Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood

Third Edition

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

Introduction: How to Use This Book

This book is intended to be used like an encyclopedia, and for this reason, there is no index. We use a uniform format to present information on all of the various syndromes. A complete list of subheadings follows. If there is no relevant information for one or more of the subheadings for a given syndrome, the heading is excluded. The only exception is the subheading “Anesthetic Considerations,” which is included even when there are no apparent anesthetic implications. This information is important for the clinician to know. “MIM #” refers to the listing number(s) of the syndrome in McKusick's *Mendelian Inheritance in Man* (see Preface). We have tried to list all possible findings associated with a particular syndrome. This might include findings noted in a small number of patients which might not be a consequence of the syndrome, but which have been reported. In addition, not all patients with a specific syndrome are expected to have all, or even most, of the possible findings. We list these as things to be aware of and to look for, not necessarily things that will be found. When preceded by “occasional,” “can have,” or a similar notation, the implication is that this is a particularly uncommon finding. The references are a bibliography and may or may not be directly referred to in the text. Sources in the bibliography are listed in reverse chronologic order.

Name

Synonym(s)

MIM #

HEENT/Airway

Chest

Cardiovascular

Neuromuscular

Orthopedic

GI/GU

Other

Miscellaneous

Anesthetic Considerations

Bibliography

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Glossary

A

Aclasis:

Pathologic tissue originates from, and is continuous with, normal tissue, providing continuity of structure.

Acro-:

Refers to distal or extreme.

Acrocephaly:

Pointed cranium, secondary to coronal and lambdoidal synostosis.

Acrodysostosis:

Congenital malformation of the distal bones of the extremities.

Acromelic:

Pertaining to the distal segment of long bones.

Adactyly:

A developmental anomaly characterized by absence of the fingers or the toes.

Allele:

One of two or more alternative forms of a gene which occupy corresponding loci on homologous chromosomes. More than two alternative forms of a gene are known as multiple alleles.

Ankylosis:

Stiffening or fixation of a joint, due to injury, disease, or surgical intervention.

Anosmia:

The inability to smell.

Apoptosis:

Programmed cell death.

Arhinencephaly:

Absence of the rhinencephalon (primarily involves olfactory nerves, bulbs, and tracts).

Arthrogryposis:

A fixed flexion or contracture deformity of a joint. May be congenital.

B

Bathrocephaly:

"Step" cranium, secondary to excessive bone formation at the lambdoid suture. There is a deep groove at the lambdoid suture between the occipital and parietal bones.

Blepharophimosis:

Inability to open the eyelids to their full extent secondary to lateral displacement of the inner canthi.

Brachycephaly:

Broad cranium, secondary to coronal synostosis which prevents anteroposterior skull growth.

Brachydactyly:

A developmental anomaly characterized by short fingers and toes.

C

Camptodactyly:

Permanent flexion deformity of one or both interphalangeal joints of a finger.

Camptomelic:

Pertaining to the permanent bending or bowing of one or more limbs.

Cleido-:

Refers to the clavicle (from the Greek, for hook).

Clinodactyly:

A developmental anomaly characterized by permanent lateral or medial deflection of a finger.

Coxa plana:

Osteochondrosis of the capital femoral epiphysis (head of the femur).

Coxa valga:

A hip deformity due to abnormal angulation of the femoral head such that the thigh is kept abducted (from the Latin for bowlegged). The angle between the femoral neck and the shaft is more obtuse than normal. The opposite of coxa vara.

Coxa vara:

A hip deformity due to abnormal angulation of the femoral head such that the thigh is kept in a state of adduction (from the Latin for crooked), and the leg appears shortened. The angle between the femoral neck and the shaft is more acute than normal. The opposite of coxa valga.

Craniosynostosis:

Premature closure of one or more cranial sutures.

Crus:

A general term used to refer to anything resembling a leg. For example, the depression of the external ear, paralleling the posterior border, between the helix and the antihelix.

Cryptophthalmos:

A developmental anomaly characterized by skin which is continuous over the eyeballs, without any evidence of eyelid formation.

Cryptorchidism:

A developmental defect characterized by full or partial failure of the normal descent of a testis from its fetal position in the abdomen to its postnatal position in the scrotum.

Cubitus valgus:

Lateral deviation of the extended forearm at the elbow.

Cubitus varus:

Medial deviation of the extended forearm at the elbow.

Cutis marmorata:

A transitory mottling of the skin, which is sometimes associated with exposure of the skin to cold.

Cyclopia:

Merging of both orbits into a single orbit containing one eye.

D

Diaphysis:

The shaft of a long bone.

Dolichocephaly:

Long, narrow cranium, secondary to sagittal synostosis, which prevents lateral skull growth.

Dwarf:

An abnormally small person. Dwarfism can be proportionate or disproportionate.

Dysostosis:

A defect in the ossification of (fetal) cartilage leading to malformation of individual bones.

E

Ectopia cordis:

Congenital displacement of the heart outside of the thoracic cavity.

Ectrodactyly:

("Lobster claw" deformity) A congenital deformity in which the hand, and less frequently the foot, is split down the middle and thus resembles a lobster claw.

Epiphysis:

The part of a long bone derived from an ossification center, located at the end of a long bone and usually wider than the shaft (the diaphysis). It is originally separated from the shaft of the bone by cartilage.

Equinovarus:

See talipes equinovarus.

Exome:

The part of the genome formed by exons, the coding portion of the gene that is eventually represented in the encoded protein.

Exostosis:

A benign bony tumor or growth arising from the surface of a bone, characteristically capped by cartilage.

G

Genu valgum:

"Knock-knees." A knee deformity in which there is abduction of the lower leg in relation to the thigh.

Genu varum:

"Bowlegs." A knee deformity in which there is adduction of the lower leg in relation to the thigh.

Gibbus:

A general term meaning hump. Often used to refer to a deformity of the spine.

Glossoptosis:

Downward displacement or retraction of the tongue.

H

Heterochromia:

A different color in two similar structures. Typically used to describe the situation of one brown eye and one blue eye.

Hydromyelia:

An increase in fluid in a dilated central canal of the spinal cord.

Hyperkeratosis:

Hypertrophy of the stratum corneum layer of skin.

Hyperostosis:

Hypertrophy of bone.

Hypertelorism:

Abnormally increased distance between two paired organs or parts. Used almost exclusively to describe ocular hypertelorism, where the eyes are abnormally far apart.

Hypertrichosis:

Excessive growth of hair, typically in places which normally have minimal or no hair.

Hypotelorism:

Abnormally decreased distance between two paired organs or parts. Used almost exclusively to describe ocular hypotelorism, where the eyes are abnormally close together.

K

Keratoconus:

A noninflammatory, abnormal protrusion of the cornea.

Keratosis pilaris:

Development of keratotic plugs in hair follicles causing discrete follicular papules, usually occurring on the arms and thighs.

L

Lissencephaly:

Smooth brain with lack of normal sulci and gyri.

Livedo reticularis:

A diffuse flat purple to red vascular discoloration of the skin. It is lacy, in the form of a reticulum ("net-like").

M

Macrocephaly:

Abnormally large head.

Megalencephaly:

Abnormally large brain. This is in contradistinction to hydrocephalus in which the intracranial volume is enlarged, but due to excessive cerebrospinal fluid rather than overgrowth of neural tissue.

Mesomelic:

Pertaining to the middle segment of long bones.

Metaphysis:

The part of the shaft of a long bone (the diaphysis) where it joins the epiphysis.

Metatarsus varus:

Inward deviation of the sole of the foot, such that the individual must walk on the outer border of the foot.

Microcephaly:

Abnormally small head, usually associated with mental retardation.

Micrognathia:

Abnormally small mandible.

Micromelia:

A developmental anomaly characterized by abnormally short limbs.

Mosaicism:

A situation in which two or more cell lines are derived from a single zygote, but are genotypically distinct.

O

Oligodactyly:

A developmental anomaly characterized by the presence of fewer than five digits on an extremity.

Opisthotonos:

A form of spasm in which the body arches backward.

Osteochondrodysplasia:

Abnormal development of bone or cartilage.

Osteochondrosis:

Degeneration of the ossification centers in children, followed by regeneration or recalcification.

P

p:

Symbol for the short arm of a chromosome.

Pachygyria:

Abnormal brain development resulting in thickened convolutions (gyri) and fewer sulci.

Periostosis:

Abnormal deposition of periosteal bone.

Pes cavus:

Exaggeration of the height of the longitudinal arch of the foot.

Pes planus:

"Flatfoot." Flattening of the longitudinal arch of the foot.

Phocomelia:

A developmental anomaly characterized by proximal segment shortening of the long bones, such that the hands and feet are attached close to the trunk. A classic example is the "thalidomide baby."

Pinguecula:

A yellowish fibrous thickening of the cornea, usually located on the medial side. Occurs often in the elderly.

Plagiocephaly:

Slanted cranium, secondary to unilateral coronal synostosis.

Platyspondyly:

Flattened vertebral bodies.

Poikiloderma:

An atrophic skin condition in which there are also pigmentary changes, giving the skin a mottled appearance.

Polydactyly:

A developmental anomaly characterized by extra digits (fingers or toes). Polydactyly may be preaxial or postaxial (see below).

Porencephaly:

The presence of one or more cavities (cysts) in the brain which may or may not communicate with the subarachnoid space.

Postaxial:

Posterior to the axis of the body or a limb—specifically the medial (ulnar) side of the upper extremities and the lateral (fibular) side of the lower extremities.

Preaxial:

Anterior to the axis of the body or a limb—specifically the lateral (radial) side of the upper extremities and the medial (tibial) side of the lower extremities.

Prognathia:

Large and/or protruding mandible.

Pseudoarthrosis:

A "false joint" as a result of a pathologic fracture in a long bone such that there is movement at a point along the diaphysis of the long bone.

Pseudocamptodactyly:

A flexion deformity of the fingers that occurs only with wrist extension. A result of short flexor muscles and tendons rather than a fixed flexion deformity.

Pseudohermaphrodite:

An individual whose gonads are definitively male or female, but whose external genitalia are ambiguous, indeterminate, or inconsistent. Female pseudohermaphrodites have ovaries and male pseudohermaphrodites have testes.

Pterygium:

An abnormal skin web.

Q

q:

Symbol for the long arm of a chromosome.

R

Rachitic:

Bony changes similar to those seen with rickets.

Retrognathia:

Abnormally positioned mandible, such that the mandible is behind the frontal plane of the forehead.

Rhizomelic:

Pertaining to the hip or shoulder joints (from the Greek, referring to the root of a limb).

S

Scaphocephaly:

"Boat-shaped" cranium, secondary to sagittal synostosis which prevents lateral skull growth.

Schizencephaly:

Abnormal clefts in the brain.

Spondylo-:

Refers to the vertebrae or spinal column.

Symphalangism:

Congenital end-to-end fusion of contiguous phalanges of a digit.

Syndactyly:

Webbing together of adjacent fingers or toes.

Synophrys:

Eyebrows that overgrow and fuse in the midline.

Synostosis:

The osseous union of bones that are normally distinct.

T

Talipes equinovarus:

One of the most common of the clubfoot deformities. There is a combination of an equinus deformity (plantar extension) and a varus deformity (inversion of the foot).

Telecanthus:

Abnormally increased distance between the medial canthi of the eyelids.

Torticollis:

"Wry-neck." Cervical muscle contracture leading to twisting of the neck so that the head is pulled to one side with the chin pointing to the opposite side.

Trident hand:

A congenital deformity in which the hand is three-pronged.

Trigonocephaly:

Triangular cranium, secondary to metopic synostosis.

Turricephaly:

Tower-shaped cranium, secondary to coronal and lambdoidal synostosis.

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Syndromes Starting with Numerals

2-Methylacetoacetyl-CoA thiolase deficiency

See Beta-ketothiolase deficiency

3ß-Hydroxysteroid dehydrogenase deficiency

Included in Congenital adrenal hyperplasia

3-Hydroxy-3-methylglutaryl-CoA lyase deficiency

See Hydroxymethylglutaric aciduria

3-Ketothiolase deficiency

See Beta-ketothiolase deficiency

3MC syndrome

See Malpuech syndrome

3-MCCD

See 3-Methylcrotonyl-CoA carboxylase I deficiency

3-Methylcrotonyl-CoA carboxylase I deficiency

Synonym: 3-MCCD; 3-Methylcrotonylglycinuria I

MIM #: 210200

This autosomal recessive disorder of leucine catabolism results in the accumulation of 3-methylcrotonylglycine and other acid metabolites in the urine. A mutation in the gene encoding the alpha-subunit of 3-methylcrotonyl-CoA carboxylase leads to accumulation of 3-methylcrotonyl-CoA, which is then converted into 3-methylcrotonylglycine, 3-methylcrotonic acid, and 3-hydroxyisovaleric acid. Secondary carnitine deficiency may occur as carnitine is consumed in conjugating these acid metabolites. Carnitine deficiency leads to impaired ß-oxidation of fatty acids, which has a significant effect on cardiac and skeletal muscle function as both rely in great part on fatty acid metabolism for energy. Recent expansion of newborn screening methods has led to increased detection of 3-methylcrotonyl-CoA carboxylase I deficiency, which has now become recognized as a common cause of organic aciduria. Treatment of the disorder consists of a protein-restricted diet and carnitine supplementation.

Cardiovascular: Cardiomyopathy. Arrhythmias.

Neuromuscular: Hypotonia and muscle atrophy. Developmental delay, intellectual disability. Apnea. Seizures.

GI/GU: Dysphagia. Gastroesophageal reflux.

Other: Failure to thrive. Metabolic acidosis, which can be profound. Hypoglycemia, hyperammonemia, neutrophilia. Secondary carnitine deficiency.

Figure: See **Appendix D**

Anesthetic Considerations: Consider evaluation of carnitine levels preoperatively. Patients are at risk for metabolic decompensation, hypoglycemia, and acidosis. Acute exacerbations should be treated with glucose and bicarbonate. Extended perioperative fasts must be avoided. Patients with cardiomyopathy require an appropriately tailored anesthetic. Propofol should be used cautiously as it can further impair mitochondrial ß-oxidation by inhibiting mitochondrial function. Bupivacaine should also be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

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3-Methylcrotonylglycinuria I

See 3-Methylcrotonyl-CoA carboxylase I deficiency

3-Oxothiolase deficiency

See Beta-ketothiolase deficiency

4-Hydroxyphenylpyruvic acid dioxygenase (oxidase) deficiency

See Tyrosinemia III

4p-syndrome

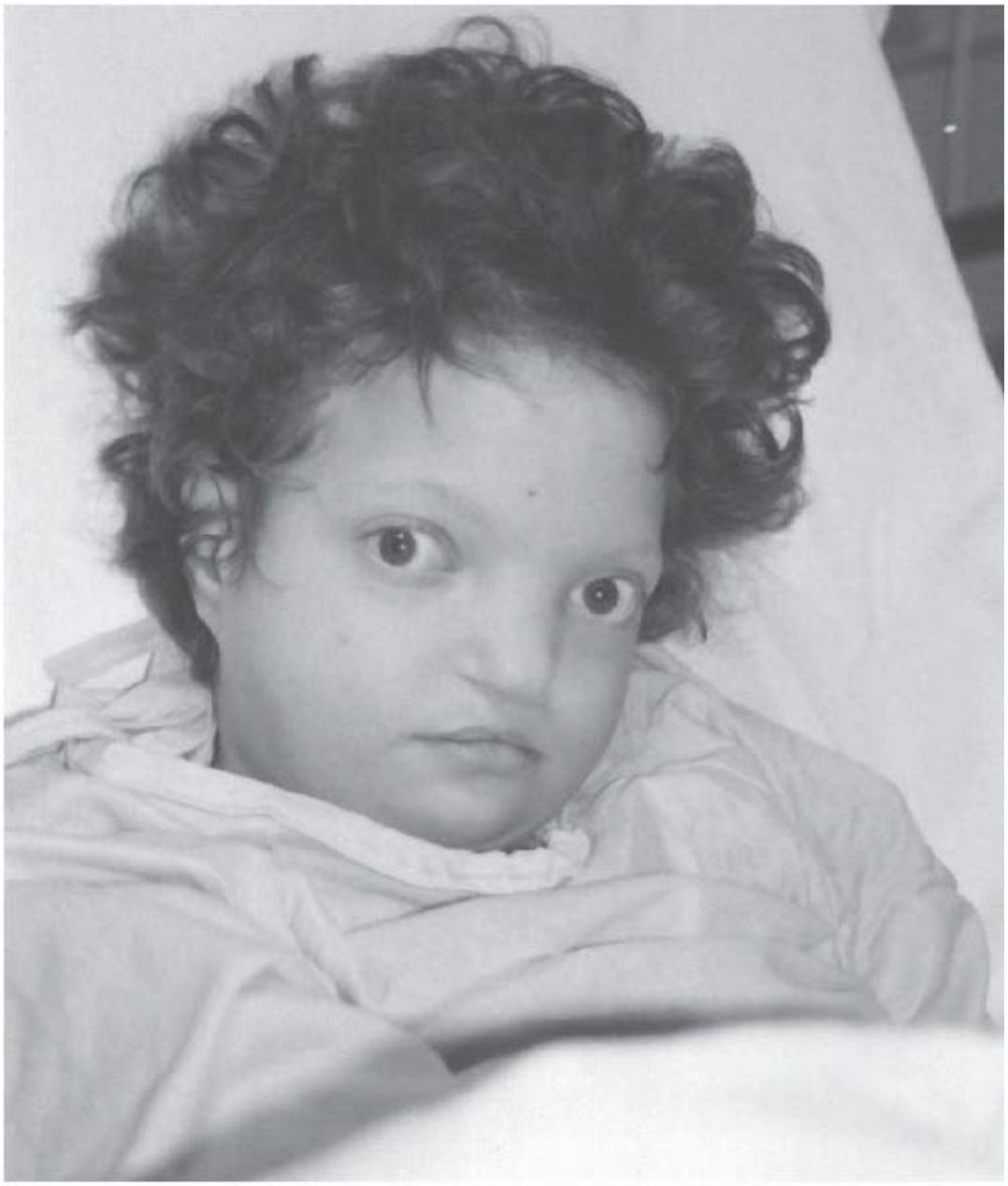
Synonym: Wolf-Hirschhorn syndrome (Includes Pitt-Rogers-Danks syndrome)

MIM #: 194190

This syndrome is due to a deletion of the short arm of chromosome 4 (deletion of chromosome 4p16.3). It is marked by a variety of midline fusion defects, and close to one-third die by 2 years of age. Deletions are of variable sizes. Deletions tend to be paternally derived while translocations tend to be maternally derived. **Pitt-Rogers-Danks syndrome** (another 4p deletion syndrome) is probably a milder clinical variation of Wolf-Hirschhorn syndrome.

HEENT/Airway: Microcephaly, prominent glabella (area of the forehead just above the nose—"Greek helmet facies"), midline scalp defects. Hypertelorism, epicanthal folds, strabismus, iris coloboma, and high-arched eyebrows. Simple, low-set ears with preauricular pits or tags. Short upper lip and philtrum, downturned fishlike mouth, fused teeth, delayed tooth eruption and shedding of deciduous teeth, bilateral cleft lip and cleft palate. Micrognathia. Webbed neck.

Chest: Patients often have recurrent aspiration secondary to severe neurologic disability. Recurrent respiratory tract infections. May have diaphragmatic hernia, pulmonary isomerism (symmetric right and left lung).



4p-syndrome. This 10-year-old girl with 4p-syndrome has characteristic facies. She has profound psychomotor retardation. She does not walk or talk.

Cardiovascular: Atrial and ventricular septal defects, pulmonary stenosis.

Neuromuscular: Severe mental and motor delay. Hypotonia, seizures. Seizures often severe in infancy and decrease in frequency after age 5 years. May have absent septum pellucidum, agenesis of the corpus callosum, lateral and third ventricle enlargement, interventricular cysts.

Orthopedic: Scoliosis. Simian crease, hyperconvex nails, polydactyly. Absent pubic rami, congenital hip dislocation, metatarsus adductus, clubfoot deformity. Fused or bifid vertebrae. Short stature.

GI/GU: Malrotation of the gut. Hypospadias, cryptorchidism, absent uterus. Renal hypoplasia.

Other: Intrauterine growth retardation. Precocious puberty. May have variable deficiency of one of several immunoglobulins.

Anesthetic Considerations: Micrognathia may make direct laryngoscopy and tracheal intubation difficult. A single case of malignant hyperthermia in a young child with Wolf-Hirschhorn syndrome has been reported (6), but there is no other evidence that malignant hyperthermia is associated with the syndrome (2,5).

Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Care must be taken in positioning because of scoliosis and possible congenital hip dislocation. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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5α-Reductase deficiency

Synonym: Pseudovaginal perineoscrotal hypospadias; Steroid 5α-reductase 2 deficiency; Pseudohermaphroditism, male

MIM #: 264600

This male-limited autosomal recessive disease is another cause of male pseudohermaphroditism. A mutation in the steroid 5α-reductase 2 gene results in defective conversion of testosterone to dihydrotestosterone. Thus, levels of

testosterone are normal. At least 45 distinct mutations have been described. Masculinization at puberty is due to retained activity of the 5α-reductase 1 gene.

GI/GU: Ambiguous genitalia. Small phallus, a bifid scrotum, and perineal hypospadias. Histologically normal testes, epididymides, and vasa deferentia. Underdeveloped seminal vesicles that lead into a vagina, which usually ends blindly. Absent or rudimentary prostate. Can have a urogenital sinus. Sperm production is minimal or absent, and fertility usually requires *in vitro* intervention.

Other: With puberty, there is masculinization with deepening voice, phallic enlargement, and a scanty beard. Affected 46, XY males raised as females often revert to male gender identity at the time of expected puberty.

Miscellaneous: Inhibition of 5α-reductase has been suggested for the prevention of male pattern baldness and for the treatment of resistant acne, benign prostatic hypertrophy, and idiopathic hirsutism. *Middlesex*, by Jeffrey Eugenides, the winner of the 2003 Pulitzer Prize for fiction, is told from the perspective of the protagonist, who had 5α-reductase deficiency. In a New Guinea population, the disorder is common enough that affected individuals are recognized early and assigned to a third sex. However, they face the same problems when forced to adjust to adult gender roles.

Anesthetic Considerations: A certain degree of sensitivity is required when speaking with patients, or families of patients, with intersex disorders.

Figure: See **Appendix A**

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5p-Syndrome

See Cri-du-chat syndrome

5,10-Methylene tetrahydrofolate reductase deficiency

Synonym: MTHFR deficiency; Methylene tetrahydrofolate reductase deficiency

MIM #: 236250

This autosomal recessive disorder is due to a defect in 5,10-methylene tetrahydrofolate reductase (MTHFR) and leads to increased homocysteine levels. MTHFR is a cytoplasmic enzyme involved in the metabolism of the sulfur-containing amino acids. Specifically, it catalyzes the conversion of 5,10-methylene tetrahydrofolate to 5-methyl tetrahydrofolate. The methyl group is donated to homocysteine (catalyzed by methionine synthase) to form methionine. The clinical severity mirrors the degree of enzyme activity deficiency and the age of onset varies from infancy to adulthood. Two-thirds of patients are female. The disease can have findings similar to homocystinuria,

and defects in this enzyme are referred to as homocystinuria type III. The disease is generally very difficult to treat. Certain specific mutations can be a risk factor for spina bifida and anencephaly. The C667T single nucleotide polymorphism (SNP) (the thermolabile variant) is relatively common and associated with a hypercoagulable state. It has also been associated with preeclampsia. Most patients are heterozygous for several substitutions in the gene (compound heterozygotes).

HEENT/Airway: Microcephaly. Lens dislocation.

Cardiovascular: High levels of homocysteine have been implicated as a cardiovascular risk factor due to increased thrombogenesis. MTHFR deficiency may be implicated in the development of coronary artery disease. The C667T SNP, which is relatively common in the population, has been shown to be associated with increased risk of asymptomatic carotid artery disease in postmenopausal women.

Neuromuscular: Mild developmental delay and intellectual disability. Hallucinations, delusions, catatonia. Waddling gate, seizures. Proximal muscle weakness. The neuropathologic findings include dilated ventricles, microgyria, demyelination, macrophage infiltration, and gliosis. Arterial and venous cerebrovascular thrombosis can be fatal. Risk of spina bifida and anencephaly. There is variability in the age of onset of symptoms and the severity of symptoms.

Other: Vascular thrombosis and vascular changes similar to those of homocystinuria (see later). The prothrombotic state can result in both arterial and venous thromboses. Patients have elevated homocysteine levels and homocystinuria, although to a far lesser degree than in the disease homocystinuria. A megaloblastic anemia only rarely develops in these patients. This defect may predispose to preeclampsia.

Miscellaneous: The increased risk of spina bifida and anencephaly with certain mutations may account, at least in part, for the effect of maternal dietary folate supplementation in decreasing the risk of these defects in fetuses of normal women. Because arsenic is detoxified by demethylation, the decreased availability of methyl donors in this disease has been suggested to increase the neurotoxicity of arsenic.

Anesthetic Considerations: 5,10-Methylene tetrahydrofolate reductase immediately precedes methionine synthetase in the pathway involved with methionine synthesis. Given the inhibitory effect of nitrous oxide on the latter enzyme (via irreversible oxidation of the cobalt atom of vitamin B_{12}), nitrous oxide is usually avoided in these patients, and neurologic deterioration (6) as well as death have been reported after anesthesia with nitrous oxide (7). However, in a recent prospective study, 98 patients homozygous for an *MTHFR* gene variant received nitrous oxide intraoperatively without an increase in perioperative morbidity or mortality (1). These patients may be at increased risk for perioperative vascular thrombosis/embolization and merit meticulous attention to hydration and homeostasis. Patients may be on anticoagulants and require perioperative conversion to heparin. Patients should be monitored postoperatively for pulmonary emboli and myocardial infarction, although the most recent study did not show any increase in postoperative cardiac injury in patients with MHTFR (1).

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9p-Syndrome

MIM #: 158170

This syndrome is due to a deletion of the short arm of chromosome 9. The clinical picture is variable, but craniosynostosis, a long philtrum, hernias, and digital abnormalities are always present.

HEENT/Airway: Craniosynostosis (particularly of metopic suture), flat occiput. Trigonocephaly. Upward-slanting palpebral fissures, epicanthal folds, prominent eyes due to hypoplastic supraorbital ridges, highly arched eyebrows. Poorly formed, posteriorly rotated ears with adherent earlobes. Midface hypoplasia with short nose, flat nasal bridge, and anteverted nostrils. Choanal atresia. Long philtrum, small mouth, cleft palate, high-arched palate. Micrognathia. Short, broad neck with low posterior hairline.

Chest: Diaphragmatic hernia.

Cardiovascular: Congenital cardiac defects, most frequently ventricular septal defect, patent ductus arteriosus, or pulmonic stenosis.

Neuromuscular: Moderate to severe intellectual disability, but often with good social adaptation, and psychological similarities to those of Williams syndrome (see later) have been noted. Poor memory, visual-motor skills, and visual-spatial skills.

Orthopedic: Normal growth, scoliosis. Long middle phalanges, short distal phalanges, simian crease,

postaxial polydactyly. Foot positioning defects. Long fingers and toes.

GI/GU: Diastasis recti, inguinal and umbilical hernias. Micropenis, cryptorchidism, hypoplastic labia majora. Hydronephrosis.

Other: Nonketotic hyperglycinemia (see later) has been observed in a patient with 9p-syndrome, suggesting at

least one of the genes for that syndrome resides on the short arm of chromosome 9.

Miscellaneous: Acute leukemia has been associated with partial deletion of the short arm of chromosome 9, and the affected gene is usually maternally derived. 9p deletion has also been implicated in the development of other cancers.

Anesthetic Considerations: The small mouth, micrognathia, and short neck may make direct laryngoscopy and tracheal intubation difficult (1). Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

Bibliography:

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10 qter Deletion syndrome

MIM #: 609625

This syndrome involves a deletion of the terminal portion of the long arm of chromosome 10. Patients have characteristic facies, variable intellectual disability, and cardiac and anogenital anomalies. Most patients have been female.

HEENT/Airway: Microcephaly. Facial asymmetry. Upward-slanting palpebral fissures, hypertelorism. Broad, beaklike nose. Micrognathia. Short neck.

Cardiovascular: Congenital cardiac defects of a wide variety of types.

Neuromuscular: Variable intellectual disability.

Orthopedic: Growth retardation. May have digital abnormalities.

GI/GU: Can have bladder obstruction and urethral reflux and secondary urinary tract infections. Anogenital anomalies.

Anesthetic Considerations: Micrognathia and short neck may make laryngoscopy and tracheal intubation difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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11ß-Hydroxylase deficiency

Included in Congenital adrenal hyperplasia

11ß-Hydroxysteroid dehydrogenase deficiency

Synonym: 11ß-ketoreductase deficiency; Apparent mineralocorticoid excess

MIM #: 218030

This autosomal recessive defect in 11ß-hydroxysteroid dehydrogenase results in low renin hypertension, metabolic alkalosis, and hypokalemia. This enzyme has two functional isoforms, one of which catalyzes the conversion of cortisol to cortisone (dehydrogenase activity) and the conversion of cortisone to cortisol (oxoreductase activity). The other isoform catalyzes just the conversion of cortisol to cortisone. In this disease, there is decreased conversion of cortisol to cortisone. Other features of the defect suggest a primary mineralocorticoid excess, which cannot be documented, and the defect is also known as the syndrome of apparent mineralocorticoid excess (AME) because of a defect in the first isoform type. Apparently, the defect prevents cortisol from acting as a ligand for the mineralocorticoid receptor. Symptoms can be partially or fully reversed with spironolactone.

HEENT/Airway: Hypertensive retinopathy.

Cardiovascular: Low renin hypertension. Left ventricular hypertrophy from systemic hypertension.

Other: Hypokalemia. Low aldosterone levels.

Miscellaneous: Inhibition of this enzyme may be the mechanism of licorice-induced hypertension (very uncommon in the United States, where almost all domestic licorice is artificially flavored) (2). Similar inhibition can be caused by compounds in grapefruit juice. Activity of this enzyme may be related to the development of the metabolic syndrome, obesity, and type 2 diabetes.

Anesthetic Considerations: Patients may have significant hypertension with end-organ involvement. Blood pressure must be controlled before elective surgery. Serum potassium level should be determined preoperatively. Steroid replacement therapy should be continued perioperatively.

Figure: See **Appendix A**

Bibliography:

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11ß-Ketoreductase deficiency

See 11ß-hydroxysteroid dehydrogenase deficiency

11q-Syndrome

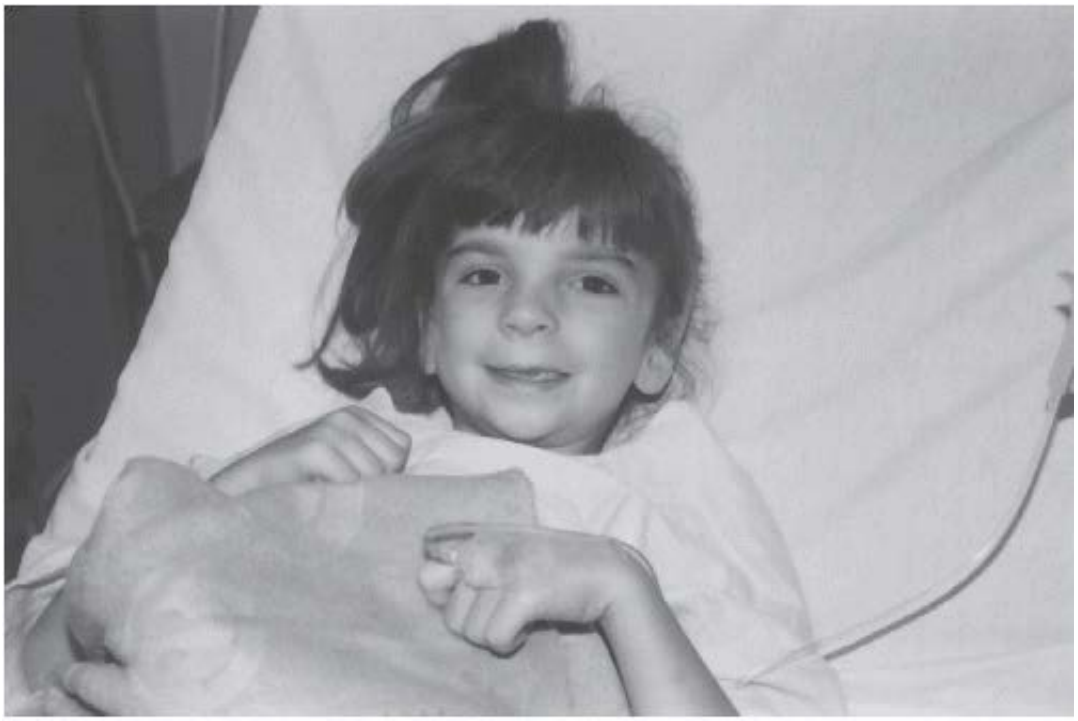
Synonym: Jacobsen syndrome

MIM #: 147791

This syndrome is due to deletion of the terminal band of the long arm of chromosome 11. This fragment of the chromosome is known to contain a heritable folate-sensitive fragile site. Two-thirds of affected children are girls. The syndrome is characterized by intrauterine and postnatal growth retardation, trigonocephaly, carp-shaped mouth, and intellectual disability.

HEENT/Airway: Trigonocephaly (see C syndrome for illustration). Microcephaly; less commonly macrocephaly. Epicanthal folds, telecanthus, hypertelorism, ptosis, strabismus, coloboma of iris or retina, retinal dysplasia. Low-set or malformed ears. Flat nasal bridge, short nose with upturned tip. Carp-shaped mouth. Micrognathia. Short neck.

Chest: Frequent respiratory infections. Pectus excavatum. Missing ribs.



11q-syndrome. This 8-year-old girl with 11q-syndrome has thrombocytopenia as well as a chronic low white

blood cell count. She has dysmorphic facies, mild intellectual disability, and congenital heart disease (parachute mitral valve and bicuspid aortic valve). She also has decreased pain sensation.

Cardiovascular: A variety of congenital cardiac defects.

Neuromuscular: Moderate to severe intellectual disability. Hypotonia in infancy, hypertonicity when older. Sleep disturbances.

Orthopedic: Growth retardation. Joint contractures. Fifth finger clinodactyly, brachydactyly. Hammer toe. Bilateral camptodactyly. Short fingers.

GI/GU: Pyloric stenosis, inguinal hernia. Annular pancreas. Hypospadias, cryptorchidism, hypoplasia of labia and clitoris, vesicoanal fistula.

Other: Intrauterine growth retardation, failure to thrive. Isoimmune thrombocytopenia is common. May have pancytopenia.

Anesthetic Considerations: Tracheal intubation may be difficult due to the short neck and micrognathia. Contractures may make optimal positioning difficult. Baseline platelet count should be obtained. Bleeding from thrombocytopenia is a very real concern. In addition to platelet transfusion, DDAVP has been suggested for minor surgery. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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1. Easley RB, Sanders D, McElrath-Schwartz J, et al. Anesthetic implications of Jacobsen syndrome. *Paediatr Anaesth* 2006; 16:66-71.

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13q-Syndrome

MIM #: 613884

The phenotype and natural history of this syndrome is variable, based on the specific chromosomal section deleted. Patients have characteristic facies and variable degrees of intellectual disability. It is frequently associated with the development of retinoblastoma.

HEENT/Airway: Microcephaly. May have trigonocephaly or facial asymmetry. High forehead. Hypertelorism, ptosis, epicanthal folds, microphthalmia. May have colobomas. Retinoblastomas, often bilateral. May have dysplastic retina or optic nerve. Anteverted earlobes. Prominent nasal bridge, short bulbous nose. Prominent maxilla. Long philtrum. Large mouth. Micrognathia. May have narrow palate. Short webbed neck.

Cardiovascular: Cardiac defects.

Neuromuscular: Intellectual disability. May have holoprosencephalic type of brain defects.

Orthopedic: Growth deficiency, often of prenatal onset. Small or absent thumbs, clinodactyly of fifth finger, fused fourth and fifth metacarpals. Talipes equinovarus, short hallux. Focal lumbar agenesis.

GI/GU: May have imperforate anus or Hirschsprung disease. Hypospadias, cryptorchidism. May have bifid scrotum or renal anomalies.

Anesthetic Considerations: Tracheal intubation may be difficult due to prominent maxilla, micrognathia, and short neck. May come to the operating room for Hirschsprung disease or the development of retinoblastoma requiring enucleation. In two case reports, tracheal intubation was not difficult.

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2. Mayhew JF, Fernandez M, Wheaton M. Anesthesia in a child with deletion 13q syndrome [Letter]. *Paediatr Anaesth* 2005;15:350.

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17α-Hydroxylase deficiency

Included in Congenital adrenal hyperplasia

17β-Hydroxysteroid dehydrogenase deficiency

See 17-Ketosteroid reductase deficiency

17-Ketosteroid reductase deficiency

Synonym: 17β-hydroxysteroid dehydrogenase deficiency; Pseudohermaphroditism, male

MIM #: 614279

This autosomal recessive disorder, due to inadequate function of the gene for 17-ketosteroid reductase, results in male pseudohermaphroditism. This enzyme is required for the final step in androgen production. These children are XY males, with testes, but have female external genitalia. There is virilization with normal male secondary sex characteristics at puberty. Of interest, this enzyme is nonfunctional until puberty, when there is a progressive increase in activity, with increases in testosterone to almost normal levels. Children are usually raised as girls, and removal of the testes can prevent the pubertal masculinization. In genetic females, this defect can result in polycystic ovaries and hirsutism. The findings in this disorder are very similar to those of 5α-reductase deficiency.

GI/GU: Male pseudohermaphroditism—there are female-appearing external genitalia at birth, though the genitalia may be somewhat ambiguous. Inguinal testes, with normal virilization at puberty.

Other: Gynecomastia, infertility, hypothyroidism.

Anesthetic Considerations: Patients may be hypothyroid. Otherwise, there are no metabolic consequences of particular importance to anesthesia. However, a particular degree of sensitivity is needed when speaking to girls and boys with gender ambiguity.

Figure: See **Appendix A**

Bibliography:

1. Castro-Magana M, Anguo M, Uy J. Male hypogonadism with gynecomastia caused by late-onset deficiency of testicular 17-ketosteroid reductase. *N Engl J Med* 1993;328:1297-1301.

17,20-Desmolase (lyase) deficiency

Synonym: Desmolase deficiency; Pseudohermaphroditism, male

MIM #: 309150

This X-linked (probably recessive) disorder is due to the absence of the enzyme 17,20-desmolase, which is involved in steroid biosynthesis. Because this enzyme is not involved in the pathway for hydrocortisone, the adrenogenital syndrome does not occur. This enzyme, as well as other enzymes of steroidogenesis, is a cytochrome P450 oxidase, and is also known as P450c17. Absence of the desmolase activity results in deficient gonadal sex hormone production. Genetic boys have female external genitalia (male pseudohermaphroditism), and girls are phenotypically normal but fail to undergo adrenarche and puberty.

Although deficient 17,20-desmolase and 17α-hydroxylase activities can occur separately and were thought to represent two distinct enzymes, they are currently known to reside in a single protein. The gene for this protein has been localized to chromosome 10, and at least 16 distinct mutations have been described.

GI/GU: Ambiguous genitalia in boys and pubertal developmental failure in girls. Adrenal hyperplasia.

Anesthetic Considerations: There are no metabolic consequences of particular importance to anesthesia. However, a particular degree of sensitivity is needed when speaking to girls and boys with gender ambiguity.

Figure: See **Appendix A**

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1. Zachmann M. Prismatic cases: 17,20-desmolase (17,20-lyase) deficiency. *J Clin Endocrinol Metab* 1996;81:457-459.

17p-Syndrome

See Smith-Magenis syndrome

18-Hydroxylase deficiency

Synonym: Corticosterone methyl oxidase I deficiency

MIM #: 203400

This autosomal recessive disorder in steroid biosynthesis results in aldosterone deficiency. This enzyme (possibly part of a multifunctional enzyme P450C11) is responsible for the conversion of corticosterone to aldosterone.

GI/GU: Poor feeding with occasional vomiting.

Other: Failure to thrive, dehydration, and intermittent fever. Hypernatremia. Hypokalemia.

Anesthetic Considerations: Patients should have baseline electrolyte and hydration status evaluated. Patients with a history of poor feeding and vomiting are at increased risk for perioperative aspiration. Patients should receive stress dose steroids perioperatively and then continue on steroid replacement therapy.

Figure: See **Appendix A**

Bibliography:

1. White PC, New MI, Dupont B. Congenital adrenal hyperplasia. *N Engl J Med* 1987;316:1580-1586.

18p-Syndrome

MIM #: 146390

This syndrome is due to deletion of the short arm of chromosome 18. The hallmark findings are intellectual disability, growth deficiency, and prominent ears. However, there may be significant variability in expression.

HEENT/Airway: Microcephaly, rounded face. Ptosis, epicanthal folds, loss of hair of outer eyebrows, hypertelorism, cataracts, strabismus. Large, protruding ears. Low nasal bridge. Wide mouth with downturned corners, dental caries, cleft palate. Micrognathia. Webbed neck.

Chest: Pectus excavatum, broad chest.

Cardiovascular: Congenital heart disease.

Neuromuscular: Mild to severe intellectual disability, particularly poor language skills. Restlessness, emotional lability, fear of strangers. Hypotonia. May have holoprosencephaly.

Orthopedic: Mild to moderate growth deficiency. Kyphoscoliosis. Small hands and feet, clinodactyly of fifth finger, simian crease. Cubitus valgus, dislocated hip, clubfoot deformity. Rheumatoid arthritis-like picture, polymyositis.

GI/GU: Inguinal hernia. Genital anomalies.

Other: May have immunoglobulin A (IgA) deficiency. Hypopituitarism. Alopecia, hypopigmentation.

Anesthetic Considerations: Although not reported, micrognathia might make direct laryngoscopy and tracheal intubation difficult. Behavioral problems may complicate preoperative management. Patients with IgA deficiency

may have allergic reactions to the IgA found in transfused blood. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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1. Wester U, Bondeson ML, Edeby C, et al. Clinical and molecular characterization of individuals with 18p deletion: a genotype-phenotype correlation. *Am J Med Genet A* 2006;140:1164-1171.

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18q-Syndrome

MIM #: 601808

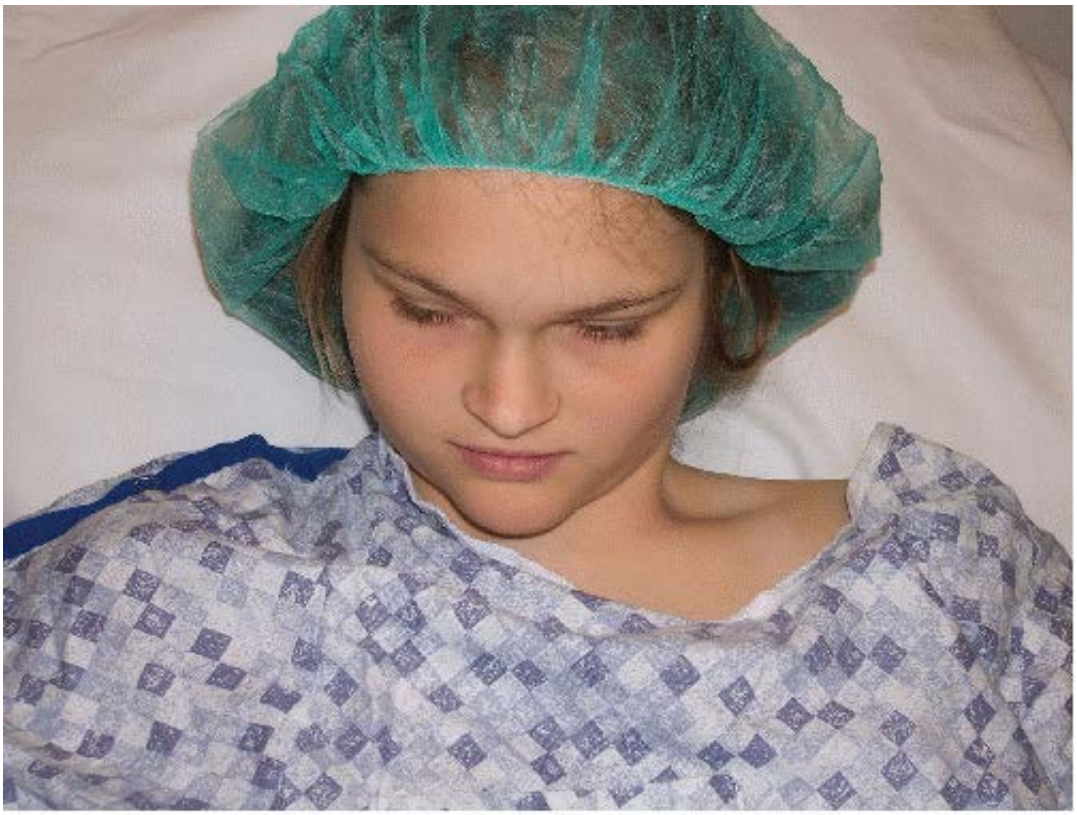
This syndrome is due to a deletion of the long arm of chromosome 18. There is significant clinical variability. In general, the size of the deletion correlates with the severity of the disease. The primary findings are intellectual disability, small stature, hypotonia, midface hypoplasia, and clubfoot deformities.

HEENT/Airway: Microcephaly, midface hypoplasia. Deep-set eyes, epicanthal folds, slanted palpebral fissures, hypertelorism, microphthalmia, hypoplasia of iris, cataracts, retinal defect, myopia, nystagmus. Prominent antihelix or antitragus, narrow or atretic external auditory canal with conductive deafness. Can have sensorineural hearing loss. Carp-shaped mouth. Narrow palate, cleft lip or palate.

Chest: Extra rib. Widely spaced nipples.

Cardiovascular: Congenital heart disease, including absent pulmonary valve.

Neuromuscular: Moderate to severe intellectual disability. Hypotonia, poor coordination. May have seizures, choreoathetosis, atrophy of olfactory and optic tracts, poorly myelinated central white matter tracts, hydrocephalus, porencephalic cysts, cerebellar hypoplasia. Behavioral problems.



18q-syndrome. FIG. 1. This shy 15-year-old required repeat surgery for a cavus foot deformity. She has a markedly diminished sensitivity to pain and has refused a nerve block or regional block as unnecessary. She also has some hearing loss and growth hormone deficiency.

18q-syndrome. FIG. 2. Lateral view.

Orthopedic: Small stature. Long hands, tapered fingers, short first metacarpals, simian crease. Hypoplastic tapering of distal legs, abnormal placement of toes, clubfoot deformity. Dimpled skin over acromion and knuckles.

GI/GU: Horseshoe kidney. Hypoplastic labia majora. Cryptorchidism, micropenis.

Other: May have immunoglobulin A (IgA) deficiency. Eczema. Hypothyroidism.

Anesthetic Considerations: Behavioral problems may complicate preoperative care. The anesthesiologist should be sensitive to possible hearing or visual deficits. Patients with IgA deficiency may have allergic reactions to the IgA found in transfused blood. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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21-Hydroxylase deficiency

Included in Congenital adrenal hyperplasia

22q11.2 Deletion syndrome

See DiGeorge syndrome

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

A

AADC deficiency

See Aromatic l-amino acid decarboxylase deficiency

Aarskog syndrome

Synonym: Aarskog-Scott syndrome; Faciodigitogenital syndrome

MIM #: 305400

This syndrome is characterized by short stature, hypertelorism, and shawl scrotum. It appears to be inherited in an X-linked recessive pattern, with female carriers expressing mild features of the syndrome in their face and hands. However, there is some evidence of autosomal dominant inheritance with a strong sex influence accounting for the preponderance of affected boys. This syndrome is caused by a mutation in the *FDG1* (faciodigitogenital) gene, which encodes the FDGY protein. This protein is a guanine nucleotide exchange factor. By activating a GTPase, it stimulates fibroblasts to form filopodia, cellular elements involved in signaling, adhesion, and migration. It also activates a kinase pathway that regulates cell growth, apoptosis, and cellular differentiation.

HEENT/Airway: Normocephalic. Rounded facies. Hypertelorism with possible ptosis of eyelids and downward slant of palpebral fissures. Widow's peak. Upper helices of the ears overfolded. Small nose, anteverted nares. Long philtrum. Maxillary hypoplasia. Slight crease below the lower lip. Delayed dental eruption. Permanent teeth characterized by broad central incisors. Short neck, occasionally with webbing. May have cleft lip and cleft palate.

Chest: Pectus excavatum.

Cardiovascular: Congenital heart disease (small ventricular septal defect) has been reported, but is uncommon.

Neuromuscular: Occasional mild to moderate intellectual disability. Attention deficit hyperactivity disorder (ADHD) common. Hypermobility of the cervical spine in association with ligamentous laxity or odontoid hypoplasia can result in neurologic deficit.

Orthopedic: Ligamentous laxity. Short stature with distally shortened limbs. Possible hypoplasia or synostosis of one or more cervical vertebrae. Brachydactyly with clinodactyly of the fifth finger, simian crease, interdigital webbing, hyperextensible fingers. Broad thumbs and great toes, flat feet. Possible spina bifida occulta. Calcified intervertebral disks. Delayed bone age.

GI/GU: “Shawl” scrotum. Cryptorchidism. Umbilical and inguinal hernias common.

Other: Isolated growth hormone deficiency. Delayed puberty.

Miscellaneous: Dagfinn Aarskog is a Norwegian pediatric endocrinologist.

Anesthetic Considerations: Although perioperative complications have not been described, the presence of vertebral laxity and/or odontoid abnormalities suggests that care should be taken to prevent excessive neck manipulation during positioning and laryngoscopy. Care must be taken in overall positioning because of generalized ligamentous laxity. Patients with congenital heart disease should receive an appropriately tailored anesthetic. ADHD can require additional attention to the preinduction period.

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Aarskog-Scott syndrome

See Aarskog syndrome

Aase syndrome

Included in Diamond-Blackfan anemia

Aase-Smith syndrome I

MIM #: 147800

This autosomal dominant syndrome is characterized by severe joint contractures (including limited ability to open the mouth), hydrocephalus, and cleft palate. There is also an Aase-Smith syndrome II, which is the same as Diamond-Blackfan anemia (see later).

HEENT/Airway: May have ptosis. External ear abnormalities. Cleft palate. Limited ability to open the mouth.

Cardiovascular: May have ventricular septal defect or multiple ventricular septal defects.

Neuromuscular: Dandy-Walker malformation with associated hydrocephalus.

Orthopedic: Severe joint contractures. Thin fingers. Absent knuckles with reduced interphalangeal creases. Inability to make a complete fist. Hypoplastic dermal ridges. Limited extension of the elbows and knees. Clubfoot deformity.

Other: Can be stillborn or die in infancy. Congenital neuroblastoma has been reported.

Anesthetic Considerations: Limitations in mouth opening persist after the induction of anesthesia (2) and may make direct laryngoscopy and tracheal intubation difficult. Patients must be carefully positioned and padded

perioperatively secondary to joint contractures and other joint abnormalities. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

Bibliography:

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2. Patton MA, Sharma A, Winter RM. The Aase-Smith syndrome. *Clin Genet* 1985;28:521-525.

Aase-Smith syndrome II

See Diamond-Blackfan anemia

Abetalipoproteinemia

Synonym: Acanthocytosis

MIM #: 200100

This autosomal recessive disease is due to the absence of apolipoprotein B, secondary to a deficiency in the microsomal triglyceride transfer protein (MTP). This is the sole apoprotein of low density lipoprotein (LDL) and one of the components of very low density lipoprotein (VLDL), so patients lack LDL and VLDL. The classic finding is the presence of acanthocytes on a blood smear (from the Greek *acanthi*, for thorn).

HEENT/Airway: Pigmentary degeneration of the retina. Ophthalmoplegia, ptosis, and anisocoria, presumably secondary to neuropathy, have been described.

Cardiovascular: Fatal cardiomyopathy has been described in a patient.

Neuromuscular: Ataxia, demyelination, and decreased deep tendon reflexes in adolescents and adults. Neurologic findings may be severe in untreated patients, with eventual inability to stand unaided. Peripheral sensory neuropathy. In general, the cranial nerves are spared, but involvement of oculomotor nerves and degeneration of the tongue have been reported. There may be muscle weakness, which can be difficult to appreciate in the presence of denervation.

Orthopedic: Untreated patients can have muscle contractures, pes cavus, clubfoot deformity, and kyphoscoliosis.

GI/GU: Vomiting and the celiac syndrome with defective absorption of lipids. The intestinal villi are normal. Malabsorption symptoms tend to diminish with age, probably reflecting, at least in great part, the aversion of these patients to dietary fat.

Other: Poor weight gain. Examination of a blood smear shows acanthocytes, a particular type of burr cell with protuberances. These cells do not easily form rouleaux, and the sedimentation rate is very low. Red blood cell survival is shortened, and there may be hyperbilirubinemia. Fat-soluble vitamin malabsorption (vitamins A, D, E, and K). Many of the findings of the disease are due to secondary vitamin E deficiency. Vitamin K malabsorption can result in prothrombin deficiency. Anemia, which has been described, is probably secondary to inadequate absorption of vitamin B_{12}, iron, and folic acid. Serum cholesterol is very low, and serum beta lipoprotein is absent.

Miscellaneous: Acanthocytes, although constituting from 50% to 100% of peripheral red blood cells, are absent in the marrow, suggesting that their formation requires exposure to plasma. The defect in the red blood cell membrane morphology can be reversed by chlorpromazine.

Anesthetic Considerations: Fat-soluble vitamins may be deficient secondary to malabsorption. The prothrombin time may be abnormal secondary to vitamin K deficiency. Patients have been said to show diminished response to local anesthetics. There are no reports of the efficacy of neuraxial blockade. The presence of denervation is a likely contraindication for succinylcholine, secondary to the risk of exaggerated hyperkalemia.

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Acanthocytosis

See Abetalipoproteinemia

Acetyl-CoA acetyltransferase 1 deficiency

See Beta-ketothiolase deficiency

Achondrogenesis

(Includes Houston-Harris achondrogenesis, Parenti-Fraccaro achondrogenesis, and Langer-Saldino achondrogenesis)

MIM #: 200600, 200610, 600972

This early lethal chondrodystrophy has been described in three forms (type IA, type IB, and type II). Type IA is also known as **Houston-Harris achondrogenesis**, and type IB is also known as **Parenti-Fraccaro achondrogenesis.** Type II achondrogenesis is also known as **Langer-Saldino achondrogenesis.** A nonlethal form of chondrodystrophy that was called achondrogenesis by Grebe is now referred to as Grebe syndrome (see later).

All patients with achondrogenesis die *in utero* or shortly after birth. Types IA, IB, and II can be distinguished on the grounds of clinical, radiologic, and histopathologic examination, but all involve severe defects in the development of cartilage and bone.

Types IA and IB achondrogenesis are inherited in an autosomal recessive fashion. Type IA is caused by a mutation in the *TRIP11* gene, which encodes the Golgi microtubule-associated protein 210 (GMAP-210). A mutation in the diastrophic dysplasia sulfate transporter gene (*DTDST*) has been shown to be the cause of type IB achondrogenesis. Thus, type IB achondrogenesis and diastrophic dysplasia (see later) are allelic disorders. Type II achondrogenesis is likely inherited in an autosomal dominant fashion, although most of the reported cases have occurred in otherwise normal families, presumably reflecting fresh mutations. A mutation in the *COL2A1* gene, leading to abnormal type II collagen, causes type II achondrogenesis. Mutations in the *COL2A1* gene are also responsible for Kniest syndrome,

spondyloepiphyseal dysplasia congenita, and Stickler syndrome (see later).

HEENT/Airway: Types IA/IB: Large poorly ossified cranium, maxillary hypoplasia or high palate, low nasal bridge, micrognathia.

Type II: Large cranium with particularly large anterior and posterior fontanelles, prominent forehead, maxillary hypoplasia or high palate, flat nasal bridge, small anteverted nares, micrognathia.

Chest: Type IA: Barrel chest. Multiple broken ribs. Hypoplastic scapulae.

Type II: Pulmonary hypoplasia.

Orthopedic: Types IA/IB: Extreme short stature. Micromelia. Short ribs. Bony ossification clearly abnormal, especially in the hands, feet, lower spine, and pelvic bones. Types IA and IB can be distinguished by radiographic features. For example, type IA involves multiple rib fractures, whereas type IB does not.

Type II: Extreme short stature. Micromelia. Short ribs, without fractures. Short, broad long bones. Bony ossification varies from normal to virtually absent in the lower spine and pelvis.

Miscellaneous: A form of type I achondrogenesis was described in 1986 and is referred to as “schnecken-becken dysplasia” (German for “snail's pelvis”; *MIM #:* 269250). It is unclear if the screenwriter of the film *The Birdcage*, who penned the line “When the schnecken beckons,” was aware of this entity (*schnecken* is a type of sweet roll).

Anesthetic Considerations: Patients are unlikely to benefit from surgery/anesthesia because of the early lethality of this disorder. Direct laryngoscopy and tracheal intubation may be difficult because of micrognathia. Care must be taken in positioning because of the severe chondrodysplasia and possibility of fractures.

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Achondroplasia

MIM #: 100800

The most common type of short-limbed dwarfism (0.36 to 0.60 per 10,000 live births in the United States), this autosomal dominant disease results from failure in development of endochondral bone primarily at the epiphyseal growth plates and the base of the skull. There is premature fusion of bones. The underlying defect is a mutation in the gene encoding fibroblast growth factor receptor 3 (*FGFR3)*. Histologic evaluation at the epiphyseal line shows short cartilaginous columns that lack the usual linear arrangement and some cartilage cells that appear to be

undergoing a mucinoid degeneration. Close to 90% of cases represent spontaneous gene mutations (affected children are born to parents without achondroplasia), with advanced paternal age an increased risk for gene mutation. The homozygous form is usually fatal within the first few weeks of life secondary to respiratory insufficiency or severe neurologic impairment from hydrocephalus. People with the heterozygous form have normal intelligence, but their average life expectancy is shorter by 10 years. Surgical decompression of the cervicomedullary junction may be performed during the first few years of life, although the timing and necessity of such intervention are still debated. Hypochondroplasia and thanatophoric dysplasia (see later) are allelic disorders.

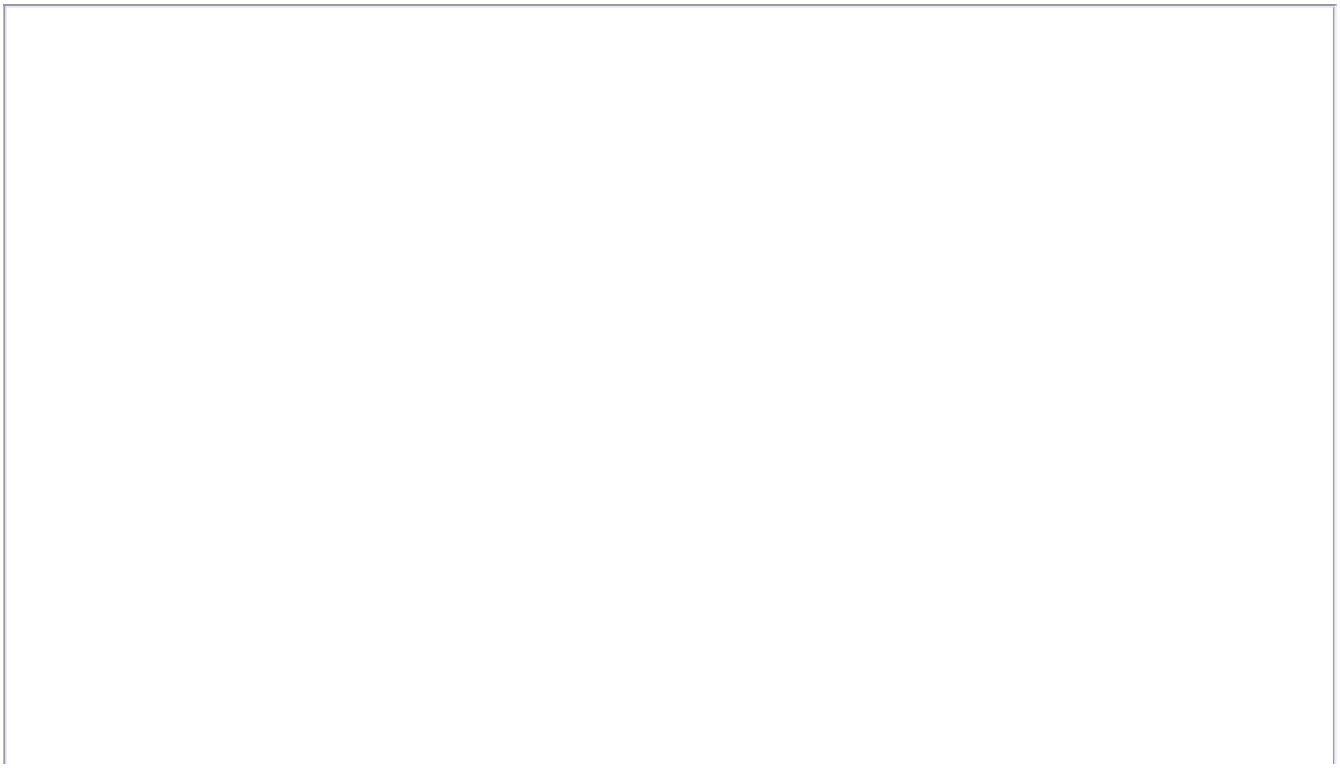
HEENT/Airway: Macrocephaly, short cranial base with small foramen magnum, prominent forehead, flattened midface. Short eustachian tubes can lead to conductive hearing loss secondary to chronic recurrent otitis media. Saddle nose, narrow nasal passages, choanal stenosis. Long, narrow mouth with high-arched palate, macroglossia, prominent mandible. May have tracheomalacia. Obstructive sleep apnea is common. Tonsillectomy and adenoidectomy can improve symptoms of sleep apnea.

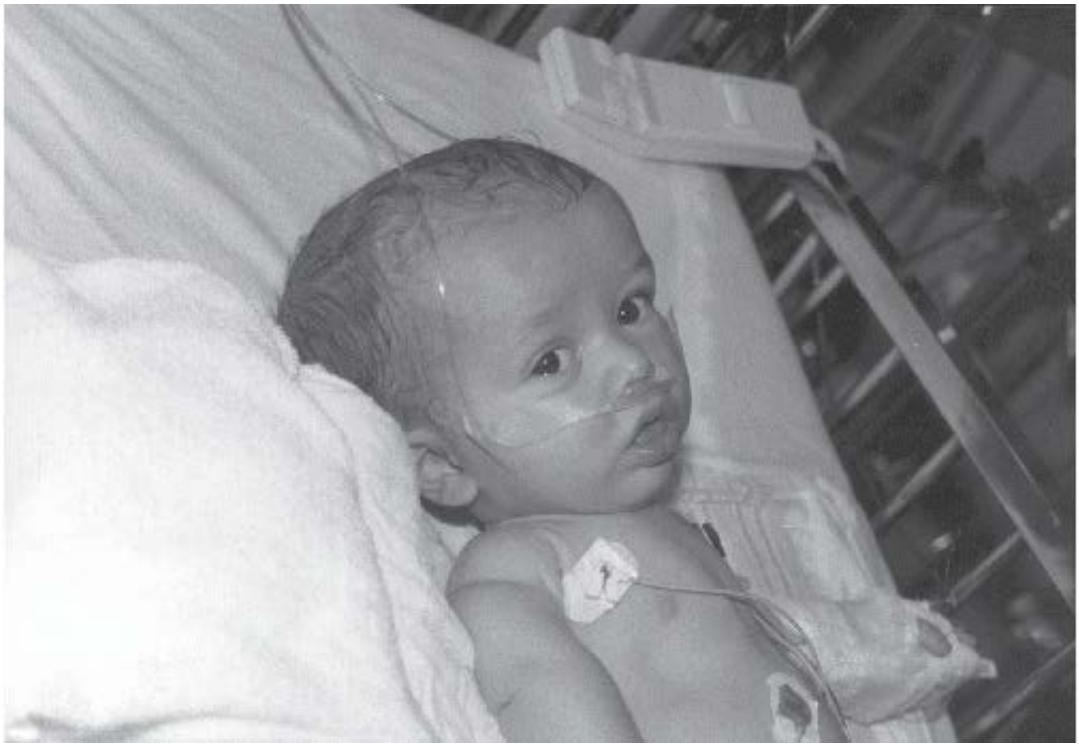
Chest: Chest wall deformities in children include abnormal spinal curvature and a small rib cage that can lead to impaired respiratory function secondary to a constrictive thoracic cage. Restrictive lung disease can be severe enough to cause hypoxemia or hypercapnia, and can be present in childhood. May have bronchomalacia. Thoracic cage constriction improves over time, and adults have an almost normal chest wall configuration.

Cardiovascular: Can develop pulmonary artery hypertension, and right ventricular hypertrophy with strain.

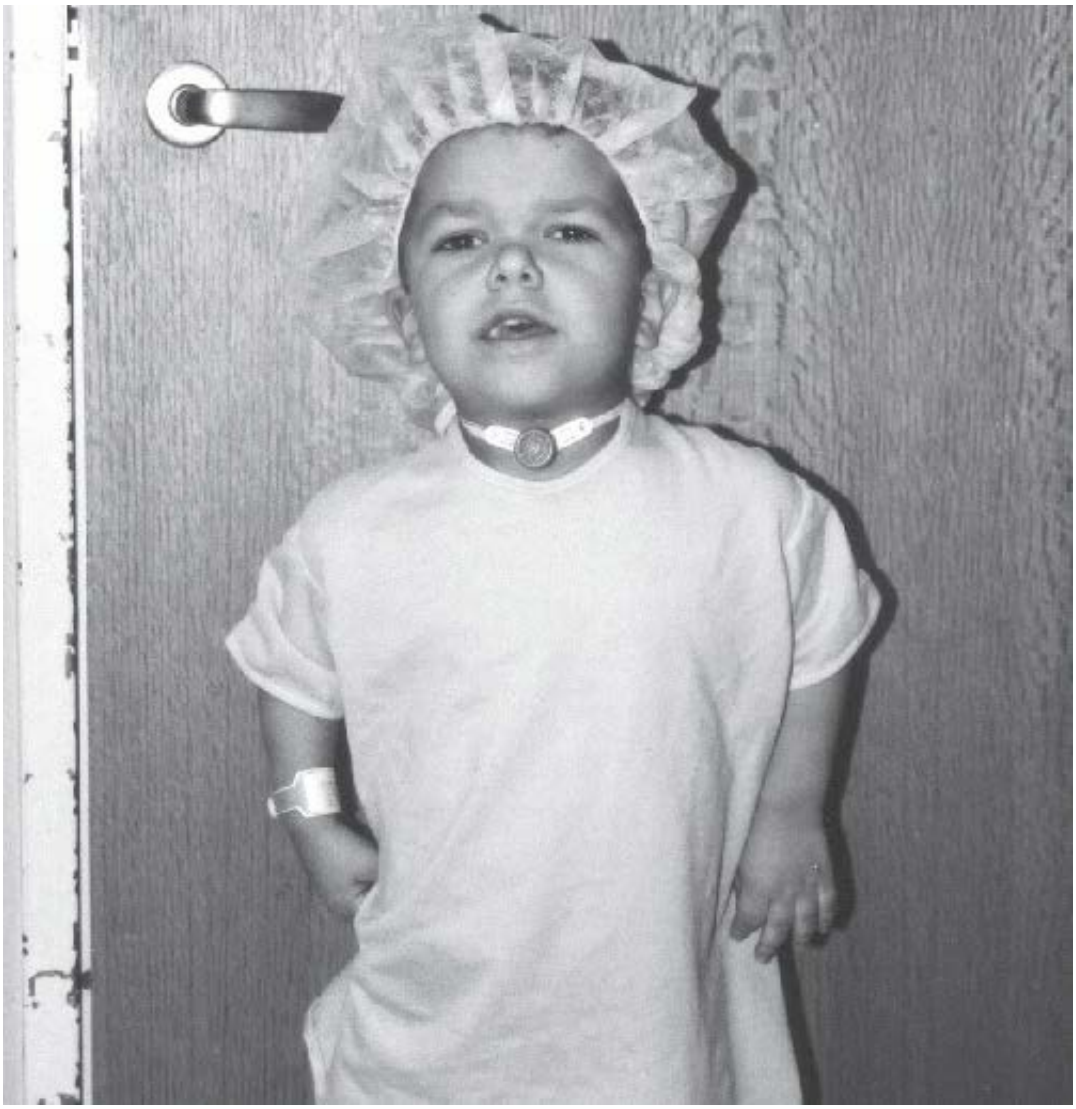
Neuromuscular: Foramen magnum is small and funnel shaped. Brainstem compression at the level of the foramen magnum can cause central apnea. Multiple cervical spine abnormalities, including instability, stenosis, and fusion. Persistent thoracolumbar kyphosis can compress the spinal cord. Small intervertebral foramina can cause compression of individual nerve roots. There is progressive narrowing of the spinal canal caudally. Possible cauda equina syndrome. Spinal cord or root compression can occur at any level and can result in hyperreflexia, sustained clonus, hypertonia, paresis, or asymmetry of movement or strength.

Narrowed foramen magnum can result in hydrocephalus. Motor development is often delayed.





Achondroplasia. FIG. 1. A young infant with achondroplasia. His head and ventricles are large, although his head circumference is within normal limits for a child with achondroplasia. He had a history of apneic spells, and had "trimming" of his epiglottis. During a later tonsillectomy, he had a presumably vagally mediated asystolic arrest.



Achondroplasia. FIG. 2. The same patient at 7 years of age. He has had a tracheostomy in the interval as well as surgical straightening of his tibias and fibulae.

Orthopedic: Short stature, secondary to rhizomelic shortening of the arms and legs. Trunk length is normal. Long bones are shortened. Incomplete extension at the elbow. Hyperextensibility of other joints, especially the knees. Trident hands. Thoracolumbar kyphosis and severe lumbar lordosis. Small pelvis. Bowing of the lower extremities. Occipitalization of C-1. Patients can have a variety of spine abnormalities (see Neuromuscular).

Other: Obesity is often present in both sexes. Glucose intolerance is common. The small maternal pelvis, exaggerated lumbar lordosis, and near-normal fetal size make delivery of women with achondroplasia by cesarean section preferable. The relatively large fetus causes more than usual impingement of the uterus on the diaphragm during pregnancy with reduction in functional residual capacity.

Miscellaneous: Achondroplastic skeletal remains have been identified in Egypt, which date to 4500 BCE, and achondroplastic dwarf figurines have been discovered among pre-Columbian art dating from approximately 500 BCE.

Anesthetic Considerations: Recall that despite the child-size stature, patients have intelligence and social skills normal for their chronologic age.

Instability of the cervical spine is rare, but possible. Compression at the cervicomedullary junction can occur in the supine position when the large occiput displaces the head sufficiently forward so that the prominent posterior margin of the foramen magnum impinges on the upper spinal cord or medulla. This can be prevented by placing a bolster under the shoulders. Forty-six percent of patients have spinal involvement, so perioperative neurologic and orthopedic examinations are critical. Monitoring somatosensory evoked potentials may help identify early cord compression in surgery requiring abnormal positioning (14), but false-negative results with a brainstem infarction and with a C-1 cord level have been reported (19), although the data in that case may have been corrupted by excessive isoflurane.

Visualization of the larynx is usually uncomplicated but may be very difficult if there is limited cervical extension. Patients can usually be ventilated by mask, but a good mask fit may be difficult to obtain. The narrow nasopharynx or choanal stenosis can preclude placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Macroglossia can obstruct the airway, and obstruction can resolve with an oropharyngeal airway. Endotracheal tubes smaller than that estimated by age are often needed, and an approximation based on weight may be more appropriate (19).

Low functional residual capacity can lead to rapid desaturation with the induction of anesthesia. Respiratory status could necessitate an arterial catheter. Patients may have pulmonary hypertension. The presence of tracheo/bronchomalacia and/or obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period (1,6). Patients may require postoperative ventilation, and pain control is critical to postoperative respiratory status.

Obesity can predispose to gastroesophageal reflux. Excess skin and subcutaneous tissue may make placement of venous catheters more difficult. Limb deformities may make venous and arterial access difficult. Careful positioning is required because of the hyperextensibility of most joints, especially the knee. Short, thick upper arms can make fixation of an appropriate-sized blood pressure cuff difficult, and falsely high pressures can be displayed by noninvasive monitors. An appropriate blood pressure cuff should cover two-thirds of the upper arm length.

A retrospective study reported very few problems in the management of general anesthesia for patients with achondroplasia (13). Apparent dexmedetomidine-induced polyuric syndrome has been reported in an achondroplastic patient but is unlikely to be related directly to his achondroplasia (2). Despite spinal abnormalities and possible technical difficulties (4), regional anesthesia for cesarean section has been reported, although lower-than-normal volumes of anesthetic are required because of the short stature (approximately 5 to 12 mL) (5,10,12,15,16,17,18). Given this range, incremental dosing is important.

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Acid maltase deficiency

See Pompe disease

Acroosteolysis syndrome

See Hajdu-Cheney syndrome

Acrocallosal syndrome

MIM #: 200990

This autosomal recessive disorder is marked by polydactyly, intellectual disability, and agenesis of the corpus callosum. The syndrome is caused by mutations in the gene *KIF7*.

HEENT/Airway: Macrocephaly, protruding occiput and forehead, large anterior fontanelle, defect in the calvarium. Hypoplastic midface. Strabismus, hypertelorism, downslanting palpebral fissures, nystagmus, decreased retinal pigmentation, optic atrophy. Small nose. Malformed ears. Retro- or micrognathia, cleft lip, cleft palate, high-arched palate.

Cardiovascular: Congenital heart defects.

Neuromuscular: Severe intellectual disability, agenesis of the corpus callosum, Dandy-Walker malformation (see later), hypotonia, arachnoid cysts, seizures, temporal lobe hypoplasia.

Orthopedic: Pre- and postaxial polydactyly, duplication of hallux. Tapered fingers. Toe syndactyly. Bipartite clavicle.

GI/GU: Umbilical and inguinal hernias. Hypospadias, cryptorchidism, micropenis. Rectovaginal fistula.

Other: Postnatal growth retardation.

Miscellaneous: The gene *GLI3* is analogous to a gene in Drosophila that regulates, among other genes, the gooseberry gene.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult because of a high-arched palate, micrognathia, and crowded dentition related to midface hypoplasia. A laryngeal mask airway has been used

successfully when intubation was not possible (2). Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Anticonvulsant medications should be continued through the perioperative period. Chronic use of anticonvulsant medications as well as abnormal liver function may affect the metabolism of some anesthetic and other drugs.

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Acrocephalopolysyndactyly type II

See Carpenter syndrome

Acrocephalosyndactyly type I

See Apert syndrome

Acrocephalosyndactyly type II

Included in Apert syndrome

Acrocephalosyndactyly type III

See Saethre-Chotzen syndrome

Acrocephalosyndactyly type V

See Pfeiffer syndrome

Acrodysostosis I and II

MIM #: 101800, 614613

This autosomal dominant disorder is characterized by intellectual disability, short hands and feet with acrodysostosis (progressive defects in ossification distally), distinctive facies (including a small nose and prominent mandible), and endocrine abnormalities. **Acrodysostosis I** is due to a heterozygous mutation in the protein kinase A gene (*PRKAR1A*). Although it had been suggested that this disorder is a variant of pseudohypoparathyroidism (see later), genetic studies have shown that the two disorders are distinct (2,3). Recently, a mutation in the cAMP-

specific phosphodiesterase 4D gene (*PDE4D*) has been identified as another cause of acrodysostosis (**acrodysostosis II**). Patients with acrodysostosis II are less likely to exhibit endocrine abnormalities.

HEENT/Airway: Brachycephaly. Hypertelorism, optic atrophy, strabismus. Blue eyes have been described in Japanese patients. Small, broad, upturned nose with a low nasal bridge. Hearing deficit common. Flat midface and prominent mandible.

Neuromuscular: Intellectual disability common. Occasional hydrocephalus.

Orthopedic: Mild to moderate short stature is common. Advanced bone age. Upper limbs relatively shorter than lower limbs. Abnormally small vertebrae are susceptible to compression. Scoliosis. Spinal canal stenosis. Short limbs with acrodysostosis. Epiphyses are cone shaped. Short, broad hands, feet, fingers, and toes. Short metatarsals.

GI/GU: Rare renal anomalies. Cryptorchidism. Hypogonadism.

Other: Endocrine abnormalities, including resistance to parathyroid hormone, thyrotropin, calcitonin, gonadotropin, and growth hormone-releasing hormone. Wrinkling of the dorsum of the hands. Pigmented nevi.

Anesthetic Considerations: May have preoperative endocrine abnormalities, particularly hypocalcemia and hyperphosphatemia. Restriction of movement in the hands and spine may present problems in positioning the patient, and wrinkling of the skin of the hands could make intravenous catheter placement more difficult.

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Acromesomelic dwarfism

See Acromesomelic dysplasia

Acromesomelic dysplasia

Synonym: Acromesomelic dwarfism. (Includes Hunter-Thompson and Maroteaux types)

MIM #: 201250, 602875

These autosomal recessive disorders are characterized by short-limbed dwarfism, a prominent forehead, and lower thoracic kyphosis. The **Maroteaux type** is caused by a defect in the natriuretic peptide receptor B gene (*NPR2*). The **Hunter-Thompson type** is caused by a defect in the gene that encodes growth/differentiation factor-5 (*GDF5*), also known as cartilage-derived morphogenetic protein 1 (*CDMP1*), a member of the transforming growth

factor-beta (TGF-beta) superfamily. Acromesomelic disorders have disproportionate shortening of the middle (forearms and lower legs) and distal (hands and feet) skeleton. In the Hunter-Thompson form, skeletal elements of the hands or feet are fused, while in the Maroteaux type, all elements are present but have abnormal growth. A third acromesomelic dysplasia is Grebe syndrome (see later).

HEENT/Airway: Macrocephaly, prominent forehead. May have corneal opacities. May have a short nose.

Chest: Lower thoracic kyphosis. Clavicles are curved superiorly and thus appear high.

Neuromuscular: Intelligence is normal. Motor development is often delayed.

Orthopedic: Extreme short stature. Short limbs, which are more pronounced distally—the forearms and hands are relatively shorter than the upper arms, and the lower legs are shorter than the upper legs. Short, broad metacarpals, metatarsals, and phalanges. Bowed radius, dislocation of the radial head, limited elbow extension. Joint laxity. Epiphyses are cone shaped. Metaphyses of long bones are flared. Hypoplasia of the ilia and acetabular region in childhood may lead to early osteoarthritis of the hip. Lumbar lordosis. Gibbus deformity.

Miscellaneous: This Hunter and Thompson are presumably not Hunter Thompson the deceased “gonzo” journalist.

Anesthetic Considerations: Recall that despite the child-size stature, patients have intelligence that is normal for their chronologic age. Patients might require a smaller than expected endotracheal tube if sized for age. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Radial anomalies may make placement of a radial arterial catheter more difficult. Careful positioning is required secondary to limited elbow extension and hyperextensibility of most other joints. Spine deformities might make neuraxial techniques more difficult.

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ADA deficiency

See Adenosine deaminase deficiency

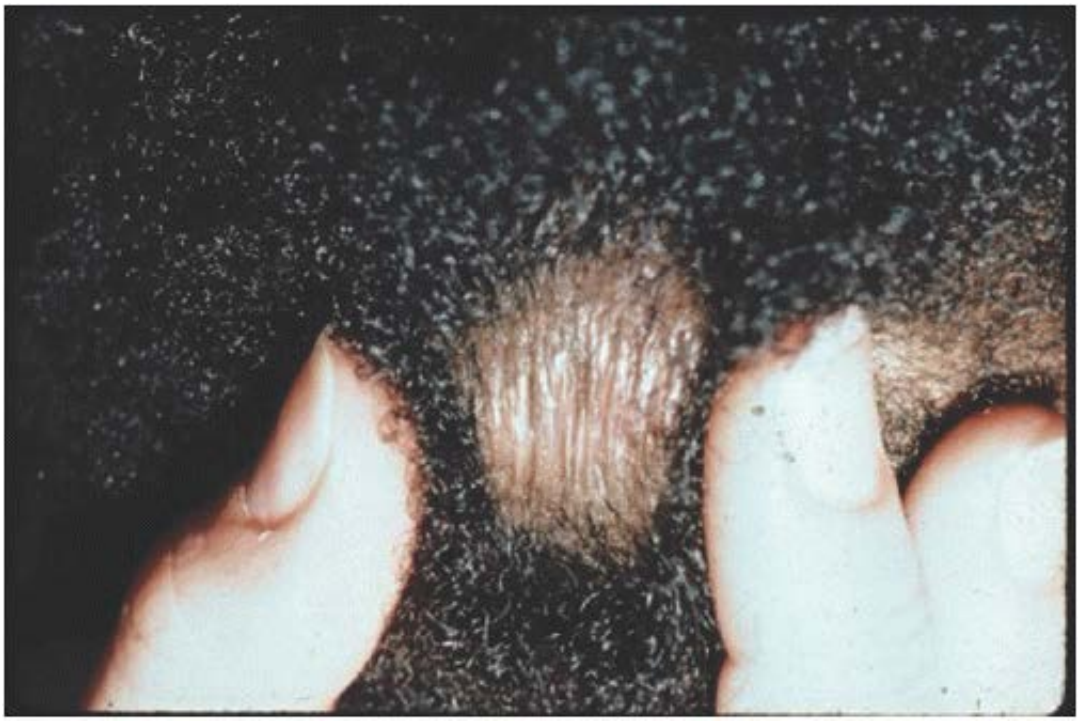
Adams-Oliver syndrome

Synonym: Aplasia cutis congenita; Cutis aplasia

MIM #: 100300

This usually autosomal dominant disorder involves failure of skin development over an area of the scalp (aplasia cutis congenita) and various limb reduction defects. There is wide variability in expression, with some affected people showing only subclinical (i.e., radiographic) evidence of the disease. This disorder is genetically heterogeneous and can be caused by mutations in the *ARHGAP31*, *RBPJ*, *DOCK6*, and *EOGT* genes.

HEENT/Airway: Failure of development of the skin overlying an area of the scalp (aplasia cutis congenita), usually in the parietal region. There may be single or multiple defects. Defects are usually covered by a thin membrane or by scar tissue or may be ulcerated. Skin grafting may be needed. Skull defects can underlie the scalp defect. Occasional frontonasal cysts. Occasional microphthalmia. Occasional cleft lip or palate.

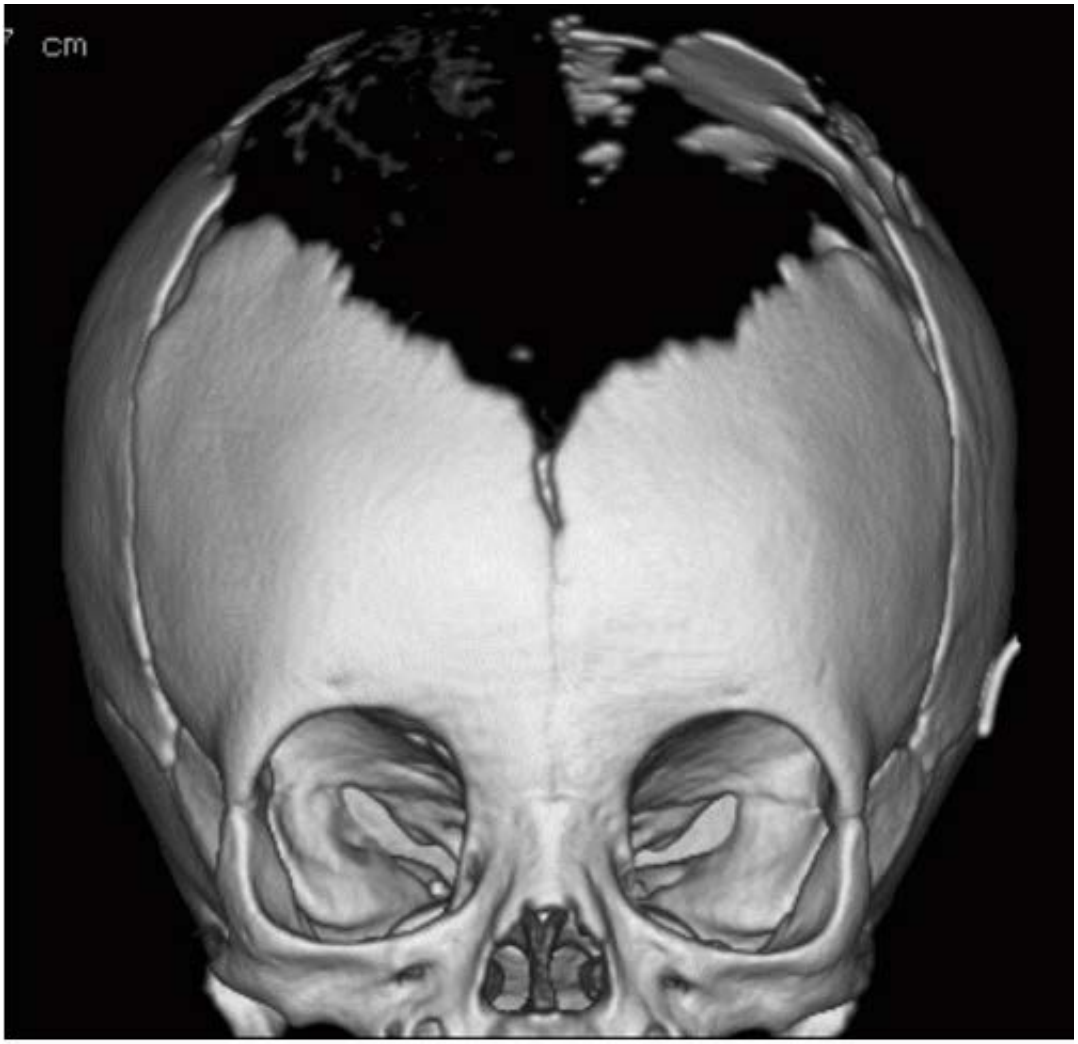


Adams-Oliver syndrome. FIG. 1. Typical scalp defect in Adams-Oliver syndrome. (Courtesy of Dr. Neil Prose, Department of Dermatology, Duke University.)

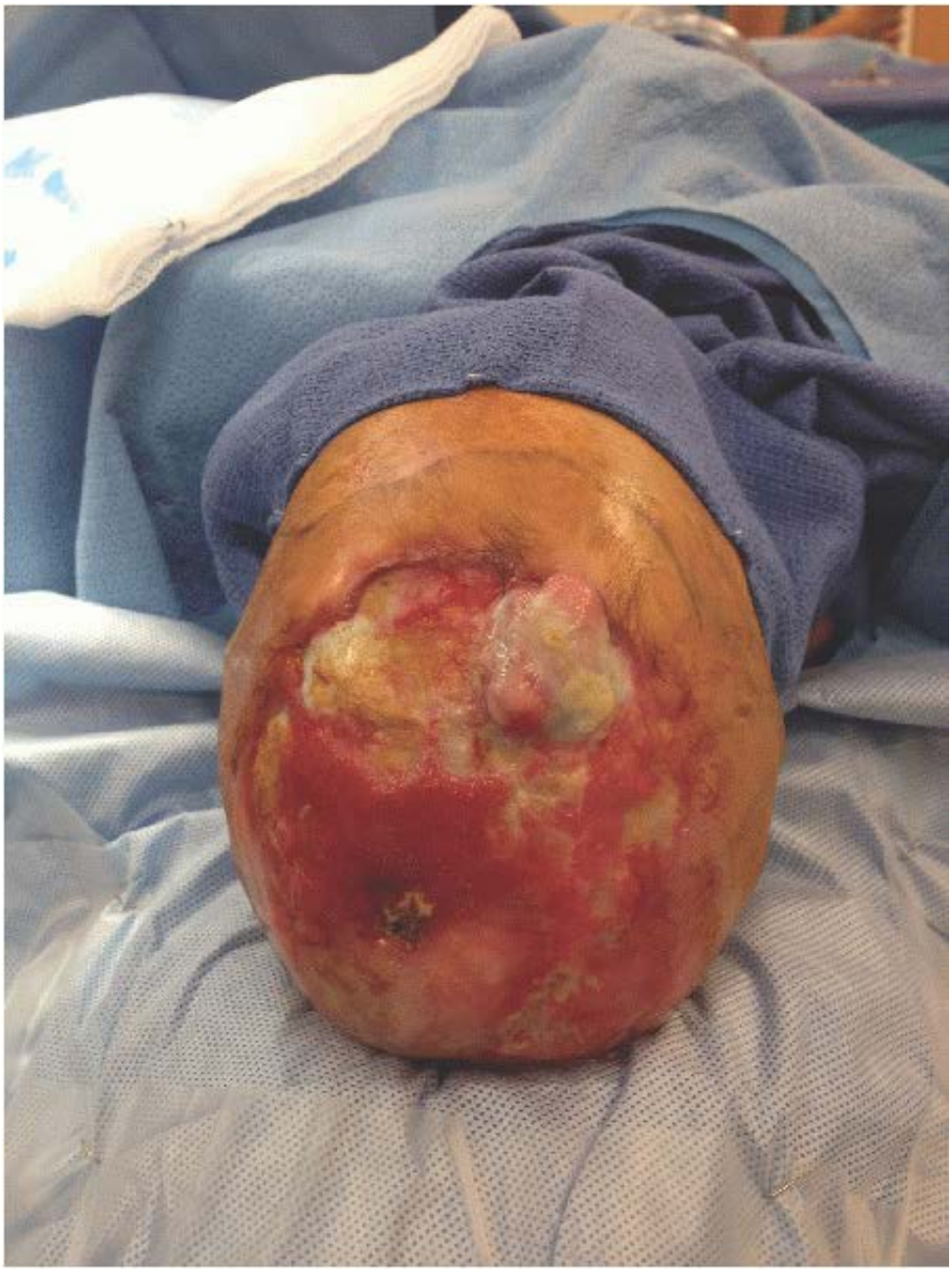
Cardiovascular: Occasional cardiac defects. May have pulmonary hypertension.

Neuromuscular: There is a risk of hemorrhage or meningitis when the superior sagittal sinus or the dura is exposed by an overlying bony defect. Despite the sometimes large defects in the skull, underlying central nervous system abnormalities have only on occasion been associated with this syndrome. Intelligence is normal.

Orthopedic: Mild growth deficiency. Various limb reduction defects including absence of the lower extremity below midcalf. Absence or hypoplasia of the metacarpals, metatarsals, and phalanges. Short terminal phalanges, hypoplastic nails.



Adams-Oliver syndrome. FIG. 2. A CT scan from a more severely affected infant.



Adams-Oliver syndrome. FIG. 3. This shows brain herniation in the infant whose CT scan is shown in Figure 2.

GI/GU: Occasional duplicated renal collecting system.

Other: Cutis marmorata. Dilated scalp veins.

Miscellaneous: Cutis marmorata and dilated scalp veins suggest that embryonic vascular disruption may play a role in the pathogenesis of the Adams-Oliver syndrome. Aplasia cutis congenita and limb reduction defects are consistent with this hypothesis.

Anesthetic Considerations: Care should be taken to avoid hemorrhage or infection when the superior sagittal sinus

or the dura is exposed by an overlying bony defect. Because of the abnormal local vascularity, skin grafts rather than flaps will be required to close scalp defects. Both scalp and limb reduction defects may make intravenous access more difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Addison-Schilder disease

See Adrenoleukodystrophy

Adenosine deaminase deficiency

Synonym: ADA deficiency

MIM #: 102700

This autosomal recessive enzyme deficiency causes one type of severe combined immunodeficiency syndrome (SCIDS, see later) with combined B- and T-cell defects and accounts for approximately one-third of the autosomal recessive cases of SCIDS. The adenosine deaminase (ADA) gene is located on the long arm of chromosome 20, and dozens of mutations have been described. Some mutations allow partial enzyme activity with later onset and survival into adulthood, although with an increased incidence of severe infections. ADA catalyzes the conversion of adenosine to inosine and deoxyadenosine to deoxyinosine. In the absence of adenosine deaminase, the cell converts deoxyadenosine to deoxyadenosine triphosphate (deoxy-ATP), which is toxic to cells by activating enzymes that deplete the cell of ATP and other adenosine nucleotides. Lymphocytes are particularly efficient at this, and in essence poison themselves.

HEENT/Airway: Chronic or recurrent sinus infections.

Chest: Chronic or recurrent pulmonary infections, asthma.

Orthopedic: Skeletal dysplasia.

GI/GU: Can have hepatic dysfunction—hepatitis with hyperbilirubinemia that resolves with enzyme treatment.

Other: Decreased B, T, and CD4 lymphocytes; recurrent candidiasis; warts; and herpes zoster. Severe susceptibility to disease from live virus immunizations (polio, measles) and bacillus Calmette-Guerin (BCG) vaccine. Variable humoral immunity (normal, hyperactive, or reduced). Can have autoimmune hemolytic anemia. Can develop B-cell lymphoma.

Miscellaneous: Adenosine deaminase has also been found to be lacking in patients with cartilage-hair hypoplasia syndrome (see later). Patients have been treated successfully with bone marrow transplantation, polyethylene glycol-modified adenosine deaminase (very expensive), and gene therapy with retroviral vectors.

Adenosine deaminase is found in all mammals with the exception of the horse.

Anesthetic Considerations: Careful aseptic technique is particularly important. Transfusion of nonirradiated blood can cause graft versus host disease.

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Adrenogenital syndrome

See Congenital adrenal hyperplasia

Adrenoleukodystrophy

Synonym: Addison-Schilder disease; Siemerling-Creutzfeldt disease. (Includes adrenomyeloneuropathy and neonatal adrenoleukodystrophy)

MIM #: 300100

This X-linked recessive disorder is characterized by adrenal cortical insufficiency and central nervous system demyelination due to the accumulation of very-long-chain fatty acids. Presumably, accumulation of 24- to 30-carbon very-long-chain fatty acids interferes with both myelin formation and adrenal steroid synthesis leading to progressive demyelination and adrenal insufficiency. Stem cell transplantation and gene therapy have led to disease stabilization in early trials. Significant phenotypic variation has been described in identical twins with adrenoleukodystrophy, suggesting that nongenetic factors are important in the phenotypic expression. At least seven phenotypic types have been described in males and five in female carriers. One phenotypic variant has been termed **adrenomyeloneuropathy** (*MIM #:* 300100). Patients with adrenomyeloneuropathy present with neurologic findings in adulthood, and with evidence of long-standing hypersecretion of adrenocorticotropic hormone (ACTH). The gene responsible for adrenoleukodystrophy is *ABCD1*, which is a member of the ATP-binding cassette superfamily. These produce a variety of proteins, which translocate a variety of proteins across intra- and

extracellular membranes. The gene responsible for cystic fibrosis is another member of this family.

Adrenoleukodystrophy is one of the leukodystrophies, the others of which are metachromatic leukodystrophy, Krabbe disease, Canavan disease, Pelizaeus-Merzbacher disease, and Alexander disease (see later for all).

Neonatal adrenoleukodystrophy (*MIM #:* 601539) is an autosomal recessive peroxisomal biogenesis disorder, related to Zellweger syndrome and infantile Refsum disease (see later for both). Various mutations in the peroxin gene-1 (*PEX1*), which is required for transportation of proteins into peroxisomes, lead to infantile Refsum disease, neonatal adrenoleukodystrophy, and Zellweger syndrome. Together, these disorders may represent a continuum of peroxisome biogenesis disorders, with Zellweger syndrome being the most severe, neonatal adrenoleukodystrophy intermediate, and infantile Refsum disease the least severe. Neonatal adrenoleukodystrophy leads to absent or nearly absent peroxisomes, with a deficiency of all of the peroxisomal ß-oxidation enzymes. Functions of peroxisomes include synthesis of cell membrane components (particularly constituents of myelin), bile acid synthesis, and fatty acid metabolism. Children with neonatal adrenoleukodystrophy do not usually live beyond their teens.

HEENT/Airway: Adrenoleukodystrophy: Visual disturbances, including decreased acuity with or without visual field defects, optic atrophy. May have Balint syndrome (a neuropsychological paralysis of visual fixation, optic ataxia, and relatively intact vision). There is an increased incidence of color blindness, presumably because of a very close linkage with the color blindness gene(s). Cognitive hearing loss.

Neonatal adrenoleukodystrophy: Retinopathy, impaired hearing. Neonatal cataracts. Esotropia. Broad nasal bridge. Low-set ears. High-arched palate.

Neuromuscular: Adrenoleukodystrophy: Severe mental and motor delay, and patients may lose milestones between 3 and 5 years of age. Severe hypotonia. Enlarged ventricles, atrophy of the pons and cerebellum. May have seizures. May have behavioral disturbances, difficulty understanding speech in a noisy environment (impaired auditory discrimination), parietal disturbances (including dressing apraxia), poor body orientation in space, diminished graphesthesia. May have spastic paraplegia, peripheral neuropathy, limb and truncal ataxia. Nerve conduction studies may be abnormal. Treatment of adrenal insufficiency with steroids does not affect the severity or progression of the neurologic disease.

Neonatal adrenoleukodystrophy: Intellectual disability, motor delay, seizures. Extent of neurologic involvement is variable, ranging from a stable handicap with some intellectual disability to severe intellectual disability, psychomotor delay, and seizures.

GI/GU: Liver function is typically abnormal (but not as abnormal as in the related Zellweger syndrome). Patients may have gastroesophageal reflux. Hypogonadism with impotence.

Other: The adrenal response to an ACTH challenge may be abnormal, but adrenal insufficiency is less common. Hyperpigmentation of the skin from oversecretion of ACTH.

Miscellaneous: Purported success in treating this disease with a dietary supplement (“Lorenzo's oil”) was the basis for a popular film (of the same name) in 1992. While this therapy can normalize very-long-chain fatty acids in blood, it does not affect disease progression. It may, however, reduce the risk of developing brain abnormalities on MRI scan in asymptomatic boys. Bone marrow transplantation and gene therapy have been investigated as treatments.

Thomas Addison (the same Addison of Addison's disease) committed suicide in 1860 at the age of 65 by jumping out of a window of his villa.

Anesthetic Considerations: Keep in mind that patients will likely have impaired vision and/or hearing. Patients

may have electrolyte imbalances secondary to chronic steroid replacement therapy. Sedative premedication increases the risk of airway obstruction in patients with significant hypotonia. Patients are at risk for perioperative aspiration because of airway hypotonia and gastroesophageal reflux. The risk of excessive potassium release with succinylcholine is unknown but is theoretically possible in bedridden patients with atrophic muscles. One patient has been reported with limited mouth opening who required fiberoptic intubation (5). Patients require careful perioperative positioning and padding secondary to demineralization of bones and ligamentous laxity due to the hypotonia. Patients should be observed closely in the postanesthesia care unit for evidence of airway obstruction from residual anesthetic.

Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers may exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects. Propofol should be used with caution in patients with peroxisomal disorders as they may be at higher risk for developing propofol infusion syndrome (1). Anticonvulsant medications should be continued through the perioperative period. Chronic use of anticonvulsant medications as well as abnormal liver function may affect the metabolism of some anesthetic and other drugs. Adrenal response to stress may be inadequate, and patients may require perioperative stress doses of steroids.

Because insults or injuries to the brain may accelerate demyelination and exacerbate neurologic symptoms, the risk of neurologic surgery is unknown. A teenage patient with only minimal symptoms experienced significant worsening of his disease after cardiopulmonary bypass to correct a ventricular septal defect (9). On the other hand, hemodynamic and hormonal responses to anesthesia and minor surgery were normal in an otherwise asymptomatic child (11).

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Adrenomyeloneuropathy

Included in adrenoleukodystrophy

AEC syndrome

Synonym: Hay-Wells ectodermal dysplasia

MIM #: 106260

This autosomal dominant ectodermal dysplasia is associated with cleft lip and palate and congenital filiform fusion of the eyelids. AEC stands for **A**nkyloblepharon, **E**ctodermal defects, and **C**left lip and palate. The syndrome is due to defects in the tumor protein gene *TP63*. There is marked variability of clinical expression. Patients with Rapp-Hodgkin ectodermal dysplasia (see later) and some patients with EEC syndrome (see later) have defects in the same gene.

HEENT/Airway: Oval facies with flattened midface and broad nasal bridge. Scalp erosions. Congenital

adhesions between the eyelids with filamentous bands (ankyloblepharon filiforme adnatum). Anomalies of the eye not associated with the tissue bands. Thin eyelashes. Photophobia common. Atretic lacrimal ducts. Otitis media is common. Conductive hearing loss, atretic external auditory canals. Cup-shaped ears. Abnormal dentition, including conical and widely spaced teeth, hypodontia, anodontia. Cleft lip or palate. May have trismus.

Cardiovascular: Rare patent ductus arteriosus or ventricular septal defect.

Orthopedic: Syndactyly, hammer toe deformities.

GI/GU: Hypospadias, micropenis, vaginal dryness.

Other: Ectodermal defects including hyperkeratosis and palmar and plantar keratoderma. Red, cracking skin at

birth. Hyperpigmentation. Coarse, wiry, and sparse hair. Dystrophic, hypoplastic, thin, or absent nails. Sweat gland deficiency or dysfunction. Sparse body hair. Scalp infections are common. Supernumerary nipples.

Anesthetic Considerations: Heat intolerance is common because of poorly functioning sweat glands. There is some capacity to produce sweat, so hyperthermia is not usually a problem. Teeth should be assessed carefully preoperatively because of the likelihood of abnormal dentition.

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Aglossia-adactyly syndrome

See Oromandibular-limb hypogenesis

Aicardi syndrome

MIM #: 304050

This syndrome is seen only in girls (with the exception of one boy with an XXY karyotype), indicating an X-linked dominant mode of inheritance that is lethal in the hemizygous male. The main features are infantile spasms, agenesis of the corpus callosum, and chorioretinopathy. The gene responsible for this disorder is located on the short arm of the X chromosome (Xp22). The gene product is unknown. Most patients die in adolescence or early adulthood.

HEENT/Airway: Microcephaly. Facial asymmetry. Chorioretinopathy marked by chorioretinal lacunae (holes). Microphthalmia, small optic nerves, and chiasm. Retinal detachment. Cataracts. Coloboma. Nystagmus. Prominent premaxilla, upturned nasal tip. Occasional cleft lip or palate.

Chest: Kyphoscoliosis may adversely affect pulmonary status. Rib abnormalities include absent, extra, fused, or bifid ribs.

Neuromuscular: Microcephaly, severe intellectual disability. Partial or total agenesis of the corpus callosum. Electroencephalographic evidence of independent activity of right and left hemispheres. Abnormalities of the cerebrum, cerebellum, and ventricles. Polymicrogyria, intracranial cysts. Infantile spasms progressing to other seizure types by 2 years of age. Hypotonia. May be associated with the development of central nervous system tumors. Dandy-Walker or Arnold-Chiari malformations.

Orthopedic: Kyphoscoliosis. Vertebral anomalies include spina bifida, hemivertebrae, and abnormally shaped vertebrae. Scoliosis. Proximally placed thumbs.

GI/GU: Hiatal hernia.

Other: Scalp lipomas. Cavernous hemangiomas. Precocious puberty. A variety of tumors including hepatoblastoma, teratoma, embryonal carcinoma, and angiosarcoma.

Anesthetic Considerations: Craniofacial features may make direct laryngoscopy and tracheal intubation difficult. Because of their neurologic status, patients are at risk for aspiration. Recurrent pneumonia is common, and pulmonary status can be further compromised by kyphoscoliosis. Patients usually have significant visual impairment. In one reported case in the anesthesia literature, caudal block was impossible due to abnormal vertebral anatomy, and intravenous cannulation was not possible due to “generalized hypotrophia” of subcutaneous tissues (6). Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs.

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Alagille syndrome

Synonym: Arteriohepatic dysplasia

MIM #: 118450

This disease involves primarily the liver (a paucity of intrahepatic bile ducts), heart, and pulmonary arteries. Additional features include characteristic facies, skeletal abnormalities, and renal anomalies. It is an autosomal dominant disorder with incomplete penetrance leading to marked variability in expression. There is genetic heterogeneity, with most cases being due to a defect in the gene Jagged 1 (*JAG1*), which produces a ligand for the protein “Notch 1,” a transmembrane receptor involved in cell fate decisions. *JAG1* is highly expressed in the developing heart and vascular structures, corresponding to the areas of observed clinical defects. A smaller number of patients have a defect in the *NOTCH2* gene. Renal involvement is common, and explained by the fact that Notch signaling is involved in the development of the renal system. Liver transplantation has been used successfully in this disorder.

HEENT/Airway: Broad forehead. Long, thin face. Eccentric pupils, deep-set eyes, chorioretinal atrophy, and pigment clumping. Posterior embryotoxon of the eye. Bulbous tip of the nose. Pointed mandible.

Cardiovascular: Pulmonary valvar and peripheral pulmonary artery stenosis. Occasional tetralogy of Fallot, atrial septal defect, or ventricular septal defect. Abdominal coarctation has been reported.

Neuromuscular: Poor school performance. Absent deep tendon reflexes. Intracranial hemorrhage has been reported spontaneously or after minor trauma. Hepatic encephalopathy with severe hepatic disease. Can have carotid and intracranial artery aneurysms.

Orthopedic: Growth retardation. Butterfly vertebrae, decrease in the interpedicular distances of the lumbar spine. Foreshortening of the fingers. Recurrent and/or poorly healing long bone fractures.

GI/GU: Intrahepatic biliary hypoplasia or atresia with cholestasis. The absence of intrahepatic biliary ducts is not congenital. There appears to be early cholestasis, portal inflammation, and inflammation of intralobular bile ducts, followed by loss of biliary ducts. Patients can have cirrhosis with portal hypertension and hypersplenism. Hepatocellular carcinoma can develop. Renal dysplasia, renal tubular acidosis, vesicoureteral reflux. There can be renal artery stenosis with systemic hypertension.

Alagille syndrome. This 12-month-old girl has a secundum atrial septal defect and a mild hepatic duct problem. She has a history of easily becoming hypoglycemic. (The blue mark over her eye is a pen mark to indicate the side of surgery.)

Other: Hypercholesterolemia and hyperlipidemia with xanthomas of the skin. Essential fatty acid deficiency and vitamin K deficiency from inadequate absorption. Pruritus from cholestasis. A bleeding dyscrasia is not limited solely to intracranial bleeding. Abnormal and excessive bleeding can occur spontaneously or can be intraoperative. Bleeding postoperatively, even after a minor procedure, has been fatal. The etiology is unclear, and hemostatic tests are normal. The dyscrasia could be related to the defect in *JAG1*, which is widely expressed in endothelium and megakaryocytes.

Anesthetic Considerations: Baseline cardiac status should be evaluated preoperatively. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Renal and hepatic function can be abnormal. Renal insufficiency has implications for perioperative fluid management and the choice of anesthetic drugs. Hepatic dysfunction can

lead to abnormalities in the protein binding of some anesthetic drugs. Vitamin K deficiency (from malabsorption) can lead to clotting abnormalities. Regional anesthesia techniques are contraindicated in the face of abnormal coagulation. Esophageal varices can develop in patients with cirrhosis, so nasogastric tubes and transesophageal echocardiography probes should be passed with caution. Excessive perioperative bleeding is possible.

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Albers-Schönberg disease

See Osteopetrosis

Albinism

MIM #: 203100, 606952, 203200

There are a variety of types of albinism, as a number of genes are involved in the full melanin biochemical and metabolic pathway. The most common forms are the types of oculocutaneous albinism, which are autosomal recessive. Type I oculocutaneous albinism is due to an abnormality in the gene for tyrosinase. Tyrosinase catalyzes the conversion of tyrosine into dopa (3,4-dihydroxyphenylalanine), which is a precursor of melanin. Patients with type IA disease never synthesize melanin in any tissue. Patients with type IB disease have a mutation that allows some residual synthetic activity. This form has more phenotypic variability, and in some people, pigmentation can approach normal. One variant of type IB is temperature sensitive, with pigmented arm and leg hair, but white scalp and axillary hair. Type II disease is particularly common in equatorial Africa. It has been suggested that the responsible gene for type II disease is a human analog of the mouse pink-eyed dilution gene. There is phenotypic variation with type II disease, and the phenotype can also be affected by the underlying constitutional pigment background. Albinism occurs in all racial groups.

HEENT/Airway: Absence of retinal pigment (producing a pronounced red reflex). The iris is blue, thin, without a cartwheel effect, and the lens can be seen through it. Some iris pigment can develop in type IB and in type II. Photophobia, nystagmus, strabismus, hypoplasia of the fovea, visual loss.

Other: The skin and hair lack pigmentation in type IA. In type IB, there can be some pigment developing with time. The hair is white or, after prolonged exposure to sunlight, very, very light blond in type IA and can become blond or brown in type IB. Hair can on occasion be reddish in type II and can also darken with age. Melanocytes are present but do not contain pigment. There is increased susceptibility to skin neoplasia, but less so in subtypes in which lentigines, or pigmented freckles, can develop.

Miscellaneous: Well-known albinos include (purportedly) Noah, of flood fame (4) and the Reverend Dr. Spooner, who gave his name to the term “spoonerism.” It is suggested that his speech aberration was related to his nystagmus, which caused a jumbling of information on the printed page. Albinism was one of the four inborn errors of metabolism (the others being alkaptonuria, cystinuria, and pentosuria) discussed by Garrod in his famous series of lectures in 1902 (5).

It is thought that the temperature-sensitive type IB disease is analogous to that in Siamese cats and the Himalayan mouse, which have tyrosinase mutations that make the enzyme sensitive to higher temperatures, such that melanin synthesis takes place in the cooler areas of the body.

Anesthetic Considerations: Consideration should be given to patients with photophobia in brightly lit operating rooms.

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Albright hereditary osteodystrophy

See Pseudohypoparathyroidism

Note: This is a distinct entity from McCune-Albright syndrome.

Albright syndrome

See McCune-Albright syndrome

Alcaptonuria

See Alkaptonuria

Alcohol

See Fetal alcohol syndrome

Aldehyde oxidase deficiency

Included in Molybdenum cofactor deficiency

Alexander disease

MIM #: 203450

This likely autosomal dominant leukodystrophy is characterized by megalencephaly (a large head) in infancy and progressive spasticity and dementia. Its features are similar to Canavan disease (see later). The responsible gene encodes glial fibrillary acidic protein (*GFAP*), which is the primary intermediate filament protein synthesized in mature astrocytes. There are infantile, juvenile, and adult forms, all having defects in this gene. The infantile form is most common. Most patients die within 10 years of diagnosis. The juvenile form is more slowly progressive, and the adult form is more heterogeneous.

The other leukodystrophies include adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, Canavan disease, and Pelizaeus-Merzbacher disease.

HEENT/Airway: Megalencephaly in infancy. Copious oral secretions.

Neuromuscular: Seizures, choreoathetosis, progressive spasticity and dementia, demyelination, ataxia. Can have hydrocephalus.

GI/GU: Increased incidence of gastroesophageal reflux.

Miscellaneous: Histologically, Alexander disease is characterized by the presence of Rosenthal fibers (tapered

eosinophilic rods) in cortical white matter astrocytes.

Anesthetic Considerations: Gastroesophageal reflux, copious oral secretions, and poor airway tone increase the risk of perioperative aspiration. Consideration should be given to anticholinergic premedication to dry oral secretions. Careful perioperative positioning and padding is important in these patients with poor nutrition. The risk of excessive potassium release with succinylcholine is unknown but is theoretically possible in bedridden patients with atrophic muscles. Anticonvulsant medications need to be continued (or a parenteral form substituted) in the perioperative period and may alter the metabolism of some anesthetic drugs. Copious secretions and airway hypotonia make close postoperative observation of airway adequacy particularly important.

Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers should be avoided because they may exacerbate movement disorders. Ondansetron ought to be safe as an antiemetic because it does not have antidopaminergic effects.

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Alkaptonuria

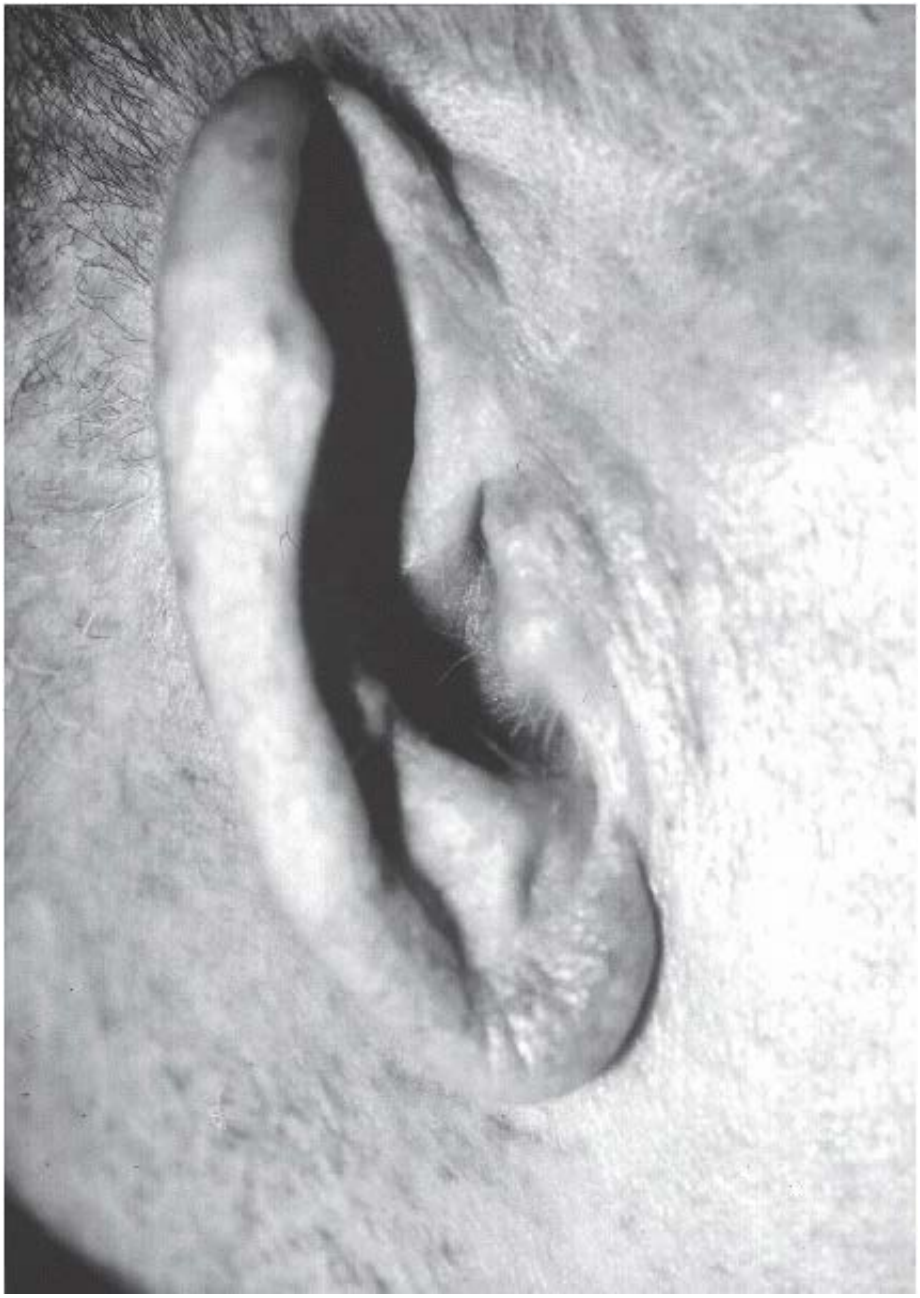
Synonym: Alcaptonuria

MIM #: 203500

This autosomal recessive disease is due to an abnormality in the gene for homogentisic acid oxidase (homogentisate 1,2-dioxygenase). This enzyme is part of the tyrosine and phenylalanine degradation pathways and catalyzes the conversion of homogentisic acid to maleylacetoacetic acid. Deficiency of this enzyme causes accumulation of homogentisic acid ("alkapton"). There is abnormal pigmentation (ochronosis) of a variety of tissues. Pigmentary changes are probably due to a polymer derived from homogentisic acid, although its exact structure is not known.

HEENT/Airway: Corneal pigmentation in older adults. One of the hallmarks of the early descriptions was dark (ochronotic) staining of the ear cartilage, also seen primarily in adults. Ear cartilage can calcify.

Cardiovascular: Ochronosis of the aortic valve has been described, and mitral involvement has also been described. Aortic staining. There is increased generalized atherosclerosis and coronary artery calcification, and aortic and mitral annular calcification. May develop aortic valve stenosis.



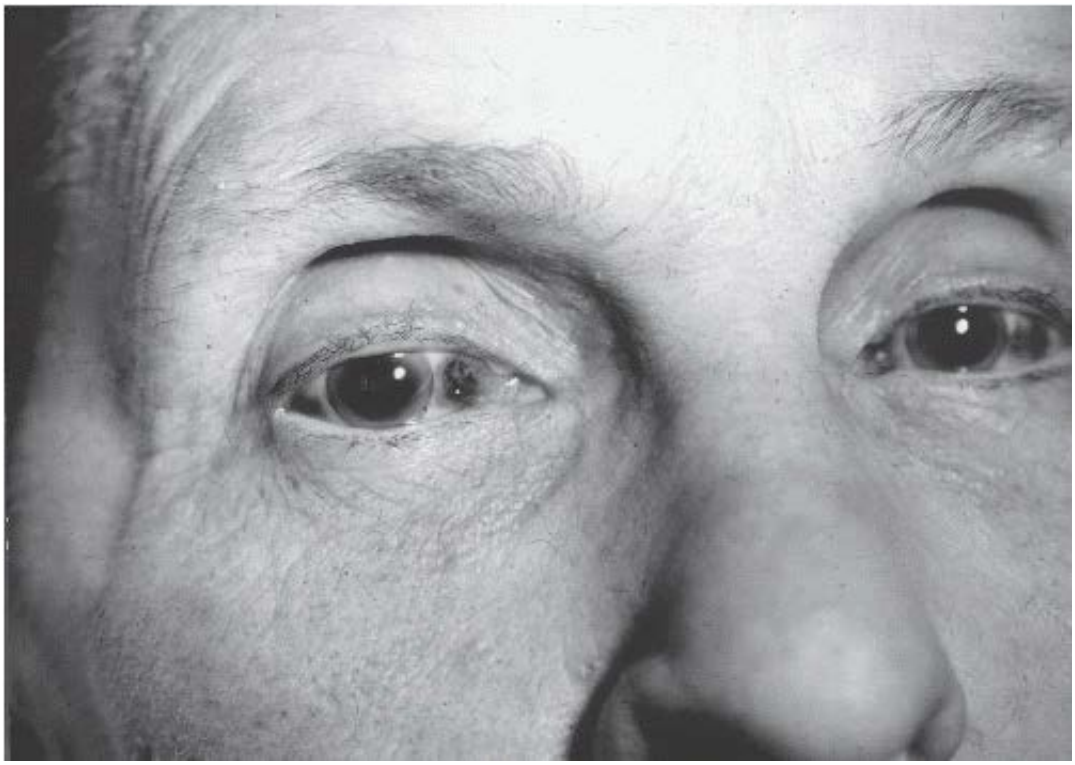
Alcaptonuria. FIG. 1. Ochronotic staining of the external ear in an adult with alkaptonuria. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Orthopedic: Osteoarthritis, including hips, knees, and spine, beyond the second or third decade. Arthritis is more severe, and appears at a younger age, in male patients. The radiographic changes in the spine are said to be almost pathognomonic. There is an increased incidence of ruptured intervertebral discs. Patients requiring joint replacement do so at a mean age of 55 years. There is dark (ochronotic) pigmentation of cartilage.

GI/GU: Urine that darkens with standing or high pH, although some patients may not have this manifestation. Rarely, renal failure in adults. There is an increased incidence of prostatitis.

Other: The pigment also appears in sweat, and can stain clothes.

Miscellaneous: This disorder is of significant historical interest because it was one of the first four human disorders suggested by Garrod to be a recessive inborn error of metabolism (the others being albinism, cystinuria, and pentosuria) (6). Alkaptonuria (with homogentisic acid pigmentation) has been described in an Egyptian mummy and has been diagnosed during coronary bypass surgery due to the observation of a black aorta. Alkaptonuria is a term derived from the alkaline urine's avid uptake of oxygen. Urine turns darker with alkalinization—if soap is used to wash diapers of these infants, the discoloration worsens, rather than being removed. In older tests for urinary glucose (or, more correctly, reducing sugars) using Benedict's reagent, this urine showed falsely elevated sugar.



Alcaptonuria. FIG. 2. Ochronotic staining of the conjunctivae in an adult with alkaptonuria. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Ochronosis is from the Greek *ochros* (“sallow”) and *nosos* (“disease”). It was so named by Virchow because microscopically the grossly bluish-black pigmentation is ochre colored (yellowish). A phenotypically similar disorder (exogenous ochronosis) occurs with topically applied phenols, such as occurred with the prolonged application of carbolic acid surgical dressings.

Anesthetic Considerations: There are few specific anesthetic concerns. Laryngeal and tracheal cartilages may have significant pigment deposition, and a smaller than expected endotracheal tube may be indicated. One should not be alarmed when the urine in the Foley catheter collection bag turns dark. Patients should be carefully positioned and padded to prevent injury to the arthritic joints and the spine. Lumbosacral arthritis and ankylosis may be a relative contraindication to regional anesthesia.

Figure: See **Appendix B**

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Alpers disease

MIM #: 203700

Alpers disease is a progressive autosomal recessive neurologic disorder beginning with seizures and progressing to spasticity, myoclonus, and dementia. Cirrhosis of the liver is also common. Clinical manifestations can be induced or exacerbated by concurrent infection or other stress. Death is usually by 3 years of age. The responsible gene is the nuclear gene encoding mitochondrial DNA polymerase gamma (*POLG*).

HEENT/Airway: Progressive microcephaly. Cortical blindness. Micrognathia has been reported.

Chest: Recurrent aspiration pneumonia.

Cardiovascular: Cardiorespiratory arrest may be a final outcome.

Neuromuscular: Intractable seizures, including epilepsia partialis continua. Status epilepticus is often the terminal event. Progressive spasticity, ataxia, hypotonia, myoclonus, and dementia.

Orthopedic: Prenatal onset of decreased mobility can result in postnatal joint limitation.

GI/GU: Swallowing difficulties. Hepatic cirrhosis with jaundice. Liver failure can be rapidly progressive and fatal in early childhood. Treatment of seizures with valproate can accelerate fulminant hepatic failure.

Anesthetic Considerations: Because of swallowing difficulties, patients are at increased risk for aspiration. Anticonvulsant medications should be continued perioperatively and may affect the metabolism of some anesthetic

drugs. Hepatic dysfunction can lead to clotting abnormalities or abnormalities in the protein binding of anesthetic drugs. Stress (and presumably surgery) can exacerbate symptoms. Patients must be carefully positioned perioperatively secondary to hypotonia and possibly limited joint mobility.

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Alpha$_1$-antitrypsin deficiency

MIM #: 613490

This autosomal recessive disease is due to an abnormality in the gene for alpha$_1$-antitrypsin (*SERPINA1*). Alpha$_1$-antitrypsin does inhibit pancreatic trypsin, but it is far more effective in inhibiting other serine proteases. Its primary role is lung protection by inhibition of neutrophil elastase. Deficiency of alpha$_1$-antitrypsin leads primarily to pulmonary and hepatic abnormalities. A variety of different mutations in the gene *SERPINA1* (at least 60) have been described, with the subtypes exhibiting a spectrum of clinical manifestations. Gene therapy and protein replacement therapy using parenteral alpha$_1$-antitrypsin prepared from pooled human plasma have been trialed in the treatment of this disorder. Neither approach has been proven effective.

Chest: Emphysema, primarily of the lung bases. Homozygotes develop severe degenerative lung disease, primarily emphysema, but also chronic bronchitis and recurrent pneumonia. Heterozygotes with certain subtypes are predisposed to chronic obstructive lung disease. There is also an increased incidence of sclerosing alveolitis. Pulmonary degeneration is significantly exacerbated by smoking. Onset of dyspnea is at 45 to 55 years in nonsmokers and 35 years in smokers. Emphysema in childhood is extremely rare.

Cardiovascular: Cor pulmonale can develop secondary to pulmonary disease.

GI/GU: Hepatic involvement occurs with certain subtypes. There may be neonatal cholestasis, sometimes leading to infantile cirrhosis with eventual portal fibrosis and esophageal varices. Hepatic intracellular inclusions. There is an increased incidence of hepatocellular carcinoma. With some subtypes, heterozygotes can also have liver disease. Liver disease can be subclinical and can present in adults with no history of neonatal disease. A patient who also had pancreatic fibrosis (but without pancreatic exocrine dysfunction) has been reported, and it has been suggested that one phenotype may make the pancreas more susceptible to chronic pancreatitis. Contrary to the earliest reports that suggested a very poor outcome for children with liver disease, it appears that approximately two-thirds will show some recovery. Panniculitis.

Miscellaneous: One in ten people of European descent is a carrier of one of the two mutations that result in partial deficiency of this protein. Liver transplantation has been successful in patients, even children, who have terminal or preterminal hepatic disease without pulmonary emphysema. Similarly, single lung transplantation has been used successfully.

Anesthetic Considerations: Pulmonary function should be assessed preoperatively. Hemodynamically significant air trapping can occur perioperatively in patients with severe emphysema. Hepatic dysfunction may lead to clotting abnormalities or abnormalities in the protein binding of anesthetic drugs. Patients with cirrhosis can develop esophageal varices, and nasogastric tubes or transesophageal echocardiography probes should be passed with caution. Levels of $alpha_1$-antitrypsin are normally increased during episodes of fever or inflammation because $alpha_1$-antitrypsin is an acute-phase reactant. Therefore, perioperative control of patient temperature and perioperative management of inflammation would seem to be reasonable goals.

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Alpha-galactosidase A deficiency

See Fabry disease

Alpha-galactosidase B deficiency

See Schindler disease

Alpha-1,4-glucan:alpha-1,4-glucan-6-alpha-glucosyltransferase deficiency

See Brancher deficiency

Alpha-1,4-glucosidase deficiency

See Pompe disease

Alpha-*N*-acetylgalactosaminidase deficiency

See Schindler disease

Alpha-mannosidosis

See Mannosidosis

Alpha-methylacetoacetic aciduria

See Beta-ketothiolase deficiency

Alpha-thalassemia/mental retardation syndrome

See ATR-X syndrome

Alport syndrome

Synonym: Progressive hereditary nephritis

MIM #: 301050, 104200, 203780

This syndrome involves progressive renal disease and hearing loss. X-linked dominant, autosomal dominant, and autosomal recessive forms have been described. There is significant variability in the age of onset and the severity of symptoms. Also, the extent of renal impairment does not correlate with the extent of auditory impairment. Up to 3% of children with chronic renal failure have Alport syndrome. This syndrome is caused by a defect in the glomerular basement membrane, which appears irregularly thickened by microscopy. Mutations in a variety of genes encoding type IV collagen, which is necessary for basement membrane integrity, are responsible for this syndrome.

HEENT/Airway: Asymmetric progressive sensorineural hearing loss—usually not detected until mid-childhood. May have cataracts, keratoconus, myopia, retinal detachment, nystagmus.

Cardiovascular: Hypertension may occur in patients with renal failure.

Neuromuscular: Rarely, myopathy or polyneuropathy has been reported in association with Alport syndrome.

GI/GU: Progressive nephritis and eventual renal failure. Hematuria—either microscopic or gross. May have proteinuria, hypophosphatemia, or nephrocalcinosis. Nephrotic syndrome is rare. Alport syndrome lacks the glomerular basement membrane protein, which is the purported antigen for the autoimmune Goodpasture syndrome. A small number of patients will develop anti-basement membrane nephritis after renal transplantation and will reject the kidney.

Other: Rarely, thrombocytopenia has been reported in association with Alport syndrome, although this could represent Fechtner syndrome (see later).

Diffuse leiomyomatosis has been reported in patients with X-linked Alport syndrome, and is probably the consequence of contiguous gene deletions.

Miscellaneous: Arthur Cecil Alport owned a small gold mine near Johannesburg. Unlike the other Cecil (Rhodes), Alport's gold mine proved to be nonlucrative, so he had to persist with medicine. Later in his career, Alport resigned from the Royal College of Physicians because he felt that they were not supporting him in his efforts to reform rampant corruption in Cairo, where he had been chair of medicine in the mid-1940s.

Anesthetic Considerations: Keep in mind that these patients will likely have significant hearing loss. Renal disease affects perioperative fluid management. Renally excreted drugs may be contraindicated. Aminoglycoside antibiotics, which are both ototoxic and nephrotoxic, should be avoided in these patients. Patients with advanced renal disease may be hypertensive. Consider having an interpreter present perioperatively for patients who are deaf. Rarely, myopathy, polyneuropathy, or thrombocytopenia has been reported in association with Alport syndrome. Myopathy would be a contraindication to the use of succinylcholine.

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Alström syndrome

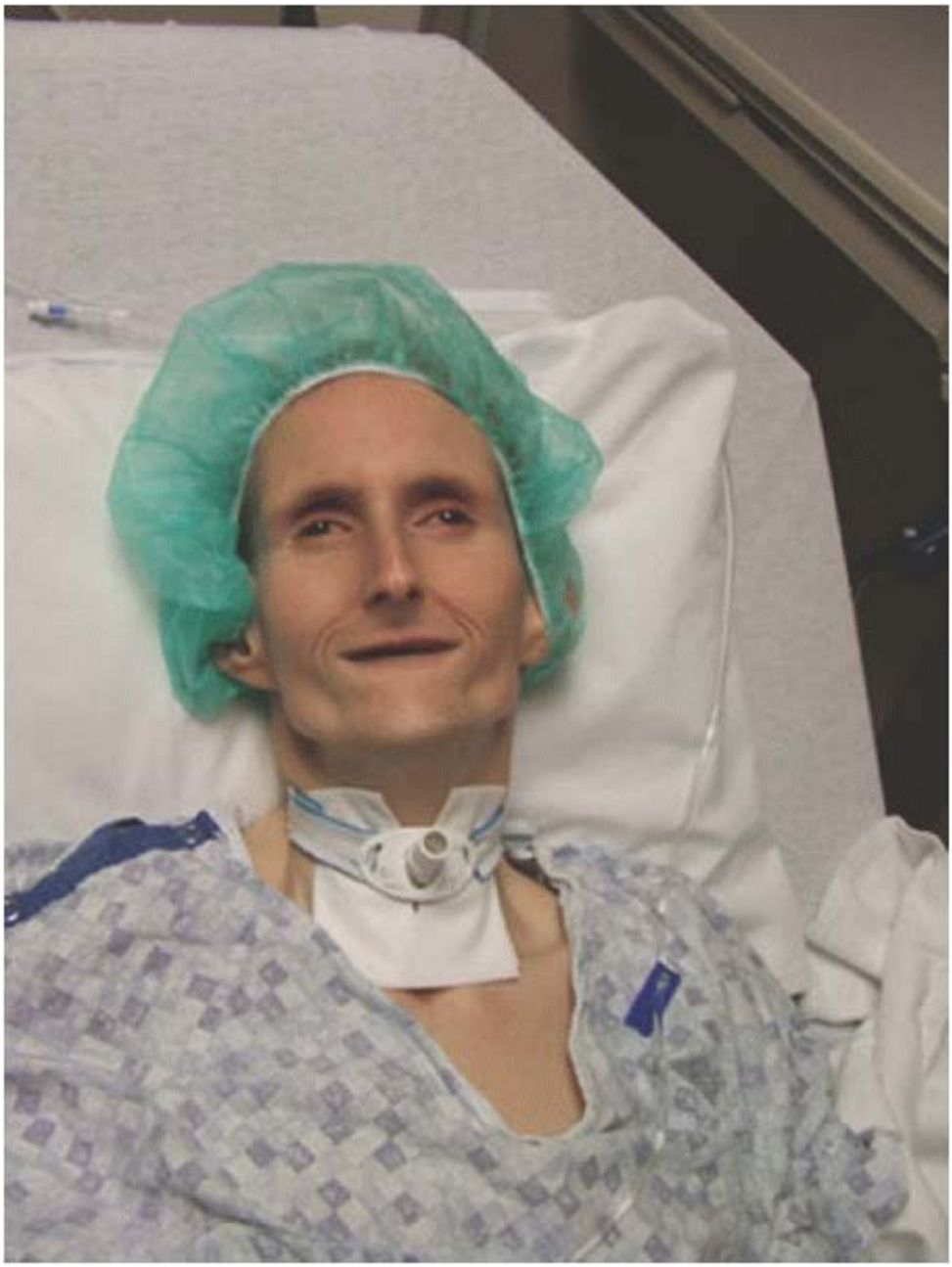
MIM #: 203800

A distinct but clinically similar syndrome to Bardet-Biedl syndrome; the hallmarks of this autosomal recessive disorder are retinitis pigmentosa, hearing loss, obesity, diabetes, and renal insufficiency. Unlike the Bardet-Biedl syndrome, there is no intellectual disability, polydactyly, or hypogenitalism. The defect is due to a mutation in the gene *ALMS1*. The gene product is unknown but likely plays a role in normal ciliary function.

HEENT/Airway: Retinitis pigmentosa, central vision loss, nystagmus, severe vision loss in the first decade with eventual blindness. Photophobia. Sensorineural hearing loss. Subcapsular cataracts.

Chest: Chronic obstructive pulmonary disease. Recurrent pneumonia. Pulmonary fibrosis.

Cardiovascular: Dilated cardiomyopathy. Atherosclerosis. Hypertension.



Alström syndrome. This 24-year-old man has severe visual impairment, type 2 diabetes, microcephaly, and cryptogenic cirrhosis with a history of esophageal variceal bleeding. In addition, he has pancytopenia and residua from multiple episodes of severe pneumonia with sepsis. He has developmental delay and graduated from the 12th grade in a special education program. A sister had similar vision problems and died at age 10 years.

Neuromuscular: Can have normal intelligence, but can have motor or language delay. Tics and absence seizures.

Orthopedic: Advanced bone age. Short adult height with pubertal onset of short stature. Kyphosis. Scoliosis.

GI/GU: Obesity can predispose to gastroesophageal reflux. Can have hepatic dysfunction. Chronic active hepatitis.

Pancreatitis. Progressive nephropathy with nephritis and renal failure. Recurrent urinary tract infections and abnormal voiding patterns.

Other: Truncal obesity with childhood onset. Hyperinsulinism followed by insulin-resistant diabetes mellitus. There can be end-organ unresponsiveness to other polypeptide hormones, including hypergonadotrophic hypogonadism in boys, menstrual irregularities in women, hypothyroidism, diabetes insipidus, and growth hormone deficiency. Gynecomastia. Hypertriglyceridemia. Acanthosis nigricans of skin. Alopecia.

Miscellaneous: Carl Alström was a Swedish psychiatrist.

Anesthetic Considerations: Keep in mind that patients can have significant visual or hearing impairment. Patients with photophobia will be uncomfortable in a brightly lit operating room. Baseline cardiac status should be evaluated, as symptomatic cardiomyopathy can be of early or delayed onset. Baseline pulmonary status should be evaluated. Baseline renal status should be evaluated. Renal disease can affect perioperative fluid management and the use of renally excreted drugs. The presence of diabetes mellitus requires attention to glucose status. Venous access and identification of landmarks for regional anesthesia can be difficult secondary to obesity. Obesity can result in desaturation with the induction of anesthesia due to increased airway closure and decreased functional residual capacity. Obesity is also a risk factor for gastroesophageal reflux and perioperative aspiration. Obese patients require lower than expected drug doses on a per kilogram basis. The patient's history should be reviewed for associated endocrinopathies, as delineated above. Serum glucose levels should be monitored perioperatively in those patients with diabetes.

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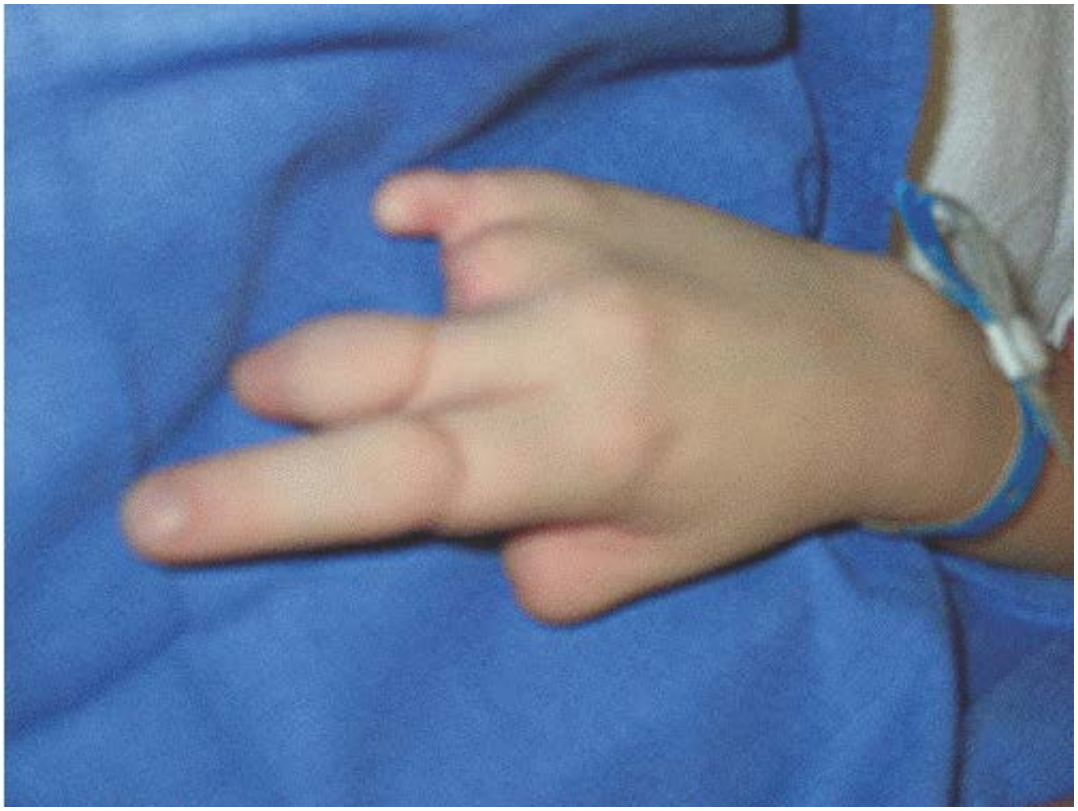
Amniotic band sequence

MIM #: 217100

This sequence occurs sporadically, with no discernible inheritance pattern. It is a consequence of amniotic membrane rupture after which loose bands of amnion wrap around parts of the developing fetus. Amniotic membrane rupture and subsequent amniotic band formation may occur at any time during gestation, but are most likely to occur in the first trimester when the amniotic membrane is most fragile. Because amniotic bands occur as a random event, there is no pattern to the deformations that can result. Most commonly the fetal limbs are involved, but occasionally, bands of amnion encircle the umbilical cord and lead to constriction of umbilical blood flow. When bands of amnion encircle the fetal limbs, various limb reduction defects can occur. Occasionally, amniotic bands lead to angulation deformities and other limb deformities by restricting normal fetal movement when a limb becomes tethered, even though it is not actually constricted.



Amniotic band sequence. The severely affected hand of an 8-year-old boy (unfortunately somewhat out of focus). In addition, he had syndactyly of his toes, an omphalocele, and cleft lip and palate.

In addition to band formation, leakage of amniotic fluid after amniotic membrane rupture can lead to limb and even vertebral abnormalities secondary to limitation of the normal movements in the fetus. In addition, significant loss of amniotic fluid can lead to lung hypoplasia secondary to lack of fluid movement with fetal "respirations." However, most patients are normal other than the typical band-related deformities.

HEENT/Airway: Several cases involving cleft lip or palate have been reported.

Neuromuscular: Rare encephalocele.

Orthopedic: Evidence of amniotic bands constricting one or more limbs, with amputation of all or part of a limb, amputation of one or more digits, ringlike constriction defects without amputation, distal limb hypoplasia, distal limb edema or pseudosyndactyly (secondary to compression that prevents separation of the digits), angulation deformities.

GI/GU: Rare omphalocele, gastroschisis.

Anesthetic Considerations: Limb reduction defects may make vascular access difficult.

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Amylo-1,6-glucosidase deficiency

See Debrancher deficiency

Amyoplasia congenita disruptive syndrome

Included in arthrogryposis

Andersen disease

See Brancher deficiency

Note: There is also an Andersen syndrome and an Anderson disease.

Andersen syndrome

Included in Long QT syndrome

Note: There is also an Andersen disease and Anderson disease

Andersen-Tawil syndrome

Included in long QT syndrome

Anderson disease

Synonym: Chylomicron retention disease

MIM #: 246700

Note: There is also an Andersen disease and Andersen syndrome.

This autosomal recessive disease results in a defect of intestinal lipid transport with subsequent fat malabsorption. The disorder is caused by a mutation in the *SAR1B* gene, leading to low levels of apolipoproteins A1 and B.

HEENT/Airway: Mild color vision defect.

Neuromuscular: Intellectual disability, decreased deep tendon reflexes, diminished vibratory sense. Peripheral neuropathy.

GI/GU: Severe childhood diarrhea and steatorrhea. Failure to thrive. Steatorrhea can be treated by substituting medium-chain for long-chain triglycerides in the diet.

Other: Growth retardation and malnutrition. Hypoalbuminemia. Hypocholesterolemia. Absent chylomicron formation. Fat-soluble vitamin deficiency—vitamin A and E deficiencies have been documented. Recurrent infections.

Anesthetic Considerations: Hypoalbuminemia can affect the binding of some anesthetic drugs. Vitamin A and E deficiencies have been documented. One can only speculate about other fat-soluble vitamin deficiencies— in particular, vitamin K deficiency with an attendant risk of bleeding.

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Anderson-Fabry disease

See Fabry disease

Angelman syndrome

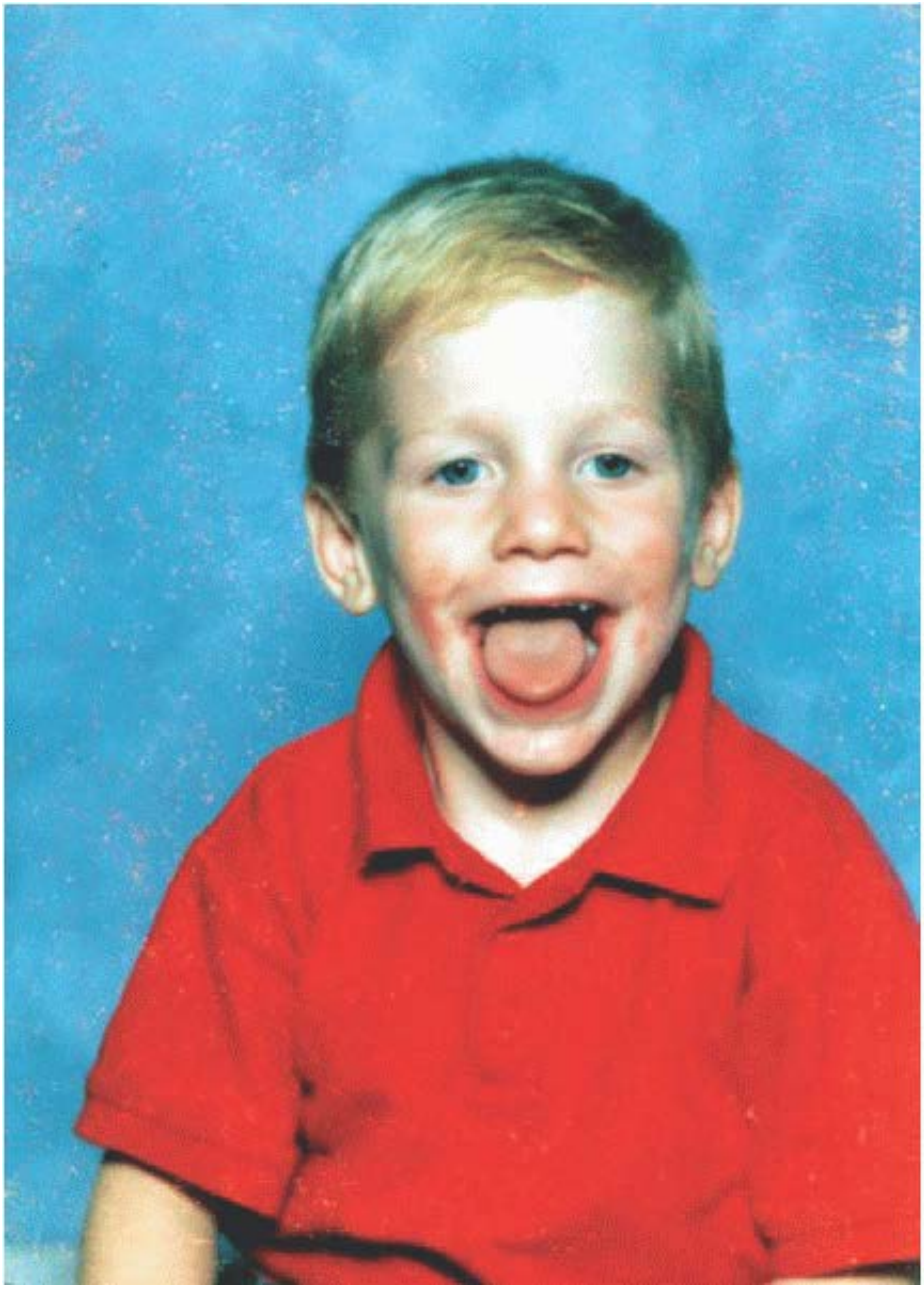
Synonym: Happy puppet syndrome

MIM #: 105830

This usually sporadically occurring syndrome is distinguished by characteristic facies, fits of laughter, and a puppet-like gait, hence the designation “happy puppet.” Laughter is generally in response to an appropriate stimulus, but the response is disproportionate. Seventy percent of patients with the syndrome have a chromosomal deletion between 15q11 and 15q13. The deletion always includes the gene encoding ubiquitin-protein ligase (*UBE3A*), which is the gene responsible for Angelman syndrome. Similar deletions are present in the Prader-Willi syndrome (see later); however, the origin of the chromosomal deletion is maternal in Angelman syndrome and paternal in Prader-Willi syndrome. Another 25% of patients with the syndrome have a mutation in *UBE3A*. *UBE3A* has biparental expression in most tissues but maternal expression in the brain. The remaining patients with Angelman syndrome have imprinting defects or uniparental disomy. Patients with chromosomal deletion defects may also lose the genes encoding for $GABA_A$ receptor subunits. Loss of these receptor subunits increases the severity of seizures and other neurologic deficits.

HEENT/Airway: Brachycephaly. Occipital depression or groove. Flat midface with deep-set eyes.

Decreased pigmentation of the iris that gives rise to blue eyes in most patients. Occasional strabismus. Wide mouth (macrostomia), characteristically open with a protruding tongue. Widely spaced teeth. Prognathia.



Angelman syndrome. A happy young boy with Angelman syndrome.

Neuromuscular: Severe intellectual disability. Marked motor and speech delay. Recurrent fits of laughter, which are not necessarily a reflection of the patient's mood but are more likely due to a defect at the level of the brainstem. Vagal hypertonia. Wide-based gait with ataxic arm and leg movements resulting in a puppet-like gait. Abnormal electroencephalogram. Seizures in the vast majority. Hypotonia. Occasional hyperreflexia. Cerebral or cerebellar atrophy by computed tomography scan.

Orthopedic: Occasional scoliosis.

Other: Often have blond hair and hypopigmentation.

Miscellaneous: Pronounced “Angel man.” The French refer to this syndrome as the *marionette joyeuse*. Because Angelman was unable to establish scientific proof that three children he had seen all had the same condition, he was reticent to publish an article about them. However, when on holiday in Italy, Angelman saw an oil painting in the Castelvecchio museum in Verona called “Boy with a Puppet.” The boy's laughing face and the fact that Angelman's patients exhibited jerky movements gave him the idea of writing an article about the three children with a title of “Puppet Children.”

Anesthetic Considerations: Severe intellectual impairment and speech delay present a challenge perioperatively, particularly at the time of induction. Induction through an intramuscular injection of ketamine may be the best option in many cases. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs. Intraoperative bradycardia for no apparent reason has been reported (6,11). This may be due to the increased vagal tone, and consideration should be given to anticholinergic pretreatment. Although GABA agonist anesthetic agents could theoretically be problematic in these patients with GABA dysregulation, there are many reports of the uneventful use of benzodiazepines, propofol, and volatile anesthetic agents (1,3,5,7,8).

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Aniridia-Wilms tumor association

Synonym: WAGR syndrome

MIM #: 194072

The association between aniridia and Wilms tumor has been recognized for many years. It is currently estimated that 1% to 2% of patients with aniridia

also have Wilms tumor. Aniridia and Wilms tumor have also been associated with genitourinary anomalies and intellectual disability, which has been termed **W**AGR syndrome, which is autosomal dominant: **W**ilms tumor, **A**niridia, **G**enitourinary anomalies or gonadoblastoma, and **R**etardation. Hemihypertrophy has also been described in some of these patients. The WAGR syndrome is a classic example of a contiguous gene syndrome. Aniridia, Wilms tumor/other genitourinary abnormalities, and intellectual disability are all due to mutations in separate, but contiguous, genes in the region of 11p13. For example, Wilms tumor and other genitourinary abnormalities are probably due to a mutation in the Wilms tumor suppressor gene (*WT1*).

HEENT/Airway: May have microcephaly. Aniridia, cataracts, nystagmus, ptosis, blindness. Hypoplastic ears. Protuberant lips. Micrognathia.

Cardiovascular: Occasional ventricular septal defect.

Neuromuscular: Moderate to severe intellectual disability.

Orthopedic: May have hemihypertrophy. May have short stature.

GI/GU: Wilms tumor. Renal failure. Genitourinary anomalies including ambiguous genitalia, cryptorchidism, and hypospadias. Gonadoblastoma also reported. Uterine malformations. Streak ovaries.

Other: Obesity

Miscellaneous: Max Wilms was an early 20th century German surgeon. He died of diphtheria at the age of 51.

Anesthetic Considerations: When meeting the patient before surgery, recall that he or she may have significant visual impairment. Micrognathia is usually mild, but can make tracheal intubation more difficult. Patients may be receiving chemotherapeutic agents for either Wilms tumor or gonadoblastoma. Patients may have renal dysfunction, which has implications for perioperative fluid management and choice of anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Antithrombin III deficiency

Synonym: Hereditary antithrombin deficiency

MIM #: 613118

Antithrombin III deficiency is one of the causes of hereditary thrombophilia, a familial propensity to develop venous thromboembolism. Antithrombin III deficiency is usually inherited in an autosomal dominant fashion. It is caused by a mutation in the antithrombin III gene (*AT3*), and over 150 different gene mutations have been described to date. Antithrombin III inactivates thrombin and factor Xa by binding to them and forming thrombin-antithrombin III and factor Xa-antithrombin III complexes, thereby permitting fibrinolysis. Two major subtypes of antithrombin III deficiency have been described. Type I deficiency is characterized by diminished synthesis of normal antithrombin III. Type II deficiency is characterized by near normal levels of dysfunctional antithrombin III. Type II deficiency is associated with a lower risk of thrombosis. Thrombotic events are rare in affected children, which may be due in part to a protective effect of elevated levels of alpha-2-macroglobulin during childhood, but 70% of patients will develop thrombosis before the age of 50. Acquired deficiencies of antithrombin III are very common, therefore the definitive diagnosis of a hereditary deficiency of antithrombin III is often difficult to make. Often the diagnosis is dependent on finding the disorder in multiple family members. A recombinant human antithrombin III (antithrombin alpha) has been developed for the treatment of this disorder.

Cardiovascular: Recurrent thrombosis of the deep veins of the legs and the mesenteric veins. Approximately 40% will develop pulmonary emboli. Infants can rarely develop cerebral venous thrombosis. Onset of thrombotic events is usually after puberty.

Miscellaneous: First described in 1965 by Egeberg who presented a Norwegian family in which members of three consecutive generations exhibited recurrent thromboembolic events and had plasma concentrations of antithrombin III that were approximately 50% of normal.

Anesthetic Considerations: Routine preoperative screening for hypercoagulable states such as antithrombin III deficiency has not been shown to improve perioperative outcome. Prophylactic perioperative anticoagulation is already recommended for all patients where warranted, and identification of a hypercoagulable state would not alter this recommendation. Hypovolemia, hypotension, and hypothermia should be avoided as they may increase the risk of thrombosis. Neuraxial anesthesia should be avoided in patients who are anticoagulated. Recombinant human antithrombin

III can be used during periods of acute thromboembolism. The use of recombinant antithrombin III during the peripartum period for patients with antithrombin III deficiency is increasing and has fewer implications for regional anesthesia than does peripartum anticoagulation (1). Patients who are deficient in antithrombin III will have incomplete anticoagulation from heparin prior to cardiopulmonary bypass. This is resolved with the administration

of exogenous antithrombin III.

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Antley-Bixler syndrome

Synonym: Multisynostotic osteodysgenesis; Trapezoidocephaly-synostosis syndrome

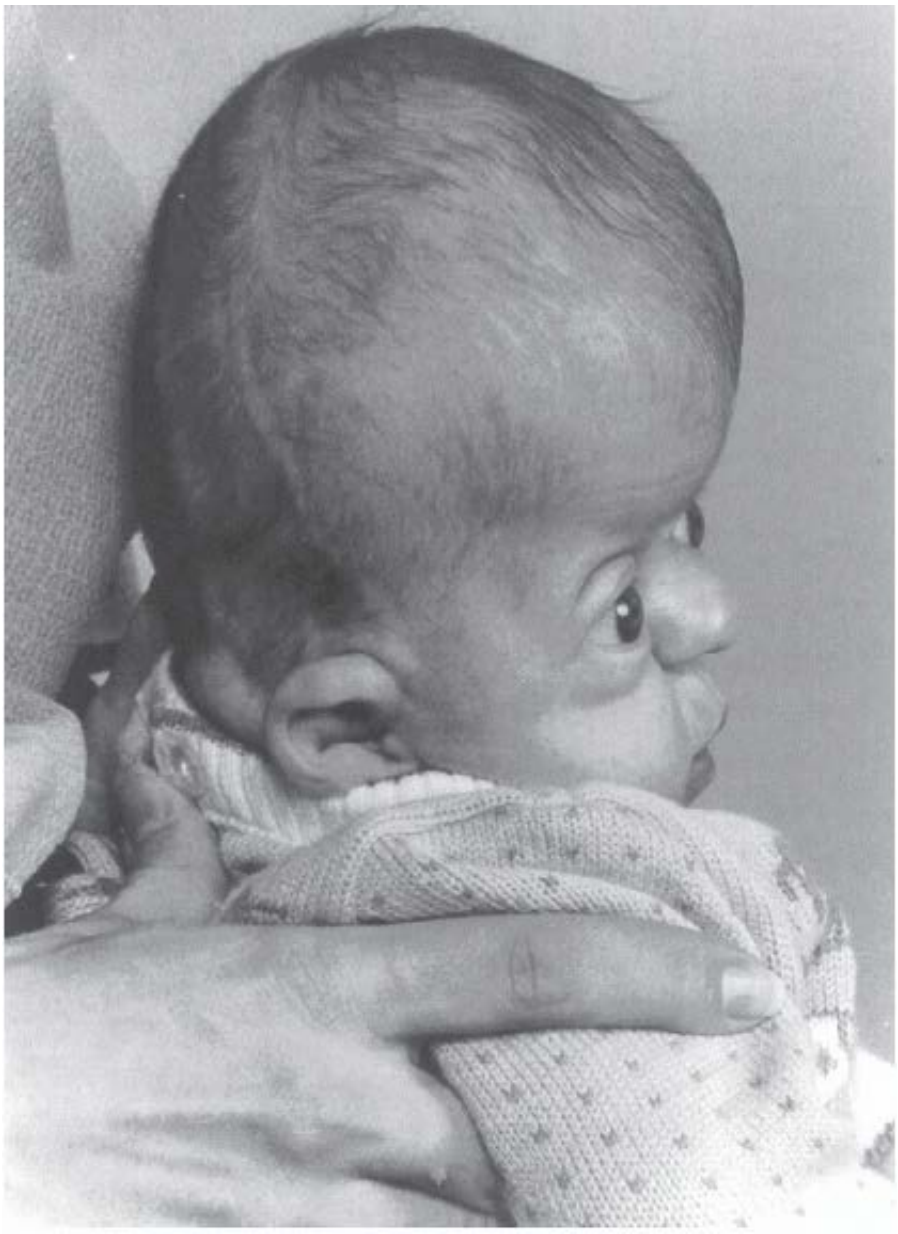
MIM #: 207410

This autosomal recessive disorder is characterized by trapezoidocephaly, choanal atresia, and radiohumeral synostosis. The defect is due to mutations in a fibroblast growth factor receptor gene, *FGFR2*. Mutations in this gene are also responsible for Apert syndrome, Crouzon syndrome, Beare-Stevenson syndrome, and some cases of Pfeiffer syndrome, which have many phenotypic similarities.

A phenotypically similar syndrome with ambiguous genitalia and abnormal steroidogenesis is due to abnormalities

in the gene encoding cytochrome P450 oxidoreductase (*MIM #:* 201750).

HEENT/Airway: Trapezoidocephaly with severe frontal bossing. Coronal and lambdoidal craniosynostosis. Large anterior fontanelle. Brachycephaly. Proptosis. Depressed nasal bridge and maxillary hypoplasia. Long philtrum. Dysplastic ears with stenotic external auditory canals. Choanal stenosis or atresia.



Antley-Bixler syndrome. A 6-week-old boy with Antley-Bixler syndrome. Craniosynostosis and midface hypoplasia are evident. (From LeBard SE, Thiemann LJ. Antley-Bixler syndrome: a case report and discussion. *Paediatr Anaesth* 1998;8:89-91, with permission.)

Many patients exhibit severe upper airway obstruction secondary to choanal stenosis or atresia immediately after

birth. Without a tracheostomy, more than half die before 3 months of age secondary to airway obstruction and associated apnea.

Chest: May have a narrow chest.

Cardiovascular: Occasional atrial septal defect.

Neuromuscular: Occasional hydrocephalus. Variable intellectual disability. At least some patients show normal intelligence, suggesting that craniosynostosis repair should be undertaken when necessary to allow for normal brain development.

Orthopedic: Radiohumeral synostosis. Femoral and ulnar bowing. Multiple joint contractures with severely limited range of motion in the hands, wrists, hips, knees, and ankles. Arachnodactyly. Slender nails. Camptodactyly. Rocker-bottom feet. May have skeletal fractures as a neonate. Narrow pelvis.

GI/GU: Occasional renal or urogenital defects including vaginal atresia and hypoplastic or fused labia.

Anesthetic Considerations: Upper airway obstruction may require immediate intervention at birth. An oral airway or choanal stenting may be helpful. Tracheostomy can be required for definitive treatment of airway obstruction. Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. A laryngeal mask airway (LMA) has been used successfully intraoperatively.

Meticulous perioperative eye protection is necessary in patients with significant proptosis. Careful perioperative positioning is required secondary to multiple joint contractures. Multiple joint contractures may limit vascular access. Skeletal fractures have not been reported outside of the neonatal period.

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Apert syndrome

Synonym: Acrocephalosyndactyly type I. (Includes Apert-Crouzon syndrome [acrocephalosyndactyly type II])

MIM #: 101200

This autosomal dominant disorder is characterized by craniosynostosis and acrocephaly, midfacial hypoplasia, and syndactyly. This syndrome is caused by mutations in the fibroblast growth factor receptor-2 gene (*FGFR2*). Most cases occur sporadically and are thought to be due to a new gene mutation. Two distinct causative mutations have thus far been identified. Different mutations of the same gene cause Crouzon syndrome, Antley-Bixler syndrome, Beare-Stevenson syndrome, and some cases of Pfeiffer syndrome, syndromes that have many phenotypic similarities. The findings in Apert syndrome tend to be more severe and more widespread than with the other craniosynostosis syndromes. Patients with the hand/foot malformations characteristic of Apert disease and the facial features of Crouzon disease (see later) have been labeled **Apert-Crouzon syndrome** (acrocephalosyndactyly type II).

HEENT/Airway: Acrocephaly, high forehead, flat occiput. Horizontal forehead groove. Irregular craniosynostosis. Large fontanelles. Midfacial hypoplasia. Hypertelorism, shallow orbits, proptosis. Down-slanting palpebral fissures. Strabismus, myopia. Can have hearing loss. Occasional choanal stenosis or atresia. Small beaked nose and nasopharynx. High, narrow palate. Can have cleft palate. Can have tracheal stenosis or abnormal tracheal cartilage.

Apert syndrome. FIG. 1. An infant with Apert syndrome scheduled for craniofacial surgery.

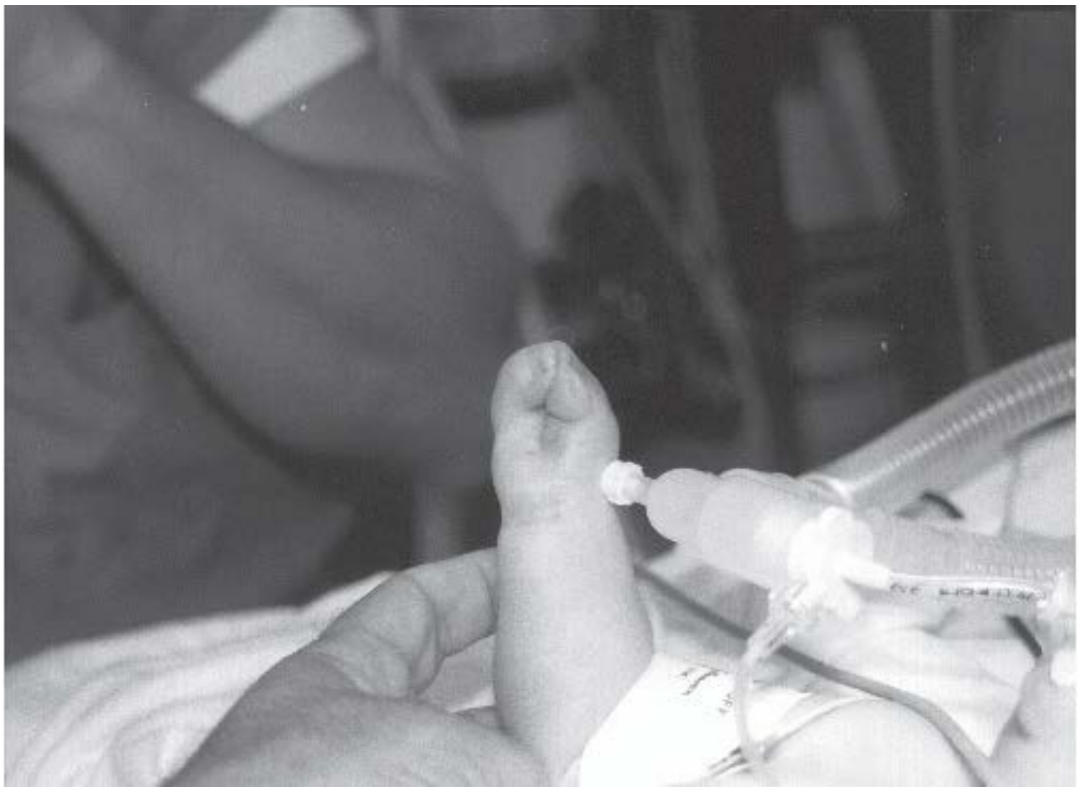
Upper airway compromise can occur secondary to the small nasopharynx, choanal stenosis or atresia, tracheal stenosis, or abnormal tracheal cartilage.

Chest: Narrowed trachea with fused tracheal rings. Rare anomalous tracheal cartilage or pulmonary aplasia, which can result in respiratory compromise. Nearly 50% have obstructive sleep apnea.

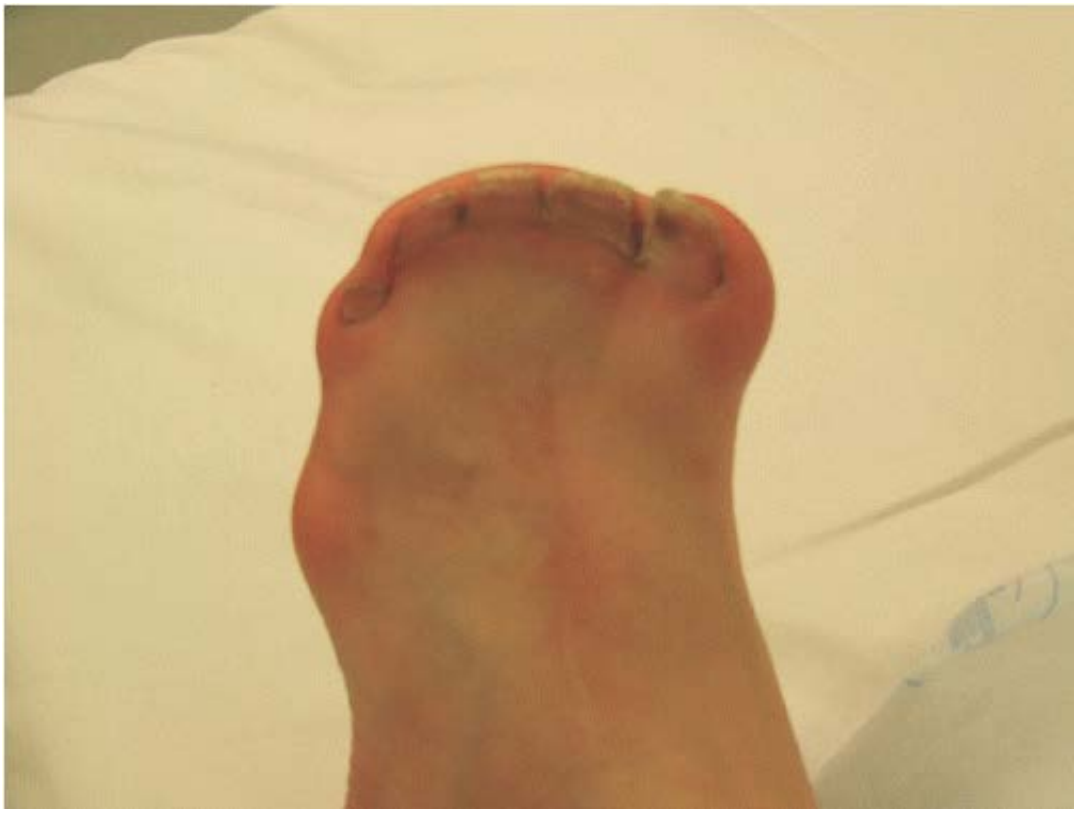
Cardiovascular: Ten percent incidence of congenital cardiac defects, which include pulmonary stenosis, overriding aorta, and ventricular septal defect.

Neuromuscular: Variable intellectual disability. Intelligence can be normal. Can have hydrocephalus or increased intracranial pressure. Craniosynostosis

repair should be undertaken when indicated to maximize brain development. However, craniosynostosis repair alone does not prevent intellectual disability. There is a high incidence of brain malformations, including agenesis of the corpus callosum, anomalies of the septum pellucidum, and gyral and hippocampal abnormalities.

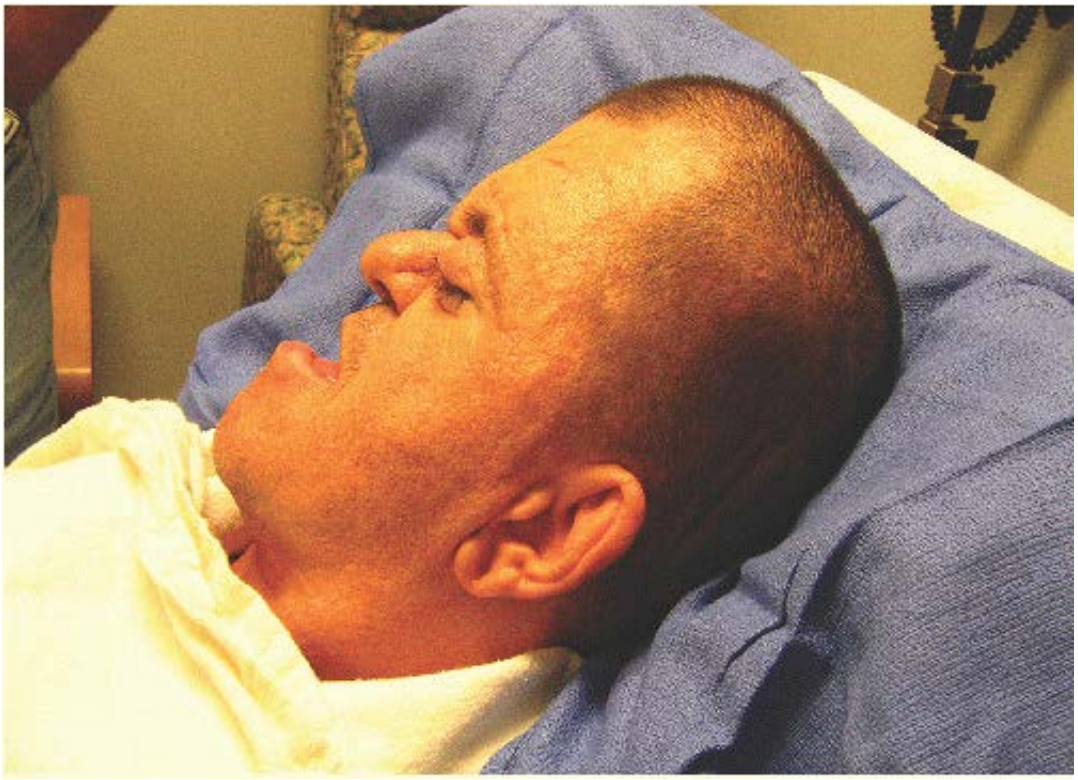


Apert syndrome. FIG. 2. Hands of the patient in Figure 1, showing syndactyly. Establishing adequate venous access in this child was challenging.



Apert syndrome. FIG. 3. An example of severe synostosis in a 9-year-old who required revision of craniofacial surgery. He has had a two level cervical fusion but had an uncomplicated intubation.

Orthopedic: Syndactyly—partial or total, osseous, or cutaneous; most commonly in digits 2 through 4. Fingers usually more severely affected than toes. Broad distal phalanx of the thumb and great toe. Occasional radiohumeral synostosis. Progressive synostosis can occur at other joints. Fusion of single or multiple cervical vertebrae, C5-6 most commonly.



Apert syndrome. FIG. 4. A 47-year-old gentleman with Apert syndrome. He is profoundly intellectually disabled. (Courtesy of Dr. William Arnold, Department of Anesthesiology, University of Virginia Health System.)

GI/GU: Ten percent incidence of genitourinary anomalies, including polycystic kidneys, hydronephrosis, bicornuate uterus, vaginal atresia, and cryptorchidism.

Other: Growth deceleration in childhood, which becomes more striking after puberty. Severe acne on face and forearms at puberty. Hyperhidrosis.

Miscellaneous: Apert was a French pediatrician, first at Hôpital Saint-Louis and later at Hôpital des Enfants-Malades. “His” syndrome was actually first reported in 1894 by Wheaton. In 1906, Apert summarized nine cases.

Anesthetic Considerations: Laryngoscopy and endotracheal intubation may be difficult, particularly if the patient has a small nasopharynx or cervical spine fusion. Guided video intubation using an Airtraq device has been described (2). Because cervical anomalies can complicate an already compromised airway in Apert syndrome, Kreiborg et al. (9) concluded that it is imperative to obtain radiographs of the cervical spine before undertaking anesthesia and surgery in these patients. Placement of a maxillary distraction device can increase the difficulty of tracheal intubation (4,6), and difficult intubation following midface distraction surgery has been ascribed to temporalis muscle fibrosis (6). Tracheal stenosis or abnormal tracheal cartilage can result in a reduced ability to clear secretions, an increased risk of tracheal injury during suctioning, or respiratory compromise (1,3,8). Choanal stenosis or atresia precludes placement of a nasal airway or a nasogastric tube. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. One series reported a high incidence of perioperative wheezing (5), which was not confirmed in a subsequent series (1). Consider preoperative evaluation of renal function in patients with a history

of renal abnormalities that predispose to renal insufficiency. Meticulous perioperative eye protection is necessary in patients with significant proptosis. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Patients can have elevated intracranial pressure, in which case precautions should be taken to avoid further elevations in pressure. Excessive premedication and intraoperative hypoventilation may exacerbate preexisting increases in intracranial pressure. Vascular access may be difficult.

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Apert-Crouzon syndrome

Included in Apert syndrome

Aplasia cutis congenita

See Adams-Oliver syndrome

Apparent mineralocorticoid excess, syndrome of

See 11ß-Hydroxysteroid dehydrogenase deficiency

ARC syndrome

MIM #: 208085

This autosomal recessive syndrome of **A**rthrogryposis, **R**enal dysfunction, and **C**holestasis is due to mutation of the gene *VPS33B*, which is involved in Golgi to lysosomal transfer, or mutation of the gene *VIPAR*, which is involved in intracellular sorting and trafficking of lysosomal proteins. Neonatal death is common.

HEENT/Airway: Can have deafness. Can have high-arched palate. Can have redundant nuchal skin.

Cardiovascular: Can have congenital heart disease.

Neuromuscular: Rarefaction of the anterior horn of the spinal cord. Developmental delay.

Orthopedic: Arthrogryposis multiplex congenita (see Arthrogryposis, later), on a neurogenic basis. Proximally placed thumbs.

GI/GU: Cholestatic liver disease. Intrahepatic biliary hypoplasia. Eventual progression to cirrhosis. Diarrhea, probably secondary to fat malabsorption. Nephropathy. Renal tubular acidosis (Fanconi syndrome, see later). May have nephrogenic diabetes insipidus.

Other: Abnormal platelet morphology and function, similar to gray platelet syndrome (not discussed in this text). Ichthyosis. Recurrent febrile illnesses. Failure to thrive. May have cryptorchidism.

Anesthetic Considerations: Severe and fatal hemorrhage has been reported after liver and kidney biopsies. Children may die before renal manifestations become clinically important. Since there is evidence of muscle denervation, succinylcholine should be avoided in these patients. Isosthenuria (fixed specific gravity, neither concentrated nor dilute) or polyuria can complicate perioperative fluid management. Protracted preoperative fasting should be avoided to prevent dehydration. Urine output may be a poor indicator of intravascular fluid status, so central venous pressure monitoring might be appropriate in these patients if surgery will involve major fluid shifts. Chronic renal failure has implications for the choice and dosages of anesthetic and other drugs. Intravenous fluids may be supplemented with bicarbonate or potassium. May require more water in intravenous fluids because of excessive and relatively dilute urine.

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Arginase deficiency

Synonym: Argininemia

MIM #: 207800

This autosomal recessive disorder is one of the urea cycle defects, and is a potential cause of hyperammonemia. The urea cycle degrades amino acids to urea. Because arginase appears relatively late in the urea cycle, the disease may be less severe than other urea cycle defects. This disorder is caused by mutations in the liver arginase gene (*ARG1*). Symptoms can be triggered by stress, such as surgery or infection, or episodes of protein catabolism, such as involution of the postpartum uterus. Unlike the other urea cycle defects, the most common findings with arginase deficiency are neurologic. Pharmacologic therapy, using parenteral phenylacetate and benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors. Liver transplantation is curative.

Neuromuscular: Spastic tetraplegia is often the presenting finding with arginase deficiency. These children are often originally diagnosed with cerebral palsy,

but the progressive nature of the neurologic disease differentiates arginase deficiency from cerebral palsy. The legs are much more severely affected than are the arms. Can have psychomotor retardation, hyperactivity, seizures. Hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and proceeds through stages of lethargy and agitation to coma with cerebral edema.

GI/GU: Possible hepatomegaly.

Other: Growth failure. Episodes of hyperammonemia are not as severe or as frequent as with the other urea cycle defects. During episodes of hyperammonemia, ammonia levels are lower than with the other urea cycle defects.

Anesthetic Considerations: Acute metabolic encephalopathy can develop perioperatively. Acute metabolic encephalopathy may be associated with cerebral edema and increased intracranial pressure. Patients should have high carbohydrate intake (and low protein intake) perioperatively. Protracted preoperative fasting should be avoided in order to avert a catabolic state. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load and trigger an acute decompensation. It has been postulated, but not clinically observed, that elevated levels of arginine might produce vasodilation and exacerbate the hypotensive effects of anesthetic medications (1).

Figure: See **Appendix C**

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Argininemia

See Arginase deficiency

Argininosuccinic acid lyase deficiency

Synonym: Argininosuccinic aciduria

MIM #: 207900

This autosomal recessive disorder is the second most common urea cycle defect and is a potential cause of hyperammonemia. The urea cycle degrades amino acids to urea. Both early-onset (severe) and later-onset (less severe) types of argininosuccinic acid lyase deficiency have been described. This disorder is caused by a mutation in the argininosuccinate lyase gene (*ASL*). In addition to a decrease in urea production, patients with argininosuccinic acid lyase deficiency have a decrease in nitric oxide production, and treatment with nitric oxide supplements has been investigated (1). Symptoms can be triggered by stress, such as surgery or infection, or episodes of protein catabolism, such as involution of the postpartum uterus.

The clinical presentations of the urea cycle defects carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, and argininosuccinic acid lyase deficiencies are essentially identical. Pharmacologic therapy, using parenteral phenylacetate and sodium benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors. Liver transplantation is curative.

Neuromuscular: Intellectual disability, seizures. Hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and proceeds through stages of lethargy and agitation, to coma with cerebral edema.

GI/GU: Hepatomegaly. Hepatic synthetic function is normal, although there may be elevations in serum transaminases, both during and between episodes of hyperammonemia.

Other: Particular to this specific urea cycle defect is the presence of brittle hair (which fluoresces red) in approximately one-half of patients, possibly related to a low-protein diet. Skin on the dorsum of the hands and arms is rough. Episodes of hyperammonemia begin with anorexia and lethargy, and can progress through agitation, irritability, and confusion. Vomiting and headaches can be prominent. Untreated, central nervous system deterioration ensues with worsening encephalopathy and eventually results in coma with cerebral edema and death.

Miscellaneous: This enzyme has structural as well as enzymatic activity. It can accumulate in high concentration without precipitating, making it transparent, and it is found in particularly high concentration in duck lens.

Anesthetic Considerations: Acute metabolic encephalopathy can develop perioperatively. Acute metabolic encephalopathy may be associated with

cerebral edema and increased intracranial pressure. Patients should have high carbohydrate intake (and low protein intake) perioperatively. Protracted preoperative fasting should be avoided in order to avert a catabolic state. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. An orogastric

tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load, triggering an acute decompensation. A case of fatality on the first postoperative day of an otherwise stable child with the disease following inguinal herniorrhaphy with enflurane anesthesia has been reported (5).

Figure: See **Appendix C**

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Argininosuccinic acid synthetase deficiency

Synonym: Citrullinuria; Citrullinemia

MIM #: 215700

This autosomal recessive disorder is one of the urea cycle defects and is a potential cause of hyperammonemia. The urea cycle degrades amino acids to urea. This disorder is caused by a mutation in the argininosuccinate synthetase gene (*ASS1*). Symptoms can be triggered by stress, such as surgery or infection, or episodes of protein catabolism, such as involution of the postpartum uterus. Onset is usually in the neonatal period, but a late-onset form of the disease has been described in Japan.

The clinical presentations of the urea cycle defects carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, and argininosuccinic acid lyase deficiencies are essentially identical. Pharmacologic therapy, using parenteral phenylacetate and sodium benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors. Liver transplantation is curative.

Neuromuscular: Intellectual disability, developmental delay. Seizures. Lethargy, episodic coma. Hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and proceeds through stages of lethargy and agitation to coma with cerebral edema.

GI/GU: Vomiting, diarrhea. Hepatic synthetic function is normal, although there can be elevations in serum transaminases, both during and between episodes of hyperammonemia.

Other: Episodes of hyperammonemia begin with anorexia and lethargy and can progress through agitation, irritability, and confusion. Vomiting and headaches can be prominent. Untreated, central nervous system deterioration ensues with worsening encephalopathy and eventually results in coma with cerebral edema and death.

Miscellaneous: The amino acid citrulline derives its name from its high concentrations in the watermelon *Citrullus vulgaris*. The disorder has also been reported in a strain of Australian dairy cows.

Anesthetic Considerations: Acute metabolic encephalopathy can develop perioperatively. Acute metabolic encephalopathy may be associated with cerebral edema and increased intracranial pressure. Patients should have high-carbohydrate intake (and low-protein intake) perioperatively. Protracted preoperative fasting should be avoided in order to avert a catabolic state. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load, triggering an acute decompensation. Worsening encephalopathy has been reported in patients receiving glycerol for cerebral edema.

Figure: See **Appendix C**

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Argininosuccinic aciduria

See Argininosuccinic acid lyase deficiency

Arima syndrome

Synonym: Cerebrooculohepatorenal syndrome

MIM #: 243910

This autosomal recessive syndrome shares phenotypic characteristics with Joubert syndrome (see later). Characteristics include aplasia of the cerebellar vermis, abnormalities of the eyes, and cystic kidney disease. Patients can also have liver disease. The gene and gene product are not known.

HEENT/Airway: Abnormal eye movements. Leber congenital amaurosis (see later). Chorioretinal coloboma. Abnormal eye movements. Rhythmic tongue protrusion. Large mouth.

Chest: Episodic hyperventilation.

Neuromuscular: Aplasia of the cerebellar vermis, ataxia, hypotonia, intellectual disability. Can have brainstem malformations including pachygyria.

Orthopedic: Postaxial polydactyly of hands and feet.

GI/GU: Can have liver disease. Infantile polycystic disease of the kidneys. Renal failure.

Anesthetic Considerations: Hepatic and renal dysfunction can affect metabolism of a variety of anesthetic medications. There have been reports of difficult airway management. A laryngeal mask airway (LMA) has been used successfully. A case of intraoperative hyperkalemia has been reported, but the etiology is unclear, as the child had renal failure with baseline hyperkalemia.

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Arnold-Chiari malformation

Synonym: Chiari II malformation

MIM #: 207950

Chiari malformations are subdivided into four types, depending on the extent of caudal displacement of the hindbrain and brainstem. Patients with type I have protrusion of the cerebellar tonsils through the foramen magnum and are usually asymptomatic. Patients with type II (Arnold-Chiari malformation) have displacement of the cerebellar tonsils, the cerebellar vermis, and other portions of the cerebellum and lower brainstem through the foramen magnum. The fourth ventricle may also be displaced. These patients usually become symptomatic, often before the age of 3 months. Patients with type III have protrusion of the cerebellum and brainstem through the foramen magnum and into the spinal cord and are almost always symptomatic before the age of 3 months. Patients with type IV, which is rare, have cerebellar hypoplasia. The Arnold-Chiari (Chiari II) malformation is the most common anomaly of the hindbrain. The etiology of this malformation appears to be multifactorial. The Arnold-Chiari malformation is present in virtually all children with meningomyelocele. Symptoms are a result of impairment of the lower cranial nerves, the brainstem, the cerebellum, and occasionally the cervical spinal cord.

The most common symptoms are vocal cord paralysis, dysphagia, stridor, apnea, upper extremity weakness, and opisthotonos. In older children and adults, the Arnold-Chiari malformation can be associated with syringomyelia.

HEENT/Airway: Vocal cord paralysis, dysphagia.

Chest: Stridor, respiratory distress, apnea (central or obstructive). Abnormal swallowing increases the risk of pulmonary aspiration.

Cardiovascular: Significant brainstem involvement can be reflected in changes in heart rate or rhythm.

Neuromuscular: Can have cranial nerve VI, VII, IX, X, XI, or XII; brainstem; cerebellar; or cervical cord dysfunction, with various manifestations. Headaches are common. Diminished or absent gag reflex. Central apnea. Ataxia, vertigo, nystagmus. Paresthesias, weakness, or spasticity of an extremity. Opisthotonos. Symptomatic patients may benefit from surgical decompression of the posterior fossa.

Brainstem compression may lead to complete obstruction of the foramina of Luschka and Magendie and to progressive hydrocephalus. Possible increased intracranial pressure. Syringomyelia. Patients with symptomatic hydrocephalus benefit from placement of a ventriculoperitoneal shunt.

Orthopedic: May have cervical spondylolysis or other deformities.

Miscellaneous: In 1883, John Cleland described the basilar impression syndrome, now known as the Arnold-Chiari malformation, 8 years prior to Chiari (1891) and 11 years prior to Arnold (1894).

Anesthetic Considerations: Patients are at increased risk of aspiration secondary to swallowing difficulties with pooling of oral secretions, diminished or absent gag reflex, and vocal cord paralysis. Patients with a history of recurrent aspiration may have chronic lung disease. Patients may also have other cranial nerve defects. Brainstem dysfunction can result in an abnormal response to hypoxia and hypercarbia or frank apnea. Intraoperative controlled ventilation is necessary in patients with frequent apneic episodes. Significant brainstem compression has been associated with intraoperative refractory hypotension and bigeminy (7). Precautions against elevations in intracranial pressure are indicated in some patients. Spinal and epidural anesthesia for cesarean section have been reported several times for women with type I lesions. If elevated intracranial pressure is present, it may be prudent to avoid subarachnoid needle entry.

Posterior fossa decompression surgery is usually performed with the patient in the prone position with the neck flexed. Care should be taken in positioning because extreme neck flexion can cause brainstem compression or endobronchial intubation. If prone, the patient's face and eyes should be well padded. There is the potential for the development of an air embolism during posterior fossa surgery.

After posterior fossa decompression, the recovery of neurologic function takes time. Patients with inability to maintain or protect their airway preoperatively (vocal cord paralysis, absent gag reflex) will not have immediate improvement in function and will need to remain intubated until adequate function returns.

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Aromatic l-amino acid decarboxylase deficiency

Synonym: AADC deficiency

MIM #: 608643

This autosomal recessive disorder, due to mutations in the gene *AADC*, is a disorder of neurotransmitter synthesis. This enzyme decarboxylates l-DOPA to dopamine and 5-hydroxytryptophan to serotonin. There are low levels of multiple catecholamine neurotransmitters, including dopamine, epinephrine, norepinephrine, and serotonin. Parasympathetic function is intact, leading to an autonomic imbalance with parasympathetic predominance. Diagnosis is made by finding low levels of these neurotransmitters in the spinal fluid or blood. Plasma enzyme activity can also be assayed. Treatment may include ropinirole (a D_2 dopamine receptor agonist), pergolid (a dopamine receptor agonist), pyridoxine (a cofactor of the enzyme), cholinergics, monoamine oxidase inhibitors, and serotonergic agents. Treatment response has been variable (mostly poor), and patients appear to segregate into responder and nonresponder groups. Interestingly the responders have all been boys, whereas the nonresponders have been a mix of boys and girls.

HEENT/Airway: Ptosis, miosis. Nasal congestion. Drooling.

Cardiovascular: Impaired heart rate and blood pressure control. Hypotension. Bradycardia.

Neuromuscular: Severe autonomic dysregulation. Severe intellectual disability. Markedly diminished voluntary movements. Truncal hypotonia, limb hyperreflexia, intermittent oculogyric crises, dystonic posturing. Myoclonus. Emotional lability.

GI/GU: Gastroesophageal reflux, constipation, diarrhea.

Other: Temperature instability. Hypoglycemia. Diaphoresis.

Anesthetic Considerations: The autonomic imbalance produces significant challenges to perioperative homeostasis. There is decreased ability to respond appropriately to hypovolemia. Prophylactic atropine has been suggested, given the propensity to bradycardia. Patients can develop hypothermia or hyperthermia (not malignant hyperthermia related). Painful stimuli can result in bradycardia and cardiorespiratory arrest due to unopposed vagal tone. Infusion of dopamine at 5 μg/kg/min resulted in an excessive hypertensive and tachycardic response in one child. Doses of 1 to 2 μg/kg/min of dopamine were tolerated (2). It is unclear if this was due to an abnormal expression of dopaminergic receptors or an interaction with dopaminergic medications the patient was receiving. Phenylephrine can result in profound reflex bradycardia. Ephedrine will

have diminished effect due to its indirect mechanism of action. It has been suggested that treatment responders may maintain more hemodynamic stability under anesthesia than do nonresponders (3). Arterial catheters should be considered for procedures with possible blood or fluid loss. Blood glucose should be followed perioperatively. Hemodynamic monitoring should be continued into the postoperative period. There can be delayed gastric emptying.

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Arrhythmogenic right ventricular dysplasia

See Uhl anomaly

Arteriohepatic dysplasia

See Alagille syndrome

Arthrodentoosteo dysplasia

See Hajdu-Cheney syndrome

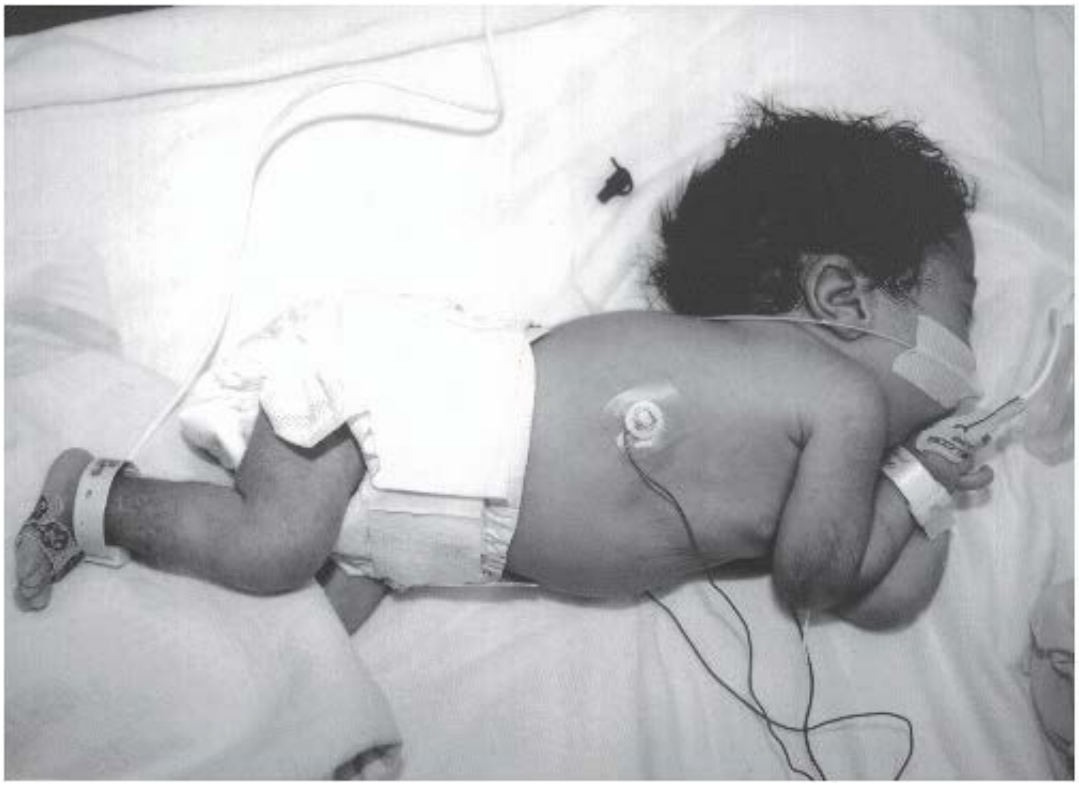
Arthrogryposis

Synonym: Arthrogryposis multiplex congenita (AMC). (Includes amyoplasia congenita disruptive syndrome and distal arthrogryposis)

MIM #: 108120, 108145, 114300, 601680, 609128

Arthrogryposis, meaning “curved joints,” is a general term that describes congenital contractures affecting

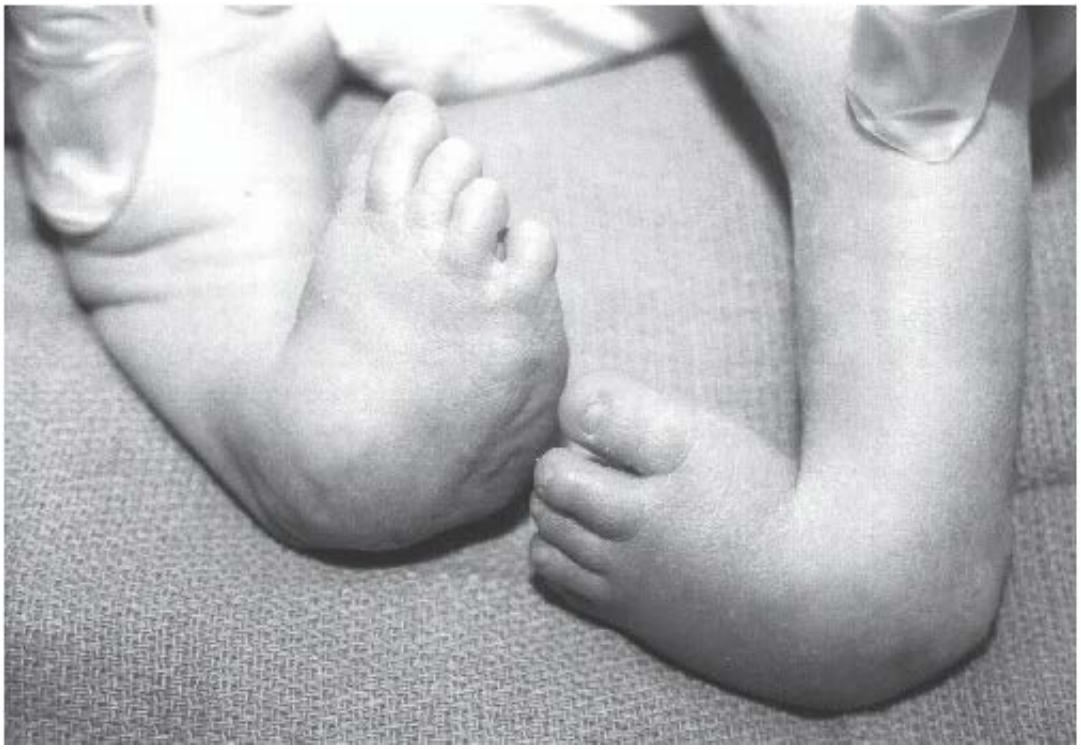
multiple (two or more) joints in a single patient. Arthrogryposis can be found associated with a variety of diseases. It can be the result of a fetal myopathy, a fetal neuropathy, or severe oligohydramnios resulting in intrauterine constraint. Whistling face syndrome (Freeman-Sheldon syndrome, see later) is a progressive form of myopathic arthrogryposis. In the sporadic disorder **amyoplasia congenita disruptive syndrome**, the arthrogryposis is thought to be a result of an intrauterine vascular accident that affects the developing anterior horn cells of the fetal spinal cord. These patients typically exhibit fixed extension at the elbow, flexion of the hands and wrists, internal rotation of the shoulders, flexion or dislocation of the hips, and clubfeet.



Arthrogryposis. FIG. 1. The neck is in fixed extension in this infant with arthrogryposis.

Distal arthrogryposis describes autosomal dominantly inherited arthrogryposis in which there is involvement primarily of the distal joints (hands and feet). There are at least 10 forms of distal arthrogryposis, with marked phenotypic variability. Typical features include congenital contractures that primarily affect the distal joints, clenched fists with medially overlapping fingers in the neonate (similar to the hand positioning noted in trisomy 18), ulnar deviation of the fingers, and clubfeet. Mutations in genes encoding myocyte contractile elements have been identified as causative agents in distal arthrogryposis, including the genes *TPM2*, *TNNI2*, *TNNT3*, *MYH3*, and *MYH8*. Distal arthrogryposis, type 2A is also known as whistling face syndrome (see later) and distal arthrogryposis, type 7 is also known as Dutch-Kentucky syndrome (see later).

HEENT/Airway: Patients can have associated ptosis, cleft lip or palate, micrognathia, short neck, trismus.



Arthrogryposis. FIG. 2. Fixed foot deformity in arthrogryposis.

Arthrogryposis. FIG. 3. The fixed knee deformity is obvious in this girl with arthrogryposis.

Chest: Myopathy, a poor cough, and skeletal deformities can result in alveolar hypoventilation, atelectasis, and restrictive lung disease and may increase the risk of aspiration.

Cardiovascular: A variety of congenital heart defects have been noted in a small percentage of patients. Severe respiratory disease can result in cor pulmonale.

Neuromuscular: Intelligence is usually normal. Spinal stenosis has been reported.

Orthopedic: Multiple joints exhibit fixed flexion or contracture deformities, severely limiting joint mobility. The

affected extremities are often atrophic. There can be webbing of the overlying skin. Joints often exhibit a good response to physical therapy. Hip involvement is common—congenital dislocation, decreased abduction, mild flexion contracture deformities. Clubfeet in most. Occasional scoliosis. Occasional fusion of cervical vertebrae. Occasional short stature.

Neonates' hands are clenched tightly in a fist, with medially overlapping fingers and thumb. Ulnar deviation of the fingers and camptodactyly occur in the adult, after the hands have unclenched.

Miscellaneous: Arthrogryposis can be seen in any circumstance in which there is immobilization of the developing fetal joints. An unusual example is treatment of a mother with curare for tetanus.

Anesthetic Considerations: Micrognathia or limited mandibular excursion, a short neck, or fusion of the cervical vertebrae can make laryngoscopy and tracheal intubation difficult (6,7). Difficult intubations have not been reported in patients with isolated limb findings. Central and peripheral regional techniques may be challenging due to vertebral and limb abnormalities, but successful blocks have been reported even in neonates (1,5). Intravenous access and appropriate positioning may be difficult because of flexion or contracture deformities, especially of the distal extremities. Fractures can occur with improper positioning. Patients may have cardiac or pulmonary disease, but their occurrence is rare. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemia. This disease is not associated with malignant hyperthermia. The hypermetabolism and hyperthermia sometimes seen in association with anesthesia are not believed to represent malignant hyperthermia (1,4,10,12).

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Arthrogryposis multiplex congenita (AMC)

See Arthrogryposis

Asperger syndrome

Included in Autism spectrum disorder

Asphyxiating thoracic dystrophy

See Jeune syndrome

Asplenia

Synonym: Ivemark syndrome; Heterotaxy syndrome.

MIM #: 208530

Asplenia and the related syndrome of polysplenia (see later) are often thought of as disorders of laterality: patients with asplenia are bilaterally right sided (right-sided isomerism, i.e., they have two copies of right-sided structures, and they lack normal left-sided structures, the spleen being one), and patients who are polysplenic are bilaterally left sided. Thus, they have neither situs solitus nor situs inversus but are said to have situs ambiguus. Asplenia is often associated with a primitive heart and right-sided obstruction. Sudden death, particularly during the first few years of life, is primarily due to sepsis, complex cardiac disease, or less commonly arrhythmias. Autosomal recessive familial cases have been reported and linked to the gene *GDF1*. The sequence of events leading to asymmetric morphogenesis remains unknown.

Chest: There are two right lungs [trilobed with the bronchial-arterial relationship of the right lung (pulmonary artery superior to the bronchus)].

Cardiovascular: There are two right atria, and thus two sinoatrial nodes producing a wandering atrial pacemaker from the two foci. A common atrium, a single ventricle with a single atrioventricular canal type valve, or a single ventricle variant with pulmonary stenosis or atresia may occur. Because there is no left atrium for the pulmonary veins to return to, there is usually some type of anomalous pulmonary venous return. Systemic venous anomalies include bilateral superior vena cavae, bilateral hepatic venous connections directly to the ipsilateral atrium, and unroofing of the coronary sinus. The aorta and inferior vena cava run together on the same side of the spine (normally the inferior vena cava is to the right and the aorta to the left). Cardiopulmonary anatomy is reviewed in reference (1).

GI/GU: There is laterality to the "tacking down" of the fetal GI tract in normal fetuses (that is why the appendix fairly reliably ends up in the right lower quadrant). In this disease of abnormal laterality, there may be malrotation of the gut, which can present with volvulus. There are two right lobes of the liver, and on radiographs, the abnormal liver can be seen interposed between the air-filled stomach and the base of the left lung. The stomach and pancreas can be left sided, right sided, or midline. There is, of course, no spleen. Can have horseshoe kidney. May have horseshoe adrenal gland.

Other: Because of absence of the spleen, patients are immunoincompetent and are susceptible to infection with encapsulated organisms. They should have received the pneumococcal and *Haemophilus* vaccines, and probably also the meningococcal vaccine if over 2 years of age. Patients are also at increased risk for fatal malaria and severe babesiosis. Red cell inclusions, particularly Howell-Jolly bodies, can be seen in the peripheral blood smear of patients with asplenia.

Anesthetic Considerations: Meticulous aseptic technique is imperative in these patients with an immune deficiency and appropriate antibiotic prophylaxis particularly important. Specific anesthetic management varies with the individual cardiac lesion. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Although not reported, it might be expected that a left-sided double-lumen endobronchial tube might occlude the takeoff of the left upper lobe bronchus, which would arise more proximally than usual in this left-sided lung that has the anatomy of a right lung.

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Asymmetric crying facies

Synonym: Cayler syndrome

MIM #: 125520

This syndrome is due to congenital unilateral hypoplasia or absence of the depressor anguli oris muscle, resulting in asymmetry of the mouth during crying or laughing. It is hypothesized to be either an autosomal dominant or a multifactorial trait. It can occur in isolation or in association with defects in other organs,

most commonly ventricular septal defects of the heart. The specific gene and gene product are not known. It is thought that the syndrome might represent another manifestation of the 22q11.2 deletion syndrome (see DiGeorge syndrome).

HEENT/Airway: Variable microcephaly. Asymmetry of the lower lip, seen particularly with crying or laughing.

Cardiovascular: Ventricular septal defect.

Neuromuscular: Rare intellectual disability. May have dysgenesis of the corpus callosum.

Other: May have failure to thrive.

Miscellaneous: Glenn Cayler, who first described this disorder, was a pediatric cardiologist who noted an "epidemic of congenital facial paresis and heart disease."

Anesthetic Considerations: Patients with congenital heart disease should receive an appropriately tailored anesthetic. The asymmetric facies should be documented preoperatively to avoid miscommunication postoperatively.

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Ataxia-telangiectasia

Synonym: Louis-Bar syndrome

MIM #: 208900

This autosomal recessive disorder involves oculocutaneous telangiectasis, variable immunodeficiency, cerebellar ataxia, and a predisposition to malignancy. Ataxia-telangiectasia is caused by a mutation in the *ATM* gene (ataxia-telangiectasia mutated gene), which encodes a protein in the phosphatidylinositol-3 kinase family of proteins. The phosphatidylinositol-3 kinase proteins respond to DNA damage by phosphorylating substances involved in DNA repair or cell cycle control. Patients with ataxia-telangiectasia have defective DNA repair after x-irradiation, and their cells have increased chromosomal breakage. Survival, which used to be uncommon into the teenager years, is now often into adulthood in the United States.

HEENT/Airway: Telangiectasis first appears on the conjunctivae, at approximately 3 to 5 years of age. Nystagmus. Oculomotor apraxia (inability to make purposeful movements). Recurrent sinusitis. Dysarthria, hypersalivation, drooling.

Chest: Recurrent pulmonary infections and bronchiectasis. These are with "routine" pathogens and not opportunistic organisms. Chronic lung disease is a significant cause of morbidity and death. Thymus remains embryonic.

Neuromuscular: Progressive cerebellar ataxia with difficulty in learning to walk is typically the initial presentation, followed by choreoathetosis, myoclonic jerks, and oculomotor abnormalities. Abnormal fetal cerebellar Purkinje cell migration and degeneration. Progressive muscle weakness from degeneration of peripheral nerve Schwann cells. Patients have normal intelligence, but severe short-term memory loss has been reported in older adults. Progressive spinal muscle atrophy may develop in adults.

Orthopedic: Interosseous muscle atrophy of the hands, in combination with dystonia, leads to a combination of flexion-extension contractures of the hands in adults.

GI/GU: May have elevated liver enzymes associated with fatty infiltration and round cell infiltration of the portal area. There is hypogonadism, more so in female than in male patients. Delayed development of secondary sexual characteristics in girls is associated with absent or hypoplastic ovaries. Can have premature menopause.

Other: Telangiectases appear on the skin, particularly on sun-exposed areas and areas of trauma. There are also areas of vitiligo, café au lait spots, early loss of subcutaneous fat, and premature graying of the hair. Endocrine abnormalities are common, and most patients have some degree of glucose intolerance. There is an increased incidence of malignancy of a variety of types, often leukemia or lymphoma, and approximately 15% of patients eventually die of malignant disease. A variety of immunologic defects are seen, variable even within the same family. These include IgA deficiency in most patients (interestingly, all of the patients in whom carcinoma of the stomach develops are IgA deficient), IgE deficiency, IgG subtype deficiency, an abnormal IgM (7S monomorphic form rather than the usual 19S pentameric form), anergy to delayed hypersensitivity skin testing, depressed lymphocyte proliferative responses to mitogens or viral pathogens, and abnormalities in helper T-cell function. Despite these abnormalities, systemic viral, bacterial, and fungal infections are uncommon. Premature aging. Can have hypertrichosis.

Miscellaneous: These patients are extremely sensitive to x-irradiation, and treatment of malignancies with conventional doses of radiation therapy may be fatal. DNA repair mechanisms are abnormal in four other inherited diseases: xeroderma pigmentosum, Fanconi anemia, Bloom syndrome, and Cockayne syndrome.

Louis-Bar is one person (Denise Louis-Bar). She began using the hyphenated surname after she was married.

Anesthetic Considerations: Perioperative x-ray studies are indicated only when absolutely necessary. Patients may have glucose intolerance, and perioperative serum glucose levels can be elevated. The likelihood of an immunodeficiency suggests that particularly good aseptic technique is obligatory. Transfusion of nonirradiated blood can cause graft versus host disease. Patients with IgA deficiency may have allergic reactions to the IgA found

in transfused blood. Significant neuromuscular disease, dysphagia, and hypersalivation may increase the risk of perioperative aspiration. Patients may benefit from anticholinergic medication for excessive drooling. Succinylcholine may cause hyperkalemia in patients with a significant neuropathy and muscle weakness. Patients may have chronic lung disease secondary to recurrent sinopulmonary infection. No major perioperative complications were detected in a recent review of 34 anesthetics in 21 patients (1).

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ATP synthetase (ATPase) deficiency

See Complex V deficiency

ATR-X syndrome

Synonym: Alpha-thalassemia/mental retardation syndrome; X-linked alpha-thalassemia/mental retardation syndrome

MIM #: 301040

This **X**-linked recessive disorder of **a**lpha-**t**halassemia, mental **r**etardation, genital abnormalities, and characteristic facies is due to a defect in the gene encoding X-linked helicase-2. Helicases are involved in a wide variety of intracellular functions, including DNA recombination and repair and regulation of transcription, including regulation of alpha-globin expression. The typical facies of patients with this syndrome are similar to that seen with Coffin-Lowry syndrome. Specific mutations in this gene can result in dysmorphic features and mental retardation without thalassemia. A second, less common, and more phenotypically variable form of this syndrome is due to a partial deletion of chromosome 16 that involves hemoglobin α-1 and α-2 genes.

HEENT/Airway: Microcephaly, midface hypoplasia. Can have absent frontal sinuses. Telecanthus, epicanthal folds. Small or malformed, low-set ears. Small, triangular nose, anteverted nostrils, alae nasi extend below columella and septum, flat nasal bridge. Carp-shaped mouth, large, protuberant tongue, full lips.

Chest: Missing rib.

Cardiovascular: Occasional ventricular septal defect.

Neuromuscular: Severe intellectual and gross motor retardation, almost absent speech. Hypotonia. Seizures.

Orthopedic: Clinodactyly. Occasional clubfoot deformity. Occasional growth retardation.

GI/GU: Gastroesophageal reflux is common. Genital anomalies including shawl scrotum, cryptorchidism, and hypospadias. Recurrent urinary tract infections. Occasional renal agenesis, hydronephrosis, hydroureter.

Other: Alpha-thalassemia (see later, under Thalassemia). Cells containing hemoglobin H inclusions are detectable in a peripheral blood smear. Hematologic abnormalities tend to be relatively minor.

Anesthetic Considerations: A preoperative hematocrit should be obtained. Severe intellectual disability and absent speech may make the induction of anesthesia more challenging. Gastroesophageal reflux is common, increasing the risk of perioperative aspiration. Patients may have renal dysfunction, which has implications for perioperative fluid management and choice of anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Autism spectrum disorder

Synonym: Autistic disorder; Kanner syndrome. (Includes Asperger syndrome.)

MIM #: 209850, 608638

Autism spectrum disorder is a pervasive developmental disorder that is characterized by an inability to socialize and form normal relationships, severe limitations in verbal and nonverbal communication skills, and stereotypical repetitive patterns of behavior. Intelligence testing in children with autism spectrum disorder usually places them in the normal to slightly below normal range. Occasionally, autistic children display isolated, but remarkable, talents—analogous to that of the adult savant. Autism spectrum disorder is usually diagnosed between 18 months and 3 years of age, but in some cases, symptoms may not become fully apparent until later, when social demands on the patient exceed their capacity. Autism spectrum disorder is more common in males than in females (3 to 4:1). Autism spectrum disorder may be associated with other neurologic disorders, particularly seizure disorders. It has also been linked to tuberous sclerosis, fragile X syndrome, Angelman syndrome, and untreated phenylketonuria (see later). There is controversy over whether the incidence of autism spectrum disorder is increasing. The cause of autism spectrum disorder is multifactorial. There appears to be no association between the use of the measles-mumps-rubella (MMR) vaccine and autism spectrum disorder (3,7). Family and twin studies have shown that genetic factors play a significant role. The disease is genetically heterogeneous, but there is evidence that chromosomal copy number variations (CNVs) are involved in its pathogenesis. Specifically implicated are CNVs that disrupt genes involved in synapse development, axon targeting, and neuron motility—suggesting that disruption of synaptogenesis may be central to the development of autism spectrum disorder.

Asperger syndrome has traditionally been thought of as a distinct form of childhood autism. Children with Asperger syndrome exhibit impaired social interactions and repetitive behaviors, but lack the severe language impairments that characterize many children with autism spectrum disorder. Also, intelligence in children with Asperger syndrome is almost always in the normal range. Asperger syndrome is often diagnosed at a later age than autism spectrum disorder. There has been ongoing debate as to whether Asperger syndrome is a separate disorder or whether it represents the "high-functioning" end of the spectrum of autism. The updated *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, released by the American Psychiatric Association in May 2013, officially eliminates Asperger syndrome as a separate entity and incorporates it into the single diagnosis of autism spectrum disorder. Asperger syndrome is still defined as a separate entity in the *World Health Organization ICD-10*, and it is likely to remain in common usage to describe high-functioning patients with autism spectrum disorder.

Neuromuscular: May have macrocephaly. May have seizure disorder. Studies have demonstrated structural anatomic changes in the brains of patients with autism, none of which are diagnostic for autism. Structural changes may be demonstrable in the hippocampus, the temporal lobe, the cerebellum, the reticular activating system, or the anterior cingulate gyrus, an area of the brain that is associated with processing feelings and thoughts and with decision making. Abnormal neurotransmitter levels have also been implicated in autism, with particular interest focused on the dopamine, catecholamine, and serotonin pathways.

Other: Higher functioning autistic children and children with Asperger syndrome may be at greater risk for having other psychiatric disorders, particularly oppositional-defiant disorder, obsessive-compulsive disorder, and anxiety or mood disorders. In some patients, autistic spectrum disorder may be associated with mitochondrial dysfunction.

Miscellaneous: Leo Kanner, an Austrian psychiatrist who practiced in the United States, was the first to describe autism. In 1943, he wrote of a disorder in which children showed "an innate inability to form the usual, biologically provided affective contact with people." Kanner noted that in most cases, the child's behavior was abnormal from early infancy, which suggested to him that the disorder was genetically based. In 1944, the Austrian pediatrician Hans Asperger described a syndrome in which children exhibited impaired social interaction coupled with seemingly normal intelligence. He dubbed this disorder "autistic psychopathy." Asperger was a prolific writer, publishing more than 350 articles in his lifetime, and an indefatigable academician, lecturing 6 days prior to his death at the age of 74 years.

Anesthetic Considerations: Patients with autism spectrum disorder often become particularly difficult to manage in the hospital setting because they react poorly to changes in their routine. There is great variability in the severity of autism and in the needs of individuals with autism. Early and comprehensive communication with the patient's family and a willingness to be flexible with the anesthetic plan are imperative. Oral midazolam has been shown to be an effective premedicant for milder cases, and oral ketamine a reliable premedicant for moderate to severe cases (5,9,10). It is important to

return the patient as quickly as possible to their baseline state. To that end, the intravenous cannula should be removed as soon as is clinically acceptable, and the patient should be discharged as quickly as possible (ideally on the same day as surgery). Developmental regression may be observed postoperatively.

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Autistic disorder

See Autism spectrum disorder

Autonomic neuropathy with insensitivity to pain

See Congenital insensitivity to pain with anhidrosis

Axenfeld syndrome

See Axenfeld-Rieger syndrome

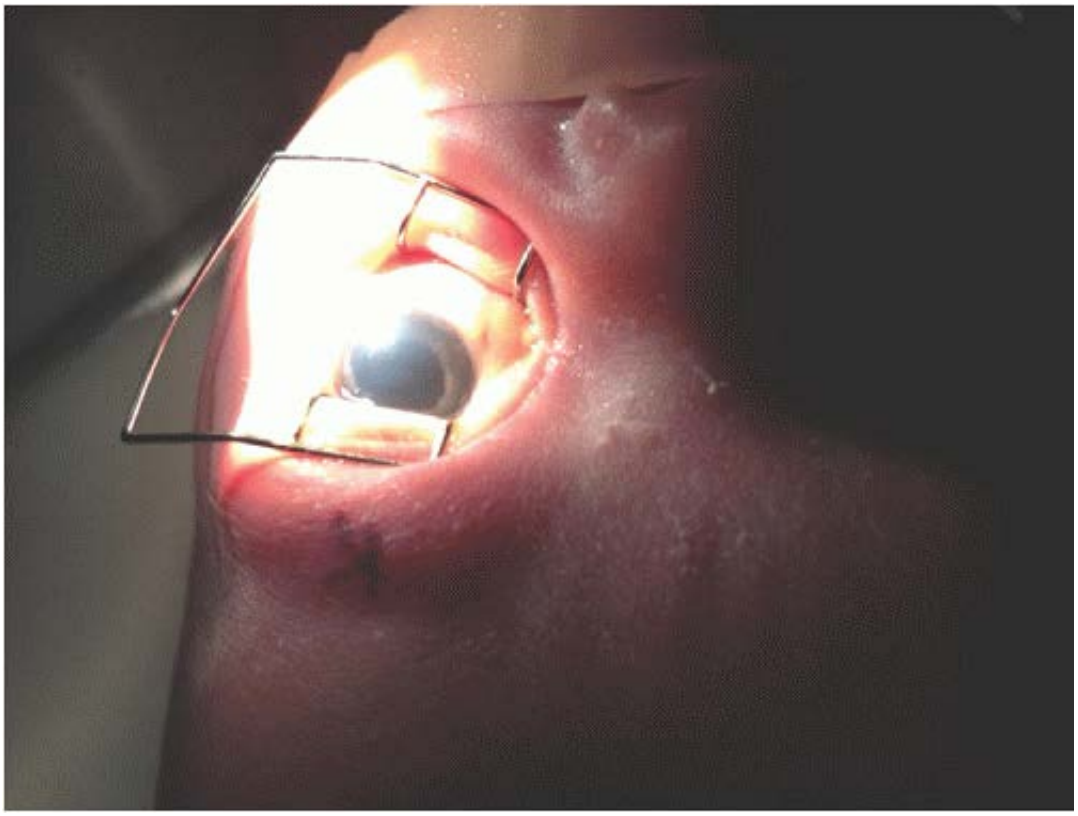
Axenfeld-Rieger syndrome

Synonym: Axenfeld syndrome

See also Rieger syndrome

MIM #: 180500

This autosomal dominant disorder is similar to Rieger syndrome (see later) and probably represents a different manifestation of the same genetic defect. Axenfeld-Rieger syndrome involves Axenfeld and Rieger anomalies of the anterior segment of the eye, which commonly lead to glaucoma, along with other facial and skeletal anomalies. This syndrome is most often due to a mutation in the gene *PITX2*. Closely related diseases, sometimes grouped as Axenfeld-Rieger syndrome types 2 and 3, are mapped to 13q14 (type 2) and the gene *FOXC1* (type 3).



Axenfeld-Rieger syndrome. This 2-week-old infant with Axenfeld anomaly had findings limited to the eyes, with congenital glaucoma, irregular pupil, mild proptosis, and mydriasis (the eye was not pharmacologically dilated). (Courtesy of Dr. George Politis, Department of Anesthesiology, University of Virginia.)

The similarity of anterior chamber angle abnormalities in Axenfeld anomaly, Rieger anomaly, and Rieger syndrome has led to the conjecture that these three categories represent a spectrum of developmental disorders. Ophthalmologists use the term Axenfeld-Rieger syndrome to categorize most of these patients, based on clinical findings. Patients may have surgery shortly after birth or later in childhood, for glaucoma or other ocular problems.

HEENT/Airway: Brachycephaly. Prominent forehead with flat midface. Facial asymmetry. Abnormalities of the anterior chamber, absent eye muscles, proptosis, hypertelorism. Glaucoma, blindness. Mild sensorineural deafness. Maxillary hypoplasia.

Cardiovascular: Can be associated with a variety of congenital cardiac defects, particularly outflow tract

malformations.

Neuromuscular: May have communicating hydrocephalus or psychomotor retardation. Hypotonia. Absent corpus callosum. May have pituitary anomalies.

Orthopedic: Flat femoral epiphyses. Coxa valga. Hip dislocation. Hypoplastic shoulder. Lax joints. Short stature.

Anesthetic Considerations: Keep in mind that patients may have impaired vision. Care must be taken perioperatively to protect the proptotic eyes from trauma. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

B

Baller-Gerold syndrome

Synonym: Craniosynostosis-radial aplasia syndrome

MIM #: 218600

This autosomal recessive disorder has as its main features craniosynostosis, radial aplasia, absent or hypoplastic thumbs, and growth retardation. Death during infancy is common. There is phenotypic overlap with both Fanconi anemia and Saethre-Chotzen syndrome (see later), and misdiagnosis may occur. Baller-Gerold syndrome is caused by mutations in the DNA helicase gene *RECQL4* and is allelic with Rothmund-Thomson syndrome caused by defects in the same gene (see later).

HEENT/Airway: Craniosynostosis involving single or multiple sutures. Flattened forehead. Downslanting palpebral fissures, epicanthal folds, hypertelorism. Low-set and posteriorly rotated ears. Prominent nasal bridge. Micrognathia with small mouth. Occasional cleft palate or choanal stenosis.

Cardiovascular: Twenty-five percent incidence of cardiac anomalies including subaortic hypertrophy, ventricular septal defect, tetralogy of Fallot.

Neuromuscular: Intellectual disability is common. Occasional seizures, hydrocephalus, absent corpus callosum.

Orthopedic: Growth retardation. Absent or hypoplastic radius. Ulnar hypoplasia and curvature. Absent or hypoplastic thumbs. Malformed or absent carpals. Occasional humeral hypoplasia, vertebral and pelvic defects, fused ribs, scoliosis.

GI/GU: Anal anomalies common, including anteriorly placed anus and imperforate anus. Renal anomalies common, including ectopic, hypoplastic, dysplastic, or absent kidneys.

Anesthetic Considerations: Patients must be evaluated for congenital cardiac defects. Micrognathia or small mouth may make direct laryngoscopy difficult. Choanal stenosis precludes nasal intubation or placement of a nasogastric tube. Vascular access may be difficult secondary to radial aplasia and humeral hypoplasia. Radial anomalies may also make placement of a radial arterial catheter more difficult. Patients with renal dysfunction require careful titration of perioperative fluids and judicious use of renally excreted drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Bannayan-Riley-Ruvalcaba syndrome

See Riley-Smith syndrome

Bannayan-Zonana syndrome

See Riley-Smith syndrome

Baraitser-Burn syndrome

Included in Oral-facial-digital syndrome, type I

Bardet-Biedl syndrome

MIM #: 209900

This is an autosomal recessive disorder with marked variability of clinical expression. The classic findings are intellectual disability, retinal dystrophy, obesity, polydactyly, hypogenitalism, and renal insufficiency. This is a genetically heterogeneous disorder, with

linkage analysis in different families implicating at least 18 different loci on 14 different chromosomes. Some may require a recessive mutation in one locus plus an additional mutation in a second locus, though this is likely rare. It has been suggested that the involved proteins attach to the basal body of ciliated cells, making this a ciliary dysfunction disorder. This disorder is similar to, but possibly distinct from, the Laurence-Moon syndrome (see later). Unlike the patients described by Bardet and Biedl, the patients described by Laurence and Moon had spastic paraplegia and did not have obesity or polydactyly. The two syndromes have sometimes been recognized as distinct and have sometimes not. Thus, the literature contains many references to the Laurence-Moon-Biedl syndrome or the Laurence-Moon-Biedl-Bardet syndrome (or other permutations).

HEENT/Airway: Occasional macrocephaly. Retinal dystrophy and pigmentation result in problems with night vision, peripheral vision, color vision, and visual acuity. Most patients are blind by age 20 years. Astigmatism, nystagmus, cataracts. Occasional glaucoma. Partial or complete loss of sense of smell. High-arched palate with tooth crowding. Hypodontia with small tooth roots. May have bifid epiglottis.

Cardiovascular: Hypertension is common, particularly in patients with renal disease. A variety of minor cardiac defects have been described. May have hypertrophy of the interventricular septum and/or dilated cardiomyopathy.

Neuromuscular: Mild to moderate intellectual disability. Behavioral problems and flat affect are common. Delayed speech. Ataxia. Poor coordination. Decreased peripheral sensation.

Orthopedic: Postaxial polydactyly. Syndactyly. Brachydactyly of hands. Short, broad feet.

GI/GU: Hirschsprung disease (see later) has been reported in several patients. Can develop hepatic fibrosis.

Hypogenitalism—male patients appear to be sterile, but some affected women have given birth. Multiple renal anomalies have been reported, including abnormal calyces, calyceal diverticula, abnormal lobulations, renal cysts, cortical loss, and scarring. Most patients exhibit mild renal insufficiency, and renal failure develops in some patients. Nephrogenic diabetes insipidus.

Other: Morbid obesity. Occasional diabetes mellitus. Poor wound healing.

Miscellaneous: Biedl was a prominent Hungarian endocrinologist who practiced in Germany. He can be considered the founder of modern endocrinology.

Anesthetic Considerations: Behavioral problems may make the smooth induction of anesthesia a challenge. Keep in mind that patients will likely have impaired vision. Patients should be evaluated for cardiovascular disease, particularly hypertension. Venous access and identification of landmarks for regional anesthesia may be difficult secondary to morbid obesity. Obesity may result in desaturation with induction of anesthesia because of increased airway closure and decreased functional residual capacity. Obesity is also a risk factor for perioperative aspiration. Drug doses (on a per kilogram basis) should be reduced in cases of massive obesity. Patients with renal dysfunction need careful titration of perioperative fluids and judicious use of renally excreted drugs.

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248.

Bare lymphocyte syndrome

Included in Severe combined immunodeficiency syndrome

Barth syndrome

MIM #: 302060

This X-linked recessive disorder of dilated cardiomyopathy, neutropenia, skeletal myopathy, and abnormal mitochondria is due to mutations in the gene *TAZ* (also known as G4.5). The role of the protein product, tafazzin, is unknown, but it is possibly an acyltransferase. The phenotype is widely variable, and the syndrome is suspected to be underdiagnosed. An etiologic role may be played by cardiolipin. There is abnormal

cardiolipin, a phospholipid structural component of the mitochondrial inner membrane, resulting in leaky mitochondria with abnormal ATP production.

HEENT: Recurrent mouth ulcers related to neutropenia.

Cardiovascular: Dilated cardiomyopathy, usually presenting in infancy. Endocardial fibroelastosis. Left ventricular noncompaction. Cardiac function tends to improve in preadolescence, worsen during the teenage years, and then improve yet again. Can develop ventricular arrhythmias.

Neuromuscular: Myopathy. Hypotonia. Sparing of bulbar and ocular muscles. Weakness, myalgia.

Orthopedic: Moderate growth retardation. Growth velocity increases during the teenage years.

Other: Intermittent lactic acidemia. Cyclic neutropenia. Recurrent infections in infancy and early childhood. Structurally abnormal mitochondria. Elevated levels of urinary 3-methylglutaconic acid.

Anesthetic Considerations: Because cardiac function can fluctuate, a cardiac evaluation should be performed in proximity to anesthesia and surgery. Cardiac medications should be continued perioperatively. Anesthetic technique may need to be modified in the presence of cardiac dysfunction. Careful aseptic technique is indicated in patients with neutropenia. Patients with lactic acidemia should not receive lactated Ringer's solution. Succinylcholine is contraindicated in this myopathy secondary to the risk of exaggerated hyperkalemia. Patients with advanced muscle weakness may require postoperative ventilation. Patients needing prolonged orotracheal intubation will require good mouth care because of the presence of oral ulcers.

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Bartter syndrome

Synonym: Hyperprostaglandin E syndrome. (Includes Gitelman syndrome)

MIM #: 601678, 241200, 607364, 602522, 613090

This clinical syndrome of salt-losing renal tubulopathies has various autosomal recessive types, all linked by hyperreninemic hypokalemic metabolic alkalosis. There is inadequate salt reabsorption from the thick ascending loop of Henle. Autosomal recessive antenatal Bartter syndrome type 1 is due to abnormalities in the Na^+-K^+-$2Cl^-$ cotransporter gene *SLC12A1*. It is marked by a hypokalemic, hypochloremic metabolic alkalosis, high levels of renin and aldosterone, and the absence of hypertension. The clinically and biochemically indistinguishable antenatal Bartter syndrome type 2 is caused by a mutation in the gene for the ATP-sensitive inwardly rectifying potassium channel ROMK and is associated with high levels of prostaglandin E. Classic Bartter syndrome (type 3) is caused by defects in the kidney chloride channel B gene (*CLCNKB*). Infantile Bartter syndrome with sensorineural deafness (type 4) is caused by defects in the gene *BSND*, which is present in the inner ear as well as the kidney, or by simultaneous mutations in *CLCNKA* and *CLCNKB*. Neonatal disease presents with antenatal onset. Similar hypokalemic alkalosis in older children and adults but with hypocalciuria is known as **Gitelman syndrome** (*MIM #:* 263800) and is caused by defects in the thiazide-sensitive sodium-chloride cotransporter *SLC12A3*. Gitelman syndrome also has episodes of muscle weakness and tetany with hypokalemia, hypomagnesemia, and hypocalciuria. Unlike the other forms, which affect the ascending loop of Henle, the defect in Gitelman syndrome affects the distal tubule.

Neuromuscular: Intellectual disability. Muscular weakness, muscle cramps.

Orthopedic: Short stature, rickets.

GI/GU: Hypokalemia can result in ileus, delayed gastric emptying, or constipation. The primary renal defect is diminished chloride reabsorption in the ascending loop of Henle. Excessive sodium delivery (as sodium chloride) to the collecting duct causes excessive potassium secretion, which is enhanced by the hyperaldosteronism. Increased urinary prostaglandin E_2 (a secondary phenomenon from protracted potassium depletion). There is juxtaglomerular cell hyperplasia. Hypokalemia inhibits renal tubular function, resulting in polyuria and polydipsia. Nephrocalcinosis (not in the classic type). Hypercalciuria.

Other: Anorexia, failure to thrive. In addition to the hypokalemic, hypochloremic metabolic alkalosis, there is also hypomagnesemia, hypocalcemia, hypercalciuria, and hyperuricemia. Electrolyte abnormalities may result in prolonged QTc and risk of arrhythmia. There is hyperaldosteronism and hyperreninemia, but no hypertension. There is an impaired vasopressor response to angiotensin II. There may be platelet dysfunction due to abnormalities in prostaglandins. Type 2 disease can be associated with transient neonatal hyperkalemia.

Miscellaneous: Bartter also described the syndrome of inappropriate antidiuretic hormone (SIADH). Because this less common syndrome was described first, it retains the eponymous association. It has been speculated that given the lack of severity of Bartter's original patients, they may have actually had Gitelman syndrome.

Bartter was an expert on mushrooms and an authority in the diagnosis and treatment of amanita-type mushroom poisoning.

Anesthetic Considerations: Neonates in particular can have severe intravascular volume depletion. Preoperative medications should be continued until surgery and reinstituted as soon as possible thereafter. Medications may include a prostaglandin synthetase inhibitor (such as indomethacin), spironolactone, potassium chloride, ammonium chloride, and sodium chloride, but treatment rarely totally corrects the hypokalemia. Serum

electrolytes should be evaluated preoperatively and monitored appropriately. A nonkaliuretic diuretic should be chosen, if possible. However, chronic hypokalemia does not carry the same risk of arrhythmia as does acute hypokalemia. Hypovolemia should be avoided and prophylactic volume expansion considered. Prostaglandin synthetase inhibitors can also additionally inhibit platelet function, and the potential for dysfunctional platelets needs to be considered. Patients may be volume contracted at baseline, and the hematocrit may fall with volume expansion.

Decreased gastric motility from hypokalemia may increase aspiration risk. Aggressive ventilation with respiratory alkalosis may worsen a preexisting metabolic alkalosis and may also further lower serum potassium. The effects of muscle relaxants may be potentiated by the hypotonia. Renal dysfunction has implications for the choice of anesthetic medications. The urinary concentrating defect may make urinary output a poor guide to intravascular volume. Propofol may increase urinary uric acid excretion in normal patients (9), and propofol may therefore be contraindicated for prolonged anesthesia or sedation in patients with Bartter syndrome.

Consider obtaining a preoperative ECG to evaluate the QT interval. Avoid perioperative medications, which might prolong the QTc. Patients with significant electrolyte abnormalities may suffer arrhythmias and/or cardiac arrest (3,4). Patients are at risk for intraoperative hypotension, and a patient with abnormal baroreceptor responses has been described (13). Patients may exhibit a decreased response to vasopressors (1,3). Perioperative changes in plasma renin activity, angiotensin-II, and plasma aldosterone responses all mirror changes seen in unaffected patients.

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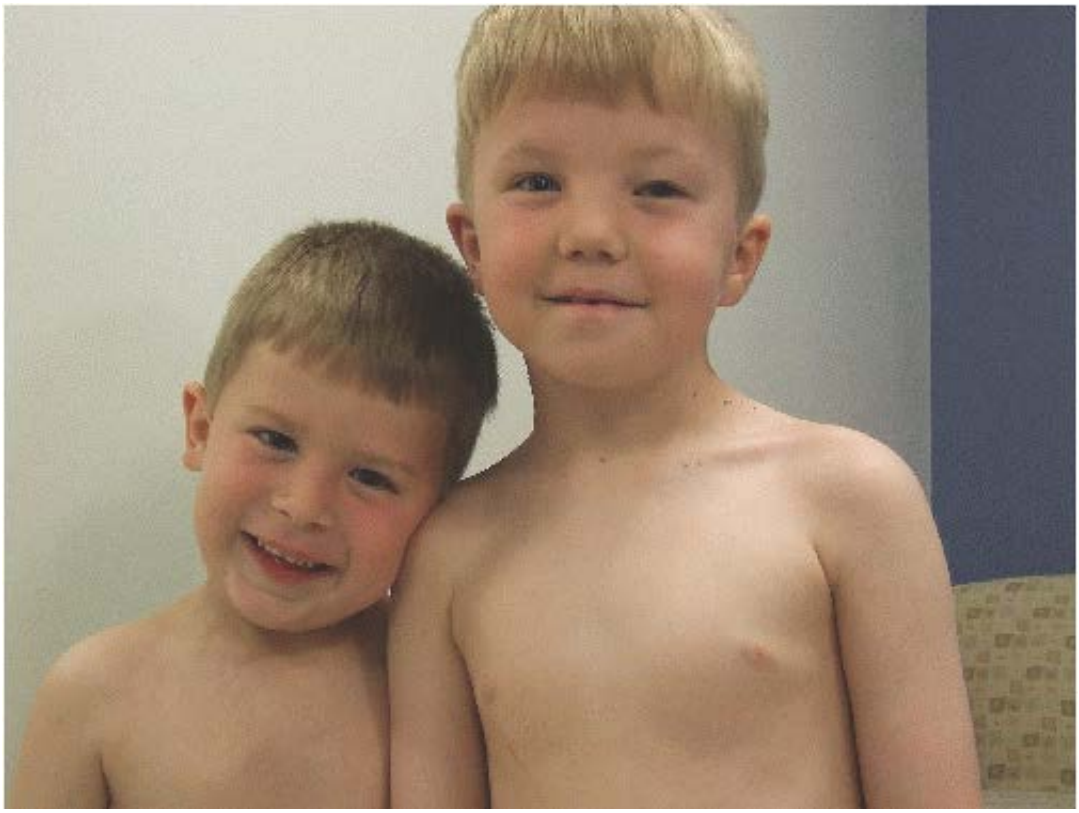
Basal cell nevus syndrome

Synonym: Gorlin-Goltz syndrome; Gorlin-Gold syndrome; Gorlin syndrome; Nevoid basal cell carcinoma syndrome

MIM #: 109400

This autosomal dominant disorder results in the development of multiple nevoid basal cell carcinomas, along with characteristic facies, rib anomalies, and mandibular cysts. Penetrance is variable but seems similar within a family. Many cases represent fresh mutations, and advanced paternal age probably plays a role in these new mutations. The syndrome is caused by a mutation in the gene *PTCH*, the human homolog of the *Drosophila* "patched" gene. *PTCH*, which is expressed in the developing tissues that are involved in the clinical syndrome, encodes a transmembrane signaling protein and functions as a tumor suppressor gene.

HEENT/Airway: Macrocephaly. Bony bridging of the sella turcica. Frontal bossing and prominent supraorbital ridges, with thick eyebrows overlying. Hypertelorism. Cataracts. Strabismus. Iris coloboma. Broad nasal bridge. May have cleft lip or palate. Abnormally shaped teeth. Dental caries is common. Prognathism. Mandibular cysts, which may enlarge during puberty.



Basal cell nevus syndrome. Two brothers with basal cell nevus syndrome. Their mother also has it and has had multiple jaw cysts. The 6-year-old has multiple small nevi and an undefined clotting disorder. The 5-year-old has just a few small nevi under his eyes and on his abdomen. He also has mild pectus excavatum.

Chest: Bifid ribs or other rib anomalies. May have pectus excavatum. Congenital lung cysts.

Cardiovascular: Occasional cardiac fibromas.

Neuromuscular: May have intellectual disability, hydrocephalus. May have calcification of the falx cerebri, falx cerebelli, petroclinoid ligament, dura, pia, or choroid plexus. Occasional agenesis of the corpus callosum. At risk for medulloblastoma, astrocytoma.

Orthopedic: Scoliosis. May have cervical vertebral anomalies. Kyphoscoliosis. Sloping, narrow shoulders. Short fourth metacarpals. Occasional polydactyly, arachnodactyly.

GI/GU: Lymphomesenteric cysts. Hamartomatous stomach polyps. Ovarian fibromas—these may contain vasoactive substances. Ovarian sarcomas. Occasional hypogonadism in male patients. Occasional renal anomalies.

Other: Multiple (up to several hundred) nevoid basal cell carcinomas, especially over the face, neck, arms, and chest. The nevi are rarely present at birth, but begin to proliferate at puberty. Basal cell carcinomas usually develop between age 15 and 35 years but have appeared as early as age 2 years. Milia. Palmar and plantar pits. Epidermal cysts. Occasional calcification of subcutaneous tissue. May have discrete patches of long pigmented hair. Can have a marfanoid habitus.

Other neoplasms may develop, including medulloblastoma, astrocytoma, meningioma, melanoma, lipoma, fibroma, breast cancer, ovarian cancer, lung cancer, chronic lymphoid leukemia, and non-Hodgkin lymphoma.

Miscellaneous: Patients are extremely radiosensitive, and therapeutic doses of ionizing radiation have led to the development of large numbers of basal cell carcinomas. African Americans are less likely to have basal cell carcinomas than are European Americans, even though other components of the syndrome are expressed equivalently. Increased skin pigmentation in African Americans is presumably protective against the effects of ultraviolet radiation in these very radiosensitive patients. The protein product of *PTCH* in *Drosophila* is a transmembrane receptor for the ligand Sonic Hedgehog.

Robert Gorlin was a dentist and a leading dysmorphologist. His *Syndromes of the Head and Neck* is a classic reference text.

Anesthetic Considerations: Dental abnormalities/dental caries may predispose to dental loss during laryngoscopy. Teeth should be inventoried before laryngoscopy. Patients may require extreme care in positioning and laryngoscopy if cervical vertebral anomalies are present. Patients may have unrecognized hydrocephalus.

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Batten disease

See Jansky-Bielschowsky disease and Spielmeyer-Vogt disease

Beals contractural arachnodactyly syndrome

See Beals syndrome

Beals syndrome

Synonym: Beals contractural arachnodactyly syndrome

MIM #: 121050

This autosomal dominant syndrome has as its main features joint contractures, arachnodactyly, and a “crumpled”-appearing ear. The responsible gene is likely fibrillin-2 (*FBN2*). It is somewhat phenotypically similar to Marfan

syndrome, caused by abnormalities in the gene fibrillin-1.

HEENT/Airway: May have scaphocephaly, brachycephaly, or dolichocephaly. May have frontal bossing. Occasional iris coloboma. “Crumpled”-appearing ear. Micrognathia. Short neck. High-arched palate.

Chest: Occasional sternal defects. May have pectus carinatum.

Cardiovascular: Mitral prolapse with regurgitation. Occasional atrial septal defect, ventricular septal defect, or aortic hypoplasia.

Orthopedic: Congenital joint contractures, especially of the elbows, hips and knees. Can also have contractures of the fingers. Joint mobility improves over time. Long, slim limbs with arachnodactyly. Camptodactyly. Ulnar deviation of the fingers. Calf muscle hypoplasia. May have mild clubfoot deformity. Generalized osteopenia. Thoracolumbar kyphoscoliosis—can be congenital and usually progressive over time.

Miscellaneous: Beals and Hecht, who originally described this syndrome in 1971, have suggested that the patient described by Marfan in 1896 actually had contractural arachnodactyly syndrome rather than the syndrome now known as Marfan syndrome. Because the ocular and cardiovascular complications of Marfan syndrome do not occur or are different in contractural arachnodactyly syndrome, the distinction between these two syndromes has clinical significance to the anesthesiologist.

Anesthetic Considerations: Relatively short neck and mild micrognathia have not been associated with difficult direct laryngoscopy or intubation. Careful perioperative positioning is required secondary to multiple joint contractures. Thoracolumbar scoliosis may be severe enough to cause restrictive lung disease. Patients may have mitral regurgitation, but significant aortic disease (as with Marfan syndrome) has not been reported.

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Bean syndrome

See Blue rubber bleb nevus syndrome

Beare-Stevenson syndrome

Synonym: Cutis gyrata syndrome of Beare-Stevenson

MIM #: 123790

This autosomal dominant disorder has as its primary components craniofacial, skin, and genital abnormalities. The most typical finding is cutis gyrata (widespread heavily corrugated skin folds), particularly of the scalp. The syndrome is associated with increased paternal age. It is due to defects in the gene encoding fibroblast growth factor receptor 2 (*FGFR2*), although the inability to document a defect in this gene in several patients suggests that there may be some heterogeneity. Death usually occurs in childhood. Different mutations of this gene cause

Apert syndrome, Crouzon syndrome, Antley-Bixler syndrome, and some cases of Pfeiffer syndrome, syndromes which have many phenotypic similarities.

HEENT/Airway: Cloverleaf skull (kleeblattschaedel), craniosynostosis, midface hypoplasia, hypertelorism, proptosis, downward-slanting palpebral fissures, low-set ears, choanal stenosis or atresia, high-arched and narrow palate. Can have cleft palate.

Chest: Can have recurrent pulmonary infections. Tracheal stenosis has been reported.

Neuromuscular: Hydrocephalus. Can have agenesis of the corpus callosum. Arnold-Chiari malformation. Developmental delay. Central sleep apnea requiring nighttime oxygen has been reported in one infant.

Orthopedic: Can have limited elbow extension.

GI/GU: Prominent umbilical stump. Anteriorly placed anus. Bifid scrotum. Heavily wrinkled labia majora.

Other: Cutis gyrata, furrowed palms and soles, acanthosis nigricans.

Anesthetic Considerations: Craniofacial abnormalities may be associated with difficult intubation. Neonates with choanal stenosis or atresia can have airway obstruction with or without apnea. Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Arnold-Chiari malformation and/or hydrocephalus can predispose to apnea, and patients need to

be observed closely postoperatively. Cervical spine abnormalities have not been reported but can be seen in other disorders due to *FGFR2* mutations. Proptosis requires close attention to eye protection perioperatively. Intravenous access may be challenging due to cutis gyrata.

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Becker disease

Synonym: Becker type myotonia congenita

MIM #: 255700

This disease is a separate entity from Becker muscular dystrophy. It is an autosomal recessive myotonia due to an abnormality in the skeletal muscle chloride channel gene (*CLCN1*). It is sometimes also called myotonia congenita, but the autosomal dominant type (Thomsen type myotonia congenita, see later under myotonia congenita) is more frequently referred to as myotonia congenita. Thomsen disease is caused by mutations in the same gene. Becker

disease does not become clinically apparent until 4 to 12 years of age, and sometimes even later in boys.

HEENT/Airway: Lid lag.

Neuromuscular: Clumsiness, muscle cramping. The hallmark finding, myotonia, refers to delayed relaxation of contracted muscle. Examples include the inability to release a handshake ("action myotonia") or the sustained contraction with direct tapping or stimulation of a tendon reflex ("percussion myotonia"—best elicited by tapping the thenar eminence or finger extensors). Severe myotonia affects the legs first. It progresses to the arms and finally the facial and masticatory muscles. Muscle dystrophy may be seen on muscle biopsy. Hypertrophy of lower limb muscles. Asymptomatic heterozygotes may have electromyographic evidence of myotonia.

Miscellaneous: Peter Emil Becker was a German neurologist and geneticist.

Anesthetic Considerations: Anesthetic or surgical manipulations can induce myotonic contractions as can cold and shivering. Even the pain from an intravenous injection of propofol can cause myotonic contractions, as can cold or shivering. These patients can have abnormal drug reactions.

Neither regional anesthesia nor muscle relaxants prevent or reverse myotonic contractions. Drugs that have been used to attenuate the contractions are quinine, procainamide, phenytoin, volatile anesthetics, and steroids. When all else fails, direct infiltration of the muscle with a local anesthetic has been recommended. Succinylcholine can induce sustained contraction of chest wall muscles, making positive pressure ventilation difficult even in the intubated patient. Because of dystrophic muscle changes, it is possible that in advanced cases, succinylcholine might result in an exaggerated hyperkalemic response— another reason to avoid the drug. Responses to nondepolarizing muscle relaxants are normal, but nondepolarizing muscle relaxants will not counteract myotonic contractions that have already been provoked. Anticholinesterase drugs used to reverse muscle relaxants can precipitate myotonia, and the use of shorter-acting muscle relaxants that do not require reversal has been suggested.

Succinylcholine-induced muscle rigidity without myoglobinuria or hyperthermia, but with a positive halothane contracture test, has been reported in two sisters (5).

Figure: See **Myotonic dystrophy, Figure 1**

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Becker muscular dystrophy

MIM #: 300376

This X-linked muscular dystrophy is similar to Duchenne muscular dystrophy. Whereas patients with Duchenne muscular dystrophy (see later) lack detectable dystrophin in skeletal muscle because of genetic defects that disrupt transcription of the gene, patients with Becker muscular dystrophy have dystrophin of altered size or reduced abundance because the genetic defect allows continued transcription of the gene. Dystrophin is responsible for connecting the sarcolemma to the extracellular matrix. Patients with Becker muscular dystrophy have a more benign disease course

than do those with Duchenne muscular dystrophy. The age of onset is later, and the progression of the disease is slower.

Chest: Respiratory muscle weakness and swallowing difficulties late in the disease can lead to recurrent respiratory infections.

Cardiovascular: Patients may have a dilated cardiomyopathy. There may be alterations in cardiac conductivity. A full cardiologic evaluation demonstrates that a significant percentage of patients with mild or subclinical skeletal muscle involvement have cardiac involvement, typically beginning in the right ventricle (12).

Neuromuscular: Generalized myopathy. Pseudohypertrophy of calf muscles. Serum creatine kinase levels are elevated, but not as high as in Duchenne muscular dystrophy. Onset of weakness is delayed compared with Duchenne muscular dystrophy, with loss of ambulation in the third to fifth decade.

Orthopedic: Pes cavus (high-arched foot).

GI/GU: Increased incidence of infertility.

Anesthetic Considerations: Neuromuscular blockade is often unnecessary because of preexisting muscle weakness. Succinylcholine has resulted in fatal rhabdomyolysis with hyperkalemia (15). Because of the risk of hyperkalemia, succinylcholine should never be administered to patients with Becker muscular dystrophy. Acute rhabdomyolysis which is not associated with malignant hyperthermia can occur in patients with dystrophinopathies when exposed to inhalational agents (3,6,7,9).

Patients with advanced disease may have swallowing difficulties and are at increased risk for perioperative aspiration. Patients with advanced disease are also at risk for perioperative respiratory complications, secondary to respiratory muscle weakness. A preoperative cardiac evaluation should be done to evaluate for cardiomyopathy and conduction disturbances. Myocardial depressant agents should be avoided in patients with a significant cardiomyopathy. An association between Becker muscular dystrophy and malignant hyperthermia has been suggested in the past but is unlikely (1,5,7,9). *In vitro* contracture testing may be positive, but it has been suggested that *in vitro* muscle testing may not be accurate with neuromuscular diseases (14).

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Becker-type myotonia congenita

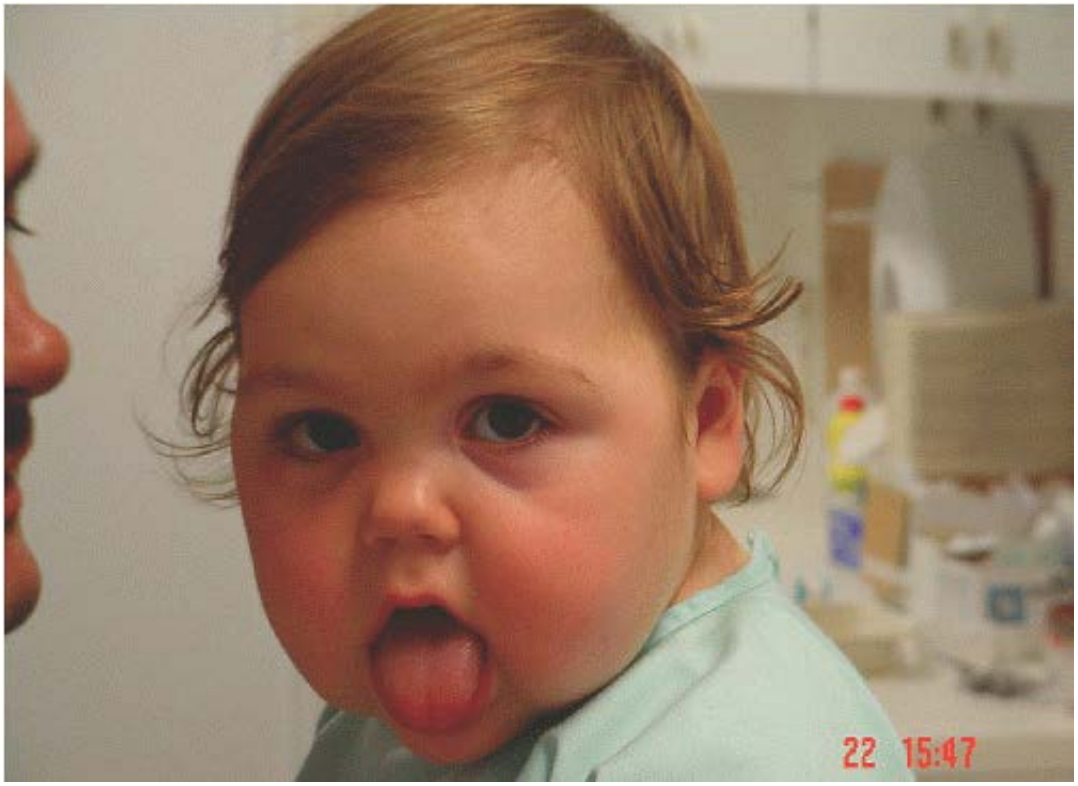
See Becker disease

Beckwith-Wiedemann syndrome

MIM #: 130650

The main features of this syndrome are macrosomia, visceromegaly, macroglossia, omphalocele, and earlobe creases. Although Beckwith-Wiedemann syndrome is likely inherited in an autosomal dominant fashion, there may be incomplete penetrance, or there may be other genetic factors that influence the clinical manifestations of this syndrome. Most cases occur sporadically. Gene duplications or deletions in the region 11p15.5 have been documented in patients with Beckwith-Wiedemann syndrome. Mutations in multiple different genes have been implicated. Underexpression of the p57 gene (*KIP2*), which encodes a protein that is a negative regulator of cell proliferation, and overexpression of the insulin-like growth factor-2 gene (*IGF2*) probably play an important role in cellular and tissue overgrowth

in this syndrome. It may be that the disease is the result of inheriting two paternal copies of the gene.



Beckwith-Wiedemann syndrome. The macroglossia in this young infant with Beckwith-Wiedemann

syndrome is apparent. (Courtesy of Dr. Michel Sommer, Department of Anesthesiology, University of Maastricht, The Netherlands.)

HEENT/Airway: Metopic ridge, large fontanelles, prominent occiput. Microcephaly can develop in later childhood. Capillary hemangioma on central forehead and eyelids. Relative exophthalmos. Linear earlobe creases or indentations of the external helix. Macroglossia—often severe enough to cause upper airway obstruction or feeding problems. Malocclusion. Prognathism.

Cardiovascular: Cor pulmonale from chronic airway obstruction. A variety of congenital defects have been described. Cardiomegaly, asymptomatic and resolving by 6 months of age, can be part of the visceromegaly.

Neuromuscular: May have mild to moderate intellectual disability. Problems with extrauterine transition have occurred, resulting in apnea or seizures. Rare posterior fossa abnormalities.

Orthopedic: Increased muscle mass and subcutaneous tissue (macrosomia). Accelerated osseous maturation leads to advanced bone age during childhood.

GI/GU: Visceromegaly—may involve kidneys, pancreas, adrenals, liver, and gonads. Omphalocele or other umbilical abnormality. Overgrowth of the external genitalia. Dysplasia of the renal medulla. Increased risk of intra-abdominal tumors, such as Wilms tumor, hepatoblastoma, adrenocortical carcinoma, neuroblastoma, rhabdomyosarcoma, nephroblastoma, or gonadoblastoma.

Other: Occasional hemihypertrophy. Premature birth common. Large for gestational age. May have neonatal polycythemia. High incidence of neonatal hypoglycemia, potentially very severe, secondary to hyperinsulinism from pancreatic islet cell hyperplasia or nesidioblastosis. Hypoglycemia usually subsides by 4 months of age and is usually responsive to therapy with corticosteroids but may require a central venous infusion of glucose or a partial pancreatectomy. Gigantism may develop later in childhood. Occasional immunodeficiency. Increased incidence (7.5% to 10%) of early childhood cancer, especially Wilms tumor and hepatoblastoma.

Miscellaneous: Wiedemann, a professor of pediatrics at Kiel (Germany), was one of the first to bring attention to the thalidomide disaster.

Anesthetic Considerations: Macroglossia can cause upper airway obstruction, which may worsen with the induction of anesthesia. Airway obstruction is also a risk in a lethargic patient after extubation. Placing the patient face down or on his or her side may help relieve the obstruction. As the patient grows, there is relatively more room for the oversized tongue. However, partial glossectomy is sometimes necessary. Macroglossia may make visualization of the vocal cords difficult during direct laryngoscopy. Both laryngeal mask airway (6) and GlideScope (2) have been used successfully. Patients with tracheas larger than would be estimated by their age and height have been described (3). Visceromegaly may reduce functional residual capacity and/or impede ventilation.

There is a high incidence of neonatal hypoglycemia, which may be severe. Serum glucose must be closely monitored in these patients, and neonates and young infants may require perioperative glucose infusions. Infants treated with steroids may require perioperative stress doses. Intravenous access may be difficult. Care may be complicated by concurrent diseases and conditions of prematurity.

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Béguez César syndrome

See Chédiak-Higashi syndrome

Berardinelli lipodystrophy

See Lipodystrophy

Berardinelli-Seip syndrome

See Lipodystrophy

Bernard-Soulier syndrome

MIM #: 231200

This autosomal recessive disorder of platelets results in variable degrees of mucocutaneous bleeding and is due to deficiencies in one of three genes encoding platelet surface glycoproteins. Most patients have episodes that are severe enough to require transfusion. Platelet aggregation remains normal in response to adenosine diphosphate, collagen, and epinephrine but abnormal in response to plasma or ristocetin. These platelets are deficient in all the

platelet surface glycoprotein Ib members: Ibα and IbB, V and IX, and lack binding sites for von Willebrand factor (glycoprotein Ib).

HEENT/Airway: Epistaxis.

GI/GU: Gastrointestinal bleeding. Menorrhagia.

Other: Purpuric skin lesions. The platelet count is normal or moderately decreased. Platelets are large, but otherwise morphologically normal. Bone marrow megakaryocytes are normal or increased. The bleeding dyscrasia can worsen during adolescence and adulthood.

Miscellaneous: In abnormalities of platelets, total platelet mass, rather than platelet number or concentration, tends to be preserved. Thus, perhaps, the low platelet concentration in this disorder with large platelets.

During the German occupation of France during WWII, Bernard was a member of the French resistance. He was arrested, and during his imprisonment, he composed poetry that was later published.

Anesthetic Considerations: Assess platelet count (usually close to normal) and bleeding time preoperatively. Preparations should be made for surgical bleeding, which is expected to be excessive. Nasal intubation should be avoided if possible. Arginine vasopressin (DDAVP) may improve, but not normalize, the platelet function. Aspirin, nonsteroidal drugs, and other inhibitors of platelet function should be avoided. Neuraxial techniques are probably contraindicated. Platelet transfusions usually control bleeding. Patients may have developed antiplatelet antibodies from prior platelet transfusions, complicating therapy. Recombinant factor VIIa has been used successfully to treat severe bleeding episodes.

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Bernheimer-Seitelberger disease

Included in Tay-Sachs disease

Beta-glucuronidase deficiency

See Sly syndrome

Beta-ketothiolase deficiency

Synonym: Acetyl-CoA acetyltransferase-1 deficiency; Alpha-methylacetoacetic aciduria; Mitochondrial acetoacetyl-CoA thiolase deficiency; 3-ketothiolase deficiency; 3-oxothiolase deficiency; 2-methylacetoacetyl-CoA thiolase deficiency

MIM #: 203750

This autosomal recessive disorder of branched-chain amino acid metabolism is due to deficiencies in the enzyme acetyl-CoA acetyltransferase-1 (also known as methylacetoacetyl-CoA thiolase, beta-ketothiolase, or 3-oxothiolase), which is responsible for the penultimate step in isoleucine catabolism, the

conversion of 2-methylacetoacetyl-CoA into acetyl-CoA and propionyl-CoA. Symptomatic presentation is variable but typically involves intermittent metabolic acidosis and ketosis with vomiting, worsened by increased protein intake. With appropriate management of acute episodes, long-term prognosis is good.

Cardiovascular: Cardiomyopathy has been reported.

Neuromuscular: Coma can accompany severe episodes after upper respiratory or gastrointestinal infections or increased protein intake. Headaches and ataxia have been reported as a chronic problem in older children.

GI/GU: Vomiting with acidotic episodes. Diarrhea, often bloody.

Other: Intermittent severe metabolic acidosis and ketosis.

Miscellaneous: One method of salicylate measurement gives a false-positive salicylate reaction because of the high levels of acetoacetic acid present. Salicylate toxicity is also a cause of metabolic acidosis in the 1- to 2-year-old, the age when most of these patients first show the effects of the disorder.

Anesthetic Considerations: Fasting hypoglycemia may occur. Serum glucose levels should be monitored perioperatively, and perioperative glucose-containing intravenous fluid should be administered as needed. Acute episodes of acidosis and ketosis are treated with bicarbonate and glucose and restriction of protein. Infections can precipitate acute acidotic episodes. It is not known if they can be precipitated by the stress of surgery. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load, triggering decompensation. Patients with cardiomyopathy should receive an appropriately tailored anesthetic.

Figure: See **Appendix D**

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Biotinidase deficiency

Synonym: Multiple carboxylase deficiency

MIM #: 253260

This autosomal recessive neurocutaneous disorder is a form of multiple carboxylase deficiency. The primary defect is a mutation in the biotinidase gene leading to the inability to cleave biocytin, a proteolytic degradation product of the carboxylase enzymes, with failure to liberate biotin (a water-soluble vitamin). This results in biotin deficiency and functional deficiency of the four carboxylases, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase, pyruvate carboxylase, and acetyl-CoA carboxylase. Disease severity can be similar to the organic acidemias, with potentially fatal episodes of ketoacidosis early in life, or the disease may be less severe. Treatment with biotin should correct all symptoms (unless fixed, such as optic atrophy). A neonatal form is due to defects in the gene encoding holocarboxylase synthetase (see later, holocarboxylase synthetase deficiency). There is considerable interpatient variability, even within a family.

HEENT/Airway: Conjunctivitis, optic atrophy, myopia, abnormal retinal pigment. Auditory nerve atrophy with hearing loss is common and variable. Laryngeal stridor.

Chest: Hyperventilation, apnea.

Neuromuscular: Intellectual disability, developmental delay, hypotonia, ataxia, myoclonic and other seizures, lethargy, coma, basal ganglia calcifications. Spastic paraparesis. Cerebral and cerebellar atrophy.

Other: Lactic acidosis with ketosis. Mild hyperammonemia. Seborrheic dermatitis, alopecia, acrodermatitis enteropathica. Abnormal cellular immunity. Recurrent fungal infections.

Anesthetic Considerations: Laryngeal stridor may be the presenting finding (3). Abnormal cellular immunity suggests that careful aseptic technique is essential. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients should receive appropriate parenteral biotin intake if they are to be on prolonged intravenous fluids. Intravenous hyperalimentation must include biotin.

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Blackfan-Diamond syndrome

See Diamond-Blackfan anemia

Blepharophimosis syndrome

Synonym: Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES syndrome)

MIM #: 110100

This autosomal dominant disorder predominantly affects the eyelids and is characterized by blepharophimosis, ptosis, and epicanthus inversus. There are two types of blepharophimosis syndrome, with type I additionally involving infertility in women from premature ovarian failure. The infertility is inherited as an autosomal dominant sex-limited trait, as occurs in the Stein-Leventhal syndrome. Both types of blepharophimosis syndrome are due to defects in the gene *FOXL2* (forkhead transcription factor). This is a nuclear protein expressed in the clinically involved tissues. Plastic surgery is often required to preserve ocular function.

HEENT/Airway: Blepharophimosis—short palpebral fissures secondary to lateral displacement of the inner canthi. Ptosis. Epicanthus inversus (a fold of skin curving in the mediolateral direction, inferior to the inner canthus). Arched eyebrows. Hypoplasia of the levator palpebrae muscle. Strabismus. Amblyopia is very common. Occasional ocular abnormalities, including microphthalmia, optic nerve hypoplasia, and nystagmus. Simple ears, with cupping. Flat nasal bridge. Small oral cavity and high-arched palate. One patient has been reported with a small larynx.

Cardiovascular: Occasional cardiac defects.

Neuromuscular: May exhibit hypotonia in infancy. Rare intellectual disability.

GI/GU: Menstrual irregularity leading to amenorrhea and infertility in women with type I blepharophimosis syndrome. Scant pubic and axillary hair in females. One patient has been reported with severe, chronic feeding difficulties.

Anesthetic Considerations: Patients must receive meticulous perioperative eye care to prevent the occurrence of corneal injuries. In one case, the small oral cavity and high-arched palate precluded successful laryngeal mask airway (LMA) placement (1).

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Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES syndrome)

See Blepharophimosis syndrome

Bloch-Sulzberger syndrome

See Incontinentia pigmenti

Bloom syndrome

MIM #: 210900

This autosomal recessive disorder is marked by short stature, malar hypoplasia, facial telangiectasis, photosensitivity, and a predisposition to malignancy. Many affected people are of Ashkenazic Jewish ancestry. This syndrome is due to mutations in the gene encoding DNA helicase RecQ protein-like-3.

HEENT/Airway: Mild microcephaly with dolichocephaly. Malar hypoplasia. Recurrent otitis. May have small nose. Facial, sun-sensitive telangiectasis and chronic erythema involving the butterfly midface region, exacerbated by sunlight. The rash is rarely present at birth, becomes noticeable during the first year, and improves with age. Occasional absence of upper lateral incisors. Occasional high-pitched voice.

Chest: May have bronchiectasis or pulmonary fibrosis after repeated lung infections.

Neuromuscular: Occasional mild intellectual disability. Occasional attention deficit disorder or learning disabilities.

Orthopedic: Proportionate very short stature.

GI/GU: Can have episodes of diarrhea and vomiting in infancy leading to dehydration. Infertility in males from failure of spermatogenesis, decreased fertility in

female patients, however pregnancy can occur, and premature delivery may be common.

Bloom syndrome. This young girl with Bloom syndrome has obvious malar hypoplasia. She also has a history of ADHD, recurrent otitis media, and conductive hearing loss. Note the presence of a sun hat to protect her sun-sensitive skin.

Other: Predisposition to malignancy—usually solid tumors or leukemia. Hypersensitivity to sunlight. Patchy areas of hypopigmentation or hyperpigmentation. May have immunoglobulin deficiency, with increased susceptibility to infection, which appears to resolve with age. May acquire non-insulin-dependent diabetes. Growth retardation and wasting; of prenatal onset with low birth weights. Decreased subcutaneous fatty tissue.

Miscellaneous: There is evidence of multiple chromosomal breaks and sister chromatid exchanges, which probably account for the predisposition to malignancy. Excess of diagnosed male to female patients is probably secondary to underdiagnosis of this disorder in women, in whom the skin lesion tends to be milder. DNA repair mechanisms are abnormal in four other inherited diseases: ataxia-telangiectasia, Fanconi anemia, xeroderma pigmentosum, and Cockayne syndrome.

Anesthetic Considerations: Patients should be addressed in a manner appropriate to their chronologic and developmental age, not their "height age." Attention to good aseptic technique is particularly important in patients with immunoglobulin deficiency.

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Blount disease

MIM #: 259200

This disease, which is essentially tibia vara, has been ascribed to both autosomal recessive and multifactorial causes. It is due to disordered growth of the proximal medial physis and metaphysis resulting in a localized tibia vara deformity and is often associated with tibial torsion. The incidence of tibia vara is higher in African Americans and increased in association with obesity, where the deformity is thought to be due to mechanical stress converting physiologic (and transient) bowlegs to a fixed tibia vara. Treatment is by bracing, and then surgical osteotomy if unsuccessful.

Orthopedic: Genu varum (bowlegs).

Miscellaneous: Walter Blount was a leading American pediatric orthopedic surgeon.

Anesthetic Considerations: There are no anesthetic implications of Blount disease; however, a good number of patients are obese, with attendant aspiration risk and possible difficulty with venous access.

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Blue diaper syndrome

MIM #: 211000

This is a defect in intestinal tryptophan transport. Bacterial degradation of the excessive tryptophan results in increased indole production, and eventually in the production of indigo blue, which stains the diapers (hence the name of the syndrome). The disease is probably inherited as an autosomal recessive, although X-linkage cannot be excluded.

HEENT/Airway: Microconia, hypoplastic optic disks, and abnormal eye movements have been described in one patient.

GI/GU: Nephrocalcinosis.

Other: Hypercalcemia.

Miscellaneous: A false-positive diagnosis has been ascribed to the presence of blue pigments of *Pseudomonas* in stool, also coloring diapers blue.

Anesthetic Considerations: It is important to provide adequate intravenous fluid perioperatively to maintain a reasonable diuresis in the face of hypercalcemia. The role of calciuretic diuretics in potentiating nephrocalcinosis is unknown.

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Blue rubber bleb nevus syndrome

Synonym: Bean syndrome

MIM #: 112200

This syndrome of large cutaneous and gastrointestinal venous malformations has been reported both within families and sporadically. These lesions are congenital malformations and are not neoplastic. Bleeding from hemangiomas is a major concern. A similar syndrome related to abnormalities in the *TEK* gene (tyrosine kinase receptor, epithelial specific) has been reported, and may be the same or very similar.

HEENT/Airway: Can involve the oropharynx. Can involve the orbit with visual impairment.

Chest: Endobronchial involvement has been reported.

Cardiovascular: May have thromboembolic pulmonary hypertension.

Neuromuscular: May develop cerebellar medulloblastoma. Can have central nervous system involvement with seizures or intracerebral hemorrhage.

Orthopedic: A case with angiomatous gigantism of an affected arm requiring amputation has been reported.

GI/GU: Bleeding hemangiomas distributed throughout the gastrointestinal tract from the oropharynx to the anus that can lead to acute and chronic bleeding. Has been the leading point for intussusception. Can have hepatic hemangiomas.

Other: The hemangiomas are found particularly on the trunk and upper arms. They are large, rubbery, and promptly refill following compression. Iron deficiency anemia. Disseminated intravascular coagulation from a consumption coagulopathy has been reported. Because the gastrointestinal venous malformations are diffusely distributed throughout the length of the gastrointestinal system, they cannot all be addressed via either upper or lower endoscopy. Lesions have been treated with a combination of prednisone, interferon, and, most recently, sirolimus. A technique combining endoscopy with endoscopic examination via open laparotomy and enterotomy has been described.

Anesthetic Considerations: Patients can have chronic and/or acute anemia. Coagulation status could be abnormal, contraindicating regional techniques. The potential for intraoperative bleeding should be recognized.

Particular care must be exercised during laryngoscopy when there is oropharyngeal involvement. Nasal intubation should be avoided if possible. A case of venous air embolism during distension of the bowel lumen with air during endoscopic visualization has been reported (3). In a single case, disseminated intravascular coagulation has been treated successfully with interferon beta.

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BOFS

See Branchiooculofacial syndrome

Bohring-Opitz syndrome

Included in C syndrome

BOR syndrome

See Melnick-Fraser syndrome

Börjeson syndrome

See Börjeson-Forssman-Lehmann syndrome

Börjeson-Forssman-Lehmann syndrome

Synonym: Börjeson syndrome

MIM #: 301900

This syndrome involves severe intellectual disability, seizures, large ears, hypogonadism, and obesity. The

syndrome is inherited in an X-linked recessive fashion. An abnormality of neuronal migration leads to the central nervous system manifestations. The gene responsible for this disorder is *PHF6*. This gene, active in the embryonic central nervous system, probably has a role in transcription. Female carriers of the gene defect may show some characteristics of the syndrome.

HEENT/Airway: Microcephaly. Coarse facies. Prominent supraorbital ridges and deep-set eyes. Nystagmus, ptosis, narrow palpebral fissures, and decreased vision. Retinal or optic nerve abnormalities. Large ears. Subcutaneous tissue of the face is swollen.

Chest: Two patients died of bronchopneumonia, but there is no apparent increased susceptibility to respiratory infections.

Cardiovascular: Dilated cardiomyopathy has been described in one patient.

Neuromuscular: Severe intellectual disability. Hypotonia. Significant motor and speech delay. Abnormal electroencephalogram—seizures are common. Narrow cervical spinal canal. It has been suggested that there might be abnormalities of midline neurodevelopment, including the hypothalamic-pituitary axis.

Orthopedic: Short stature. Vertebral osteochondrosis. Mild scoliosis or kyphosis. Hypoplasia of the distal and middle phalanges. Fingers are tapered. Short, widely spaced and flexed toes. Subcutaneous tissue of the hands is swollen.

GI/GU: Hypogonadotropic hypogonadism. Cryptorchidism. Small penis.

Other: Obesity. Postpubertal gynecomastia.

Anesthetic Considerations: Severe intellectual disability may complicate preoperative management. Intravenous access may be difficult secondary to obesity and swelling of the subcutaneous tissue of the hands. Patients who are obese are at increased risk for aspiration and may warrant a rapid sequence induction of anesthesia. Obesity may result in desaturation with induction of anesthesia because of increased airway closure and decreased functional residual capacity. Obese patients require lower than expected drug doses on a per kilogram basis. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. The narrowed cervical spinal canal has not been associated with spinal cord abnormalities.

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BPES syndrome

See Blepharophimosis syndrome

Brachmann-de Lange syndrome

See Cornelia de Lange syndrome

Brancher deficiency

Synonym: Glycogen storage disease type IV; Andersen disease; Alpha-1,4-glucan:alpha-1,4-glucan-6-alpha-glucosyltransferase deficiency

MIM #: 232500

This relatively uncommon form of glycogen storage disease is an autosomal recessive disease that is due to abnormalities in gene encoding the brancher enzyme (*GBE1*), which results in insufficient branching of glycogen as it is synthesized. Glucose release from this abnormal glycogen is abnormal. This type of glycogen storage disease is differentiated from the other forms by early development of hepatic failure with cirrhosis. Liver transplantation is the only successful therapy. It resolves the cirrhosis (obviously) and may decrease amylopectin storage in the heart; however, progressive cardiac failure after liver transplantation has been reported. A neuromuscular presentation also exists.

Cardiovascular: Congestive heart failure is rare and is due to amylopectin storage in the heart.

Neuromuscular: Hypotonia, muscle atrophy, delayed milestones. An adult patient has been described who had symptoms of limb-girdle muscular dystrophy with hyperlordotic posture, waddling gait, and proximal limb weakness.

Orthopedic: Growth retardation.

GI/GU: Hepatomegaly, hepatic failure with cirrhosis, ascites, portal hypertension with splenomegaly. Esophageal varices. In some, liver disease may not be progressive.

Other: Fasting hypoglycemia may occur. Failure to thrive.

Anesthetic Considerations: Although congestive heart failure is rare, a thorough preoperative cardiac examination is indicated. Liver function should be evaluated preoperatively. Hepatic failure may lead to abnormal coagulation and may affect protein binding of some anesthetic drugs. Regional anesthesia techniques are contraindicated in the face of abnormal coagulation. Esophageal probes and catheters should be placed with caution as varices can be present. Fasting hypoglycemia may occur. Serum glucose levels should be monitored perioperatively, and perioperative glucose-containing intravenous fluids would seem appropriate. Succinylcholine should be used with caution in patients with muscle atrophy because of the risk of exaggerated hyperkalemia.

Figure: See **Appendix E**

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Branchiooculofacial syndrome

Synonym: BOFS

MIM #: 113620

This autosomal dominant disorder involves defects of the branchial arch products, eyes, and face. The most consistent abnormalities are branchial cleft sinuses, nasolacrimal duct obstruction, and pseudocleft lip (looks like a surgically repaired cleft lip). The defects are caused by a mutation in the gene for transcription factor AP2-alpha (*TFAP2A*).

HEENT/Airway: Subcutaneous scalp cysts. Nasolacrimal duct obstruction, strabismus, coloboma, microphthalmia, cataracts, hemangiomatous cysts of the orbit. Malformed ears, ear pits, postauricular linear skin lesions, conductive hearing loss. Mastoid hypoplasia. Fusion of ear ossicles. Broad nasal bridge, flat nasal tip, broad philtrum. Pseudocleft lip, high-arched palate, cleft lip or palate, carp-shaped mouth, lip pits, dental anomalies, mild micrognathia. Nasal speech. Branchial cleft sinuses (of the neck).

Chest: Supernumerary nipples.

Neuromuscular: Most have normal intelligence. Rare mild intellectual disability.

Orthopedic: Growth retardation. Polydactyly, clinodactyly. Hypoplastic fingernails.

GI/GU: Renal anomalies, including agenesis and cysts. Hydronephrosis.

Other: Low birth weight, premature graying. Ectopic thymus.

Miscellaneous: The phenotypically similar BOR syndrome (Melnick-Fraser syndrome, see later) can be distinguished from BOF syndrome on CT scan—the cochlea and internal auditory canals are usually normal in BOF syndrome but are always abnormal in BOR syndrome.

Anesthetic Considerations: In the absence of renal involvement, there are no specific anesthetic considerations.

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Branchiootorenal syndrome

See Melnick-Fraser syndrome

Brugada syndrome

MIM #: 601144, 611777, 611875, 611876, 612838, 613119, 613120, 613123

This genetically heterogeneous autosomal dominant syndrome (with low penetrance) is manifest by an abnormal EKG. Brugada syndrome is a major cause of sudden unexplained death (from ventricular fibrillation) in patients with structurally normal hearts. The mean age at sudden death is 41 years, but it can occur in infants and children. Most of those affected are males. There are eight distinct types, all due to mutations in different genes: Brugada syndrome-1 (BRGDA1) is due to a mutation in the sodium channel pore-forming subunit gene *SCN5A*; BRGDA2 is caused by a mutation in *GPD1L*, the glycerol-3-phosphate dehydrogenase 1-like gene; BRGDA3 and BRGDA4 are caused

by mutations in the genes *CACNA1C* and *CACNB2*, respectively, encoding subunits of the L-type voltage-dependent calcium channel and both have a short QT interval; BRGDA5 is due to a mutation in the gene *SNC1B*, encoding a sodium channel subunit; BRGDA6 is due to a mutation in the gene *KCNE3*, encoding a potassium channel subunit; BRGDA7 is due to a mutation in the sodium channel subunit gene *SCN3B*; and BRGDA8 is caused by a mutation in the gene *HCN4*, encoding a cyclic nucleotide-gated potassium channel. In addition, polymorphisms in the genes *SCN10A*, *HEY2* and *SCN5A* have been shown to have an effect on disease susceptibility in BRGDA1. Inducibility on programmed electrical stimulation is a poor predictor of subsequent ventricular fibrillation.

Cardiovascular: ST segment elevation in the right precordial leads. There is an upsloping ST segment (early repolarization) with right bundle branch block and T-wave inversion. Ventricular fibrillation. ST segment elevation may change with autonomic tone; it can disappear with isoproterenol or exercise, may be exaggerated with beta blockade, and can be unmasked with sodium channel blockers.

Miscellaneous: Symptoms most often occur at night, and many cultures have stories and terms for young men with *Lai Tai* (Thailand), *Bangungut* (Philippines) or *Pokkuri* (Japan) who scream, thrash, and die suddenly in their beds.

Anesthetic Considerations: Patients with an implanted defibrillator will need to be evaluated and probably reprogrammed perioperatively. External defibrillator pads should be applied in the absence of a functioning implanted defibrillator.

There are conflicting data regarding the clinical safety of a variety of drugs and anesthetic techniques. A variety of general anesthetic techniques have been used successfully, despite certain drugs being cautioned against (see http://www.brugadadrugs.org). Anesthetic drugs cautioned against include bupivacaine, procaine, and propofol, as well as edrophonium and metoclopramide (Class IIa for all). Other drugs to be avoided include ketamine and tramadol (Class IIb for both). Alpha-agonists and beta-blockers should be avoided. A Brugada-like EKG pattern has been seen in the propofol infusion syndrome, and a chronically propofol-abusing anesthesia trainee was noted to have a Brugada pattern followed by fatal ventricular fibrillation while injecting propofol. On the other hand, sedation with propofol for a cardiac electrophysiologic case induced a Brugada-like pattern but could not be

induced with other agents and genetic testing was negative. A patient was reported who developed two episodes of Brugada EKG (once with a ventricular arrhythmia) with two bupivacaine epidurals. Another patient developed a ventricular arrhythmia with a ropivacaine paravertebral block. Although lidocaine has been generally well tolerated, a patient with a specific double missense mutation in *SCN5A*, without evidence of Brugada syndrome at rest, developed a ventricular arrhythmia when treated with 70 mg intravenous lidocaine for seizures. Other sodium channel blockers are contraindicated. Electrolyte abnormalities (hypokalemia, hyperkalemia, or hypercalcemia) should be corrected preoperatively. Hyperthermia, bradycardia, and autonomic changes should be avoided. Fortunately, the incidence of serious perioperative events appears to be low (3).

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

C

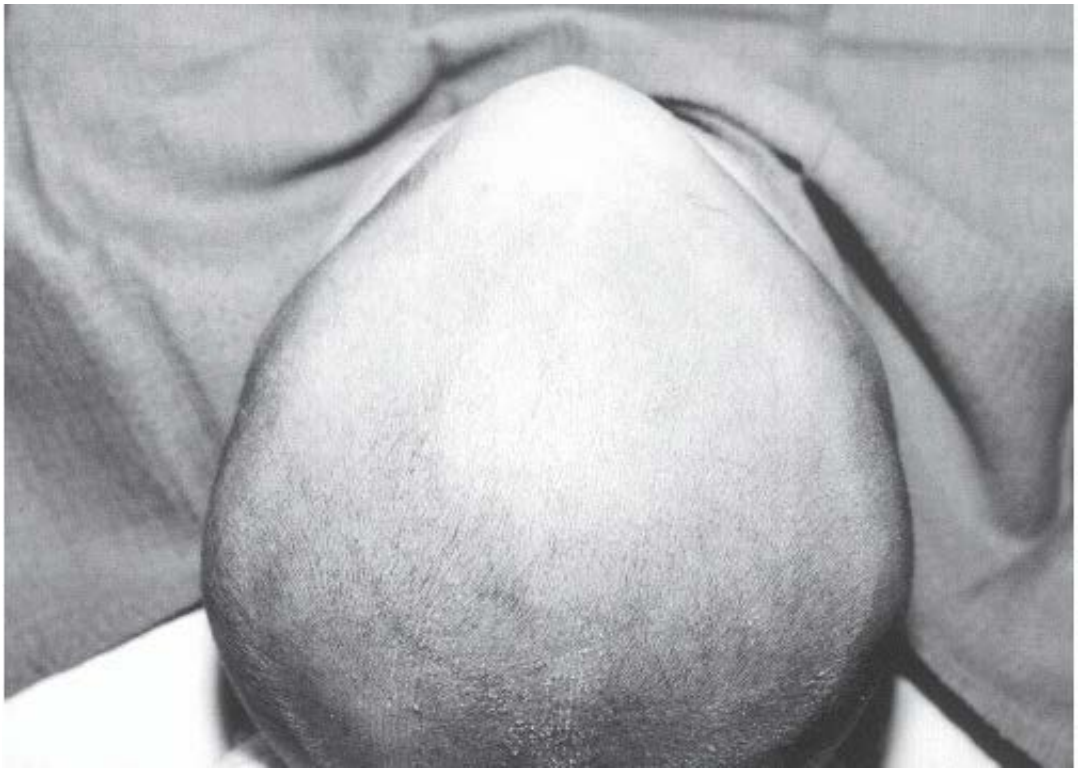
C syndrome

Synonym: Opitz trigonocephaly syndrome. (Includes Bohring-Opitz syndrome)

MIM #: 211750

The prominent features of this autosomal recessive disorder are trigonocephaly, unusual facies, polydactyly, flexion deformities, cardiac abnormalities, short stature, and intellectual disability. When viewed from above, the widened biparietal diameter and narrow forehead give the appearance of a triangular cranium (trigonocephaly). In many cases, the responsible gene is *CD96*, located on the long arm of chromosome 3. A syndrome that is phenotypically similar, but genetically distinct, has recently been delineated. The sporadically

occurring **Bohring-Opitz syndrome** (*MIM #*: 605039) is characterized by greater severity of the characteristic features and is caused by a mutation in the *ASXL1* gene located on the long arm of chromosome 20. Trigonocephaly can be found in other disorders as well.



C syndrome. Trigonocephaly, viewed from above. (Courtesy of K. Lin, MD and the Craniofacial Anomalies Clinic, University of Virginia Health System.)

HEENT/Airway: Abnormal skull with trigonocephaly, synostosis of the metopic suture, narrow pointed forehead, and biparietal widening. Up-slanting palpebral fissures, strabismus. Low-set ears with abnormal helix. Hypoplastic nasal root. Deeply furrowed palate. Short neck. Micrognathia with large mouth.

Chest: Pectus deformities. Anomalous ribs.

Cardiovascular: Congenital heart defects, of a variety of types.

Neuromuscular: Intellectual disability, hypotonia.

Orthopedic: Polydactyly, syndactyly. Ulnar deviation of the fingers. Syndactyly. Flexion deformities of the elbows, wrists, and fingers. Short stature. Dislocated hips.

GI/GU: Omphalocele. Hepatomegaly. Cryptorchidism; prominent labia majora and clitoris.

Other: Loose skin. Death can occur in childhood.

Miscellaneous: The term “C syndrome” comes from Opitz's use of a patient's initials to refer to this syndrome.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult (3). Flexion deformities may make correct positioning difficult. Likewise, skeletal anomalies may make regional anesthesia technically difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Two children have died during or shortly after craniosynostosis repair, suggesting increased perioperative risk in these patients (1).

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C1 esterase inhibitor deficiency

See Hereditary angioedema

Caffey disease

Synonym: Infantile cortical hyperostosis

MIM #: 114000

This probably autosomal dominant disease involves apparent inflammatory swelling of a variety of bones. It is due to mutations in the collagen gene *COL1A1*. Oddly for a genetic disorder, signs and symptoms are often not present at birth, appear, and then regress. It usually presents at about 5 months of age and is gone by age 2 years, although a case with recurrences through adolescence has been reported. A severe phenotype with prenatal onset and perinatal death has also been reported.

HEENT/Airway: The mandible is the most commonly affected bone, and may be very tender, warm and swollen.

Orthopedic: Inflammatory changes in bone and periosteum, which eventually resolve. Bones are tender, warm, and swollen. The mandible, ribs, and scapulae are most commonly affected. There is infiltration of the periosteum by round cells with periosteal thickening. There is cortical hyperostosis and cortical irregularity. In some cases, the bony deformities persist. May have short stature.

Other: Fever.

Miscellaneous: John Caffey was the dean of American pediatric radiologists. He worked until the

day of his death at age 83. Caffey played a critical role in the recognition of the battered baby syndrome of child abuse.

Anesthetic Considerations: There are no specific anesthetic considerations, although mandibular tenderness is an indication for extreme gentleness during physical examination of the airway, and gentle positioning would seem appropriate.

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Campomelic dwarfism

See Campomelic dysplasia

Campomelic dysplasia

Synonym: Campomelic dwarfism

MIM #: 114290

This disorder is distinguished by short stature, flat facies, hypoplastic scapulae, and bowed limbs. It was once thought to be autosomal recessive, but is now thought to be autosomal dominant with lethality in most cases.

Campomelic dysplasia is due to mutations of the *SOX9* gene. This gene is involved in cartilage formation, testicular development, and sex determination. Although approximately half possess an X,Y karyotype, up to two-thirds are phenotypically female due to sex reversal. Most patients with campomelic dysplasia die in early infancy secondary to respiratory insufficiency or critical airway narrowing.

HEENT/Airway: Macrocephaly, large anterior fontanelle. Flat facies, high forehead. Hypertelorism, short palpebral fissures. Abnormal or low-set ears. May have hearing loss. Low nasal bridge. Cleft palate. Micrognathia. Short neck.

Chest: Small thorax and thoracic kyphoscoliosis may lead to restrictive lung disease. Missing or hypoplastic ribs. May have tracheobronchomalacia with intrathoracic airway obstruction. Small thoracic cage. Eleven pairs of ribs.

Cardiovascular: Rare cardiac defects.

Neuromuscular: Gross abnormalities may be found in the cerebral cortex, thalamus, and caudate nucleus. Significant central nervous system abnormalities, including apnea. Hydrocephalus. Hypoplastic olfactory tracts. Hypotonia.

Orthopedic: Short stature. Short-limbed dwarfism. Abnormal vertebrae, particularly in the cervical region. Hypoplastic scapulae. Bowed limbs, especially the tibiae, with pretibial skin dimpling. Short fibulae. Abnormal hand positioning. Narrow, tall pelvis. Hip dislocation. Delayed osseous maturation. Clubfoot deformity.

GI/GU: May have hydronephrosis. Many XY individuals have sex reversal (patients have male gonadal dysgenesis and develop normal female external genitalia).

Miscellaneous: “Camptomelique” was introduced in the French literature to describe this syndrome. The name derives from the Greek *camptos* (“bent”) and *melos* (“limb”).

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia and short neck. Patients might require a smaller-than-expected endotracheal tube if sized for age. Patients may have significant cervical vertebral abnormalities and may have an unstable cervical spine. Respiratory insufficiency is common, and patients are at risk for perioperative respiratory complications. Patients with tracheobronchomalacia often have airway obstruction, which may require a tracheostomy. Patients are at risk for perioperative apnea. Regional anesthesia may be technically difficult due to the skeletal anomalies. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency.

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Camurati-Engelmann syndrome

Synonym: Progressive diaphyseal dysplasia; Engelmann-Camurati syndrome

MIM #: 131300

This autosomal dominant syndrome is marked by diaphyseal dysplasia with leg pain and weakness. There is wide variability in expression, and some patients may manifest only radiographic evidence of the disease.

Microscopically, osteoblastic hyperactivity has been demonstrated in the diaphyseal portions of most long bones, leading to hyperostosis and sclerosis. Bony overgrowth may lead to cranial nerve compression and/or bone marrow compromise. This disorder is progressive through adolescence and then stabilizes during adulthood. The disorder is due to specific mutations in the gene encoding transforming growth factor ß1. A second type of the disease, Camurati-Engelmann syndrome type II, is not associated with defects in this gene.

HEENT/Airway: Occasional sclerosis of the cranium, mandible. May have optic nerve compression secondary to hyperostosis of the skull. Exophthalmos. May develop limited mouth opening and neck extension. May have hearing loss from nerve compression.

Neuromuscular: May have cranial nerve compression secondary to hyperostosis of the skull. Muscle weakness, particularly of the pelvic girdle.

Orthopedic: Progressive diaphyseal dysplasia, including diaphyseal widening with cortical thickening and irregularity. The diaphyseal dysplasia is bilateral and symmetric. The femur and tibia are most affected. The medullary canal is narrowed, even though overall the bone is widened. Waddling gait. Leg pain and weakness. Occasional scoliosis. Over years, the disease may also affect the upper extremities and the spine.

GI/GU: Hepatosplenomegaly. Hypogonadism. Delayed puberty.

Other: Patients are typically tall, thin, and “malnourished” appearing. May be anemic, leukopenic.

Miscellaneous: Mario Camurati was an Italian orthopedic surgeon. Engelmann practiced orthopedics primarily in Vienna. Camurati published his discussion several years before Engelmann. Cockayne actually probably published the first case report of this syndrome and considered syphilitic osteitis in the differential.

Anesthetic Considerations: Patients are often taking steroids for symptomatic relief of bone pain and clinical improvement of their bone disease. These patients require perioperative stress doses of steroids. In advanced disease, limited neck extension and mouth opening may make direct laryngoscopy and tracheal intubation difficult. In advanced disease, spine abnormalities may make neuraxial techniques difficult, although successful spinal anesthesia for cesarean section has been reported (4). Meticulous perioperative eye care is indicated in patients with exophthalmos. Careful perioperative positioning is important in these patients with bone pain. Neuromuscular blockade should be used with caution because of preexisting muscle weakness. There may be excessive perioperative heat loss in these very thin patients.

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Canavan disease

MIM #: 271900

This autosomal recessive leukodystrophy is due to a defect in the gene for aspartoacylase (*ASPA*), with resultant accumulation of *N*-acetylaspartic acid in the brain. The disease affects myelin formation. Patients' brains show spongiform degeneration. Congenital, infantile (the most common), and juvenile forms have been described. Its features are similar to those of Alexander disease (see earlier). Onset is typically in the first 2 months of life with death in the first decade. Recently, gene therapy has led to disease stabilization in a number of patients.

The other leukodystrophies include adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, Alexander disease, and Pelizaeus-Merzbacher disease.

HEENT/Airway: Macrocephaly. Delayed closure of the anterior fontanelle. Absence of blinking to visual threat. Optic atrophy. Blindness. Deafness. Copious oral secretions.

Neuromuscular: Hypotonia early in life, followed by hypertonicity and decerebrate or decorticate posturing. Arrested developmental milestones. Seizures, spastic diplegia or quadriplegia, choreoathetosis, opisthotonic posturing.

GI/GU: Increased incidence of gastroesophageal reflux. Poor nutrition.

Miscellaneous: A disproportionate number of patients with Canavan disease have been Ashkenazic Jews of eastern European descent.

Anesthetic Considerations: Macrocephaly may be severe enough to require elevation of the rest of the body to obtain the “sniffing” position. Patients are

at risk for perioperative aspiration because of airway hypotonia, gastroesophageal reflux, and copious oral secretions. Consideration should be given to anticholinergic premedication to dry oral secretions. Care must be taken around the patient's eyes perioperatively because their blink reflex is impaired. Careful perioperative positioning and padding are important in these patients with poor nutrition. Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers may exacerbate movement disorders. Ondansetron should be safe to use as an antiemetic because it does not have antidopaminergic effects. Anticonvulsant medications must be continued (or a parenteral form substituted) perioperatively, and chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Postoperative respiratory observation is particularly important because of airway hypotonia. Increased risk from succinylcholine has not been demonstrated, but it seems reasonable to avoid it if appropriate because of the potential for hyperkalemia.

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Cantrell's pentalogy

See Pentalogy of Cantrell

Carbamoyl phosphate synthetase deficiency

See Carbamoyl phosphate synthetase deficiency

Carbamoyl phosphate synthetase deficiency

Synonym: Carbamoyl phosphate synthetase deficiency

MIM #: 237300

This autosomal recessive disorder is one of the urea cycle defects and is a potential cause of hyperammonemia. The urea cycle degrades amino acids to urea. Urea cycle disorders are marked by hyperammonemia, encephalopathy, and respiratory alkalosis. This particular disorder is caused by a mutation in the gene encoding the mitochondrial enzyme carbamoyl phosphate synthetase (*CPS1*). Symptoms similar to those of hepatic encephalopathy can be triggered by stress such as surgery or infection or episodes of protein catabolism such as involution of the postpartum uterus. Patients may self-select a low-protein diet. There are two types of the disease: a lethal neonatal type and a less severe type with delayed onset.

The clinical presentations of the urea cycle defects carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, and argininosuccinic acid lyase deficiencies are essentially identical. Pharmacologic therapy, using parenteral phenylacetate and sodium benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors. Liver transplantation is curative.

Chest: Neonatal respiratory distress.

Neuromuscular: Muscle weakness with acute episodes. Seizures, ataxia. Developmental delay. May have stroke-like episodes. Untreated hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and proceeds through stages of lethargy and agitation, to coma with cerebral edema.

GI/GU: Vomiting and mild abdominal pain with exacerbations. Hepatic synthetic function is normal, although there may be elevations in serum transaminases, both during and between episodes of hyperammonemia.

Other: Episodes of hyperammonemia begin with anorexia and lethargy, and may progress through agitation, irritability, and confusion. Vomiting and headaches may be prominent.

Miscellaneous: Carbamoyl phosphate synthetase is a large protein that constitutes 15% to 30% of mitochondrial protein.

Anesthetic Considerations: Acute metabolic encephalopathy can develop perioperatively. Acute metabolic encephalopathy may be associated with cerebral edema and increased intracranial pressure. Patients should have high carbohydrate intake (and low protein intake) perioperatively. Protracted preoperative fasting should be avoided in order to avert a catabolic state. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load.

Figure: See **Appendix C**

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Cardiac-limb syndrome

See Holt-Oram syndrome

Cardiofaciocutaneous syndrome

Synonym: CFC syndrome

MIM #: 115150

This sporadically occurring syndrome includes congenital cardiac defects, frontal bossing, ectodermal defects, neurologic abnormalities, and growth failure. There is phenotypic overlap with Costello syndrome and Noonan syndrome (see later), but the syndromes are now recognized to be genetically distinct. Cardiofaciocutaneous syndrome can be caused by a mutation in the *BRAF* gene and is associated with advanced paternal age.

HEENT/Airway: Macrocephaly, bitemporal narrowing, frontal bossing. Shallow orbital ridges, hypoplastic supraorbital ridges, hypertelorism, down-slanting palpebral fissures, exophthalmos, ptosis, strabismus, nystagmus. Absent eyebrows and eyelashes. Abnormal external ears, which are posteriorly rotated. May have hearing loss. Depressed nasal bridge, short, upturned nose. Wide, long philtrum. May have submucous cleft palate.

Micrognathia.

Chest: Pectus carinatum or excavatum.

Cardiovascular: Cardiac myxomas. Atrial septal defect and pulmonic stenosis are the most common of the congenital cardiac defects. May have hypertrophic cardiomyopathy.

Neuromuscular: Intellectual disability. Developmental delay. Hypotonia. Cortical atrophy, brainstem atrophy, mild hydrocephalus. Seizures may develop.

Orthopedic: Growth retardation, short stature. Thin nails. Hyperextensible fingers. Multiple palmar creases.

Other: Abnormalities of the skin, including atopic dermatitis, hyperkeratosis, and ichthyosis. Sparse, friable, slow-growing hair. Decreased sweating (hypohidrosis).

Anesthetic Considerations: Micrognathia can make direct laryngoscopy and tracheal intubation difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients may have heat intolerance secondary to sweat gland dysfunction.

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Carnevale syndrome

See Malpuech syndrome

Carney complex

MIM #: 160980, 605244

This autosomal dominant multiple neoplasia syndrome is due to mutations in the gene *PRKAR1A,* a cyclic AMP-dependent protein kinase A regulatory gene that is a tumor-suppressing gene. A second form, type 2, is linked to chromosome 2. The disease is marked by spotty skin pigmentation, cardiac and other myxomas, endocrine tumors, and melanotic schwannomas.

HEENT/Airway: Spotty pigmentation on the lips and face. Scleral and conjunctival pigmentation. Eyelid myxoma. May have obstructive sleep apnea.

Cardiovascular: Atrial and ventricular myxomas. May develop cardiomyopathy.

Other: Profuse ephelides, or freckles and lentigines, and other pigmented skin lesions and nevi. Blue nevi.

Cushing's disease, acromegaly. Red hair. A variety of thyroid gland abnormalities. Neoplasias include myxoid cutaneous tumors, adrenocortical nodular hyperplasia, Sertoli cell tumor of testes, pituitary adenoma, mammary ductal fibroadenoma, schwannoma, and pheochromocytoma.

Miscellaneous: Prior to acquiring its eponymous name, Carney complex was known as NAME syndrome (**N**evi, **A**trial myxoma, **M**yxoid neurofibroma,

and **E**phelides) or as LAMB syndrome (**L**entigines, **A**trial **M**yxoma, and **B**lue nevi).

In 1995, Carney published an account of his search for Harvey Cushing's patient Minnie G, who was reported in Cushing's 1912 monograph on the pituitary and its disorders. Carney believed that this patient might have had “his” syndrome. Carney succeeded in identifying her, locating her death certificate, and finding her family. However, the cause of her Cushing's syndrome remains unknown.

Anesthetic Considerations: Patients should be screened preoperatively for the presence of cardiac myxomas. Luckily, these are relatively easily diagnosed by echocardiography. These tumors are often pedunculated and can obstruct valve orifices with changes in body position. They can also directly affect valve function. In rare cases, they can embolize. Intraoperative transesophageal echocardiography (TEE) may be very helpful. Cardiac myxomas are the primary cause of death in patients with Carney complex, and perioperative sudden cardiac death has been described. Central venous catheters and pulmonary artery catheters are contraindicated in the face of right-sided cardiac myxomas. Patients can present with the biochemical abnormalities of Cushing's disease, with hypertension, hyperglycemia, weakness, and obesity. If acromegaly has developed, there is concern about difficult laryngoscopy and intubation, as well as obstructive sleep apnea and cardiomyopathy. Although schwannomas can develop, there is inadequate information currently to contraindicate regional techniques.

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Carnitine palmitoyltransferase deficiency

MIM #: 255120, 600650

This disorder is due to two distinct and separate autosomal recessive mutations. There are two carnitine palmitoyltransferase (CPT) enzymes. Both are involved in the transfer of fatty acids into the mitochondria. To cross the mitochondrial membrane, fatty acids are first activated by coenzyme-A (CoA) and are then reversibly conjugated with l-carnitine. CPT I converts fatty acyl-CoA into a fatty acylcarnitine, which is required for transport through the mitochondrial membrane. CPT II, on the inner aspect of the membrane, liberates carnitine and, in association with several other enzymes, makes the fatty acyl-CoA available for beta-oxidation.

Carnitine palmitoyltransferase I deficiency is marked by hypoketotic hypoglycemia and potentially with seizures and coma. Attacks are precipitated by fasting, exercise, cold exposure, infection, stress, or a high-fat and low-carbohydrate diet. It usually presents at 8 to 18 months of age.

Carnitine palmitoyltransferase II is found in a variety of tissues, but the clinical manifestations are restricted to muscle. This represents the most common inherited disorder of long-chain fatty acid oxidation. It usually presents in young adults, but there is also a neonatal-onset type that is severe and presents with (potentially fatal) cardiomyopathy, weakness, and coma. The milder adult form has muscle weakness and episodes of rhabdomyolysis triggered by exercise, prolonged fasting, cold, or by conditions of stress that are associated with increased supply of energy as lipid to muscle.

Medium-chain triglycerides bypass the CPT-mediated transfer process.

Chest: CPT I: Acute respiratory failure.

Cardiovascular: CPT I: Cardiomyopathy.

CPT II (neonatal form): Arrhythmia, cardiomyopathy.

Neuromuscular: CPT I: Muscle aching and stiffness, rhabdomyolysis. This form does not have muscle weakness. Episodes similar to hepatic encephalopathy progressing eventually to coma.

CPT II: Episodes of rhabdomyolysis and myoglobinuria are associated with aching muscle pain and elevations in creatine phosphokinase. Muscle weakness following exercise.

GI/GU: CPT I: Hepatomegaly with fatty infiltration. After acute episodes, there are major abnormalities in liver function tests and serum bilirubin that remain abnormal for several weeks. There may also be transient renal tubular acidosis because fatty acids are an energy source for the kidney.

CPT II: Episodic pancreatitis, even without myoglobinuria. Episodes of rhabdomyolysis and myoglobinuria can lead to renal dysfunction.

Other: CPT I: Hypoketotic hypoglycemia, hyperammonemia, Reye syndrome-like episodes.

CPT II (neonatal form): Hypoketotic hypoglycemia.

Miscellaneous: Mothers carrying fetuses with CPT I can develop acute fatty liver of pregnancy or

HELLP syndrome. This is also the case with other acyl-CoA dehydrogenase deficiencies, such as long-chain acyl-CoA dehydrogenase deficiency (see later). Presumably, abnormal fetal metabolites overwhelm the ability of the heterozygote mother's mitochondria to oxidize them.

Anesthetic Considerations: Protracted perioperative fasting must be avoided because it may lead to hypoketotic hypoglycemia. Perioperative intravenous fluids should include glucose. In patients who are hypoglycemic, 5% dextrose may be inadequate. The limitations of caloric intake as supplied by intravenous lipids are unclear.

Medium-chain triglycerides are fully metabolized and are an appropriate energy source. Hepatic function should be evaluated preoperatively. Patients with cardiomyopathy should receive an appropriately tailored anesthetic. Anesthesia and/or surgical stress can precipitate an attack of rhabdomyolysis (9,10) or hepatic coma (5). Regional anesthesia/analgesia may be used to blunt the stress response. The consequences of succinylcholine use in the presence of this myopathy are not known. One group of researchers has suggested that a subset of patients who are susceptible to malignant hyperthermia are CPT deficient (1,8). This was not supported by a larger study of malignant hyperthermia susceptible patients (3).

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Carpenter syndrome

Synonym: Acrocephalopolysyndactyly type II. (Includes Summitt syndrome)

MIM #: 201000

This autosomal recessive disorder is characterized by craniosynostosis, acrocephaly, lateral displacement of the inner canthi, syndactyly of the hands, polydactyly of the feet, and cardiac defects. Carpenter syndrome can be caused by mutation in the *RAB23* gene. A variant, known as **Summitt syndrome** (*MIM #:* 272350), has been described with the findings of Carpenter syndrome with obesity and normal intelligence.

HEENT/Airway: Craniosynostosis (coronal, sagittal, and lambdoid). Acrocephaly, brachycephaly, or Kleeblattschaedel deformity (see later). Hypoplastic supraorbital ridges. Flat midface. Lateral displacement of the inner canthi; may have inner canthal folds. Proptosis, microcornea, cataracts. Low-set, malformed ears. May have conductive or sensorineural hearing loss. Flat nasal bridge. High-arched palate. Abnormal dentition, including missing teeth, delayed loss of deciduous teeth, and delayed emergence of teeth. Hypoplastic mandible. May have short neck.

Cardiovascular: Congenital cardiac defects occur in approximately half and include atrial septal defect, ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, and transposition of the great vessels.

Neuromuscular: Variable intellectual disability, from none to severe. May have speech delay. May have cerebral malformations. May have elevated intracranial pressure if craniosynostosis is severe.

Orthopedic: Growth retardation. Hands show syndactyly, brachydactyly, clinodactyly, camptodactyly. Single palmar crease. Feet show preaxial polydactyly, partial syndactyly. Hypoplastic or missing middle phalanges of fingers and toes. Coxa valga. Angulation deformities at the knees. Metatarsus varus.

GI/GU: Umbilical hernia, omphalocele. Cryptorchidism, hypogonadism. May have hydronephrosis or hydroureter.

Other: Obesity. Precocious puberty.

Miscellaneous: George Carpenter described a patient with “his” syndrome thus: “When looked at from the front, the face and skull form an ace of diamonds shaped figure, the eyes protruding frog-like, the eyeballs being kept in position merely by their lids, so that it is possible to readily dislocate the globes and permit the organs to hang suspended by their muscular and nerve attachments.”

Anesthetic Considerations: The hypoplastic mandible may make direct laryngoscopy and tracheal

intubation difficult. Because of the incidence of dental anomalies, dentition should be carefully assessed preoperatively. Meticulous perioperative eye protection is necessary in patients with significant proptosis. Patients may have elevated intracranial pressure, in which case precautions should be taken to avoid further elevations in pressure. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Abnormal airway anatomy may predispose to postoperative respiratory obstruction.

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Cartilage-hair hypoplasia syndrome

Synonym: Metaphyseal chondrodysplasia, McKusick type; Metaphyseal dysplasia, McKusick type

MIM #: 250250

There are many types of metaphyseal chondrodysplasia—see also Jansen, Pyle, Schmid, Shwachman, and Spahr type [Spahr type not included in this text (*MIM #*: 250400)]. This autosomal recessive form of metaphyseal chondrodysplasia is characterized by flared and irregular metaphyses, mild bowing of the legs, and fine, sparse hair. The hematologic and immunologic abnormalities that can be seen with this syndrome are similar to those seen in Shwachman syndrome (see later). The gene responsible for this disorder, *RMRP*, is interesting. The product of this gene, mitochondrial RNA-processing endoribonuclease, cleaves mitochondrial RNA. The enzyme is a ribonucleoprotein whose RNA component is produced by a nuclear gene and imported into the mitochondria. The *RNRP* gene is untranslated—it encodes an RNA, not a protein.

HEENT/Airway: May have abnormal dentition and dental caries.

Chest: Prominent sternum. Mild flaring of the ribs at the costochondral junction. May have bronchiectasis.

Orthopedic: Growth deficiency and short stature with short limbs and long trunk. Mild bowing of the legs. Long fibula distally relative to the tibia. Incomplete extension of the elbow. Flared and irregular metaphyses, with epiphyses essentially normal. Short hands. Lax joints in the hands. Flat feet. Small pelvic inlet. Genu varum. Scoliosis, lumbar lordosis.

GI/GU: May have esophageal atresia, intestinal malabsorption, Hirschsprung disease (see later), anal stenosis. May have impaired spermatogenesis.

Other: Fine, sparse, hypopigmented hair. Abnormal cellular immune function and neutropenia lead to significantly increased risk of serious infection, with a noted susceptibility to varicella infection (chicken pox). Humeral immune deficiency of a variety of immunoglobulin types and subtypes. Mild macrocytic anemia. Rare congenital hypoplastic anemia that is usually transient, but occasionally persistent. May have thrombocytosis. Malignancy, particularly non-Hodgkin's lymphoma and basal cell carcinoma, may develop, presumably due to the immunologic defect. May develop obesity.

Miscellaneous: Particularly common in Old Order Amish and in Finland.

Anesthetic Considerations: A baseline hematocrit should be obtained. Carious teeth can be dislodged during laryngoscopy. Attention to good aseptic technique is indicated because patients may have a significant immunologic abnormality. Neuraxial anesthesia/analgesia may be technically difficult secondary to scoliosis and/or

lordosis. Patients must be carefully positioned and padded secondary to orthopedic abnormalities. Patients with concomitant Hirschsprung disease are at increased risk for postoperative morbidity and mortality.

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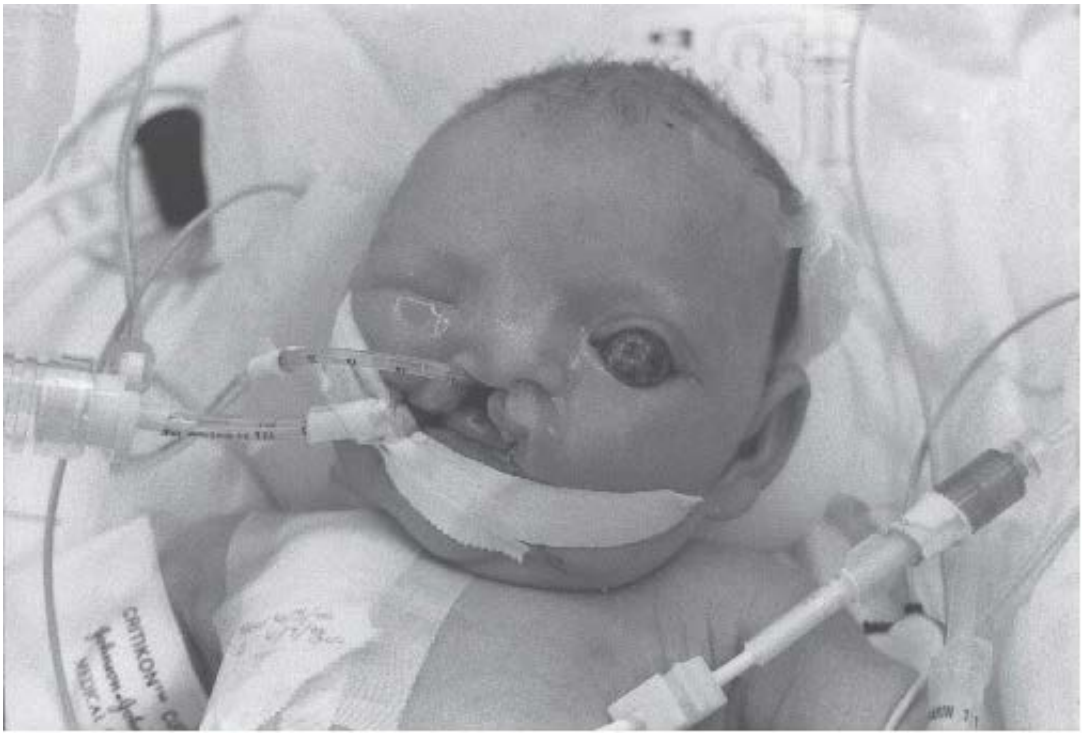
Cat eye syndrome

MIM #: 115470

This autosomal dominant syndrome classically involves colobomas of the iris and anal atresia. However, there is wide phenotypic variability and many patients with this syndrome exhibit only one of

the characteristic features. Genetic studies have been able to confirm atypical cases in which only one of the classic features is present. This syndrome is due to the presence of a partial extra chromosome or a duplication of the 22q11 region, including the centromere. Patients may have mosaicism.



Cat eye syndrome. In addition to the expected ocular findings, this 5-day-old infant with cat eye syndrome has complex cyanotic congenital heart disease, anal atresia, cleft lip and palate, and brainstem hypoplasia.

HEENT/Airway: Mild hypertelorism, down-slanting palpebral fissures. Inferior coloboma of the iris. May have colobomas of the choroid or optic nerve. Inner epicanthal folds, microphthalmia, strabismus. May have abnormal external ear, atresia of the external auditory canal, preauricular tags/pits. Flat nasal bridge. May have choanal atresia. May have cleft palate. Mild micrognathia.

Chest: Absence or synostosis of ribs.

Cardiovascular: Congenital cardiac defects, including persistence of the left superior vena cava, tetralogy of Fallot, and total anomalous pulmonary venous return.

Neuromuscular: Intelligence is normal or near normal.

Orthopedic: May have growth retardation. May have radial aplasia, duplication of the hallux.

GI/GU: Anal atresia with a fistula from the rectum to the bladder, vagina, urethra, or peritoneum. May have inguinal hernias, malrotation of the gut, Meckel's diverticulum, Hirschsprung disease (see later), and biliary atresia. Renal abnormalities include hypoplasia, unilateral or bilateral agenesis, hydronephrosis, supernumerary kidneys.

Miscellaneous: The association of coloboma of the iris and anal atresia was first reported by Haab in 1879. It was later named cat eye syndrome because inferior iris colobomas cause the pupils to be keyhole shaped, much like a cat's eye.

Anesthetic Considerations: Patients invariably need surgical correction of anal atresia. Difficult intubation has been reported, with successful use of a laryngeal mask airway (LMA) or awake nasal fiberoptic intubation. Renal

abnormalities are common, and renal insufficiency has implications for perioperative fluid management and the choice of anesthetic drugs. Radial anomalies may make placement of a radial arterial catheter more difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Choanal atresia, although uncommon, precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube.

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Catel-Manzke syndrome

MIM #: 302380

This sporadic, possibly X-linked recessive disorder is characterized by severe micrognathia, cleft palate, glossoptosis, and anomalies of the index finger. The responsible gene and gene product are not known.

HEENT/Airway: May have hypertelorism. Abnormal or posteriorly rotated external ears. Large tongue. Cleft palate, glossoptosis, severe micrognathia (Pierre Robin anomaly). May have cleft lip. Short neck.

Chest: May have pectus excavatum or carinatum.

Cardiovascular: Cardiac defects are common and include atrial septal defects, ventricular septal defects, overriding aorta, coarctation of the aortic, and dextrocardia.

Neuromuscular: Intelligence is normal. Occasional developmental delay, seizures. May have facial paresis.

Orthopedic: Prenatal and postnatal growth failure. Accessory bone at the base of the index finger, with resultant ulnar deviation (bilateral duplication of the proximal phalanges of the index fingers—hyperphalangism).

Hypoplasia of the associated metacarpal. Over time, the accessory bone fuses to the proximal phalangeal epiphysis. Clinodactyly. Single palmar crease. May have radial defects. Dislocatable knees. Camptodactyly. Clubfoot.

GI/GU: May have umbilical and inguinal hernias. Cryptorchidism.

Other: Failure to thrive secondary to respiratory problems or cardiac anomalies.

Anesthetic Considerations: Endotracheal intubation may be extremely difficult or impossible secondary to severe micrognathia. Alternatives to direct laryngoscopy, such as fiberoptic intubation, retrograde intubation, blind nasal intubation, and the laryngeal mask airway, must be considered. Patients may have significant upper airway obstruction even without the induction of anesthesia. Placing the patient prone so that the tongue does not fall

posteriorly into the pharynx may improve spontaneous ventilation. Radial anomalies may make placement of a radial arterial catheter more difficult. Patients must be closely observed after surgery for evidence of airway obstruction. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Caudal regression syndrome

Synonym: Sacral agenesis. (Includes sirenomelia)

MIM #: None

This syndrome involves a spectrum of abnormalities of the sacrum and lower extremities (the caudal region). There is no discernible Mendelian inheritance pattern. The syndrome is probably secondary to a defect in neural plate and neural tube development or fetal vascular supply. Infants of diabetic mothers are at increased risk for development of this syndrome. The more severely affected patients have complete sacral agenesis, and their prognosis is poor. **Sirenomelia**, a congenital anomaly characterized by fusion of the lower extremities (mermaid malformation), is thought to be at the extreme end of the caudal regression spectrum.

HEENT/Airway: May have cleft lip or palate.

Cardiovascular: Rare congenital heart disease.

Neuromuscular: Disruption of the distal spinal cord secondary to sacral or lumbar defects may lead to neurogenic bladder, fecal incontinence, and lower extremity paralysis. May have microcephaly, meningomyelocele.

Orthopedic: Varying degrees of sacral and lower extremity hypoplasia. The buttocks are shortened and flattened. May have hypoplasia of the lumbar vertebrae. May have hypoplasia of the femur, defects of the tibiae/fibulae. The most extreme cases have sacral agenesis, flexion and abduction deformities of the lower extremities, popliteal webs, or fusion of the lower extremities. Clubfoot deformity is common.

GI/GU: May have imperforate anus. May have renal anomalies.

Anesthetic Considerations: Baseline renal function should be evaluated if neurogenic bladder is present or renal anomalies are suspected. Self-catheterization for neurogenic bladder is a major risk factor for the development of latex allergy. Lower lumbar and caudal anesthesia/analgesia are technically difficult or impossible with the complete absence of those structures. The patient's lower extremities may need to be carefully positioned and padded secondary to contracture deformities.

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Cayler syndrome

See Asymmetric crying facies

Central core disease

MIM #: 117000

This autosomal dominant congenital myopathy is characterized by nonprogressive, primarily proximal muscle weakness and susceptibility to malignant hyperthermia. The name is derived from the fact that there is decreased stain uptake in the central areas (cores) of muscle fibers on histologic examination. This is a result of quantitative and qualitative abnormalities of mitochondria, sarcoplasmic reticulum, and glycogen in these areas. This disorder is due to one of several reported defects in the ryanodine receptor-1 gene (*RYR1*), a calcium channel gene that has been mapped

to the long arm of chromosome 19. As a consequence of the defect, less calcium is maintained in the sarcoplasmic reticulum and elevated calcium concentrations are found in the muscle fiber cytosol, leading to reduced calcium release during excitation-contraction coupling and muscle weakness. Additionally, there is evidence that the calcium channel is hyposensitive, contributing to the uncoupling of excitation-contraction. The resultant myopathy is relatively mild. The abnormality appears to be limited to Type 1 muscle fibers.

The other congenital myopathies are minicore myopathy (not covered in this text), myotubular myopathy (see later), and nemaline rod myopathy (see later).

HEENT/Airway: Mandibular hypoplasia and a short neck may occur secondary to congenital muscle weakness.

Neuromuscular: Proximal or, more rarely, diffuse, nonprogressive myopathy. Hypotonia in infancy. Delayed motor development. Intelligence is normal. Cranial nerve function is normal.

Orthopedic: May have kyphoscoliosis, dislocated hips, pes cavus, joint contractures, clubfoot deformity.

Anesthetic Considerations: Central core disease is one of the few diseases where patients are clearly susceptible to the development of malignant hyperthermia (see later). Patients with central core disease must always receive a nontriggering anesthetic. Interestingly, both central core disease and malignant hyperthermia susceptibility are due to mutations in *RYR1*. However, malignant hyperthermia susceptibility does not always correlate with central core disease, and central core disease does not always cosegregate with the identified region on chromosome 19 (10).

Mandibular hypoplasia and short neck can make direct laryngoscopy and tracheal intubation difficult.

Nondepolarizing neuromuscular blocking agents may cause prolonged neuromuscular blockade. Patients with significant respiratory muscle weakness may require postoperative ventilatory support. Although statin drugs have been associated with rhabdomyolysis and myopathy, there is an isolated report of uncomplicated use in a patient for coronary bypass surgery (9).

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Central hypoventilation syndrome

See Ondine's curse

Centronuclear myopathy

See Myotubular myopathy

Cerebral gigantism

See Sotos syndrome

Cerebrocostomandibular syndrome

MIM #: 117650

This autosomal recessive (sometimes autosomal dominant) disorder consists of intellectual disability, rib gap defects, and severe micrognathia. Patients have a very small thoracic cage, and usually die during early childhood of respiratory insufficiency. The responsible gene and gene product are not known.

HEENT/Airway: May have microcephaly. Severe micrognathia, large tongue. May have hearing loss. Cleft palate. Dental anomalies. May have abnormal cartilaginous tracheal rings.

Chest: Defects (gaps) in ribs between the posterior incompletely ossified ribs and the anterior cartilaginous ribs, with resultant small, bell-shaped thoracic cage. The defects become pseudoarthroses over time. Ribs may be aberrantly attached to the vertebrae posteriorly. Sternum and clavicles may be hypoplastic. Rib defects may cause flail chest.

Cardiovascular: May have ventricular septal defect.

Neuromuscular: Intellectualdisability. Porencephaly. Speech delay. May have meningomyelocele.

Orthopedic: Growth retardation. Vertebral defects, scoliosis may be severe. May have sacral fusion, congenital hip dislocation, clubfoot deformity. May have hypoplastic humerus.

GI/GU: May have cystic renal disease.

Anesthetic Considerations: Endotracheal intubation can be extremely difficult or impossible secondary to severe micrognathia. Alternatives to direct laryngoscopy, such as fiberoptic intubation, retrograde intubation, blind nasal intubation, and the laryngeal mask airway should be considered. Patients have severe restrictive lung disease secondary to thoracic cage defects. These patients are at increased risk for perioperative respiratory complications. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Vertebral anomalies may make neuraxial techniques difficult. Renal disease is rare but, when present, has implications for perioperative fluid management and the choice of anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Cerebrohepatorenal syndrome

See Zellweger syndrome

Cerebrooculofacioskeletal syndrome

Synonym: COFS syndrome; Pena-Shokeir syndrome, type II

MIM #: 214150

This autosomal recessive syndrome consists of microcephaly, microphthalmia, arthrogryposis, and failure to thrive. It is a progressive disorder involving degeneration of the brain and spinal cord. Evidence of the degenerative process is usually present at birth. Most patients die in early childhood. The disorder is due to mutations in the gene *ERCC6*, which is involved in DNA repair. Defects in this gene are also responsible for the late-onset type of Cockayne syndrome (see later).

HEENT/Airway: Microcephaly. Microphthalmia, blepharophimosis, cataracts, nystagmus. Large ears. Can have decreased hearing, and abnormal inner ear pathology has been described. Broad nasal root. Mild micrognathia. Overhanging upper lip.

Chest: Pulmonary infections are common, particularly as malnutrition progresses. Widely spaced nipples.

Neuromuscular: Degeneration of white matter. Cerebellar degeneration. Intellectual disability. Hypotonia, hyporeflexia. May have seizures, infantile spasms. Focal gliosis of the third ventricle, focal microgyria, hypoplastic optic tracts and chiasm, agenesis of the corpus callosum, intracranial calcifications.

Orthopedic: Severe growth deficiency. Arthrogryposis, particularly of elbows and knees. Camptodactyly. Coxa valga. Rocker bottom feet. Kyphoscoliosis. Osteoporosis.

GI/GU: May have renal abnormalities.

Other: Severe failure to thrive with progressive malnutrition. Photosensitivity. Hirsutism.

Anesthetic Considerations: Patients exhibit progressive neurologic degeneration and may be at risk for hyperkalemia with the administration of succinylcholine. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Micrognathia is usually mild and should not interfere with ease of intubation. Pulmonary infections are common. Patients must be carefully positioned and padded secondary to joint contractures and osteoporosis.

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Cerebrooculohepatorenal syndrome

See Arima syndrome

Cerebroside lipidosis

See Krabbe disease

Ceroid lipofuscinosis

See Jansky-Bielschowsky disease and Spielmeyer-Vogt disease

Cervicooculoacoustic syndrome

See Wildervanck syndrome

CFC syndrome

See Cardiofaciocutaneous syndrome

Charcot-Marie-Tooth disease

MIM #: 118200, 118210, 118220, 302800

This hereditary peripheral neuropathy is the most common form of peripheral neuropathy in children but is genetically and clinically heterogeneous. Patients exhibit distal motor and sensory nerve dysfunction, with the primary manifestation being peroneal muscle atrophy. The sympathetic postganglionic fibers may also be involved, leading to autonomic dysfunction. Symptoms are usually evident by the mid-teen years and are slowly progressive with periods of remission and exacerbation. Life expectancy is unaffected. Exacerbations of symptoms can occur during pregnancy.

A relatively common autosomal dominant form of Charcot-Marie-Tooth syndrome (CMT type 1) is a peripheral demyelinating disease with bilaterally slowed motor nerve conduction velocities. It presents in the second or third decade of life with progressive disease. Overexpression of the *PMP22* gene results in CMT type 1A. CMT type 1B is caused by mutations in the gene *MPZ* and is related clinically and genetically to Dejerine-Sottas syndrome (see later). Both the *PMP22* and *MPZ* genes encode a peripheral myelin protein. There are many other subtypes of CMT type 1 that have been associated with defects in a variety of other genes. Another dominant form, CMT type 2, is caused by mutations in the gene *K1F1B* (whose gene product transports mitochondria along microtubules) or the gene *MFN2* (which regulates mitochondrial fusion). CMT type 2 presents later in life than CMT type 1. An X-linked dominant form is due to mutations in the gene *GJB1,* which encodes connexin-32, a gap junction protein.

HEENT/Airway: May have vocal cord paresis.

Chest: Severe disease can result in respiratory insufficiency in adults secondary to respiratory muscle involvement.

The presence of proximal arm weakness may be a marker for respiratory muscle involvement.

Cardiovascular: Rare cardiac conduction abnormalities, cardiomyopathy.

Neuromuscular: Slowly progressive neuropathy with muscle wasting and early loss of deep tendon reflexes. Muscle weakness begins in the feet and legs. Peroneal muscle atrophy is a hallmark finding, with foot drop. Involvement of the sympathetic postganglionic fibers impairs autonomic function. Weakness and wasting of intrinsic muscles of the hands in severe disease. Difficulty manipulating thumb for tasks that require thumb opposition or fine motor movements. Thickened ulnar and peroneal nerves. Tremor.

Orthopedic: High-arched feet (pes cavus), clubfoot deformity, hammer toe deformity. Foot deformities may precede muscle atrophy by many years.

Other: Temperature regulation by sweating may be impaired secondary to autonomic dysfunction. The neuropathy may be exacerbated by pregnancy. Symptoms often, but not always, return to baseline after delivery. Some patients may have new or exacerbated symptoms postpartum. Alcohol can exacerbate symptoms in CMT 1 disease, and all patients are very sensitive to vincristine. Vitamin C reduced the severity and progression of neuropathy in a mouse model of Charcot-Marie Tooth Disease Type 1A but has shown no significant effect in human trials.

Miscellaneous: Described separately by Charcot and Marie in France and Tooth in England. Charcot and Marie thought it to be a primary muscular disease, but Tooth correctly identified it as a peripheral neuropathy.

Anesthetic Considerations: Neurologic function should be assessed preoperatively. Use of regional anesthesia is controversial in this demyelinating disease but has been used successfully in cases where the benefits were thought to outweigh the risks (3,4). Spinal and epidural anesthesia have also been used successfully in these patients (9,17). Both depolarizing and nondepolarizing muscle relaxants have been used uneventfully in these patients (2,7,13,15,18,19). Hypersensitivity did occur in a patient with advanced disease (20). It has been suggested that succinylcholine be avoided, particularly during acute exacerbations, because of the risk of hyperkalemia secondary to denervation muscle atrophy. Succinylcholine has been used during stable disease without problems (19). Concern exists over the use of nitrous oxide (possible toxicity and worsening neuropathy), but a recent review found no reports of adverse effects or worsening neuropathy in patients who received nitrous oxide (5). Sensitivity to thiopental has been reported (16). Temperature regulation by sweating may be impaired secondary to autonomic dysfunction, leading to thermal lability and mottled cyanosis. Vocal cord paresis is well tolerated in adults but has resulted in tracheostomies in children. Respiratory muscle dysfunction can occur in

advanced cases. Pregnancies have resulted in a higher incidence of emergency and instrumented deliveries. There is no association between Charcot-Marie-Tooth syndrome and malignant hyperthermia.

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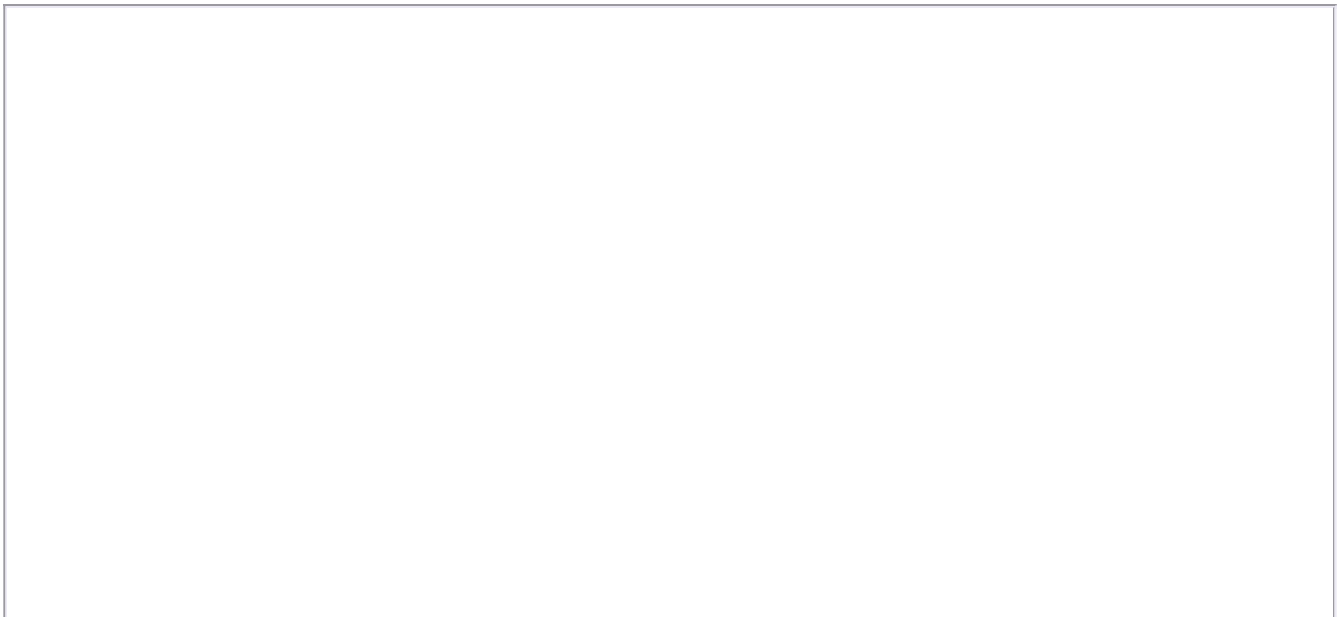
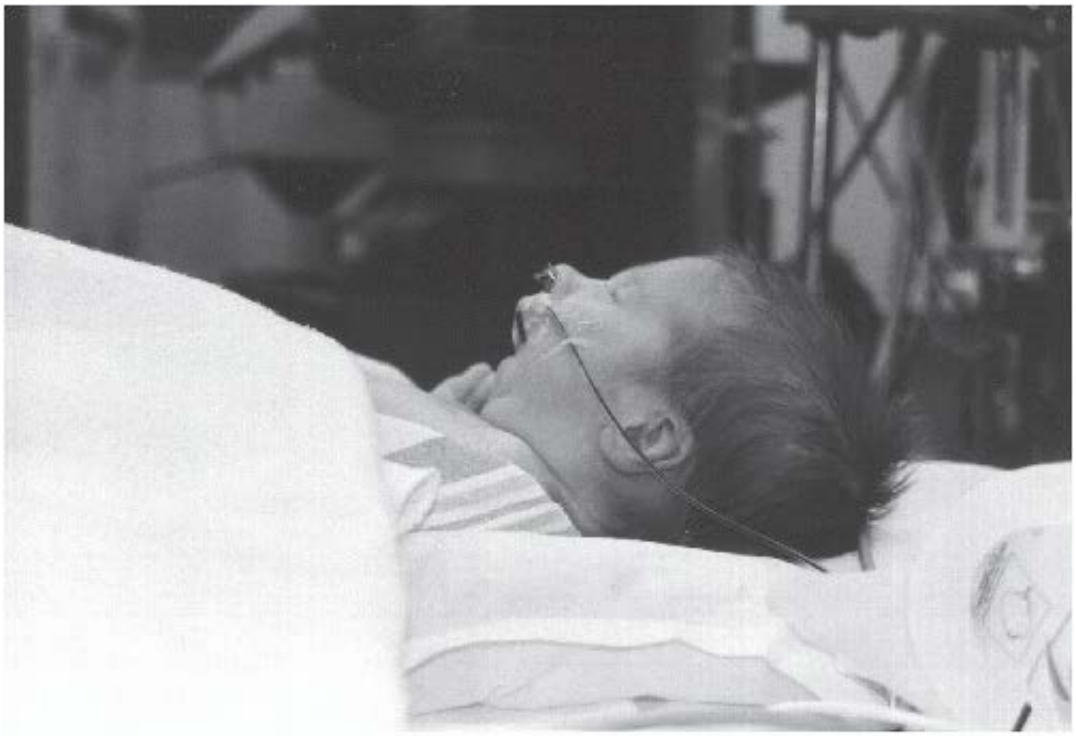
CHARGE syndrome

MIM #: 214800

The acronym CHARGE stands for **C**olobomas of the eye, **H**eart disease, **A**tresia of the choanae, **R**etarded growth and/or intellectual development, **G**enital anomalies and/or hypogonadism, and **E**ar anomalies and/or deafness. These anomalies are frequently seen in non-random association, and traditionally at least four abnormalities need to be present to make the diagnosis. All of the organ systems involved are at a critical stage of development during the second month of gestation, and it has been hypothesized that a midline developmental abnormality during the second month of gestation is responsible for the variety of defects seen with the CHARGE association. The association is due to abnormalities in one of two genes, *CHD7* (chromodomain helicase DNA-binding protein 7) or *SEMA3E* (semaphorin 3E). *CHD7* is a transcriptional regulator, and *SEMA3E* is involved in embryonic endothelial and vasculature development. Most cases are sporadic, but autosomal dominant transmission has been described.





CHARGE syndrome. This neonate presented for choanal atresia repair. The micrognathia is obvious. She was extubated without difficulty, but when she required additional surgery 2 weeks later, neither the anesthesiologist nor the otolaryngologist could visualize the vocal cords, and the trachea was intubated through a laryngeal mask airway.

HEENT/Airway: Microcephaly. Colobomas of the eye (iris, choroid, retina, disc, or optic nerve). May have morning glory anomaly (see later, Papillorenal syndrome). Up-slanting palpebral fissures. May have anophthalmia. External ear abnormalities, sensorineural or conductive hearing loss—semicircular canal agenesis is common. Choanal atresia or stenosis. Cleft lip or palate. Velopharyngeal incompetence. May have single maxillary central incisor. Micrognathia, which may be severe. Short neck. Laryngomalacia. Subglottic stenosis. May have esophageal atresia, tracheoesophageal fistula.

Chest: May have rib anomalies, pectus carinatum, respiratory insufficiency.

Cardiovascular: Congenital heart disease, including tetralogy of Fallot (most commonly), patent ductus arteriosus, atrial septal defect, ventricular septal defect, double-outlet right ventricle with an atrioventricular canal, right-sided aortic arch.

Neuromuscular: Variable intellectual disability. Developmental delay. Cranial nerve abnormalities may result in facial nerve palsy, swallowing difficulties, abnormal gag reflex, sensorineural hearing loss. Severe cases may manifest arhinencephaly, holoprosencephaly.

Orthopedic: Growth retardation. May have syndactyly, nail hypoplasia. May have limb defects.

GI/GU: Gastroesophageal reflux. May have omphalocele, anal atresia, or stenosis. Genital anomalies or hypogonadism. Renal anomalies.

Other: Failure to thrive. May have parathyroid hypoplasia. May have immunologic abnormalities.

Anesthetic Considerations: Consider having an interpreter present before surgery to ease communication with those patients who are deaf. In addition, many patients have visual defects. Micrognathia can make direct laryngoscopy and tracheal intubation difficult. Intubation can become more difficult with increasing age. Patients with laryngomalacia may have trouble maintaining an airway while ventilating through a mask or a laryngeal mask airway without additional positive end-expiratory pressure. They may do better in the lateral position. Patients with subglottic stenosis require a smaller-than-expected endotracheal tube. Choanal atresia may cause severe respiratory distress in the newborn and precludes the use of a nasal airway or nasogastric tube. Upper airway dysfunction and frequent intubations may lead to arytenoid dislocation/subluxation in these patients (1).

Gastroesophageal reflux is common, and some patients also have an impaired gag reflex. Patients are at high risk for perioperative aspiration. These patients are also at high risk for postoperative airway events such as decreased oxygen saturation, stridor, airway obstruction, aspiration, and failed extubation (3). Patients with congenital heart disease should receive an appropriately tailored anesthetic. Patients with renal disease need careful titration of perioperative fluids and consideration of the mode of metabolism in choosing anesthetic drugs.

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Chédiak-Higashi syndrome

Synonym: Béguez César syndrome

MIM #: 214500

This autosomal recessive disorder involves granular cells. It is characterized by the presence of large intracellular inclusions, best seen in neutrophils, monocytes, and lymphocytes, but present in a variety of other granular cells, such as renal tubular epithelium, gastric mucosa, Schwann cells, and melanocytes. The disorder is characterized by immune dysfunction, partial oculocutaneous albinism, and peripheral neuropathy. Death is usually secondary to infection or a lymphoreticular malignancy occurring during an accelerated phase of the disease. During an accelerated phase, patients can also develop anemia, thrombocytopenia, and qualitative platelet defects.

The disorder is due to mutations in the gene *LYST*, a lysosomal trafficking regulator gene, which is likely responsible for sorting lysosomal proteins.

HEENT/Airway: Partial oculocutaneous albinism with abnormal pigmentation of the eyes. Photophobia and nystagmus, particularly in patients with light-colored eyes. Decreased retinal pigmentation. Abnormal electroretinogram and auditory and visual evoked responses, suggesting abnormal neural routing. Epistaxis. Gingivitis.

Chest: Recurrent upper and lower respiratory tract infections.

Neuromuscular: Cranial nerve abnormalities. Peripheral neuropathy (late, perhaps due to invasion by lymphohistiocytic cells or as a consequence of the lysosomal defect in neurons and glial cells). Abnormal electroencephalogram, electromyogram, and nerve conduction velocity. May have disorders of muscle function secondary to neuropathy. May have seizures. Diffuse brain and spinal cord atrophy. Ataxia.

GI/GU: Hepatosplenomegaly. Gastrointestinal tract bleeding. Abnormal liver function as a late finding during the accelerated phase.

Other: Partial albinism. Hair has an abnormal metallic, frosted-gray sheen and has been described as ashen or silvery-blond. Even darker hair has a silvery appearance. Skin color varies from light to slate gray, and burns easily on exposure to sunlight. Pigmented and papillary skin lesions are common. Patients are highly susceptible to bacterial infections, usually staphylococcal or streptococcal, and to infection with Epstein-Barr virus. Infections are related to both quantitative and qualitative neutrophil, monocyte, and natural killer cell defects. May have lymphoma-like lymphoproliferative disease. Quantitative and qualitative abnormalities of platelet function, easy bruising/bleeding. In late stages can have lymphohistiocytic infiltrates and erythrophagocytosis.

Miscellaneous: Chédiak-Higashi syndrome is a disease of Aleutian mink, Hereford cattle, killer whales, cats, beige mice, and humans.

Anesthetic Considerations: Patients are highly susceptible to bacterial infections, and good perioperative aseptic technique is imperative. Patients often have photophobia and may be sensitive to the bright operating room lights. Bleeding dyscrasia is a contraindication to neuraxial anesthesia. Excessive operative blood loss may occur secondary to quantitative or qualitative defects in platelet function. Succinylcholine may be relatively

contraindicated in patients with a significant neuropathy because of the risk of hyperkalemia. Patients taking steroids to ameliorate the symptoms of the accelerated phase should receive perioperative stress dose steroids.

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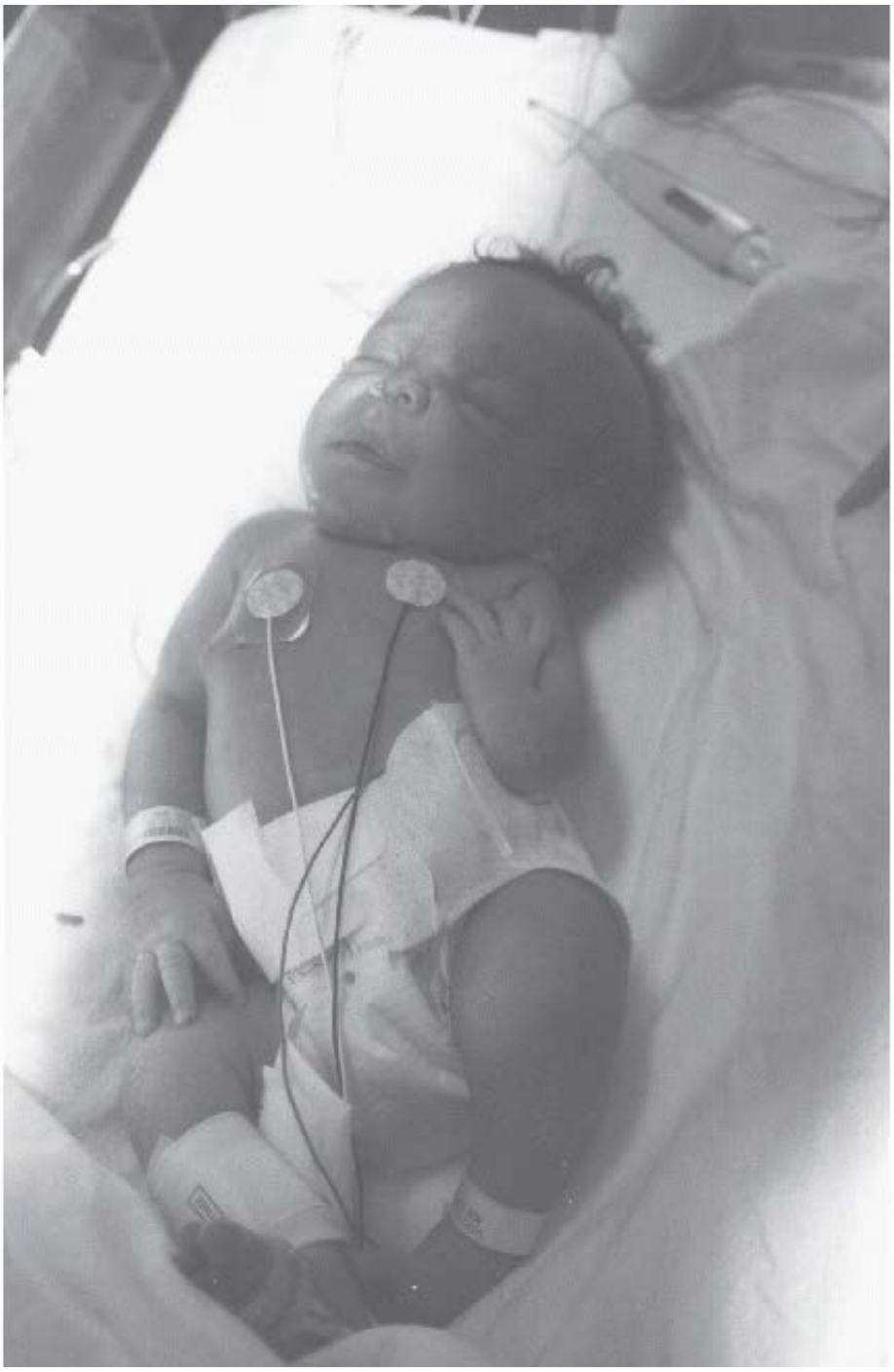
Chiari II malformation

See Arnold-Chiari malformation

CHILD syndrome

MIM #: 308050

CHILD is an acronym for **C**ongenital **H**emidysplasia with **I**chthyosiform erythroderma and **L**imb **D**efects. Congenital cardiac defects are also common. Most cases have been female, suggesting X-linked dominant inheritance with lethality in boys. The disorder is due to mutations in the gene *NSDHL* [NAD(P)H steroid dehydrogenase-like protein], which may be involved in cholesterol synthesis. Interestingly, the right side of the body is more often affected than the left. Left-sided disease is associated with cardiac defects. A variety of organs can be asymmetrically hypoplastic, ipsilateral to the side of ichthyosis and limb malformations.



CHILD syndrome. This 2.3-kg 16-day-old infant with complex congenital heart disease has CHILD syndrome. Note that her left humerus is shorter than the right and her left forearm is also shortened. Her left femur is shorter than her right, and she has bilateral clubfoot deformity and four fingers on her left hand.

HEENT/Airway: May have hearing loss. May have cleft lip. May have unilateral mandibular hypoplasia.

Chest: May have unilateral pulmonary hypoplasia. May have unilateral clavicular, scapular, or rib hypoplasia.

Cardiovascular: Congenital cardiac defects, especially atrial septal defects, ventricular septal defects, single coronary ostium, single ventricle.

Neuromuscular: May have mild intellectual disability. May have unilateral cortical, cranial nerve, brainstem, or spinal cord hypoplasia. Rare meningomyelocele.

Orthopedic: Unilateral hypomelia, varying from phalangeal hypoplasia to complete absence of a limb. Ipsilateral nail dysplasia. May have hypoplastic mandible, clavicle, scapula, ribs, or vertebrae ipsilateral to the affected limb. Joint contractures, webbing at the elbows and knees. May have scoliosis. May have unilateral pelvic hypoplasia.

GI/GU: May have umbilical hernia. Unilateral renal agenesis. Unilateral ovarian hypoplasia or fallopian tube hypoplasia.

Other: Congenital unilateral ichthyosiform erythroderma—erythematous, scaling skin, present at birth or soon thereafter. There is a sharp demarcation in the midline between normal and abnormal skin. Unilateral alopecia, hyperkeratosis. The face is usually spared. May have unilateral thyroid or adrenal hypoplasia.

Miscellaneous: Although the snappy acronym followed by many decades, the first description was by Otto Sachs in 1903.

Anesthetic Considerations: Peripheral intravenous access is limited in patients with significant limb defects. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Difficult laryngoscopy secondary to mandibular hypoplasia has not yet been reported. Renal insufficiency affects perioperative fluid management and the kinetics of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Patients with pulmonary hypoplasia may require heightened attention to perioperative ventilation.

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Cholesterol ester storage disease

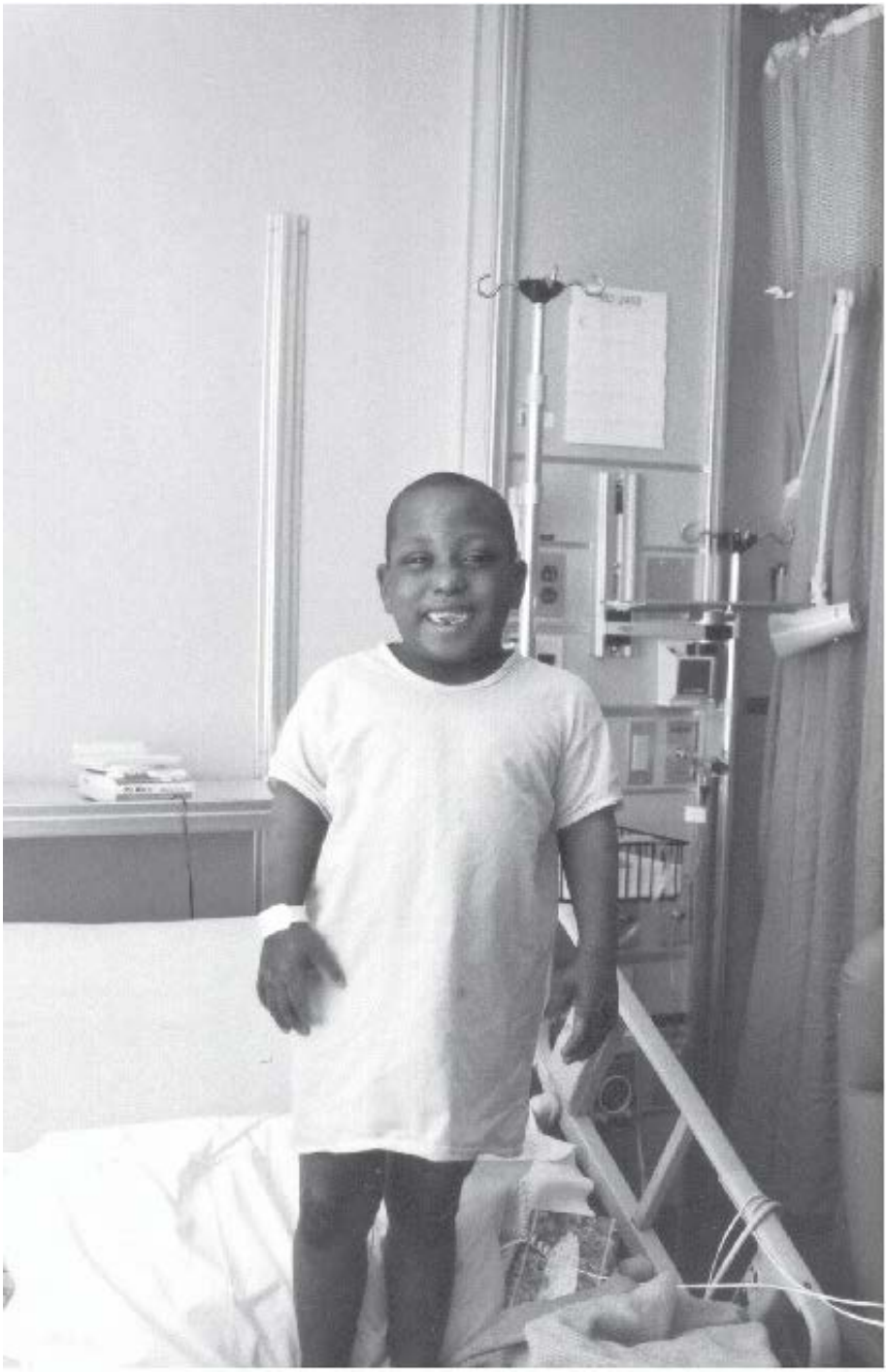
Included in Wolman disease

Chondrodysplasia punctata—autosomal recessive type

Synonym: Rhizomelic chondrodysplasia punctata

MIM #: 215100

This autosomal recessive type of chondrodysplasia punctata is characterized by rhizomelic limb shortening, vertebral clefting, and punctate epiphyseal calcifications.



Chondrodysplasia punctata—autosomal recessive type. This young boy with autosomal recessive chondrodysplasia punctata has obvious rhizomelic asymmetry of his arms. He is hyperactive with developmental delay.

Patients usually die in infancy or childhood. This disorder is due to a mutation in the *PEX7* gene, which encodes the peroxisomal type 2 targeting signal receptor, leading to quantitative or qualitative defects in peroxisomes. There are also X-linked dominant, autosomal dominant, and X-linked recessive types of chondrodysplasia punctata (see

following). The fetal warfarin syndrome (see later) is phenotypically similar to chondrodysplasia punctata.

HEENT/Airway: May have microcephaly. Frontal bossing. Flat facies. Bilateral cataracts. May have upward-slanting palpebral fissures. Flat nasal bridge with small nares. May have micrognathia. May have cleft palate.

Chest: Neonates are prone to respiratory insufficiency.

Neuromuscular: Severe intellectual disability. May exhibit spasticity. Cortical atrophy. Severely delayed myelination. Seizures.

Orthopedic: Dwarfism. Rhizomelic limb shortening (proximal limb shortening). Hypoplastic distal phalanges.

Coronal clefting of the vertebrae. Vertebrae may be dysplastic. Punctate epiphyseal calcifications and irregularity. Metaphyseal splaying. Joint contractures.

Other: Ichthyosis, which develops postnatally. May have alopecia. Laboratory abnormalities (elevated plasma phytanic acid and decreased red blood cell plasmalogen) can aide in diagnosis.

Miscellaneous: Chondrodysplasia punctata has also been described in the beagle.

Anesthetic Considerations: Neonates are prone to respiratory insufficiency. Patients must be carefully positioned perioperatively secondary to joint contractures. Patients with ichthyosis may be using topical agents with an oily base that prevents adhesives from sticking to their skin. Tubes and catheters may need to be sewn or tied into place perioperatively. In patients with severe ichthyosis, temperature regulation may be impaired. Small nares may impede passage of nasal or nasogastric tubes.

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Chondrodysplasia punctata— X-linked dominant and autosomal dominant types

Synonym: Conradi-Hünermann syndrome

MIM #: 302960, 118650

Also known as Conradi-Hünermann syndrome, this X-linked dominant type of chondrodysplasia punctata is characterized by asymmetric limb shortening and punctate epiphyseal calcifications that usually improve in the first year of life. The long-term prognosis is good because intelligence is usually normal, and the epiphyseal

abnormalities usually improve with age. The X-linked dominant form is due to defects in the emopamil binding protein gene (*EBP*), leading to elevated levels of sterol precursors. The autosomal dominant form is also referred to, perhaps inappropriately, as Conradi-Hünermann syndrome. The specific gene and gene product are unknown. There is an X-linked recessive form (*MIM #:* 302950) which is due to defects in the gene encoding arylsulfatase E (*ARSE*). There is also an autosomal recessive type of chondrodysplasia punctata (see preceding). The fetal warfarin syndrome (see later) is phenotypically similar to chondrodysplasia punctata.

HEENT/Airway: Frontal bossing. Flat facies. Down-slanting palpebral fissures. May have cataracts. May have abnormal external ears. May have hearing loss. May have microphthalmia, glaucoma. Low nasal bridge. Micrognathia. Short neck. Laryngeal and tracheal calcifications with associated tracheal stenosis. Laryngomalacia.

Cardiovascular: May have congenital cardiac defects, including patent ductus arteriosus, atrial septal defects, ventricular septal defects, pulmonary artery stenosis.

Neuromuscular: May have intellectual disability.

Orthopedic: May have mild to moderate growth deficiency. Asymmetric limb shortening related to areas of punctate epiphyseal calcification, but limb length not as profoundly shortened as in the autosomal recessive type. Scoliosis, related to areas of punctate calcification. May have joint contractures. May have vertebral anomalies, including hypoplasia, aplasia, clefting. May have odontoid hypoplasia or agenesis with atlantoaxial instability.

GI/GU: May have renal anomalies.

Other: Congenital ichthyosis. Large skin pores. Coarse, sparse hair. May have alopecia. May have failure to thrive in infancy. Elevated sterol precursor levels.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to the short neck and micrognathia. Patients who have laryngeal and tracheal calcifications with associated tracheal stenosis may need a smaller-than-expected endotracheal tube. Laryngomalacia may cause perioperative upper airway obstruction, which is usually responsive to positive pressure (positive end-expiratory pressure, continuous positive airway pressure). Patients with odontoid hypoplasia or agenesis may have atlantoaxial instability and an unstable cervical spine.

Patients with ichthyosis may be using topical agents on their skin. The oily base in these agents prevents adhesives from sticking to the skin. Perioperatively, tubes and catheters may need to be sewn or tied into place. In patients with severe ichthyosis, temperature regulation may be impaired. Patients must be carefully positioned and padded perioperatively secondary

to asymmetric limb shortening and joint contractures. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Chondrodystrophica myotonia

See Schwartz-Jampel syndrome

Chondroectodermal dysplasia

See Ellis-van Creveld syndrome

Christmas disease

See Hemophilia B

Chronic granulomatous disease

MIM #: 306400

Chronic granulomatous disease describes a genetically heterogeneous group of immunodeficiency disorders in which neutrophils are unable to deliver activated oxygen to the phagocytic vacuole. Thus, neutrophils can phagocytize but cannot kill fungi or catalase-negative bacteria, resulting in severe fungal or bacterial infections in a variety of organs and tissues. Chronic infections can lead to the formation of noncaseating granulomas. Most cases are X-linked recessive and caused by abnormalities in each of five polypeptides required for NADPH oxidase (phox) activity. Rare forms are autosomal recessive. Very rarely, this can disease present for the first time in previously healthy, older adults.

HEENT/Airway: Ulcerative stomatitis and gingivitis.

Chest: There may be sequelae of chronic pulmonary infections with granulomatous infiltration or fibrosis.

Orthopedic: Osteomyelitis.

GI/GU: There may be granulomas throughout the gastrointestinal tract leading to local complications. Esophageal strictures. There may be splenic infections and perirectal and perianal abscesses and fistulae. There may be granulomatous ureteral strictures, or bladder involvement with urinary obstruction. Tubo-ovarian abscesses may develop in female patients.

Other: May have cutaneous granulomas, lymphadenitis, lymphadenopathy. Discoid lupus in carriers or in adults with mild disease. Large deletions may also affect the Kell red blood cell blood group system, which lies adjacent on the X chromosome.

Miscellaneous: Originally known as fatal granulomatous disease of childhood, with the development of effective treatment it has become known as chronic granulomatous disease. The disease has been treated with gamma-interferon, bone marrow transplantation, and gene therapy.

Anesthetic Considerations: Good aseptic technique is of particular importance, as is maintaining any antibiotic/antifungal dosing schedule. Chronic use of aminoglycosides or amphotericin can affect renal function. Potential sites of infection (e.g., wound, catheter) must be monitored carefully postoperatively. Double-lumen endobronchial tubes may be of use in thoracic surgery to minimize spillage of infectious materials from one lung to the other. Granulomatous lesions of the gastrointestinal tract may involve the gastroesophageal sphincter or may delay gastric emptying. For this reason, rapid sequence induction of anesthesia has been recommended (3). A small number of patients may have abnormalities in the Kell red blood cell blood group system. This could delay the availability of blood or limit the amount of blood that can be made available.

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Citrullinemia

See Argininosuccinic acid synthetase deficiency

Citrullinuria

See Argininosuccinic acid synthetase deficiency

Cleidocranial dysostosis

See Cleidocranial dysplasia

Cleidocranial dysplasia

Synonym: Cleidocranial dysostosis

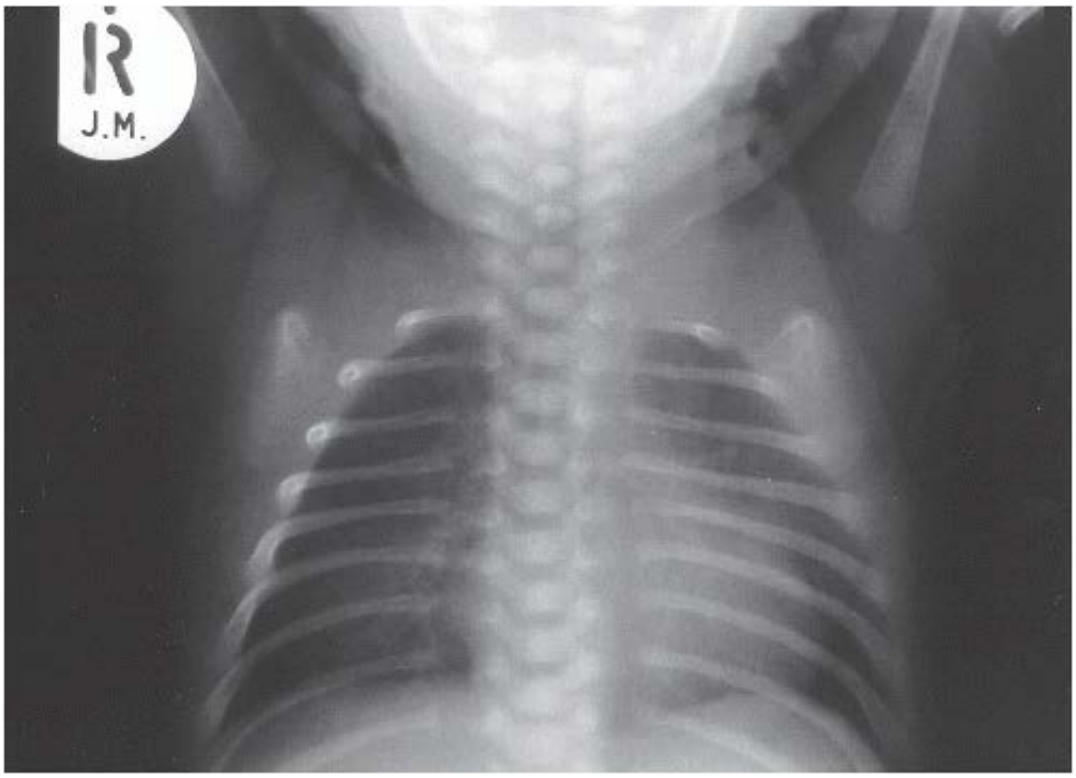
MIM #: 119600

This autosomal dominant disorder is characterized by dysplasia of osseous and dental tissue. The most frequent defects are seen in the clavicle and the cranium, hence the name “cleidocranial.” There is wide variability in the clinical expression of this syndrome. The gene responsible for this disorder encodes transcription factor CBFA1, and the gene is known as *RUNX2*. *RUNX2* (homologous to the “runt domain”) is an osteoblast-specific transcription factor. It is the osteogenic “master switch” and is a regulator of osteoblast differentiation. One-third of patients represent a new mutation.

HEENT/Airway: Brachycephaly, thick calvarium, delayed and poor calcification of cranial sutures, wormian bones.

Frontal, parietal, and occipital bossing. Very delayed closure of the fontanelles; may be open in adults. Midfacial hypoplasia. Hypoplastic sinuses and mastoid air cells. Hypertelorism. May have hearing loss. Low nasal bridge. High-arched palate; may have cleft palate. Dental abnormalities, including delayed eruption, enamel hypoplasia, root abnormalities, dental caries. May have micrognathia. May have abnormality of temporomandibular joint. Hypoplastic hyoid bone.

Cleidocranial dysplasia. FIG. 1. This brother and sister have cleidocranial dysplasia. Note the narrow upper chest and sloping shoulders.



Cleidocranial dysplasia. FIG. 2. Chest radiograph of a child with cleidocranial dysplasia. Note the absent clavicles. (Courtesy of Dr. Philip A. Henning, Neonatal Service, Tygerberg Children's Hospital, Cape Town, South Africa.)

Chest: Small, narrow thoracic cage with short ribs. Cervical ribs. Aplastic or hypoplastic clavicles. Neonatal respiratory distress.

Cardiovascular: May have subclavian artery damage from the clavicular anomaly.

Neuromuscular: Intelligence is usually normal. Syringomyelia. Large foramen magnum.

Orthopedic: Short stature. Hypoplastic or aplastic clavicles. May have hypoplastic phalanges. Joint hypermobility. Delayed calcification of pubic bone with wide symphysis pubis. Hypoplastic iliac bones, narrow pelvis. May have coxa vara. Vertebral abnormalities, scoliosis, kyphosis, spondylosis, spondylolisthesis. Bones susceptible to fracture.

Miscellaneous: A Neanderthal skull with features of cleidocranial dysostosis has been described (6). It has also been postulated that Thersites, a character in the *Iliad*, had this disorder (5).

Anesthetic Considerations: Hypoplasia or aplasia of the clavicles alters the landmarks for insertion of a subclavian intravenous catheter or placement of an infraclavicular block. Vertebral abnormalities may

make neuraxial techniques difficult. Dental abnormalities should be documented preoperatively. Root abnormalities or severe dental caries predispose the teeth to loss during direct laryngoscopy. A single patient with limited mouth opening secondary to temporomandibular joint deformity has been reported. Patients should be

carefully positioned and padded because their joints are lax and their bones are fragile and susceptible to fracture. Given the single reported case of an adult with arm ischemia from impingement of the subclavian artery, documentation of arm pulses after positioning is encouraged. A narrow thoracic cage can lead to respiratory distress in early infancy and decreased perioperative respiratory reserve at any age.

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Clouston syndrome

MIM #: 129500

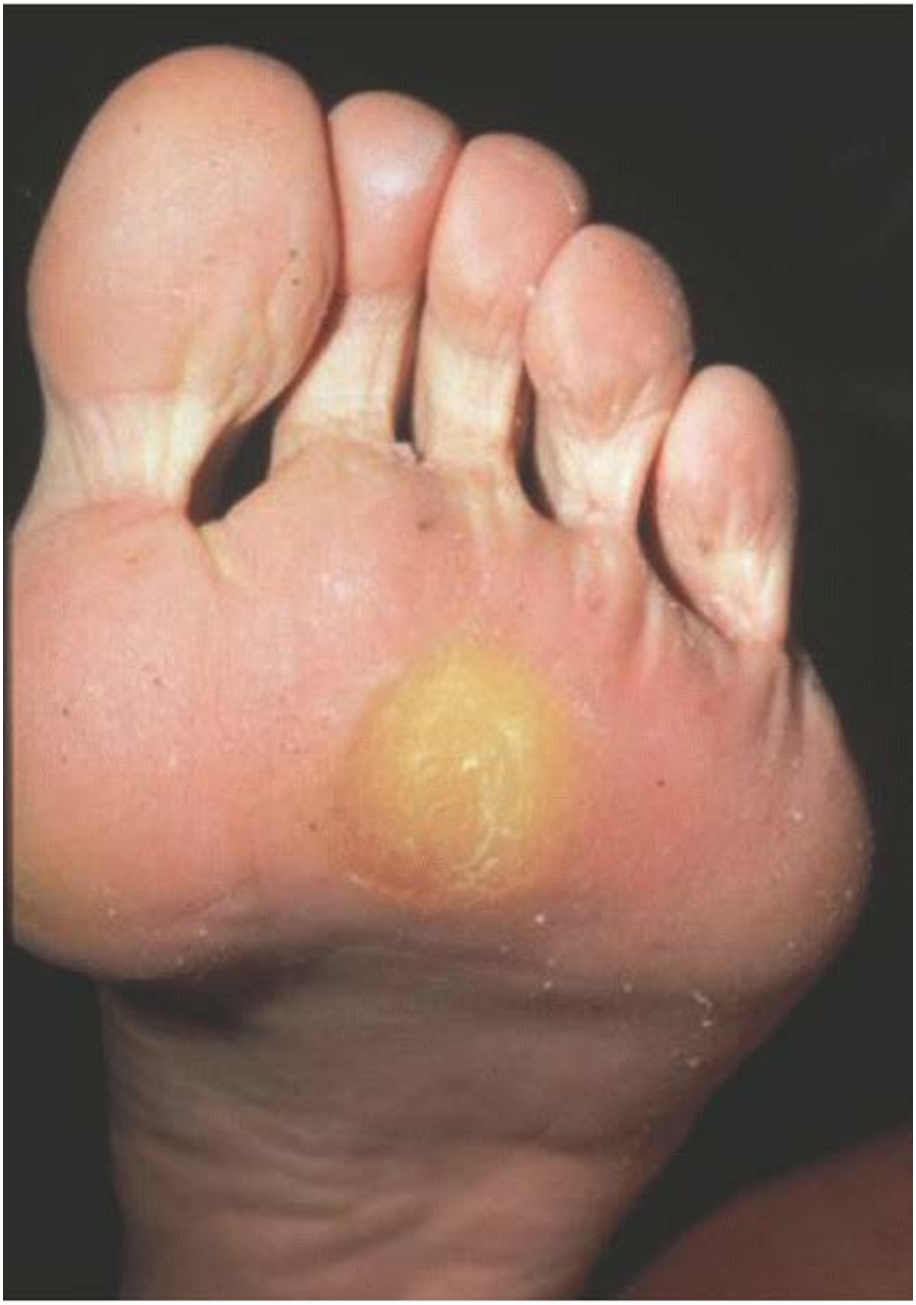
This autosomal dominant hidrotic ectodermal dysplasia consists of nail dysplasia, palmar and plantar dyskeratosis, and alopecia. It is caused by mutations in the gene *GJB6* (gap junction protein, beta-6), which encodes a connexin. Connexins are the protein subunits for gap junctions. Unlike forms of hypohidrotic ectodermal dysplasia, patients with hidrotic ectodermal dysplasia have normal sweat and sebaceous gland function.

HEENT/Airway: Thick skull. Hypoplastic or absent eyebrows and eyelashes, strabismus. May have cataracts or photophobia. Teeth are normal.

Neuromuscular: May have intellectual disability.

Orthopedic: May have short stature. Nail dysplasia. May have clubbing of the fingers.

Other: Thickened palmar and plantar dyskeratosis. Hair hypoplasia. Alopecia or fine, brittle hair. Alopecia may be more total in females. Hyperpigmentation over joints and intertriginous areas. Sweat production is normal. Severe nail changes with onychodystrophy, onycholysis, nail hypoplasia, and thick, discolored nails.



Clouston syndrome. Dyskeratosis on the sole in Clouston syndrome. (Courtesy of Dr. Neil Prose, Department of Dermatology, Duke University.)

Anesthetic Considerations: Dental abnormalities, typical of other ectodermal dysplasias, are not seen in Clouston syndrome. Sweat production is normal, so perioperative thermoregulation is maintained. Patients with photophobia may be sensitive to bright operating room lights.

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Cloverleaf skull

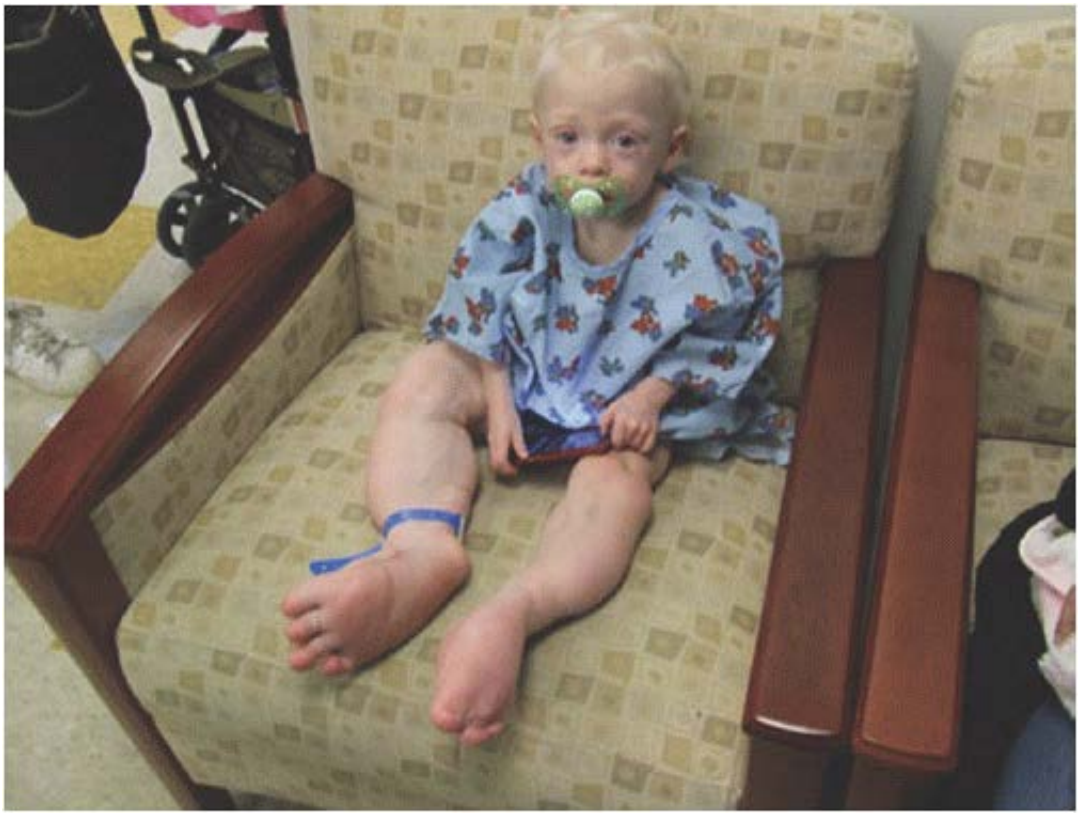
See Kleeblattschaedel

CLOVES syndrome

MIM #: 612918

This syndrome consists of **C**ongenital **L**ipomatous **O**vergrowth, **V**ascular malformations, **E**pidermal nevi and **S**keletal/spinal abnormalities. It is due to postzygotic somatic activating mutations (with

mosaicism) for the gene *PIK3CA*, encoding a subunit of phosphatidylinositol 3-kinase. Mutations in this gene can be found also in patients with Klippel-Trenaunay-Weber syndrome, which has features overlapping with CLOVES syndrome, and in some cancer cells. The low rate of malignant transformation in CLOVES syndrome is thought to be due to the endogenous presence of some enzyme activity due to the mosaicism. Hemihypertrophy is a major feature.



CLOVES syndrome. FIG. 1. This 2-year-old girl has obvious lipomatous changes of her feet and legs, as well as an enlarged left kidney.

HEENT/Airway: Hyperostosis of the skull.

Cardiovascular: Progressive arteriovenous malformations with skin involvement. Venous, capillary, and lymphatic malformations. Rare venous thrombosis or thromboembolism.

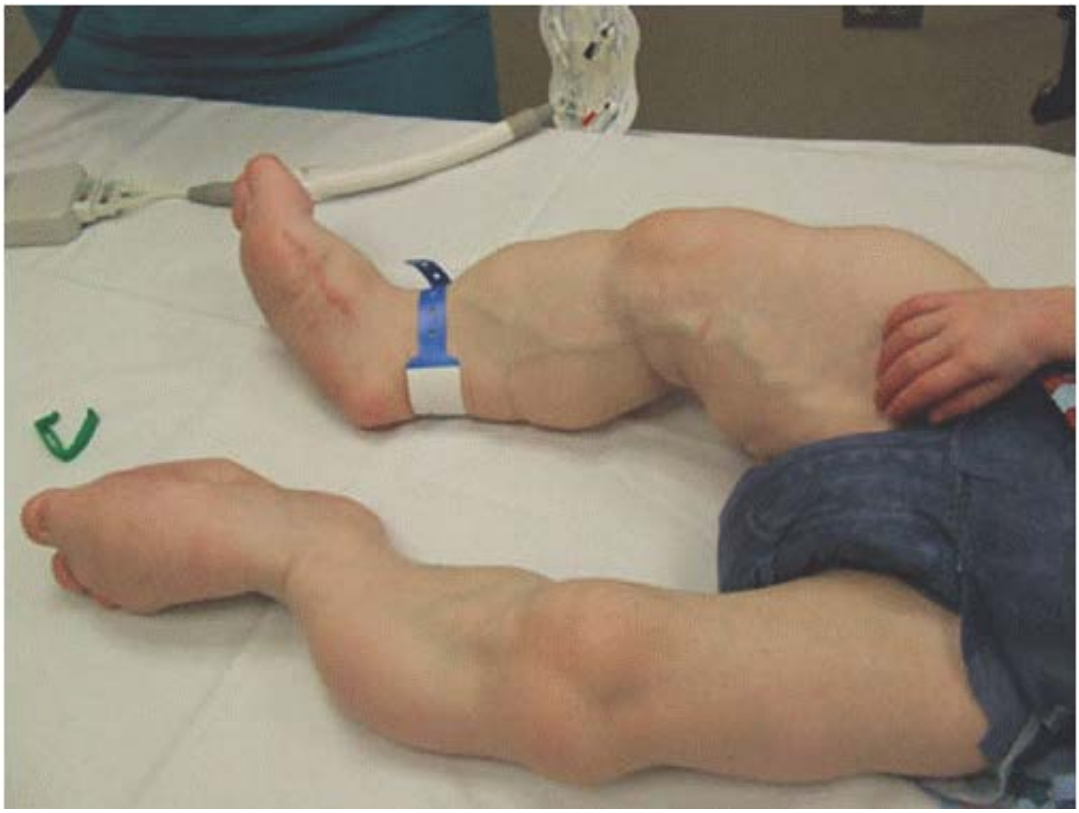
Neuromuscular: Can have perispinal vascular malformations. Uncommon neural tube defects.

Orthopedic: Hemihypertrophy. Wide hands and feet. Large “sandal gap” deformity. Macrodactyly. Can have scoliosis. Uncommon patellar chondromalacia or dislocation. Can have soft tissue lipomas or lipohypoplasia.

GI/GU: Splenomegaly, splenic cysts. Testicular cysts. Can have renal hypoplasia or agenesis.

Other: Overgrowth of palmar skin and furrowed skin over soles of the feet.

Miscellaneous: This acronym was selected in part because it is a Middle English word for weight, about 8 pounds, although the connection escapes us.



CLOVES syndrome. FIG. 2. A close up of the leg changes of the girl in Figure 1.

Anesthetic Considerations: There is an increased incidence of perioperative pulmonary embolism. Thoracic phlebectasia could complicate central venous catheter placement, particularly via the subclavian route. The potential presence of perispinal vascular malformations mandates caution when considering neuraxial blocks.

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Cobalamin (A-G) deficiency

MIM #: 251100, 251110, 277400, 277410, 236270, 277380, 250940

There are seven distinct autosomal recessive abnormalities that result in defective intracellular metabolism of cobalamin. The cobalamins (Cbl) are cobalt-containing organometallic substances. The basic structure of the

cobalamins is vitamin B_{12}. Once absorbed from the gastrointestinal tract and transported to the cells [complexed with transcobalamin II (see later, Transcobalamin II deficiency)], cells endocytose the complexes, dissociate the transcobalamin II, and either methylate cobalamin in the cytoplasm (forming Me Cbl, required for the enzyme methylmalonyl CoA mutase) or adenosylate it in the mitochondria (forming Ado Cbl, required for *N*-5-methyltetrahydrofolate methyltransferase).

Cobalamin A and B defects lead to abnormal adenosylcobalamin synthesis and result in methylmalonic

acidemia (see later). Treatment with cobalamin (cyanocobalamin or hydroxocobalamin) results in improvement for most cobalamin A patients and some cobalamin B patients. Cobalamin E and G abnormalities affect only Me Cbl and produce homocystinuria with hypomethioninemia (see later). Treatment with cobalamin corrects the clinical problem. Cobalamin C, D, and F abnormalities affect the synthesis of both Me Cbl and Ado Cbl. Patients with cobalamin C and D mutations have methylmalonic aciduria and homocystinuria. Patients with cobalamin C defects tend to be more severely affected. Cobalamin F results in mild methylmalonic acidemia.

Other: In general, disorders affecting only Ado Cbl produce metabolic ketoacidosis in young infants. Me Cbl defects present as failure to thrive and megaloblastic changes. Disorders affecting both forms result in a variable combination of the two phenotypes.

Miscellaneous: Cobalamin was first described as “extrinsic factor,” the complement to “intrinsic factor,” which is the transport factor necessary for the absorption of vitamin B_{12} in the distal ileum. The discoverers of this factor won the Nobel Prize in Medicine in 1934.

Anesthetic Considerations: See under the specific type of amino acid disorder caused, methylmalonic acidemia or homocystinuria.

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Cocaine

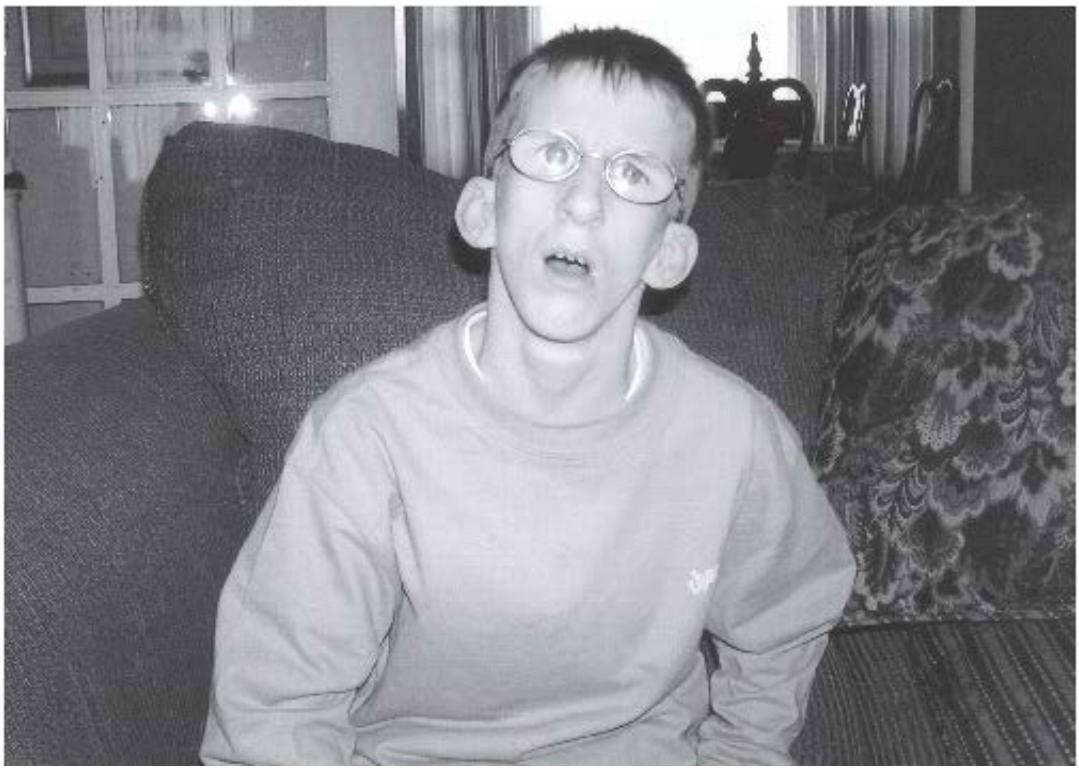
See Fetal cocaine effect

Cockayne syndrome

MIM #: 216400, 133540

This autosomal recessive disease has multisystem findings, including precocious senile-like changes, growth failure, intellectual disability, accelerated atherosclerosis, retinal degeneration, optic atrophy, sensorineural hearing loss, and photosensitivity dermatitis. Cockayne syndrome has been divided into an early-onset form (congenital) and a late-onset form (onset in early childhood). The pathogenesis of both forms appears to be similar. There is decreased ability to repair ultraviolet light-induced damage to DNA strands. The two types of the disorder are due to mutations in the DNA repair genes *ERCC8* (Type A) or *ERCC6* (Type B). Patients with the early-onset form of

Cockayne syndrome usually die in childhood, those with the late-onset form die in their early teens. DNA repair mechanisms are abnormal in four other inherited diseases: ataxia-telangiectasia, Fanconi anemia, Bloom syndrome, and xeroderma pigmentosum.



Cockayne syndrome. Typical facies in a young man with Cockayne syndrome.

HEENT/Airway: Microcephaly, thick calvarium. Gaunt face (lacking subcutaneous fat) with a long, slender nose. Retinal degeneration, cataracts, optic atrophy, nystagmus, miotic pupils. Decreased lacrimation. Sensorineural hearing loss. Dental abnormalities include delayed eruption, missing teeth, hypoplastic teeth, dental caries, malocclusion. Small mandible.

Chest: Pneumonia is common, and often is a contributing cause of death.

Cardiovascular: Premature hypertension, coronary atherosclerosis, and peripheral vascular disease. May have cardiac arrhythmias.

Neuromuscular: Progressive intellectual disability. Intracranial calcifications, especially in the basal ganglia, resulting in unsteady gait, ataxia, tremor, incoordination, dysarthric speech. Muscle atrophy. May have increased ventricular size, cerebral atrophy, demyelination of subcortical white matter, peripheral neuropathy. Seizures may develop. May have accelerated cerebral atherosclerosis.

Orthopedic: Growth failure. Relatively short trunk such that the limbs appear inappropriately long. Limited joint mobility with formation of flexion contractures. Vertebral abnormalities, kyphosis. Osteoporosis may develop.

GI/GU: Gastroesophageal reflux. Progressive renal disease in some. May have hepatomegaly, splenomegaly.

Other: Photosensitivity dermatitis. Thin, dry skin. Thin, dry, prematurely gray hair. Absence of subcutaneous fat. Impaired sweat production. Cool hands and feet, which sometimes appear cyanotic. Rare basal cell carcinomas.

Miscellaneous: Edward Cockayne, of the Great Ormond Street Hospital, London, was a pioneer in the study of genetic diseases and the skin. As a hobby, he developed a very large collection of butterflies and moths and was in fact awarded the Order of the British Empire for his services to entomology.

Anesthetic Considerations: A small mandible and normal (for age)-sized teeth has made direct laryngoscopy difficult (8,9). Fiberoptic intubation using a laryngeal mask has been successful (8). The trachea may be smaller than expected and may require a smaller-than-expected endotracheal tube (1,7). Gastroesophageal reflux is common, and patients may be at increased risk for perioperative aspiration. However, mask inductions and laryngeal mask airways (LMAs) have been used successfully (7,8). Dental abnormalities should be documented before surgery. Decreased lacrimation increases the risk of corneal abrasion, and the eyes should be adequately protected. Note that the pupils may be miotic at baseline. Impaired sweat production may lead to perioperative hyperthermia. The hands may be cool and cyanotic appearing, even when there is no arterial desaturation. Patients must be carefully positioned and padded secondary to contractures. Contractures may make vascular access more challenging.

Patients may have hypertension or peripheral vascular disease. Accelerated coronary atherosclerosis and cardiac arrhythmias are of particular concern. Consideration should be given to evaluating for ischemic cardiac disease. A report suggested that nifedipine-induced hypotension may have caused transient cerebral ischemia, possibly related to cerebral atherosclerotic disease (6).

Patients with significant renal disease need careful titration of perioperative fluids and consideration of the mode of metabolism in choosing anesthetic drugs. Chronic use of anticonvulsant medication alters the metabolism of some anesthetic drugs. Succinylcholine-induced hyperkalemia has not been reported but is a potential concern in patients with muscle atrophy or advanced renal disease. Prolonged anesthetic recovery has been reported in one patient.

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Coenzyme Q-cytochrome c reductase deficiency

See Complex III deficiency

Coffin-Lowry syndrome

MIM #: 303600

This X-linked dominant disorder is characterized by intellectual disability, short stature, coarse facies, down-slanting palpebral fissures, a bulbous nose, and puffy hands with tapering fingers. Most cases occur sporadically. This disorder is caused by mutations in the *RSK2* gene. The RSK genes encode growth factor-regulated serine-threonine kinases. Female heterozygotes have more mild manifestations.

HEENT/Airway: May have microcephaly, thick calvarium, delayed closure of anterior fontanelle. Hypoplastic sinuses. Coarse facies, which worsen with age. Midfacial hypoplasia. Down-slanting palpebral fissures, hypertelorism. Heavy arched eyebrows. Large, protuberant ears. May have sensorineural hearing loss. Short, broad, bulbous nose, anteverted nares. Wide mouth, thick lower lip. Dental abnormalities including hypoplastic teeth, malocclusion, premature loss, and large medial incisors.

Chest: Short bifid sternum. Pectus carinatum or excavatum.

Cardiovascular: May have mitral regurgitation. May have dilated cardiomyopathy. Rare restrictive cardiomyopathy.

Neuromuscular: Severe intellectual disability. Severe speech delay—may never acquire speech. Hypotonia. May have dilated lateral ventricles, seizures. May have calcification of the ligamentum flavum, with resultant

narrowing of the spinal canal and subsequent radiculopathy. Can have nonepileptic drop attacks, with features of cataplexy and hyperekplexia.

Orthopedic: Short stature. Puffy hands with tapering fingers. Small fingernails. “Drumstick” terminal phalanges. May have simian creases. Flat feet. Hypermobile joints. Vertebral dysplasia. Cervical lordosis. Thoracolumbar kyphoscoliosis. Characteristic stooped posture.

GI/GU: Inguinal hernia. Rectal or uterine prolapse.

Other: Cutis marmorata. Dependent acrocyanosis.

Miscellaneous: This syndrome was described by Coffin et al. in 1966 and then by Lowry et al. in 1971. These were later recognized as the same syndrome.

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Patients are prone to premature tooth loss. Peripheral vascular access may be difficult secondary to puffy hands. Patients must be carefully positioned secondary to hypermobile joints. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients with cardiomyopathy require an appropriately tailored anesthetic. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

Calcification of the ligamentum flavum has been reported, with resultant narrowing of the spinal canal and subsequent radiculopathy. It may be wise to avoid regional anesthesia if there is evidence of a radiculopathy. If regional anesthesia is undertaken, note that there may be technical difficulties finding the epidural or subarachnoid space and that a decreased amount of drug may be needed in the narrowed subarachnoid space.

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Coffin-Siris syndrome

MIM #: 135900

This possibly autosomal recessive syndrome is characterized by intellectual disability, coarse facies, hypoplastic to absent fifth fingers, and hypoplastic toenails. The clinical features are highly variable, and multiple genes have been implicated in the Coffin-Siris phenotype. Most affected individuals are females. Similar nail changes have been observed in the fetal hydantoin syndrome.

HEENT/Airway: Microcephaly. Coarse facies. Thick eyebrows, long eyelashes. May have hypotelorism, ptosis, strabismus, nystagmus. May have hearing loss. Preauricular skin tag. Depressed nasal bridge, broad nose, anteverted nares. Long philtrum. Wide mouth, thick lips, macroglossia. May have choanal atresia, cleft palate. Delayed dentition. Short neck.

Chest: Recurrent upper and lower respiratory tract infections are common. May have diaphragmatic hernia.

Cardiovascular: May have a congenital cardiac defect, including patent ductus arteriosus, atrial septal defect, ventricular septal defect, tetralogy of Fallot.

Neuromuscular: Intellectual disability. Speech delay. May exhibit aggressive behavior. Hypotonia. May have agenesis of the corpus callosum, Dandy-Walker malformation. Seizures.

Orthopedic: Short stature. Hypoplastic or absent digits, especially the fifth finger and fifth toe. Hypoplastic toenails. Clinodactyly. Hypermobility of joints. Radial dislocation at the elbow. Coxa valga. May have vertebral abnormalities. Sacral dimple.

GI/GU: May have inguinal or umbilical hernias, intussusception, malrotation of the gut, gastric outlet obstruction, duodenal redundancy. May have renal anomalies including hydronephrosis, ureteral stenosis, microureter, ectopic kidney. Cryptorchidism, absent uterus.

Other: Sparse scalp hair with generalized hirsutism. Cutis marmorata. One patient has been reported in whom recurrent hypoglycemia developed.

Anesthetic Considerations: A smooth induction of anesthesia may be difficult in patients with aggressive behavioral characteristics. Direct laryngoscopy and tracheal intubation may be difficult secondary to facial dysmorphism (1). It has been suggested that the dysmorphic features worsen with age, and a patient has been reported who underwent uncomplicated anesthesia as a child but whose trachea could not be successfully intubated as a 45-year-old (5). Upper and lower respiratory tract infections are common in these patients. Acutely, this may lead to cancellation of an anesthetic. Chronically, this may indicate the presence of residual lung disease in patients, with subsequent

increased risk of postoperative pulmonary complications. Choanal atresia, if present, precludes the use of a nasal airway or a nasogastric tube. Patients must be carefully positioned secondary to hypermobility of the joints. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

One patient has been reported who had recurrent hypoglycemia. The cause of the hypoglycemia is unknown. The possibility of perioperative hypoglycemia should be kept in mind, particularly during a general anesthetic.

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COFS syndrome

See Cerebrooculofacioskeletal syndrome

Cohen syndrome

MIM #: 216550

This autosomal recessive disorder is distinguished by intellectual disability, hypotonia, muscle weakness, obesity, and prominent upper central incisors. The disorder is due to abnormalities in the gene *COH1*. The exact role of the large, complex protein product of this gene is unknown, but it may be a Golgi-specific matrix protein that is required for Golgi integrity.

HEENT/Airway: Microcephaly. Malar hypoplasia, down-slanting palpebral fissures. Poor vision, retinal anomalies, strabismus. May have microphthalmia, coloboma. Large ears. High nasal bridge. Short philtrum. Prominent upper central incisors, open mouth. High-arched palate. Mild micrognathia. May have increased susceptibility to oral cavity infections.

Cardiovascular: May have a cardiac anomaly, especially mitral valve prolapse.

Neuromuscular: Intellectual disability, hypotonia, and muscle weakness. Motor delay. Cheerful disposition. May have cerebellar hypoplasia. May have seizures. Autistic-like behavioral problems.

Orthopedic: May have short stature. Narrow hands and feet, long fingers and toes. Simian creases. Joint hypermobility. Genu valgus, cubitus valgus. Lumbar lordosis, scoliosis. Narrow feet.

GI/GU: May have hiatal hernia with gastroesophageal reflux. May have periureteral obstruction.

Other: Central obesity starting in childhood. May have intermittent neutropenia. Delayed puberty.

Miscellaneous: Cohen syndrome is relatively common in Finland.

Anesthetic Considerations: The prominent upper central incisors must be carefully avoided during laryngoscopy. Difficult laryngoscopy and intubation has been reported in an adult (1). Venous access and identification of landmarks for regional anesthesia may be difficult secondary to obesity. Obesity may result in desaturation with induction of anesthesia because of increased airway closure and decreased functional residual capacity. Obesity is also a risk factor for perioperative aspiration. Patients must be carefully positioned perioperatively secondary to hyperextensibility of the joints. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Patients with hypotonia and muscle weakness might be at risk for hyperkalemia after the administration of succinylcholine. Although patients may have intermittent neutropenia, they do not appear to have an increased risk of infection. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Collodion membranes

Included in Ichthyosis

Complex I deficiency

Synonym: NADH-coenzyme Q reductase deficiency; NADH-ubiquinone oxidoreductase

MIM #: 252010

There are a total of five protein complexes that make up the mitochondrial electron transport chain. Complex I has at least 36 polypeptide subunits that are encoded by nuclear DNA and 7 that are encoded by mitochondrial DNA. Thus, both nuclear and mitochondrial gene defects can lead to defects in complex I. Electrons are transferred independently by complexes I and II to coenzyme Q and then sequentially to complexes III and IV. Complex V converts ADP to ATP. Complex I is capable of utilizing both pyruvate (when complexed to malate) and glutamate as carbon sources. Complex II can only utilize succinate. Complex I deficiency is the most common oxidative phosphorylation enzymatic defect. Specific mutations can present as Leber hereditary optic neuropathy, Leigh disease, or MELAS (see later for each). Complex I deficiency is also commonly seen in combination with deficiencies in other complexes in the electron transport chain. The phenotype is highly variable.

HEENT: Macrocephaly. Leber hereditary optic neuropathy (see later).

Chest: Neonatal respiratory distress.

Cardiovascular: Cardiomyopathy, biventricular hypertrophy.

Neuromuscular: Encephalopathy, seizures. Myopathy, with generalized muscle weakness and muscle wasting. Fatigue to exercise, fasting, and ethanol. Mitochondria in muscles have abnormal morphology with inner and outer membranes arranged in whirls.

GI/GU: Poor feeding, vomiting. Hypospadias, micropenis.

Other: Hypoglycemia. Lactic acidemia, worse with exercise.

Anesthetic Considerations: Patients are at risk for perioperative respiratory failure and must be monitored closely both during and after surgery for signs of respiratory insufficiency. There is a report of three patients with Leigh disease (which can occur in complex I deficiency) in whom respiratory failure was precipitated by general

anesthesia, leading to death. All three patients had preoperative respiratory abnormalities. Patients with complex I deficiency can have a cardiomyopathy, so cardiac function should be evaluated preoperatively and the anesthetic should be tailored appropriately. Patients should not undergo a protracted perioperative fast without concomitantly receiving an intravenous glucose-containing solution. Patients with lactic acidemia should not receive lactated Ringer's solution. Perioperative serum glucose levels should be monitored closely. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemia. Patients may be sensitive to nondepolarizing neuromuscular blocking agents. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates, propofol, and volatile anesthetics can inhibit mitochondrial respiration, anesthesia with each of these drugs has been used without any complications in patients with mitochondrial defects. Patients with complex I deficiency have been shown to be sensitive to isoflurane and sevoflurane (2,5), but sevoflurane has been used successfully. Propofol has been used successfully as the primary anesthetic (6), although some would avoid it in these patients. Mitochondrial myopathy does not convey an increased susceptibility to malignant hyperthermia.

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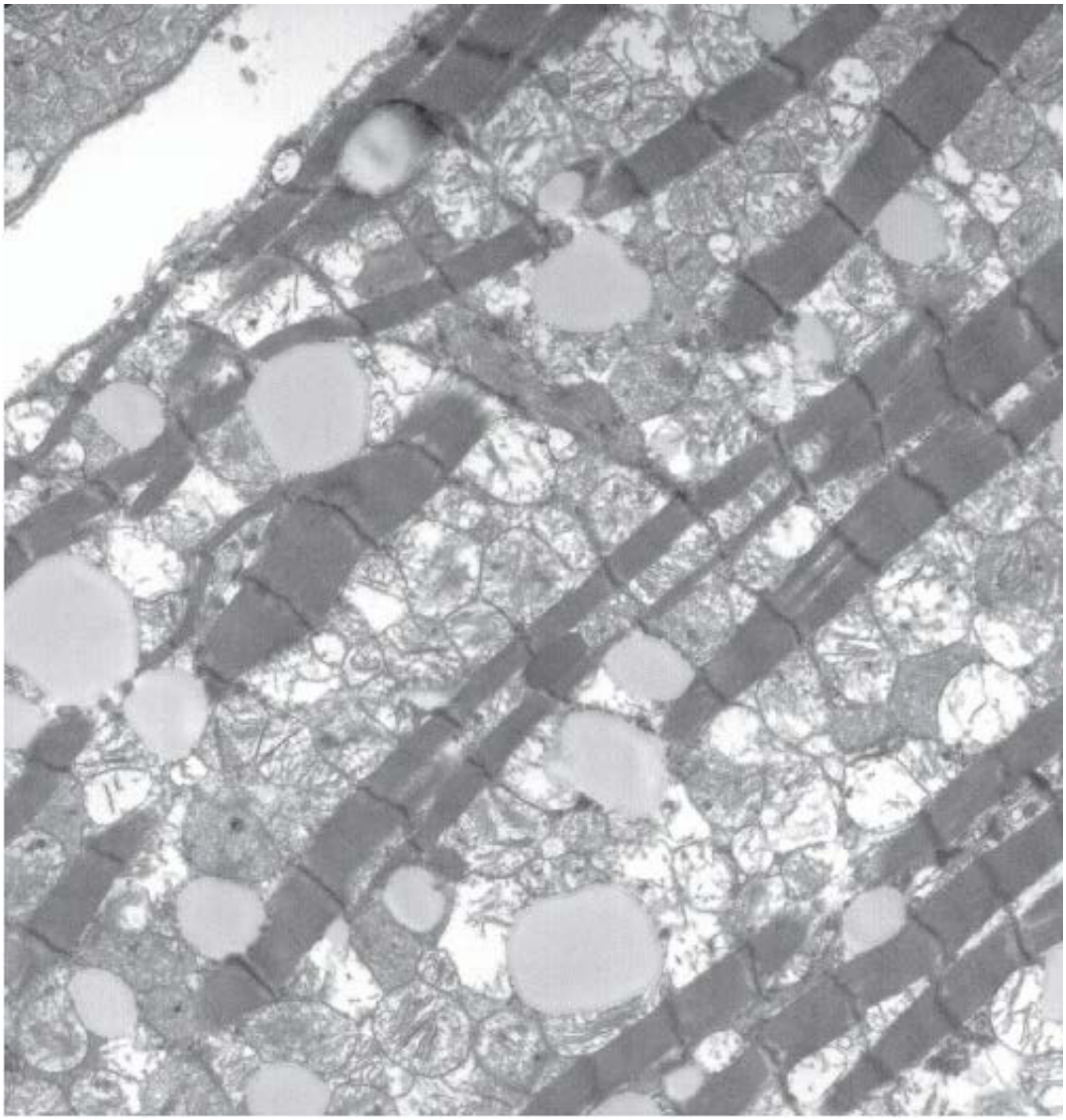
Complex II deficiency

Synonym: Succinate-coenzyme Q reductase deficiency

MIM #: 252011

This autosomal recessive disorder involves one of the five protein complexes that make up the mitochondrial electron transport chain. Unlike the other four, this enzyme is coded for solely by nuclear (and not a combination of nuclear and mitochondrial) DNA. Four nuclear-encoded proteins form the complex. Electrons are transferred independently by complexes I and II to coenzyme Q and then sequentially to complexes III and IV. Complex V converts ADP to ATP. Complex I is capable of utilizing both pyruvate (when complexed to malate) and glutamate as carbon sources. Complex II can only utilize succinate.



Complex II deficiency. Cardiac pathology from a 2-year-old girl with complex II deficiency who died while awaiting heart transplantation. This electron micrograph shows a proliferation of large abnormal mitochondria with simplified architecture of the cristae.

Cardiovascular: May have isolated hypertrophic cardiomyopathy.

Neuromuscular: Progressive encephalopathy with dementia. Myoclonic seizures. Spastic quadriplegia.

Orthopedic: Small stature.

GI/GU: Hepatic cirrhosis has been reported in a patient with complex II/III deficiency.

Other: Lactic acidemia.

Anesthetic Considerations: Patients with complex II deficiency can have a hypertrophic cardiomyopathy, so cardiac function should be evaluated preoperatively. Patients should not undergo a protracted perioperative fast without concomitantly receiving an intravenous glucose-containing solution. Patients with lactic acidemia should not receive lactated Ringer's solution. Perioperative serum glucose levels should be monitored closely. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemia. Patients may be sensitive to nondepolarizing neuromuscular blocking agents. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates, propofol, and volatile anesthetics can inhibit mitochondrial respiration, anesthesia with each of these drugs has been used without any complications in patients with mitochondrial defects. However, complex II deficiency has been implicated in a case of a child who developed metabolic acidosis from the propofol infusion syndrome (4). Hepatic disease can affect the binding and metabolism of some anesthetic drugs. Mitochondrial myopathy does not convey an increased susceptibility to malignant hyperthermia.

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Complex III deficiency

Synonym: Coenzyme Q-cytochrome c reductase deficiency; Ubiquinone-cytochrome c oxidoreductase deficiency

MIM #: 516020

Complex III includes mitochondrial cytochrome b and is one of five protein complexes that make up the mitochondrial electron transport chain. This is the second enzyme in the sequence, and catalyzes the transfer of electrons from reduced coenzyme Q10 to cytochrome c. The energy generated is used to translocate protons from the inside to the outside of the mitochondrial inner membrane. This disorder may be inherited as a mitochondrial gene defect, and thus, it can be maternally transmitted. It is one of the least commonly identified respiratory chain disorders. Specific mutations can present as Leber hereditary optic neuropathy (see later). Onset of symptoms is in the second and third decades.

HEENT/Airway: External ophthalmoplegia or other ocular myopathy, ptosis, sudden swollen optic disc, Leber hereditary optic neuropathy (see later) with sudden central field defect.

Cardiovascular: Cardiomyopathy with evidence of abnormal accumulations of mitochondria.

Neuromuscular: Headaches. Myopathy, easy fatigability, areflexia. Encephalopathy, dementia.

GI/GU: Dysphagia. Hepatic cirrhosis has been reported in a patient with complex II/III deficiency.

Other: Lactic acidemia.

Anesthetic Considerations: Patients with complex III deficiency can have a cardiomyopathy, so cardiac function should be evaluated preoperatively. Patients should not undergo a protracted perioperative fast without concomitantly receiving an intravenous glucose-containing solution. Patients with lactic acidemia should not receive lactated Ringer's solution. Perioperative serum glucose levels should be monitored closely. Patients with significant dysphagia are at increased risk for perioperative aspiration. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemic arrest. Patients may be sensitive to nondepolarizing neuromuscular blocking agents.

Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates, propofol, and volatile anesthetics can inhibit mitochondrial respiration, anesthesia with each of these drugs has been used without any complications in patients with mitochondrial defects. Hepatic disease can affect the binding and metabolism of some anesthetic drugs. Mitochondrial myopathy does not convey an increased susceptibility to malignant hyperthermia.

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Complex IV deficiency

Synonym: Cytochrome c oxidase deficiency

MIM #: 220110

Complex IV is one of five protein complexes that make up the mitochondrial electron transport chain. Electrons are transferred independently by complexes I and II to coenzyme Q and then sequentially to complexes III and IV. Complex IV collects electrons from cytochrome c and transfers them to oxygen to produce water. Complex V converts ADP to ATP. There are said to be up to nine distinct clinical presentations of this disorder; thus, the clinical findings given here are inclusive and will not all be seen in every patient. This complex is encoded by both nuclear and mitochondrial DNA, and therefore, some cases are inherited as a mitochondrial gene defect (i.e., they are maternally transmitted). Most cases, however, are due to nuclear gene mutations. In addition, complex IV deficiency can occur secondarily in diseases such as Menkes kinky hair syndrome (see later). Specific mutations can present in the neonate as Fanconi syndrome, Leber hereditary optic neuropathy, or Leigh disease (see later for each).

HEENT/Airway: Leber hereditary optic neuropathy (see later) with sudden central visual loss, swollen optic disc. Sensorineural hearing loss.

Chest: Respiratory failure due to muscle weakness.

Cardiovascular: Hypertrophic cardiomyopathy (*COX10* mitochondrial gene defect only).

Neuromuscular: Headaches. Fatal neonatal myopathy, hypotonia, hyporeflexia. Ataxia. Delayed development. Seizures. Abnormal mitochondria in muscles.

GI/GU: Early and fatal liver dysfunction has been reported. Neonatal renal dysfunction. Fanconi syndrome (see later).

Other: Lactic acidosis. Failure to thrive. Anemia (*COX10* mitochondrial gene defect only).

Anesthetic Considerations: Patients are at risk for perioperative respiratory failure and must be monitored closely both during and after surgery for signs of respiratory insufficiency. There is a report of three patients with Leigh disease (which may occur in complex IV deficiency) in whom respiratory failure was precipitated by general anesthesia, leading to death. All three patients had preoperative respiratory abnormalities. Patients with the *COX10* mitochondrial gene defect can have a cardiomyopathy, so cardiac function should be evaluated preoperatively. Patients should not undergo a protracted perioperative fast without concomitantly receiving an intravenous glucose-containing solution. Perioperative serum glucose levels should be monitored closely. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemia. Patients may be sensitive to nondepolarizing neuromuscular blocking agents. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates, propofol, and volatile anesthetics can inhibit mitochondrial

in patients with mitochondrial defects. Hepatic disease can affect the binding and metabolism of some anesthetic drugs. Careful attention must be paid to intravascular volume, electrolyte, and acid-base status in patients with Fanconi syndrome. Mitochondrial myopathy does not convey an increased susceptibility to malignant hyperthermia.

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Complex V deficiency

Synonym: ATP synthetase deficiency

MIM #: 516060

There are a total of five protein complexes that make up the mitochondrial electron transport chain. Electrons are transferred independently by complexes I and II to coenzyme Q and then sequentially to complexes III and IV. Complex V converts ADP to ATP. Complex V has 10 to 16 polypeptide subunits encoded by nuclear DNA and 2 polypeptide subunits encoded by mitochondrial DNA. Mitochondrial, autosomal recessive, and X-linked forms have been described. Specific mutations can present as Leber hereditary optic neuropathy, NARP syndrome, or Leigh disease (see later for each).

HEENT/Airway: Retinitis pigmentosa, nystagmus, and other abnormalities in eye movements, Leber hereditary optic neuropathy (see later) with sudden central field defect, sluggish pupils, blindness.

Chest: Hyperventilation, dyspnea, Cheyne-Stokes respirations, respiratory failure.

Cardiovascular: Hypertrophic cardiomyopathy.

Neuromuscular: Intellectual disability. Seizures, apnea, ataxia, hypotonia, tremor, areflexia, spastic quadriplegia, chorea. Neurodegenerative disease of brainstem and basal ganglia, intermittent coma.

GI/GU: Dysphagia. Failure to thrive.

Other: Intermittent lactic acidosis.

Miscellaneous: Accumulation of a subunit of ATP synthase has been found very early in the development of neurofibrillary degeneration in Alzheimer disease.

Anesthetic Considerations: Patients are at risk for perioperative respiratory failure and must be monitored closely

both during and after surgery for signs of respiratory insufficiency. There is a report of three patients with Leigh disease (which may occur in complex V deficiency) in whom respiratory failure was precipitated by general anesthesia, leading to death. All three patients had preoperative respiratory abnormalities. Patients with complex V deficiency can have a hypertrophic cardiomyopathy, so cardiac function should be evaluated preoperatively.

Patients should not undergo a protracted perioperative fast without concomitantly receiving an intravenous glucose-containing solution. Perioperative serum glucose levels should be monitored closely. Patients with significant dysphagia are at increased risk for perioperative aspiration. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of hyperkalemia. Patients may be sensitive to non-depolarizing neuromuscular blocking agents. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates, propofol and volatile anesthetics can inhibit mitochondrial respiration, anesthesia with each of these drugs has been used without any complications in patients with mitochondrial defects. Mitochondrial myopathy does not convey an increased susceptibility to malignant hyperthermia.

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Complex glycerol kinase deficiency

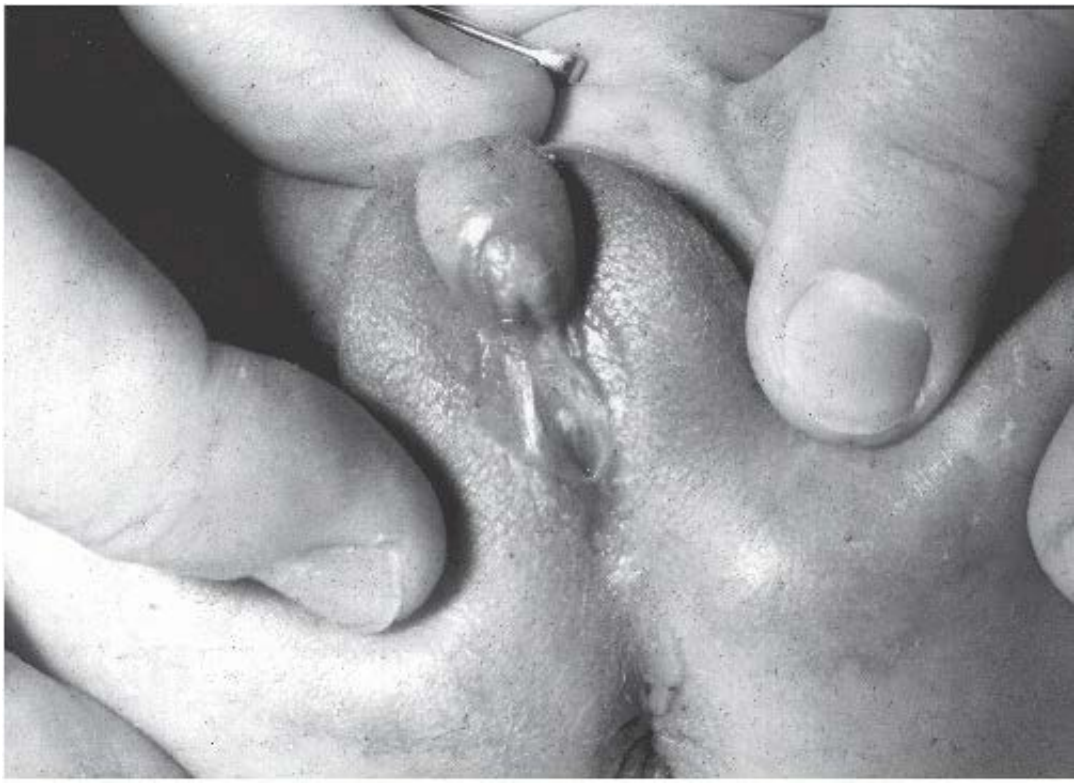
Included in Glycerol kinase deficiency

Congenital absence of the rods and cones

See Leber congenital amaurosis

Congenital adrenal hyperplasia

Synonym: Adrenogenital syndrome. (Includes 21-hydroxylase deficiency, 11β-hydroxylase deficiency, 17α-hydroxylase deficiency, and 3β-hydroxysteroid dehydrogenase deficiency)



Congenital adrenal hyperplasia. Masculinized female external genitalia in a newborn girl with congenital adrenal hyperplasia. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

MIM #: 201910, 202010, 202110, 201810

Congenital adrenal hyperplasia is an autosomal recessive disease resulting from a defect in one of the enzymes of cortisol biosynthesis. In approximately 95% of cases, it is due to 21-hydroxylase deficiency in the adrenal cortex, so unless another enzyme deficiency is specifically mentioned, "congenital adrenal hyperplasia" refers to **21-hydroxylase deficiency.** Because of the defect in cortisol synthesis, adrenocorticotropic hormone levels rise, resulting in overproduction of cortisol precursors, particularly 17-OH progesterone, which causes excessive androgen production, and results in fetal virilization. There are four clinical types of 21-hydroxylase deficiency: classic salt wasting, classic simple virilizing, nonclassic, and late onset (also called attenuated, or acquired). The different types are due to different allelic mutations in the 21-hydroxylase gene.

This clinical disease can also be secondary to abnormal function of the gene for **11ß-hydroxylase**, which is also an autosomal recessive defect. 11ß-Hydroxylase is the final step in aldosterone synthesis. There is accumulation of 11-deoxycorticosterone, a potent salt retainer, with consequent hypertension, which differentiates it clinically from congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Patients respond well to supplemental mineralocorticoids.

An alternative cause of this syndrome is **17α-hydroxylase deficiency.** Excessive production of corticosterone and deoxycorticosterone result in hypokalemic alkalosis. There is almost complete absence of aldosterone synthesis. There is estrogen deficiency, resulting in primary amenorrhea and absent sexual maturation in girls. Although

deficient 17,20-desmolase (see earlier) and 17α-hydroxylase activities can occur separately and these were thought to represent two distinct enzymes, they are now known to reside in a single protein. The gene for this protein has been localized to chromosome 10, and at least 16 distinct mutations have been described.

Congenital adrenal hyperplasia can also be due to a deficiency of the enzyme **3ß-hydroxysteroid dehydrogenase.** This variant of the disease has much less marked virilization, suggesting the gene product has testicular as well as adrenal activity. Boys with this type can have hypospadias or even pseudohermaphroditism, and salt wasting may be severe, or even fatal.

Cardiovascular: Hypertension, depending on the defect. Cortisol deficiency can contribute to poor cardiac function and diminished vascular response to catecholamines. When combined with hypovolemia, this can result in shock.

Orthopedic: Untreated, children have early rapid growth, with early epiphyseal closure and eventual short stature.

GI/GU: Newborn girls have masculinization of the external genitalia, but the degree of masculinization depends on the specific enzyme deficiency. Girls have normal female internal genitalia. Boys have normal male external and internal genitalia. Untreated, boys and girls have penile or clitoral enlargement. There is also precocious adrenarche and centrally mediated precocious puberty.

Other: Approximately half of all patients with 21-hydroxylase deficiency have an additional defect in aldosterone synthesis (conversion of progesterone to 11-deoxycorticosterone). Some 21-hydroxylase precursors can act as mineralocorticoid antagonists, worsening the effects of aldosterone deficiency. If left untreated, this can cause severe salt wasting and death (analogous to Addisonian crisis). Adrenal medullary development is partially dependent on glucocorticoids, so patients with salt-wasting 21-hydroxylase deficiency can also be catecholamine deficient, potentially exacerbating shock. Patients can also have hypoglycemia. A mild form can present in adults with hirsutism as the only manifestation. Patients may be hyperkalemic, which can be symptomatic. Girls are reported to have boy-like behavior in childhood, but their adult gender and sexual identity is as females.

Patients with 17α-hydroxylase deficiency have hypertension and hypokalemic alkalosis. They can also have non-life-threatening, mild symptoms of glucocorticoid deficiency.

Patients with 3ß-hydroxysteroid dehydrogenase deficiency can have severe and fatal salt wasting, which may not respond to apparently appropriate adrenal replacement therapy.

Miscellaneous: The Yupik-speaking Eskimos of Alaska have the highest prevalence of 21-hydroxylase deficiency in the world.

Anesthetic Considerations: Serum electrolytes, hydration status, and glucose should be followed closely perioperatively. Hyperkalemia can be a cause of ventricular arrhythmias and cardiac arrest (5,6). Patients may be hypertensive, therefore blood pressure should be monitored closely. Etomidate should be used with caution as it suppresses steroid biosynthesis by binding with high affinity to 11 beta-hydroxylase. Steroid therapy must be continued perioperatively, and patients should receive perioperative stress doses of corticosteroids as indicated. Parenteral corticosteroids may need to be substituted for the usual oral preparations. Stress-dose hydrocortisone is 2 mg/kg every 6 hours. The acute treatment of salt-losing crises includes the administration of salt-containing intravenous fluids, intravenous mineralocorticoid (such as fludrocortisone), and intravenous cortisol. Pregnancy is possible for many women, but delivery is often via Cesarean section. A certain amount of sensitivity is required when speaking with patients or families whose children have intersex disorders.

Figure: See **Appendix A**

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Congenital cutis laxa

See Cutis laxa

Congenital insensitivity to pain with anhidrosis

Synonym: Familial dysautonomia, type II; Hereditary sensory and autonomic neuropathy IV (HSAN IV); Autonomic neuropathy with insensitivity to pain

MIM #: 256800

This autosomal recessive disease is caused by mutations in the gene *NTRK1*, which encodes a tyrosine kinase receptor of nerve growth factor. Peripheral unmyelinated nerve fibers and small myelinated fibers are markedly diminished in number, or even absent. There are at least five genetically distinct hereditary sensory and autonomic neuropathies (HSANs). This type and HSAN type III (familial dysautonomia, see later) are the most common types. This disease is marked by insensitivity to superficial and deep visceral pain, with concomitant anhidrosis due to lack of innervation of otherwise normal sweat glands. Tactile sensation remains primarily intact. Patients can have self-mutilation of the mouth and hands. Recurrent episodes of hyperpyrexia are common, and may result in death in up to 20% of infants and young children.

HEENT/Airway: Hypotrichosis of the scalp. Can have absent corneal sensation with secondary corneal opacities,

abrasions, and scarring. Poor corneal healing. Normal lacrimation. Accidental oral trauma from decreased sensation. Self-mutilation of the lips and tongue.

Cardiovascular: Postural hypotension with reflex tachycardia, though not as marked as in familial dysautonomia. Absent innervation of vessel walls, although in one report baroreceptor function was intact.

Neuromuscular: Developmental delay, intellectual disability. Hyperactivity. Rage attacks. Diffuse autonomic dysfunction. Insensitivity to pain, particularly superficial and deep visceral pain. Absent or diminished deep tendon reflexes. Temperature insensitivity. Episodic fever, sometimes severe [109°F (42.8°C)] has been reported. Decreased small unmyelinated and myelinated fibers. Loss of sympathetic innervation of eccrine sweat glands.

Orthopedic: Neuropathic arthropathy. Distal ulceration and osteomyelitis of fingers and toes leading to autoamputation. Fractures.

Other: Anhidrosis or markedly diminished sweating, thick calloused skin and palms. Skin ulcers. Dystrophic nails. Delayed wound healing, rare humoral immunodeficiency. Absent flare response to injection of subcutaneous histamine.

Miscellaneous: This disease has a particularly high incidence in a group of Israeli Bedouins.

Anesthetic Considerations: Most patients will not require opioids perioperatively. However, despite the congenital analgesia, anesthesia is required to maintain

amnesia, surgical immobility, and hemodynamic stability. Reported anesthetics have been largely uneventful, and patients have generally required standard doses of anesthetic agents. Transient bradycardia and hypotension have been observed. Corneal protective reflexes may be absent even prior to the induction of anesthesia. Autonomic nervous system abnormalities may lead to delayed gastric emptying with the risk of perioperative regurgitation and aspiration. Perioperative thermoregulation is a primary concern. Temperature can usually be controlled by the customary means. Operating room temperature should be controlled and forced air warmers and cooling mattresses used as necessary. Adequate preoperative sedation will ameliorate fever caused by excitement. Atropine use has not resulted in excessive temperature elevations. Postoperative hyperthermia can develop. Nonsteroidal anti-inflammatory drugs are ineffective in lowering temperature. Patients will not feel pain and may be susceptible to additional orthopedic trauma from excessive postoperative movement: sedation might be required.

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Congenital methemoglobinemia

See Methemoglobinemia

Congenital myotonic dystrophy

Included in Myotonic dystrophy

Congenital spherocytosis

See Hereditary spherocytosis

Conradi-Hünermann syndrome

See Chondrodysplasia punctata—X-linked dominant and autosomal dominant types

Cooley's anemia

Included in Thalassemia

Cori disease

See Debrancher deficiency

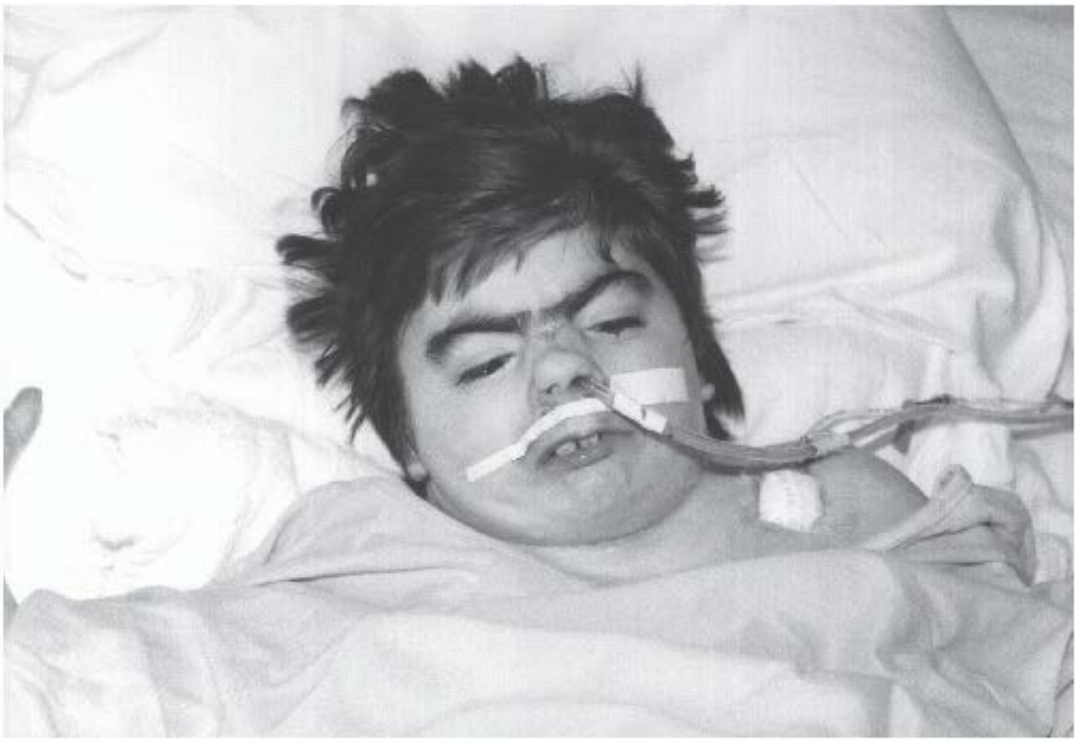
Cornelia de Lange syndrome

Synonym: de Lange syndrome; Brachmann-de Lange syndrome

MIM #: 122470

This syndrome is characterized by small stature, severe intellectual disability, eyebrow fusion, a thin upper lip with a long philtrum, down-turned angles of the mouth, and micromelia. Approximately half of all cases are due to a defect in the human homolog of the Drosophila gene *Nipped-B*. The protein product of this

gene has acquired the name delangin. Inheritance is thought to be autosomal dominant.



Cornelia de Lange syndrome. This 30-year-old woman with Cornelia de Lange syndrome was hospitalized for cecal volvulus. She is only slightly over 90 cm (3 feet) tall and weighs 20 kg. She is unable to talk or walk.

HEENT/Airway: Microbrachycephaly. Low anterior and posterior hairlines. Bushy eyebrows that fuse in the midline (synophrys). Long eyelashes. Myopia, ptosis, nystagmus. Low-set ears. Chronic otitis media. Hearing loss. Depressed nasal bridge, upturned nasal tip, anteverted nares. Thin upper lip with long philtrum, down-turned angles of the mouth. High-arched palate. Occasional choanal atresia, cleft palate. Teeth erupt late and are widely spaced. Micrognathia. Short neck.

Chest: Short sternum. Thirteen ribs. May contract lung disease secondary to repeated aspiration.

Cardiovascular: Occasional ventricular septal defect, valvular pulmonary stenosis.

Neuromuscular: Severe mental and motor delay. Hypertonia. May have seizures. Risk of apnea in infancy. Delayed speech is sometimes secondary to hearing loss. May exhibit autistic, stereotypical, self-destructive, or antisocial behavior. Broad-based gait.

Orthopedic: Prenatal and postnatal growth deficiency. Micromelia of the upper extremities. Simian crease. Proximal origination of the thumbs. Clinodactyly. Flexion contractures at the elbows. Dislocated or hypoplastic radial head. Syndactyly of the second and third toes. Delayed osseous maturation.

GI/GU: Gastroesophageal reflux. Bowel anomalies, including duplication of the gut, malrotation with volvulus, pyloric stenosis. Occasional hiatal hernia, diaphragmatic hernia, inguinal hernia. Hypospadias. Cryptorchidism.

Other: Characteristic weak, low-pitched, growling cry in infancy. Cutis marmorata (transient skin mottling). Perioral cyanosis without arterial desaturation. Hirsutism. Occasional thrombocytopenia.

Miscellaneous: Cornelia de Lange qualified as a physician in 1897, very much in discord with the expected gender roles of her time. She went on to become a leading Dutch pediatrician and originally reported this syndrome in 1933. Brachmann had described a child with similar features at autopsy in 1916, and this syndrome is sometimes known as the Brachmann-de Lange syndrome. It was Opitz, in 1963, who discovered Brachmann's description of the syndrome, when a volume of the journal *Jahrbuch fur Kinderheilkunde* was brought to his attention because it had been damaged by water such that it only opened in one place. He was then “startled to find out that here was an article on the Cornelia de Lange syndrome written 17 years before de Lange's first paper of 1933. The author, Dr. W. Brachmann, was then a young physician in training, who apologized that his study of this remarkable case was interrupted by sudden orders to report for active duty (in the German Army)” (11). Brachmann was killed in World War I, and his portrait and most of his academic papers were destroyed in World War II.

Anesthetic Considerations: Severe intellectual disability and behavioral characteristics make smooth induction of anesthesia a challenge. Patients with Cornelia de Lange syndrome may have decreased anesthetic requirements (10). Infants are at risk for perioperative apnea. Micrognathia, high-arched palate, and short neck may make direct laryngoscopy difficult. Choanal atresia, if present, precludes the use of a nasal airway or a nasogastric tube. Because of the high incidence of gastroesophageal reflux, these patients are at significant risk for pulmonary aspiration. Cutis marmorata (transient skin mottling) and perioral cyanosis without arterial desaturation can be misleading perioperatively. Peripheral vascular access can be difficult secondary to micromelia, and the shortened arm may require use of a narrower-than-usual blood pressure cuff. The short neck may make central venous access more difficult. Chronic use of anticonvulsant medications affects the kinetics of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Careful perioperative positioning may be necessary because of flexion contractures.

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Corticosterone methyl oxidase I deficiency

See 18-hydroxylase deficiency

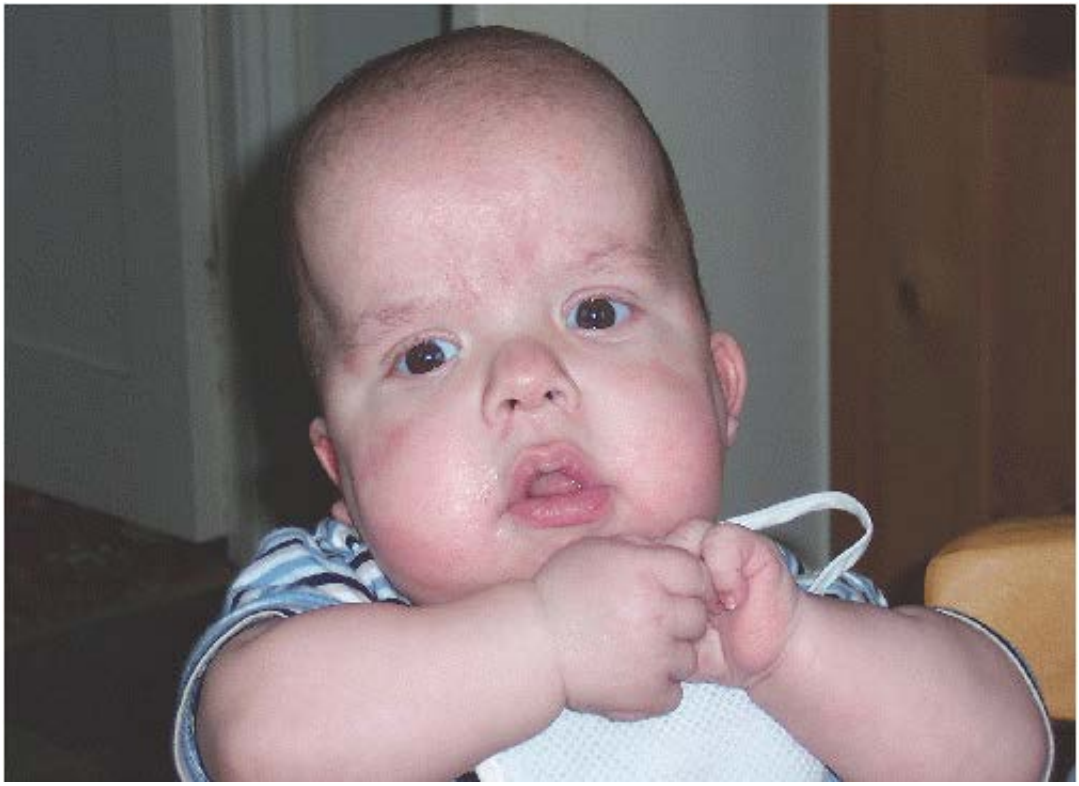
Costello syndrome

MIM #: 218040

This likely autosomal dominant disorder is characterized by intellectual disability, coarse facies, poor postnatal growth, hypertrophic cardiomyopathy, and perioral, nasal, and anal papillomas. The defect can be caused by

mutations in the gene *HRAS*. *HRAS* is homologous to a retroviral oncogene. Malignancies frequently develop, particularly rhabdomyosarcoma, neuroblastoma, and bladder cancer. There is an association with older paternal age, suggesting a possible autosomal dominant inheritance with germ line mosaicism. There is phenotypic overlap with cardiofaciocutaneous syndrome (see earlier).

HEENT/Airway: Macrocephaly. Coarse and characteristic facies that worsen with age. Epicanthal folds, strabismus, down-slanting palpebral fissures. Low-set ears with thick lobes. Flat nasal bridge with upturned nose. May have choanal atresia. Thick lips. Macroglossia. May have high-arched palate. Short neck. Hypertrophied supraglottic tissue. Hoarse voice. Perioral and nasal papillomas with onset during childhood. Rare laryngeal papillomas. The papillomas may become malignant. The craniofacial phenotype resembles that of the lysosomal storage diseases. Obstructive sleep apnea is common.



Costello syndrome. FIG. 1. A 15-month-old boy with difficulty swallowing and gastroesophageal reflux. He later required a fundoplication and a gastrostomy tube.

Chest: Barrel chest. May have copious tracheobronchial secretions. Pulmonary deposits of abnormal collagen and elastic fibers have been reported.

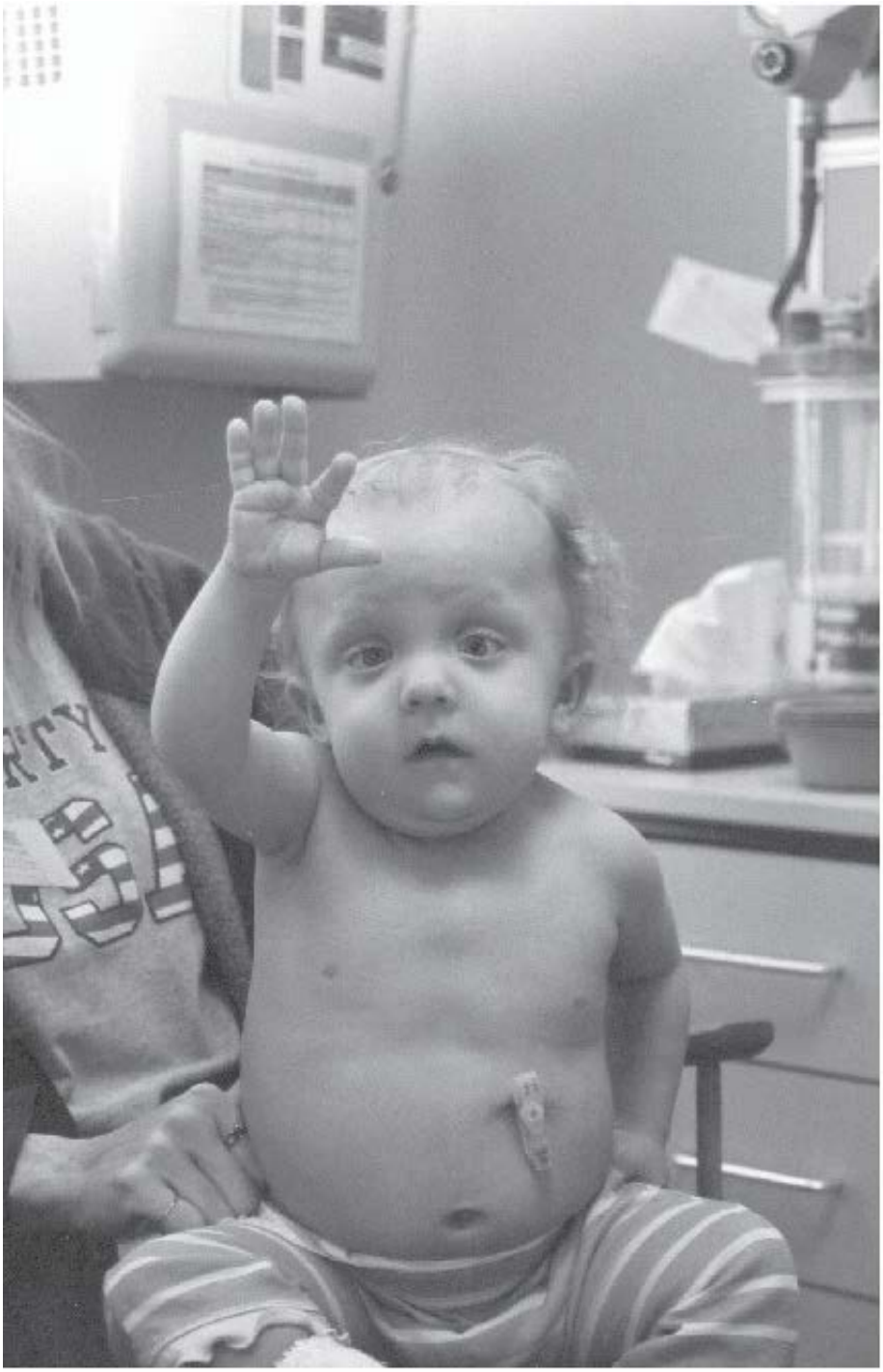
Cardiovascular: Hypertrophic cardiomyopathy, which can be associated with fatal dysrhythmias. Supraventricular tachyarrhythmias have also been reported, primarily during infancy. Cardiomyocytes contain accumulations of chondroitin-6-sulfate. May have ventricular septal defect, mitral valve prolapse, pulmonic stenosis.

Neuromuscular: Moderate to severe intellectual disability. Speech delay. Hypotonia. Cheerful personality. Cerebral atrophy. May have seizures.

Orthopedic: Short stature. Characteristic hand posture with ulnar deviation at the wrist. Decreased mobility at the elbow. Hyperextensible fingers. Deep palmar and plantar creases. Loose skin on hands and feet. Brittle nails. Dislocated hip. Short Achilles tendon. Clubfoot deformity. Unsteady gait.

GI/GU: Swallowing difficulties. Gastroesophageal reflux. May have hypertrophic pyloric stenosis.

May have hepatosplenomegaly. May have inguinal hernias. Undescended testes. Perianal papillomas. The papillomas can become malignant.



Costello syndrome. FIG. 2. A 3-year-old with congenital heart disease and cardiomyopathy, developmental delay, and strabismus. A severe gag reflex required feeding via a gastric tube.

Other: Polyhydramnios. Fetal macrosomia. Feeding problems and failure to thrive in infancy. Obesity in childhood. Cutis laxa, particularly of the neck, hands, and feet. Hyperkeratotic palms and soles. Darkly pigmented skin. Sparse, curly hair. Acanthosis nigricans. Can have deficiency of growth hormone. Can have abnormal glucose metabolism, with fasting hypoglycemia and postprandial hyperglycemia. May be associated with malignancies, particularly rhabdomyosarcoma, neuroblastoma and bladder cancer. Sudden death.

Anesthetic Considerations: Swallowing difficulties and gastroesophageal reflux are common, and patients are at increased risk for perioperative aspiration. Copious tracheobronchial secretions have also been described. Macroglossia and short neck may impact airway management. Thickened aryepiglottic folds have complicated laryngoscopy and tracheal intubation (8). Laryngeal papillomas and a tracheal web have also been described. Nasal papillomatosis may be a contraindication to nasotracheal intubation. Additionally, patients may have choanal atresia preventing nasal intubation. Obstructive sleep apnea is common and patients are at risk for perioperative respiratory compromise.

Patients often have hypertrophic cardiomyopathy, and are at risk for fatal dysrhythmias. It has been suggested that all children with Costello syndrome receive an electrocardiogram, a 24-hour Holter monitor, and an echocardiogram (2,4). If not yet done, it would seem prudent to complete these studies prior to elective surgery. Patients with congenital heart disease should receive an appropriately tailored anesthetic. In at least one instance, Costello syndrome has been associated with fasting hypoglycemia. Perioperative hyperthermia has been described, but has not been associated with malignant hyperthermia (7,8).

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Coumarin

See Fetal warfarin syndrome

Cowden syndrome

MIM #: 158350

This autosomal dominant disease is a disease of multiple hamartomas and a variety of benign and malignant tumors. It is caused by a germ line mutation in the gene *PTEN* (phosphatase and tensin homolog gene). *PTEN* is a tumor suppressor gene. Cowden syndrome has been only poorly described in young children. It has been suggested that the defect is allelic with Riley-Smith syndrome (Bannayan-Riley-Ruvalcaba syndrome) (see later), with which it has overlapping clinical features. However, unlike Cowden syndrome, malignant transformation has not been described in Riley-Smith syndrome. There is a high incidence of breast cancer in affected women, and also a significant risk of thyroid cancer in both men and women, although the majority of tumors of those organs will be benign.

HEENT/Airway: Progressive macrocephaly, “birdlike facies,” multiple facial papules, cataracts, myopia, angioid streaks, hearing loss, hypoplastic mandible and maxilla, microstomia, high-arched palate, scrotal tongue, oral papules and papillomas.

Chest: Pectus excavatum, gynecomastia in boys, breast fibrocystic disease, breast cancer.

Neuromuscular: Seizures, intention tremor, mild to moderate intellectual and psychomotor delay, cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease).

Orthopedic: Kyphosis, scoliosis.

GI/GU: Hamartomatous polyps, colonic diverticulae. Polyps and adenomas can involve esophagus and stomach. Hydrocele, varicocele. Ovarian cysts, uterine leiomyomas.

Other: Multiple skin tags and palmoplantar keratoses. Subcutaneous lipomas. Trichilemmomas (hamartomas of the hair follicle). Cutaneous hemangiomas. Endocrinopathies include goiter, thyroid adenoma and follicular cell cancer, hyperthyroidism and thyroiditis. Other neoplasias include ovarian carcinoma, cervical

carcinoma, uterine adenocarcinoma, transitional cell cancer of the bladder, testicular cancer, adenocarcinoma of the colon, and meningioma.

Miscellaneous: The first major report was that of Weary et al. from the University of Virginia. The disease is named after the first reported case, Ms. Rachel Cowden.

Anesthetic Considerations: Patients with thyroid disease should have their thyroid function evaluated

preoperatively. Patients with benign or malignant gastrointestinal disease should be evaluated preoperatively for anemia. Oropharyngeal papillomas can make laryngoscopy and intubation difficult (2). These can be friable. Chronic use of anticonvulsant medications can affect the kinetics of some anesthetic drugs.

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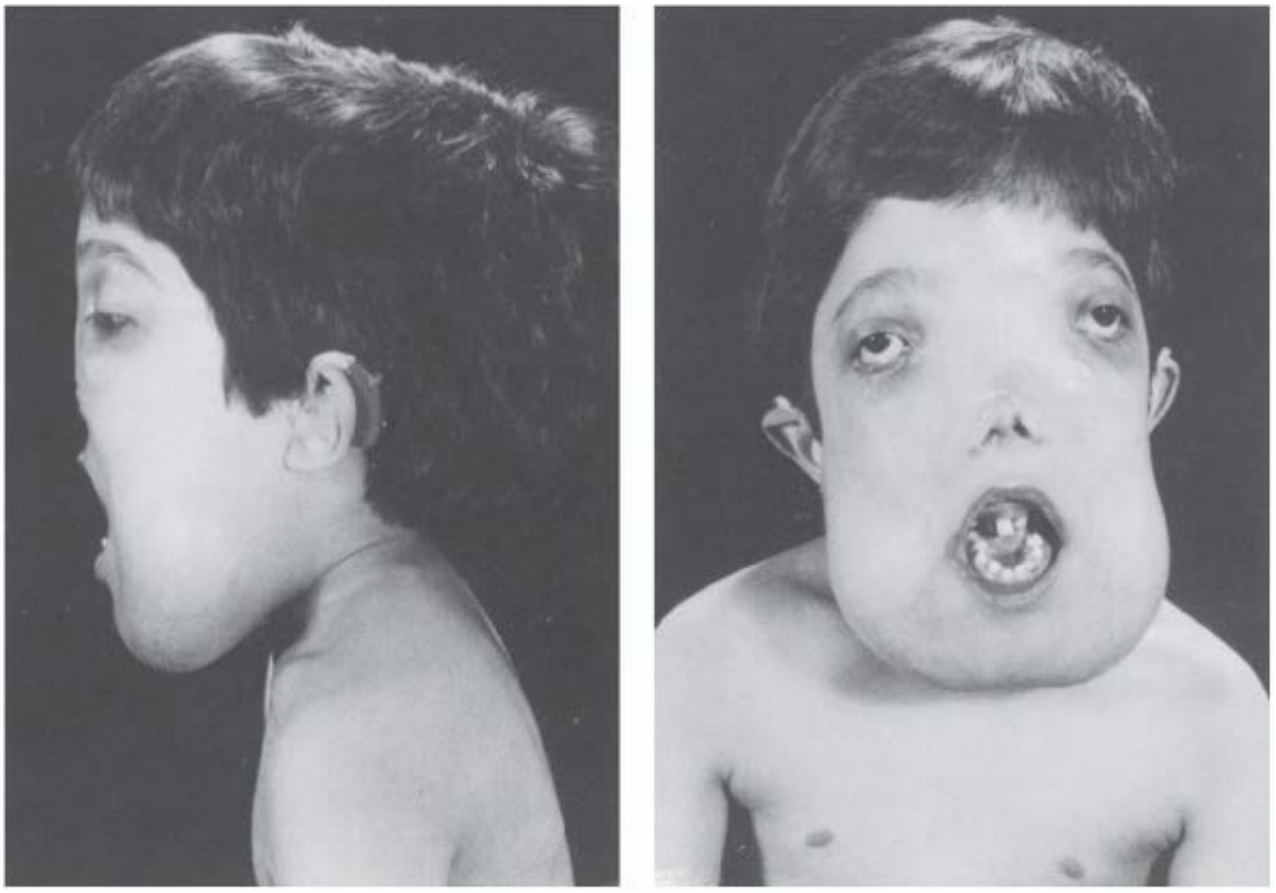
Craniocarpotarsal dysplasia

See Whistling face syndrome



Craniodiaphyseal dysplasia. A young boy with craniodiaphyseal dysplasia. (From Ref. 2, with permission.)

Craniodiaphyseal dysplasia

MIM #: 218300, 122860

This metabolic bone disease leads to massive hyperostosis (progressive thickening) and sclerosis of multiple bones, particularly the craniofacial bones and the long tubular bones. Both autosomal recessive and autosomal dominant forms have been reported. The autosomal dominant form is caused by a mutation in the *SOST* gene. Impingement on cranial foramina can result in a variety of problems.

HEENT/Airway: Bony overgrowth of the skull, mandible, and maxilla. Calvarial thickness of 4 cm has been reported. Hypertelorism. May have vision loss. Hearing loss. Choanal stenosis. Respiratory distress can occur secondary to narrowing of the nasal passages, and patients eventually become obligate mouth breathers. Obliterated sinuses. Limited mouth opening.

Chest: Thickening of the ribs and clavicles.

Cardiovascular: Bony overgrowth can impede jugular venous drainage.

Neuromuscular: May have intellectual disability. May develop increased intracranial pressure. Encroachment of

the foramina may cause compression and impairment of cranial nerves IX and X. Stenosis of the cervical canal has led to quadraparesis in an adult.

Orthopedic: Restricted cervical spine and atlantoaxial mobility. Hyperostosis and sclerosis of the diaphyses, with diaphyseal widening. No metaphyseal flaring. Pelvic bones can also be involved. Bone pain.

Other: May have hyperparathyroidism.

Anesthetic Considerations: Direct laryngoscopy and visualization of the larynx may be extremely difficult. Fiberoptic intubation through a laryngeal mask airway has been successful (2). The large mandible, bulky occiput and limited cervical spine mobility may severely limit the ability to flex the neck. Massive mandibular overgrowth may prevent placement of a tracheostomy because the jaw can extend down to the level of the manubrium. Choanal stenosis may preclude placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Hypercapnea should be avoided in the presence of increased intracranial pressure. Bone reduction surgery can result in significant blood loss.

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Craniofacial dysostosis

See Crouzon syndrome

Craniofrontonasal dysplasia

MIM #: 304110

This likely X-linked dominant disorder is characterized by brachycephaly, hypertelorism, down-slanting palpebral fissures, cleft nasal tip, and digital anomalies. Curiously, unlike other X-linked disorders, girls are far more severely affected than are boys. The gene responsible for this disorder is *EFNB1*, although there may be additional etiologies. *EFNB1* is a receptor for a protein-tyrosine kinase.

HEENT/Airway: Coronal synostosis with brachycephaly in females. Low posterior hairline. Facial asymmetry. Frontal bossing, down-slanting palpebral fissures, nystagmus, all in females. Hypertelorism in males. Broad nasal root, cleft nasal tip. High-arched palate. May have cleft lip or palate. May have webbed neck.

Chest: Pectus excavatum in males. Clavicular pseudoarthrosis in males. Sprengel deformity (winged scapula) in females. May have diaphragmatic hernia. Unilateral breast hypoplasia.

Neuromuscular: May have intellectual disability.

Orthopedic: Short stature. Asymmetric lower limb shortness. Digital anomalies, including syndactyly (females), brachydactyly (males), clinodactyly, broad toes. Longitudinally grooved fingernails. May have limited forearm pronation, limited hip and shoulder abduction. Joint laxity.

GI/GU: Hypospadias. Shawl scrotum.

Other: Thick, wiry hair (females). Widow's peak.

Anesthetic Considerations: Although not reported, direct laryngoscopy and tracheal intubation may be difficult secondary to palatal abnormalities. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Limited hip, shoulder, and arm mobility may occasionally affect positioning. Infants may have diaphragmatic hernia.

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Craniometaphyseal dysplasia

MIM #: 123000, 218400

This syndrome is similar to Pyle metaphyseal dysplasia (see later) but involves greater craniofacial hyperostosis and less metaphyseal splaying than is seen with Pyle disease. Craniometaphyseal dysplasia can be inherited in an autosomal dominant or an autosomal recessive fashion. The autosomal dominant form is due to mutations in the gene *ANKH*, the homolog

of the mouse progressive ankylosis gene. The autosomal recessive type is due to a mutation in the gene *GJA1*, and is more rare and more severe. Specifically, it is more likely to result in hearing loss, facial paralysis, and loss of vision.

HEENT/Airway: Macrocephaly. Thick calvarium and skull base. Hypertelorism, proptosis. The recessive form can have optic atrophy. May have conductive hearing loss. Bony wedge over the bridge of the nose. Progressive flattening of the nose. Narrow nasal passages, chronic rhinitis. Prognathism, mandibular asymmetry. Malaligned teeth. Delayed eruption of permanent teeth in the recessive form. May have obstructive sleep apnea.

Neuromuscular: Intelligence is usually normal. Hyperostosis can lead to obstructive hydrocephalus, cranial nerve compression, and headaches. Cranial nerve compression can result in hearing loss (cranial nerve VIII), facial paralysis (cranial nerve VII), and loss of vision (cranial nerve II). Stenosis of the foramen magnum can occur—cerebellomedullary compression has been reported.

Orthopedic: Mild metaphyseal splaying. “Erlenmeyer flask” deformity of distal femur in childhood, club-shaped distal femur in adulthood. Diaphyseal sclerosis.

Anesthetic Considerations: Patients with proptosis or facial paralysis may not be able to close their eyelids fully over their eyes. Meticulous perioperative eye care is necessary to prevent corneal abrasions. Patients may have extremely narrow nasal passages or have nasal obstruction. In either case, it may be impossible to place a nasal airway, a nasotracheal tube, or a nasogastric tube. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

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Cranioorofacial digital syndrome

See Otopalatodigital syndrome, type II

Craniosynostosis-radial aplasia syndrome

See Baller-Gerold syndrome

Cri du chat syndrome

Synonym: 5p-syndrome

MIM #: 123450

This chromosomal disorder is due to a partial deletion of the short arm of chromosome 5. It is thought that many of the phenotypic changes are specifically due to the loss of the gene *TERT*, the telomerase reverse transcriptase gene. Cri du chat is one of the most common chromosomal deletion syndromes and is characterized by microcephaly, intellectual disability, downward-slanting palpebral fissures, and a distinctive cat-like cry in infancy. The abnormal cry is caused by laryngeal deformity. The larynx normalizes with aging, and the distinctive cry diminishes. Most cases are the result of new deletions. Most patients die in early childhood.

HEENT/Airway: Microcephaly, round face, facial asymmetry. Downward-slanting palpebral fissures, hypertelorism, epicanthal folds, strabismus. Abnormal, low-set ears. May have cleft lip or palate. May have dental abnormalities, including delayed eruption, malocclusion. Micrognathia. Long, floppy epiglottis. Laryngeal deformity, consisting of diamond-shaped vocal cords on inspiration with a large air space in the area of the posterior commissure. May have short neck.

Chest: May have recurrent aspiration.

Cri du chat syndrome. An 18-year-old girl with cri du chat syndrome (giving a thumbs-up). She is hypotonic and nonverbal. She has had prior surgery to resect excessive epicanthal folds.

Cardiovascular: Congenital heart disease in one-third, predominantly patent ductus arteriosus, ventricular septal defect and tetralogy of Fallot.

Neuromuscular: Severe intellectual disability. Hypotonia. Brainstem atrophy.

Orthopedic: Growth retardation. Scoliosis. Simian crease. May have hemivertebrae. May have flat feet.

GI/GU: May have inguinal hernia.

Miscellaneous: The name “cri du chat” (“cat cry”) comes from the plaintive, high-pitched cry reminiscent of the mewing of a cat.

Anesthetic Considerations: Severe intellectual disability may make the smooth induction of anesthesia a challenge. Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia, a short neck, a long, floppy epiglottis, and a small, narrow larynx. A variety of alternative laryngoscope blades and intubation techniques should be available. A laryngeal mask airway has been used during a thoracotomy in a young child who could not be otherwise successfully intubated (7).

Patients are at risk for perioperative aspiration. Those patients who have a history of recurrent aspiration may

have chronic lung disease. Hypotonia can include the pharyngeal muscles, and patients should be observed closely perioperatively for airway obstruction. It has been suggested that intraoperative maintenance of body temperature is particularly difficult in these patients (1,6). There is no known association with malignant hyperthermia or succinylcholine-induced rhabdomyolysis. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications can affect the kinetics of some anesthetic drugs.

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Crigler-Najjar syndrome

MIM #: 218800, 606785

This usually autosomal recessive disease is due to a defect in the enzyme uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase) resulting in unconjugated hyperbilirubinemia. In type I disease, there is absent enzyme activity. In type II disease, there is markedly diminished activity, and both autosomal dominant inheritance with incomplete penetrance and autosomal recessive inheritance have been suggested. Type I disease can be treated with phototherapy, often for many hours a day, which converts bilirubin to more polar compounds that can be excreted without conjugation. Phototherapy usually becomes less effective at around the time of puberty due to skin changes and a decreased surface to mass ratio. Type II disease is often less severe and is responsive to therapy with phenobarbital, which induces hepatic microsomal enzymes.

Acute exacerbations of the disease can occur with trauma or other stresses such as surgery or infection, and have been treated with plasmapheresis and plasma exchange. Without treatment, death occurs from kernicterus, often in young childhood but as late as adolescence in some. Transplantation of isolated hepatocytes has met with some success, but has not been sufficient to correct the disease. Liver transplantation is curative.

Gilbert syndrome (see later) is also due to a defect in the enzyme UDP-glucuronosyltransferase, and the two syndromes are likely allelic. Other diseases of hepatic bilirubin metabolism include the Dubin-Johnson and Rotor syndromes (see later).

Neuromuscular: Kernicterus, if not treated. Late bilirubin encephalopathy can develop in older patients who were otherwise doing well with the exception of jaundice. Acute stress can raise bilirubin levels, even in type II, with the development of new neurologic manifestations.

GI/GU: Congenital nonhemolytic unconjugated hyperbilirubinemia with otherwise normal hepatic function and histology, although canalicular and biliary duct cholestasis has been described, probably from excretion of unconjugated bilirubin with phototherapy. There is essentially no conjugated bilirubin. Although the bile is pale, stool color is normal because of normal fecal urobilinogen. Jaundice appears within the first days of life.

Miscellaneous: Phototherapy for hyperbilirubinemia was first appreciated by a nurse in an English nursery who noticed that infants near the windows were less likely to have jaundice. Indeed, the bilirubin levels of these patients can go down during the summertime.

The family of one of the first reported cases was fairly inbred and also harbored other recessive diseases including Morquio syndrome, homocystinuria, metachromatic leukodystrophy, and Seckel syndrome.

Anesthetic Considerations: Phototherapy should be continued as long as possible perioperatively, and has even been used intraoperatively (5). Phenobarbital therapy should also be continued perioperatively. Fasting increases bilirubin levels. The stress of surgery or a perioperative infection can exacerbate the hyperbilirubinemia. Hemolysis of transfused blood can exacerbate the hyperbilirubinemia.

Perioperatively, it is imperative to avoid physiologic stresses and medications that increase free serum bilirubin levels, as this may result in bilirubin crossing the blood-brain barrier and causing irreversible damage. The physiologic stresses most likely to lead to increased serum bilirubin levels include dehydration, hypercarbia, and acidosis. Sulfonamides, ampicillin, some cephalosporins, salicylates, furosemide, and intravenous contrast agents can increase free bilirubin levels by displacing bilirubin from albumin. No anesthetic agents in current use are known to displace bilirubin significantly enough to contraindicate their use. Some patients may be on long-term phenobarbital therapy, which can affect the metabolism of some anesthetic drugs. Morphine is metabolized by a different glucuronosyltransferase system and can be used in these patients. Hepatic synthetic function is normal in these patients.

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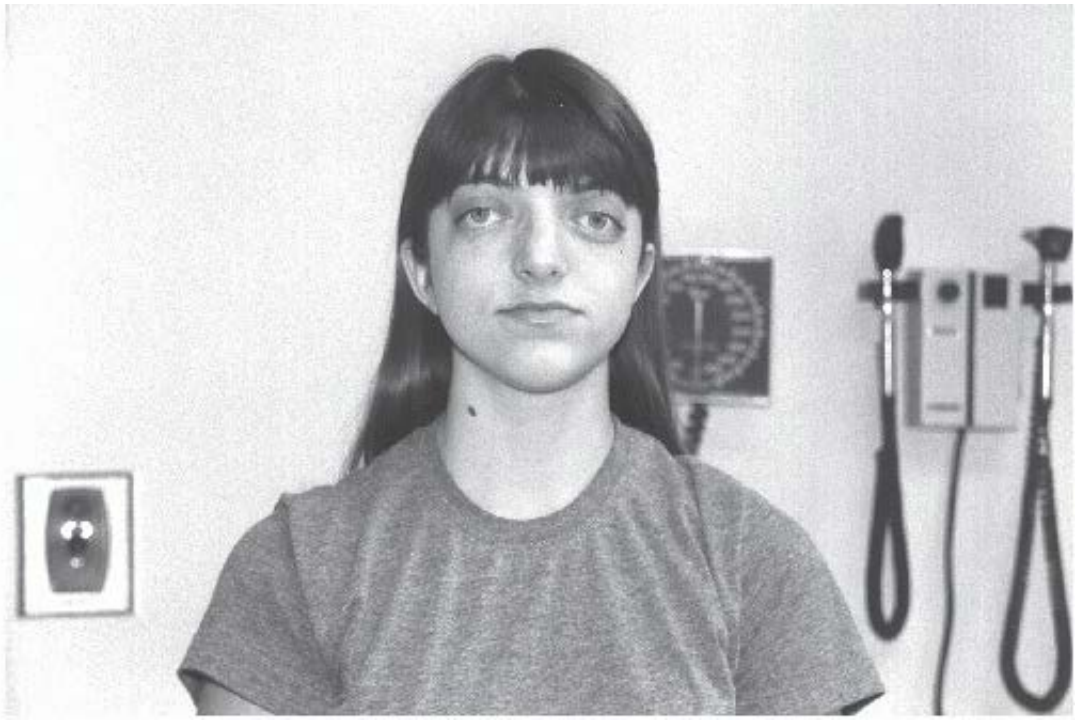
Crouzon syndrome

Synonym: Craniofacial dysostosis

MIM #: 123500

This autosomal dominant craniofacial dysmorphic syndrome is inherited in an autosomal fashion, but there is wide variability in expression. Anomalies are confined to the craniofacial region and include craniosynostosis, hypertelorism, shallow orbits with ocular proptosis, maxillary hypoplasia, and a parrot-like beaked nose. Craniofacial surgery is undertaken to correct elevated intracranial pressure and to allow for normal brain development, or strictly for cosmetic reasons.



Crouzon syndrome. FIG. 1. A young girl with Crouzon syndrome.

Crouzon syndrome results from mutations in the fibroblast growth factor receptor-2 gene (*FGFR2*). About half of all cases are new mutations with a suggestion of advanced paternal age. Different mutations of the same gene cause Apert syndrome, Antley-Bixler syndrome, Beare-Stevenson syndrome, and some cases of Pfeiffer syndrome. Crouzon syndrome with acanthosis nigricans (*MIM #:* 612247) results from a mutation in the fibroblast growth factor receptor-3 gene (*FGFR3*).

HEENT/Airway: Craniosynostosis, especially of coronal, lambdoid, and sagittal sutures. Frontal bossing. Hypertelorism, shallow orbits with ocular proptosis. Exposure keratitis or conjunctivitis is common. May have strabismus, nystagmus, optic atrophy. Mild to moderate conductive hearing loss. May have external auditory canal atresia. Hypoplastic maxilla. Parrot-like beaked nose. Choanal atresia has been described in Crouzon syndrome with acanthosis nigricans. Short philtrum. High-arched palate, occasional cleft lip or palate. Dental crowding. Relative prognathism.

Crouzon syndrome with acanthosis nigricans may be associated with cementomas of the jaw.

Crouzon syndrome. FIG. 2. Lateral view of the girl in Figure 1.

Upper airway obstruction is common—many patients become obligate mouth breathers, but acute respiratory distress develops only rarely. May develop sleep apnea.

Neuromuscular: Intelligence is normal. Rarely, may have intellectual disability, hydrocephalus, or increased intracranial pressure secondary to abnormal suture closure. May have seizures, agenesis of the corpus callosum.

Orthopedic: May have dislocation of the radial head. Cervical spine fusion, typically C2-C3. Scoliosis and spinal stenosis may occur in Crouzon syndrome with acanthosis nigricans.

Other: May have acanthosis nigricans involving skin of the head and neck.

Miscellaneous: Octave Crouzon was a leading French neurologist during the first part of the 20th century.

Anesthetic Considerations: Mask ventilation may be difficult in patients with mid-face hypoplasia because of inadequate mask fit. Tracheal intubation may be difficult secondary to the craniofacial and cervical anomalies. Placement of a maxillary distraction device may increase the difficulty of tracheal intubation (3). Ocular proptosis often leads to exposure keratitis or conjunctivitis. Meticulous perioperative eye care is indicated. Patients may have elevated intracranial pressure, in which case precautions should be taken to avoid further elevations in pressure. Airway anomalies are less common than in the related Apert and Pfeiffer syndromes.

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Cryptophthalmos syndrome

See Fraser syndrome

Cryptophthalmos-syndactyly syndrome

See Fraser syndrome

Cutis gyrata syndrome of Beare-Stevenson

See Beare-Stevenson syndrome

Cutis laxa

Synonym: Congenital cutis laxa. (Includes de Barsy syndrome)

MIM #: 123700, 219100, 219150, 219200

Cutis laxa is a rare congenital disorder of elastin synthesis, affecting both skin and internal organs. Inheritance may be autosomal recessive or, more rarely, autosomal dominant. The recessive and some of the dominant forms are due to abnormalities in the fibulin gene *FBLN5*. It has been suggested that *FBLN5* is a vascular ligand for integrin receptors and is involved in vascular development and remodeling. Autosomal recessive cutis laxa has been subdivided into three types. Type I involves lung atelectasis and emphysema, and can be fatal. Type II is associated with bony abnormalities, and type III (also known as **de Barsy syndrome**) includes eye abnormalities and intellectual disability. The dominant form is usually less severe, with rare pulmonary manifestations. Most cases of autosomal dominant cutis laxa are caused by a mutation in the gene encoding elastin. There is also an acquired form of cutis laxa, called generalized elastolysis. Skin biopsy specimens show deficient and disorganized elastin fibers in the dermis and vascular walls. X-linked cutis laxa is also referred to as Ehlers-Danlos syndrome, type IX (see later).

HEENT/Airway: Delayed closure of fontanelles. May have ocular anomalies. May have hoarse cry from vocal cord laxity.

Chest: Diaphragmatic atony, diaphragmatic hernia. Lung atelectasis, emphysema. Rare pulmonary hypertension in the recessive form.

Cardiovascular: Aneurysmal aortic dilatation or aortic and arterial tortuosity, peripheral pulmonary artery stenosis, valvular insufficiency. Cor pulmonale may develop in patients with significant pulmonary hypertension. Acquired form may have severe coronary artery disease. Renal artery dysplasia.

Orthopedic: Less joint hypermobility than in the clinically similar Ehlers-Danlos syndrome. Hip dislocation. Generalized osteoporosis.

GI/GU: Umbilical, inguinal hernias. Gastroesophageal reflux. GI and GU diverticulae, including esophageal and bladder diverticulae. Rectal prolapse in recessive form.

Other: Skin hangs on the body in loose, pendulous folds like an ill-fitting suit. Child may look prematurely wrinkled and aged. Skin is usually thickened, does not bruise easily, and heals normally (unlike skin in Ehlers-Danlos syndrome).

Anesthetic Considerations: Abnormal skin may make vascular access and the determination of landmarks for regional anesthesia more difficult. Patients may have significant pulmonary disease, aortic or coronary artery disease. Patients with gastroesophageal reflux may be at increased risk for perioperative aspiration. Nasogastric tubes should be placed with care because of possible esophageal diverticula. Consider avoiding the use of nitrous oxide in patients with severe emphysematous disease. Patients who are receiving chronic steroid treatment require perioperative stress doses of steroids. Perioperative hyperthermia has been described but has not been associated with malignant hyperthermia (2).

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Cyclic neutropenia

MIM #: 162800

This autosomal dominant disease is characterized by regular cyclic variations in neutrophils, monocytes, eosinophils, lymphocytes, platelets, and reticulocytes. Cycles among individuals vary from approximately 15 to 35 days. It is due to mutations in the gene encoding neutrophil elastase. Kostmann disease (see later) is an allelic disorder. Patients may be treated with granulocyte colony-stimulating factor (G-CSF).

HEENT/Airway: Recurring mucosal ulcers.

Other: Recurrent fever and malaise. There may be serious skin and other infections during periods of neutropenia.

Miscellaneous: A very similar disease occurs in gray collie dogs.

Anesthetic Considerations: Careful aseptic technique is required, particularly during periods of neutropenia. Patients with mucosal ulcers will require extra care during laryngoscopy and intubation.

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Cystic fibrosis

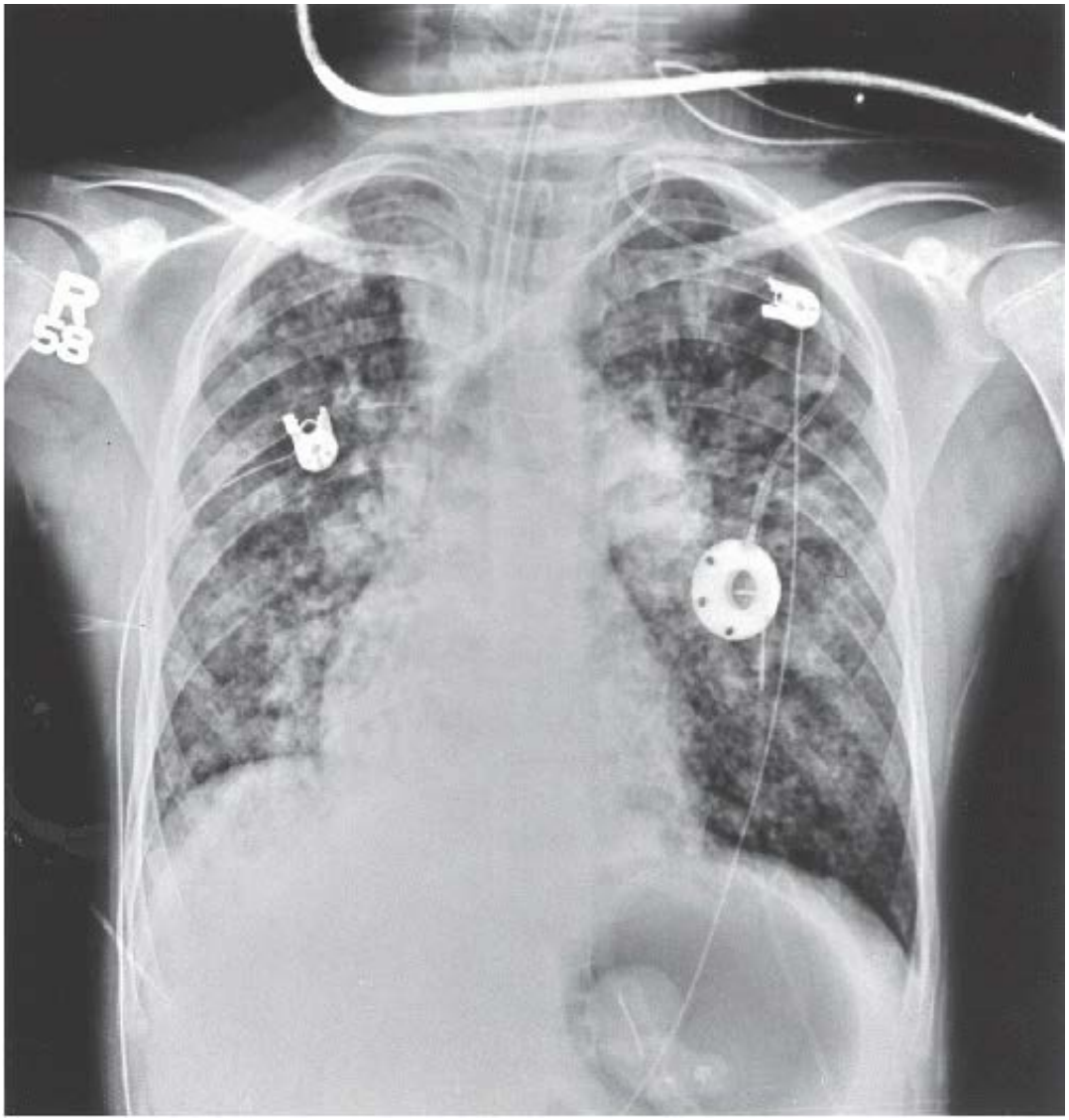
Synonym: Mucoviscidosis

MIM #: 219700

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by copious viscid mucous production that affects multiple organ systems, particularly the lungs and the exocrine pancreas. This disorder is due to a defect in the cystic fibrosis transmembrane

conductance regulator gene (*CFTR*). The protein product of the gene functions as a chloride ion channel in apical cell membranes of the exocrine glands. Since the discovery of the CF gene, more than 1500 *CFTR* gene mutations

that lead to the disease have been identified. Genetic defects are varied and can be single nucleotide polymorphisms or large deletions and can affect channel synthesis, maturation, regulation, conductance, or stability. The mutation that accounts for approximately 70% of defective *CFTR* alleles and 90% of CF cases in the United States is known as the ΔF508 mutation. This mutation causes a deletion of phenylalanine at position 508 in the protein product of the gene. The abnormal protein is recognized as misfolded and is rapidly degraded before it can reach its site of action at the cell membrane. It has been proposed that polymorphisms, or minor variations, in other genes, specifically in *TGFß1* (the gene encoding transforming growth factor ß1) or a nearby upstream region, can modify the clinical severity of lung disease.



Cystic fibrosis. Chest radiograph of a 15-year-old boy with end-stage cystic fibrosis. This film was taken shortly after tracheal intubation. His arterial PCO_2 before intubation was 104 mm Hg. The following day he underwent bilateral, living unrelated donor pulmonary lobe transplantation.

Cystic fibrosis most often occurs in people of European descent, where the incidence is 1:2000 to 1:5000, making it the most common autosomal recessive disease in that population. The *CFTR* gene has been constructed *in vitro*, and work is ongoing to determine a viral or nonviral vector that is capable of delivering and inserting the normal gene into a patient's cells to correct the genetic defect. Although gene therapy for CF has not yet been successful, recent investigations focusing on *CFTR* potentiator medications have shown promise. In January 2012, the United States Food and Drug Administration approved the *CFTR* potentiator medication ivacaftor, which has been shown to increase chloride secretion and airway surface liquid and has been associated with improvements in lung function in clinical trials in CF patients with at least one copy of the *G551D* mutation. Unfortunately, only 4% to 5% of patients with CF have the *G551D* mutation. However, additional similar compounds that may have broader applicability are currently undergoing clinical trials.

HEENT/Airway: Chronic sinusitis. Nasal polyps occur in older children and adults, and are usually asymptomatic but may cause nasal obstruction or epistaxis. With advanced disease, the trachea may enlarge and become flaccid.

Chest: Recurrent or persistent chest infections are the rule. Electrolyte abnormalities and mucous gland and goblet cell hypertrophy lead to viscid mucous. Viscid mucous is hard to clear, leading to mucous plugging and patchy atelectasis. The lungs become colonized with bacteria, typically *Pseudomonas* or *Staphylococcus* species. Colonization and intermittent infection contribute to lung damage through inflammation and destruction of lung tissue. Bronchopulmonary aspergillosis may also develop. Bronchial hyperreactivity causes additional gas trapping and hyperinflation. In addition, there is decreased ciliary clearance. The incidence of spontaneous pneumothorax increases with age and has a high recurrence rate without pleurodesis. Minor hemoptysis is common; major hemoptysis requiring bronchial artery embolization is rare.

Cardiovascular: Chronic respiratory disease and hypoxemia may result in cor pulmonale. Left ventricular dysfunction has also been reported.

GI/GU: The neonate may present with meconium ileus (secondary to abnormally viscid meconium).

Eighty-five percent of patients have pancreatic exocrine insufficiency secondary to viscid secretions, which causes ductal obstruction. Pancreatic exocrine insufficiency leads to steatorrhea and malabsorption. Malabsorption is usually successfully treated with oral pancreatic enzymes and fat-soluble vitamin supplements. Adults may have intermittent small bowel obstruction, only rarely requiring surgery, but exclusion of other surgical diseases may be difficult. There is an increased incidence of rectal prolapse in children, often recurrent. There is an increased incidence of gastroesophageal reflux.

Pancreatic insufficiency disrupts the enterohepatic circulation of bile acids, and there is an increased incidence of cholelithiasis. Biliary cirrhosis leading to portal hypertension can occur. Hepatic cirrhosis may develop.

Frequent aminoglycoside use has caused renal insufficiency.

Men are infertile; women have decreased fertility.

Other: Malnutrition. Anemia of chronic disease. Delayed skeletal maturation. Digital clubbing. Vitamin K deficiency and prolonged prothrombin time only in severe malabsorption. Progressive pancreatic damage can result in glucose intolerance or even frank diabetes in teenagers and adults. Oral hypoglycemics are rarely useful, and insulin may be needed. High sweat electrolyte losses (the basis of the diagnostic sweat test) can cause heat prostration, particularly with exertion in hot weather.

Miscellaneous: Cystic fibrosis has been recognized in European folklore since the 1600s. References such as “the child will soon die whose forehead tastes salty when kissed” have appeared in songs and stories from northern Europe for centuries. Curcumin, a major component of the spice turmeric, can correct ΔF508 processing and has prolonged life in mice homozygous for this gene. Heterozygotes are relatively immune to typhoid, which requires a

normal *CFTR* gene to enter cells.

Anesthetic Considerations: In the early part of the last century, CF was uniformly fatal in infancy or early childhood. Today, most patients reach adulthood, with a mean survival age of 38 years. Anesthesiologists are therefore more likely to see CF patients in the operating room, either for surgery related to their disease (nasal polypectomy, lung transplant) or for unrelated surgeries. The patient's medical condition should be optimized prior to any elective surgery. Most patients with CF have a good understanding of their own disease and will be a good source of information for the anesthesiologist. Many patients with CF have frequent need for medical consultation and intervention and may have developed anxiety or aversion to certain encounters. Emerging literature underscores the prevalence of procedural pain and chronic pain in patients with CF. Proper assessment and treatment of pain in patients with CF is critical to maintaining quality of life, regular exercise and chest physiotherapy. Poor pain control has been associated with pulmonary exacerbations and decreased survival (2).

Over 90% of CF patients die from respiratory complications. Patients uniformly have obstructive disease (secondary to mucous plugging and hyperreactivity), but many also have restrictive disease (secondary to chronic lung destruction). Approximately 40% of patients will respond to bronchodilators. Pulmonary infections are common and should be resolved before undertaking elective surgery. Clinical evaluation and sputum culture can be misleading—a preoperative chest radiograph may be helpful. Preoperative blood gas and pulmonary function testing may be useful in assessing the severity of the lung disease. Elevated $PaCO_2$ is an indication of severe disease. Patients are likely to have a prolonged FEV_1 secondary to obstructive disease and increased residual volume secondary to gas trapping. Ventilation-perfusion mismatching may lead to hypoxemia.

Pulmonary disease may prolong induction of anesthesia by volatile agents. Nasal polyposis is a contraindication to nasal intubation and may complicate nasogastric tube placement. Some patients depend on hypoxic respiratory drive and may hypoventilate with supplemental oxygen. Intraoperative assisted or controlled ventilation is recommended. High airway pressures should be avoided if possible, particularly in the presence of known bullae. The anesthesiologist should maintain a high index of suspicion for pneumothorax. Consideration should be given to avoiding the use of nitrous oxide. Perioperative intubation is rarely contraindicated, but prolonged intubation carries the risk of infection and barotrauma.

Perioperative treatment of secretions is usually the anesthesiologist's greatest challenge. Good perioperative chest percussion therapy is critically important. It may be prudent to delay the patient's procedure until midmorning to maximize clearance of secretions. Intraoperative chest physiotherapy may be indicated (7). Inspired gases should be humidified. Adequate hydration must be assured. Anticholinergic medications decrease the volume of secretions but will not thicken them. Ketamine may increase bronchial secretions and should be avoided. Intubation may be necessary for pulmonary toilet in longer cases; LMA placement may be appropriate in shorter cases. Intubated patients require frequent suctioning of the airway. Nebulized saline, mucolytic agents (*N*-acetylcysteine), or recombinant human DNase (which degrades neutrophil DNA and decreases the viscosity of secretions) may be helpful.

Perioperative bronchial hyperreactivity may also be challenging. Coughing and laryngospasm are common. Unfortunately, bronchodilators do not reliably improve air flow, and in some patients, they may even exacerbate airway obstruction by causing airway instability during expiration secondary to smooth muscle relaxation.

Patients should receive a cardiac evaluation and a preoperative echocardiogram if cor pulmonale is suspected. Gastroesophageal reflux is common, and these patients are at increased risk for perioperative aspiration. Aminoglycosides can prolong the action of nondepolarizing muscle relaxants. Patients with a history of frequent aminoglycoside use may have renal insufficiency. Patients with liver disease may develop a coagulopathy and/or demonstrate altered drug metabolism. Patients with pulmonary aspergillosis may be taking steroids, and require

perioperative stress doses of steroids.

Venous access may be difficult in these patients who require frequent intravenous lines for antibiotic administration. Preoperative laboratory assessment may reveal hyponatremia, anemia, or elevated blood glucose. Some patients will have glucose intolerance or diabetes and will require appropriate perioperative glucose management.

A primary postoperative goal is the rapid restoration of the patient's ability to cough, deep breathe, mobilize, and resume chest physiotherapy. To this end, short-acting anesthetic agents are ideal. Sedative and opioid medications should be minimized, with appropriate alternatives utilized. Regional anesthesia or analgesia should be strongly considered, particularly when it has the potential to improve postoperative respiratory function.

High-dose ibuprofen, when taken chronically, has been shown to slow the progression of mild pulmonary disease in some patients with cystic fibrosis, presumably through its anti-inflammatory effects (6). There is no evidence that acute ingestion of nonsteroidal inflammatory drugs has any beneficial effect.

The cardiopulmonary demands of pregnancy may be life threatening to patients with CF, and the incidence

of preterm delivery is increased. Nevertheless, successful outcomes have been reported (8,9,11).

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Cystinosis

MIM #: 219750, 219800, 219900

Note: This syndrome is distinct from cystinuria.

This autosomal recessive inborn error of amino acid metabolism consists of three types, an infantile (nephrotic) form, an adolescent form, and an adult form. All three types are due to mutations in the gene *CTNS*, which encodes cystinosin, the lysosomal membrane transport protein for cystine. Multiple specific mutations have been described. There is accumulation of intracellular cystine in a wide variety of organs, but the primary clinical manifestations involve alterations in renal function. In the juvenile form, eye findings present early with renal findings presenting with a generally milder course in or after the second decade. The adult form has only eye manifestations. Treatment is with cysteamine, which combines with cystine in the lysosome. The mixed disulfide leaves the lysosome via the lysine transport system. Early treatment with cysteamine has improved the outcome significantly.

HEENT/Airway: Deposition of cystine crystals in the cornea and conjunctivae may cause photophobia or recurrent corneal erosions. Patchy depigmentation of the retina. Decreased visual acuity with aging. Recurrent epistaxis has been described in dialyzed patients. May have choking and gagging due to myopathy.

Cardiovascular: Hypertension secondary to renal failure.

Neuromuscular: Poor school performance, seizures, impaired visual memory, and cerebral atrophy may develop with aging. Severely affected patients may have hypotonia, swallowing and speech difficulties, pyramidal and cerebellar signs, and strokes. Ischemic strokes have been seen only in adults. Pseudotumor cerebri has been reported. A myopathy of both proximal and distal muscles, with particular involvement of the interossei and muscles of the thenar eminence, has been described. Some myopathy is due to cystine deposits in muscles, but some may be due to excessive carnitine losses in the urine.

Orthopedic: Severe rickets with the infantile form, if inadequately treated. Short stature.

GI/GU: Involvement of the liver can result in cirrhosis with portal hypertension and esophageal varices. Hepatic enlargement can be due in part to large Kupffer cells that contain cystine crystals and become large foam cells.

There can be hypersplenism. Can have pancreatic exocrine dysfunction. Males may have hypogonadism. Cysteamine, used to treat cystinosis, carries a high incidence of gastrointestinal symptoms, which are often acid mediated.

The infantile form presents with progressive renal failure, beginning with the Fanconi syndrome (see later) with polyuria, followed by glomerular and renal failure requiring dialysis or transplantation. In addition to multiple amino acid and electrolyte losses in the urine, patients also lose vitamin D and carnitine, which need to be replaced. The urine is pale and cloudy with a particular odor, probably due to the aminoaciduria. The adolescent form presents with renal dysfunction in the second decade of life, whereas the adult form has normal renal function. Bartter syndrome (see earlier) can develop in some children. Progression of the renal failure can result in a regression of Fanconi syndrome secondary to decreased glomerular filtrate being presented to the proximal tubules. Dialysis and renal transplantation are routine. Fanconi syndrome does not recur in transplanted kidneys, even though cystine crystals are present, because they are located within macrophages or leukocytes.

Male patients may have an abnormal pituitary-testicular axis with incomplete maturation and infertility. Female patients have normal gonadal function.

Other: Pancreatic involvement by cystine deposition can result in diabetes mellitus, and thyroid involvement

can result in hypothyroidism. Thyroid dysfunction is common, particularly in adulthood. Pancreatic exocrine function is normal. Decreased sweating may result in heat intolerance, hyperthermia, and flushing with exercise. May have anemia from renal failure. Caucasian patients will have skin and hair pigmentation lighter than their siblings. May have thrombocytosis.

Miscellaneous: Many children crave the four P's of salt-rich (and child-friendly) foods: pizza, pickles, pretzels, and potato chips (3).

Anesthetic Considerations: Because of possible Fanconi or Bartter syndromes involving renal electrolyte losses, preoperative measurement of serum electrolytes, calcium, phosphorus, and magnesium is appropriate. Electrolytes may need to be followed perioperatively. The patient's usual doses of electrolytes can be given orally before surgery, if tolerated. If oral medications are inappropriate, alternative parenteral dosing is necessary. These might include supplemental calcium, bicarbonate, carnitine, and cysteamine, which depletes lysosomal cystine.

Isosthenuria (fixed specific gravity, neither concentrated nor dilute) or polyuria may complicate perioperative fluid management. Protracted preoperative fasting should be avoided to prevent dehydration. Urine output may be a poor indicator of intravascular fluid status, so central venous pressure monitoring might be appropriate in these patients if surgery will involve major fluid shifts. Indomethacin significantly diminishes urinary water and electrolyte losses. Chronic renal failure has implications for the choice and dosages of anesthetic and other drugs. Intravenous fluids may be supplemented with bicarbonate or potassium. Because of excessive relatively dilute urine, patients may require more free water in intravenous fluids. Thirst and salt-sensing mechanisms are intact, and if otherwise appropriate, patients should have free access to water and salt.

When clinically indicated, patients should have thyroid and hepatic function evaluated preoperatively. Patients may have esophageal varices. If diabetes mellitus is suspected, the serum glucose should be measured. Preoperative blood counts should be obtained in patients with chronic renal failure or hypersplenism. Nasal tubes should be avoided in patients with recurrent epistaxis. Patients with photophobia may be bothered by bright operating room lights. Patients may have recurrent corneal erosions, and perioperative eye care is particularly important. If poorly nourished, these patients may have difficulty maintaining their intraoperative body temperature. Poor nutrition is an indication for careful positioning and padding of pressure points. Decreased sweating may result in perioperative hyperthermia. A child with intraoperative hyperthermia, thought not to be related to malignant hyperthermia, has been reported (4). Succinylcholine should presumably be avoided in

patients with myopathy due to the potential of an exaggerated hyperkalemic response.

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Cystinuria

MIM #: 220100

Note: This syndrome is distinct from cystinosis.

Cystinuria is due to a mutation in the renal amino acid transporter gene. This transporter is involved in the renal and gastrointestinal epithelial transport of cystine, lysine, arginine, and ornithine. Cystinuria is inherited in an autosomal recessive fashion, and there are three clinical phenotypes. Type I disease is due to defects in the gene *SLC3A1*, which encodes the heavy subunit of the protein. Types II and III are due to mutations in the gene *SLC7A9*, which encodes the light subunit. The main clinical manifestation in all three types is the formation of cystine renal stones with subsequent sequelae related to obstructive uropathy. Patients with type I disease excrete large amounts of cystine, lysine, arginine, and ornithine in the urine. Heterozygotes with type I disease have no abnormal aminoaciduria. Patients with type II disease excrete excessive amounts of cystine and lysine in the urine. Heterozygotes with type II disease also have excessive excretion of cystine and lysine. Patients with type III disease excrete slightly increased amounts of cystine in the urine. Because of the particularly low solubility of cystine, all three types can form cystine stones. Although compliance is an issue, excretion of cystine is diminished with a diet limiting protein and salt.

Neuromuscular: May have intellectual disability.

GI/GU: Radiopaque nephrolithiasis. May develop obstructive uropathy, recurrent pyelonephritis and renal insufficiency secondary to high chronic stone burden. Renal transplantation is curative.

Miscellaneous: An abnormal renal stone was first identified by Wollaston in 1810. It was an odd stone and he named the substance cystic oxide, because it

came from the bladder. It turns out he was incorrect on both accounts—it was not restricted to the bladder (stones also occur in the kidney) and it is an amine, not an oxide. Later analysis showed it was a sulfur-containing amino

acid, and so this stone eventually was responsible for the names of the amino acids cystine and cysteine. This was one of the four inborn errors of metabolism (the others being albinism, alkaptonuria, and pentosuria) discussed by Garrod in his famous series of lectures in 1902 (3). Cystinuric patients also excrete large amounts of cadaverine and putrescine.

Anesthetic Considerations: Children may well have had multiple urologic interventions. Urine output should be maintained. Perioperative hydration to maintain a diuresis should be continued. Renal disease affects the choice of anesthetic drugs. Cystine solubility is low at acidic urine pH, but does not significantly increase until the urine pH is over 7.5. Cystine stones are not as easily destroyed by extracorporeal lithotripsy as other types of stones, and percutaneous lithotripsy is more effective, although extracorporeal lithotripsy may be more effective in children.

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Cytochrome c oxidase deficiency

See Complex IV deficiency

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

D

Dandy-Walker Malformation

MIM #: 220200

Dandy-Walker malformation is characterized by cerebellar hypoplasia and cystic dilation of the fourth ventricle. Inheritance of this malformation is heterogeneous and unlikely Mendelian, although some possibly autosomal recessive cases have been described. Approximately half of the patients have other associated congenital anomalies.

HEENT/Airway: Hypertelorism, cleft lip, microglossia, and micrognathia have been associated in some patients but are not primary manifestations.

Chest: Central respiratory failure with periodic breathing or apnea.

Neuromuscular: Cerebellar hypoplasia (agenesis of the cerebellar vermis), and dilation of the fourth ventricle, often with a posterior fossa cyst, which enlarges the posterior fossa. Obstructive hydrocephalus with enlargement of the third and lateral ventricles is common. There may be associated agenesis of the corpus callosum, poor intellectual development, or interference with medullary control of respiration with apnea and respiratory failure. Most patients will be diagnosed within the first year of life and will require shunting to relieve intracranial pressure, but there can be asymptomatic adults (2,5). There may be posterior fossa signs such as cranial nerve palsies, nystagmus, and truncal ataxia.

Orthopedic: Syndactyly, polydactyly, and limb and vertebral anomalies have been described in some patients.

Miscellaneous: This syndrome was first described by Dandy and Blackfan, who incorrectly ascribed it to atresia of the foramina of Luschka and Magendie. Dandy was a surgeon, and Blackfan was a pediatrician and the most outstanding pediatric hematologist of his generation (e.g., see Diamond-Blackfan anemia). Taggart and Walker described it almost 30 years later, and 40 years after the original description, the current name was suggested.

In 1913, at the age of 27 years, Dandy published a masterful description of the pathogenesis and management of hydrocephalus. His mentor, Halsted, commented that “Dandy will never do anything equal to this again. Few men make more than one great contribution to medicine.” Halsted was wrong.

Anesthetic Considerations: Associated micrognathia is rare but may complicate laryngoscopy and tracheal intubation (4,7). Obstructive hydrocephalus can increase intracranial pressure. Precautions should be taken in patients with increased intracranial pressure to avoid further perioperative increases in pressure. Laryngeal incompetence and vocal cord paralysis with postextubation upper airway obstruction have been reported, presumably due to brainstem compression after surgical drainage (8). Apnea is possible, and patients should be closely observed perioperatively to ensure adequate control of ventilation.

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De Barsy syndrome

See cutis laxa

Debrancher deficiency

Synonym: Glycogen storage disease type III; Amylo-1,6-glucosidase deficiency; Cori disease; Forbes disease

MIM #: 232400

This autosomal recessive glycogen storage disease may involve the liver or muscle. It is caused by a mutation in the gene encoding the glycogen debrancher enzyme (*AGL*). The enzyme defect precludes full degradation of glycogen, which results in hypoglycemia and storage of a polysaccharide with short branches in all tissues. Unlike von Gierke disease (glycogen storage disease type I), hypoglycemia can be partially ameliorated by gluconeogenesis and

ketogenesis. Gluconeogenesis, however, may rob muscles of protein. Most patients have involvement of both liver and muscle (skeletal and cardiac) (type IIIa), but some only have hepatic involvement (type IIIb). Patients with liver involvement and myopathy lack enzyme activity in both liver and muscle. Patients with liver involvement lack only hepatic but not muscle enzyme. There is marked clinical variability, and in infancy, it may be indistinguishable clinically from von Gierke disease. Clinical symptoms and hepatomegaly often improve after puberty. There is a report of a patient who developed respiratory failure at age 47 years after a period of fasting.

HEENT/Airway: Doll-like facies. Macroglossia.

Cardiovascular: Cardiomyopathy, often subclinical but may be progressive in adults.

Neuromuscular: Muscle weakness and wasting. The myopathy can be mild in childhood but becomes more pronounced in adulthood with muscle wasting. Muscle wasting is both myopathic and neuropathic.

Orthopedic: Growth retardation.

GI/GU: Hepatomegaly, which can be massive. Periportal fibrosis and nodular cirrhosis are rare and may not be progressive. Progressive liver failure is particularly common in Japanese patients. Hepatic adenomas, without malignant transformation. Liver manifestations, including hepatomegaly, usually improve with age and may be gone completely after puberty. Renal tubular acidosis is very rare. Polycystic ovary with normal fertility.

Other: Hypoglycemia. Ketoacidosis with stress. Elevated cholesterol and beta-lipoprotein. Truncal obesity. Hypoglycemia risk decreases with aging.

Miscellaneous: Glycogen storage disease type III was the first glycogen storage disease to be described (by van Creveld), a year before von Gierke and 4 years before Pompe described their now eponymous diseases. The disease also occurs in dogs, in whom it is much more severe.

Anesthetic Considerations: Because of the risk of cardiomyopathy, a careful preoperative cardiac examination should be done. Liver function should be evaluated preoperatively. Hepatic failure may lead to abnormal coagulation and may affect protein binding of some anesthetic drugs. A protracted preoperative fast without supplemental glucose must be avoided. Serum glucose should be monitored perioperatively, and perioperative intravenous fluids should contain glucose. Young children can be obese, which can increase the perioperative aspiration risk and make vascular access more challenging. Succinylcholine should be used cautiously, if at all, in patients with myopathy and muscle wasting because of the risk of an exaggerated hyperkalemic response. Patients with advanced myopathy may require postoperative ventilation.

Figure: See **Appendix E**

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Degos disease

See Malignant atrophic papulosis

Dejerine-Sottas syndrome

MIM #: 145900

There are both autosomal dominant and recessive forms of this motor and sensory neuropathy that is characterized by enlarged nerves with slow conduction, nystagmus, hearing loss, and ataxia. Symptoms first occur in infancy, and the course is progressive, although marked by acute exacerbations and remissions. This disorder can be due to mutations in the genes *MPZ*, *PMP22*, *PRX*, or *ERG2*. *MPZ*, *PMP22*, and *PRX* encode structural proteins in peripheral myelin. *ERG2* induces these three other genes. Different mutations in some of these genes can also cause Charcot-Marie-Tooth syndrome (see earlier), but Dejerine-Sottas syndrome is more clinically severe.

HEENT/Airway: Nystagmus. Hearing loss.

Neuromuscular: Enlarged nerves secondary to hypertrophic interstitial neuropathy. Demyelination and slow nerve conduction. Muscle weakness and atrophy begins distally and spreads proximally. Lower limbs affected before upper limbs. Muscle weakness eventually involves the bulbar muscles. Ataxia. Delayed motor development. Loss of deep tendon reflexes. Foot drop. Sensory deficits accompany the motor deficits. May also have autonomic deficits with thermal lability and mottled cyanosis. Eventual muscle atrophy. Normal intelligence.

Orthopedic: Kyphoscoliosis. Pes cavus. Hammer toes. Clubfoot deformity.

Miscellaneous: Joseph Dejerine was a French neuropathologist. Jules Sottas was his student.

Anesthetic Considerations: Patients may be at risk for an exaggerated hyperkalemic response after the administration of succinylcholine secondary to denervation muscle atrophy. Temperature regulation by sweating may be impaired secondary to autonomic dysfunction, leading to thermal lability and mottled cyanosis. Epidural anesthesia has been used successfully. There is no association between Dejerine-Sottas syndrome and malignant hyperthermia.

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de Lange syndrome

See Cornelia de Lange syndrome

Delleman syndrome

Synonym: Oculocerebrocutaneous syndrome

MIM #: 164180

This is a sporadically occurring disease whose primary manifestations are central nervous system cysts or hydrocephalus, orbital cysts or microphthalmia, and focal skin defects. It has been suggested that it may be a consequence of disruption of the anterior neuroectodermal plate. Another possibility is an autosomal dominant lethal mutation, survivable only in mosaics. Males are more commonly affected, and the left side is more commonly involved than is the right.

HEENT/Airway: Periorbital skin appendages, orbital cysts, unilateral anophthalmia, or microphthalmia. May have bilateral anophthalmia. Colobomas. Punched-out lesions over the alae nasi.

Neuromuscular: A variety of cerebral malformations including intracranial cysts, polymicrogyria, agenesis of the corpus callosum, and hydrocephalus. Psychomotor developmental delay and seizures, which can be neonatal in onset.

Other: Focal dermal hypoplasia or aplasia.

Anesthetic Considerations: Neonatal seizures can be difficult to appreciate and aspiration risk can be increased with seizures and feeding problems. Chronic use of anticonvulsant medications can affect the kinetics of some anesthetic drugs.

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de Morsier syndrome

See Septooptic dysplasia

Denys-Drash syndrome

de Sanctis-Cacchione syndrome

MIM #: 278800

This autosomal recessive disorder is a form of xeroderma pigmentosum (see later) involving xeroderma pigmentosum, neurologic abnormalities, growth deficiency, and hypogonadism. There is slow somatic growth and variable progressive neurologic dysfunction. Skin deterioration begins in infancy and is progressive thereafter, exacerbated by sun exposure. Life span is shortened secondary to neurologic deterioration or malignancy. As with other forms of xeroderma pigmentosum, there is a defect in DNA repair after ultraviolet radiation-induced damage. Patients with de Sanctis-Cacchione syndrome are most often in xeroderma pigmentosum complementation group A. The disorder can be due to mutations in the gene *ERCC6*. This gene is part of the nuclear excision repair network, which eliminates damaged DNA. Mutations in this gene can also result in a type of Cockayne syndrome (see earlier).

HEENT/Airway: Microcephaly. Photophobia. Keratitis. Occasional sensorineural hearing loss.

Neuromuscular: Progressive neurologic dysfunction—choreoathetosis, ataxia, hypo- or areflexia, spasticity, seizures, peripheral neuropathy. Cerebral and olivopontocerebellar atrophy.

Orthopedic: Growth deficiency.

GI/GU: Hypogonadotropic hypogonadism.

Other: Xeroderma pigmentosum. Telangiectasis. Keratoses. Angiomas. Extreme sunlight sensitivity, with progressive skin deterioration. Eventually, basal cell carcinomas, squamous cell carcinomas, or melanomas develop. Internal malignancies can develop, including solid organ tumors and leukemia. May exhibit immune dysfunction and frequent infections.

Miscellaneous: de Sanctis and Cacchione originally proposed (in Italian) a somewhat less sensitive synonym: xerodermic idiocy. Needless to say, this synonym is no longer routinely used.

Anesthetic Considerations: Neurologic dysfunction may make the smooth induction of general anesthesia challenging. Chronic use of anticonvulsant medications can affect the kinetics of some anesthetic drugs. Care must be taken in positioning and padding the patient secondary to atrophic skin changes and the potential for injury to the skin. Patients with photophobia may be sensitive to bright operating room lights.

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Desmolase deficiency

See 17,20-Desmolase deficiency

de Toni-Debre-Fanconi syndrome

See Fanconi syndrome

Diamond-Blackfan anemia

Synonym: Blackfan-Diamond syndrome; Aase-Smith syndrome II. (Includes Aase syndrome)

MIM #: 105650

This disease of congenital red blood cell hypoplasia appears to have multiple etiologies. It can be autosomal dominant or recessive. Many cases are sporadic. Approximately 25% are due to defects in the gene encoding ribosomal protein S19, found on the long arm of chromosome 19. Other loci have been mapped to chromosomes 3, 8, 10, and 12. Forty to fifty percent of patients have associated anomalies, primarily cardiac, craniofacial, orthopedic, or genitourinary. Short stature and an increased risk of malignancy are also commonly associated. **Aase syndrome** is a form of Diamond-Blackfan anemia that involves congenital anemia and radial/thumb abnormalities. It is caused by a mutation in the gene encoding ribosomal protein L5 (*RPL5*). It is likely autosomal recessive but may be autosomal dominant.

HEENT/Airway: Hypertelorism. Snub nose. Thick upper lip. May have high arched or cleft palate. May have micrognathia or retrognathia. May have short neck.

Orthopedic: Short stature. May have radial anomalies. May have triphalangeal thumbs or other hand anomalies.

GI/GU: Hepatosplenomegaly. Congenital malformations of the urinary system.

Other: Congenital red blood cell hypoplasia leading to normochromic macrocytic anemia. This may be steroid responsive and may require chronic transfusions. Transfusion-related complications may occur. There is an increased risk of leukemia. Fetal anemia can present with hydrops fetalis.

Miscellaneous: Dr. Louis Diamond was responsible for introducing exchange transfusion as a successful treatment for hemolytic disease of the newborn (Rh sensitization). He is also the Diamond of Shwachman-Diamond syndrome. Dr. Blackfan was the first (with Dandy) to describe Dandy-Walker malformation. He was offered, and refused, the deanship of the Harvard Medical School, in order to remain active clinically.

Anesthetic Considerations: The patient's hematocrit should be obtained before any procedure with the potential for significant blood loss. Oxygen-carrying capacity must be maintained perioperatively. Direct laryngoscopy and tracheal intubation may be difficult in patients with craniofacial abnormalities. Patients who are on chronic steroid therapy need perioperative stress doses of steroids. Chronic transfusion can potentially result in iron overload, with cardiomyopathy. Radial anomalies may limit peripheral vascular access and make placement of a radial arterial catheter more difficult.

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Diaphyseal aclasis

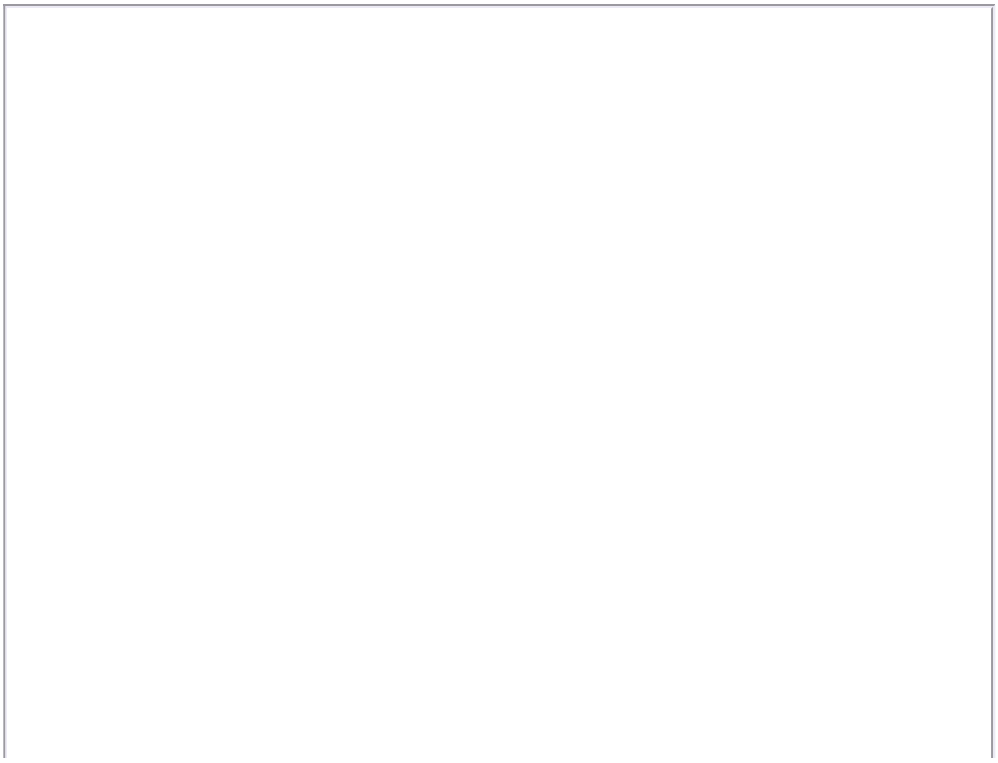
See Multiple exostoses syndrome

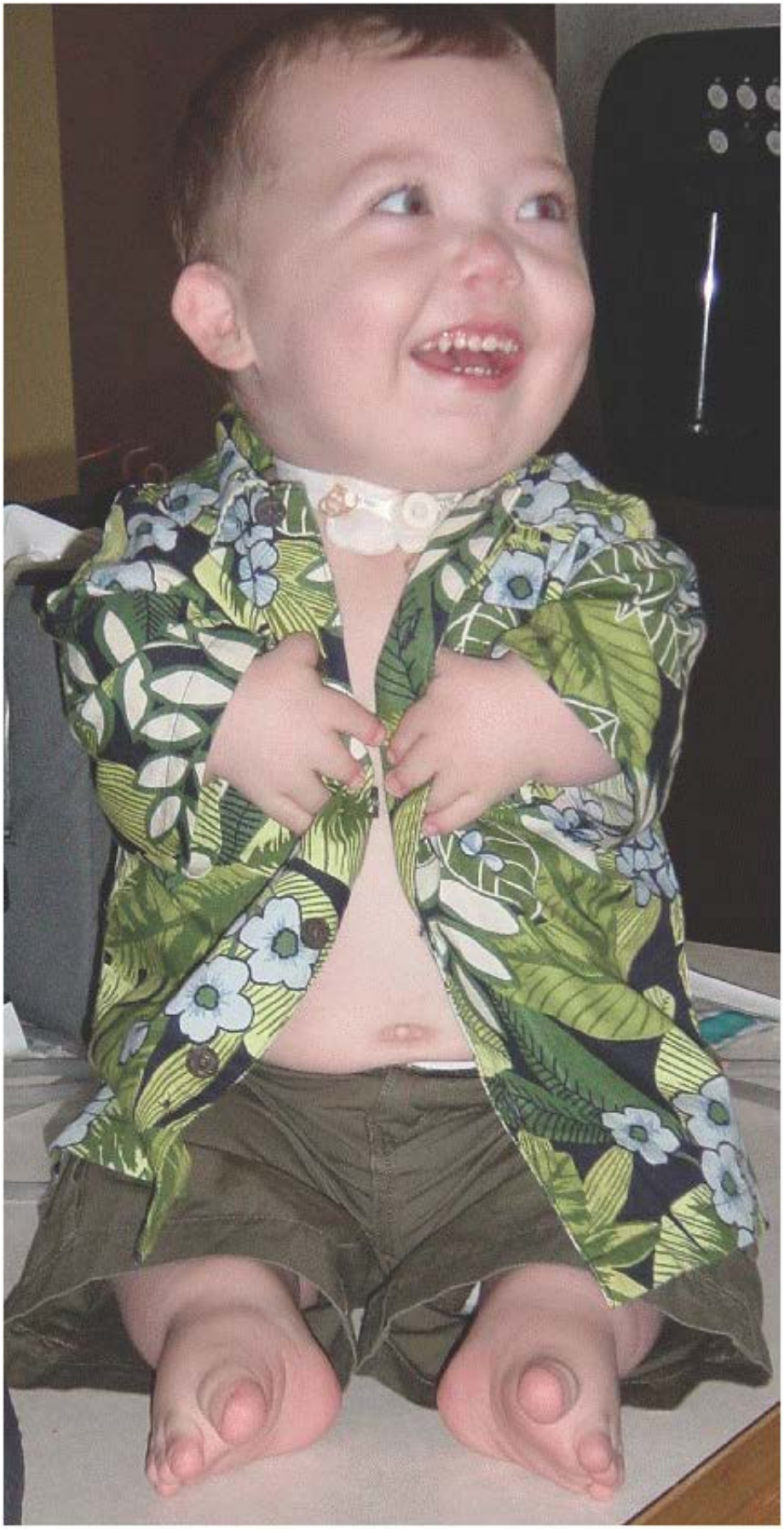
Diastrophic dysplasia

Synonym: Diastrophic nanism

MIM #: 222600

This autosomal recessive, short-limbed dwarfism is further characterized by generalized joint dysplasia, decreased joint mobility, spine anomalies, clubfeet, and hypertrophic auricular cartilage. There is a significant amount of phenotypic variability with this syndrome. The gene for this disorder, *SLC26A2 (DTDST)*, is a sulfate transporter gene. The gene appears to encode a novel sulfate transporter. Mutations in the *DTDST* gene also cause achondrogenesis type IB (see earlier) and multiple epiphyseal dysplasia (see later); therefore, these disorders are allelic. It is also allelic with atelosteogenesis type II (not discussed in this text).





Diastrophic dysplasia. This young boy has diastrophic dysplasia.

HEENT/Airway: Hypertrophic auricular cartilage— may eventually become ossified. Conductive hearing loss. Micrognathia. Malocclusion and occasional hypodontia. Cleft palate. Laryngomalacia, tracheomalacia, and/or bronchomalacia; laryngotracheal stenosis—may cause airway obstruction. Hoarse voice.

Chest: Premature calcification of the costal cartilages. Accessory manubrial ossification center. Severe kyphoscoliosis leads to restrictive lung disease in some.

Small rib cage and tracheal instability can lead to serious neonatal respiratory compromise.

Neuromuscular: Intelligence is normal. Spinal cord compression can occur as a consequence of severe kyphoscoliosis. Occasional intracranial calcifications.

Orthopedic: Progressive and marked short stature from lack of pubertal growth spurt. Short limbs. Cervical vertebral hypoplasia or kyphosis with occasional subluxation of C2-3, which may resolve by adulthood (mid-cervical kyphosis is unique to diastrophic dysplasia). Cervical spina bifida. May have odontoid hypoplasia. Broadening of the cervical spine. Cervical lordosis and degenerative changes in adults. Scoliosis. Marked lumbar lordosis and thoracic kyphoscoliosis. Spina bifida occulta in midcervical to upper thoracic vertebrae. Interpeduncular narrowing of L1-5. Generalized joint dysplasia with decreased joint mobility, especially at the elbows, hips, and knees. Early hip degeneration. May have joint webbing. Patellar subluxation. Abduction of the thumbs (hitchhiker thumbs) and great toes. Clubfeet that are particularly difficult to correct surgically.

Miscellaneous: "Diastrophic" is from the Greek, meaning tortuous or crooked, referring to the kyphoscoliosis. It was appropriated from geology, where diastrophism is the process of bending the earth's crust. The disorder is particularly prevalent in Finns. Matt Roloff, the father on the American reality television series *Little People, Big World* has diastrophic dysplasia.

The location of the *DTDST* gene was found fortuitously by a group mapping the gene for Treacher Collins syndrome.

Anesthetic Considerations: Patients may have airway obstruction secondary to laryngotracheobronchomalacia or laryngotracheal stenosis. Up to 25% of infants die of airway complications. Airway complications may be exacerbated by general anesthesia. Patients with laryngotracheal stenosis may require a smaller-than-predicted endotracheal tube. Micrognathia can further complicate laryngoscopy and tracheal intubation. Patients may have restrictive lung disease. Patients may require a period of postoperative ventilation secondary to airway obstruction and/or lung disease.

These patients are at risk for subluxation at C2-3, in addition to baseline cord compression. The head must be carefully positioned during laryngoscopy to avoid hyperextension. Patients must be carefully positioned and padded for the procedure because of limited joint mobility.

Because of their relatively short limbs, these patients may require a smaller than normal blood pressure cuff. An appropriately sized cuff should cover two-thirds of the length of the upper arm. Peripheral intravenous access may be difficult.

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Diastrophic nanism

See Diastrophic dysplasia

Dibasic amino aciduria type 2

See Lysinuric protein intolerance

DIDMOAD syndrome

Synonym: Wolfram syndrome

MIM #: 222300

Diabetes **I**nsipidus, **D**iabetes **M**ellitus, **O**ptic **A**trophy, and **D**eafness is likely an autosomal recessive disorder. Only insulin-dependent diabetes mellitus and optic atrophy are required to make the diagnosis. Diabetes mellitus is often the presenting problem, usually in the first decade of life. This autosomal recessive disorder is due to mutations in the gene *WFS1*, which encodes the protein wolframin, an endoplasmic reticulum membrane glycoprotein, but has also been associated with abnormalities at a different locus on chromosome 4. There may also be a mitochondrial form of the syndrome. The syndrome is clinically variable.

HEENT/Airway: Optic atrophy, ptosis, nystagmus. Progressive sensorineural hearing loss and deafness.

Cardiovascular: May develop cardiomyopathy.

Neuromuscular: Autonomic dysfunction, intellectual disability, dementia, seizures. Ataxia, tremor, peripheral neuropathy. Dysphagia, dysarthria. Magnetic resonance imaging scans show widespread atrophic brain changes. Brainstem atrophy can lead to central respiratory failure (often the terminal condition). Psychiatric illness. Patients may be compulsive or physically aggressive. There is an increased risk of suicide.

GI/GU: Hydronephrosis, hydroureter, and distended bladder without vesicoureteral reflux. May have testicular atrophy.

Other: Insulin-dependent diabetes mellitus, central diabetes insipidus. Megaloblastic anemia (thiamine responsive) has been reported. May have hypothyroidism.

Anesthetic Considerations: Psychiatric illness may make preanesthetic management more difficult. When meeting

the patient before surgery, be sensitive to the possibility that they have hearing or visual loss. Glucose control (insulin-dependent diabetes mellitus) and water balance (central diabetes insipidus) are critical. Patients with significant brainstem dysfunction may have dysphagia and/or abnormal control of respiratory function. Patients may have autonomic dysfunction. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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DiGeorge syndrome

Synonym: 22q11.2 deletion syndrome

MIM #: 188400

This well-known syndrome has been shown in most cases to be due to microdeletions of chromosome 22 (22q11.2). Most cases are sporadic, but autosomal dominant inheritance has been demonstrated in up to 25% of cases. Mutations in the gene *TBX1*, located in the middle of the microdeletion region, is thought to be involved in producing some of the features. This gene, a transcription factor, is involved in developmental processes. The phenotypic presentation can vary, and the same deletion(s) can result in Shprintzen syndrome (velocardiofacial syndrome, see later), conotruncal anomaly face syndrome (Takao syndrome, not discussed in this text), and isolated conotruncal cardiac defects (truncus arteriosus, tetralogy of Fallot, or interrupted aortic arch). Identical twins have had the same genotype, but a different phenotypic presentation. DiGeorge syndrome has also been associated with prenatal exposure to alcohol and to isotretinoin (Accutane).

Approximately 80% of affected people will have cardiovascular anomalies and 50% will have otolaryngologic manifestations. Up to 60% will have at least transient hypocalcemia, but only 2% will have major immunologic insufficiency.

Most features can be traced back to abnormalities of the third and fourth pharyngeal pouches and fourth branchial arch *in utero*, and include defects in the development of the thymus, parathyroids (leading to hypocalcemia), and great vessels. Neonatal morbidity and mortality are associated with the cardiac defects, sequelae of T-cell immunodeficiency, and seizures related to hypocalcemia.

HEENT/Airway: Telecanthus/lateral displacement of inner canthi and short palpebral fissures with either an upward or a downward slant. Sclerocornea, other ocular anomalies. Low-set ears with lower-than-usual vertical dimension and abnormal folding of the pinna. Hearing deficits. Bulbous nose. Choanal atresia with velopharyngeal incompetence. The philtrum is short and the mouth small. Overt or submucous cleft palate. Micrognathia in infancy. Laryngomalacia, tracheomalacia. Trachea may be short.

Cardiovascular: A variety of conotruncal cardiac defects, namely truncus arteriosus, tetralogy of Fallot, and interrupted aortic arch. Truncus arteriosus and tetralogy of Fallot are often associated with a right aortic arch.

Aberrant subclavian arteries.

Chest: May have recurrent pulmonary infections. Occasional bronchomalacia.

Neuromuscular: Hypocalcemic tetany or seizures in neonates. Polymicrogyria. Intellectual disability of mild or moderate degree. About 20% of adults carry a psychiatric diagnosis, particularly schizophrenia.

GI/GU: Occasional esophageal atresia with tracheoesophageal fistula, imperforate anus, diaphragmatic hernia. It has been suggested that there is an increase in feeding difficulties due to pharyngeal and esophageal dysmotility. Renal dysplasia, hydronephrosis, unilateral renal agenesis.

Other: Neonatal hypocalcemia (and subsequent seizures), which can be intermittent, secondary to hypoplastic or absent parathyroid glands. The hypocalcemia typically resolves in early childhood. Abnormal parathyroid function in up to 70%, but abnormal parathyroid function can only be documented in some children and in adults with provocative tests. Cell-mediated immune deficiency from a T-cell deficiency secondary to a hypoplastic or aplastic thymus gland may result in severe infections. May have short stature, and growth hormone deficiency has recently been documented in some patients. May have hypothyroidism.

Miscellaneous: In past years, the absence of some features of the syndrome in any particular patient led to the diagnosis of a “forme fruste” of the syndrome. Approximately one in eight children with tetralogy of Fallot, and one in five with truncus arteriosus, will have DiGeorge syndrome.

Anesthetic Considerations: Micrognathia, if present, may make direct laryngoscopy and tracheal intubation difficult. A short trachea can result in inadvertent endobronchial intubation. Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Subclavian access may be difficult in patients with aberrant subclavian arteries. Neonates should have their serum calcium level evaluated preoperatively. Hyperventilation may worsen hypocalcemia, as may the infusion of citrated blood products. Blood products should be irradiated to prevent graft versus host disease. Careful aseptic technique is indicated. Patients with congenital heart disease should receive an appropriately tailored anesthetic. If present, renal disease affects perioperative fluid management and the choice of anesthetic drugs. This region of chromosome 22 also includes the gene encoding catechol-*O*-methyltransferase (*COMT*), responsible for degrading catecholamines. A patient has been reported with unexpected tachycardia from epinephrine containing local analgesic given during dental surgery, possibly from being hemizygous for *COMT*.

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Dilantin

See Fetal hydantoin syndrome

Disseminated lipogranulomatosis

See Farber disease

Distal arthrogryposis

Included in arthrogryposis

Distal arthrogryposis, type 2A

See Whistling face syndrome

Distal arthrogryposis, type 7

See Dutch-Kentucky syndrome

Distichiasis-lymphedema syndrome

See lymphedema-distichiasis syndrome

DK-phocomelia syndrome

Synonym: von Voss-Cherstvoy syndrome

MIM #: 223340

This possibly autosomal recessive disorder is characterized by phocomelia, thrombocytopenia, encephalocele, and urogenital anomalies. The responsible gene and gene product are not known.

HEENT/Airway: Facial asymmetry (particularly in patients with encephalocele). One patient has been described with choanal atresia. May have cleft palate.

Cardiovascular: May have valvular defects. May have abnormal branching of coronary arteries.

Chest: May have abnormal lung lobation. May have agenesis of the diaphragm.

Neuromuscular: Occipital or parietooccipital encephalocele. May have seizures.

Orthopedic: Phocomelia. May have congenitally dislocated hips.

GI/GU: Renal anomalies—including horseshoe kidney, renal aplasia. Genital anomalies, including ambiguous genitalia. May have omphalocele, anal atresia, accessory spleens.

Other: Thrombocytopenia.

Miscellaneous: The "DK" in the synonym DK-phocomelia comes from the surnames of the two original patients. The syndrome was initially thought to be lethal in infancy but has since been recognized in older children and even in an adult (1).

Anesthetic Considerations: A platelet count should be obtained preoperatively. Phocomelia may make fixation of an appropriate-sized blood pressure cuff difficult, and falsely high pressures may be displayed by noninvasive monitors. An appropriately sized blood pressure cuff should cover two-thirds of the upper arm length. Renal anomalies, if they affect renal function, have implications for perioperative fluid management and the choice of anesthetic drugs.

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Donohue syndrome

See Leprechaunism

Down syndrome

Synonym: Trisomy 21

MIM #: 190685

Trisomy 21 is almost certainly the most widely appreciated chromosomal disease among nongeneticists. Besides the distinctive facies, there are significant airway and cardiac findings, and there is variable intellectual disability.

HEENT/Airway: Brachycephaly. Upslanting palpebral fissures. Brushfield spots are seen on the iris. Strabismus is sometimes present. Small external ear canals. Narrowed nasopharynx. Flat nasal bridge. Furrowed tongue. Macroglossia and pharyngeal muscle hypotonia tend to cause upper airway obstruction. High-arched palate; tonsillar and adenoidal hypertrophy. Micrognathia. Teeth may be small or fused. Short, broad neck. Small hypopharynx. Trachea may be small, even in adults without congenital heart disease.

Down syndrome. FIG. 1. A young boy with typical Down syndrome facies. He has a history of congenital duodenal atresia, hypothyroidism, and subglottic stenosis. He has no cardiac disease. He has obvious macroglossia and suffers from obstructive sleep apnea.

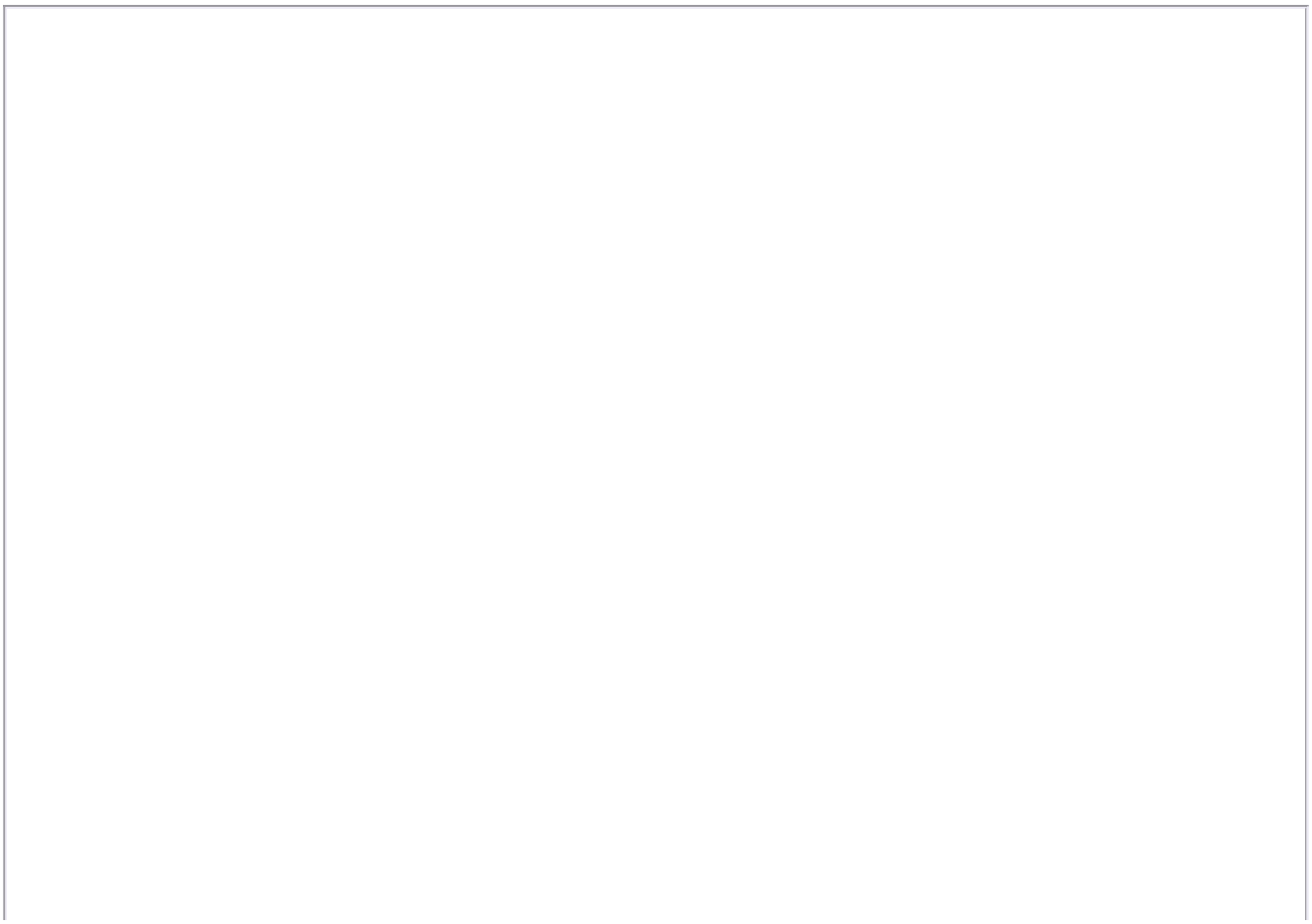
Chest: May have chronic upper airway obstruction with hypoventilation and obstructive sleep apnea. Recurrent pulmonary infections may develop.

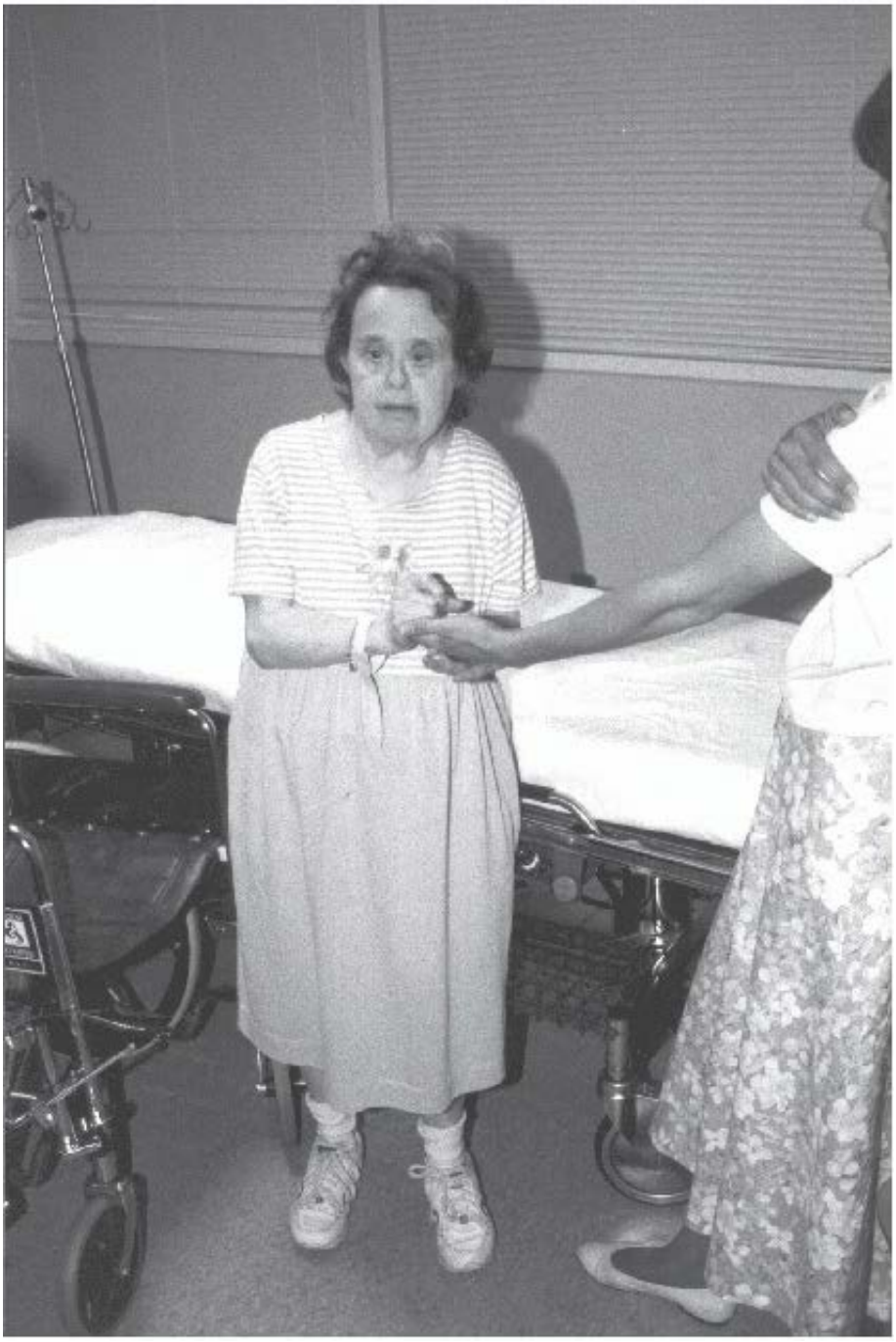
Cardiovascular: Approximately one-half have congenital heart disease. Of those, approximately one-half have endocardial cushion defects (including complete atrioventricular canal), and the remaining half have a variety of defects, typically atrial septal defect, ventricular septal defect, or patent ductus arteriosus. Tetralogy of Fallot can also be seen. Children with congenital heart disease with left-to-right shunting are thought to acquire pulmonary hypertension and pulmonary vascular disease at an earlier stage than children with a similar cardiac lesion without Down syndrome. This is clouded by upper airway obstruction and hypoventilation that many of these patients have, which can also increase pulmonary arterial pressure.

Neuromuscular: Hypotonia and variable intellectual disability. Children raised at home typically do better than those raised in institutions, which is uncommon today. These children are often very friendly. Dementia and Parkinsonism in older adults. Intellectual decline with aging to middle age and older.

Orthopedic: Height (and weight) below those of normal children. Growth charts for Down syndrome

children are available. Joint laxity. Lax cervical ligaments can result in atlantooccipital or atlantoaxial instability and dislocation. Bony abnormalities such as flattening of the occipital condyles can also increase the risk of atlantooccipital instability. There can also be C2 and odontoid abnormalities, which can increase the risk of cervical instability. Atlantoaxial instability can be demonstrated in 7% to 36% of children radiographically. The incidence of atlantooccipital instability is approximately 8.5%. Lax ligaments can affect any joint. Patients have clinodactyly of the fifth finger; short, stubby hands; and simian creases (horizontal palmar creases that cross the palm in a single crease).





Down syndrome. FIG. 2. A 66-year-old woman with Down syndrome. Other than recurrent pulmonary infections and hypothyroidism, she has been healthy. Her only surgery was a cholecystectomy. Like other adults with Down syndrome, her facial features have lost some of the classic features of children with Down syndrome.

GI/GU: There is a well-known association with congenital duodenal atresia or stenosis. Increased incidence of Hirschsprung disease (see later). Males are infertile. Females have decreased fertility.

Other: May have abnormal cellular immune function predisposing to infection. May have high white blood cell

counts in response to infection (leukemoid reaction). The incidence of true leukemia is also elevated, particularly acute megakaryoblastic leukemia and B-cell ALL (acute lymphoblastic leukemia). There is an increased incidence of congenital hypothyroidism and the development of antithyroid antibodies. May develop obesity.

Miscellaneous: John Langdon Down was very progressive for his time, and he publically challenged the popular belief that women who sought higher educational degrees were more likely to bear children who would be intellectually deficient. In his original report (1866) on what would become known as Down syndrome, Down tried to differentiate these patients from infants with hypothyroidism ("cretins"). Waardenburg first observed that the disorder might be due to a chromosomal abnormality, which was confirmed by Lejeune in 1959.

Figures with features of Down syndrome have been discovered on pre-Columbian pottery dating from approximately 500 BCE. Simian creases can be found as normal variants in non-Down patients. One of us once knew a genetics fellow with bilateral simian creases.

Anesthetic Considerations: Intellectual disability or behavioral problems may affect the choice of technique for the induction of anesthesia. Mask ventilation may be difficult secondary to macroglossia, midface hypoplasia, and pharyngeal muscle hypotonia—an oral airway is usually helpful. Laryngoscopy and tracheal intubation may be difficult secondary to macroglossia and a small hypopharynx. Some patients will also have micrognathia. Difficult laryngoscopy due to lingual tonsillar hypertrophy has been reported (10). Children with Down syndrome have smaller tracheas than age-matched controls. Expect to use an endotracheal tube one to two sizes smaller than that predicted by age (12). Adults can also have relatively small tracheas. Postoperative stridor and respiratory complications are more common than in the general population. Preexisting obstructive sleep apnea, macroglossia, and pharyngeal muscle hypotonia may lead to upper airway obstruction, and patients must be observed closely in the postanesthesia care unit.

Although atlantoaxial instability can occur after approximately 4 years of age, many thousands of children have had laryngoscopy and intubation without untoward incident. However, there are case reports of subluxation after intubation (15,18,20,21). The diagnosis of instability is difficult (8) and involves flexion-extension views. Laryngoscopy should be done with care to minimize flexion or extension of the neck. Recommendations by some for routine preoperative flexion, neutral, and extension lateral radiographs of the neck seem excessive to most practitioners. Currently, only a small percentage would obtain radiographs in asymptomatic patients (13), and x-ray criteria are not

predictive of a tendency to dislocate. Rotary cervical dislocations can be related to surgical positioning, often for otolaryngologic surgery. If possible, the patient and table should be rotated as a unit with rotation of the head kept to a minimum. Dislocations are typically preceded by signs or symptoms (19), so a thorough preoperative history and physical examination are essential. The preoperative history should include questions about head or neck pain and any recent changes in gross and fine motor function, and the physical exam should screen for abnormal gait and hyperreflexia.

A significant number of these patients have congenital heart disease. Some patients also have some degree of pulmonary hypertension, due to either heart disease or chronic upper airway obstruction, or a combination of both. A quick screen for endocardial cushion defects (present in approximately 25%) is a superior QRS axis. An increased incidence of bradycardia during induction has been reported in children with Down syndrome, irrespective of whether or not they have known congenital heart disease (2,3,9,11). In the majority of cases, the heart rate has responded promptly to a lowering of the volatile anesthetic agent. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

These patients are more sensitive to the mydriatic and chronotropic effects of atropine (because of altered sensitivity of cholinergic receptors, an imbalance of cholinergic and adrenergic receptors, or altered distribution of

the drug), but no ill effects have been seen with normal doses of atropine. Hypothyroidism, when present, could result in delayed gastric emptying, alterations in drug metabolism, and impaired temperature regulation.

Excess subdermal fat in the extremities, prominent skin folds, and abnormal vascular patterns contribute to the vascular access difficulties common in these patients. These patients can be relatively challenging to sedate for cases requiring monitored anesthesia care, without causing hypoventilation.

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Note: Although we have endeavored to include essentially all papers in the English language anesthesia literature relevant to specific syndromes, there are too many dealing with anesthesia and Down syndrome to make that practical, and we have had to be selective.

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Drash syndrome

Synonym: Denys-Drash syndrome

MIM #: 194080

This autosomal dominant syndrome is characterized by pseudohermaphroditism, Wilms tumor, degenerative renal disease, and hypertension. The disorder is due to a mutation in the Wilms tumor suppressor gene (*WT1*). This gene is a transcription activator or repressor and is required for normal formation of the genitourinary system and mesothelial tissues. There is phenotypic overlap with aniridia-Wilms tumor association (see earlier) and Frasier syndrome (see later), which is also due to abnormalities of *WT1*.

Cardiovascular: Hypertension secondary to renal failure.

GI/GU: Wilms tumor, usually bilateral. Male pseudohermaphroditism. Ambiguous female genitalia with

gonadal dysgenesis, both testicular and ovarian tissue present. Renal failure with mesangial sclerosis presenting as proteinuria and often nephrotic syndrome, and progressing to end-stage renal failure in young childhood. Gonadoblastoma. Primary amenorrhea.

Anesthetic Considerations: Renal function should be evaluated preoperatively. Electrolytes and hematocrit should be evaluated preoperatively in patients with chronic renal failure. Patients with renal dysfunction need careful titration of perioperative fluids, and avoidance or reduced dosages of renally excreted drugs. Nephrotoxic medications should be avoided. A certain degree of sensitivity is required when speaking with patients, or families of patients, with intersex disorders.

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Dubin-Johnson syndrome

MIM #: 237500

This is an autosomal recessive disease of hyperbilirubinemia, mostly conjugated. Penetrance is reduced in females, so males are more often affected. Most patients are asymptomatic. There is a defect in hepatocellular secretion of bilirubin glucuronide and other organic ions. Hepatic cells are stained with a black pigment. The disorder is due to abnormalities in the gene *CMOAT* (canalicular multispecific organic anion transporter), first described in rats. It is also known as *MRP2*, a multidrug resistance protein, which is related to resistance to some chemotherapeutic

drugs. Clinically, this syndrome is similar to Rotor syndrome (see later). Other diseases of hepatic bilirubin metabolism include Crigler-Najjar syndrome (see earlier) and Gilbert syndrome (see later).

GI/GU: Hyperbilirubinemia without pruritus. Serum bilirubin is typically between 2 and 5 mg/dL but may be as high as 25 mg/dL. Occasional hepatomegaly, abdominal pain, or splenomegaly. The degree of hyperbilirubinemia can be markedly increased by intercurrent stress, illness, pregnancy, or birth control pills. Black liver. Cholestasis.

Miscellaneous: This disease is particularly common among Iranian Jews, where it is also associated with factor VII deficiency.

Nathan Dubin, chair of pathology at the Medical College of Pennsylvania, often published humorous verse and limericks under a pseudonym. Frank Johnson became curator of the Armed Forces Medical Museum.

Anesthetic Considerations: These patients are asymptomatic, and there are no specific anesthetic considerations. Although sulfonamides, some cephalosporins, and intravenous contrast agents can increase free bilirubin levels by displacing bilirubin from albumin, no currently used anesthetic agents are known to displace bilirubin to a degree that would contraindicate their use. The stress of surgery or a perioperative infection can exacerbate the hyperbilirubinemia. Hepatic synthetic function is normal in these patients.

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Dubowitz syndrome

MIM #: 223370

This likely autosomal recessive disorder is distinguished by characteristic facies, microcephaly, infantile eczema, growth deficiency, and intellectual disability. The facies have been likened to those of the fetal alcohol syndrome (see later). The responsible gene and gene product are not known.

HEENT/Airway: Microcephaly. Characteristic small facies with indistinct supraorbital ridge. Facial asymmetry. Short palpebral fissures with telecanthus and apparent hypertelorism. May have ptosis, epicanthal folds, blepharophimosis, strabismus, microphthalmia, hypoplasia of the iris, or colobomas. Malformed ears. Broad nasal tip. Dental abnormalities, including late eruption, caries, and missing teeth. Micrognathia. Occasional submucosal cleft palate, velopharyngeal insufficiency.

Cardiovascular: Occasional cardiac defect. Occlusion of the internal carotid artery and an aberrant right subclavian artery have been documented in two patients. Stenosis of the coronary arteries has been described in a 19-year-old patient.

Neuromuscular: Variable degree of intellectual disability. Variable hypotonia. High-pitched, hoarse cry in infancy. Delayed speech. Hyperactivity or attention deficit in most. Other behavioral problems. Cervical vertebral anomalies have been described.

Orthopedic: Growth deficiency. Delayed osseous maturation. Brachyclinodactyly of the fifth fingers. Syndactyly of the second and third toes.

GI/GU: Frequent vomiting. Chronic diarrhea. Gastroesophageal reflux. Inguinal hernia. Cryptorchidism. Pilonidal dimple. May have hypospadias.

Other: Intrauterine growth retardation. Eczema, noted on the face and flexural areas of infants, has usually cleared by age 2 to 4 years, with occasional flare-ups. Sparse scalp and eyebrow hair. Occasional bone marrow hypoplasia or aplastic anemia. Occasional immunoglobulin deficiency with recurrent respiratory and gastrointestinal infections. Occasional malignancy, including neuroblastoma, lymphoma, and leukemia.

Anesthetic Considerations: Behavioral problems may affect the choice of technique for the induction of anesthesia. Missing or loose teeth should be documented before the induction of anesthesia. Patients with gastroesophageal reflux or frequent vomiting are at increased risk for perioperative aspiration. Micrognathia could potentially result in difficulty with laryngoscopy and intubation, and submental intubation has been reported in a single patient in the Dutch literature. Cervical spine abnormalities have been reported, so care should be exercised during intubation and positioning. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Duchenne muscular dystrophy

MIM #: 310200

This X-linked muscular dystrophy is biochemically closely related to both Becker muscular dystrophy (see earlier) and X-linked dilated cardiomyopathy (not discussed in this text). Duchenne muscular dystrophy is a progressive myopathy involving skeletal, smooth, and cardiac muscle, with the inevitable development of severe respiratory and myocardial disease by the mid to late teens. Female carriers can have mild clinical manifestations. Patients with Duchenne muscular dystrophy have deletion mutations in the dystrophin gene that prevent any expression of dystrophin in skeletal muscles (frame shifts or stop codons). Patients with Becker muscular dystrophy have dystrophin of altered size or reduced abundance because of deletion mutations that maintain the reading frame during gene transcription. Patients with X-linked cardiomyopathy have defects in a cardiac-specific promotor region or have altered mRNA splicing, such that only cardiac, but not striated, muscle dystrophin is affected.

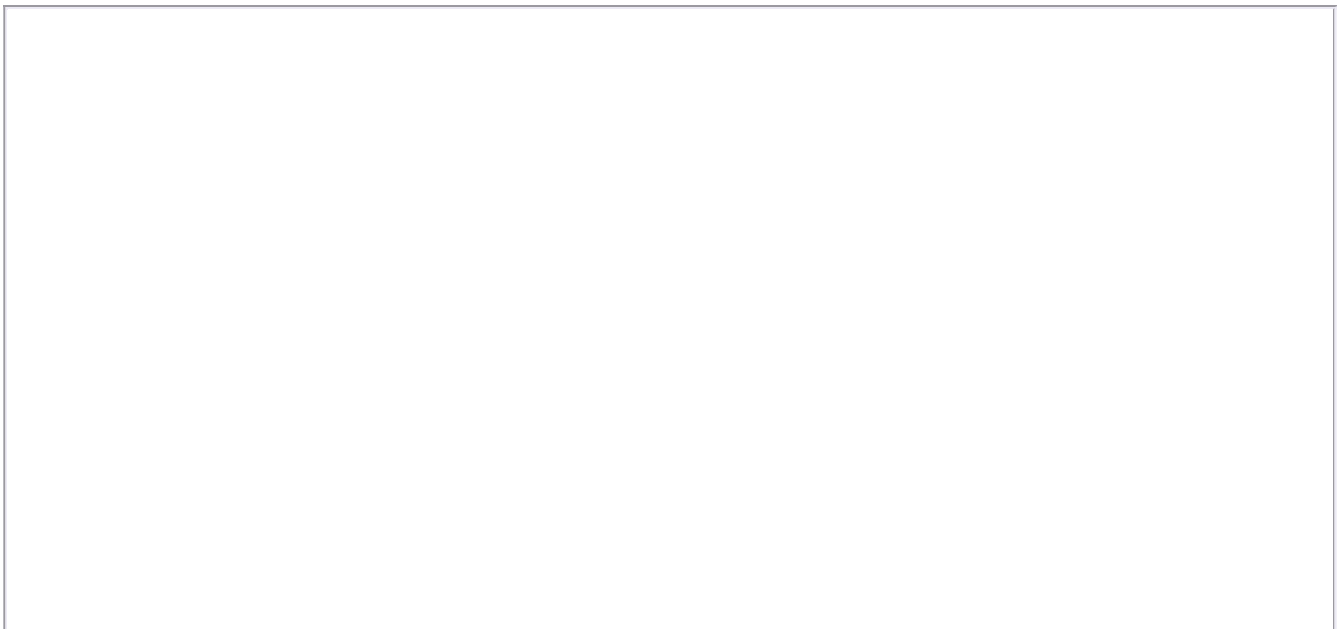
Dystrophin is a very large protein (accounting for the relatively large number of spontaneous mutations) that resides immediately adjacent to the cell membrane and serves to help anchor the contractile apparatus. Dystrophin is responsible for connecting the sarcolemma to the extracellular matrix. It is found in striated muscle, smooth muscle, and cardiac muscle. Very large deletions in the dystrophin gene can also affect two nearby genes, leading to hyperglycerolemia (see later) and congenital adrenal hypoplasia (*not* hyperplasia).

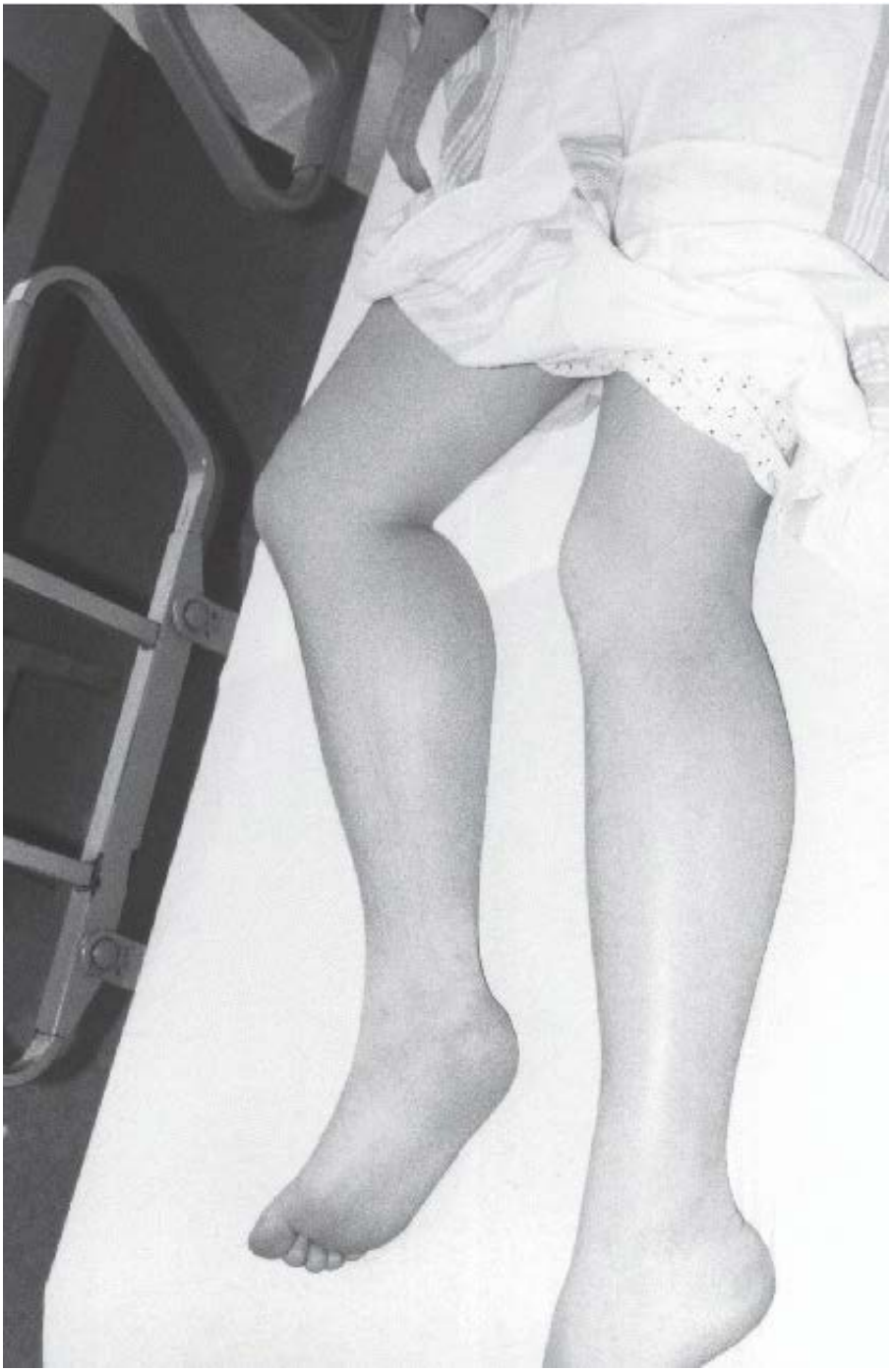
HEENT/Airway: Large tongue. Red-green color defect (secondary to downstream deletion).

Chest: Respiratory muscle weakness and swallowing difficulties can lead to recurrent respiratory infections. Abdominal muscle weakness results in earlier expiratory muscle weakness. Early diaphragmatic preservation preserves inspiratory function through the first decade. Scoliosis may cause restrictive lung disease. Most patients eventually die a respiratory death.

Cardiovascular: Dilated cardiomyopathy. Ninety percent have a typical abnormal electrocardiogram with tall R waves in the right precordium, deep Q waves in the left precordial leads, biventricular hypertrophy, and sinus tachycardia at rest. Heart block or arrhythmias can develop from fibrosis of the conduction system. Heart failure occurs in adolescence. Patients may be relatively asymptomatic for the degree of myocardial dysfunction because they have limited activity. The severity of the cardiomyopathy does not mirror the severity of the peripheral muscular disease. Female carriers also can have a cardiomyopathy, which develops in adulthood.

Neuromuscular: Generalized myopathy. A classic finding is pseudohypertrophy of the calf muscles. Resting elevations in creatine kinase. Some patients may have mild intellectual disability.





Duchenne muscular dystrophy. Calf pseudohypertrophy in a 12-year-old girl with Duchenne muscular dystrophy. She has mild to moderate muscle weakness, pes cavus, a mild learning disability, and hypothyroidism.

Orthopedic: Flexion contractures. Scoliosis, lordosis.

GI/GU: There may be gastric hypomotility with delayed gastric emptying. In the extreme, there may be gastric dilatation with the risk of aspiration, or abdominal distention from small bowel ileus. Constipation. Myoglobinuria

may result in renal impairment.

Other: The dystrophin gene is closely linked to the gene for glycerol kinase, and patients with Duchenne muscular dystrophy can also have hyperglycerolemia (see later). Typically, those patients with mild intellectual disability are most likely also to have hyperglycerolemia and congenital adrenal hypoplasia. Thrombotic events have been reported in some patients.

Miscellaneous: Unexpected rhabdomyolysis with hyperkalemic arrest after succinylcholine in boys with undiagnosed Duchenne muscular dystrophy was the primary reason behind the change in the package labeling in the United States for succinylcholine several years ago, cautioning against its use in children. As a consequence of muscle regeneration (not specifically of dystrophic muscle), there is postsynaptic expression of both fetal and mature nicotinic acetylcholine receptors. Mice have a similar genetic defect but do not become dystrophic. It is thought that a related protein, eutrophin, somehow substitutes function for the missing dystrophin. The gene for eutrophin is active in mouse muscle. It is present but inactive in human muscle.

Separated from his only child after his wife's death, Duchenne led a lonely existence in Paris working primarily in charity clinics. He pursued his clinical neurologic studies outside of mainstream Parisian medicine, and was never given any official recognition by the *Académie de Médecine* or the *Institut de France*, although he was made an honorary member of the medical academies in Rome, Madrid, Stockholm, St. Petersburg, Geneva, and Leipzig.

Anesthetic Considerations: Perioperative complications may be life threatening. Preoperative evaluation of pulmonary and cardiac function usually involves room air pulse oximetry, arterial blood gas analysis, pulmonary function testing, a chest x-ray, an electrocardiogram, and an echocardiogram. Airway management may be difficult secondary to a large tongue and joint contractures (3). A patient has been reported who repeatedly had tracheal occlusion when placed in the prone position because of impingement of the trachea between the sternum and a lordotic thoracic spine (26). Postoperative respiratory complications are common secondary to the combination of scoliosis, poor cough, and muscle weakness. Prolonged postoperative ventilation may be necessary. Opioids should be titrated with caution. Regional anesthesia/analgesia should be strongly considered (particularly when it has the potential to improve postoperative respiratory function), although regional techniques may be difficult to perform due to kyphoscoliosis and joint contractures. Epidural anesthesia has been used with success using normal dosing (30). Patients may have gastric hypomotility with delayed gastric emptying and are at increased risk for perioperative aspiration. An intraoperative nasogastric tube may be indicated. Vascular access may be difficult in patients with joint contractures. Patients with joint contractures must be positioned and padded carefully.

Heart block or arrhythmias can develop from fibrosis of the conduction system. Heart failure can develop in adolescence, and acute onset of heart failure intraoperatively in a previously (cardiac) asymptomatic patient with a normal preoperative resting echocardiogram has been reported. Anesthetic agents that depress cardiac function should be avoided. Cardiac arrest has also been reported after total intravenous anesthesia (23). Female carriers of the abnormal gene can also have a cardiomyopathy, but usually not until adulthood.

Neuromuscular blockade is often unnecessary because of preexisting muscle weakness. Although a

normal response to succinylcholine has been reported, hyperkalemic cardiac arrest secondary to rhabdomyolysis is a well-known response, and the use of succinylcholine is contraindicated in these patients. All of the commonly available nondepolarizing muscle relaxants have been used successfully in patients with Duchenne muscular dystrophy. There are a couple of reports documenting mild increases in sensitivity to nondepolarizing muscle relaxants (24,27). More common are reports of prolonged onset time (3,10,17), which must be taken into account when trying to secure the airway rapidly. Finally, prolonged duration of action has been reported after the use of nondepolarizing muscle relaxants (10,15,17,24). It appears that the response to nondepolarizing muscle relaxants

may depend on the degree of disease progression (6).

An association between Duchenne muscular dystrophy and malignant hyperthermia has been discussed in the past but is unlikely (5,7). *In vitro* contracture testing can be positive, but it has been suggested that *in vitro* muscle testing may not be accurate in patients with neuromuscular diseases (7,11). However, clear cases of rhabdomyolysis after the use of halothane, enflurane, isoflurane, sevoflurane, and desflurane have been reported—even without the concurrent use of succinylcholine (14,16,19,21,29). Most of these episodes have occurred in the postoperative period. This phenomenon has been called “anesthesia-induced rhabdomyolysis” (AIR). Myoglobinuria, elevated plasma creatine kinase levels, and EKG changes have been observed postoperatively. Hyperkalemic arrests, sometimes fatal, have occurred on or shortly following emergence. Because of the perioperative risk of rhabdomyolysis, it is now recommended that volatile anesthetic agents be avoided in patients with known Duchenne muscular dystrophy (2,7,11).

Patients who also have congenital adrenal hypoplasia will be on chronic maintenance glucocorticoid and mineralocorticoid replacement therapy and will need perioperative stress doses. Prednisone and anabolic steroids have also been used to improve symptomatology of the myopathy, and these patients will similarly need perioperative stress doses of steroid.

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Dutch-Kentucky syndrome

Synonym: Distal arthrogryposis, type 7; Trismus-pseudocamptodactyly syndrome; Hecht-Beals syndrome; Hecht syndrome

MIM #: 158300

This autosomal dominant disease is characterized by limited mouth opening and deformities of the extremities. The disease is due to mutations in the gene *MYH8*, which encodes myosin heavy chain 8, which is a perinatal myosin that is active during early skeletal muscle development.

HEENT/Airway: Macrocephaly, ptosis. Malformed ears, deep philtrum. Severely limited mouth opening. The limitation may be due to an enlarged coronoid process of the mandible or to an abnormal ligament from the maxilla to the mandible, anterior to the masseter muscles. Limitation in mouth opening may be so severe as to preclude solid foods.

Cardiovascular: May have mitral valve prolapse, aortic root dilatation.

Orthopedic: Extremity deformities are secondary to short flexor muscles and tendons, which lead to flexion deformities. Pseudocamptodactyly—a flexion deformity of the fingers that occurs with wrist extension. May also have flexion deformities of the feet such as down-turned toes, metatarsus adductus, clubfoot deformity. Congenital hip dysplasia, kyphoscoliosis. Short stature. Hands are clenched at birth but loosen during infancy.

Miscellaneous: Although doctors Hecht (a pediatrician and medical geneticist) and Beals (an orthopedic surgeon) were in different fields, they were assigned to share an office because of a shortage of space. Because of their physical proximity, they collaborated on a number of academic projects. The name of this syndrome was suggested after the evaluation of an extensive pedigree of a family in Kentucky was traced back as far as a Dutch girl who emigrated to the United States in 1780 and who was described as having “crooked hands and a small mouth.”

Anesthetic Considerations: Mask ventilation has not been reported to be difficult; however, tracheal intubation may be extremely difficult. The limitation in mouth opening is anatomic and will not resolve with muscle relaxants. Various techniques, including indirect laryngoscopy, blind nasal intubation, fiberoptic intubation, and retrograde guidewire-assisted nasal fiberoptic intubation, have been reported (2,3,4,6). Use of the laryngeal mask has not been reported but might be useful since the anatomy of the glottis and upper airway are normal. However, introduction of an adequate sized device might be difficult or impossible with the very restricted mouth opening. It may be advisable to have a person present for induction who is skilled in obtaining a surgical airway.

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Dyggve-Melchior-Clausen syndrome

MIM #: 223800, 304950

This syndrome, marked by short-trunk dwarfism, characteristic progressive skeletal changes, limited joint mobility, and intellectual disability, is usually inherited in an autosomal recessive fashion. However, a family with X-linked transmission has been described. Superficially, patients resemble those with Hurler and Morquio syndromes. There are some patients who manifest the characteristic skeletal changes (particularly the radiographic and pathologic changes of the iliac crests) but who have no intellectual disability. The autosomal recessive disorder is due to abnormalities in the gene *DYM*, which encodes dymeclin, a ubiquitous transmembrane protein associated with Golgi organization and protein secretory pathways that are essential to bone formation during early development. Mutations in this same gene are responsible for Smith-McCort dysplasia (not discussed in this text). Patients with Smith-McCort dysplasia do not have intellectual disability.

HEENT/Airway: Microcephaly. Thickened calvarium. Deformed sella turcica. Coarse facies. Relatively large facial bones, prognathism. Odontoid hypoplasia. Very short neck.

Chest: Barrel chest. Wide costochondral junctions. May develop restrictive lung disease secondary to thoracic and spine deformities.

Neuromuscular: Psychomotor retardation varies from moderate to severe. Atlantoaxial instability secondary to odontoid hypoplasia can lead to spinal cord compression.

Orthopedic: Short-trunk dwarfism. Multiple progressive skeletal changes involving the limbs, vertebrae, and pelvis. Rhizomelic limb shortening. Broad hands and feet. Multiple proximal ossification centers of the humerus and femur. Limited joint mobility, especially of the elbows, hips, and knees. Flattened vertebrae with ossification defects. Scoliosis, kyphosis, lordosis. Irregularly calcified iliac crests. Dysplastic acetabulae. Laterally displaced capital femoral epiphyses. Dislocated hips. Waddling gait.

Anesthetic Considerations: The head must be carefully positioned during laryngoscopy secondary to possible odontoid hypoplasia and atlantoaxial instability. The very short neck can make direct laryngoscopy difficult, particularly in the face of possible atlantoaxial instability. Fiberoptic intubation should be considered as an alternative intubation technique. Patients may have restrictive lung disease. Spine deformities might make neuraxial techniques more difficult. The patient should be carefully positioned and padded secondary to limited joint mobility and the risk of hip subluxation.

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Dyschondrosteosis

See Leri-Weill dyschondrosteosis

Dysencephalia splanchnocystica

See Meckel-Gruber syndrome

Dyskeratosis congenital

MIM #: 305000, 127550, 224230

This usually X-linked recessive disorder involves dysplasia of the skin, mucous membranes, and bone marrow. Its main features are reticular skin hyperpigmentation, hyperkeratosis, nail dystrophy, generalized leukoplakia, nasolacrimal duct obstruction, and pancytopenia. Except for skin hyperpigmentation (present at birth), the features of this disease do not become apparent until late childhood. However, the disease is relentless, and most patients die by 30 years of age, primarily from pancytopenia but also from malignant transformation of the leukoplakia or opportunistic infections. Although usually inherited in an X-linked recessive fashion, autosomal dominant as well as autosomal recessive inheritance has been documented. The autosomal dominant form tends to result in a milder phenotype. The X-linked type is due to mutations in the gene *DKC1*, which encodes dyskerin, a protein likely involved in cell cycle and nucleolar function. The autosomal dominant form is due to mutations in the gene *TERC*, which encodes the RNA component of telomerase.

HEENT/Airway: Premalignant leukoplakia on the lips, mouth, conjunctivae. Nasolacrimal duct obstruction. May have abnormal hearing. Nasopharyngeal strictures, stenosis. Dental caries, gingival recession, alveolar bone loss, tooth mobility. Esophageal strictures.

Chest: May have restrictive lung disease, may have pulmonary fibrosis.

Neuromuscular: Occasional intellectual disability. Intracranial calcifications.

Orthopedic: Osteoporosis. Avascular necrosis of the femoral head. May have growth deficiency.

GI/GU: Premalignant leukoplakia on the anus, urethra. Occasional hepatic cirrhosis. Ureteral, urethral, vaginal, or anal strictures. Testicular hypoplasia.

Other: Skin hyperpigmentation, particularly of the neck, trunk, and upper arms. Palmar and plantar hyperkeratosis. Telangiectasis. Atrophic skin. Nail dystrophy. Thin, sparse hair. Pancytopenia. May have

immunologic abnormalities. Leukoplakia often exhibits malignant transformation (squamous cell carcinoma). Other malignancies can develop, including Hodgkin's lymphoma, pancreatic adenocarcinoma, cervical carcinoma, and esophageal carcinoma. Patients have shortened telomeres.

Miscellaneous: There may be an increased risk of leukemia in the female carrier of the X-linked gene.

Anesthetic Considerations: A complete preoperative blood count should be obtained. The presence of neutropenia mandates good aseptic technique. The teeth should be examined preoperatively for loss or excessive mobility. Patients may have restrictive lung

disease. Nasotracheal and nasogastric tubes must be placed carefully because of the possibility of nasopharyngeal or esophageal strictures. Patients should be carefully positioned and padded secondary to osteoporosis and possible bone fragility.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

E

Eagle-Barrett syndrome

See Prune belly syndrome

Eastman-Bixler syndrome

See Faciocardiorenal syndrome

Ectodermal dysplasia

See AEC syndrome, EEC syndrome, Ellis-van Creveld syndrome, Marshall syndrome, Rapp-Hodgkin ectodermal dysplasia, pachyonychia congenita, and Rothmund syndrome

Ectrodactyly-ectodermal dysplasia-clefting syndrome

See EEC syndrome

Edwards syndrome

See Trisomy 18

EEC syndrome

Synonym: Ectrodactyly-ectodermal dysplasia-clefting syndrome

MIM #: 604292, 129900

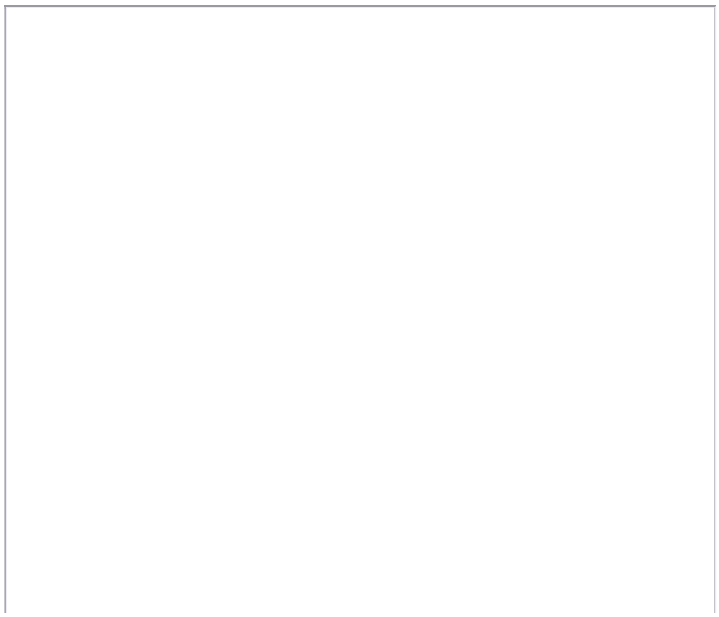
This dysmorphic syndrome is defined by the triad of **E**ctrodactyly (“lobster claw” deformity), **E**ctodermal dysplasia, and **C**left lip and palate. It is likely inherited in an autosomal dominant fashion. There is marked variability in expression; for example, ectrodactyly is not a constant feature. Three forms have been described (EEC1-3), but the majority of cases appear to belong to EEC3. EEC3 is due to abnormalities in the gene encoding tumor protein *TP63*. Mutations in this gene can also result in the AEC syndrome (see earlier) and Rapp-Hodgkin syndrome (see later).

HEENT/Airway: Ectodermal dysplasia affects hair, eyes, and teeth. Thin, sparse hair. Maxillary hypoplasia. Lacrimal duct hypoplasia. Dacryocystitis, keratitis, blepharophimosis, blepharitis, and conjunctivitis. Photophobia. Conductive or sensorineural hearing loss. Small, malformed ears. Occasional choanal atresia. Cleft lip and palate. Hypoplastic “peg-shaped” teeth, dental caries. Xerostomia. Absence of Stensen duct of the parotid gland.

Chest: May have recurrent respiratory infections even after repair of cleft lip and palate.

Neuromuscular: Usually normal intelligence.

Orthopedic: Ectrodactyly (“lobster-claw” deformity) of the hands and feet. Less severe variants have syndactyly or clinodactyly.



EEC syndrome. This happy young boy has obvious ectrodactyly.

GI/GU: Rare abdominal wall defects, anal atresia. Genitourinary anomalies are frequent, including cryptorchidism, hypospadias, duplicated collecting system, vesicoureteral reflux, hydronephrosis, and renal dysplasia. Bladder diverticulae. Transverse vaginal septum.

Other: Ectodermal dysplasia affects the skin, sweat glands, and nails. Skin is fair and thin, and prone to ulceration. Mild hyperkeratosis. Hypoplasia of the sweat glands. Mild nail dysplasia. Hypoplastic nipples. Patients may be malnourished and anemic secondary to poor oral intake and loss of protein through skin ulcers. Occasional central diabetes insipidus, growth hormone deficiency, or hypogonadotrophic hypogonadism.

Anesthetic Considerations: Recall when meeting the patient before surgery that he or she may have hearing loss. Because of hypoplasia of the sweat glands and abnormal temperature regulation, atropine premedication should be avoided. For the same reason, perioperative hyperthermia may occur. Dental loss and mobility should be documented preoperatively. The eyes need to be protected with ointment because of inadequate tear production. Patients with photophobia may be sensitive to the bright operating room lights. The skin must be well padded because of its fragility. Choanal atresia, if present, precludes the use of a nasal airway or a nasogastric tube. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency.

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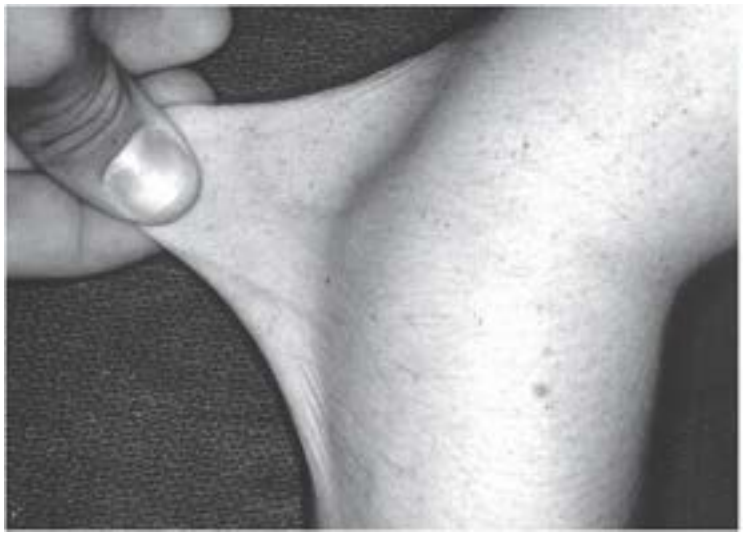
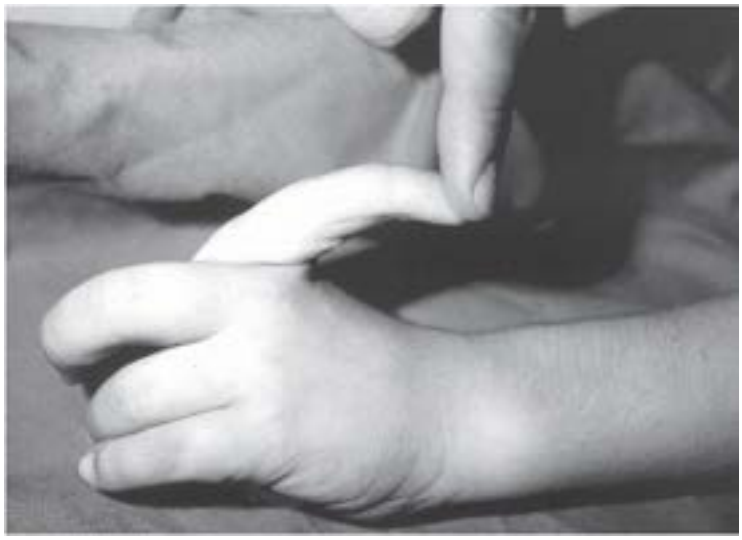
Ehlers-Danlos syndrome

MIM #: 130000 and others (see Table 1)

There are 10 distinct forms of the Ehlers-Danlos syndrome (EDS), varying from mild to severe. The hallmarks of the syndrome are lax joints, hyperextensibility of the skin, and easy bruising and bleeding. Most types are inherited in an autosomal dominant fashion, with wide variability in expression. At least some cases are caused by mutations in the genes *COL1A1*/*COL1A2*, *COL3A1*, or *COL5A1*/*COL5A2*, the genes encoding collagen types I, III or V; the gene *PLOD*, which encodes lysyl hydroxylase in collagens and other proteins; and the gene encoding tenascin-X (*TNXB*), a noncollagen protein that may regulate collagen synthesis or deposition. Several of the different clinical types are due to different mutations of the same gene, and thus are allelic. Type I is described in detail in the text, and the other types are outlined in Table 1. Type IV disease is associated with premature death, with an estimated median survival of 48 years. Although Table 1 presents the classical description of the Ehlers-Danlos types, a simplified nosology exists that divides the syndrome into six types—classical (EDS I and II), hypermobility (EDS III), vascular (EDS IV), kyphoscoliosis (EDS VI), arthrochalasia (EDS VIIA and VIIB) and dermatosparaxis (EDS VIIC).



Ehlers-Danlos syndrome. FIG. 1. Marked skin laxity seen in patients with Ehlers-Danlos syndrome. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)



Ehlers-Danlos syndrome. FIG. 2. Ligamentous laxity seen in patients with Ehlers-Danlos syndrome. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

TABLE 1. Types of Ehlers-Danlos syndrome

	Type	Skin hyperextensibility	Joint hypermobility	Skin fragility	Bruising; bleeding	Other	Inheritance	Enzyme defect	MIM #
I.	Gravis—severe classic form	Marked	Marked	Marked	Moderate	Prematurity, varicose veins, hernias	Autosomal dominant	Defect in the *COL5A1, COL5A2 or COL1A1* genes	130000
II.	Mitis—mild classic form	Moderate	Moderate	Moderate	Moderate		Autosomal dominant	Defect in the *COL5A1 or COL5A2* genes	130010
III.	Benign hypermobility	Variable	Striking joint hypermobility, frequent joint dislocation, premature osteoarthritis	Soft, but otherwise normal skin	Minimal		Autosomal dominant	Defects in the genes *COL3A1* or *TNXB*	130020
IV.	Ecchymotic or vascular type; death before the fifth decade	Minimal	Normal joint mobility, except the small joints of the hands are hypermobile	Thin, translucent skin with easily visible underlying veins/easy bruising	Marked	Characteristic facies with large eyes, a thin, pinched nose and thin lips. Spontaneous carotid-cavernous fistulae, intracranial aneurysms, carotid artery aneurysms. Bowel or arterial rupture leading to death. Uterine rupture during pregnancy	Autosomal dominant and autosomal recessive	Type III collagen gene *COL3A1* defect leads to a defect in type III collagen	130050
V.	X-linked-clinically similar to type II; female carriers are asymptomatic	Marked	Digits only	Minimal	Minimal		X-linked recessive	Unknown. Lysyl oxidase deficiency has been suggested	305200
VI.	Ocular-scoliotic type—Lysyl hydroxylase deficiency	Soft, hyperextensible skin with moderate scarring	Marked	Minimal	Easy bruising	Muscle hypotonia, scoliosis. Corneal and scleral fragility, keratoconus	Autosomal recessive	*PLOD* gene defect leads to lysyl hydroxylase deficiency, resulting in hydroxylysine-deficient collagen	225400

VII.	Procollagen proteinase deficiency	Moderate	Marked joint hypermobility, congenital hip dislocation	Moderate	Moderate	Short stature	Subclassified into three types: EDS VII A, mutation in the *COL1A1* gene, autosomal-dominant EDS VII B, mutation in the *COL1A2* gene, autosomal dominant		130060,
							EDS VII C, deficiency in procollagen N-proteinase activity, autosomal recessive		225410
VIII.	Ehlers-Danlos syndrome with periodontitis	Minimal	Minimal joint hypermobility except the small joints of the hands show marked hypermobility	Marked	Marked, poor wound healing	Generalized periodontitis	Autosomal dominant	Unknown	130080
IX.	Ehlers-Danlos syndrome with occipital horns	Soft, mildly extensible skin				Occipital hornlike exostoses, short humeri, short, broad clavicles. Chronic diarrhea, bladder diverticula, with a propensity for bladder rupture	X-linked recessive	Defect in alpha peptide of Cu^{2+}-transporting ATPase (same as Menke syndrome)	304150
X.	Ehlers-Danlos syndrome with fibronectin defect	Minimal	Joint hypermobility and dislocation	Moderate	Poor wound healing	Platelet aggregation defect that corrects with the addition of fibronectin	Autosomal recessive	Unknown	225310

Modified from Arendt-Nielsen L, Kaalund S, Bjerring P. Insufficient effect of local analgesics in Ehlers Danlos type III patients (connective tissue disorder). *Acta Anaesthesiol Scand* 1990;34:358-361.

HEENT/Airway: May have epicanthal folds, blue sclerae, microcornea, keratoconus, glaucoma, dislocated lens, retinal detachment, myopia. Easy upper eyelid eversion (Méténier's sign). Hypermobile ears—"lop ears." May have hypoplastic, irregularly spaced teeth. Able to touch tip of nose with tongue (Gorlin's sign). May have tracheal dilatation.

Chest: Hemoptysis. Downsloping ribs. Lung cysts can be associated with pneumothorax.

Cardiovascular: Cardiovascular abnormalities include valvular prolapse or insufficiency (usually mitral or tricuspid), a variety of congenital structural defects (most commonly atrial septal defect), and conduction defects. Aortic root dilatation can occur. Aortic dissection secondary to poor vessel integrity has occurred. Intraoperative ischemia from asymptomatic coronary disease in a relatively young adult has been reported (13). Can have postural acrocyanosis. Arterial rupture in type IV disease—teenage boys seem most at risk, which can be fatal. The postoperative period is also a high-risk period, possibly due to increased collagenase activity.

Neuromuscular: Rare intellectual disability.

Orthopedic: Joint laxity with the possibility of dislocation. Joint laxity may also result in spinal or foot deformities. Atlantoaxial instability may occur in type IV disease. Stiffened joints and arthritis may occur with aging. Slim build, long neck. Mucinoid-containing subcutaneous nodules develop in areas of frequent trauma.

GI/GU: Gastrointestinal bleeding. Inguinal hernias are common. Occasional diaphragmatic hernia, dilatation of the esophagus or intestine, intestinal diverticulae. Umbilical hernia. Spontaneous bowel rupture in type IV disease. Occasional renal tubular acidosis. Uterine rupture in type IV disease.

Other: The skin is hyperextensible and fragile. May have acrocyanosis. Wound healing is poor and results in friable "cigarette-paper" scars. Abnormal vessel integrity and platelet dysfunction cause easy bruising or hemarthroses. Chronic pain. Premature delivery can be secondary to premature rupture of fragile fetal membranes (affected infant)

or lax maternal tissues (affected mother). Other obstetric complications include uterine rupture (in type IV disease), postpartum hemorrhage, separation of the symphysis pubis, and uterine prolapse.

Miscellaneous: Edvard Ehlers was a Danish dermatologist and Henri Danlos was a French dermatologist at the turn of the last century. This disorder was described by Ehlers several years before Danlos, but in fact there had been several prior descriptions, as early as 1657. The Russian Rschernogobow inferred a systemic defect in connective tissue as early as 1892. It has been suggested that the famous violinist Paganini may have had Ehlers-Danlos syndrome, thus explaining his unusual dexterity and extensive reach.

Anesthetic Considerations: The integrity of the skin and blood vessels is poor. Careful positioning is required to avoid trauma to the skin, dislocation of the joints, and nerve injury (1). Intramuscular medications should be avoided if possible. Untoward hypertension may cause rupture of an unknown vascular aneurysm. Subcutaneous fluids from an infiltrated intravenous catheter may not be discernible because of the extreme distensibility of tissues. Arterial and large central venous catheters should be avoided if possible because of the risk of hematoma formation or arterial aneurysm formation. In addition, the risk of catheter erosion through the vein wall is probably significantly increased. The use of ultrasound for central venous cannulation to minimize the risk of carotid puncture is suggested. Ensure that adequate blood is available because blood loss may be out of the ordinary. Prolonged hemorrhage may occur after trauma. Poor tissue integrity can be problematic for the surgeon intraoperatively, and tissue can be torn by routine clamps and sutures. Wound healing is slow and poor. There is an increased risk of wound dehiscence. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

Endotracheal intubation may be difficult secondary to collapsible tissue and temporomandibular joint dysfunction (4). Endotracheal intubation carries with it a risk of oral, laryngeal, or tracheal trauma and hematoma formation. One instance of postintubation tracheal rupture has been described (2). If tracheal intubation is required, adequate relaxation is encouraged to minimize the risk of trauma to the airway and decrease the risk of temporomandibular joint dislocation. Patients with type IV disease may have atlantoaxial instability and an unstable cervical spine. Patients may have tracheal dilatation. Airway pressures should be kept as low as possible to minimize the risk of pneumothorax. Spontaneous ventilation, if appropriate, is preferred. Postoperative pleural effusions have been reported in a significant number of patients.

Vessel fragility and subsequent bleeding is a relative contraindication to regional anesthesia. Although patients are at increased risk for hematoma formation, neuraxial anesthesia has been performed successfully (3,9,10,12,15).

Patients with type III disease have markedly diminished duration of analgesia with lidocaine infiltration, even with the addition of vasoconstrictors. As a result, they may have inadequate pain relief during dental or cutaneous procedures such as dental work or episiotomy repairs. EMLA cream (a eutectic mixture of local anesthetics) also provides inadequate cutaneous analgesia in these patients (16). In contrast, a recent case report describes four successful brachial plexus blocks in a patient with type III disease, suggesting that the relative failure of infiltrative and cutaneous anesthesia is not secondary to resistance to local anesthetics by the nerves (5).

Patients with congenital heart disease should receive an appropriately tailored anesthetic. Intraoperative ischemia from asymptomatic coronary disease in a relatively young adult has been reported (13).

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Elastin arteriopathy

See Williams syndrome

Electron transfer flavoprotein (ETF) deficiency

Included in Glutaric acidemia type II

Electron transfer flavoprotein: Ubiquinone oxidoreductase (ETF-QO) deficiency

Included in Glutaric acidemia type II

Ellis-van Creveld syndrome

Synonym: Chondroectodermal dysplasia

MIM #: 225500

An autosomal recessive dysmorphic syndrome, Ellis-van Creveld syndrome leads to dwarfism, postaxial polydactyly, nail dysplasia, and cardiothoracic malformations. Cardiothoracic malformations are the primary cause of death. The disorder is due to mutations in the gene *EVC*, although it can also be due to a defect in a closely linked gene *EVC2*.

HEENT/Airway: Neonatal teeth, hypoplastic or missing teeth. Alveolar ridge hypoplasia. Multiple maxillary and mandibular frenula attach to the alveolar ridge. Short upper lip ("partial harelip"). May have micrognathia, cleft lip, or cleft palate. May have a short trachea.

Chest: Long, narrow thorax with short ribs. Restrictive lung disease and pulmonary hypoplasia. Bronchial cartilage hypoplasia with lobar emphysema is possible. May have recurrent pneumonia.

Cardiovascular: Congenital cardiac defects common, especially atrial septal defect (may have single atrium), ventricular septal defect, and other endocardial cushion defects. Also transposition of the great arteries, pulmonary stenosis, and obstructive left-sided lesions.

Neuromuscular: Usually normal intelligence. May have Dandy-Walker malformation.

Orthopedic: Short stature, predominantly due to short legs. Progressive shortening of the long bones,

predominantly the distal segments. Postaxial polydactyly. Cone-shaped epiphyses of phalanges 2 to 5. Genu valgum. Dysplastic nails. Patients often have limited hand function. Pelvic dysplasia.

Ellis-van Creveld syndrome. Postaxial polydactyly and dysplastic nails of a child with **Ellis-van Creveld syndrome.** (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

GI/GU: May have nephrotic syndrome, renal medullary dysplasia, renal failure. May have epispadias, hypospadias, cryptorchidism. May have cholestatic disease, cirrhosis.

Miscellaneous: The first case of Ellis-van Creveld syndrome was probably reported in 1670, a description of a "polydactylous monster" found drowned in an Amsterdam canal. The name "six-fingered dwarfism" was proposed at one time to describe this syndrome. This synonym has fallen into disuse in favor of more tactful ones. There is a large Old Order Amish community in Lancaster County, Pennsylvania, United States with a high prevalence of Ellis-van Creveld syndrome.

This disorder is named after Richard WB Ellis of Guy's Hospital, London, and Simon van Creveld of the University of Amsterdam. The anecdotal story is that Ellis and van Creveld met fortuitously in a railway car on their way to a medical meeting and during the course of their conversation realized they were both considering publication of the same disorder. They decided to publish jointly (in 1940), with Ellis's name first for reasons of alphabetization and euphony.

In 1941 the Nazis removed Simon van Creveld from his position as Chair of Paediatrics at the University of Amsterdam and condemned him to a concentration camp. He survived his incarceration and at the end of the war was reinstated to his former position.

Anesthetic Considerations: Dental abnormalities are common, and should be noted preoperatively. Peripheral intravenous access may be difficult secondary to short-limbed dwarfism. Endotracheal intubation may be difficult secondary to micrognathia and clefting. There is a single report of congenital stridor due to an upper airway cyst (3). A short trachea may result in inadvertent endobronchial intubation. Neuraxial anesthesia/analgesia may be technically difficult secondary to dwarfism (2). Patients may have significant restrictive lung disease, and a period of postoperative ventilation may be necessary. Renal disease affects perioperative fluid management and the choice of anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Emery-Dreifuss muscular dystrophy

MIM #: 310300

This X-linked muscular dystrophy is differentiated from Duchenne muscular dystrophy by its more benign course and early contractures, and from Becker muscular dystrophy by the presence of contractures and the higher incidence of cardiac problems, particularly cardiac conduction problems. It typically presents in late childhood or early adolescence. Rare cases have been inherited in an autosomal dominant fashion with occurrences in girls. There are many distinct mutations of the *EMD* gene. The gene product of the Emery-Dreifuss muscular dystrophy gene has been termed emerin. It is located on the inner nuclear membrane, and although its specific physiologic role is unknown, it has been conjectured to play an important role in cardiac conduction. Autosomal dominant disease can be due to mutations in the gene encoding lamin A/C, which, like emerin, is located in the nuclear envelope, on the nucleoplasmic surface of the inner nuclear membrane.

HEENT/Airway: Neck flexion can be limited due to contractures of the posterior cervical muscles.

Cardiovascular: Cardiomyopathy, often presenting as heart block, typically developing during the third decade of life. Third-degree heart block, which can be fatal, can be preceded by sinus bradycardia or

first-degree heart block. May have atrial standstill. Cardiomyopathy with poor ventricular function is less common than are conduction abnormalities. The degree of cardiac involvement does not correlate with the degree of skeletal muscle involvement. Female carriers can have cardiac problems in the absence of any muscle abnormality.

Neuromuscular: Slowly progressive muscle wasting and weakness with a humeroperoneal distribution (proximal distribution in the upper extremities and distal distribution in the lower extremities) in the earliest phases, followed by hip and knee extensors and the distal upper limb. Progression is slow, and patients only rarely lose the ability to walk. Muscle wasting is associated with elevations in creatine kinase, but only to 3 to 10 times normal, much lower than in Duchenne muscular dystrophy.

Orthopedic: Early contractures of the elbows, Achilles tendons (causing toe walking), and posterior cervical muscles. Contractures can appear before muscle weakness. Hypoplasia of the third to fifth cervical vertebral bodies and intervertebral discs with fusion of the apophyseal joints has been described. This is thought to be secondary to the immobilization and disuse caused by stiffness of the posterior cervical muscles.

Miscellaneous: Although reported by Dreifuss and colleagues in the 1960s, it was probably described as early as 1902. Born in Germany, Fritz Dreifuss grew up in New Zealand and was a scarfie (ask your New Zealand colleagues) at the University of Otago in New Zealand. He spent the bulk of his professional career on the neurology faculty at the University of Virginia, where he was uniformly liked and respected. He died in 1997.

Anesthetic Considerations: Endotracheal intubation can be difficult because of neck stiffness and decreased cervical mobility. A preoperative cardiac evaluation should be

done to evaluate for cardiomyopathy and conduction disturbances. Temporary cardiac pacing must be available at all times perioperatively. Patients with significant conduction defects may already have an implanted pacemaker or an automatic implantable cardiac defibrillator (AICD) in place. Myocardial depressant agents should be avoided in patients with a significant cardiomyopathy. Patients with advanced disease are also at risk for perioperative respiratory complications, secondary to respiratory muscle weakness.

Neuromuscular blockade is often unnecessary because of preexisting muscle weakness. Succinylcholine is contraindicated in this myopathic condition because of the risk of an exaggerated hyperkalemic response. Patients must be carefully positioned and padded perioperatively secondary to multiple joint contractures. Malignant hyperthermia has not been reported in association with this disease. Spine deformity secondary to myopathy and contractures may make neuraxial techniques difficult.

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Engelmann-Camurati syndrome

See Camurati-Engelmann syndrome

Eosinophilic granuloma

Included in Langerhans cell histiocytosis

Epidermal nevus syndrome

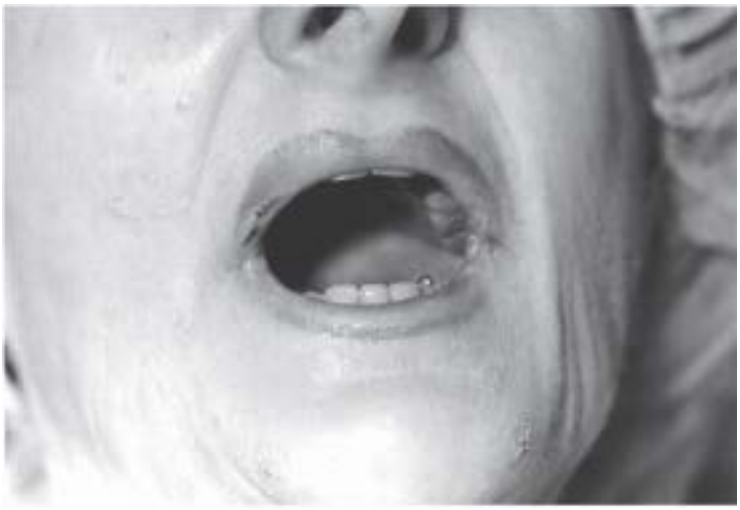
See Nevus sebaceus of Jadassohn

Epidermolysis bullosa

MIM #: 131750, 131800, 131900, 226600, 226650, 226700, and many others

Epidermolysis bullosa is a family of disorders that involve the epidermis and mucous membranes resulting in separation of skin layers with formation of bullae after even trivial local trauma. The disease is due to abnormalities in one of several attachment complexes anchoring the epidermis to the underlying dermis. There are approximately 30 separate subtypes, both autosomal dominant and recessive, which are divisible into three main groups. In simplex types, the pathologic process occurs above the basement membrane layer of skin, and lesions heal without scarring. In junctional epidermolysis bullosa the pathologic process occurs at the level of

the basement membrane. Junctional epidermolysis bullosa has been subdivided into non-Herlitz and Herlitz types, allelic disorders in which the Herlitz subtype is much more severe. In the Herlitz subtype, the laryngotracheal mucosa is affected to such an extent that granulation tissue and scarring can cause airway obstruction, often resulting in death during the first year. In the dystrophic types of epidermolysis bullosa, the disease occurs at or below the basement membrane, and lesions of the dystrophic types heal with scarring (Table 2). Recessive dystrophic epidermolysis bullosa (RDEB) is the type encountered most frequently by anesthesiologists.



Epidermolysis bullosa. FIG. 1. Photograph of a 62-year-old woman with epidermolysis bullosa showing markedly diminished maximal mouth opening. (Courtesy of Dr. Alison S. Carr, Department of Anaesthesia, Derriford Hospital, Plymouth, England.)

HEENT/Airway: Disease involving the corneal epithelium can lead to bullae that cause corneal ulceration or perforation. In the severe forms, scarring of healed bullae in the oral cavity can limit mouth opening and limit tongue mobility by adhering the tongue to the floor of the mouth. Acute pharyngeal bullae can cause airway obstruction or hemorrhage. Nasal mucosa tends to be less affected. Teeth may be dysplastic and prone to caries. Older patients are typically edentulous. Glottic or subglottic bullae or scarring may require tracheostomy. Even though the tracheal epithelium is histologically different, tracheal bullae and scarring can occur.

Cardiovascular: May be associated with mitral valve prolapse. May be associated with dilated cardiomyopathy, possibly related to selenium or carnitine deficiency.

Neuromuscular: One type, due to abnormalities in the gene *PLEC1*, an adhesion protein found in epidermis and sarcolemma, is associated with late-onset muscular dystrophy.

Epidermolysis bullosa. FIG. 2. Photograph of the same patient as in Figure 1 showing markedly atrophic skin on the arms with atrophy and pseudosyndactyly of the fingers. (Courtesy of Dr. Alison S. Carr, Department of Anaesthesia, Derriford Hospital, Plymouth, England.)

Orthopedic: Pseudosyndactyly of the fingers.

GI/GU: Esophageal strictures, diverticulae, and perforation may occur. Gastroesophageal reflux. Esophageal scarring resulting in dysmotility. There may also be anal involvement, often causing chronic constipation. One specific type, due to mutations in specific integrin genes, is associated with congenital pyloric atresia. Glomerulonephritis may develop from streptococcal skin infections.

Other: Skin lesions can be painful, and many patients are being treated for chronic pain. There may be neoplastic degeneration of skin lesions. Patients may be malnourished and hypoalbuminemic, and acquire anemia of chronic disease. Hair and nails may be atrophic. The anemia is not responsive to treatment with iron but has responded to therapy with iron and erythropoietin. Stem cell therapy has been used for palliation, and allogeneic bone marrow transplantation for patients with epidermolysis bullosa dystrophica is currently undergoing clinical trials.

Miscellaneous: A presumed association with porphyria was probably due to misdiagnosis of patients with porphyria cutanea tarda as epidermolysis bullosa.

Anesthetic Considerations: The overall perioperative goal is to avoid friction and shearing forces that lead to skin layer separation and fresh blisters. Do not use tape to attach monitors or catheters, and remove adhesive patches from electrocardiograph leads and pulse oximeter probes (or use clip-on oximeter probes). If only stick-on oximeter probes are available, the finger

can be covered first with nonadhesive plastic film. EKG leads without adhesive can be secured with Mepilex, Mepitel, or Mepitac. Alternatively, needle electrodes may be used. Some clinicians prefer to omit EKG monitoring, and instead follow the heart rate on the oximetry monitor. Monitors and intravenous catheters can be secured with Webril, Kerlix, or Coban (crinkly, stretchy tape that adheres to itself without adhesive). Noninvasive blood pressure cuffs can be used because they tend to cause direct pressure rather than shearing force, but the cuff should be cushioned with flannel gauze. Orthopedic limb tourniquets can also be used if well padded (26). Chronic scarring of the hands and feet can result in fusion of the fingers and toes (pseudosyndactyly), so that the pulse oximeter may need to be placed on the ear. Scarring of the hands and arms with parchment-like skin may make venous access difficult. Avoid wiping the skin during preparation for placing vascular or epidural catheters. A tourniquet used to aid in intravenous catheter placement may cause bullae. Ultrasound or transillumination may be helpful. The internal and external jugular veins have been used without any problems. Central venous and arterial cannulae should be sutured rather than taped in place. Patients should position themselves on the operating table to minimize trauma. Pressure points must be well padded and lubricated (including heels). The operating table must be well padded, as by a sheepskin or other padding. Skin traction (e.g., restraining an infant or toddler) must be avoided—pharmacologic premedication should be strongly considered, and intramuscular or rectal inductions may occasionally be preferred.

TABLE 2. Types of epidermolysis bullosa

Major types	Level of pathology	Major subtypes	Features	Inheritance	Affected gene product
Epidermolysis bullosa simplex (EBS)	Epidermal	EBS, generalized (Koebner type) *MIM #:* 131900	Onset at birth or in infancy. Generalized bullae without scarring. Normal teeth and nails.	Autosomal dominant	Keratin 5, keratin 14
		EBS localized (Weber-Cockayne type) *MIM #:* 131800	Onset after infancy. Bullae on limbs only without oral lesions. No scarring.	Autosomal dominant	Keratin 5, keratin 14
Junctional epidermolysis bullosa (JEB)	Lamina lucida	Non-Herlitz type *MIM #:* 226650	Onset at birth or in infancy. Generalized bullae, including hands and feet. Blisters tend to heal with scarring. Oral mucosal blisters. Dental and nail defects.	Autosomal recessive	Reduced laminin 332
		Herlitz type *MIM #:* 226700	Onset at birth or in infancy. Generalized bullae, minimal involvement of hands and feet. Mucosal, scalp and perioral involvement. Secondary infections with granuloma formation can lead to scarring. Severe anemia and growth failure. Death before 1 year of age common.	Autosomal recessive	Absent laminin 332
Epidermolysis bullosa dystrophica (DEB)	Dermis (sub-lamina densa)	Dominant type *MIM #:* 131750	Onset at birth. Limb but not oral involvement. Bullae heal with scarring, which may be hypertrophic.	Autosomal dominant	Type VII collagen
		Recessive type (RDEB) *MIM #:* 226600	Onset at birth. Generalized bullae, particularly of the limbs, and may develop acquired syndactyly, microstomia. Esophageal involvement common. Healed, scarred bullae can be atrophic. Dystrophic nails. Dysplastic teeth.	Autosomal recessive	Type VII collagen

Pressure from a face mask or hands holding a face mask can cause facial bullae. Mask cuffs should be covered with Xeroform, Vaseline gauze or petroleum jelly. Hands holding

a face mask should be gloved and lubricated with petroleum jelly to decrease skin trauma. Alternatively, silicone-based padding (Safetac) can be applied to the face, in which case the mask and the anesthesiologist's hands do not need to be lubricated (11). The tongue is often scarred and small, and less likely to cause obstruction during mask ventilation. On the other hand, neck and perioral scarring may cause neck contractures and limited mouth opening—rendering direct laryngoscopy and intubation very difficult or impossible. Fiberoptic nasal intubation is often the technique of choice in these patients. Nasal intubation has the additional advantage that nasal mucosa is comprised of specialized epithelium that is less vulnerable to bullae formation. Nasotracheal tubes may be affixed to a head wrap and foam block, secured by Coban tape tied to the tube and

wrapped around the neck, or sutured into place. An oral RAE tube might be easier to keep in place when untied or untapped (19). Placement of oral airways, endotracheal intubation, or oropharyngeal suctioning can result in oropharyngeal, lingual, or tracheal bullae. Oropharyngeal suctioning should be done, if at all, under direct vision without touching the mucosa. Laryngoscope blades should be well lubricated with a water-soluble gel and the endotracheal tube should be well lubricated, undersized (0.5 mm smaller than anticipated for age), and uncuffed. In several large series, with good care, there were no major tracheal complications from airway management or intubation (6,9,15,19,24), although new oral lesions were frequently noted. Tracheal tube cuffs, if present, should be inflated gently and carefully. The laryngeal mask airway (LMA) has been used successfully (4,21) and if possible should be removed in young children prior to awakening to minimize airway trauma. Ketamine infusion has been used to avoid airway manipulation if muscle relaxation is not required (12,29), and total intravenous anesthesia with blow-by oxygen is an attractive alternative if clinically appropriate.

Esophageal disease may increase the risk of aspiration and is an indication for a rapid sequence induction with cricoid pressure (using a lubricated gloved hand and lubrication to the neck). Pressure must be applied with no sideways movement. Nasogastric tubes are relatively contraindicated because of the risk of causing pharyngeal and esophageal bullae.

Contractures about the eyes may prevent complete eye closure during anesthesia. The eyes should be protected with a pad of ophthalmologic gel rather than tape. Eye ointment may cause blurry vision upon emergence, with the unfortunate consequence that the patient will want to rub the eyes.

Despite theoretical risks, caudal (27), spinal (23), brachial plexus (1,5,18), and lateral cutaneous nerve of the thigh blocks have been used in children, and regional techniques have been used in adults (20,28). However, contracted limbs may limit appropriate access, and care needs to be taken to avoid skin trauma during skin preparation. There is a single case report of an epidural catheter in a child that was tunneled and sutured to avoid skin tape. Subcutaneous infiltration with local anesthetics should be avoided, but intramuscular injections have not been associated with the formation of bullae. Rectal analgesics must be carefully administered because of the risk of perianal trauma. Patients may have chronic pain and may require long-term opioid therapy (7).

Fasciculations from succinylcholine might be capable of causing skin trauma, but one large series reported no significant skin trauma after the use of succinylcholine (26). The operating environment should be kept warm, as these patients are at risk for heat loss due to open skin lesions and limited subcutaneous fat secondary to malnourishment. Infection is a persistent risk—aseptic technique must be maintained and antibiotics must be appropriately timed. Hypoalbuminemia and decreased protein binding may require decreased doses of drugs that are protein bound, such as muscle relaxants. Patients with recessive dystrophic epidermolysis bullosa (RDEB) may rarely have a cardiomyopathy, and would require an appropriately tailored anesthetic (16). Bleeding oropharyngeal bullae can be treated with the application of epinephrine-soaked sponges (1:200,000). Finally, care should always be taken when transferring patients to avoid shearing forces on the skin.

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Note: Although we have endeavored to include essentially all papers in the English language anesthesia literature relevant to specific syndromes, there are too many dealing with anesthesia and epidermolysis bullosa to make that practical, and we have had to be selective.

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Epstein syndrome

Included in Fechtner syndrome

Escobar syndrome

See Multiple pterygium syndrome

Essential fructosuria

Synonym: Fructosuria; Fructokinase deficiency

MIM #: 229800

This autosomal recessive disorder is due to deficient activity of hepatic fructokinase (ketohexokinase). This enzyme catalyzes the conversion of fructose to fructose-1-phosphate, the first step in the metabolism of fructose. This enzyme is actually better termed a hexokinase because it is not specific for fructose. Accumulation of fructose in this disease is benign. It is the accumulation of fructose-1-phosphate, as occurs in hereditary fructose intolerance (see later), that leads to toxicity.

GI/GU: Reducing substance (fructose) in the urine.

Miscellaneous: These patients are asymptomatic and are usually discovered fortuitously when a reducing substance is found in the urine. This may happen less frequently now that urine test strips that measure reducing sugars have been replaced by test strips that are specific for glucose.

Anesthetic Considerations: There are no specific anesthetic considerations.

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Eulenburg disease

See Paramyotonia congenita

Exstrophy of the bladder sequence

MIM #: 600057

Abnormal development of the anterior abdominal wall mesoderm is the cause of this developmental defect. Failure of the infraumbilical mesenchyme to migrate into the infraumbilical region gives rise to a midline defect of the lower abdominal wall, with exposed bladder, failed fusion of the symphysis pubis, incomplete fusion of the genital tubercles, often with epispadias, and sometimes inguinal hernias. The defect is nearly twice as common in boys as it is in girls. Nearly three-quarters of the cases are isolated, and advanced maternal age appears to play a role. The remaining cases appear to have an autosomal dominant mode of inheritance. The defects can be surgically repaired, which requires a period of immobility postoperatively. Although the incidence of persistent genitourinary abnormalities after surgical repair is low, some patients will be incontinent. Pseudoexstrophy of the bladder is a rare occurrence of a healed omphalocele with a defect in the hypogastric area, but an intact bladder.

Orthopedic: Failed fusion of the symphysis pubis. Diastasis of rectus abdominis muscles.

GI/GU: Bladder exstrophy. Epispadias, bifid clitoris. May have inguinal hernias, anteriorly displaced anus. May have horseshoe kidney, renal agenesis.

Miscellaneous: The word exstrophy derives from the Greek ekstriphein, which translates as “turn inside out.”

Anesthetic Considerations: Surgical repair can be prolonged, and patients may experience significant fluid loss intraoperatively. Renal disease affects perioperative fluid management and the choice of anesthetic drugs.

A working epidural catheter can provide good intraoperative and postoperative analgesia. Good postoperative analgesia is particularly desirable in these patients who require a period of postoperative immobility.

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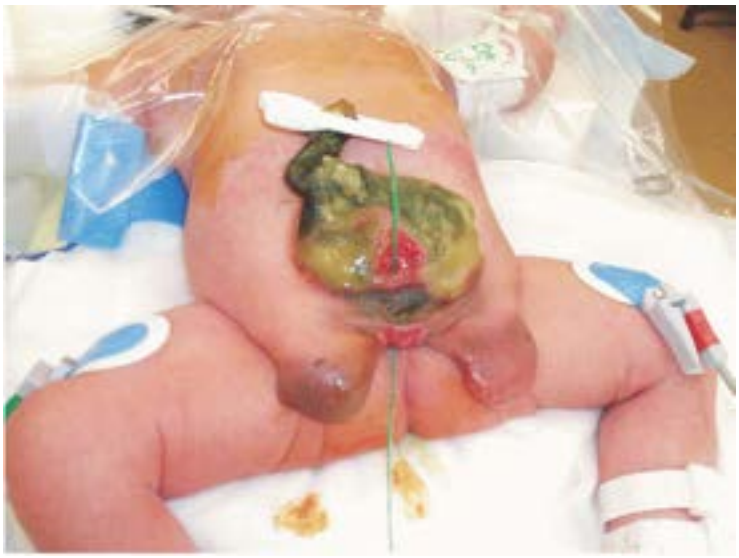
Exstrophy of the cloaca sequence

Synonym: OEIS complex

MIM #: 258040

This developmental disorder is caused by defects in the mesenchyme that will form the lower abdominal wall, the cloacal septum, and the lumbosacral vertebrae. As a result, there is a midline defect of the lower abdominal wall, and defects of the lower genitourinary tract and pubis. It has also been referred to as the OEIS complex— for **O**mphalocele, **E**xstrophy of the cloaca, **I**mperforate anus, and **S**pinal defects. The defects can be surgically ameliorated, but there are likely to be persistent genitourinary and sometimes gastrointestinal abnormalities, such as urinary incontinence, the need for gender reassignment in severely affected male patients, and malnutrition in patients with significantly shortened bowel.



Exstrophy of the cloaca. This neonate with exstrophy of the cloaca still has remnants of the mesenchymal membrane covering the defect. There is a small open bladder connecting to a prolapsed bladder neck (due to the widened symphysis pubis). There is also a common epispadias, a bifid scrotum, and an unusual skin bridge across the two pubic tubercles. There is also an imperforate anus, not well seen here. (Courtesy Dr. R. Cartland Burns, Department of Surgery, Nemours Children's Hospital, Orlando, Florida.)

Orthopedic: Failed fusion of the symphysis pubis. Incomplete development of the lumbosacral vertebrae with hydromyelia. May have anomalies of the lower extremities, including limb hypoplasia, congenital hip dislocation, clubfoot, and other deformities.

GI/GU: Imperforate anus. Short bowel syndrome. May have an omphalocele. Exstrophy of the cloaca (failure of cloacal division with persistence of a single exit point for the ureters and the hindgut), failed fusion of the genital tubercles with severe epispadias. Cryptorchidism. Renal anomalies, including renal agenesis and polycystic kidneys.

Miscellaneous: The word exstrophy derives from the Greek ekstriphein, which translates as “turn inside out.”

Anesthetic Considerations: Surgical repair can be prolonged, and patients may experience significant fluid loss intraoperatively. Renal disease affects perioperative fluid management and the choice of anesthetic drugs. Lower lumbar and caudal anesthesia/analgesia may be technically difficult.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

F

Fabry disease

Synonym: Alpha-galactosidase A deficiency; Anderson-Fabry disease

MIM #: 301500

This X-linked lysosomal storage disorder, due to deficient lysosomal alpha-galactosidase A, typically presents in boys during puberty or adolescence. This enzyme splits galactose from the cerebroside ceramide

trihexoside, and its deficiency results in storage of glycosphingolipids with terminal alpha-galactosyl moieties in a variety of tissues, particularly vascular endothelium and smooth muscle. It is closely related to other sphingolipidoses, such as Gaucher disease, in which glucose cannot be split from cerebroside. Because of random X chromosome inactivation, some girls may have some of the manifestations of the disease, such as extremity pain (acroparesthesia) and skin lesions (angiokeratoma). On rare occasions, girls can be as severely affected as boys. Death is usually in adulthood from renal, cardiac, or cerebrovascular complications. There is also a cardiac variant, where vascular disease is absent. Residual enzyme activity has been enhanced in the cardiac variant, and cardiac function improved, with infusions of galactose. However, the greatest success has been obtained with recombinant enzyme replacement therapy.

HEENT/Airway: Corneal and lens opacities. Whorl-like corneal epithelial changes visible by slit-lamp examination. These changes are typical for this disease and are alone almost diagnostic. Tortuous retinal and conjunctival vessels with aneurysmal dilatations of venules seen on the conjunctivae. There may be involvement of the temporomandibular joint with limitation of movement.

Chest: Progressive intrinsic airway disease. May have chronic bronchitis, obstructive lung disease, dyspnea. Progressive pulmonary disease significantly worse in smokers.

Cardiovascular: Endothelial accumulation leading to ischemia and infarction. Ischemic cardiovascular disease. Occasionally, electrocardiographic changes consistent with infarction are not due to ischemia but instead due to glycolipid deposition in the myocardium. Renovascular hypertension, left ventricular asymmetric hypertrophy with hypertrophic obstructive cardiomyopathy. Valvular abnormalities, including mitral valve prolapse and insufficiency. Conduction abnormalities, including short PR interval and episodic supraventricular tachycardia secondary to progressive glycolipid deposition in the AV node and bundle of His. Cerebrovascular disease. Cardiac disease in the cardiac variant presents with milder disease at an older age but is progressive and eventually fatal.

Neuromuscular: Recurrent pain crises of the extremities, characterized by burning pain of the palms and soles. With time, pain may radiate to the proximal extremities and to other parts of the body. These pain crises are provoked by cold, exertion, fever, emotional stress, or rapid changes in temperature or humidity. They tend to diminish in intensity and frequency with aging. In some patients, the pain can be excruciating. Acroparesthesias. Abnormal temperature sensation in the extremities. Crises of extremity pain are probably due to accumulation of

glycolipid in autonomic nervous system ganglion cells. Chronic diphenylhydantoin or carbamazepine may be used for pain. Cerebrovascular disease may cause transient ischemic attacks or stroke, which may occur before age 30.

Orthopedic: Arthralgia. Lymphedema of the legs (without hypoproteinemia), presumably due to glycolipid deposition in lymphatic vessels. There are multiple ossifications at the insertion of fibrous structures to bone, and articular erosions. A typical defect is limited extension of the distal interphalangeal joints. There can be avascular necrosis of the head of the femur or the talus and small infarction-like areas of involvement of the metatarsals, metacarpals, and temporomandibular joint.

GI/GU: Diarrhea, hemorrhoids, and episodic flank pain. The pain is presumably due to deposition in the small intestinal vessels or the autonomic ganglia. Priapism. Renal insufficiency beginning with proteinuria, and hyposthenuria (inability to concentrate urine), progressing to uremia and hypertension.

Other: Hypohidrosis (decreased sweating), probably due to accumulation of glycolipid in autonomic nervous system ganglion cells. Angiokeratoma skin lesions are characteristic, although not diagnostic, because they also occur in other lysosomal storage disorders. Angiokeratomas are due to blood vessel ectasia and are most commonly found between the lower abdomen and the knees and on the mucous membranes of the mouth and the cornea. They are small, dark red to blue-black, slightly raised, superficial, nonblanching lesions. Episodes of pain can be associated with fever and an elevated erythrocyte sedimentation rate.

Miscellaneous: Fabry, a German dermatologist, was probably not the first to describe this disorder. Fabry's description of the skin lesions as “purpura papulosa haemorrhagica Hebrae” implies that it was previously described by Hebra (Hebra was Moritz Kaposi's father-in-law). Anderson described this disorder in the same year. A third case was described in an Egyptian man who had scrotal lesions. Madden, the physician, was unable to make a diagnosis, but consulted Osler, who was then convalescing in Egypt. He also could not make a diagnosis but suggested that scrotal irradiation might be helpful (ouch!). The typical corneal lesions are identical to those seen with chronic chloroquine or amiodarone therapy.

Anesthetic Considerations: Attacks of abdominal pain may be incorrectly ascribed to a surgical abdomen or renal colic. Anticholinergic drugs may exacerbate hypohidrosis, and are best avoided perioperatively.

Limited mouth opening can occur secondary to temporomandibular joint disease and may make direct laryngoscopy more difficult. The degree of pulmonary involvement should be assessed preoperatively. Cardiac status should be carefully evaluated preoperatively, as hypertrophic cardiomyopathy and conduction abnormalities are common. The possibility of ischemic neurovascular disease should be considered. Renal insufficiency affects perioperative fluid management and the metabolism of renally excreted drugs. Patients may have polyuria, making urine output a poor indicator of intravascular volume status. Recurrent extremity pain may be a relative contraindication to regional techniques. Chronic diphenylhydantoin or carbamazepine therapy, used to alleviate extremity pain, may affect the metabolism of some anesthetic drugs. Amiodarone can induce lysosomal abnormalities, so its use could theoretically exacerbate abnormalities in this lysosomal disorder.

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Facioaudiosymphalangism syndrome

See Multiple synostoses syndrome

Facioauriculovertebral syndrome

See Goldenhar syndrome

Faciocardiorenal syndrome

Synonym: Eastman-Bixler syndrome

MIM #: 227280

This autosomal recessive disorder involves anomalies of the face, the heart, and the kidneys. Because of the small number of patients described, it is not clear if the additional findings are specific to this syndrome. The responsible gene and gene product are not known.

HEENT/Airway: Facial anomalies, including broad nasal bridge, malar hypoplasia, long philtrum, open mouth. May have cleft palate, micrognathia.

Cardiovascular: Cardiac anomalies, including conduction defects, endocardial fibroelastosis, cardiomegaly.

Neuromuscular: Severe intellectual disability. Hyperactive reflexes, ankle clonus. Bilateral Babinski reflex.

Orthopedic: May have growth retardation.

GI/GU: Renal anomalies, including horseshoe kidney.

Other: May have growth hormone deficiency.

Anesthetic Considerations: Severe intellectual disability may make preoperative management and the induction of anesthesia challenging. The perioperative electrocardiogram should be monitored closely for evidence of conduction abnormalities. Patients with endocardial fibroelastosis may have diminished myocardial function. Renal disease affects perioperative fluid management and the choice of anesthetic drugs.

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Faciodigitogenital syndrome

See Aarskog syndrome

Faciogenitopopliteal syndrome

See Popliteal pterygium syndrome

Facioscapulohumeral muscular dystrophy

Synonym: Landouzy-Dejerine disease

MIM #: 158900

This autosomal dominant disease is the most clinically benign of the muscular dystrophies. It is caused by contraction of a D4Z4 repeat array on the long arm of chromosome 4. The name indicates the areas of major involvement. The incidence is only 1/50 that of Duchenne muscular dystrophy. The disorder is highly variable. Weakness usually first involves the face, scapulae, and upper arms followed by the foot flexors and the hip girdle.

HEENT/Airway: Weakness of the orbicularis oris and oculi muscles with ptosis. Weakness of the perioral muscles leads to, for example, inability to whistle or blow through a straw. Protruding lips, a result of facial muscle weakness, have been termed “tapir's mouth.” Facial muscle weakness leads to a relatively inanimate face, with decreased ability to frown or smile. Retinal vasculopathy with telangiectases, microaneurysms, and capillary leak. Sensorineural hearing loss.

Cardiovascular: Absence of electrocardiographic and other cardiac findings differentiates this from the other forms of muscular dystrophy.

Neuromuscular: The primary muscles involved are those of the face, neck, shoulder, and upper arms. The lower abdominal muscles, as well as the peroneal and proximal muscles of the leg, can also be involved. The bulbar, extraocular, and respiratory muscles are spared. Intelligence is normal.

Orthopedic: Kyphoscoliosis. The clavicles slope downward, resulting in drooping shoulders. Winged scapula.

GI/GU: May have swallowing abnormalities.

Miscellaneous: Duchenne actually differentiated the infantile form of this disease from typical Duchenne muscular dystrophy 20 years before its description by Landouzy and Dejerine. Joseph Landouzy was a French physician who became Dean of Medicine at the University of Paris in 1901. Joseph Dejerine was a French neuropathologist. The autopsy result of one of their original patients (from 1886) was reported in 1964. At that time, the pedigree extended through seven generations.

Anesthetic Considerations: Muscular dystrophy places these patients at risk for hyperkalemic arrest with the administration of succinylcholine. Patients with dysphagia may be at higher risk for perioperative aspiration. In a single patient, sensitivity to atracurium was found to be normal while recovery was found to be faster (4). Similarly, a single patient was reported to have normal sensitivity, but rapid recovery, from vecuronium (2). Baseline weakness of the neck muscles means that the ability to sustain a head lift may not be an appropriate marker of adequate reversal of muscle relaxation. Malignant hyperthermia has not been reported in association

with this disease.

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Factor V Leiden mutation

MIM #: 188055

Factor V Leiden mutation is the most common cause of hereditary thrombophilia, a familial propensity to develop venous thromboembolism. It is present in approximately 5% to 8% of people of European descent. The factor V Leiden mutation involves a substitution of glutamine for arginine in the 506 position of factor V. This point mutation stops the cleavage of procoagulant factor Va by activated protein C (APC). The mutated factor V protein exhibits normal procoagulant function *in vitro* but is resistant to inactivation by APC in a PTT assay. It is the most frequent cause of APC resistance. Most affected patients are heterozygous for the factor V Leiden mutation. Homozygotes are at higher thrombotic risk. Also at higher risk are patients heterozygous for the factor V Leiden mutation combined with mutations in the genes for protein C, protein S, or antithrombin III. The genes for factor V and antithrombin III are both located on the long arm of chromosome 1 and are not infrequently inherited together. Approximately 10% of persons carrying the factor V Leiden mutation experience clinically significant thrombosis in their lifetime.

Cardiovascular: Recurrent venous thrombosis, cerebral sinus thrombosis, renal transplant rejection, venous thrombosis during pregnancy/delivery. Risk of thromboembolism is increased in the presence of other risk factors (smoking, pregnancy, contraceptive pill use, surgery, trauma, immobilization, malignancy). There appears to be no increased risk of arterial thrombotic events.

Miscellaneous: In 1987, investigators from Leiden launched the Leiden Thrombophilia Study, a large case-control study designed to define the risk of venous thromboembolism associated with protein C deficiency in the Dutch population. Instead, the study is better remembered (and credited) for identifying this important cause of venous thromboembolism.

Factor V Leiden mutation is so rare as to be essentially nonexistent in persons of Chinese, Japanese, black African, or Native American descent. Because of the genetic distribution, it has been estimated that

the mutation must have originated approximately 30,000 years ago, after the evolutionary divergence of European, African, and Asian populations.

Anesthetic Considerations: Venous thrombosis is an important cause of postoperative morbidity and occasionally also mortality. Factor V Leiden mutation is potentially an additive risk factor for this postoperative complication; however, it appears that its contribution is so small as to be clinically insignificant in the face of other perioperative risk factors (especially pregnancy, trauma, surgery, immobility) and in particular in the presence of prophylactic perioperative anticoagulation. It is unnecessary to screen for Factor V Leiden mutation preoperatively, as there is currently no recommended alteration in anesthetic management. Factor V Leiden mutation may decrease the risk of blood loss in patients undergoing cardiopulmonary bypass (9) but at the same time may be a contributing factor to accelerated graft occlusion after coronary artery bypass grafting. Pregnant patients may have been on low molecular weight heparin, making the timing of epidural catheter placement an issue. Transition to unfractionated heparin late in pregnancy has been suggested. Parturients have been reported to be at increased risk for deep vein thrombosis. Increased risk of abruption, preeclampsia, and pregnancy loss have also been reported. Patients may also be at greater risk for cerebral venous sinus thrombosis.

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Fahr disease

Synonym: Idiopathic basal ganglia calcification

MIM #: 213600

This disease is characterized by nonatherosclerotic calcification of multiple (probably demyelinated) areas of the brain, with degeneration of function and eventual decerebration. Familial cases appear to be autosomal dominant and are caused by a mutation in the solute carrier family gene *SLC20A*. Some cases of Fahr disease may be the sequelae of defective iron transport, a fetal viral infection, or hypoparathyroidism.

The mineralizations contain not only calcium but also aluminum, zinc, and iron. The differences in mineral content between pericapillary and nonvascular, and between the globus pallidus and dentate nucleus of the cerebellum, suggest that mineralization is a secondary process. Single photon emission computed tomography scans show decreased blood flow to the affected areas.

HEENT/Airway: Small, round head. Prolongation of visual evoked potentials. Optic atrophy. Retinitis pigmentosa.

Neuromuscular: Calcification (actually mineralization) of widely scattered areas of the brain, including the cortex, basal ganglia, and cerebellum. Mineralization is both perivascular and within the brain substance. Progressive deterioration of mental and motor function. Basal ganglia changes lead to athetosis. Cerebellar dysarthria. Symmetric spastic paralysis. Seizures, dementia, and psychiatric disturbances. Memory problems. Astrocytoma may develop.

Other: Hypoparathyroidism.

Miscellaneous: Fahr's original patient probably did not have his eponymous disorder.

Anesthetic Considerations: Patients with dysarthria may be at increased risk for aspiration. Hypocalcemia from hypoparathyroidism should be excluded before surgery (but is specifically excluded in a narrow delineation of the disease). Chronic use

of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Succinylcholine is contraindicated in patients with advanced spastic paralysis.

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Fairbank type multiple epiphyseal dysplasia

Included in Multiple epiphyseal dysplasia

Familial adenomatous polyposis

See Gardner syndrome

Familial dysautonomia

See also Congenital insensitivity to pain with anhidrosis (familial dysautonomia, type II)

Synonym: Riley-Day syndrome; Hereditary sensory and autonomic neuropathy III (HSAN III)

MIM #: 223900

This autosomal recessive disorder affects both sensory and autonomic neurons, causing degenerative changes in multiple organ systems. The pathogenesis is not clear, although there is demyelination in the brainstem and posterior columns of the spinal cord, degeneration of the autonomic ganglia, and loss of small myelinated and unmyelinated nerve fibers. Almost all cases are due mutations in the gene *IKBKAP*. This disorder is characterized by lack of tearing, absent corneal reflexes, excessive sweating, cold hands and feet, peripheral sensory neuropathy, absent deep tendon reflexes, hypotonia, cardiovascular lability, and emotional lability. The causes of death are typically respiratory failure, renal failure or unexplained sudden death. Familial dysautonomia is seen almost exclusively in people of Ashkenazic Jewish descent. The incidence of the disease has decreased precipitously since genetic testing and population screening became available in 2001.

HEENT/Airway: Lack of tears, absent corneal reflexes. Corneal ulcerations can develop. The tongue is smooth secondary to the absence of fungiform papillae. Impaired gag reflex. Drooling.

Chest: Respiratory drive in response to hypercapnia and hypoxia is blunted. Recurrent aspiration leads to chronic lung disease. May also have restrictive lung disease from hypotonia and kyphoscoliosis.

Cardiovascular: Sympathetic and parasympathetic instability with profound fluctuations in vasomotor response and blood pressure. Paroxysmal hypertension is common. Hypersensitivity to endogenous and exogenous catecholamines. Vasovagal reflex may be exaggerated. Postural hypotension. May have prolonged QT interval.

Neuromuscular: Normal intelligence. Speech delay. Decreased pain and temperature perception, followed later by decreased vibratory sensation. Visceral and peritoneal pain perception intact. Emotional lability and immature behavior. Decreased taste. Peripheral sensory neuropathy, absent deep tendon reflexes. Poor coordination. Autonomic neuropathy. May have seizures. Decreased myelinated and unmyelinated small nerve fibers, large myelinated fibers, sympathetic ganglia neurons, and neurons in dorsal horns.

Orthopedic: Kyphoscoliosis. Peripheral sensory neuropathy eventually leads to Charcot type neuropathic joints.

GI/GU: Swallowing difficulties with abnormal esophageal and gastrointestinal motility. High incidence of gastroesophageal reflux, aspiration, protracted episodes of vomiting, abdominal pain. Constipation. Poor control of bladder function. Progressive renal dysfunction secondary to chronic volume depletion and cardiovascular lability. Tolerate dialysis poorly.

Other: Excessive sweating, blotching of the skin, cold hands and feet, acrocyanosis. Electrolyte disturbances secondary to excessive sweating, vomiting. Impairment of temperature regulation, episodic fever. Diabetes mellitus can develop.

Anesthetic Considerations: Despite relative insensitivity to pain, these children require anesthesia to provide amnesia and immobility, to ameliorate visceral pain and surgical stress, and to control dysautonomia. Emotional lability and immature behavior may be especially apparent preoperatively. Judicious use of premedication (avoiding opioid-induced hypoventilation—see later) attenuates the stress response to preoperative anxiety. Lack of tears and the absence of corneal reflexes means that these patients are at increased risk for corneal injuries. Meticulous perioperative eye care is

necessary. Impairment of the gag reflex, swallowing difficulties, and abnormal esophageal motility place these patients at very high risk for perioperative aspiration. Consider pretreatment with an H_2-receptor antagonist.

Patients should have a rapid sequence induction, and the airway should be protected with an endotracheal tube. Careful assessment of the patient's preoperative hydration and electrolyte status is necessary because patients may be dehydrated secondary to swallowing difficulties or excessive sweating. Patients may be incapable of responding appropriately to perioperative hypovolemia.

Sympathetic and parasympathetic instability may lead to profound fluctuations in blood pressure, and paroxysmal hypertension is common. Patients are hypersensitive to endogenous and exogenous catecholamines. Inotropes should be avoided unless absolutely necessary. An arterial catheter may be helpful. Premedication with a phenothiazine or a beta-blocker has been recommended to minimize the blood pressure response to circulating catecholamines perioperatively. Dexmedetomidine infusion has been used successfully intraoperatively to help achieve hemodynamic stability (1,3,6). Cardiovascular autonomic instability may make it difficult to assess accurately the anesthetic depth. It has been suggested that monitoring the depth of anesthesia using the Bispectral Index (BIS), or a similar monitor, might be helpful in these patients (3,7). The QT interval may be prolonged. The vasovagal reflex may be exaggerated. Epidural anesthesia has been used as an adjunct to general anesthesia and was thought to provide additional cardiovascular stability (8,12). Spinal anesthesia has been used as an alternative to general anesthesia, with good intraoperative cardiovascular stability and postoperative analgesia (5).

Respiratory drive in response to hypercapnia and hypoxia is blunted. Patients may be unable to compensate for opioid-induced hypoventilation. Intraoperative assisted or controlled ventilation is recommended (14). Patients may have chronic lung disease secondary to recurrent aspiration or restrictive lung disease secondary to kyphoscoliosis. Extubation in the operating room has resulted in an increased incidence of postoperative atelectasis (14).

Patients may require lower-than-expected concentrations of volatile anesthetics, probably secondary to decreased muscle tone and decreased peripheral pain sensation. There is no specific contraindication to the use of succinylcholine or nondepolarizing muscle relaxants. Temperature regulation is impaired. Patients may become hypothermic or hyperthermic perioperatively, so body temperature must be monitored and controlled as well as possible.

Postoperative complications include persistent vomiting, aspiration, orthostatic hypotension and syncope, paroxysmal hypertension, hypoxemia, hypoventilation, hyperthermia, and unintentional self-injury. There is decreased need for postoperative analgesics secondary to decreased peripheral pain sensation. Chlorpromazine has been used in the past to control postoperative nausea, hyperthermia, and hypertension (14). Diazepam has long been the drug of choice for the treatment of dysautonomic crises. More recently, clonidine has also been used successfully to treat dysautonomic crises, particularly when hypertension is a prominent feature of the crisis (9,11).

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Familial hyperkalemic periodic paralysis

See Familial periodic paralysis

Familial hypokalemic periodic paralysis

See Familial periodic paralysis

Familial hyperlysinemia

Synonym: Hyperlysinemia

MIM #: 238700

This autosomal recessive disease is due to a defect in the enzyme alpha-aminoadipic semialdehyde synthase (*AASS*). This enzyme catalyzes the deamination of lysine as a first step in the metabolism of excess lysine through the Krebs cycle to produce energy. This enzyme is present in many tissues. It actually catalyzes two separate steps in the metabolic pathway (and was previously thought to be two separate enzymes). Deficiency of this enzyme also results in saccharopinemia, an increase in saccharopine, which is another intermediary metabolite. Familial hyperlysinemia may, in fact, not have any clinical significance, because early cases were identified from among patients referred for medical care for developmental or neurologic problems, and later patients identified

prospectively have not had problems.

HEENT/Airway: Ectopia lentis.

Neuromuscular: Intellectual disability, seizures, hypotonia.

Orthopedic: Lax ligaments.

GI/GU: Episodic vomiting.

Other: Mild anemia. Significant lysinuria.

Miscellaneous: Hyperlysinemia itself is not toxic, as evidenced by the lack of effects in the fetus of a mother with the disease (lysine freely traverses the placenta).

Anesthetic Considerations: Patients with recurrent vomiting may be at risk for perioperative aspiration. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients must be carefully positioned perioperatively secondary to ligamentous laxity.

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Familial Mediterranean fever

MIM #: 249100

This autosomal recessive disease, found predominantly in patients of Eastern Mediterranean ancestry, is characterized by recurrent bouts of fever and serositis, most commonly pleuritis, peritonitis, and arthritis. Acute attacks last 1 to 4 days and can occur from several times per week to yearly. The frequency and intensity of attacks tend to lessen with aging. The disease can be accompanied by amyloidosis, even in the absence of these crises. The disease often becomes apparent in early childhood. It is treated with colchicine, which not only controls the symptoms but can arrest the development of amyloidosis. Colchicine will not abort an ongoing crisis. The disorder is due to abnormalities in the gene *MEFV*, which encodes pyrin. Pyrin is only found in mature granulocytes. Pyrin is thought to regulate the inflammatory response at the level of the leukocyte cytoskeleton.

HEENT/Airway: Transient conjunctivitis. Temporomandibular arthritis has been reported.

Chest: Recurrent pleuritis, transient pleural effusion.

Cardiovascular: Self-limited pericarditis

Neuromuscular: Uncommon benign, recurrent aseptic meningitis. Myalgia during an attack. Migraine headaches during attacks have been described.

Orthopedic: Mild arthralgia or recurrent arthritis, monoarticular or polyarticular.

GI/GU: Recurrent abdominal pain. Recurrent peritonitis, children often have associated diarrhea. Splenic amyloidosis. Recurrent orchitis. Progressive renal amyloidosis with proteinuria, eventually leading to renal failure, which can occur without overt crises.

Other: Attacks are accompanied by fever, as high as 39°C to 40°C. Many patients have an erysipelas-like skin rash, typically of the lower leg or foot. Pregnancy is associated with remission of symptoms, which resume postpartum. Leukocytosis. Elevated erythrocyte sedimentation rate. The thyroid can be involved.

Miscellaneous: Pyrin has also been called marenostrin, from the Latin for Mediterranean Sea (*mare nostrum*).

Anesthetic Considerations: Recurrent abdominal pain can be incorrectly diagnosed as an acute abdomen. In one series of children, one-third were subjected to needless surgery, most often laparotomies (6). Some suggest prophylactic laparoscopic appendectomy early in the disease course to prevent misdiagnosis of true appendicitis later. The stress of surgery and anesthesia can provoke an attack.

Temporomandibular arthritis, a rare manifestation, may impair mouth opening and make direct

laryngoscopy more difficult. Renal failure can affect perioperative fluid management and the metabolism of some anesthetic drugs. Tetrahydrocannabinol was used successfully in a patient with recurrent abdominal pain to decrease the analgesic requirement (5). Intravenous metaraminol is known to provoke attacks (in fact, it has been used as a diagnostic test for familial Mediterranean fever) and is therefore contraindicated in these patients in the perioperative period (3).

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Familial periodic paralysis

Synonym: Periodic paralysis. (Includes Hyperkalemic periodic paralysis and Hypokalemic periodic paralysis)

See also Paramyotonia congenita

MIM #: 170400, 170500, 613345

Hyperkalemic periodic paralysis (*MIM #:* 170500) is due to mutations in the *SCN4A* (alpha subunit, skeletal muscle sodium channel) gene. Hypopolarization of the membrane does not allow activation of the sodium channel. **Hypokalemic periodic paralysis** (*MIM #:* 170400, 613345) is due to mutations in the *CACNL1A3* (the dihydropyridine-sensitive calcium channel) gene or the *SCN4A* gene. Hypokalemic periodic paralysis has also been described as a rare complication of thyrotoxicosis. Both diseases are autosomal dominant and lead to episodic muscle weakness. In general, hypokalemic attacks are nocturnal or occur in the early morning and are prolonged, whereas hyperkalemic attacks occur during the daytime and are of a shorter duration. Between episodes, the serum potassium is normal in both variants.

Cardiovascular: Can be associated with arrhythmias. Concurrent use of digoxin increases the risk of arrhythmias associated with hypokalemia.

Neuromuscular: Profound weakness can be precipitated by exercise, exposure to cold, or with rest after exercise. The diaphragm is spared. Menses and pregnancy have been reported to exacerbate the condition. Respiratory and cranial muscles tend to be spared except for the worst attacks. Muscle tone is normal in the absence of an episode of weakness. Myotonia has been associated with hyperkalemic paralysis, although the myotonia may be detectable only electromyographically.

Other: Excessive intake of dietary sodium or carbohydrate can provoke an attack of weakness in hypokalemic patients.

Miscellaneous: The names “hyperkalemic” and “hypokalemic” periodic paralysis are somewhat misnomers because the serum potassium rises or falls during an episode of weakness but may remain within normal limits. The diagnosis of hyperkalemic periodic paralysis is made based on provocation by an oral potassium load. Hypokalemia in patients with hypokalemic periodic paralysis is produced by insulin and glucose administration.

Anesthetic Considerations: Hyperkalemic periodic paralysis: Prolonged preoperative fasting and potassium-containing intravenous fluids should be avoided. Intraoperative fluids should provide some dextrose and no potassium. Old banked blood can present a significant potassium load. Consider utilizing washed red cells if appropriate. Hyperkalemic paralysis may present during general anesthesia or in the postanesthesia care unit. Perioperative decreases in body temperature can provoke an attack. Hypoventilation and acidosis should be avoided as they exacerbate hyperkalemia. Episodic measures of plasma potassium should be performed perioperatively, and the patient's electrocardiogram should be monitored continuously for evidence of hyperkalemic changes. Once a hyperkalemic attack is in progress, treatment options include glucose and insulin, beta agonists, glucagon, and calcium chloride, as well as kaliuretics such as furosemide. Succinylcholine is contraindicated in patients with the hyperkalemic variant. During an episode of paralysis, a nerve stimulator will unreliably reflect the state of neuromuscular blockade. There is no contraindication to using nondepolarizing muscle relaxants, although neostigmine has been reported to increase myotonia. Spinal and epidural anesthesia have been used successfully.

Hypokalemic periodic paralysis: Hypokalemic paralysis can also be precipitated by perioperative stress or hypothermia. It has been suggested that anxiety can precipitate an attack of weakness, so appropriate premedication may be warranted. Infusions of glucose and large carbohydrate meals should be avoided in hypokalemic patients. Hyperventilation (as during delivery) could decrease serum potassium levels. Beta-adrenergic agents can decrease blood potassium levels. Perioperative potassium concentrations must

be monitored closely and intravenous potassium supplementation used. Routine oral potassium supplementation should be resumed when practical. The patient's electrocardiogram should be monitored continuously for evidence

of hypokalemic changes. Hypokalemic weakness responds to an infusion of potassium. Spinal and epidural anesthesia have been used as the sole anesthetic without complication, despite the small decrease in serum potassium accompanying conduction block. Postoperative muscle weakness has been reported after depolarizing neuromuscular blockade, but nondepolarizing agents have not been problematic.

Malignant hyperthermia with equivocal *in vitro* contracture tests has been reported (12,17), and there has been reported a single patient with positive halothane and caffeine contracture tests, but inconclusive genetic analysis of *CACNL1A3* and *SCN4A* (6). However, most information indicates that familial periodic paralysis is not associated with malignant hyperthermia. Myotonia has been associated with hyperkalemic paralysis. A single patient has been described with hypokalemic/normokalemic paralysis and myotonia, which made intubation impossible (13).

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Fanconi anemia

MIM #: 227650, and others

This mostly autosomal recessive entity (one of the types is X-linked) is due to a defect in a DNA repair mechanism, and the hallmarks are bone marrow failure, cancer susceptibility, and skeletal defects. It is distinct from Fanconi syndrome (see later). The marrow is primarily affected, along with the heart, kidney, and limbs. The disorder is related to abnormalities in one of several Fanconi anemia complementation group genes, *FANCA* through *FANCQ.* Bone marrow transplantation has been curative, but patients are overly sensitive to the conditioning regimen. Patients may or may not have associated dysmorphic features. Male heterozygotes have a three- to fourfold elevated risk of malignancy. DNA repair mechanisms are abnormal in four other inherited diseases: ataxia-telangiectasia, xeroderma pigmentosum, Bloom syndrome, and Cockayne syndrome.

HEENT/Airway: Microcephaly. Ptosis, strabismus, nystagmus, microphthalmia. Atresia of the external auditory canal.

Cardiovascular: May have congenital heart disease.

Neuromuscular: Hydrocephalus or ventriculomegaly, absent septum pellucidum, and neural tube defects have been reported.

Orthopedic: Short stature. A hallmark finding is small or aplastic thumbs and radial aplasia. Clinodactyly, syndactyly, occasional radial abnormalities. Rib and vertebral defects. Congenital hip dislocation.

GI/GU: Small penis, small testes, cryptorchidism. Hydronephrosis, absent or ectopic kidneys.

Other: Hypoplastic and eventually aplastic bone marrow. Pancytopenia, typically thrombocytopenia followed by anemia and neutropenia. Hexokinase deficiency (see later) has been reported as part of Fanconi anemia. Increased risk of malignancies—particularly acute myelogenous leukemia (AML) as a child and solid tumors if survive to adulthood. Uneven hyperpigmentation of the skin. Patients can have a variety of endocrinopathies, including growth hormone

deficiency, hypothyroidism, glucose intolerance, and clinical diabetes. Several patients have been reported with VATER association (see later) anomalies.

Miscellaneous: Fanconi was a Swiss pediatrician of international renown. His name has been attached to more than 15 diseases or genetic syndromes. Bone marrow transplantation is curative only for marrow failure and prevention of AML. There is still the risk of solid tumors of a variety of types, including squamous cell carcinomas.

Anesthetic Considerations: The hematocrit and platelet count must be evaluated before surgery. Appropriate blood products must be available perioperatively. Regional anesthetic techniques should be undertaken with caution if the patient is thrombocytopenic. Aspirin, nonsteroidal anti-inflammatory agents and other medications that interfere with platelet function should be avoided. Neutropenia suggests special attention be paid to good aseptic technique. Nitrous oxide-induced bone marrow depression is at least a theoretical concern, and consideration should be given to avoiding the use of nitrous oxide. Radial abnormalities may exclude radial artery catheter placement. Patients may have renal dysfunction, which has implications for perioperative fluid management and the choice of anesthetic drugs. Patients who are on chronic steroid therapy require perioperative stress doses of steroids.

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Fanconi syndrome

Synonym: de Toni-Debre-Fanconi syndrome

MIM #: 134600

This is a distinct entity from Fanconi anemia (see earlier). Fanconi syndrome is a disorder of proximal renal tubular dysfunction with impaired reabsorption of amino acids, glucose, phosphate, urate, potassium, and bicarbonate, as well as a vitamin D-resistant metabolic bone disease. It is a consequence of a variety of genetic diseases and toxins and as such can be inherited (autosomal dominant or recessive) or acquired. It can be seen with cystinosis, Wilson disease, galactosemia, tyrosinemia, cytochrome c oxidase deficiency, von Gierke disease, hereditary fructose intolerance, Lowe syndrome, and amyloidosis. It can also be caused by a variety of toxins, including outdated

tetracycline, cadmium, valproate, Lysol, multiple myeloma protein (Bence Jones protein), and quite a few others. The specific gene and gene product of the autosomal dominant type are not known, and it is possible that a primary, idiopathic, autosomal dominant form does not really exist.

Neuromuscular: Severe potassium depletion from urinary losses can cause muscle weakness.

Orthopedic: Short stature. Renal phosphate loss presents as vitamin D-resistant rickets in children and osteomalacia in adults. Adults may have pathologic fractures.

GI/GU: Proximal renal tubular dysfunction, with generalized aminoaciduria, normoglycemic glycosuria, hyperphosphaturia with hypophosphatemia, and excessive urinary loses of potassium, bicarbonate, and water, resulting in polyuria and polydipsia. Chronic renal failure can eventually develop.

Other: Polyuria and polydipsia. Chronic hyperchloremic metabolic acidosis from renal bicarbonate loss (renal tubular acidosis), hypokalemia.

Miscellaneous: Fanconi was a Swiss pediatrician of international renown. His name has been attached to more than 15 diseases or genetic syndromes. Fanconi syndrome was of course first described by Abderhalden. Fanconi synthesized the similarities between his case and those of de Toni and Debre in the next few years. A similar disease occurs in Basenji dogs. Fanconi syndrome from cadmium toxicity in postwar Japan was known as “Itai-Itai” or “ouch-ouch” disease.

Anesthetic Considerations: Patients have proximal renal tubular dysfunction, with aminoaciduria, glycosuria, hyperphosphaturia, and excessive urinary loses of potassium, bicarbonate, and water. Careful attention must be paid to the patient's volume, electrolyte, and acid-base status. Urine volume may be an inadequate indicator of intravascular volume. Chronic renal failure develops in some patients, which affects the metabolism of renally excreted drugs. Patients with metabolic bone disease may be at increased risk for pathologic fractures, so careful perioperative positioning is imperative.

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Farber disease

Synonym: Disseminated lipogranulomatosis

MIM #: 228000

This autosomal recessive storage disease is due to a mutation in the gene encoding the lysosomal enzyme acid ceramidase (*ASAH1*), which results in the accumulation of ceramide in the lysosomes of a wide variety of tissues. Symptoms begin in infancy. Seven subtypes have been delineated. Patients with type 1 disease usually die by 2 years of age from airway and ventilation problems. Patients with types 2 and 3 disease have a more benign course, and most of them have normal intelligence. Patients with type 4 disease, also called the neonatal type, present

like those with malignant histiocytosis and have severe hepatosplenomegaly and usually die before the age of one. Patients with type 5 disease have predominantly nervous system involvement, with visceral sparing. Types 6 and 7 are exceedingly rare. Hematopoietic stem cell transplantation has been used successfully in type 2 and 3 disease.

HEENT/Airway: Cherry-red spot on the macula. Granulomas of the conjunctivae. Granulomas occur in the oral cavity, epiglottis, and larynx causing upper airway obstruction and difficulty swallowing. The tongue may be enlarged. Involvement of the larynx may cause a hoarse cry, progressing to aphonia.

Chest: Pulmonary involvement may cause obstructive disease. Recurrent pulmonary consolidation with fever, possibly secondary to aspiration.

Cardiovascular: Granulomatous lesions of the cardiac valves.

Neuromuscular: Profound psychomotor retardation, secondary to accumulation of ceramide in neurons and glial cells. Peripheral neuropathy with diminished deep tendon reflexes, hypotonia, and muscle wasting. Muscle denervation.

Orthopedic: Multiple, progressive, painful arthropathies with eventual contractures. Swelling over bony protuberances.

GI/GU: Episodicvomiting, poor feeding. Hepatomegaly. Rare splenomegaly. May have nephropathy.

Other: Subcutaneous nodules, lymphadenopathy. Very rare cases associated with *in utero* hydrops.

Miscellaneous: Sidney Farber, of the Boston Children's Hospital, was one of the founders of pediatric pathology. The Sidney Farber Cancer Institute and the Dana-Farber Cancer Institute, both located in Boston, are named in his honor.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to the presence of airway granulomas or an enlarged tongue. Even mild postextubation laryngeal edema can compromise an already narrowed airway. Patients are at risk for hyperkalemia with the administration succinylcholine because of the presence of denervation myopathy. Patients must be carefully positioned and padded secondary to poor tissue mass, prominent subcutaneous nodules and contractures. Temperature maintenance during surgery is difficult in these patients who typically have a thin body habitus.

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Fazio-Londe disease

MIM #: 211500

This progressive bulbar palsy is inherited in an autosomal recessive fashion. Progressive deterioration of the anterior horn cells of the cranial nerves occurs, with little or no spinal cord involvement. This motor neuron disorder is due to a mutation in the *C20ORF54* gene, which may encode a riboflavin transporter. An allelic disorder, Brown-Vialetto-Van Laere syndrome (not discussed in this book), has a similar phenotype with the addition of sensorineural hearing loss. Recently, it has been shown that riboflavin supplementation stabilizes or improves the progression of both diseases.

HEENT/Airway: Weakness of the periorbital muscles with ptosis. Involvement of the extraocular muscles is very rare. Facial weakness. Absent gag reflex. Stridor. Vocal cords may be almost immobile.

Chest: Decreased diaphragmatic movement.

Neuromuscular: Bulbar palsy. The seventh cranial nerve is almost always affected. Hyperreflexia. Pyramidal tracts are uninvolved. Trunk and limb muscles also become involved as the disease progresses.

GI/GU: Swallowing difficulties.

Anesthetic Considerations: Patients are at increased risk for aspiration secondary to an absent gag reflex and swallowing difficulties. Patients often have stridor at baseline, and need to be observed closely perioperatively (particularly postoperatively) for airway obstruction. Succinylcholine is relatively contraindicated in this

neuropathy with associated muscle weakness because of the risk of an exaggerated hyperkalemic response.

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Fechtner syndrome

(Includes May-Hegglin anomaly; Sebastian syndrome; Epstein syndrome)

MIM #: 153640

This autosomal dominant disease is due to mutations in the gene encoding nonmuscle myosin heavy chain-9. It is marked by thrombocytopenia with giant platelets, leukocyte inclusion bodies, sensorineural hearing loss, and renal insufficiency. Thus, it is similar to Alport syndrome with additional hematologic findings. It is thought that Fechtner syndrome and the similar **May-Hegglin anomaly**, **Sebastian syndrome**, and **Epstein syndrome** (not discussed elsewhere in this text) are allelic expressions of the same entity.

HEENT/Airway: Congenital cataracts. High-tone sensorineural hearing loss.

GI/GU: Nephritis, ranging from microscopic hematuria to end-stage renal failure requiring dialysis.

Other: Giant platelets, symptomatic thrombocytopenia, small pale blue inclusions in neutrophils and eosinophils (Dohle bodies). Variable bleeding diathesis due to abnormal platelet-vessel wall and platelet-platelet interactions.

One patient has been described who had coexisting von Willebrand disease (8).

Miscellaneous: Fechtner was the name of the first reported family.

Anesthetic Considerations: Although the bleeding diathesis is variable, patients may exhibit excessive surgical bleeding and/or need a transfusion of platelets perioperatively. Regional anesthesia techniques are relatively contraindicated in the face of thrombocytopenia, but uncomplicated neuraxial anesthetics have been reported with and without prophylactic platelet transfusion (2,4,9,10). Patients may have developed alloimmunization from multiple prior transfusions. DDAVP therapy may play a role in minimizing operative blood loss (5,7).

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Femoral hypoplasia-facial syndrome

See Femoral hypoplasia-unusual facies syndrome

Femoral hypoplasia-unusual facies syndrome

Synonym: Femoral hypoplasia-facial syndrome

MIM #: 134780

This usually sporadic, possibly autosomal dominant, syndrome is characterized by severe femoral hypoplasia, upslanting palpebral fissures, a short nose, and cleft palate. Although the significance is unknown, many of these patients are infants of diabetic mothers.

HEENT/Airway: May have craniosynostosis. Up-slanting palpebral fissures. Short nose with a broad tip, hypoplastic alae nasi. Long philtrum, thin upper lip. Cleft palate. Low-set or malformed ears. Micrognathia.

Chest: May have Sprengel deformity, or fused or missing ribs.

Cardiovascular: May have cardiac defect, including ventricular septal defect, pulmonary stenosis, or truncus arteriosus.

Neuromuscular: Normal intelligence.

Orthopedic: Short stature and short thighs secondary to femoral hypoplasia. Femoral hypoplasia is severe and often asymmetric. A case with femoral aplasia has been reported. Variable and often asymmetric hypoplasia of the tibia and fibula. May have abnormal pelvis with hypoplastic acetabulae, large obturator foramina, and vertical ischial axis. May have humeral hypoplasia with decreased mobility at the shoulder or elbow. May have radioulnar and radiohumeral synostosis. Preaxial polydactyly. Syndactyly of the toes. Scoliosis. Vertebral dysplasia. Caudal dysplasia, similar to the caudal regression syndrome (see earlier). Clubfoot deformity.

GI/GU: Inguinal hernias. Cryptorchidism. Small penis, testes, or labia majora. Absent uterus. Polycystic kidneys, hypoplastic or absent kidneys, abnormal collecting system.

Anesthetic Considerations: Micrognathia may make direct laryngoscopy and tracheal intubation more difficult. Fiberoptic intubation through a laryngeal mask airway (LMA) has been successful in a young infant (3). Patients must be carefully positioned and padded perioperatively due to restricted joint mobility. Significant renal disease has implications for perioperative fluid management and the choice of anesthetic drugs.

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Femur-fibula-ulna syndrome

MIM #: 228200

This sporadically occurring disorder involves femoral defects in association with several rare defects of the upper extremities including unilateral or bilateral amelia (absence of the limb), peromelia (severe malformation of the limb), humeroradial synostosis and ulnar defects. Defects are more likely to be unilateral than bilateral and are more likely to be right sided. The upper limbs are usually more severely affected than are the lower limbs. The particular upper limb abnormalities associated with this syndrome are rarely seen in association with other multiple malformation syndromes, lending credence to this as a unique malformation syndrome. The cause is unknown.

Orthopedic: Femoral defects, including peromelia at the level of the femur. Fibular defects. Unilateral or bilateral amelia or peromelia of the upper extremities. Humeroradial synostosis. Ulnar defects.

Anesthetic Considerations: Limb abnormalities may make vascular access more challenging. Ultrasound has been used in a child with femur-fibula-ulna syndrome to perform a local anesthetic block of the brachial plexus at the level of the interscalenes.

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Fetal akinesia deformation sequence (FADS)

See Fetal akinesia/hypokinesia sequence

Fetal akinesia/hypokinesia sequence

Synonym: Fetal akinesia deformation sequence (FADS); Pena-Shokeir syndrome, type I

MIM #: 208150

This usually autosomal recessive disorder is marked by arthrogryposis and pulmonary hypoplasia. Most patients are stillborn or die in the neonatal period as a consequence of pulmonary hypoplasia. Mutations in the genes *RAPSB* or *DOK7* cause fetal akinesia/hypokinesia, likely as a result of congenital myasthenia. Additionally, the syndrome phenotype can occur when there has been decreased fetal movement for any reason. Thus, this disorder is etiologically heterogeneous and could be considered a fetal akinesia deformation sequence. Decreased fetal movement impairs normal development of the joints. Dysfunction of the diaphragm and intercostal muscles leads to pulmonary hypoplasia.

HEENT/Airway: Rigid, expressionless face. Hypertelorism, prominent eyes, epicanthal folds. Ptosis. Simple, posteriorly rotated ears. Flattened nasal tip. Small mouth, high-arched palate. May have cleft palate. Micrognathia. Apparent short neck.

Chest: Pulmonary hypoplasia. Small thorax. Thin ribs.

Cardiovascular: May have congenital cardiac defect.

Neuromuscular: May have hydrocephalus, microgyri, cerebellar hypoplasia, absent septum pellucidum.

Orthopedic: Arthrogryposis of multiple joints, including elbows, hips, knees, and ankles. May have osseous hypoplasia. Ulnar deviation of the hands. Clenched hand positioning, similar to that seen with trisomy 18. Camptodactyly. Rocker-bottom feet, clubfeet. Can have perinatal fractures of thin, gracile long bones.

GI/GU: Short bowel syndrome with malabsorption. Cryptorchidism.

Other: Polyhydramnios secondary to impaired swallowing of amniotic fluid. Intrauterine growth retardation. A case with thymic and lymphoid hyperplasia has been reported.

Anesthetic Considerations: Micrognathia and short neck may make direct laryngoscopy and tracheal intubation difficult. Patients are likely to have significant pulmonary hypoplasia. Careful perioperative positioning is necessary secondary to multiple contractures.

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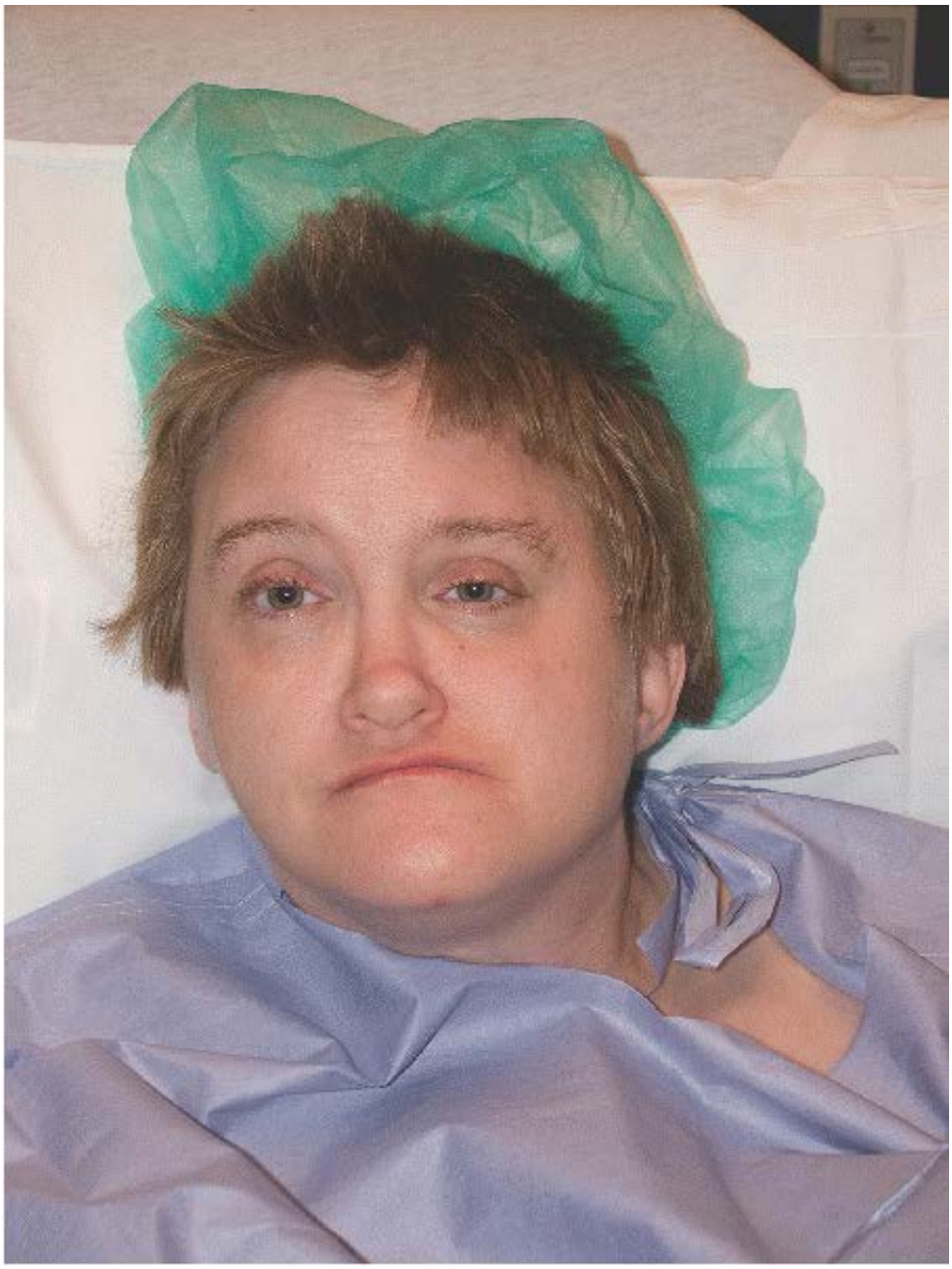
Fetal alcohol syndrome

MIM #: None

Alcohol is the most common teratogen in our society. It leads to a variety of craniofacial, growth, and central nervous system defects. The characteristic facies of fetal alcohol syndrome involve maxillary hypoplasia; short palpebral fissures; a short, upturned nose; a thin upper lip; and a long, smooth philtrum. In general, the frequency and severity of the various anomalies are dose dependent. However, it is possible to have central nervous system

effects without obvious involvement of other organs (3).

HEENT/Airway: Mild to moderate microcephaly, maxillary hypoplasia. Short palpebral fissures, ptosis, microphthalmia. Posteriorly rotated, prominent ears. May have hearing loss. Eustachian tube dysfunction. Short, upturned nose. Thin upper lip with long, smooth philtrum. Malocclusion, cleft lip or palate. Micrognathia. Short neck. May have obstructive apnea.



Fetal alcohol syndrome. FIG. 1. This 40-year-old woman was admitted for surgery for congenital cervical stenosis. She has multiple problems including asthma, obstructive sleep apnea, scoliosis, facial anomalies, visual impairment, and irritable bowel syndrome.

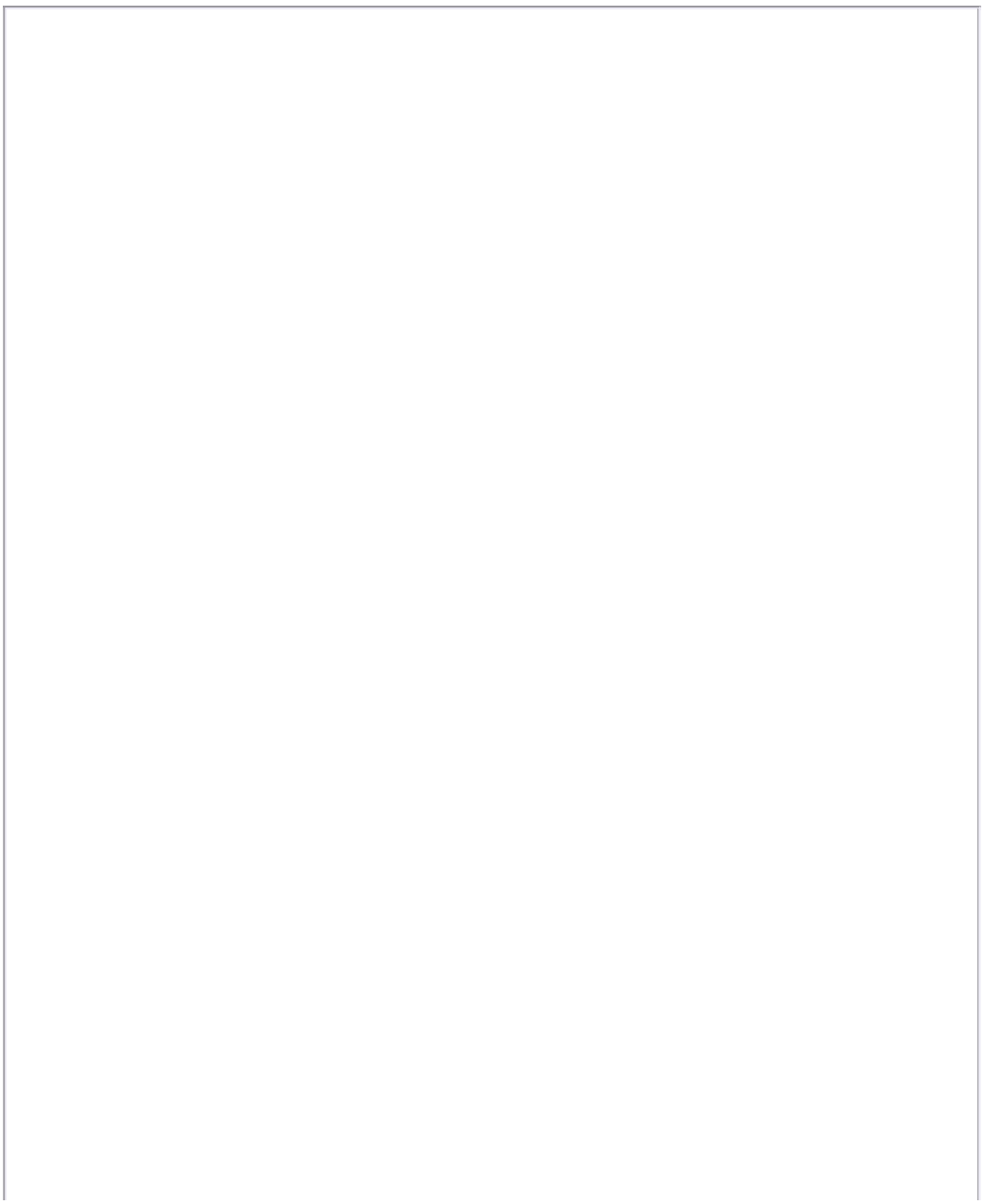
Chest: Rib anomalies.

Cardiovascular: Ventricular septal defects common. Atrial septal defects, tetralogy of Fallot, and coarctation of the aorta have also been reported.

Neuromuscular: Mild to moderate intellectual disability. Poor fine motor coordination, hypotonia. Irritability in infancy and hyperactivity in childhood. May have tremor. May have absent corpus callosum, cerebellar anomalies, meningomyelocele.

Orthopedic: Growth deficiency, of prenatal onset. Cervical vertebral anomalies. Abnormal palmar creases, short fourth and fifth metacarpals, small distal phalanges, small fifth fingernails, clinodactyly. Abnormal joint position or function.

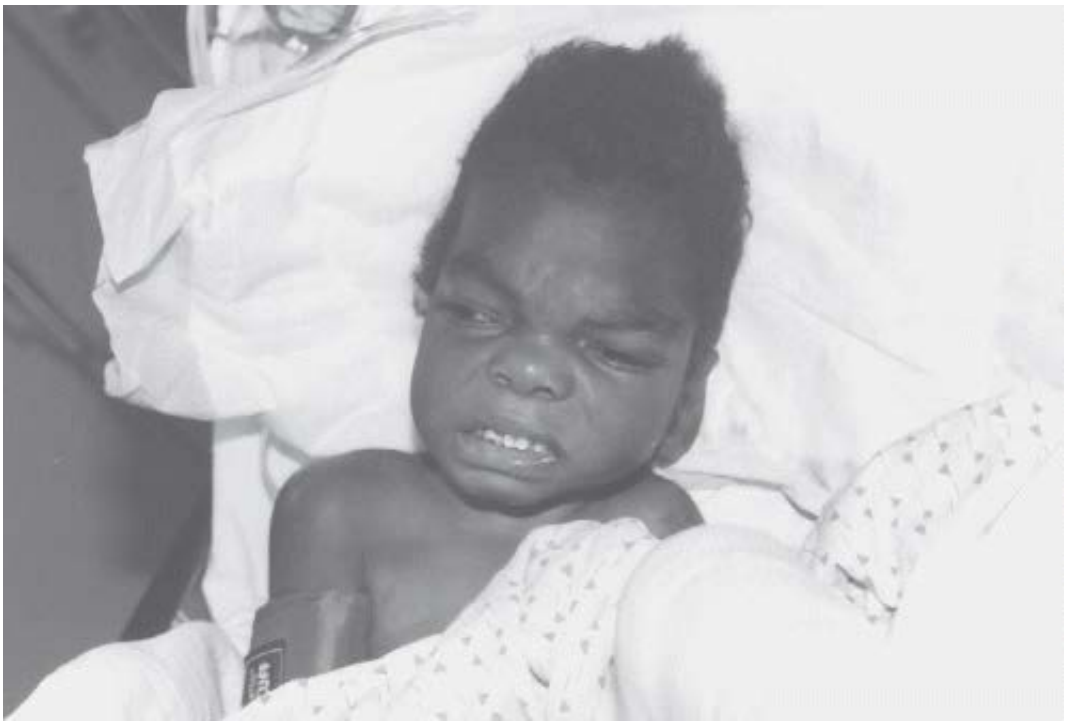
GI/GU: Hypoplastic labia majora.



Fetal alcohol syndrome. FIG. 2. The lateral view of the woman in Figure 1.

Other: Strawberry hemangiomas. Failure to thrive.

Miscellaneous: It has been estimated that 10% to 20% of people with IQs in the range of 50 to 80 have fetal alcohol syndrome.



Fetal alcohol syndrome. FIG. 3. This 5-year-old boy with fetal alcohol syndrome has typical facies. He also has hypoplasia of tooth enamel, and a fibrous trachea, sternocleidomastoid, and hyoid. He has markedly diminished neck extension. A laryngeal mask airway could not be placed successfully. The nares were small and only one side would accept a 2.7-mm fiberoptic bronchoscope, but a nasotracheal tube could not be advanced. The case was done by mask ventilation.

Anesthetic Considerations: Preoperative management may be challenging secondary to intellectual disability and hyperactivity. Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia and a short neck. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Fetal cocaine effect

MIM #: None

The prevalence of cocaine use in the obstetric population has been reported to be as high as 10%. Although a variety of isolated congenital anomalies have been reported in infants who were exposed to cocaine *in utero*, fetal cocaine exposure has not been associated with any specific pattern of teratogenesis. The underlying pathogenesis of the various anomalies is probably related to the vascular effects of cocaine, which causes uterine, placental, or fetal vasoconstriction. Disruption of the blood supply leads to altered morphogenesis of the developing structures.

HEENT/Airway: May have microcephaly. May have cleft lip.

Cardiovascular: Increased heart rate and systemic blood pressure and decreased cardiac output have been documented in cocaine-exposed newborns. May have atrial and ventricular arrhythmias. May have cardiac anomalies, including pulmonary stenosis, transposition of the great vessels, hemopericardium. May have vascular anomalies.

Neuromuscular: May have delayed fine and gross motor skills, hypotonia, irritability, abnormal reflexes, electroencephalographic abnormalities, and seizures. May have cavitary central nervous system lesions. Most neurophysiologic findings are self-limited to infancy and early childhood.

Orthopedic: May have limb reduction defects or other skeletal defects.

GI/GU: May have intestinal atresia or infarction. May have genitourinary anomalies. May have renal dysfunction.

Other: Increased incidence of intrauterine growth retardation and prematurity—probably secondary to uteroplacental insufficiency from cocaine-induced vasoconstriction. If the mother's cocaine use is recent, the infant might undergo a neonatal abstinence syndrome—hyperflexion, prolonged periods of scanning eye movements, excessive irritability, and tachypnea. Fetal cocaine syndrome may be associated with an increased risk of sudden infant death syndrome (SIDS).

Anesthetic Considerations: Cocaine-exposed newborns have increased heart rate and systemic blood pressure and decreased cardiac output compared with other newborns, consistent with either transplacental passage of maternal catecholamines or transplacental passage of cocaine, which then results in increased levels of circulating catecholamines in the newborn. These cardiovascular changes are resolved by the second day of life (4). Therefore, if an infant of a cocaine-using mother is born with a congenital anomaly that requires surgery, that surgery should be postponed until at least the second postnatal day unless the surgery is emergent, to allow the effects of cocaine to abate. It has been suggested that fetal exposure might lead to diminished ability of the neonatal heart to respond to inotropic drugs. Arrhythmias are possible, and continuous EKG monitoring is indicated. Ketamine is not a good anesthetic choice because of its sympathetic stimulatory effects.

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Fetal coumarin syndrome

See Fetal warfarin syndrome

Fetal Dilantin syndrome

See Fetal hydantoin syndrome

Fetal face syndrome

See Robinow syndrome

Fetal hydantoin syndrome

Synonym: Fetal Dilantin syndrome

MIM #: None

This syndrome is usually caused by *in utero* exposure to phenytoin (Dilantin), although a variety of anticonvulsants (including carbamazepine, mysoline, and phenobarbital) have been implicated in the etiology of this syndrome. Major features include craniofacial abnormalities, growth retardation, and phalangeal anomalies. Severity may be altered by inherited differences in fetal detoxification pathways. Exposure to multiple agents increases fetal risk. Approximately 10% of infants exposed *in utero* have the full-blown syndrome, and an additional one-third have some features. There is no known safe upper limit for maternal dosing (see also the fetal valproate syndrome, later).

HEENT/Airway: Microcephaly, wide anterior fontanelle, ridging of the metopic suture. Hypertelorism, strabismus, coloboma, glaucoma. Midface hypoplasia. Broad flat nasal bridge, short nose. Cleft lip and palate. Short neck, webbed neck, low-set hairline.

Chest: Rib anomalies, widely spaced nipples.

Cardiovascular: A variety of cardiac defects have been described.

Neuromuscular: Occasional mild intellectual disability, which may improve in childhood. Pilonidal sinus.

Orthopedic: Mild to moderate growth retardation, usually with prenatal onset. Hypoplastic distal phalanges with small nails, digitalized thumb, syndactyly, polydactyly. Hypoplastic toenails. Congenital hip dislocation.

GI/GU: Inguinal and umbilical hernias, single umbilical artery. Pyloric stenosis, duodenal atresia, anal atresia. Hypospadias, micropenis, or ambiguous genitalia. Renal malformations.

Other: Hirsutism with coarse scalp hair. Children may be at increased risk for development of cancer. Neonatal hypocalcemia has been reported.

Anesthetic Considerations: Patients with congenital heart disease should receive an appropriately tailored anesthetic. A short neck may make direct laryngoscopy and tracheal intubation more difficult. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Fetal hyperphenylalaninemia syndrome

See Maternal PKU syndrome

Fetal retinoid syndrome

See Retinoic acid embryopathy

Fetal valproate syndrome

MIM #: None

This dysmorphic syndrome is due to maternal use of the anticonvulsant valproic acid during pregnancy. *In utero* exposure to multiple anticonvulsant agents increases the risk to the fetus (see also the Fetal hydantoin syndrome, earlier). There is evidence that exposure to valproic acid *in utero* is associated with lower intelligence and that this risk is dose dependent. Valproic acid has also been implicated in the development of neural tube defects and other major and minor malformations. Not all infants who are exposed to valproic acid prenatally are affected, and the occurrence of the syndrome in several sets of twins and siblings suggests a hereditary component.

HEENT/Airway: Narrow head, high forehead. Metopic suture synostosis, trigonocephaly. Epicanthal folds. Myopia, strabismus. Low nasal bridge, short nose with anteverted nostrils. Long upper lip with shallow philtrum. Small

mouth, cleft lip. May have cleft palate. May have micrognathia.

Chest: Broad chest, bifid ribs. Supernumerary nipples.

Cardiovascular: A variety of congenital cardiac defects, including left-sided obstructive lesions, ventricular septal defect, atrial septal defect, and pulmonary atresia.

Neuromuscular: Reduced intelligence compared to unexposed controls. Autism. Meningomyelocele, spina bifida.

Orthopedic: Long, thin fingers and toes, polydactyly, triphalangeal thumbs, radial anomalies. Growth retardation.

GI/GU: Inguinal and umbilical hernias. May have omphalocele. Hypospadias.

Anesthetic Considerations: Radial anomalies may make placement of a radial arterial catheter more difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Fetal warfarin syndrome

Synonym: Fetal coumarin syndrome

MIM #: None

This dysmorphic syndrome is due to the teratogenic effects of maternal warfarin use during pregnancy. Approximately one-third of fetuses exposed during the first trimester to coumarin derivatives are affected. The effects of exposure during the second and third trimesters are unclear. Warfarin appears to inhibit the activity of

aryl sulfatase E (ARSE), the deficiency of which causes chondrodysplasia punctata, X-linked recessive type (*MIM #:* 302950). Not surprisingly, the fetal warfarin syndrome is phenotypically similar to chondrodysplasia punctata. Maternal warfarin use can also be associated with intracranial hemorrhage in the fetus, which usually results in fetal demise.

HEENT/Airway: Microcephaly. Dolichocephaly, frontal bossing. May have microphthalmia, optic nerve abnormalities. Depressed nasal bridge with nasal hypoplasia, nasal alar grooves. May have short neck. May have choanal atresia or upper airway obstruction.

Cardiovascular: Congenital heart defects.

Neuromuscular: Severe intellectual disability. Seizures. Hydrocephalus, Dandy-Walker malformation, agenesis of the corpus callosum.

Orthopedic: Rhizomelia. Calcified stippling of uncalcified epiphyses (chondrodysplasia punctata), which disappears after the first year. Mild nail hypoplasia and shortened fingers. Polydactyly. Rare spinal abnormalities. Rare atlantoaxial instability.

Other: Low birth weight with catch-up growth postnatally.

Anesthetic Considerations: Infants may present with upper airway obstruction, which can be relieved by an oral airway. Care should be taken to avoid neck hyperextension in the event of atlantoaxial instability. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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FG syndrome

Synonym: Opitz-Kaveggia syndrome

MIM #: 305450

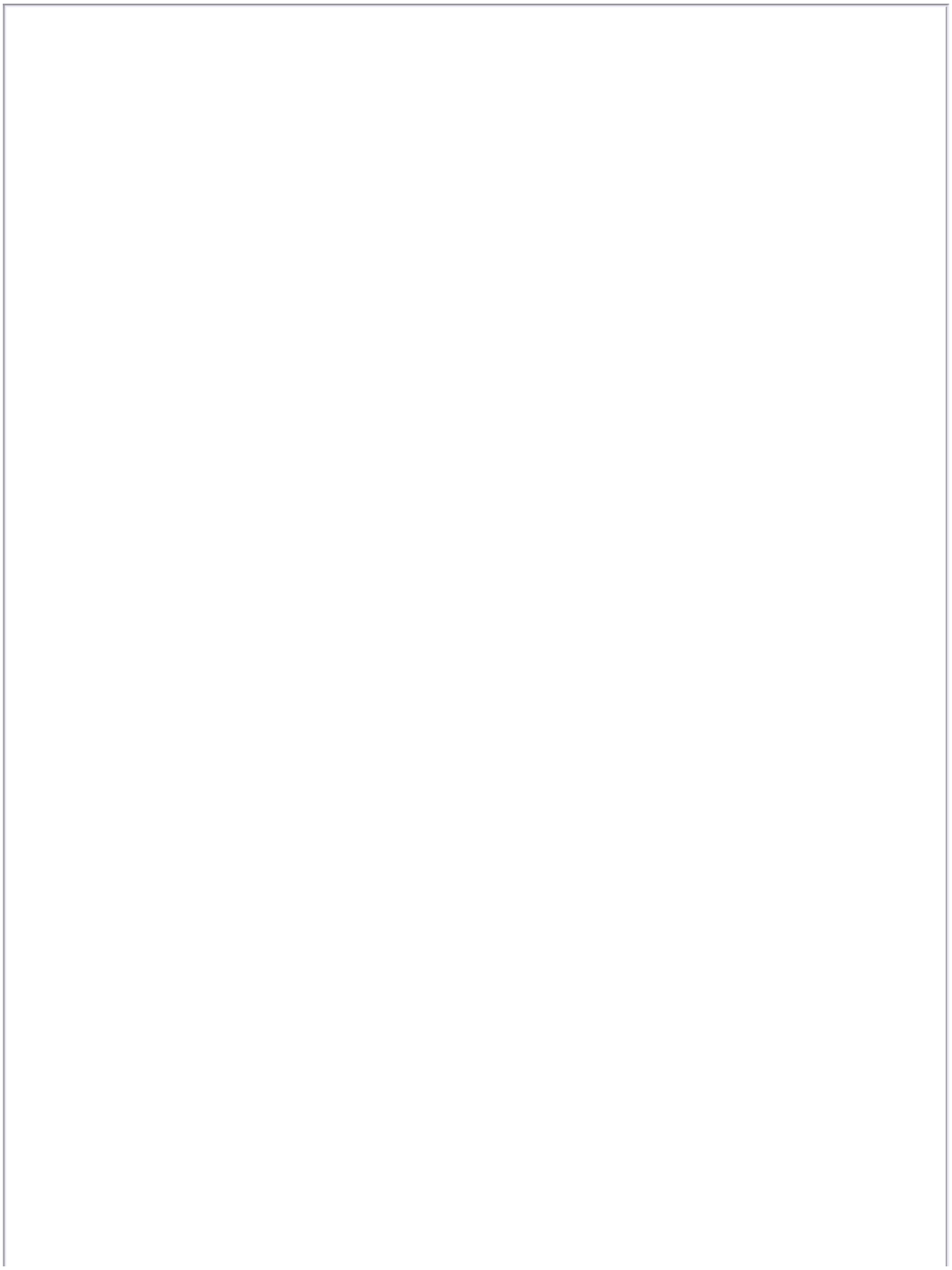
This X-linked recessive disorder is characterized by intellectual disability, macrocephaly with a prominent forehead, imperforate anus, and congenital hypotonia. It is a genetically heterogeneous disorder, although many

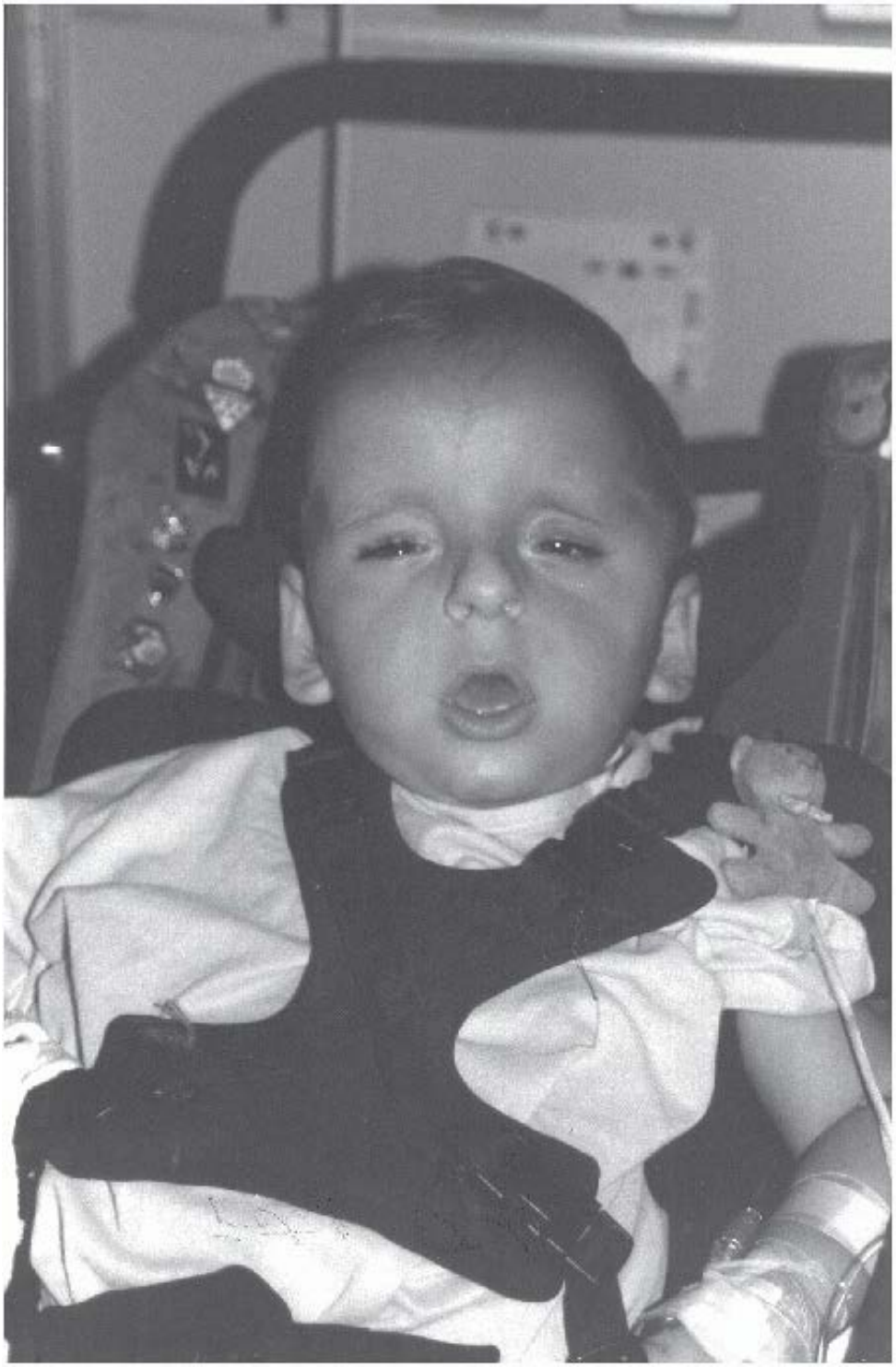
patients exhibit a mutation in the *MED12* gene on the long arm of the X chromosome.

HEENT/Airway: Macrocephaly. Prominent forehead, large anterior fontanelle. Plagiocephaly. Hypertelorism, epicanthal folds, down-slanting palpebral fissures, strabismus. Small, simple ears. May have sensorineural hearing loss. Prominent facial wrinkles, long philtrum, prominent lower lip. Narrow palate. May have choanal atresia, cleft lip/palate, short neck. High-pitched voice.

Cardiovascular: Occasional cardiac defect.

Neuromuscular: Congenital hypotonia. Usually severe intellectual disability and motor delay. Seizures. May have hydrocephalus. Agenesis of the corpus callosum. Tethered spinal cord. Pleasant personality, with attention deficit and hyperactivity. With aging, behavior may include aggressive outbursts.





FG syndrome. A young child with FG syndrome.

Orthopedic: Short stature. Broad thumbs and great toes. Clinodactyly, camptodactyly, syndactyly. Simian crease. Persistent fetal finger pads. Lax joints in infancy. Multiple joint contractures.

GI/GU: Imperforate anus, anal stenosis, or anteriorly placed anus. May have umbilical hernia, inguinal hernia.

Severe constipation. May have pyloric stenosis or malrotation. Cryptorchidism, hypospadias.

Other: Fine, thin hair. Frontal cowlick. Sociable personality.

Miscellaneous: The term “FG” comes from Opitz's use of a patient's initials to refer to this syndrome.

Anesthetic Considerations: Although intellectual disability is usually severe, patients may nonetheless be cooperative with induction because of a generally easy-going personality. Older patients may exhibit more aggressive behavior. Hypotonia increases the risk of perioperative respiratory complications and may render neuromuscular blockade unnecessary. Choanal atresia, if present, precludes the use of a nasal airway or a nasogastric tube. Patients must be carefully positioned

and padded secondary to multiple joint contractures. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Fibrodysplasia ossificans progressiva syndrome

Synonym: Myositis ossificans progressiva

MIM #: 135100

This syndrome is characterized by abnormal fibrous tissue in which there is progressive ectopic ossification. Inheritance is autosomal dominant, with most cases representing fresh mutations. It is caused by a mutation in the type 1 activin A receptor gene (*ACVR1*). The fibrodysplasia becomes apparent in most affected individuals by the age of 5 years. The initial ectopic ossification center is usually located in the neck, spine, or shoulder. Ectopic ossification usually progresses from proximal to distal and from cranial to caudal. By their mid-teens, most patients have severely limited mobility in the upper extremities secondary to ectopic ossification. The median lifespan is 40 years. Most patients experience alternating periods of exacerbations and remissions. Ectopic ossification of soft tissues can occur after trauma or surgery. Patients are often misdiagnosed, with an average time from onset of symptoms to correct diagnosis of greater than 4 years. Attempts to surgically remove the ossifications have resulted in massive new bone formation.

HEENT/Airway: Ectopic ossifications develop in the neck, spine, and shoulders, which may result in severely limited mobility. These begin as tumor-like swellings. May have secondary torticollis. Involvement of the masticatory muscles leads to limited ability to open the mouth. Abnormal temporomandibular joints with dislocation have been reported. Submandibular swelling can cause airway obstruction. Hypoplastic supraorbital ridges, infraorbital prominences, low-set ears, maxillary overbite.

Chest: Restrictive lung disease may develop secondary to ankylosis of the costovertebral joints, which limits respiratory excursion. The diaphragm is usually unaffected. The most common cause of death is pneumonia.

Cardiovascular: Approximately 30% have an abnormal electrocardiogram, with right bundle branch block, inferior lead T-wave inversion, left axis deviation, or supraventricular tachycardia.

Fibrodysplasia ossificans progressiva. FIG. 1. This 19-year-old with fibrodysplasia ossificans progressiva has such muscle stiffness that she cannot bend enough to sit and cannot brush her teeth. She walks on her tip toes. She has essentially no flexion or extension of her neck and required a nasal fiberoptic intubation.

Neuromuscular: Although the spine may be severely affected, nerve compression has not occurred. May have intellectual disability.

is pain and swelling, followed by ossification, which occurs in fascia, tendons, ligaments, joint capsules, and muscles. Joint mobility often becomes limited. There may be severe spinal involvement with cervical fusion and marked limitation of motion. Scoliosis. There may be secondary osteoporosis. Pathologic fractures may occur.

Fibrodysplasia ossificans progressiva. FIG. 2. A bony forearm nodule in the young woman in Figure 1.

GI/GU: May have inguinal hernias.

Miscellaneous: First described in 1692 by Patin, who noted a woman "*qui est devenue dure comme du bois*" ("who had become hard like wood"). It has also been referred to as "stone man disease."

Anesthetic Considerations: Head extension and mouth opening may be severely limited because of involvement of the neck, spine, and the muscles of the jaw. Direct laryngoscopy may be very difficult and may stretch the temporomandibular joint resulting in further ossification. Tracheostomy may also be difficult because of neck flexion, and should be avoided because the stoma can calcify. Nasal fiberoptic intubation is the method of choice for securing the airway (1,4,6,9,10). Patients can have severe restrictive lung disease. Poor cough requires good postoperative chest physiotherapy; however, excessive tissue injury can result in traumatic ossification.

A significant percentage of these patients have cardiac conduction abnormalities, usually right bundle branch block or supraventricular tachycardia. Patients are often on steroids to ameliorate the pain and swelling, and perioperative stress doses of steroids should be considered. Positioning should be done with care because of joint immobility. Biopsies, minor trauma, intramuscular injections, other injections (e.g., dental analgesia), and intravenous catheters can all serve as a nidus for calcification. For that reason, and because spinal abnormalities may be present, regional anesthesia is relatively contraindicated. However, ultrasound visualization has been used

successfully to identify obscured landmarks and to guide the injection of local anesthetic agents (5).

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Floating-Harbor syndrome

MIM #: 136140

This syndrome is characterized by short stature, distinctive triangular facies with a bulbous nose, and abnormalities in the acquisition of expressive language. The distinctive facial appearance is best appreciated in mid-childhood. Inheritance is likely autosomal dominant, but most cases are sporadic. The syndrome is caused by a mutation in the *SRCAP* gene.

HEENT/Airway: Triangular facies. May have trigonocephaly. Bulbous nose, large nares. Eyes appear deep-set secondary to a very prominent nasal bridge. Posteriorly rotated ears. Short philtrum. Wide mouth with thin lips. May have supernumerary upper incisor. Low posterior hairline. Short neck.

Cardiovascular: Rare pulmonary valvular stenosis.

Neuromuscular: Abnormalities in the acquisition of expressive language result in delayed speech development. Mild intellectual disability. No motor delay.

Orthopedic: Short stature with prenatal onset. Delayed bone age, joint laxity. Clinodactyly, brachydactyly, broad thumbs. May have finger clubbing.

GI/GU: May have celiac disease.

Other: Hirsutism.

Miscellaneous: The name Floating-Harbor syndrome comes from a combination of the names of the two hospitals where the initial two patients were observed (Boston Floating Hospital in Boston, Massachusetts and Harbor General Hospital in Torrance, California).

Anesthetic Considerations: Communication problems associated with expressive language delay may

occur perioperatively. Patients must be positioned carefully secondary to joint laxity.

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Focal dermal hypoplasia

See Goltz syndrome

Forbes disease

See Debrancher deficiency

Forney syndrome

MIM #: 157800

This likely autosomal dominant disorder is characterized by mitral insufficiency, deafness, and bony fusion. It has been proposed that this syndrome be renamed cardiospondylocarpofacial (CSCF) syndrome. The responsible gene and gene product are not known.

HEENT/Airway: Freckling of the iris. Facial dysmorphism. Congenital deafness from fixation of the stapes.

Cardiovascular: Congenital mitral insufficiency.

Orthopedic: Short stature. Fusion of cervical vertebrae. Fusion of carpal and tarsal bones.

Other: Facial freckling.

Anesthetic Considerations: Recall that patients are likely to be deaf. Cervical vertebral fusion may make direct laryngoscopy and tracheal intubation difficult.

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Fragile X syndrome

Synonym: Martin-Bell syndrome. (Includes fragile XE syndrome and X-associated tremor/ataxia syndrome)

MIM #: 300624

This X-linked syndrome is characterized by moderate to severe intellectual disability, large ears, and macroorchidism. The syndrome gets its name because of the fragility of the X chromosome when cells are cultured in certain media. The fragile site on the X chromosome is marked by repeats of the trinucleotide CGG. The gene at this locus is termed *FMR1*. When the repeats are long (normal allele—30 repeats, affected individuals—mean of 230 repeats), the gene becomes hypermethylated and is not transcribed. Carriers of intermediate alleles have smaller but still excessive numbers of repeats. The product of this gene, termed FMRP, is an RNA-binding protein and may be associated with neuronal plasticity. Although most of the identified patients are male, girls can be affected. This syndrome is relatively common. Up to 6% of boys with intellectual disability (and 0.3% of girls with intellectual disability) have this disorder. Presumably, fewer girls with full complements of CGG repeats manifest the full syndrome because of X-chromosome inactivation (lyonization). Fragility of the X chromosome (at Xq27.3) in these patients is caused by folate deficiency or folate antagonists. An additional gene, the fragile XE syndrome gene (*FMR2*), is located downstream from the fragile X syndrome gene. The much less common **fragile XE syndrome** (*MIM #:* 309548) is a less severe disease, with mild intellectual disability and speech delay, but without physical or behavioral problems. There is now a newborn screening assay for fragile X syndrome.

HEENT/Airway: Macrocephaly in early childhood, dolichocephaly, coarse acromegalic facies. Epicanthal folds, pale blue iris, nystagmus, strabismus, myopia. Large ears with soft cartilage. Thickened nasal bridge. Thick lips. Crowding of teeth. Submucous cleft palate. May have obstructive sleep apnea. Prognathism (actually a prominent

mandibular symphysis, or square chin). High-pitched speech. Torticollis.

Chest: Pectus excavatum.

Cardiovascular: Mitral valve prolapse, aortic dilatation.

Neuromuscular: Moderate to severe intellectual disability, which declines with aging due to decreased ability to acquire adaptive behaviors. Cluttered speech, or complete lack of speech in those severely affected. Decreased short-term abstract visual memory. Attention deficit disorder with hyperactivity. Behavioral problems with hand flapping or biting. Poor social interaction with peers. Poor eye contact. Autism. Seizures. Hypotonia. Small cortical lobes, small cerebellar vermis, enlarged fourth ventricle. A subset of males with smaller numbers of excessive repeats can present at age 50 to 70 years with progressive intention tremor or ataxia and Parkinsonian symptoms. This is called **X-associated tremor/ataxia syndrome**

(*MIM#*: 300623). Depression in women with greater than 100 repeats.

Orthopedic: Accelerated growth rate in early years. Kyphoscoliosis. Hyperextensible joints, flat feet.

GI/GU: Macroorchidism, particularly noticeable after puberty. Women with smaller numbers of excessive repeats can have premature ovarian failure.

Miscellaneous: Martin and Bell described X-linked mental retardation, but it was not until 26 years later that karyotype analysis allowed a description of the fragile X chromosomes. Julia Bell remained active until her death at age 100 years, even publishing an original paper at the age of 80. She retired at age 86. When James Martin and Marjorie Blandy (another physician) married in 1922 in England, they initially kept their marriage a secret, because in that era, women in England were forced to give up their careers after marriage.

Nucleic acid base triplet repeats are also the etiology of other diseases, including Friedreich ataxia, spinocerebellar ataxia type I, and Joseph disease.

Anesthetic Considerations: Attention deficit, hyperactivity, and behavioral problems may make preoperative management and induction challenging. Patients with obstructive sleep apnea may be at higher risk for perioperative respiratory complications. Patients must be positioned carefully secondary to joint laxity. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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Fragile XE syndrome

Included in Fragile X syndrome

Franceschetti-Klein syndrome

See Treacher Collins syndrome

Francois dyscephalic syndrome

See Hallermann-Streiff syndrome

Fraser syndrome

Synonym: Cryptophthalmos syndrome; Cryptophthalmos-syndactyly syndrome

MIM #: 219000

This autosomal recessive syndrome involves cryptophthalmos, auricular and nasal malformations, syndactyly, and genitorenal anomalies. It can be caused by mutations in the genes *FRAS1*, *FREM2*, or *GRIP1*.*FRAS1* and *FREM*2 are both likely to encode an extracellular matrix protein, and the protein encoded by *GRIP1* appears to be involved in cell signaling. Cryptophthalmos is a condition in which the palpebral fissures are absent, and skin covers the eyeballs. Often there are associated eyebrow and ocular defects. Because cryptophthalmos is a variable feature, this syndrome is most appropriately called Fraser syndrome rather than cryptophthalmos syndrome. Isolated cryptophthalmos, without the other features of Fraser syndrome, has also been reported. Nearly half of the patients with Fraser syndrome are stillborn or die in the first year of life, chiefly from laryngeal or renal anomalies. Some progress is being made in the surgical amelioration of laryngeal obstruction in the fetus. It is interesting to note that some of the anomalies in this syndrome occur when areas that are temporarily fused *in utero* fail to separate (eyelids, digits, vagina).

HEENT/Airway: Hair from the temples grows onto the lateral forehead. Cryptophthalmos. Often have associated ocular anomalies with abnormal vision. May have eyebrow anomalies. Hypertelorism. Lacrimal duct defects. Ear anomalies include microtia, stenosis or atresia of the external auditory canal, low-set ears, cup-shaped ears, absent pinna, conductive hearing loss. Nasal anomalies include narrow, notched nares, coloboma of the alae nasi, flat nasal bridge, beaked nose. High-arched palate. May have cleft lip or palate. Choanal stenosis or atresia. Micrognathia. Laryngeal or tracheal stenosis, webbing, hypoplasia, or atresia. Fusion of the vocal cords.

Chest: Occasional pulmonary hyperplasia, probably secondary to retention of amniotic fluid in the fetal lung because of laryngeal or tracheal stenosis. Widely spaced nipples.

Cardiovascular: Associated with a variety of congenital cardiac defects.

Neuromuscular: Intellectual disability not uncommon. May have meningomyelocele, encephalocele.

Orthopedic: Cutaneous syndactyly. Widely spaced symphysis pubis. Clubfeet.

GI/GU: May have umbilical anomaly, anal stenosis or atresia, malrotation of the gut. Genital anomalies include hypospadias, cryptorchidism, bicornuate uterus, vaginal atresia, enlarged clitoris. Renal agenesis or hypoplasia.

May have hypoplastic bladder, urethral valves.

Miscellaneous: The syndrome was first described as cryptophthalmos (“hidden eye”) in 1872; Fraser's contribution in 1962 was the recognition that the syndrome was also associated with a variety of other malformations. Chiari in the 19th century was the first to note the association of laryngeal atresia and cryptophthalmos.

Anesthetic Considerations: Because of stenosis, atresia, or webbing of the larynx or trachea, laryngoscopy and tracheal intubation may be very difficult or impossible (3,4,6,7). Infants may be asymptomatic but have significant subglottic stenosis. Choanal stenosis or atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Patients with renal disease need careful titration of perioperative fluids and avoidance or reduced dosages of renally excreted drugs.

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Frasier syndrome

MIM #: 136680

This autosomal dominant syndrome is characterized by pseudohermaphroditism, progressive glomerulopathy, and streak gonads. It is closely related to Drash syndrome (see earlier), and both are caused by a mutation in the *WT1*

(Wilms tumor) gene. Frasier syndrome is thought to be due to a somatic mutation in the *WT1* gene. Rather than an abnormal protein, with this mutation, there is an abnormal ratio of the two splice isoforms. Despite the defect in the Wilms tumor gene, Wilms tumor is not associated with Frasier syndrome as it is with Drash syndrome. Many patients develop gonadoblastoma.

GI/GU: Male pseudohermaphroditism, streak gonads (gonadal dysgenesis). Focal glomerular sclerosis, nephrotic syndrome, renal failure. Gonadoblastoma.

Anesthetic Considerations: Renal function should be evaluated preoperatively. Electrolytes and hematocrit should be evaluated preoperatively in patients with chronic renal failure. Patients with renal dysfunction need careful titration of perioperative fluids and avoidance or reduced dosages of renally excreted drugs. Nephrotoxic medications should be avoided. A certain degree of sensitivity is required when speaking with patients, or families of patients, with intersex disorders.

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Freeman-Sheldon syndrome

See Whistling face syndrome

Friedreich ataxia

MIM #: 229300

This autosomal recessive syndrome is characterized by neurologic degeneration with ataxia and cardiomegaly. The mean age at onset of symptoms is 15 years but can be as early as 2 years and as late as 50 years of age, with clumsiness or gait instability. There is loss of the large sensory neurons of the dorsal root ganglia, and loss of peripheral branches with loss of large myelinated fibers. There is degeneration of the posterior columns. The degree of cardiac involvement does not necessarily mirror the degree of neurologic involvement. This syndrome is due to a mutation in the gene encoding frataxin, a protein involved in iron-sulfur biogenesis and heme biosynthesis. The disorder is due to a variable number of repeats of the triplet GAA in the frataxin gene, which has been mapped to chromosome 9q (*FRDA1*). Disease severity is directly related to the number of GAA triplets, while the age at onset and the

risk of nonneurologic involvement are both inversely related to the number of GAA triplets. An additional locus has been mapped to 9p (*FRDA*2), but the gene and gene product are unknown.

HEENT/Airway: Optic atrophy later in life and retinal pigmentation. Visual field defects. Fixation instability. Nystagmus. Can develop sensorineural hearing loss late. Dysarthria.

Chest: Severe kyphoscoliosis may result in decreased pulmonary function.

Cardiovascular: Cardiomyopathy is eventually present in almost all patients, although it may remain asymptomatic in a few. There is symmetric, concentric hypertrophy. A small proportion of patients may have cardiac findings similar to hypertrophic cardiomyopathy, with asymmetric hypertrophy. The severity of the left ventricular hypertrophy is related to the number of repeats of the sequence GAA in the frataxin gene. Patients are at risk for arrhythmias and sudden death and may have had placement of an implanted cardioverter-defibrillator.

Neuromuscular: There is degeneration not only of the corticospinal and spinocerebellar tracts most prominently but also of the dorsal columns, pyramidal tracts, and, to a lesser extent, the cerebellum and medulla, so that sensory loss and lack of position and vibration sense are cardinal features. Ataxia, particularly of the legs. Dysarthria. Intention tremor. Skeletal muscle weakness. Diminished or absent deep tendon reflexes. Babinski sign. Intelligence is usually normal.

Orthopedic: Kyphoscoliosis. Pes cavus.

Other: Diabetes mellitus has been reported in some patients, and additional patients will be carbohydrate intolerant.

Miscellaneous: Nikolaus Friedreich succeeded Virchow in the chair of pathologic anatomy at Wurzburg. Nucleic acid base triplet repeats are also apparently the etiology of other diseases, including fragile X syndrome, spinocerebellar ataxia type I, and Joseph disease. Frataxin bears homology with gram negative, but not gram positive, bacteria, and may be a mitochondrial gene originally derived from protomitochondrial bacteria, which then transferred to the nucleus.

Anesthetic Considerations: Hyperkalemia has been reported after the use of succinylcholine. Nondepolarizing muscle relaxants have been used successfully (5,6) with normal responses in terms of onset time and duration, although with typical interpatient variability. Most patients have some degree of cardiomyopathy. Some patients will have diabetes mellitus or glucose intolerance. Severe kyphoscoliosis may result in decreased pulmonary function. Peripheral nerve blocks are relatively contraindicated because of the risk of exacerbating the neuropathic process. Spinal and epidural anesthesia have been used successfully, although they may be more difficult with scoliosis (8). Neurologic dysfunction may intensify postoperatively.

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Frontometaphyseal dysplasia

Synonym: Gorlin-Cohen syndrome

MIM #: 305620

This X-linked recessive disorder results in abnormalities in multiple organ systems. The most consistent features are prominent supraorbital ridges, metaphyseal dysplasia, progressive joint contractures, and restricted joint mobility. Boys are more severely affected than girls. Frontometaphyseal dysplasia is due to mutations in the gene *FLNA*, which encodes filamin A. Filamin A cross-links actin filaments and aids in anchoring membrane proteins. There are four otopalatodigital syndromes caused by mutations in *FLNA*. In order of severity, they are otopalatodigital syndrome type I (see later), frontometaphyseal dysplasia, otopalatodigital syndrome type II (see later), and Melnick-Needles syndrome (see later).

HEENT/Airway: Frontal hyperostosis leading to prominent supraorbital ridges. Wide nasal bridge. Incomplete sinus development. Hypertelorism. Down-slanting palpebral fissures. Conductive and sensorineural hearing loss. Long, thick philtrum. High-arched palate. Missing permanent teeth, retained deciduous teeth. Hypoplasia of the mandibular ramus. Small, pointed chin. May have subglottic stenosis, tracheal web, stridor. May have tracheoesophageal fistula.

Chest: Thoracic scoliosis and rib cage deformities may lead to restrictive lung disease. Malformation of the bronchial tree can result in respiratory compromise.

Cardiovascular: May have primary pulmonary hypertension. May have right bundle branch block. May have mitral valve prolapse.

Neuromuscular: Cervical vertebral anomalies or fusion. Wide foramen magnum. Anteriorly placed odontoid. May have intellectual disability. Wasting of muscles in arms and legs, especially hypothenar and interosseous muscles of the hands.

Orthopedic: Metaphyseal dysplasia. Progressive joint contractures (fingers, wrists, elbows, knees, and ankles) and restricted joint mobility. Arachnodactyly. Winged scapula. Flared pelvis. Thoracic scoliosis.

GI/GU: Obstructive uropathy. Cryptorchidism.

Other: Hirsutism of buttocks and thighs.

Anesthetic Considerations: Dental abnormalities (especially missing teeth) should be documented preoperatively. Facial anomalies may make direct laryngoscopy and tracheal intubation difficult. A smaller endotracheal tube may be necessary if the patient has subglottic stenosis. Peripheral intravenous access may be difficult because of contractures. Patients may have a history of stridor, recurrent respiratory tract infections, or chronic lung disease and are at risk for postoperative pulmonary complications. Patients with pulmonary hypertension or right bundle branch block require an appropriately tailored anesthetic. Patients must be carefully positioned and padded secondary to the presence of contractures.

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Frontonasal dysplasia sequence

See Median cleft face syndrome

Fructokinase deficiency

See Essential fructosuria

Fructose-1,6-biphosphatase deficiency (Fructose-1, 6-diphosphatase deficiency)

MIM #: 229700

This autosomal recessive disorder is due to mutations in the gene encoding fructose-1,6-biphosphatase (fructose-1,6-diphosphatase). This enzyme is one of four rate-limiting enzymes of hepatic gluconeogenesis. In this disorder, the liver is unable to convert fructose, lactate, glycerol, or amino acids into glucose. Onset of symptoms with episodic metabolic acidosis and hypoglycemia is often in the first year of life. Half of affected children have their first episode within the first 4 days of life. Later, episodes are often triggered by fasting or febrile illnesses.

Episodes have caused apnea and cardiac arrest.

Chest: Hyperventilation will often be the first sign of metabolic acidosis in infants.

Neuromuscular: Normal intelligence. Hypotonia. Episodes can be signaled by trembling, lethargy and coma. May have hypoglycemic seizures.

GI/GU: Hepatomegaly with fatty changes in the liver.

Other: Failure to thrive. Recurrent episodes of hypoglycemia and metabolic ketoacidosis precipitated by stress, infection, the ingestion of fructose or sucrose, or prolonged fasting. Severe lactic acidosis can develop during an acute episode. Ketonuria. A glucose-insulin infusion may be needed during severe episodes. Episodes of hypoglycemia and metabolic ketoacidosis occur more rarely as the patient ages. Tolerance of fasting also improves with age. Prolonged thrombin time with decreased factor VII has been reported, which normalized with infusion of glucose.

Miscellaneous: Unlike patients with hereditary fructose intolerance (see later), these patients do not have an aversion to fructose-containing foods. Glycerol can also cause a response similar to a load of fructose.

Anesthetic Considerations: Fructose should already have been eliminated from the diet. It is important to avoid any oral premedicant syrup that contains fructose. Patients also have a reduced tolerance to sorbitol, which can also be found in oral medications. Postoperatively, sucrose should be avoided (sucrose is a disaccharide of glucose and fructose). Preoperative fasting should be minimized because of the risk of hypoglycemia and metabolic ketoacidosis. Intravenous glucose should be provided perioperatively, and the amount of glucose needed may exceed the normal maintenance requirements. Blood glucose levels should

be monitored perioperatively. Persistent lactic acidemia indicates that glucose needs are not being met.

Glycerol is sometimes used to treat cerebral edema. In some countries, glycerol preparations are prepared with 5% fructose, and its use in these patients has been associated with worsening cerebral edema.

Figure: See **Appendix E**

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Fructose-1-phosphate aldolase B deficiency

See Hereditary fructose intolerance

Fructosuria

See Essential fructosuria

Fryns syndrome

MIM #: 229850

This autosomal recessive syndrome has as its main features diaphragmatic defects, lung hypoplasia, cleft lip or palate, distal limb abnormalities, and genital anomalies. Most patients are stillborn or die in early infancy. The responsible gene and gene product are not known.

HEENT/Airway: Coarse facies. Optic anomalies. Malformed ears. Olfactory anomalies. Broad, flat nasal bridge, anteverted nares. Large mouth. Cleft lip or palate. Retrognathia. Micrognathia.

Chest: Congenital diaphragmatic defects (usually hernia). Lung hypoplasia. Can have broad clavicles.

Cardiovascular: Ventricular septal defects, aortic arch anomalies.

Neuromuscular: Severe intellectual disability. Myoclonus. May have Dandy-Walker malformation, hydrocephalus, agenesis of the corpus callosum, arhinencephaly.

Orthopedic: Distal limb abnormalities including digital hypoplasia and nail dysplasia. Camptodactyly.

GI/GU: Delayed gastric emptying. May have omphalocele, malrotation of the gut, pyloric stenosis, duodenal atresia, anteriorly placed or imperforate anus. Genital anomalies include cryptorchidism, hypospadias, bifid scrotum, uterine and cervical atresia, bicornuate uterus, duplicated vagina. Renal dysplasia. Ureteral dilation.

Anesthetic Considerations: Most patients exhibit severe respiratory distress at birth secondary to diaphragmatic hernia and/or lung hypoplasia. Microretrognathia may make direct laryngoscopy and intubation difficult. Patients have delayed gastric emptying and are at risk for perioperative aspiration. Significant renal disease has implications for perioperative fluid management and the choice of anesthetic drugs. Patients with hydrocephalus may warrant precautions for increased intracranial pressure, although not necessarily so in young infants with open sutures. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Furlong syndrome

See Loeys-Dietz syndrome

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

G

G syndrome

See Hypertelorism-hypospadias syndrome

G6PD deficiency

See Glucose-6-phosphate dehydrogenase deficiency

Gabrielli syndrome

Included in Oral-facial-digital syndrome, type I

Galactocerebrosidase deficiency

See Krabbe disease

Galactokinase deficiency

MIM #: 230200

This autosomal recessive disorder is due to an abnormality in the enzyme galactokinase. Galactokinase converts galactose to galactose-1-phosphate, in the pathway that ultimately converts galactose to glucose. This enzyme deficiency is occasionally included in the term “galactosemia” (see later). Galactose is in the diet as lactose, a disaccharide of glucose and galactose. Nuclear cataracts are the only consistent clinical finding. The cataracts are thought to be due to a reduction of galactose to galactitol.

HEENT/Airway: Nuclear cataracts. Neonatal diagnosis and removal of dietary galactose can result in clearing of cataracts.

Neuromuscular: Pseudotumor cerebri has been reported.

GI/GU: Neonatal jaundice.

Other: Elevated blood galactose. Galactosuria.

Miscellaneous: Gitzelmann in 1965 was the first to identify a patient with galactokinase deficiency. The patient was 44 years of age and had a history of galactosuria after the ingestion of milk. Galactosuria had been identified in the patient 33 years earlier when he required treatment for cataracts. At that time, Fanconi had called his condition “galactose diabetes.” At age 44 years, the patient was drinking 3 quarts of milk a day and was healthy other than blindness.

The ability to make the diagnosis of this disorder easily in the newborn period has been diminished in our modern age by the substitution of urine glucose test strips that test specifically for glucose (by glucose oxidase) rather than testing for reducing substances in general (which include galactose), and by early discharge from the newborn nursery, because urine and blood tests will be positive in the newborn only after feedings are well established.

Anesthetic Considerations: There are no specific anesthetic concerns, other than consideration of possible vision loss.

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Galactose-1-phosphate uridyltransferase deficiency

See Galactosemia

Galactose epimerase deficiency

See Uridine diphosphate galactose epimerase deficiency

Galactosemia

Synonym: Galactose-1-phosphate uridyltransferase deficiency

See also Galactokinase deficiency; Uridine diphosphate galactose epimerase deficiency

MIM #: 230400

This autosomal recessive disorder is caused by a deficiency in galactose-1-phosphate uridyltransferase, one of three enzymes catalyzing the conversion of dietary galactose to glucose. Galactose-l-phosphate uridyltransferase catalyzes the conversion of galactose-1-phosphate (formed by galactokinase) and uridine diphosphate glucose (UDP-glucose) into UDP-galactose and glucose-l-phosphate. Excess galactose-1-phosphate is presumably the substance that is toxic to a wide variety of tissues. Severe disease can present in the first weeks of life with poor feeding, weight loss, vomiting, diarrhea, hypoglycemia, lethargy, and hypotonia. Partial activity of the galactose-1-phosphate uridyltransferase enzyme leads to more mild clinical manifestations of the syndrome. Two other enzyme deficiencies result in elevated blood galactose but have distinct clinical presentations (see **Galactokinase deficiency**, earlier, and **Uridine diphosphate galactose epimerase deficiency**, later). These two other enzyme deficiencies are occasionally generically referred to as “galactosemia.”

HEENT/Airway: Neonatal cataracts. Retinal and vitreous hemorrhage has been reported, presumably on the basis of coagulopathy from hepatic failure.

Neuromuscular: Intellectual disability, even with appropriate dietary restriction and resolution of acute symptoms. Verbal dyspraxia. Motor abnormalities.

GI/GU: Vomiting or diarrhea. Hepatomegaly or acute hepatic failure in the neonatal period, progressing to periportal fibrosis, cirrhosis, and decreased hepatic function. Ascites as a preterminal finding. Renal tubular acidosis, albuminuria, and aminoaciduria. Ovarian failure.

Other: Failure to thrive. Bleeding diathesis, some patients may have hemolysis. Susceptibility to *Escherichia coli* sepsis as a neonate if untreated. Hypergonadotropic hypogonadism with gonadal failure in females.

Miscellaneous: In most states, neonates are routinely screened for galactosemia. Abnormal urine levels of galactose are not identified by current urine test strips because they use glucose oxidase, which is specific for glucose. Older tablet techniques identified all reducing sugars, including galactose. Interestingly, the diagnosis of galactosemia, particularly of variants with partial activity and false-positive diagnoses, increases during the summer months. This is presumably due to degradation of enzyme activity in the blood samples in hot mailrooms and delivery trucks.

Anesthetic Considerations: Recall that patients may have impaired vision. Neonates may have a significant bleeding diathesis. Strict asepsis is imperative in neonates, as they are at risk for *Escherichia coli* sepsis. Serum glucose levels should be monitored perioperatively. Hepatic dysfunction may affect the binding or the metabolism of some anesthetic drugs. Significant albuminuria may make urine output a poor indicator of intravascular volume.

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Galactosialidosis

MIM #: 256540

This autosomal recessive lysosomal storage disease is due to mutations in the gene encoding cathepsin A. This protein is a serine protease that protects beta-galactosidase (the cause of GM_1 gangliosidosis, see later) and alpha-neuraminidase from intralysosomal proteolysis. This results in accumulation of lysosomal polysaccharide. The disease is characterized by short stature, “gargoyle” facies, intellectual disability, ataxia, seizures, macular cherry-red spot, and hearing loss. Three types of disease have been described—early infantile, the most severe form which is associated with early death (average age of death is seven months), and late juvenile and juvenile/adult, which are slowly progressive. Children with the late juvenile type tend to have more mild neurologic but more severe cardiac disease, have growth retardation, and do not die young. Most juvenile/adult patients are Japanese.

HEENT/Airway: Coarse, “gargoyle” facies. Conjunctival telangiectasis. Corneal clouding, macular cherry-red spot. Conductive hearing loss. Macroglossia. Small mouth opening, malocclusion.

Chest: Barrel chest.

Cardiovascular: Thickened mitral and aortic valves with stenosis and/or insufficiency. Cardiomyopathy.

Neuromuscular: Cervical spine instability, atlantoaxial instability. Intellectual disability. Ataxia, seizures.

Orthopedic: Skeletal dysplasias and dysostosis. Short stature.

GI/GU: May have hepatosplenomegaly.

Other: Widespread angiokeratomas, particularly in juvenile/adult type. In the extreme, it can cause hydrops fetalis. Can develop hemophagocytosis.

Anesthetic Considerations: Macroglossia, combined with cervical spine instability, can make laryngoscopy and tracheal intubation difficult. It is likely that difficulty will worsen with aging, as with other lysosomal storage disorders, in which laryngoscopy and intubation can be exceedingly difficult. The laryngeal mask airway (LMA) has been used successfully in patients with other lysosomal storage diseases. Nasal fiberoptic intubation has been used successfully, but with difficulty (1). Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients with cardiomyopathy should receive an appropriately tailored anesthetic.

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Gangliosidosis

See GM_1 gangliosidosis; GM_2 gangliosidosis (Sandhoff disease; Tay-Sachs disease)

Gardner syndrome

Synonym: Familial adenomatous polyposis

MIM #: 175100

This autosomal dominant disorder involves extensive adenomatous polyposis of the colon and upper gastrointestinal tract. The responsible gene, called the *APC* gene, is a tumor suppressor gene. This disorder is accompanied by a high incidence of colorectal cancer, but a variety of other malignancies can also occur. Individually, polyps are indistinguishable from those that appear in the general population and are no more

likely to become cancerous. However, their massive number almost guarantees that some will. Technically, Gardner syndrome refers specifically to patients with extracolonic manifestations in addition to colonic polyps, but “Gardner syndrome” and “familial adenomatous polyposis” tend to be used interchangeably.

HEENT/Airway: Skull osteomas, with overlying fibromas of the skin. Pigmented retinal lesions (congenital hypertrophy of retinal pigment) that can rarely become malignant. Jaw cysts, mandibular osteomas, dental abnormalities.

Neuromuscular: Central nervous system cancers.

Orthopedic: Multiple osteomas, osteosarcoma.

GI/GU: Extensive adenomatous polyposis, primarily of the colon, but also of the upper gastrointestinal tract, including gastric and duodenal polyposis. The incidence of gastric carcinoma is higher in Japan. Malignant transformation of the polyps leads to colorectal carcinoma, periampullary carcinoma, bile duct carcinoma, and

hepatoblastoma. There is a high incidence of colorectal cancer in early adult life. Mesenteric fibromatosis (desmoid tumors) can occur after surgery. Adrenal carcinoma.

Other: Thyroid carcinoma, other carcinomas. Sebaceous and epidermoid cysts of skin, particularly on the back. Fibromas, desmoid tumors.

Miscellaneous: Eldon Gardner made major contributions in *Drosophila* genetics.

Anesthetic Considerations: May have prophylactic colectomy. Because of the incidence of mandibular and dental anomalies, mouth opening and dentition should be carefully assessed preoperatively. Nonsteroidal anti-inflammatory drugs have been shown to suppress the development of adenomatous polyps and can cause regression of existing polyps, so patients may be on one of these drugs, including aspirin.

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Gaucher disease

Synonym: Glucocerebrosidase deficiency

MIM #: 230800, 230900, 231000

This most common of the lysosomal storage diseases is an autosomal recessive defect of the lysosomal enzyme beta-glucosidase with consequent glycolipid (glucosylceramide) storage. The major features are hematologic abnormalities, hypersplenism, and bone lesions. If symptoms begin early in infancy, death usually occurs by 1 year of age. Life expectancy is normal in those who are more mildly affected. The disease is categorized into three types. The most common type is the nonneuropathic type I, which is also the mildest type. Type II has infantile onset and severe neurologic findings. Type III is also nonneuropathic, but signs usually begin later in the first decade and progress more slowly than in type I. A variant of type III (type IIIC) is associated with cardiac manifestations, particularly aortic and mitral valve calcification.

Many people with Gaucher disease are of Ashkenazic Jewish descent.

Gaucher disease. This young boy with Gaucher disease died shortly after this photo was taken. Note retroflexion and hypertonia.

Characteristic Gaucher cells are found in the marrow and in reticuloendothelial cells. These are large, lipid-laden histiocytes whose appearance has been likened to wrinkled tissue paper. Treatment with alglucerase (Ceredase) or taliglucerase (Elelyso) enzyme replacement therapy, is available.

HEENT/Airway: Strabismus and trismus in type 2. Pingueculae can occur with greater frequency but are not collections of Gaucher cells. Can have accumulation of brown Gaucher cells at corneoscleral limbus.

Chest: Pulmonary infiltration can lead to pulmonary hypertension and cor pulmonale. May develop right to left intrapulmonary shunting as a consequence of hepatic disease. Treatment with alglucerase can be associated with pulmonary arterial hypertension in a small percentage of patients. Bronchoscopy with bronchial washing may show typical Gaucher cells in the aspirate. A small number of patients may have pulmonary disease with hypoxia. Kyphoscoliosis may cause restrictive lung disease.

Cardiovascular: Cardiac involvement is rare and occurs particularly in type IIIC disease. Calcification of the aortic and mitral valves and the ascending aorta has been reported.

Neuromuscular: Absent in type 1 disease. Cranial nerve involvement, myoclonic jerks, seizures, and apnea in the infantile type. Patients with types 2 and 3 may have trismus and opisthotonos.

Orthopedic: Decreased bone density of long bones and vertebrae, with risk of pathologic fractures. Vertebral collapse causing kyphoscoliosis. Avascular necrosis of the femoral head. Erlenmeyer flask deformity of distal femur. Episodic painful bony crises in some, which can be associated with fever. Osteolytic lesions can follow within months of splenectomy, suggesting only partial splenectomies be done.

GI/GU: Cranial nerve involvement can cause swallowing difficulties. Hepatomegaly, which can be profound, with normal hepatic function (until late). Portal hypertension with secondary hepatic failure is rare. Splenic infarcts with pain. Splenomegaly, hypersplenism, which may require splenectomy. Renal involvement is rare.

Other: Anemia and thrombocytopenia from hypersplenism. Platelet dysfunction can occur as well as thrombocytopenia. Anemia can also occur from marrow infiltration by storage material. Enlargement of lymphoid tissue, including lymph nodes, thymus, Peyer patches, and tonsils. There can be a yellow-brown pigmentation over the face or lower legs. A variety of lymphoid and bone tumors have been described. Peripheral insulin resistance.

Miscellaneous: Gaucher, a French dermatologist and venereologist, entered medicine when he failed the university entrance examinations to study natural sciences. He described this particular type of hypersplenism in his doctoral thesis in 1882. One of his more interesting papers (on Salvarsan) was titled “606 or the German Poison.”

Elelyso (taliglucerase alfa), produced by transgenic carrot cells and used to treat Gaucher disease type 1, is the first prescription medication to be certified as kosher.

It has been suggested that heterozygosity for the glucocerebrosidase gene may predispose to the development of Parkinson's disease.

Anesthetic Considerations: Both lymphoid hyperplasia and trismus have been reported to complicate airway management. Trismus and opisthotonos resolve with muscle relaxants. Patients with a history of difficult intubation may become more difficult to intubate with age. Many patients require an endotracheal tube that is

smaller than that predicted by age. Patients with swallowing difficulties are at risk for aspiration, and a rapid sequence induction is recommended. Patients should be evaluated preoperatively for anemia, thrombocytopenia and coagulation disorders. Patients with otherwise mild disease may nonetheless have a bleeding dyscrasia and unexpected perioperative bleeding. Spinal and epidural anesthesia have been used successfully (3,5,7), but bleeding dyscrasias must first be excluded. Patients must be positioned carefully perioperatively due to bony fragility. Some patients will have chronic pain concerns.

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Geleophysic dysplasia

MIM #: 231050, 614185

This usually autosomal recessive syndrome is distinguished by characteristic facies, short stature, small hands and feet, and progressive cardiac valvular disease. It has been suggested that geleophysic dysplasia is a lysosomal storage disease based on the finding of lysosomal storage vacuoles in cells from the skin, tracheal mucosa, cartilage, liver, and heart valves. A mutation in the ADAMTS-like protein 2 gene is responsible for most instances of this disorder. A mutation in the fibrillin 1 gene (*FBN1*) causes an autosomal dominant form of geleophysic dysplasia, which is allelic with the autosomal dominant form of Weill-Marchesani syndrome (see later), and these two syndromes share skeletal and joint features.

HEENT/Airway: Characteristic “happy-natured” facies: round face, upslanting palpebral fissures, thickened ears, short nose with anteverted nares, long smooth philtrum, thin inverted vermilion, wide mouth. Gradual coarsening of facial features. High-pitched voice. Tracheal stenosis can develop.

Chest: Can have stenosis of the mainstem bronchi. Can have pectus excavatum.

Cardiovascular: Progressive valvular disease (especially aortic and mitral) with valvular thickening and eventual stenosis or incompetence. Cardiomegaly.

Neuromuscular: Can have developmental delay, seizures.

Orthopedic: Short stature. Toe-walking. Small hands and feet. Progressive contractures of multiple joints, particularly fingers and wrists. Decreased bone density. Coxa valga. Shortened tubular bones.

GI/GU: Hepatomegaly.

Other: Thick skin. Small nails.

Miscellaneous: *Geleos*, meaning “happy,” and *physis*, meaning “nature” are combined to describe this syndrome that includes characteristic “happy-natured” facies.

Anesthetic Considerations: Tracheal stenosis can be progressive and lead to critical airway narrowing. A smaller-than-expected endotracheal tube invariably is needed. Cardiac valvular disease is progressive and often causes death secondary to heart failure in early childhood. Joint contractures may make proper positioning difficult.

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Gilbert syndrome

MIM #: 143500

This usually autosomal recessive, sometimes autosomal dominant, condition leads to chronic mild unconjugated hyperbilirubinemia. It is a benign disease. Bilirubin levels can rise during periods of intercurrent illness and with fasting and can be normal at other times. It is due to deficient activity of the microsomal enzyme uridine diphosphate glucuronosyltransferase (UDP-glucuronosyltransferase), which catalyzes the conversion of unconjugated bilirubin to conjugated bilirubin. The most common abnormalities are mutations in the promoter region of the gene. Patients are usually asymptomatic but can have mild, nonspecific complaints such as abdominal pain, diarrhea, fatigue, and malaise. Interestingly, increased serum bilirubin levels have been associated with a reduced risk of atherosclerotic heart disease, and it has been demonstrated that patients with Gilbert syndrome have a lower risk of developing ischemic heart disease and hypertension (4).

Gilbert syndrome is the most benign of the diseases of hepatic bilirubin metabolism, which also include Crigler-Najjar, Dubin-Johnson, and Rotor syndromes. Crigler-Najjar syndrome (see earlier) is also due to a defect in UDP-glucuronosyltransferase, and these two syndromes are likely allelic. Phenobarbital induces hepatic microsomal enzymes and lowers the serum bilirubin level. The response to phenobarbital also suggests that the genetic defect is in a control gene rather than a structural gene.

HEENT/Airway: Scleral icterus.

GI/GU: Chronic but often intermittent, low-grade, unconjugated hyperbilirubinemia. Bilirubin levels are usually less than 3 mg/dL. Urobilinogen is absent, and liver function tests and histologic appearance are normal. Patients may complain of vague abdominal discomfort. Neonates may rapidly acquire normal postnatal levels of hyperbilirubinemia.

Other: Factors that can increase serum bilirubin levels include stress, intercurrent illness, infection, exercise, fatigue, alcohol ingestion, fasting, and menstruation.

Miscellaneous: Nicolas Gilbert was a French clinical pathologist—hence the soft “G” in “Gilbert.” The Bolivian squirrel monkey (but not the Brazilian squirrel monkey) also gets Gilbert syndrome.

Anesthetic Considerations: Stress, such as with surgery, perioperative fasting, intercurrent illness, infection, exercise, or fatigue, can increase serum bilirubin levels. Elevated fasting bilirubin concentration is rapidly normalized with the administration of oral or intravenous carbohydrate, but not fat. Postoperative unconjugated hyperbilirubinemia can occur, even in a previously asymptomatic patient. Although sulfonamides, some cephalosporins, and intravenous contrast agents can increase free bilirubin levels by displacing bilirubin from albumin, no currently used anesthetic agents are known to displace bilirubin to a degree that would contraindicate their use. Some patients may be on long-term phenobarbital therapy, which can affect the metabolism of some anesthetic drugs. Morphine is metabolized by a different glucuronosyltransferase system and can be used in these patients, although a prolonged effect was described in one patient in the older literature. Hepatic synthetic function is normal in these patients.

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Gilles de la Tourette syndrome

See Tourette syndrome

Gitelman syndrome

Included in Bartter syndrome

Globoid cell leukodystrophy

See Krabbe disease

Glucocerebrosidase deficiency

See Gaucher disease

Glucose phosphate isomerase deficiency

Synonym: Glucose-6-phosphate isomerase deficiency; Phosphohexose isomerase deficiency

MIM #: 613470

This autosomal recessive disease is caused by a deficiency in the enzyme glucose phosphate isomerase (*GPI*). This enzyme catalyzes the interconversion of glucose-6-phosphate and fructose-6-phosphate, the second step of the Embden-Meyerhof glycolytic pathway. Glucose phosphate isomerase deficiency presents as a nonspherocytic hemolytic anemia.

Neuromuscular: Mixed cerebellar and sensory ataxia. Muscle weakness.

GI/GU: Gallstones, cholecystitis, splenomegaly.

Other: Hemolytic anemia with spontaneous hemolytic crises. Splenectomy may significantly improve hematocrit and transfusion requirements. Impaired granulocytic function.

Anesthetic Considerations: The patient's hematocrit should be evaluated preoperatively. Perioperative hypoglycemia is not a concern.

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Glucose-6-phosphatase deficiency

See von Gierke disease

Glucose-6-phosphate dehydrogenase deficiency

Synonym: G6PD deficiency

MIM #: 300908

This X-linked enzyme defect can result in hemolysis in response to a variety of drugs or metabolic insults. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy in humans. G6PD

is the first step in the hexose monophosphate shunt, and the only source of NADPH [the reduced form of nicotinamide-adenine dinucleotide phosphate (NADP)] in mature red blood cells, which lack the citric acid cycle. There are approximately 400 known genetic variants of this disease, which can be divided into five classes according to the level of enzyme deficiency (Table 3A) and which can exhibit several different clinical presentations. In an African form (G6PD A-), young red blood cells have normal levels of the enzyme, so the increased erythrocyte production in response to hemolysis produces more young cells and therefore limits hemolysis. An enzyme assay done at this time may be normal. In the Mediterranean and Asian forms, there is decreased enzyme activity in both young and old red blood cells, and hemolysis continues as long as the triggering agent or condition is present. Occasional rare types present with chronic, rather than episodic, hemolytic anemia. Because of early X chromosome inactivation, female heterozygotes have two populations of red blood cells, either with or without the enzyme. Total enzyme activity in female heterozygotes ranges from normal to that seen in male hemizygotes, and female heterozygotes can have hemolytic attacks.

Hemolysis after exposure to a triggering agent becomes apparent 2 to 3 days after the exposure. Anemia worsens through the seventh day. The hematocrit begins to recover on the eighth day. There is some discrepancy between the small number of drugs clearly shown to be triggers for hemolysis, and the large number of drugs that have been implicated.

Oxidant drugs are problematic because superoxide ions are normally converted by superoxide dismutase to H_2O_2 and subsequently converted by reduced glutathione to water. NADPH is required to convert glutathione back to the reduced state.

GI/GU: Abdominal pain can occur during hemolytic episodes, and the spleen may be palpable. Cholelithiasis and cholecystitis. Hemolysis can cause renal failure, which is more common in adults than it is in children. Most episodes of renal failure are transient, if supported by dialysis.

TABLE 3A. Classes of G6PD deficiency

Class	Severely deficient, chronic hemolytic	Uncommon

I	anemia	
Class II	Severely deficient, 1%-10% enzyme activity	More common in Asian and Mediterranean populations
Class III	Moderately deficient, 10%-60% enzyme activity	More common in African Americans
Class IV	Normal activity, 60%-100% enzyme activity	Uncommon
Class V	Increased activity, >150% enzyme activity	Uncommon

Other: Hemolytic episodes can be caused by infection, presumably secondary to the release of peroxides from activated phagocytes and microbial metabolic products. Neonatal hyperbilirubinemia can be severe. Some patients will have a chronic hemolytic anemia, which can worsen during periods of oxidative stress.

Miscellaneous: "Favism" refers to hemolysis in G6PD-deficient people after the ingestion of fava beans (broad beans). Its effects were first noted long ago— Pythagoras is said to have warned against eating fava beans. G6PD-deficient red blood cells are more resistant to infection by *Plasmodium falciparum* and therefore appear to provide some protection against malaria.

Anesthetic Considerations: Patients should be evaluated preoperatively for anemia. It is important to prevent oxidative stressors such as hypoxemia, acidosis, hypothermia, hyperglycemia, anxiety, pain, and infection. Drugs known to trigger hemolysis must be avoided (Table 3B). Although there have been no reports of complications with the use of EMLA cream (a eutectic mixture of local anesthetics), prilocaine, which is found in EMLA cream, is a known trigger of hemolysis. Benzodiazepines, codeine and its derivatives, fentanyl, ketamine, and propofol are not known to trigger hemolysis in these patients. Cardiopulmonary bypass can impair oxygenation and increase hemolysis (2,7). Because hemolysis may not become apparent

until 2 to 3 days after the triggering exposure, good postoperative follow-up is imperative.

TABLE 3B. Drugs and other agents that can cause hemolysis in glucose-6-phosphate dehydrogenase deficiency

Analgesics
Aspirin (only in very high doses)

Prilocaine (possibly, but only in high doses, due to increased methemoglobin production)

Antibiotics

Ciprofloxacin

Nitrofurantoin

Nalidixic acid

Sulfonamides

Antimalarials

Chloroquine

Primaquins

Other

Ascorbic acid (in massive doses)

Fava beans

Glyburide (possibly)

Hydralazine

Methylene blue

Mothballs (naphthalene) (maybe)

Nitrates

Nitroprusside (possibly because of increased methemoglobin production)

Probenecid (maybe)

Vitamin K (water-soluble analogs)

In Mediterranean form only

Chloramphenicol

Quinine

Quinidine

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http://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe.aspx

Methylene blue is ineffective as an antidote to methemoglobinemia in these patients because methylene blue is unable to reduce methemoglobin in NADPH-deficient red blood cells. As a consequence, drugs known to cause methemoglobinemia (such as benzocaine, lidocaine, prilocaine, phenacetin, and nitrates) should also be avoided in these patients.

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Glucose-6-phosphate isomerase deficiency

See Glucose phosphate isomerase deficiency

Glutaric acidemia type I (glutaric aciduria type I)

Synonym: Glutaryl-CoA dehydrogenase deficiency

MIM #: 231670

This enzyme defect results primarily in chronic neurologic deterioration, although there may be metabolic abnormalities during episodes of acute clinical deterioration. It is marked by neuronal loss in the basal ganglia. The enzyme for this autosomal recessive disease catalyzes the conversion of glutaryl-CoA to glutaconyl-CoA and glutaconyl-CoA to crotonyl-CoA, which are intermediates in the metabolism of lysine eventually to acetyl-CoA. The defect affects the degradation of lysine, hydroxylysine, and tryptophan, and the accumulated glutaryl-CoA is esterified with carnitine, which can lead to a severe secondary carnitine deficiency. This enzyme resides in the mitochondria, and it is distinct from glutaric acidemia type II (see later). Treatment is with a lysine/tryptophan-restricted diet, carnitine, and riboflavin, a cofactor of the enzyme.

HEENT/Airway: Megalencephaly, often at birth. Opisthotonos.

Neuromuscular: Rare patients are normal. Extrapyramidal signs (dystonia, choreoathetosis). Eventual hypotonia, spastic quadriparesis. Progressive atrophic signs on brain imaging, particularly of the caudate and putamen. Can have hydrocephalus or arachnoid cysts. Patients may have an acute encephalopathic crisis with intercurrent infection. With recovery, there is a loss of developmental milestones. The etiology of acute crises is unknown. Intellectual function is preserved until late in the course of the disease. Can be associated with acute and chronic subdural hematoma.

GI/GU: Vomiting and hepatomegaly with acute crises. Microvesicular fatty infiltration of the liver and kidney.

Other: Metabolic findings are minimal and are often related to the secondary carnitine deficiency. Can have acute metabolic crises during intercurrent illness, with severe hypoglycemia, ketosis, and metabolic acidosis, which can progress to an encephalopathic Reye-like syndrome. Patients respond to glucose, carnitine, and bicarbonate. Association with subdural hematomas make false allegations of child abuse possible.

Anesthetic Considerations: Despite significant neurologic dysfunction that suggests otherwise, children maintain normal intellectual function until late in the disease. Patients can have difficulty swallowing and are at increased risk for perioperative aspiration. Acute neurologic crises may be triggered by perioperative stress or infection. Adequate levels of hydration and serum glucose must be ensured perioperatively. Patients may have significant dystonia, which will relax to a great extent with the induction of anesthesia even in the absence of muscle relaxant. Phenothiazines, butyrophenones, and other dopaminergic blockers can exacerbate movement disorders. Metoclopramide can cause extrapyramidal effects and is best avoided.

Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects. Involuntary movements may be aggravated by valproic acid. Baclofen reduces involuntary movements.

Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated

cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

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Glutaric acidemia type II (Glutaric aciduria type II)

Synonym: Multiple acyl-CoA dehydrogenase deficiency (MADD). (Includes Electron transfer flavoprotein [ETF] deficiency and Electron transfer flavoprotein:ubiquinone oxidoreductase [ETF-QO] deficiency)

MIM #: 231680

This progressive neurologic disorder differs from glutaric acidemia type I (glutaric aciduria type I) in that in type II, multiple acyl-CoA dehydrogenase deficiencies result in the excretion of a variety of organic acids in addition to glutaric acid. There are several autosomal recessive abnormalities that involve diminished activity of one or more of the acyl-CoA dehydrogenases involved in the transfer of electrons from acyl-CoA dehydrogenase to coenzyme Q in the mitochondrial electron transport chain. These abnormalities result in inhibition of mitochondrial oxidation of fatty acids and some amino acids. Acyl-CoA dehydrogenases are integral to fatty acid oxidation. After mobilization from adipose tissue, fatty acids are taken up by the liver and other tissues and converted to acyl-CoA esters in the cytoplasm. These enter mitochondria as carnitine esters and then become reesterified as acyl-CoA esters. Beta-oxidation results in the liberation of electrons that are transferred to electron transfer flavoprotein (ETF). As beta-oxidation proceeds, the acyl chain is gradually shortened, and this first step in the oxidation process is catalyzed by acyl-CoA dehydrogenases with differing, but overlapping, chain length specificities. There are very-long-chain, long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases. The clinical presentation is variable. Some infants die as neonates, whereas others eventually succumb to cardiac disease. In some, episodes of a Reye-like syndrome develop.

Three clinical phenotypes have been described, which are consistent within families. They are neonatal onset without congenital anomalies, neonatal onset with congenital anomalies, and mild and/or later onset. Infants with congenital anomalies often die within the first day of life.

This disorder can also be caused by abnormalities of the alpha or beta subunit of **electron transfer flavoprotein [ETF]** or by **electron transfer flavoprotein:ubiquinone oxidoreductase [ETF-QO] deficiency.** These proteins carry the electrons generated by a variety of dehydrogenases into the mitochondria and the main electron transport chain.

Treatment with riboflavin has been used in some patients with some success.

HEENT/Airway: Macrocephaly, high forehead, large anterior fontanelle, hypoplastic midface. Hypertelorism, congenital cataracts. Low-set and malformed ears. Flat nasal bridge.

Chest: Neonatal respiratory distress. Pulmonary hypoplasia with ETF deficiency.

Cardiovascular: Fatty degeneration of the myocardium. Severe hypertrophic cardiomyopathy can be fatal.

Neuromuscular: Hypotonia, muscle weakness. Pachygyria, cerebral gliosis.

Orthopedic: Rocker-bottom feet.

GI/GU: Nausea and vomiting. Abdominal wall defects. Fatty infiltration of the liver with hepatomegaly. Fatty degeneration of the renal tubular epithelium with proximal tubule damage resulting in glycosuria and generalized aminoaciduria. Polycystic kidneys, renal dysplasia. The kidneys can be palpable in affected neonates. External genital anomalies.

Other: Nonketotic hypoglycemia, hyperammonemia, hyperuricemia. Neonatal presentation is associated with profound hypoglycemia and metabolic acidosis, and delivery is often premature. Metabolic acidosis associated with an odor of sweaty feet and stale breath.

Miscellaneous: A similar range of organic acids is excreted in the urine in Jamaican vomiting sickness, which is caused by the ingestion of unripe ackee fruit. The toxin hypoglycin in unripe ackee inhibits several acyl-CoA dehydrogenases.

Anesthetic Considerations: Perioperative fasting should be minimized because patients are prone to hypoglycemia and nonketotic metabolic acidosis during periods of fasting. Blood glucose should be followed perioperatively, and patients should receive perioperative intravenous glucose supplementation. Patients with a history of nausea and vomiting may be at increased risk for aspiration. Renal defects may make urine output a poor indicator of intravascular volume. Consideration should be given to avoiding the use of nitroprusside because cyanide inhibits electron transport, although nitroprusside has been used in a patient without apparent injury (2). Patients with pulmonary hypoplasia or cardiomyopathy require an appropriately tailored anesthetic.

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Glutaryl-CoA dehydrogenase deficiency

See Glutaric acidemia type I (glutaric aciduria type I)

Glycerol kinase deficiency

Synonym: Hyperglycerolemia (Includes Complex glycerol kinase deficiency)

MIM #: 307030

This X-linked disease is due to a deficiency of glycerol kinase and is marked by hyperglycerolemia and glyceroluria. Glycerol kinase catalyzes the first step in glycerol catabolism, the phosphorylation of glycerol to glycerol-3-phosphate. There are three clinical phenotypes: an infantile form due to a microdeletion, a juvenile form that is associated with vomiting, acidosis and stupor in the toddler age group, and an adult or benign form. There is considerable clinical heterogeneity. Glycerol-limited diets appear to be of benefit in symptomatic patients. The adult form is typically detected by “pseudohypertriglyceridemia.” Laboratories may measure triglyceride levels by quantitation of glycerol after lipolysis, and these patients have elevated levels of blood glycerol unrelated to triglyceride levels.

This gene is closely linked to the genes for Duchenne muscular dystrophy and congenital adrenal hypoplasia (note: hypoplasia, not hyperplasia), and some patients with the infantile form of glycerol kinase deficiency will have a deletion syndrome involving all three genes. This contiguous gene deletion syndrome has become known as

complex glycerol kinase deficiency or chromosome Xp21 deletion syndrome (*MIM #:* 300679).

HEENT/Airway: Esotropia.

Neuromuscular: Intellectual disability. Episodes of somnolence or stupor progressing to coma. May be associated with Duchenne muscular dystrophy, but the myopathy may be relatively mild.

Orthopedic: Osteoporosis, pathologic fractures.

GI/GU: Vomiting, poor growth. May be associated with adrenal hypoplasia.

Other: Acidemia. Hyperglycerolemia, hyperglyceroluria. Hypoglycemia. Adults with the benign form can have mild diabetes mellitus, pseudohypertriglyceridemia.

Miscellaneous: Glycerol (the same as glycerin) derives its name from the Greek *glykeros* ("sweet"), by way of the French glycerine.

Anesthetic Considerations: Perioperative medications should be checked to ensure that they do not include glycerol (glycerin) as a component of the vehicle. Since glycerol is a component of propofol emulsions, it seems prudent to avoid propofol in these patients. Adrenal function should be assessed in patients with the infantile form. Patients with associated adrenal hypoplasia should be on steroid replacement therapy with a glucocorticoid and a mineralocorticoid and require perioperative stress doses of steroids. Adequate perioperative sources of glucose should be assured. Patients must be carefully positioned and padded secondary to osteoporosis and the risk of pathologic fractures.

Given the association between the infantile form and Duchenne muscular dystrophy, it would seem safest to proceed as if these patients had Duchenne muscular dystrophy, particularly in younger boys who may not yet have the clinical manifestations of the muscular dystrophy (see Duchenne muscular dystrophy, earlier).

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Glycine encephalopathy

See Nonketotic hyperglycinemia

Glycogen storage disease type 0, liver

Synonym: Glycogen synthase deficiency. (Includes Glycogen storage disease type 0, muscle)

MIM #: 240600

This autosomal recessive glycogen storage disease is due to one of several mutations in the gene encoding hepatic glycogen synthase. It is marked by fasting ketotic hypoglycemia and postprandial hyperglycemia and hyperlactatemia. There is a varied presentation, and it is likely that many if not most patients with the disease will not have the severe manifestations delineated below. Strictly speaking, this is not a glycogen storage disease, as the disorder results in decreased glycogen stores. Treatment is with frequent protein-rich meals and nighttime addition of uncooked cornstarch.

A similar disorder has recently been described in patients with muscle glycogen synthase deficiency (**Glycogen storage disease type 0, muscle**: (*MIM #:* 611556). In addition to the neuromuscular manifestations, glycogen deficiency in cardiac muscle has led to cardiomyopathy and sudden death in these patients.

Cardiovascular: Cardiomyopathy.

Neuromuscular: Seizures, developmental delay. Morning drowsiness (prior to breakfast). Muscle cramping.

GI/GU: Hepatic steatosis.

Other: Growth failure, small for gestational age. Neonatal hypoglycemia. Fasting ketotic hypoglycemia. Postprandial hyperglycemia, hyperlactatemia and glycosuria. Episodic hyperglycemia, glycosuria, and ketonuria make a superficial misdiagnosis of diabetes tempting. Hypoglycemic episodes can resolve with aging, except during pregnancy.

Anesthetic Considerations: Protracted preoperative fasting should be avoided. Liver function should be evaluated preoperatively. Perioperative fluids should contain glucose, and serum glucose should be monitored perioperatively. These patients are not appropriate for outpatient surgery. Patients with cardiomyopathy should receive an appropriately tailored anesthetic.

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Glycogen storage disease type I (IA and IB)

See von Gierke disease

Glycogen storage disease type II

See Pompe disease

Glycogen storage disease type III

See Debrancher deficiency

Glycogen storage disease type IV

See Brancher deficiency

Glycogen storage disease type V

See McArdle syndrome

Glycogen storage disease type VI

See Hers disease

Glycogen storage disease type VII

Synonym: Phosphofructokinase deficiency; Muscle phosphofructokinase deficiency; Tarui disease

MIM #: 232800

This autosomal recessive glycogen storage disease is similar to, but more severe than, glycogen storage disease type V (see McArdle syndrome, later). There is

involvement of muscle and red blood cell energy metabolism leading to exercise intolerance, muscle cramping and hemolysis.

Phosphofructokinase catalyzes the conversion of fructose 6-phosphate to fructose 1,6-diphosphate, a rate-limiting step in glycolysis. The enzyme in mammals is a complex isozyme with three subunits each encoded by its own structural gene: L, the major form found in the liver and kidney; M, found in the liver and the only form found in muscle; and P, the platelet form. Red blood cells contain both L and M subunits, and in general have half the enzyme activity. Because red blood cells have no energy source other than glycolysis, this decrease in enzyme activity is significant and decreases red blood cell half-life. Glucose cannot be utilized, but also lowers free fatty acid levels, the primary energy source of muscles. There is a severe infantile variant of this disease that also includes central nervous system and cardiac muscle abnormalities. In the infantile form, a severe myopathy is present at birth and is often accompanied by arthrogryposis.

Chest: Death secondary to respiratory complications is common in the severe infantile form.

Cardiovascular: Cardiomyopathy in the severe infantile form.

Neuromuscular: Muscle cramps with exertion, muscle weakness. Easy fatigability, especially after high-carbohydrate meals. Infants with the neonatal form can have seizures, intellectual disability, or other central nervous system manifestations.

Orthopedic: Arthrogryposis in the neonatal form.

GI/GU: Gallstones. Mild hemolytic anemia. Myoglobinuria with extreme exertion. A case of acute renal failure from rhabdomyolysis after exercise has been reported.

Other: There is mild erythrocytosis, thought to be secondary to decreased production of 2,3-diphosphoglycerate. Hemolytic tendency with elevated reticulocyte counts and serum bilirubin. There is no associated hypoglycemia. Hyperuricemia.

Miscellaneous: Relatively common in English Springer Spaniels.

Anesthetic Considerations: Patients with the severe infantile form may have a cardiomyopathy. Patients should be screened for anemia. Muscles are unable to use glucose and do not benefit from glucose or glucagon. Muscle fatigue is worse after a high-carbohydrate meal, and exercise tolerance is worse after a glucose infusion (4). The effects of perioperative glucose infusions remain speculative. Succinylcholine may be relatively contraindicated in patients with a myopathy because of the risk of an exaggerated hyperkalemic response. Propofol may increase urinary excretion of uric acid (3), making this a potential consideration when propofol is used for prolonged anesthesia or sedation.

Figure: See **Appendix E**

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Glycogen storage disease type VIII

See Glycogen storage disease type IX

Glycogen storage disease type IX

Synonym: Phosphorylase kinase deficiency; Glycogen storage disease type VIII; Hepatic phosphorylase b kinase deficiency

MIM #: 306000

The deficient enzyme in this X-linked recessive disease is phosphorylase kinase, which is involved in phosphorylating glycogen to glucose-1-phosphate. The major finding is hypoglycemia and fasting ketosis in infancy.

There is improvement in disease severity with age, such that most adults are asymptomatic despite continued lack of enzyme activity. The confusion of the nomenclature (glycogen storage disease VIII vs. IX) is due to the fact that the enzyme complex is encoded on both the X chromosome and on autosomes. About 75% of cases are X-linked, the rest are autosomal recessive. Several subtypes have been delineated, depending on which enzyme is missing (hepatic and/or muscle).

Cardiovascular: A rare cardiac-specific enzyme deficit has been reported with death during infancy with massive cardiac glycogen deposition.

Neuromuscular: Muscles are not involved. Some patients with an autosomal lack of hepatic and muscle phosphorylase kinase deficiency will have hypotonia. Mild motor delay.

Orthopedic: Growth retardation, but normal adult height.

GI/GU: Hepatomegaly, elevated liver transaminases. Rare cirrhosis. Renal tubular acidosis has been reported.

Other: Hypercholesterolemia, hypertriglyceridemia, fasting ketosis, hypoglycemia in infancy.

Anesthetic Considerations: Liver transaminases may be elevated. Adequate levels of serum glucose must be assured perioperatively in infants and young children. Patients respond normally to glucagon. There are no specific anesthetic concerns in adults.

Figure: See **Appendix E**

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Glycogen synthase deficiency

See Glycogen storage disease type 0

GM_1 gangliosidosis

MIM #: 230500, 230600, 230650

This autosomal recessive lysosomal storage disease is due to a defect in the gene for beta-galactosidase-1 (*GLB1*), resulting in the accumulation of GM_1 ganglioside. Infantile, juvenile, and adult forms have been described, due to different mutations of the same gene. The main manifestations are neurologic. Death in the infantile form occurs by the age of 2 to 3 years.

Gangliosides have both a hydrophobic ceramide moiety and a hydrophilic oligosaccharide chain. They are components of the outer cell membrane, with the hydrophobic moiety anchoring it in the membrane and the hydrophilic chain extending into the extracellular space. Although their function is unknown, they have been

implicated as binding sites for a variety of viruses, bacterial toxins, growth factors, and interferons.

HEENT/Airway: Infantile form: Coarse facies, frontal bossing. Macular cherry-red spot. Optic atrophy. Corneal clouding. Large, low-set ears. Depressed nasal bridge. Gingival hypertrophy, mild macroglossia. Short neck.

Juvenile form: Late blindness with normal cornea, retina, and macula.

Adult form: Normal vision.

Chest: Infantile and juvenile forms: Spatulate ribs. Recurrent aspiration pneumonia.

Cardiovascular: Infantile form: May have cardiomyopathy. May have valvular heart disease. May have paroxysmal supraventricular tachycardia.

Neuromuscular: Infantile form: Severely delayed mental and motor development, hypotonia, hyperreflexia. Seizures. Eventual decerebrate rigidity within a year of life.

Juvenile form: Mental and motor deterioration. Ataxia, choreoathetosis, progressive spasticity, lethargy. Generalized muscle weakness. Seizures. Eventual decerebrate rigidity.

Adult form: Intelligence usually normal or mildly affected. Facial dystonia (grimacing) and dysarthria with normal eye movements are common. Cerebellar dysfunction, ataxia, dystonia which is eventually incapacitating. Seizures are uncommon.

Orthopedic: Infantile form: Dwarfism, thoracolumbar kyphosis, scoliosis, stiff joints, flexion contractures of knees and elbows. Periosteal new bone formation as a newborn. Hypoplastic vertebral bodies with anterior beaking, osteoporosis of cortex of most bones, iliac flaring, wedge-shaped metacarpals. The bony changes are similar to those seen with the mucopolysaccharidoses.

Juvenile form: Mild changes with inferior beaking of lumbar vertebral bodies, proximal pointing of metacarpals (particularly the fifth), mild remodeling of the pelvis.

Adult form: Minimal radiologic changes.

GI/GU: Infantile form: Hepatosplenomegaly, inguinal hernia.

Juvenile and adult forms: No hepatosplenomegaly.

Other: Infantile form: Failure to thrive, edema. Thick, rough, hirsute skin. Angiokeratomas. May have increased incidence of Mongolian spots.

Adult form: Angiokeratomas.

Miscellaneous: This disease also occurs in cats, dogs, and sheep.

Anesthetic Considerations: Although there are no reports in the anesthesia literature, given the phenotypic similarity with the mucopolysaccharidoses, laryngoscopy and tracheal intubation might be expected to be difficult. Children should be considered to be at increased risk for perioperative aspiration. Succinylcholine is relatively contraindicated in this disease because of the risk of an exaggerated hyperkalemic response. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Skeletal dystrophy and abnormal skin in the infantile form may make vascular access more challenging. Contractures may make proper positioning

more difficult. Patients with cardiomyopathy or valvular disease require an appropriately tailored anesthetic. Supraventricular tachycardia in the infantile form has been fatal.

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GM_2 gangliosidosis

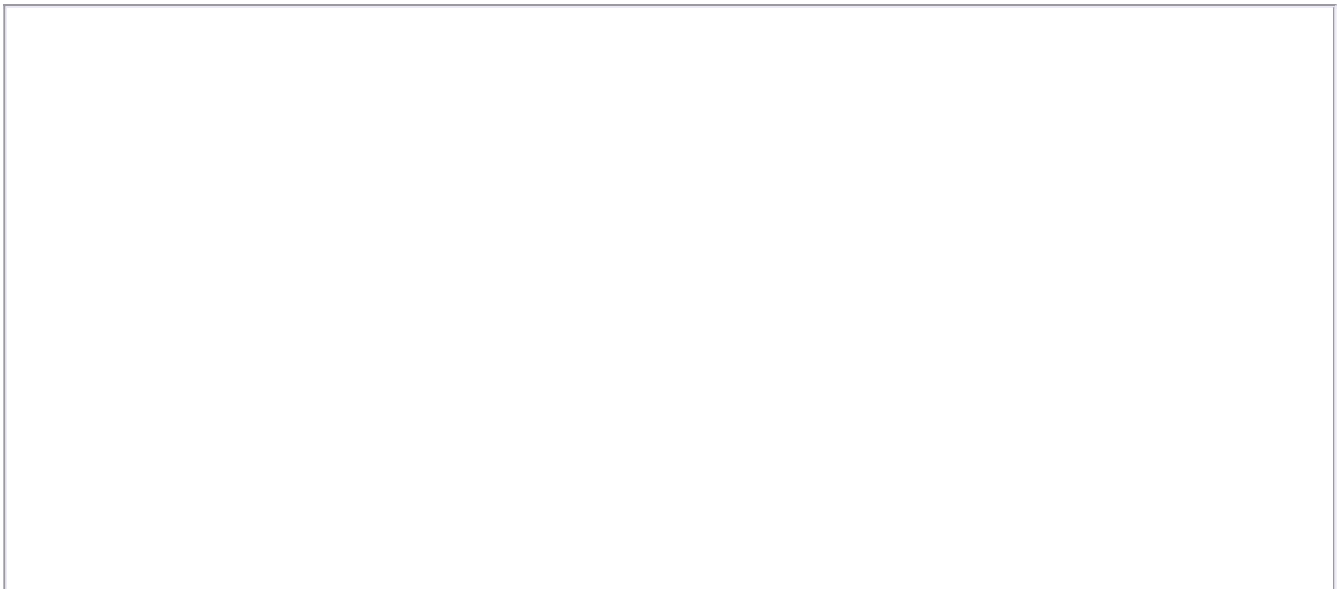
See Sandhoff disease and Tay-Sachs disease

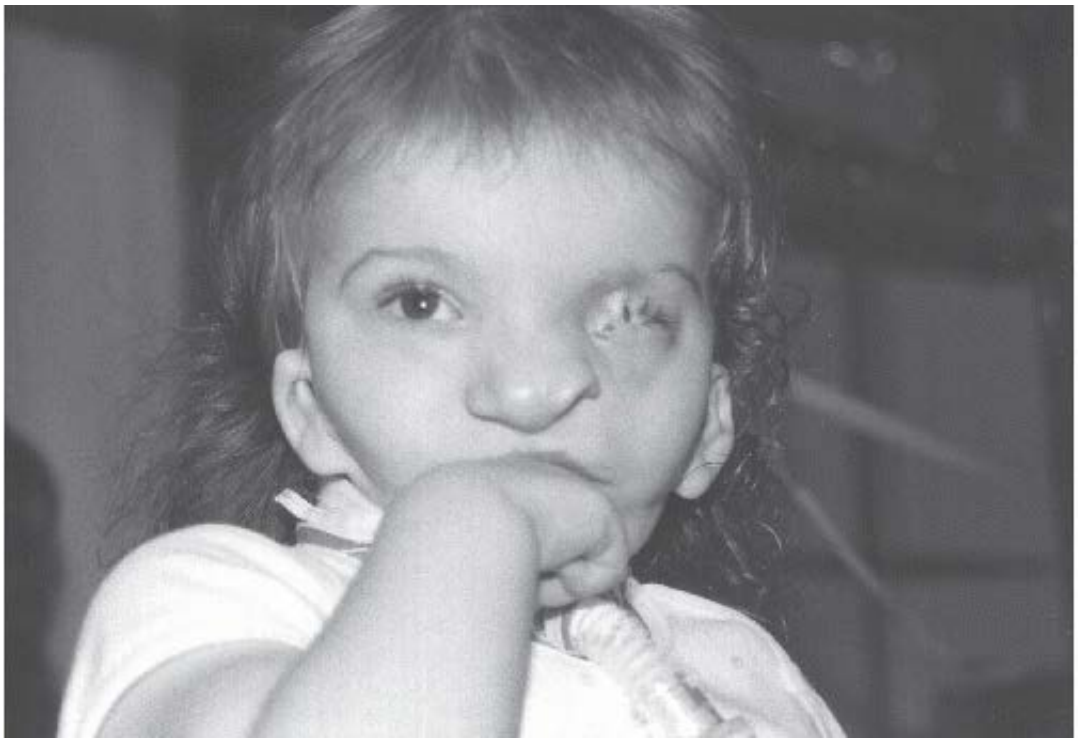
Goldenhar syndrome

Synonym: Facio-auriculo-vertebral syndrome; Hemifacial microsomia; Oculoauriculovertebral syndrome

MIM #: 164210

The main features of this sporadically occurring phenotypically variable syndrome are developmental anomalies of the first and second branchial arches, ocular anomalies, vertebral anomalies, and cardiac defects. The craniofacial anomalies are usually unilateral, or at least asymmetric, hence the term “hemifacial microsomia.” Epibulbar dermoids are common. This syndrome may represent the sequelae of a fetal vascular accident affecting the first and second branchial arches. Most cases are sporadic, but there are instances where inheritance is consistent with either autosomal dominant or autosomal recessive inheritance. There appears to be an increased risk of Goldenhar syndrome after the use of assisted reproductive technologies.



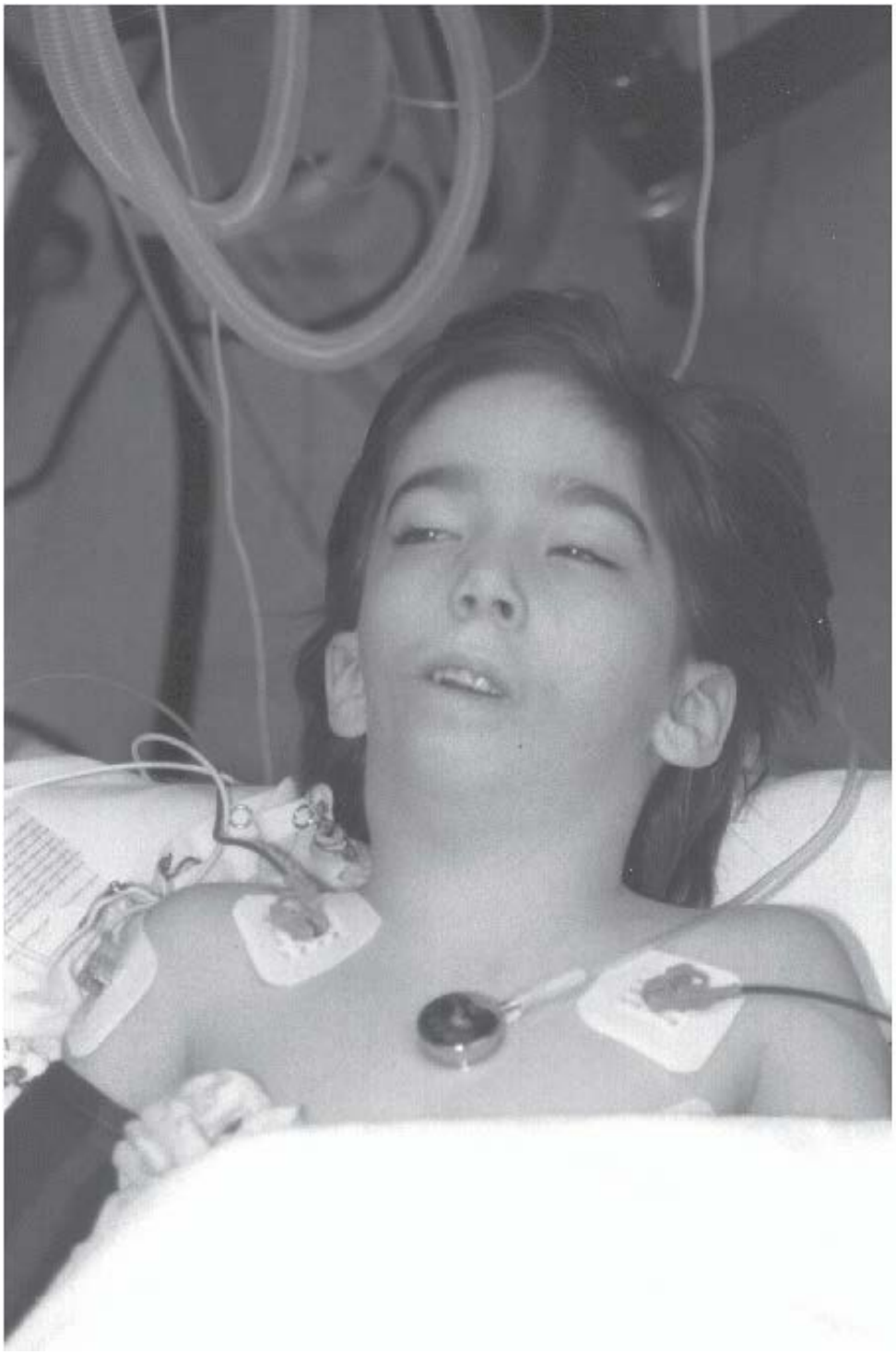


Goldenhar syndrome. FIG. 1. A young girl with Goldenhar syndrome. She has required a tracheostomy, and the eye findings are apparent.

HEENT/Airway: Unilateral or asymmetric hypoplasia of the facial bones and muscles. Epibulbar dermoids. May have upper lid coloboma, subconjunctival lipoma, strabismus, microphthalmia. Microtia and conductive hearing loss. Preauricular skin tags or pits. May have limited mouth opening, deviation of the mandible to the affected side, unilateral mandibular hypoplasia, micrognathia. May have cleft palate or high-arched palate. Abnormal tongue and palatal function. Parotid gland dysfunction. May have branchial cleft remnants in the neck. Occasional laryngeal anomaly, including tracheoesophageal fistula. May develop obstructive sleep apnea.

Chest: May have rib anomalies. Rare pulmonary hypoplasia or aplasia.

Cardiovascular: May have congenital cardiac defect, particularly ventricular septal defect, patent ductus arteriosus or tetralogy of Fallot.



Goldenhar syndrome. FIG. 2. The facial asymmetry in this young girl was more apparent after the induction of anesthesia. She has significant micrognathia with markedly diminished mouth opening. Tracheal intubation was very difficult.

Goldenhar syndrome. FIG. 3 A, B. This physician has had surgery in the past where tracheal intubation could not be done orally and he required fiberoptic intubation. Other manifestations of the syndrome include an eye coloboma, an ear tag, and slight micrognathia, none of which is immediately apparent.

Neuromuscular: Intelligence is usually normal. May have speech impairment. May have Arnold-Chiari malformation or hydrocephalus.

Orthopedic: Vertebral anomalies, especially of the cervical vertebrae, including hemivertebrae or hypoplasia. May have radial anomalies.

GI/GU: May have difficulties feeding. Renal anomalies include agenesis, ectopia, or dysplasia. May have ureteral duplication, vesicoureteral reflux.

Anesthetic Considerations: Craniofacial and vertebral anomalies can make laryngoscopy and tracheal intubation exceedingly difficult (10,14,15,16,19,20,22). The difficult airway may get progressively worse with age. Difficult intubating conditions may still occur after mandibular lengthening procedures, and prior surgery should not be considered reassuring. Correct mask fit may be difficult because of facial asymmetry. It may help to introduce the laryngoscope into the unaffected side of the mouth, where there is more room to displace the tongue. Multiple alternatives to direct laryngoscopy have been described, including suspension laryngoscopy, fiberoptic intubation, GlideScope® intubation, laryngeal mask airway, Airtraq, ProSeal, Air-Q, and retrograde intubation (1,2,3,4,7,9,10,12,15,19,22). A laryngeal mask airway has been used successfully to resolve upper airway obstruction in an awake infant (18).

It has been suggested that preoperative radiographs of the mandible are predictive of the degree of difficulty for

laryngoscopy (16). Mandibles that were merely small were least likely to be associated with a difficult intubation. Absent ramus, condyle, and temporomandibular joint had a high association with difficult intubation. Radiologic grading was not as useful with bilateral involvement. More recently, three-dimensional computed tomography airway imaging has been recommended as an aid to airway management in these patients (6,11).

Airway abnormalities can predispose to obstructive sleep apnea. One review of patients with Goldenhar syndrome found the incidence of obstructive sleep apnea to be nearly 24% (17). Care should be taken, particularly in the postanesthesia care unit, to avoid perioperative airway obstruction.

Patients undergoing corrective surgery, which may be quite extensive, can experience significant intraoperative blood loss. Patients may have hydrocephalus (20) and, if so, require appropriate management of intracranial

pressure. Radial anomalies may make placement of a radial arterial catheter more difficult. Patients with renal disease have altered metabolism of renally excreted drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Goltz syndrome

Synonym: Focal dermal hypoplasia; Goltz-Gorlin syndrome

MIM #: 305600

This X-linked dominant disorder is a disease of mesoectodermal development, with primary manifestations in skin, nails, hair, bones, and teeth. Specifically, patients exhibit pigmentary and atrophic skin changes, multiple papillomas, nail dystrophy, thin hair, syndactyly, bone hypoplasia, and small teeth with dental hypoplasia. Goltz syndrome is caused by a mutation in the *PORCN* gene located on the short arm of the X chromosome. Over 80% of affected individuals are female, suggesting that the disorder is lethal in male hemizygotes.

Note that Goltz syndrome is also known as Goltz-Gorlin syndrome. Gorlin syndrome, also known as Gorlin-Goltz syndrome, is a different syndrome that involves nevoid basal cell carcinomas (see Basal cell nevus syndrome, earlier).

HEENT/Airway: May have facial asymmetry, microcephaly. Strabismus, colobomas of the iris or choroid, microphthalmia, aniridia. Low-set ears with thin ear helix. May have hearing loss. Broad nasal tip with notched alae nasi. Small teeth with enamel hypoplasia. Delayed tooth eruption, hypodontia, oligodontia. High-arched palate. Pointed chin. Papillomas of the lip, buccal mucosa, and gingivae. Esophageal or laryngeal papillomas, which can be obstructive. May have cleft lip or palate.

Chest: Midclavicular hypoplasia or aplasia, rib hypoplasia. Supernumerary nipples. Asymmetric breasts. May have diaphragmatic hernia.

Cardiovascular: May have a congenital cardiac defect.

Neuromuscular: Occasional intellectual disability. May have spina bifida occulta.

Orthopedic: Nail dystrophy. Sparse, brittle hair. Patchy alopecia. Syndactyly, clinodactyly, brachydactyly,

polydactyly, adactyly. Aplasia or hypoplasia of the clavicles. Failure of fusion of the pelvic bones. Striated long bones. Scoliosis. Hypermobile joints. Skeletal asymmetry. May have short stature. Congenital dislocation of the hip.

GI/GU: Gastroesophageal reflux. Umbilical and inguinal hernias. Anal and vulvar papillomas. May have renal dysplasia, horseshoe kidney, bifid ureter. May have labial or clitoral hypoplasia. May have cryptorchidism.

Other: Pigmentary and atrophic skin changes. Herniation of fat through areas of severe dermal atrophy.

Hyperhidrosis. Telangiectasis. Palmar hyperkeratosis. Multiple skin and mucous membrane papillomas. Thin, brittle hair. Alopecia.

Miscellaneous: Robert Goltz is a dermatopathologist and a past president of the American Academy of Dermatology.

Anesthetic Considerations: Laryngeal papillomas can obstruct the glottic opening. Airway obstruction is so severe in some patients as to require a tracheostomy. Teeth should be examined preoperatively for number and stability. Gastroesophageal reflux is common, so precautions should be taken to minimize the risk of aspiration. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Patients should be carefully positioned and padded secondary to dermal hypoplasia and joint hypermobility. Temperature regulation may be impaired in patients with severe dermal hypoplasia.

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Goltz-Gorlin syndrome

See Goltz syndrome

Gorham syndrome

See Gorham-Stout disease

Gorham-Stout disease

Synonym: Gorham syndrome

MIM #: 123880

This is an autosomal dominant disease of massive osteolysis with replacement of bone with fibrovascular tissue resulting in pathologic fractures and secondary complications. It is sometimes referred to as the “disappearing bone disease.” The etiology is not currently understood. Onset in most cases is in the second or third decade of life but may be as early as 1 to 2 years of age. Impairment of the spine or lungs can become fatal. Bone grafts have not proven successful, but resection and replacement with artificial bone material has been effective, as has radiation therapy.

HEENT/Airway: Can have destruction of maxillary or mandibular bones, as well as orbital and cranial bones.

Chest: Relapsing pleural effusions. Respiratory failure from restrictive disease or pleural effusions. Chylothorax, which carries an approximately 50% mortality rate.

Cardiovascular: May have chylopericardium.

Neuromuscular: May have neurologic complications from spine involvement. May have unstable cervical spine.

Orthopedic: Massive osteolysis. In most patients, several adjacent bones are involved.

Other: May have hypoproteinemia secondary to chylothorax. Bone changes can be preceded by vascular skin changes.

Anesthetic Considerations: Pulmonary function and cervical spine integrity should be evaluated preoperatively. Patients with cervical spine instability require in-line cervical stabilization or a fiberoptic technique for intubation. Maxillary or mandibular involvement may make mask ventilation difficult. Succinylcholine should be avoided in patients with severely osteolytic bones due to the risk of bone fracture secondary to succinylcholine-induced fasciculations. Patients should be carefully positioned and padded perioperatively to avoid pathologic fractures.

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Gorlin syndrome

See Basal cell nevus syndrome

Gorlin-Cohen syndrome

See Frontometaphyseal dysplasia

Gorlin-Gold syndrome

See Basal cell nevus syndrome

Grebe syndrome

MIM #: 200700

This autosomal recessive syndrome is characterized by marked distal limb reduction and polydactyly and is thus a type of acromesomelic dysplasia. This chondrodysplasia results from a mutation in the gene *CDMP1*, which encodes cartilage-derived morphogenetic protein 1, a member of the transforming growth factor-beta superfamily of growth factor/signaling proteins. *CDMP1* is primarily expressed at sites of skeletal development. Heterozygotes have a milder phenotype. There are two other acromesomelic dysplasias, those of Hunter-Thompson and Maroteaux types (see Acromesomelic dysplasia, earlier).

HEENT/Airway: Normal facies.

Neuromuscular: Normal intelligence.

Orthopedic: Small stature due to limb reduction. Distal limb reduction (bones are shortened)—lower extremities affected more than upper extremities, distal bones more severely affected than proximal bones. The very short fingers resemble toes. Polydactyly. Short feet are in valgus position.

Other: May be stillborn.

Miscellaneous: Grebe is pronounced “GRAY-beh.” Hans Grebe was a university colleague of Mengele, a pupil of the racial hygienist Otmar Freiherr von Verschuer, and himself an advocate of the Nazi racial doctrines.

Anesthetic Considerations: Peripheral vascular access and regional anesthesia techniques will be challenging because of marked limb reduction defects. Patients must be carefully positioned and padded perioperatively secondary to marked chondrodysplasia.

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Greig cephalopolysyndactyly syndrome

MIM #: 175700

This autosomal dominant syndrome is distinguished by a characteristic skull shape (high forehead with frontal bossing), polydactyly, and syndactyly. This disorder is caused by mutations in the gene *GLI3*, which maps to chromosome 7. *GLI3* is homologous to the *Drosophila* cubitus interruptus gene, and this syndrome is homologous to the mouse mutant "extra toes." Frameshift mutations in this same gene result in the Pallister-Hall syndrome (see later), making these two disorders allelic.

HEENT/Airway: High forehead with frontal bossing, macrocephaly. Apparent hypertelorism, may have down-slanting palpebral fissures. Broad nasal root.

Neuromuscular: Normal intelligence. May have craniosynostosis. May have mild hydrocephalus. May have agenesis of the corpus callosum.

Orthopedic: Postaxial polydactyly in the hands, preaxial polydactyly in the feet. Syndactyly. Broad thumbs and halluces. Camptodactyly. May have hip dislocation.

Miscellaneous: Greig was a Scottish surgeon who described this entity during his tenure as the curator of the Museum of the Royal College of Surgeons of Edinburgh. He collected over 300 skulls during his lifetime, which he donated to the College Museum. Greig is pronounced "Gregg."

Anesthetic Considerations: Patients should be carefully positioned perioperatively to avoid hip dislocation.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

H

Haddad syndrome

Included in Ondine's curse

Hajdu-Cheney syndrome

Synonym: Acroosteolysis syndrome; Arthrodentoosteo dysplasia

MIM #: 102500

This autosomal dominant connective tissue disorder is characterized by acroosteolysis (dissolution of bone in the distal phalanges of the fingers and toes), lax joints, and early dental loss. The connective tissue defect primarily affects the development of skeletal tissue, and is caused by a mutation in the *NOTCH2* gene. Although the disorder begins in childhood, the diagnosis is often delayed. Patients frequently present with pain in the affected fingers, weakness, or pathologic fractures.

HEENT/Airway: Bathrocephaly. Cranial sutures may fail to ossify. Thickened cranium with wormian bones. Thick, straight scalp hair; prominent eyebrows and eyelashes. Synophrys. Absent frontal sinus. Downslanting palpebral fissures. Low-set, prominent ears. Hearing loss. Broad nose, anteverted nares, long philtrum. High, narrow palate. May have low-pitched voice. Hypoplasia of the mandibular ramus. Early dental loss. Short neck.

Cardiovascular: May have a congenital cardiac defect, especially septal defects.

Neuromuscular: Progressive basilar impaction against the foramen magnum may result in brainstem dysfunction. Hydrocephalus.

Orthopedic: Short stature that may be aggravated by vertebral osseous compression. Rare cervical instability secondary to cervical osteolysis. Biconcave vertebrae, vertebral osteopenia that may lead to collapse, narrow intervertebral disc spaces. Kyphoscoliosis. Lax joints. Dislocation of the radial head (“nursemaid's elbow”). Patellar dislocation. Acroosteolysis (shrinking fingers and toes), short distal phalanges, pseudoclubbing, short nails. Genu valgus, fibular bowing. May have osteoporosis and pathologic fractures.

GI/GU: Inguinal hernias. May have cystic renal disease.

Other: Hirsutism.

Anesthetic Considerations: Short neck and hypoplasia of the mandibular ramus may make direct visualization of the larynx difficult. Cervical instability may be present. Dental loss should be documented preoperatively. There is a report of vocal cord paralysis (6), and another report of upper airway obstruction (5) in patients with Hajdu-Cheney syndrome. In one report of a general anesthetic, the patient required an endotracheal tube one size smaller than that predicted for age (4). Spine abnormalities may make neuraxial techniques difficult, although successful spinal labor analgesia has been reported (2). Patients may have hydrocephalus. Patients must be

carefully positioned and padded to avoid hyperextension of lax joints or causing/aggravating pathologic fractures. Renal function should be assessed preoperatively in patients suspected of having cystic renal disease. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Hallermann-Streiff syndrome

Synonym: Francois dyscephalic syndrome

MIM #: 234100

This sporadic disorder is characterized by birdlike facies, ocular defects, mandibular hypoplasia, tracheomalacia, and hypotrichosis. The responsible gene and gene product are unknown.

HEENT/Airway: Small, birdlike facies with a large cranial vault and frontal bossing. Ocular defects include microphthalmia, cataracts, coloboma, nystagmus, strabismus, glaucoma, and retinal degeneration. Sparse eyebrows and eyelashes. Hypoplastic, pointed (beaked) nose with septal deviation. Malar hypoplasia. Absence of mandibular condyles. Mandibular hypoplasia and anterior displacement of the temporomandibular joints, making the mouth appear open. High-arched

palate. Narrow upper airway. May have obstructive sleep apnea. Neonatal, missing, supernumerary or hypoplastic teeth. Tracheomalacia.

Chest: Rib hypoplasia. A narrow upper airway combined with tracheomalacia frequently results in respiratory complications, including respiratory distress and recurrent infection.

Cardiovascular: Chronic upper airway obstruction and respiratory insufficiency can lead to cor pulmonale. May have congenital heart disease.

Neuromuscular: Intelligence is usually normal but may have intellectual disability. May have spina bifida, hyperactivity, choreoathetosis, seizures.

Orthopedic: Proportionate short stature. Thin, slender long bones. Clavicular hypoplasia. Hyperextensible joints. May have scoliosis, osteoporosis.

Other: Low birth weight. Hypotrichosis. Focal areas of skin atrophy over the nose and scalp.

Anesthetic Considerations: Major craniofacial abnormalities make endotracheal intubation difficult (1,2,4,5,8). The hypoplastic nose with deviated septum may make nasotracheal intubation difficult. The temporomandibular joints may be weak, allowing dislocation during laryngoscopy. Neonatal teeth (teeth present at birth) as well as deciduous and permanent teeth are brittle and can be broken easily during laryngoscopy.

Patients with significant upper airway obstruction may need a tracheostomy. Patients with recurrent respiratory infections may have chronic lung disease. These patients in particular are at risk for postoperative pulmonary complications. Patients with chronic upper airway obstruction or chronic lung disease may have cor pulmonale. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Care needs to be taken in positioning patients with hyperextensible joints. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Hallervorden-Spatz disease

Synonym: Neurodegeneration with brain iron accumulation; Pantothenate kinase-associated neurodegeneration (PKAN)

MIM #: 234200

Hallervorden-Spatz disease is an autosomal recessive progressive neurologic disease. Its pathologic hallmark is iron deposition, particularly in the globus pallidus, caudate, and substantia nigra. It typically presents in childhood with movement disorders and may rarely present in adults as Parkinsonism and dementia. It is due to mutations in the gene *PANK2*, which encodes pantothenate kinase. This enzyme is important in the synthesis of coenzyme A. Patients with the classic form have onset of signs in the first decade of life. There are also subtypes with early onset and slow progression, and late onset with rapid progression. Patients with early onset tend to have pigmentary retinopathy while those with late onset tend to have speech and psychiatric disorders.

HEENT/Airway: Optic atrophy, retinitis pigmentosa. Oromandibular rigidity from dystonia. Dysarthria and difficulty swallowing.

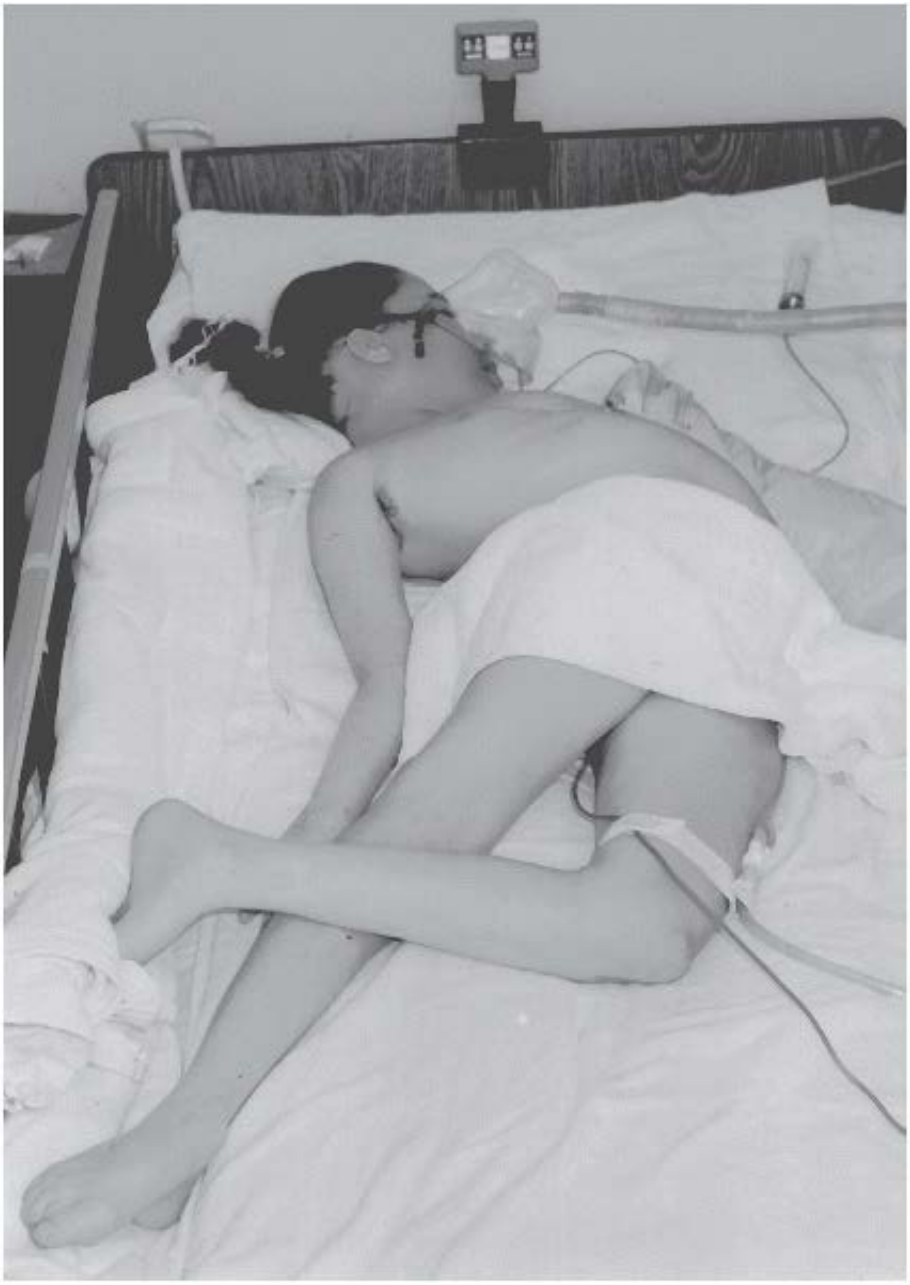
Chest: Risk of recurrent aspiration pneumonia.

Neuromuscular: Choreoathetosis. Dystonia with torticollis is common. Parkinsonian features including tremor and rigidity. Rigidity is progressive and begins in the lower extremities before progressing to the upper. Behavioral problems. Psychiatric problems. Progressive dementia. Spasticity. T_2-weighted MRI scans demonstrate a pattern of hyperintensity within the generally hypointense globus pallidus (“eye of the tiger sign”).

Orthopedic: Scoliosis is common from dystonia. Equinovarus foot deformity.

Miscellaneous: Both Hallervorden and Spatz were Nazi war criminals. A majority of the brains they investigated during the Nazi period were victims

of euthanasia, and there is good evidence that Hallervorden in particular was present at the killing of many of these people. Because of concerns regarding the origins of Hallervorden's personal pathologic collection, the collection has been removed from the Edinger Institute. It has also been suggested that this eponymous disease be renamed (4). Its primary listing in OMIM is currently “Neurodegeneration with brain iron accumulation.”



Hallervorden-Spatz disease. A 21-year-old woman with Hallervorden-Spatz disease. Scoliosis and dystonia are apparent. She had torticollis and trismus that prevented any mouth opening. Hypertonicity, including oromandibular hypertonicity and torticollis, resolved with halothane. (Courtesy of Dr. Raymond C. Roy, Department of Anesthesiology, Wake Forest University School of Medicine.)

Anesthetic Considerations: With the induction of anesthesia (even with volatile agents alone), muscle tone diminishes and leads to relaxation of oromandibular rigidity and improvement of torticollis. Dexmedetomidine has also been shown to suppress the dystonia (1). Nondepolarizing muscle relaxants can be used. Succinylcholine is contraindicated in these patients who may be bedridden and who may have unpredictable lesions involving upper motor neurons. Patients are at risk for perioperative aspiration. Extrapyramidal signs will reappear on emergence, and patients are at risk for postoperative respiratory complications (5).

Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers may exacerbate movement disorders. A patient has been reported in whom apparent neuroleptic malignant syndrome developed perioperatively, presumably secondary to decreased dopaminergic activity in the substantia nigra and the nigrostriatal projections (6).

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Hand-Schüller-Christian disease

Included in Langerhans cell histiocytosis

Hanhart syndrome

See Oromandibular-limb hypogenesis

Happy puppet syndrome

See Angelman syndrome

Hartnup disorder

MIM #: 234500

This autosomal recessive disorder involves impairment of neutral amino acid transport in the kidneys and the small

bowel. Some patients can have renal involvement only, while others have bowel involvement only. Because tryptophan is required for niacin synthesis, reduced tryptophan absorption and increased renal losses lead to secondary niacin deficiency. The skin and neurologic findings are similar to those of pellagra (the four Ds of niacin deficiency: Diarrhea, Dermatitis, Dementia, and Death). There is significant phenotypic variability. Many patients diagnosed by neonatal screening remain asymptomatic, as do most siblings of identified patients. The disorder is due to mutations in the gene *SLC6A19*.

HEENT/Airway: Nystagmus, diplopia.

Neuromuscular: Intermittent cerebellar ataxia, tremors, episodic emotional instability, seizures, psychosis. Mild intellectual disability. Most patients, however, are normal.

GI/GU: Diarrhea. Aminoaciduria. The pattern of aminoaciduria differs from the generalized hyperaminoaciduria of, for example, the Fanconi syndrome or cystinuria. Tests of renal function are otherwise normal.

Other: Pellagra-like, light-sensitive skin rash on exposed areas of the body. The rash initially blisters and eventually is scaly and depigmented. Maternal Hartnup disorder does not affect the fetus. A patient has been reported in whom a pellagra-like rash developed coincident with lactation and breast-feeding.

Miscellaneous: This disorder was named not after a Dr. Hartnup, but rather the Hartnup family, in whom it was first described. It is thought that the full-blown syndrome is not often seen in the United States because of the generally superadequate diet. Treatment with niacin or nicotinamide can often clear the rash and improve the neurologic findings, if treatment is thought necessary.

Anesthetic Considerations: Adequate hydration must be ensured in these patients who have frequent diarrhea. A protracted perioperative fast without adequate protein intake could worsen the symptoms of this disorder. Stress and sulfonamides may exacerbate symptoms.

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Hawkinsinuria

Included in Tyrosinemia III

Hay-Wells ectodermal dysplasia

See AEC syndrome

Heart-hand syndrome

See Holt-Oram syndrome

Hecht Beals syndrome

See Dutch-Kentucky syndrome

Hecht syndrome

See Dutch-Kentucky syndrome

Hemifacial microsomia

See Goldenhar syndrome

Hemoglobin H disease

Included in Thalassemia

Hemoglobin S-thalassemia

Included in Thalassemia

Hemophilia

See Hemophilia A or Hemophilia B

Hemophilia A

MIM #: 306700

This X-linked disorder is due to mutations or deletions of the gene that encodes clotting factor VIII. Over 370 distinct mutations in the gene have been described. This disorder cannot be clinically differentiated from hemophilia B (Christmas disease, see later), which is due to deficient activity of factor IX. Acquired hemophilia A is a rare condition caused by the acquisition of autoantibodies against factor VIII.

Patients with less than 1% factor VIII activity are said to have severe disease, those with 1% to 5% activity have moderate disease, and those with 6% to 30% activity have mild disease. Patients with severe disease can have spontaneous bleeding, whereas patients with mild disease usually have bleeding only after surgery or major trauma. However, life-threatening bleeding can occur in all groups. Of the approximately 17,000 people with hemophilia A in the United States, approximately 30% have the mild form and may not be aware that they have hemophilia. Female carriers usually have normal coagulation, but in some instances can have severe bleeding as well.

HEENT/Airway: Subgaleal hematoma or cephalohematoma can be seen in the newborn. Bleeding after dental procedures or trauma to the lip or tongue can be severe (saliva has significant fibrinolytic activity). Antifibrinolytics such as epsilon aminocaproic acid (Amicar) or tranexamic acid are useful for control of bleeding in the mouth.

Neuromuscular: Central nervous system bleeding, usually after trauma, but can be spontaneous. Severity of the bleeding may not become apparent until several days after the trauma.

Orthopedic: Hemarthrosis is the most common type of bleeding, especially in the knees, elbows, and ankles, but also in the shoulders, hips, and wrists. Cold packs, brief immobilization, and early physiotherapy are indicated for

hemarthrosis. Joints only rarely need to be aspirated. Recurrent bleeding can damage synovia, cartilage and bone, destroying joint function. Epiphyseal damage can cause abnormal bone growth. Bone cysts are a late complication.

GI/GU: Gastrointestinal abnormalities can be associated with excessive gastrointestinal bleeding. Retroperitoneal bleeding. Painless hematuria. Antifibrinolytics such as epsilon aminocaproic acid should be avoided in patients with hematuria to avoid causing clot formation in the ureters.

Other: Platelet function and bleeding time are normal. Previously, there was a high incidence of hepatitis B infection and human immunodeficiency virus (HIV) infection because of inadequate testing of blood and factor products and the frequency with which these patients required blood products. Since the advent of recombinant factor VIII, viral transmission through the use of human factor VIII obtained from pooled blood products is no longer a great concern.

Miscellaneous: Hemophilia was a scourge to the male offspring of Queen Victoria. It has been suggested that this was a paternal age effect because there had been no previous hemophilia in the family, and her father was 52 years old when she was born.

Anesthetic Considerations: Orotracheal intubation is preferred because of the increased risk of bleeding with nasotracheal intubation. Hemostasis after venipuncture or catheter placement in large veins may be a problem. Intramuscular injections should be avoided or given only after treatment with factor VIII. Regional anesthesia is relatively contraindicated and certainly so without prior treatment with factor VIII and documentation of posttreatment factor levels and activated partial thromboplastin time (aPTT) (2,5,6). Minimum safe factor levels have not been determined (5).

Perioperative management should be planned in consultation with the patient's hematologist. Specific therapy may vary slightly, and the following is offered only as a guideline:

For *minor surgery*, patients should receive a loading dose of human recombinant factor VIII concentrate of 50 units/kg followed by an infusion of 4 units/kg/h for 24 hours postoperatively to maintain a factor VIII level of 100%. After 24 hours, the dosage is changed to every 8 hours for 7 days.

For *major surgery*, patients should receive a loading dose of 50 units/kg of human recombinant factor VIII concentrate followed by an infusion of 4 units/kg/h for 7 days. Because of the variable rate of decay of the recombinant factor, levels must be monitored and factor dosing adjusted based on these levels. The half-life of factor VIII is shorter in younger children, and they therefore require more frequent monitoring and dosing.

For minor nonsurgical soft tissue bleeding, factor VIII activity should be replaced to 20% of normal; for hemarthroses or severe soft tissue bleeds, factor VIII activity should be replaced to at least 40% of normal; for extensive dental work, factor VIII activity should be replaced to at least 70% of normal; for central nervous system bleeds, factor VIII activity should be replaced to 80% to 100% of normal. For central nervous system or retroperitoneal bleeds, treatment may be needed for 7 to 14 days.

One unit of factor VIII per kilogram weight increases the circulating factor VIII activity by 2%. The half-life of factor VIII is 8 hours for the first dose and 12 hours thereafter. A recombinant factor VIII with a prolonged half-life is being investigated for routine preventive use. There is individual variation, so specific dosing may need to be determined by measuring blood levels.

Factor VIII is available in several preparations:

1. Human recombinant factor VIII: the concentration of factor VIII varies (usually approximately 40 units/mL). This is the preferred treatment.
2. Fresh frozen plasma: 1 unit/mL. This requires the use of excessive volumes.

3. Cryoprecipitate: 80 to 120 units/bag.

Desmopressin (DDAVP) has been used in a dose of 0.3 μg/kg for mild (and only mild) cases. DDAVP stimulates the release of von Willebrand factor, which is needed for the proper functioning of factor VIII. The addition of antifibrinolytic agents, epsilon aminocaproic acid (Amicar) or tranexamic acid, can decrease bleeding, particularly oral bleeding. Antifibrinolytics should be avoided in patients with hematuria to avoid causing clot formation in the ureters.

Upon exposure to factor VIII, approximately 30% of patients with hemophilia A will develop alloantibodies

(inhibitors) that nullify factor VIII clotting function and increase the risk of bleeding that is difficult to control. In patients in whom high titers of inhibitors have developed, use of “bypassing agents” such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII can be considered (3).

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Hemophilia B

Synonym: Christmas disease

MIM #: 306900

This type of hemophilia is due to a defect in the gene that encodes factor IX. It is inherited in an X-linked recessive fashion. Female carriers are almost never clinically affected. The clinical manifestations are identical to those of hemophilia A (factor VIII deficiency). See Hemophilia A (earlier) for a discussion of the clinical findings. The aPTT may be normal in patients with factor IX levels in the 20% to 30% range.

Miscellaneous: The second report of this disease appeared in the December 27 (Christmas) issue of *The British Medical Journal*, and reported a 5-year-old boy with the family name of Christmas (as well as other patients).

Anesthetic Considerations: See Hemophilia A (earlier) for a discussion of the general perioperative treatment of hemophilia. Perioperative management should be planned in consultation with the patient's hematologist. Specific treatment for hemophilia B requires the administration of factor IX. This is available in a variety of preparations. Recombinant factor IX preparations are now available, as are several plasma-derived preparations. One unit of factor IX per kilogram weight should increase the circulating factor IX activity by 0.8% to 1%. The half-life is 16 to 20 hours. Allergic reactions can occur. Treatment will need to be continued postoperatively. Factor IX levels can be measured with a relatively short turnaround time. Hypercoagulability has not been a problem with recombinant factor IX replacement, even when combined with antifibrinolytics. The use of fibrin sealants has enhanced surgical hemostasis and decreased the requirement for protracted postoperative treatment. A recently approved recombinant factor IX with a much longer half-life is being investigated for routine preventive use.

For muscle, soft tissue, mucous membrane or urinary tract bleeding, factor IX activity should be replaced to 40% of normal; for joint bleeding, factor IX activity should be replaced to 60% of normal; for surgery or head or neck trauma, factor IX activity should be replaced to 100% of normal. In general, a loading dose is given to reach the targeted level, followed by an infusion of 8 units/kg/h.

Upon exposure to factor IX, 1% to 6% of patients with hemophilia B will develop allo-antibodies (inhibitors) that nullify factor IX clotting function and increase the risk of bleeding that is difficult to control. In patients in whom high titers of inhibitors have developed, use of “bypassing agents” such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII can be considered (2).

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Henoch-Schönlein purpura

Synonym: Schönlein-Henoch purpura

MIM #: None

This small-vessel vasculitis is often post-infectious (usually in response to infection with streptococcal species), but there may also be a genetic susceptibility. It is the most common vasculitis in children, and occurs most frequently in the fall and winter months. It causes systemic leukocytoclastic vasculitis and deposition of immune complexes, primarily IgA and C3, in many organs. The primary findings are a nonthrombocytopenic purpuric rash of the lower

abdomen and legs, arthritis, abdominal pain, and nephritis. Most cases are self-limited and last approximately 4 weeks. Younger children usually have a shorter course and fewer recurrences. Recurrences can uncommonly occur as late as 2 years after the onset, although renal relapses are not seen after the urine becomes clear.

HEENT/Airway: Patients may have dependent edema. In infants, this tends to be scalp edema.

Chest: Pulmonary hemorrhage is rare but can be fatal.

Neuromuscular: Seizures and intracranial hemorrhage are uncommon.

Orthopedic: Arthritis or arthralgia, particularly of the feet and ankles, and also the knees. This is a periarticular process rather than a true synovitis. Dependent edema.

GI/GU: Colicky abdominal pain, vomiting. Uncommon complications are intussusception, bowel infarction or perforation, and gastrointestinal tract bleeding. Steroids decrease abdominal pain and probably decrease the incidence of intussusception. Hematuria, proteinuria. Nephritis and progressive renal failure is less common. Nephritis is usually treated with steroids. May have orchitis.

Other: Fever, malaise. Nonthrombocytopenic purpuric rash over the lower extremities, less commonly on the arms or face. Onset of the rash can follow the arthritis or abdominal pain. Nonpitting edema of the hands, feet, and face. Anemia. Normal coagulation.

Miscellaneous: Henoch initially had a poor opinion of modern bacteriology, calling it Bakterienschwindel (the swindle of bacteria) in the first edition of his primary work *Vorlesungen über Kinderkrankheiten*. Subsequent editions did not include this opinion. Schönlein published only two papers, and they were only one and three pages long, respectively. Nonetheless, it was Schönlein who coined the term “hemophilia.” Osler incorrectly thought this disorder was a consequence of anaphylaxis, and for many years, it was referred to as anaphylactoid purpura.

Anesthetic Considerations: Elective surgery should ideally be postponed until any renal involvement has resolved. Renal dysfunction can affect the metabolism of some anesthetic drugs and has implications for the perioperative titration of fluids. Patients may be whole-body fluid overloaded secondary to edema but may be intravascularly hypovolemic. Peripheral venous access can be difficult secondary to edema. Patients may be quite uncomfortable, and care in positioning will be much appreciated by them. Patients taking steroids should receive perioperative stress doses of steroids. Regional anesthetic techniques are not necessarily contraindicated, as the platelet count and coagulation cascade are normal.

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Hepatic phosphorylase b kinase deficiency

See Glycogen storage disease type IX

Hepatolenticular degeneration

See Wilson disease

Hereditary angioedema

Synonym: C1 esterase inhibitor deficiency; hereditary angioneurotic edema

MIM #: 106100

This autosomal dominant disorder is due to a deficiency of the serum inhibitor of the first component of complement (C1 esterase inhibitor), allowing uncontrolled activation of the classic complement cascade. It is caused by a mutation in the C1 inhibitor gene, *C1NH*. Type I disease has decreased levels of normal C1 esterase inhibitor, whereas the less common type 2 disease has normal or increased levels of a functionally abnormal C1 esterase inhibitor. Appropriate biologic activity is confirmed by normal C4 levels in the blood. Abnormal subepithelial edema can form in the skin, abdominal organs, and the upper airway and larynx. Attacks progress over 1 to 2 days and regress over the next 2 to 3 days. Trauma to an extremity, tonsillectomy, and tooth extraction are common initiating events, although often there will be no identifiable initiating event.

Less commonly, the deficiency can be acquired. The acquired form is more common in females than males, and can be associated with autoimmune or low-grade lymphoproliferative disorders where it is due to increased catabolism of the protein.

Long-term prophylaxis is with the modified androgens danazol (50 to 300 mg/day in adults) or stanazol (also spelled stanozol) (1 to 4 mg/day in adults). Stanazol has fewer side effects. The modified androgens increase hepatic synthesis of C1 esterase inhibitor. Antifibrinolytics have also enjoyed some success as prophylactic agents due to their ability to inhibit plasmin activity. C1 esterase inhibitor concentrate (obtained from pooled plasma) can be used for acute therapy and is now available in the United States. Other agents being investigated to control acute attacks include bradykinin B2 receptor antagonists and kallikrein inhibitors.

HEENT/Airway: Episodes of airway edema can be precipitated by trauma or emotional upset. Edema can involve the tongue, oral cavity, soft palate, pharynx, and larynx, but not the bronchi, presumably because of local breakdown of kinins by angiotensin-converting enzyme in the lungs. Prophylactic androgens and C1 esterase inhibitors for exacerbations have essentially eliminated airway deaths and airway-related intensive care unit admissions.

GI/GU: Recurrent abdominal pain is a common complaint, sometimes accompanied by nausea and vomiting, or severe diarrhea. Decreased motility can be severe enough to cause a functional bowel obstruction. One-third of patients undergo unnecessary appendectomies or laparotomies. Hypovolemic shock can develop secondary to fluid loss into the peritoneum or bowel wall. There is an increased incidence of polycystic ovaries.

Other: Erythema marginatum during an attack. Attacks can occur with menses. The incidence appears to decrease after the first trimester of pregnancy and after menopause. The disease can be exacerbated during adolescence. Dental surgery is more likely to trigger an attack than abdominal surgery. Hypercoagulability (based on the thromboelastogram) was documented in one patient who had coronary artery surgery (12).

Miscellaneous: First described by Quincke, the disease's hereditary nature was first recognized by Sir William Osler. Before modern therapeutic approaches, there was a significant incidence of fatal laryngeal edema after dental extractions, and one-third of patients eventually died secondary to airway obstruction. Stanazol figured prominently in the recent steroid abuse scandal in American major league baseball.

Anesthetic Considerations: Since stress can precipitate an acute attack of angioedema, consideration should be given to appropriate premedication. Dental, ear/nose/throat, and endoscopic manipulations are known to precipitate episodes of edema. Endotracheal intubation should be avoided if possible. Edema can develop hours to days after surgery. Mask general anesthesia and regional anesthesia have not been reported to cause problems and should be considered preferable if clinically appropriate. ACE inhibitors and tramadol have been demonstrated to precipitate attacks, otherwise there are no apparent contraindications to any routinely used anesthetic drugs. The effect of the laryngeal mask airway (LMA) is not known, but in the absence of further information, it should be considered as a source of potential airway trauma and in any event would not circumvent obstruction from laryngeal edema. If an emergency intubation is required, assistance from an otolaryngologist should be obtained, as an emergency tracheostomy is possible. Because angioedema may not manifest itself immediately, good postoperative follow-up is imperative.

Perioperative prophylaxis should be administered in conjunction with any invasive procedure. Prophylaxis involves instituting or increasing androgen therapy for 5 to 6 days before surgery until 3 days after surgery (danazol 600 mg/day in adults or stanazol 6 mg/day in adults). Antihistamines, epinephrine, and steroids are not effective in the treatment of episodes of edema or for emergency preoperative prophylaxis. If immediate prophylaxis or treatment of an exacerbation is required, or if androgens are contraindicated, as in pregnancy, C1 esterase inhibitor concentrate (obtained from pooled plasma) can be used. The dose is 25 units/kg in adults, and the effect lasts 4 to 5 days. Fresh frozen plasma (two units in adults) has been used in lieu of C1 esterase inhibitor concentrate, but the use of fresh frozen plasma in an emergency is controversial.

It does supply C1 esterase inhibitor, but it also supplies C2 and C4, which provide additional substrate, and levels of C1 esterase inhibitor can be at the same time inadequate.

Both cardiopulmonary bypass and heparin-protamine complexes activate complement, which can be disastrous, and hemodilution will dilute low but adequate levels of C1 esterase inhibitor. Mortality related to complement activation during bypass has been reported (16). However, successful cardiopulmonary bypass has been undertaken after preoperative treatment as outlined previously (5,15), and off-pump coronary artery surgery is a viable alternative (6,10,11).

C1 esterase inhibitor has been used successfully to treat nonhereditary angioedema, such as from angiotensin-converting enzyme (ACE) inhibitor (9).

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Hereditary angioneurotic edema

See Hereditary angioedema

Hereditary antithrombin deficiency

See Antithrombin III deficiency

Hereditary sensory and autonomic neuropathy (HSAN)

See Congenital insensitivity to pain with anhidrosis (HSAN IV) and Familial dysautonomia (HSAN III)

Hereditary fructose intolerance

Synonym: Fructose-1-phosphate aldolase B deficiency

MIM #: 229600

This autosomal recessive disease is caused by the inability to split fructose-1-phosphate into dihydroxyacetone phosphate and glyceraldehyde. This has several sequelae: fructose cannot be converted into glucose in the organs containing this pathway (liver, renal cortex, small bowel mucosa), and there is increased activity of the proximal enzyme in the pathway, fructokinase, so that any fructose causes accumulation of fructose-1-phosphate, which inhibits gluconeogenesis as well as glycogenolysis, causing hypoglycemia and depletion of adenosine triphosphate and guanosine triphosphate stores. Hereditary fructose intolerance is caused by a mutation in the aldolase B gene.

Ingestion of fructose is followed shortly by severe hypoglycemia and emesis. Patients are asymptomatic as long as there is no fructose in the diet, so infants do well while breast fed, but experience problems when cow's milk formula sweetened with sucrose is added, or when they are fed fruits or vegetables. Patients (or their parents) typically are aware of which foods to avoid and maintain themselves asymptomatic. The younger the child and the larger the fructose load, the more severe the symptoms. Young infants receiving only bottle feedings that are sweetened with fructose or sucrose can have a fatal reaction. The disease can be encountered occasionally in children with a Reye syndrome-like presentation. Extensive disease in older children or adults is rare.

Neuromuscular: Lethargy, dizziness, apathy, myoclonic jerks, eventually seizures.

GI/GU: Gastrointestinal discomfort, abdominal distention, diarrhea. Gastrointestinal bleeding. Hepatomegaly, jaundice, ascites. Proximal renal tubule dysfunction with renal tubular acidosis (aminoaciduria, glycosuria, phosphaturia, bicarbonaturia).

Other: Hypoglycemia (uncommon and short-lived after fructose ingestion), lactic acidosis. Hyperuricemia when fructose is not restricted. Failure to thrive, nausea, pallor. Bleeding dyscrasia. Growth retardation with chronic ingestion. Can have transient hypermagnesemia from breakdown of Mg^{2+} ATP with fructose ingestion.

Miscellaneous: Approximately one half of adult patients are completely without dental caries, presumably from decreased dietary sucrose. Strange food phobias may on occasion be considered to be a psychiatric problem. The first case reported was that of a 24-year-old “spinster.” Times change.

Anesthetic Considerations: Oral medications that are suspended or dissolved in syrup sweetened with sucrose, fructose, or sorbitol must be avoided. Inadvertent postoperative infusions of fructose, sorbitol, or invert sugar in the past have been fatal and have been reported primarily in the German literature. Hypoglycemia is unresponsive to glucagon. Fresh frozen plasma or exchange transfusion may be needed for a severe bleeding dyscrasia.

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Hereditary hemorrhagic telangiectasia

See Osler-Weber-Rendu syndrome

Hereditary onychoosteodysplasia

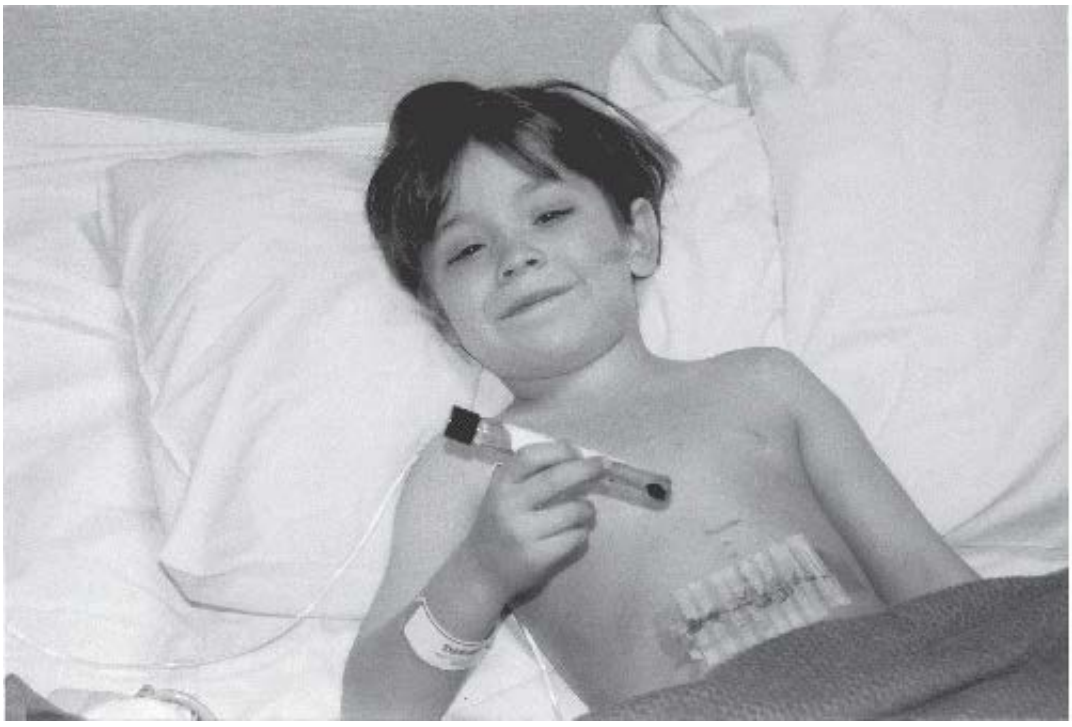
See Nail-patella syndrome

Hereditary spherocytosis

Synonym: Congenital spherocytosis; Spherocytosis

MIM #: 182900

Hereditary spherocytosis is a genetically heterogeneous autosomal dominant form of hemolytic anemia. There is incomplete penetrance with variability in the severity of disease, and 25% of cases are sporadic. The disorder is characterized by mild to moderately severe anemia, spherocytosis on the peripheral blood smear, and marked improvement after splenectomy. Most cases of hereditary spherocytosis are caused by mutations in the genes encoding for ankyrin and/or spectrin, proteins critical to the integrity of the red cell membrane. Ankyrin is the principal binding site for spectrin on the membrane. Deficiencies in ankyrin and/or spectrin lead to abnormal red cell membrane permeability to sodium, a loss of red cell membrane lipids, a decrease in red cell membrane surface area, and the formation of the characteristic spherocytes. These cells are rigid and osmotically fragile. The abnormal red blood cells are in turn removed from the circulation by the spleen, leading to the clinical picture of anemia and splenomegaly.



Spherocytosis. A young boy with congenital spherocytosis posing with his gallstones following a cholecystectomy and partial splenectomy. His hematocrit had been 22 and his total bilirubin 10.4 mg/dL (direct fraction 0.8 mg/dL).

GI/GU: Splenomegaly. Cholelithiasis.

Other: Mild to moderately severe anemia. Characteristic spherocytes in peripheral blood smear. Neonatal jaundice. May have clinically significant iron overload and formation of bilirubinate gallstones. May have leg ulcers. Clinical symptoms improve significantly after splenectomy.

Miscellaneous: Hereditary spherocytosis was first described by Vanlair and Masius in 1871 and then rediscovered 20 years later by Wilson and Minkowski.

Anesthetic Considerations: The patient's hematocrit should be evaluated preoperatively and consideration should be given to the potential need for perioperative transfusion.

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Hereditary xanthinuria

See Xanthinuria

Hermansky-Pudlak syndrome

MIM #: 203300

The hallmarks of this autosomal recessive disorder are oculocutaneous albinism, a bleeding diathesis, and abnormal pigmented reticuloendothelial cells with lysosomal accumulation of ceroid lipofuscin primarily in the lungs and gut. There can be pulmonary fibrosis or granulomatous colitis. The disorder appears to be due to an abnormality of the membranes of lysosomes, melanosomes, and platelet dense bodies. Platelet dense bodies trigger the secondary aggregation of platelets. The responsible gene is the *HPS1* gene on the long arm of chromosome 10. The gene product has not yet been identified, but it is likely to be a transmembrane protein that is a component of multiple organelles.

HEENT/Airway: Congenital nystagmus, ocular albinism, visual loss (approximately 20/200). Epistaxis. Excessive bleeding after dental extractions.

Chest: Can have pulmonary fibrosis, which is progressive, beginning with restrictive disease and often becoming fatal in the fourth or fifth decade of life.

Cardiovascular: May have cardiomyopathy.

GI/GU: Inflammatory bowel disease, especially granulomatous colitis. Abnormal pigmented hepatic reticuloendothelial cells, renal failure.

Other: Albinism with variable cutaneous hypopigmentation. Bleeding diathesis, easy bruisability, platelets lack dense bodies and have abnormal aggregation studies. Pigmented reticular cells in bone marrow and lymph glands, lysosomal accumulation of ceroid lipofuscin.

Miscellaneous: The disorder is particularly common in northwest Puerto Rico, and in a small isolated Swiss Alpine village.

Anesthetic Considerations: Although pulmonary and cardiac abnormalities are uncommon, a careful evaluation of these organ systems is required preoperatively. Restrictive lung disease can occur. Preoperative evaluation should include a platelet count and bleeding time, as patients may have normal numbers of abnormally functioning platelets. Nasal intubation or the placement of a nasogastric tube should be undertaken with caution because of the increased risk of bleeding. Aspirin-containing medications must be avoided. Desmopressin (DDAVP) may be useful in controlling bleeding by improving platelet function. Patients may require perioperative platelet transfusions. Regional anesthetic techniques are relatively contraindicated because of the bleeding diathesis. Patients who are on chronic steroid therapy require perioperative stress doses of steroids.

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report. *J Reprod Med* 2013;58:267-270.

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Hers disease

Synonym: Glycogen storage disease type VI; liver glycogen phosphorylase deficiency

MIM #: 232700

This disorder is caused by an autosomal recessive defect in liver glycogen phosphorylase, which can be partially or completely absent. This enzyme is involved in the degradation of glycogen. This is a relatively benign disorder, and most patients with Hers disease do not require specific treatment.

Cardiovascular: The heart is unaffected.

Neuromuscular: Normal development and intelligence. Muscles are unaffected with liver glycogen phosphorylase deficiency.

Orthopedic: Growth retardation.

GI/GU: Prominent hepatomegaly with the potential for the development of hepatic adenomas or malignancies. Hepatomegaly usually resolves with age and disappears around the time of puberty. Cirrhosis can develop.

Other: Patients may have mild to moderate hypoglycemia and mild ketosis. There is no hyperuricemia.

Anesthetic Considerations: A prolonged preoperative fast should be avoided. Liver function should be evaluated preoperatively. Serum glucose levels should be monitored perioperatively and adequate perioperative glucose should be assured. Patients respond normally to glucagon.

Figure: See **Appendix E**

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Heterotaxy syndrome

See Asplenia or Polysplenia

Hexokinase deficiency

MIM #: 235700

Like phosphofructokinase and pyruvate kinase, hexokinase catalyzes a rate-limiting step in glycolysis. Hexokinase

catalyzes the conversion of glucose and adenosine triphosphate to glucose 6-phosphate. Glycolysis is the only energy source available to red blood cells, and deficiency of hexokinase results in a chronic hemolytic anemia. The enzyme has four isozymes, each encoded by its own gene. A variety of alleles for this autosomal recessive disorder have been reported.

GI/GU: Cholelithiasis, cholecystitis. Splenomegaly.

Other: Chronic hemolytic anemia with jaundice. A transfusion requirement may be partly ameliorated by splenectomy.

Miscellaneous: Hexokinase deficiency has also been reported as part of Fanconi anemia, but that defect also involves deficient platelet and white blood cell hexokinase, which are normal in this hexokinase deficiency. A model in the mouse is called “downeast anemia.”

Anesthetic Considerations: The patient's hematocrit should be evaluated preoperatively, and consideration should be given to the potential need for perioperative transfusions.

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HHH syndrome

Synonym: Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

MIM #: 238970

This autosomal recessive disorder is due to mutations in the gene *SLC25A15*. This gene encodes a transporter (ORNT1) that moves ornithine across the inner mitochondrial membrane from cytosol to mitochondrial matrix, a critical step in the urea cycle. Infants do well until breast-feeding is discontinued and a protein-rich diet begun. Patients often self-select a low-protein diet and avoid milk and meat. Symptoms are related to hyperammonemia and are similar to the other urea cycle defects. It is likely that early intervention with arginine, ornithine, or citrulline may effect a favorable neurologic prognosis. Onset can be from childhood to adulthood. A second mitochondrial transporter, ORNT2, when overexpressed, can minimize the effects of the disorder.

HEENT/Airway: Retinal depigmentation.

Neuromuscular: Periodic neurologic symptoms develop with high protein intake and include episodic confusion, lethargy, ataxia, and choreoathetosis. Delayed milestones. Decreased vibratory sense. Progressive spastic paraplegia-hypotonia early, with spasticity late. Seizures. Intelligence low normal to severely impaired.

GI/GU: Episodic vomiting.

Other: Failure to thrive, growth failure. Hyperornithinemia, postprandial hyperammonemia, homocitrullinuria. A bleeding diathesis has been described in a few patients.

Anesthetic Considerations: Patients should be maintained on a low-protein diet perioperatively. Succinylcholine may be contraindicated in patients with muscle disuse because of the risk of an exaggerated hyperkalemic

response. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood in the gastrointestinal tract provides a protein load that may lead to the development of hyperammonemia. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Figure: See **Appendix C**

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Hirschsprung disease

MIM #: 142623

Hirschsprung disease is colonic aganglionosis, which results in a functional rectal or colonic obstruction. The normal *in utero* craniocaudal progression of neural crest cells is arrested in this disorder, with subsequent absence of distal myenteric and submucosal ganglia. The affected segment, of variable length, is chronically contracted. The diagnosis can be made on rectal biopsy. In infants, a colostomy is often performed for decompression, followed in approximately 1 year by a definitive “pull-through” procedure. Alternatively, the definitive “pull-through” procedure can be done in a single stage. Despite surgical correction, many patients continue to have functional problems.

Although long thought to be inherited as an autosomal recessive trait, defects in one or more genes, both autosomal dominant and autosomal recessive, can be responsible for this disease. These include the *RET* gene, the endothelin-B receptor gene, the endothelin-3 receptor gene, and the gene for glial cell line-derived neurotrophic factor. There is a male predominance.

There is an association of Hirschsprung disease with Ondine's curse, or central hypoventilation syndrome (see later). Although only a small number of patients with Hirschsprung disease have Ondine's curse, approximately 50% of children with Ondine's curse can have Hirschsprung disease. There is also an increased incidence of Hirschsprung disease in a variety of neurocristopathy and nonneurocristopathy syndromes, such as Down syndrome, Bardet-Biedl

syndrome, Smith-Lemli-Opitz syndrome, and Waardenburg syndrome, among others.

HEENT/Airway: Bicolored iris has been described.

Cardiovascular: May have congenital heart disease.

Neuromuscular: Central hypoventilation (“Ondine's curse”) has been reported.

GI/GU: Colonic or rectal aganglionosis. Failure to pass neonatal meconium. Vomiting on the first day or two of life. Patients may present with enterocolitis resembling sepsis or necrotizing enterocolitis. The affected segment is of variable length and may be very short, which makes the clinical diagnosis more challenging. A barium enema in neonates may not show the typical transition of normal to abnormal bowel seen in older patients. Therapy is an initial colostomy followed in approximately 1 year by a definitive pull-through operation, although earlier definitive repair has been proposed.

May have Meckel's diverticulum, malrotation. Increased incidence of megaureter, megacystis, cryptorchidism, cystic renal disease, bladder diverticulae, hypoplastic uterus.

Miscellaneous: The high incidence of Hirschsprung disease in association with the central hypoventilation syndrome (“Ondine curse”) has led to the suggestion of Ondine-Hirschsprung disease as a synonym for this disease, and a mutation in the receptor tyrosine kinase (RET) protooncogene has been documented in a child with Ondine-Hirschsprung disease.

Harald Hirschsprung was the first Danish pediatrician. He was appointed as director of the Queen Louisa Hospital for Children. Queen Louisa requested that Biblical texts be placed over each bed. When Hirschsprung insisted on placing pictures of animals there, the Queen refused to enter the hospital. Hirschsprung frequently offered his medical lectures only on Sunday mornings, to be certain that only those students who were truly interested would attend.

Anesthetic Considerations: Patients may have associated abnormalities such as central hypoventilation syndrome, Down syndrome, or congenital heart disease. Neonates frequently present with vomiting and are at risk for dehydration and perioperative aspiration. Neonates should have a nasogastric tube in place for decompression. Adequate preoperative intravenous rehydration should occur, and a rapid sequence induction of anesthesia should be undertaken.

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Histidinemia

MIM #: 235800

This autosomal recessive disease is due to deficient activity of the enzyme histidine ammonia-lyase (histidase). This enzyme catalyzes the first step in the deamination of histidine, the conversion of histidine to *trans*-urocanic acid. Urocanic acid has been proposed to have an ultraviolet protective effect, and urocanase is not present in the epidermis.

Despite earlier suggestions, it is now thought that this is a benign disease. Histidinemia might potentiate the central nervous system effects of other processes, such as perinatal hypoxia, explaining the abnormal findings in some patients. Alternatively, ascertainment bias is possible, because earlier cases were identified in patients who came to medical attention for other problems, such as developmental disorders. Later cases have been ascertained by neonatal screening, and there has been no increased incidence of clinical abnormalities. A histidine-restricted diet has been shown to have no effect.

Miscellaneous: This disorder is particularly common in French-Canadians and the Japanese.

Anesthetic Considerations: There are no specific anesthetic considerations.

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Histiocytosis X

See Langerhans cell histiocytosis

Holocarboxylase synthetase deficiency

Synonym: Multiple carboxylase deficiency

MIM #: 253270

This autosomal recessive disease is closely related to biotinidase deficiency (the other multiple carboxylase deficiency, see earlier). Biotin, a B vitamin, is a cofactor for four carboxylases: pyruvate carboxylase, propionyl-CoAcarboxylase, 3-methylcrotonyl-CoAcarboxylase, and acetyl-CoA carboxylase. Holocarboxylase synthetase attaches biotin to the inactive apoenzyme. Abnormalities in this enzyme result in defective activity of all of these carboxylases, and holocarboxylase synthetase deficiency is thus a cause of multiple carboxylase deficiency. Biotinidase liberates biotin from a proteolytic enzyme degradation product. While there is some overlap, holocarboxylase synthetase deficiency presents as a neonate and is usually fatal if untreated, while biotinidase deficiency typically presents after several months of life. Acute episodes are triggered by intercurrent infection or increased protein intake and involve ketoacidosis and hyperammonemia. Treatment with biotin should correct all symptoms (unless fixed, such as optic atrophy), although some poorly biotin-responsive forms have been reported. Isolated abnormalities in the carboxylase enzymes have been reported and are biotin unresponsive.

HEENT/Airway: Conjunctivitis, optic atrophy, myopia, abnormal retinal pigment. Auditory nerve atrophy with hearing loss. Laryngeal stridor has been reported in the closely related biotinidase deficiency.

Chest: Tachypnea and Kussmaul breathing from ketoacidosis.

Neuromuscular: Lethargy, hypotonia, ataxia, seizures, coma during acute episodes. May have psychomotor developmental delay. May have subependymal cysts.

GI/GU: Feeding difficulty, vomiting. Odd smelling urine.

Other: Potentially fatal episodes of ketoacidosis, lactic acidosis, and hyperammonemia. Organic aciduria. Hypothermia. Bright red, scaly rash over the body, particularly in the diaper and intertriginous areas. Alopecia totalis. Abnormal T-cell and B-cell function.

Anesthetic Considerations: Treatment with biotin should be continued perioperatively and can be given parenterally if necessary. It is not known whether perioperative stress and catabolism can provoke an acute episode in this disorder. Patients are at risk for perioperative aspiration because of the increased risk of feeding difficulties and vomiting. Good aseptic technique is indicated in these patients who are likely to have T- and B-cell dysfunction. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Intravenous hyperalimentation must include biotin.

Bibliography:

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2. Suzuki Y, Yang X, Aoki Y, et al. Mutations in the holocarboxylase synthetase gene HLCS. *Hum Mutat* 2005;26:285-290.

Holoprosencephaly sequence

MIM #: 236100

Most cases of holoprosencephaly are sporadic, and the exact cause remains unknown. Associations with at least 12

genetic loci have been proposed. Anomalous development of the prechordal mesoderm leads to failure of cleavage of the prosencephalon, which results in

midline facial defects and defects in the development of the forebrain into two hemispheres. A spectrum of anomalies can result, which can vary from severe (cyclopia with a severely malformed forebrain) to mild (hypotelorism, varying degrees of forebrain malformation). Cleft lip and palate are a frequent manifestation of the midline facial defect. Although most cases of holoprosencephaly are sporadic, this developmental disorder can be secondary to teratogenic effects, such as seen with infants of diabetic mothers, who are at increased risk for holoprosencephaly. In addition, some cases of holoprosencephaly are genetic, due to abnormalities in one of several genes, one of which is the gene *sonic hedgehog*. There is an autosomal dominant form of holoprosencephaly. Also, holoprosencephaly has been seen in association with trisomy 13, trisomy 18, some of the deletion syndromes, CHARGE syndrome, Meckel-Gruber syndrome, Pallister-Hall syndrome, Smith-Lemli-Opitz syndrome, and velocardiofacial syndrome.

HEENT/Airway: Cebocephaly ("monkey-like" head— hypotelorism, nasal defects). Microcephaly. Variable defects of midline facial development, including hypotelorism, nasal defects, absence of the philtrum, absence of the superior labial frenulum, cleft lip and palate, bifid uvula, and a single central maxillary incisor. In its most severe manifestation, cyclopia with a proboscis above the single eye.

Cardiovascular: Cardiac defects include dextrocardia and ventricular septal defects.

Neuromuscular: Arhinencephaly (absence of the rhinencephalon). Intellectual development may be extremely limited. Apnea. Seizures. Can have pituitary deficiency or absence.

GI/GU: Can have malrotation of the gut, bile duct stenosis.

Anesthetic Considerations: The oral and median facial defects may make both mask ventilation and endotracheal intubation very difficult. Perioperative temperature instability, seizures and periodic apnea, and/or bradycardia may all affect anesthetic management. Hypernatremia from acute worsening of underlying subclinical diabetes insipidus following surgical stress has been reported (3). Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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Holt-Oram syndrome

Synonym.: Cardiac-limb syndrome; Heart-hand syndrome

MIM #: 142900

This autosomal dominant disorder is characterized by cardiac anomalies, primarily atrial septal defect, and upper limb defects. There is marked variability of expression, with some affected people having only radiographic evidence of the syndrome. The severity of the limb defects does not correlate with the severity of the cardiac defect. Patients having only limb defects can have children with the full syndrome. This syndrome is due to a mutation in the gene T-box 5 (*TBX5*). Members of the T-box gene family act as transcription factors, whose expression is tissue specific. The product of *TBX5* promotes cardiomyocyte differentiation. Different mutations can apparently result in the full syndrome, or solely cardiac or limb manifestations.

HEENT/Airway: May have hypertelorism.

Chest: May have pectus excavatum, thoracic scoliosis. May have pulmonary anomalies.

Cardiovascular: Various cardiac anomalies, primarily atrial septal defect (ostium secundum type), but also ventricular septal defect, patent ductus arteriosus, mitral valve prolapse, aortic stenosis, pulmonic stenosis, and others. Conduction abnormalities may require implantation of permanent pacemaker. May have hypoplastic peripheral vasculature.

Orthopedic: Variable, often asymmetric, upper limb defects, including absent, hypoplastic, or triphalangeal thumbs, hypoplastic digits, syndactyly, polydactyly, absent carpal ossification centers, hypoplastic radius, decreased mobility at the elbows, and phocomelia. Shoulders are narrow and sloping. May have vertebral anomalies. May have absent pectoralis major muscle.

Miscellaneous: Mary Holt was Samuel Oram's assistant. Oram said that her name preceded his as she was a lady and it seemed only proper.

Anesthetic Considerations: Even patients with only minimal upper limb defects should receive a cardiac examination and possibly an echocardiogram because the severity of the limb defects does not correlate with the severity of the cardiac defect. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Peripheral vascular access may be difficult in patients with significant limb anomalies and/or hypoplastic peripheral vasculature. Upper limb defects may make fixation of an appropriate-sized blood pressure cuff difficult, and falsely high pressures may be displayed by noninvasive monitors. An appropriate blood pressure cuff should cover two-thirds of the upper arm.

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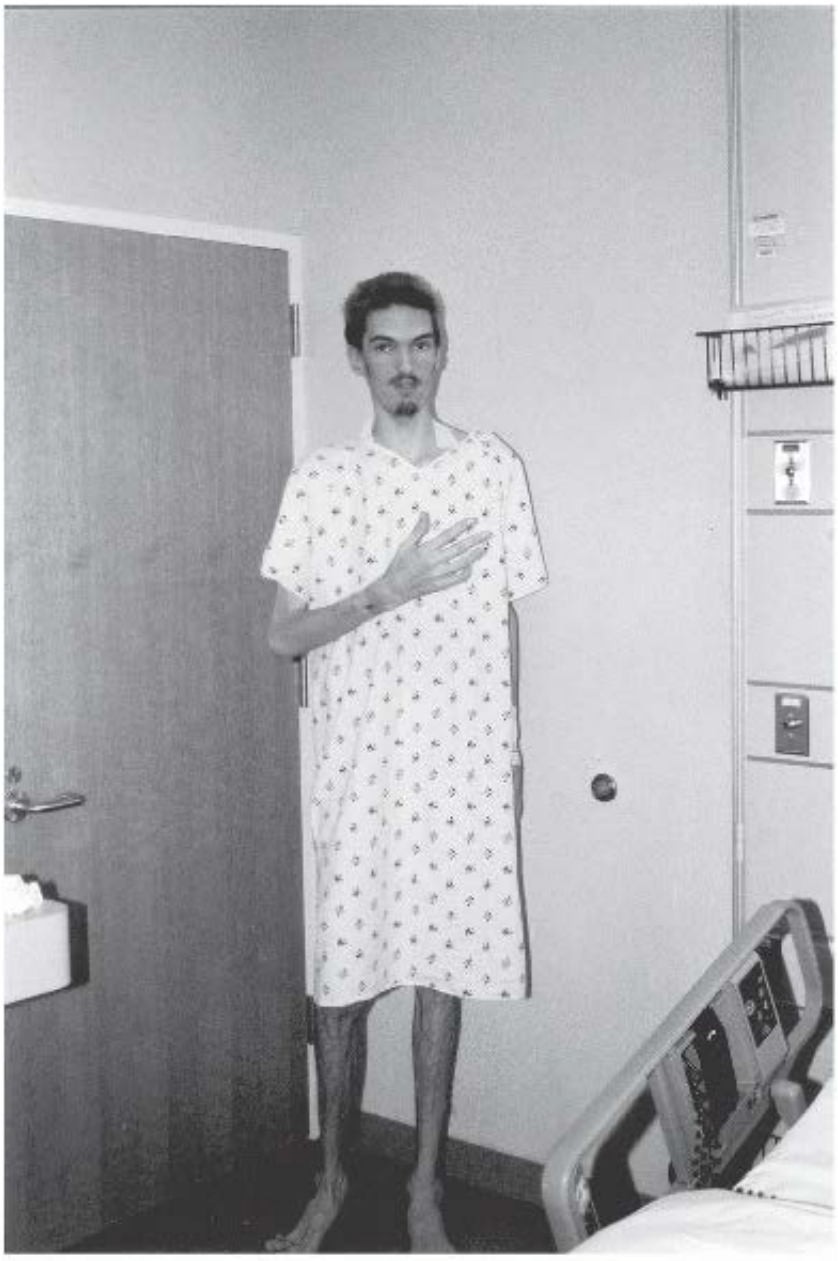
Homocystinuria

MIM #: 236200

Homocystinuria is the second most common disease of amino acid metabolism. There are three types of homocystinuria. The most common, or classic type (type I), is an autosomal recessive disease due to a defect in cystathionine beta-synthase, which catalyzes the synthesis of cystathionine from homocysteine and serine. This results in a defect in transsulfuration of the precursors of cysteine, which in turn results in weakened cross-linking of collagen. There are two variants of type I (classic) homocystinuria, one which is vitamin B_6 (pyridoxine) responsive and one which is unresponsive. Classic type homocystinuria is characterized by marfanoid habitus, myopia, optic lens dislocation, thromboembolic events, and mild intellectual disability.

Homocystinuria can also be caused by defects in the enzymes tetrahydrofolate methyltransferase (type II) or tetrahydrofolate reductase (type III) (5,10-methylene tetrahydrofolate reductase deficiency, see earlier), which are involved in the metabolism of methionine to cystathionine.



Homocystinuria. This 19-year-old with homocystinuria and scoliosis has an obvious marfanoid habitus. He is 6′ 7″ (201 cm) tall; his father is only 6′ (183 cm).

Low-methionine diets, although likely beneficial, are relatively unpalatable and poorly tolerated. There has been interest shown in treatment with betaine, a methyl donor, increasing homocysteine methylation.

HEENT/Airway: Lens dislocation is common, and uniform after 10 years of age. Myopia. Less commonly can have glaucoma, optic atrophy, retinal degeneration, cataracts. High-arched palate.

Chest: Pectus excavatum. Spontaneous pneumothorax, though rare, has been reported in pyridoxine-unresponsive patients.

Cardiovascular: Increased risk of premature coronary vascular disease with myocardial infarction. Thrombi in major arteries and veins. Thromboembolic events can occur during childhood and adolescence. Hypertrophy of the carotid wall.

Neuromuscular: May have intellectual disability; intelligence normal in approximately one-third. Seizures. Risk of thromboembolic stroke. Cerebral angiography has been associated with fatal thrombosis.

Orthopedic: Marfanoid habitus. Osteoporosis beginning in childhood or adolescence, scoliosis.

GI/GU: Pancreatitis with pseudocyst formation has been reported. The urine can have a foul odor.

Other: Spontaneous thromboemboli, presumably either from fraying of collagen in vessel media with loss of overlying endothelium or from activation of Hageman factor by homocysteine. These can be arterial or venous. This is a cause of early death. Hypercoagulability has been shown on thromboelastography. Hypopigmentation, reversible in pyridoxine-responsive disease.

There is hyperinsulinemia from pancreatic exposure to elevated levels of sulfur-containing amino acids such as methionine. There can be secondary hypoglycemia.

The disease is diagnosed by the presence of homocystine and elevated levels of methionine in the urine. Also, when tested with nitroprusside, the urine turns a magenta color.

Miscellaneous: Phenotypically somewhat similar to Marfan syndrome. One differentiating feature is that intellectual disability can be associated with homocystinuria. Another differentiating feature is that the optic lens dislocates down in homocystinuria and up in Marfan syndrome.

The incidence of premature vascular disease in homocystinuria prompted a prospective study that associated elevated homocysteine levels with increased risk of mortality in (nonhomocystinuric) adult patients with coronary artery disease (6).

Anesthetic Considerations: The cardiovascular status and risk of coronary artery disease should be evaluated preoperatively. Because of the risk of hypoglycemia in type I disease, prolonged preoperative fasting should be avoided and patients should receive glucose-containing intravenous fluid perioperatively.

Because of the risk of thromboembolism, factors encouraging tissue perfusion (good cardiac output, adequate hydration, avoidance of stasis, pneumatic stockings, early ambulation) should be encouraged. Perioperative dextran infusions have been used in an effort to decrease perioperative thrombosis. Heparin appears to be ineffective. Dipyridamole may help normalize platelet dysfunction, but results have been mixed.

Nitrous oxide inhibits the activity of the enzyme methionine synthase, which converts homocysteine to methionine, and thereby raises homocysteine levels (5). Nitrous oxide should therefore be avoided in these patients (7), and a fatal outcome in a patient with type III has been reported.

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Houston-Harris achondrogenesis

Included in Achondrogenesis

Hunter syndrome

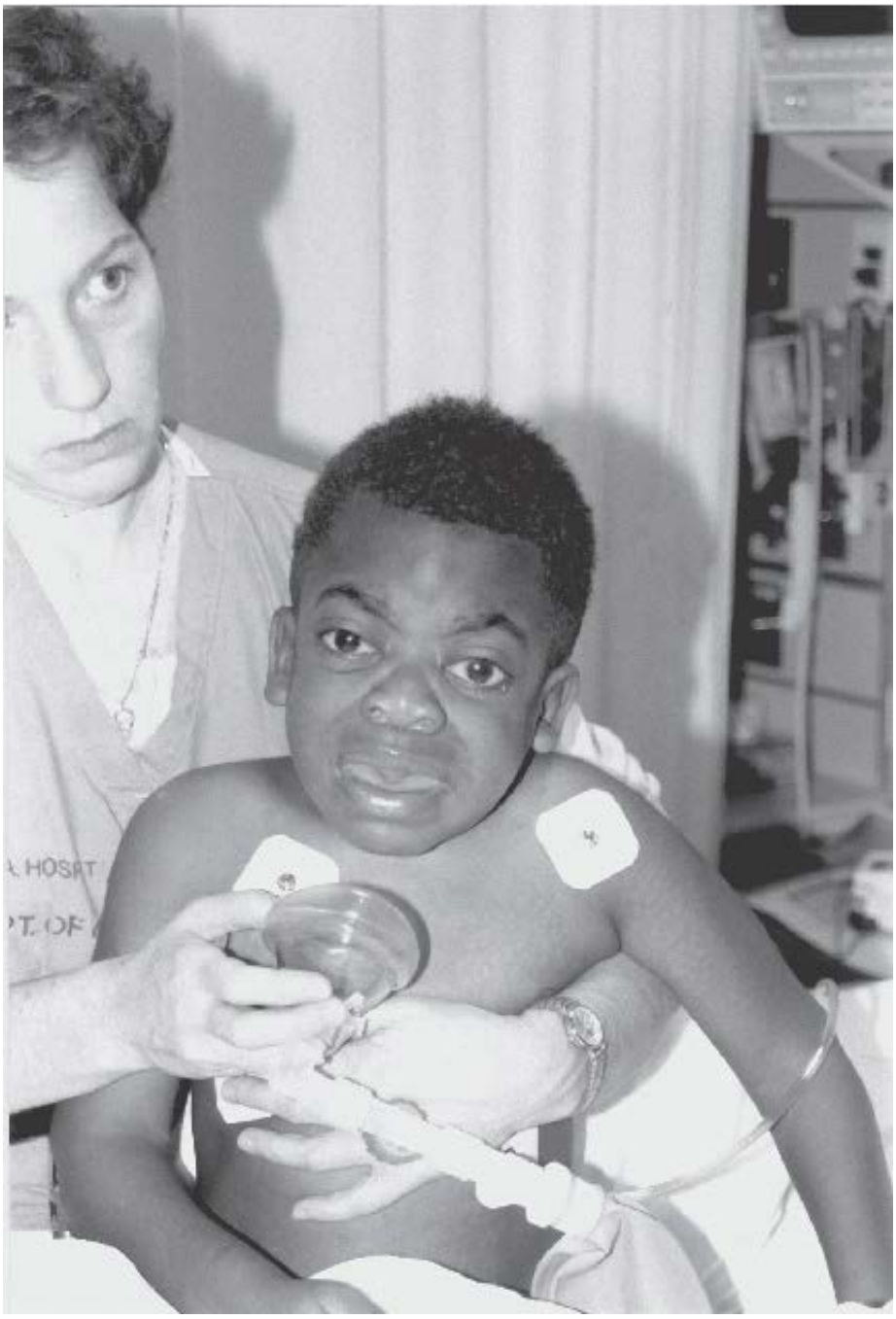
Synonym: Mucopolysaccharidosis II

MIM #: 309900

This X-linked recessive disorder is caused by the absence of the lysosomal enzyme iduronate sulfatase, with subsequent storage of dermatan sulfate and heparan sulfate in a wide variety of tissues. Characteristics of the disease usually become apparent by 2 to 4 years of age, although there is marked variability in the phenotypic manifestations, ranging from mild to severe. Death usually occurs in the late teens, but some patients with milder disease have lived into their forties. Milder Hunter syndrome is phenotypically similar to Hurler/Scheie or Scheie syndromes (see later) but can be differentiated from those syndromes by normal intelligence and slower progression of disease. Severe Hunter syndrome is phenotypically similar to Hurler syndrome (mucopolysaccharidosis IH, see later) but can be differentiated from Hurler syndrome by having generally less intellectual disability, joint disease, and organ involvement, as well as having clear corneas, no gibbus deformity of the spine, and a more gradual onset of the physical characteristics. Treatment with enzyme replacement therapy or bone marrow transplantation has had limited success.

HEENT/Airway: Macrocephaly, scaphocephaly, coarse facial features. Atypical retinitis pigmentosa. Hearing loss and recurrent ear infections. Patients often have macroglossia and are mouth breathers. The soft tissues of the mouth and lips are often stiff and can be manipulated only with difficulty. There can be

hypertrophy of the adenoids and tonsils and copious oral secretions. The temporomandibular joints are stiff. Infiltration of soft tissues can limit neck mobility. There is mucopolysaccharide deposited in the tissues of the upper airway, often leading to obstructive sleep apnea. The larynx appears to be shifted anteriorly and cephalad with the continued mucopolysaccharide deposition that occurs with aging. May have tracheal stenosis.



Hunter syndrome. This 7-year-old boy required anesthesia for a magnetic resonance imaging scan. He has a history of obstructive sleep apnea and very difficult intubations. His macroglossia is easily appreciated. He also has pebbled skin, a thickened, prolapsed mitral valve, and recurrent otitis media. The anesthetic was

performed easily using a laryngeal mask airway.

Chest: Pectus excavatum or carinatum, spatulated ribs. Recurrent upper respiratory tract infections. Patients with a mucopolysaccharidosis are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Can have coronary artery narrowing and ischemic cardiac disease. Can have thickening of cardiac valves.

Neuromuscular: Progressive mild intellectual disability, or can have normal intelligence. Communicating hydrocephalus due to meningeal thickening. Can have cervical spinal canal narrowing with cord compression.

Orthopedic: Stiff joints, carpal tunnel syndrome, kyphosis, beaking of the lumbar vertebrae.

GI/GU: Hepatosplenomegaly, prominent abdomen. Inguinal and umbilical hernias. Chronic diarrhea.

Other: Hypertrichosis, “pebbled” skin.

Miscellaneous: Charles Hunter was a Scotsman who practiced medicine in Winnipeg, Manitoba. He was for a period of time the professor of medicine at the University of Manitoba but objected to the bureaucratic administrative side of the position and resigned, but continued to teach and maintain a private practice.

Anesthetic Considerations: Laryngoscopy and tracheal intubation can be extraordinarily difficult secondary to a variety of airway problems, including copious oral secretions, macroglossia, hypertrophy of the adenoids and tonsils, stiff temporomandibular joints, limited neck mobility, and mucopolysaccharide deposits in the tissues of the upper airway, larynx, and trachea. An oropharyngeal airway can worsen airway obstruction by pushing down a long, high epiglottis over the larynx. A nasopharyngeal airway may help, but on occasion, advancement is difficult because of mucopolysaccharide deposits. The laryngeal mask airway has been used successfully in patients with mucopolysaccharidoses (1,6,12,14); however, a case of airway obstruction from a laryngeal mask airway pushing down a large laryngeal polyp has also been reported (9). Consideration should be given to administering anticholinergic premedication to dry oral secretions. Patients must be carefully positioned and padded perioperatively secondary to stiff joints. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications. Close monitoring should continue into the postoperative period, and opioids should be used with care. A case of delayed awakening after a single, small dose of fentanyl has been reported (15). Postobstructive pulmonary edema has been reported.

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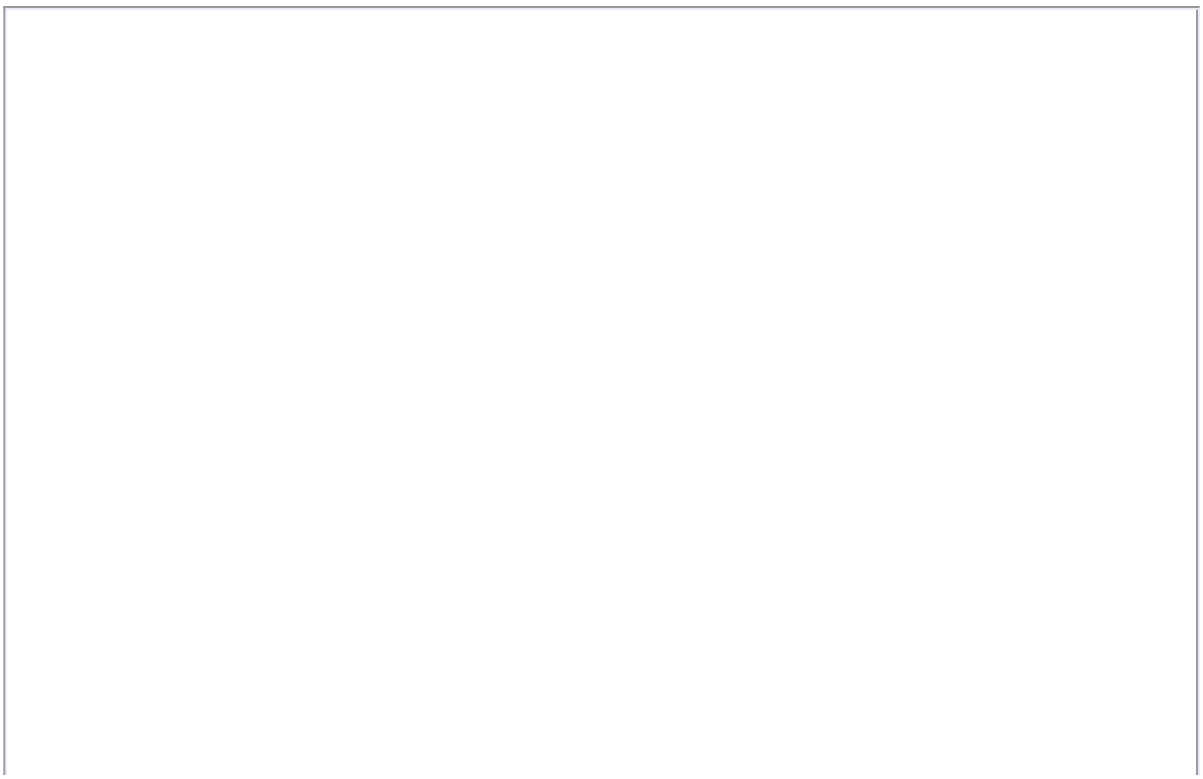
Hurler syndrome

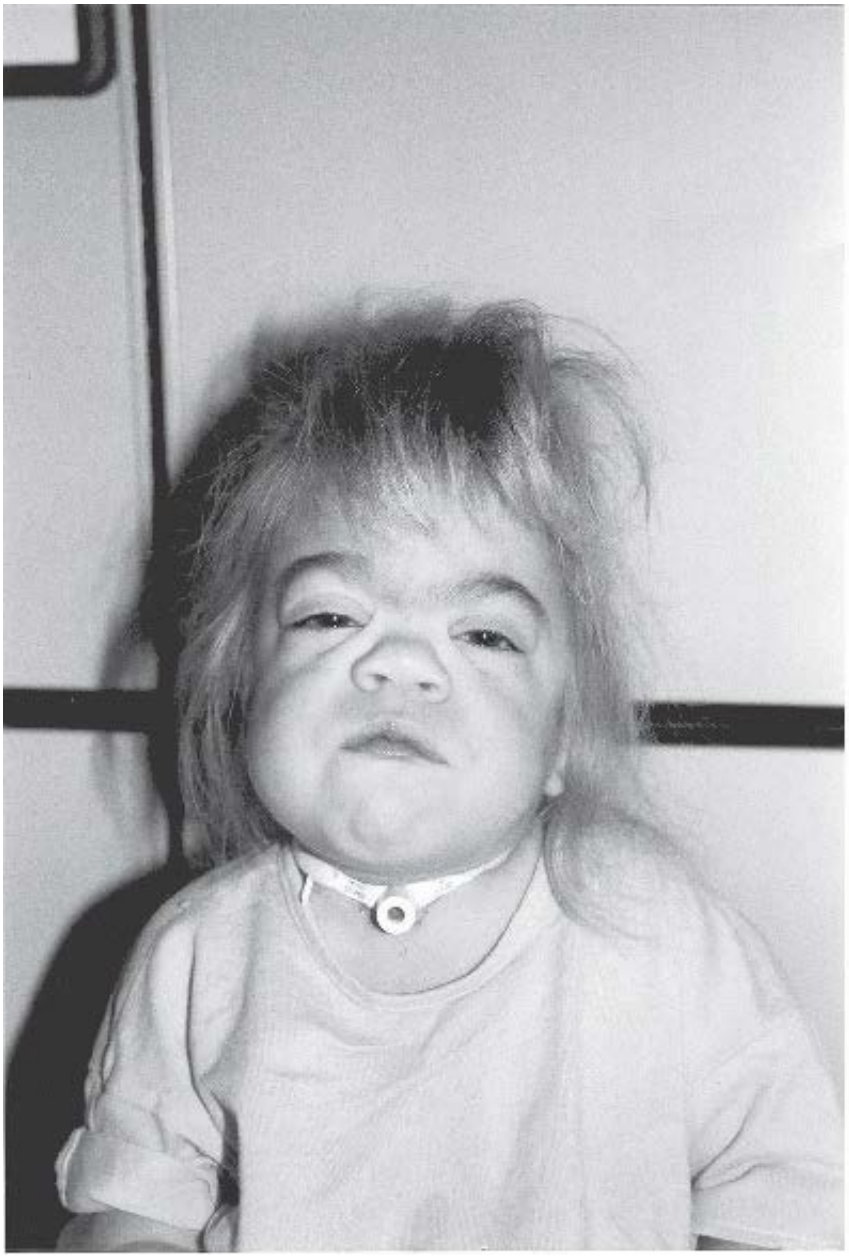
Synonym: Mucopolysaccharidosis IH

MIM #: 607014

This autosomal recessive disorder is due to an abnormality in alpha-L-iduronidase, which is involved in the degradation of glycosaminoglycans (mucopolysaccharides). Deficiency of alpha-L-iduronidase can result in three related clinical syndromes with significant phenotypic variability: Hurler, Scheie, and the intermediate Hurler-Scheie syndromes (see later for both), and these more correctly represent a spectrum of mucopolysaccharidosis I, with Hurler syndrome at the severe end of the spectrum, Scheie at the mild end, and Hurler-Scheie intermediate. Hurler syndrome can be differentiated from the phenotypically similar Hunter syndrome (mucopolysaccharidosis II, see earlier) by having a greater degree of intellectual disability, joint disease, and organ involvement, as well as corneal opacities, a gibbus deformity of the spine, and a more rapid onset of the physical characteristics.

Death is usually at several years of age from obstructive airway disease, respiratory infection, or cardiac complications. Treatment with recombinant human alpha-L-iduronidase can significantly improve some clinical manifestations of the disease, and bone marrow transplantation has provided very good long-term results. More and more older patients will be seen with this disease due to the success of these treatments. Cord blood transplantation has also been used successfully, with improved results when patients are under 2 years of age. Bone marrow transplantation appears to have minimal effect on the progression of skeletal disease.





Hurler syndrome. This 4-year-old girl with Hurler syndrome has required a recent tracheostomy.

HEENT/Airway: Macrocephaly, scaphocephaly, coarse facies. Corneal opacities. Can develop glaucoma. Hearing loss (combination of both sensorineural and conductive). Recurrent middle ear infections. The tongue, tonsils, adenoids, and lips are large. The sphenoid can approximate the hard palate, and the nasopharynx can be further occluded by adenoidal tissue. Patients are often mouth breathers and have copious nasal discharge. The teeth are widely spaced and peglike, and there are dental cysts. The trachea can be narrowed and flattened. Granulomatous tissue can be present in the trachea and lower respiratory tract. Obstructive sleep apnea. The epiglottis may be situated higher than normal because of small cervical vertebrae, and the epiglottis and aryepiglottic folds may be infiltrated. Short neck.

Chest: Oarlike ribs (broad at the sternal ends). Spine deformities and hepatosplenomegaly can inhibit pulmonary

function. Recurrent upper respiratory tract infections. Glycosaminoglycan deposition in the lower airway and pulmonary interstitium can cause obstructive disease and a diffusion defect. Distal tracheal obstruction may develop and be extremely problematic. Patients with a mucopolysaccharidosis are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Can have coronary artery narrowing and ischemic cardiac disease. Since coronary artery involvement is diffuse, the extent of disease may be underestimated by coronary angiography. Valvular defects, particularly mitral valve thickening. Infants with fatal cardiomyopathy have been reported.

Neuromuscular: Intellectual disability. Enlarged, “J”-shaped sella turcica. Communicating hydrocephalus, usually associated with increased intracranial pressure. Can have thickened meninges resulting in hydrocephalus or myelopathy from cord compression.

Orthopedic: Small stature. Can have a hypoplastic odontoid with atlantoaxial subluxation. Joint contractures. Early kyphoscoliosis, lumbar lordosis. Thoracolumbar gibbus deformity. Deformed lower thoracic and upper lumbar vertebrae, pelvic dysplasia, shortened tubular bones, expanded diaphyses with dysplastic epiphyses. Brachydactyly. Coxa valga with poorly formed pelvis and small femoral heads. Flexion deformity of the hip.

GI/GU: Hepatosplenomegaly. Inguinal and umbilical hernias. Alternating constipation and diarrhea.

Other: Thick skin, hypertrichosis.

Miscellaneous: Gertrud Hurler, a German pediatrician, pronounced her name “Hooler.” The first case was actually presented to the Munich Pediatric Society by her chief, Pfaundler, but was written up by Hurler.

Figurines with features of Hurler syndrome have been discovered among pre-Columbian artifacts. A defect in lysosomal alpha-L-iduronidase also occurs in Plott hound dogs.

Anesthetic Considerations: Hurler syndrome has been called “the worst airway problem in pediatric anesthesia” (19). Despite the successes seen with enzyme replacement therapy and bone marrow transplantation, the airway of patients with Hurler syndrome may still be very difficult to manage (2,3,7). Because of the abnormal facies, a regular pediatric mask may not fit adequately, and it has been suggested that in these cases, the mask be applied upside down, with the narrower nasal bridge over the mouth (16). Consideration should be given to administering anticholinergic premedication to dry oral secretions. Patients with odontoid hypoplasia are at risk for atlantoaxial subluxation, and cervical spine precautions should be observed. Thickening of the soft tissues, an enlarged tongue, a short, immobile neck, and limited mobility of the cervical spine and temporomandibular joints make laryngoscopy extremely difficult. Laryngoscopy may become more difficult with age, particularly after approximately 2 years of age. There is a high incidence of failed intubation. An oral airway has been reported to displace the epiglottis downward, impairing flow through the larynx. Nasal airways have proven to be more effective without this complication, but on occasion, advancement is difficult because of mucopolysaccharide deposits in the nose. Fiberoptic intubation of older children and adults has been described (6,7,18), and the laryngeal mask airway (LMA) has been used successfully (1,2,3,12,14), although a case of inability to ventilate or intubate through an LMA due to abnormal laryngeal anatomy has been reported (9). Bone marrow transplantation may decrease the difficulty of intubation when transplantation is done in the first 2 years of life (1,2). Postoperative respiratory complications are common, and the presence of obstructive sleep apnea may increase the risk of respiratory complications. Close monitoring should continue into the postoperative period and opioids should be used with care. Postobstructive pulmonary edema has been reported.

Hypercapnea should be avoided in the presence of increased intracranial pressure. Patients must be carefully positioned and padded perioperatively secondary to joint contractures. Patients may have restrictive or obstructive pulmonary disease. Patients with cardiac disease should receive an appropriately tailored anesthetic. A

case of failed epidural block despite good placement of the catheter has been reported and ascribed to possible deposition of mucopolysaccharide in the epidural space or on the nerve sheaths (11). A successful caudal anesthetic has subsequently been reported (5).

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Hurler-Scheie syndrome

Synonym: Mucopolysaccharidosis I H/S

MIM #: 607015

This is an autosomal recessive disorder of alpha-L-iduronidase, which is involved in the degradation of glycosaminoglycans (mucopolysaccharides). This disorder represents a phenotype intermediate between Hurler (see earlier) and Scheie syndromes (see later), both of which are also due to a deficiency of alpha-L-iduronidase. There is significant variability among these syndromes, which more correctly represent a spectrum of mucopolysaccharidosis I. Treatment with recombinant human alpha-L-iduronidase can significantly improve some clinical manifestations of the disease, and bone marrow transplantation has provided very good long-term results. Cord blood transplantation has also been used successfully, with improved results when patients are under 2 years of age. Bone marrow transplantation appears to have minimal effects on the progression of skeletal disease.

HEENT/Airway: Corneal clouding; may have glaucoma. Deafness (both sensorineural and conduction loss). Accumulation of mucopolysaccharides in the oropharynx, tongue, epiglottis, aryepiglottic folds, and tracheal wall.

Some patients have had micrognathia. Short neck. May have sleep apnea.

Chest: Pectus carinatum, clubbed ribs. Patients with a mucopolysaccharidosis are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Valvular stenosis or insufficiency. The mitral valve is most commonly affected, followed by the aortic and tricuspid valves.

Neuromuscular: Varying degrees of mild intellectual disability, but many have normal intelligence. May have cervical cord compression from dural mucopolysaccharide accumulation ("pachymeningitis cervicalis"). Communicating hydrocephalus is rare in patients with normal intelligence. Compression of lower spinal cord from spondylolisthesis.

Orthopedic: Dwarfism, thoracic kyphoscoliosis, lumbar gibbus, stiff joints.

GI/GU: Hepatosplenomegaly.

Miscellaneous: A defect in lysosomal alpha-L-iduronidase also occurs in Plott hound dogs.

Anesthetic Considerations: Accumulation of mucopolysaccharides in the oropharynx, tongue, epiglottis, aryepiglottic folds, and tracheal wall, in conjunction with a short neck and possible micrognathia, conspire to make laryngoscopy extremely difficult. In addition, distortion of the anatomy may not allow identification of the cricothyroid membrane for retrograde techniques (12). Airway involvement is progressive with increasing age. The laryngeal mask airway has been used with success in patients with mucopolysaccharidoses (1,2,3,7,9). Bone marrow transplantation may decrease the difficulty of intubation when transplantation is done in the first 2 years of life (1,2). Postoperative respiratory complications are common, and the presence of obstructive sleep apnea may increase the risk of respiratory complications. Close monitoring should continue into the postoperative period and opioids should be used with care. Postobstructive pulmonary edema has been reported.

Patients must be carefully positioned and padded perioperatively secondary to stiff joints. Patients with cardiac disease should receive an appropriately tailored anesthetic. Spinal anesthesia has been used successfully (13) and is an option if otherwise appropriate.

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Hutchinson-Gilford syndrome

See Progeria

Hydantoin

See fetal hydantoin syndrome

Hydroxyacyl-CoA dehydrogenase deficiency

See Long-chain hydroxyacyl-CoA dehydrogenase deficiency

Hydroxydicarboxilic acidemia

See Long-chain acyl-CoA dehydrogenase deficiency

Hydroxymethylglutaric aciduria

Synonym: Hydroxymethylglutaryl-CoA lyase deficiency; 3-hydroxy-3-methylglutaryl-CoA lyase deficiency

MIM #: 246450

This autosomal recessive disorder results in the accumulation of 3-hydroxy-3-methylglutaric acid in the urine. Deficiency of hydroxymethylglutaryl-CoA lyase leads to hydrolysis of 3-hydroxy-3-methylglutaryl-CoA to form 3-hydroxy-3-methylglutaric acid, which is excreted in the urine. 3-Hydroxy-3-methylglutaryl-CoA is derived from the catabolism of leucine and from the synthetic pathway of ketone bodies from fatty acid oxidation. Patients present with signs similar to those of Reye syndrome. Patients have been known to self-select a low-protein diet, although the limitation of dietary fat has been shown to be more effective in lowering the excretion of metabolites. There are some patients who have hydroxymethylglutaric aciduria with normal enzyme activity, and the pathogenesis of this disorder is unknown.

HEENT/Airway: Microcephaly.

Neuromuscular: Hypotonia and lethargy that may progress to coma or seizures during an acute episode. Cerebral atrophy. Most are developmentally normal.

GI/GU: Vomiting. Hepatomegaly, elevated transaminases.

Other: Metabolic acidosis, which can be profound. There is never ketosis because this enzyme is required for ketone production. However, lactic acidosis can develop in patients during severe episodes. Hyperammonemia, sometimes severe. Hypoglycemia, which can be fatal. There can be secondary carnitine deficiency. Two children who became very ill after immunizations have been reported.

Anesthetic Considerations: Extended perioperative fasts must be avoided because fasting causes hypoglycemia and increases fatty acid oxidation. Patients must receive adequate perioperative glucose. Acute exacerbations should be treated with glucose and bicarbonate. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

Figure: See **Appendix D**

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Hydroxymethyl glutaryl-CoA lyase deficiency

See Hydroxymethylglutaric aciduria

Hydroxyprolinemia

Synonym: Hyperhydroxyprolinemia

MIM #: 237000

This disorder is distinct from hyperprolinemia (see later). Hydroxyproline is derived from the breakdown of collagen. Hydroxyprolinemia is an autosomal recessive disorder due to deficient activity of hydroxyproline oxidase. Hydroxyproline oxidase is involved in the catabolism of hydroxyproline, catalyzing the conversion of 4-hydroxy-L-proline to delta-1-pyrroline-3-hydroxy-5-carboxylic acid. Proline oxidation is unaffected.

Although clinical manifestations were ascribed to the disorder in early reports, this likely reflects an ascertainment bias because these patients first came to medical attention for a clinical problem, probably unrelated. It is unclear whether this disorder has any clinical manifestations.

Neuromuscular: May have intellectual disability or psychiatric problems.

GI/GU: May have microscopic hematuria.

Anesthetic Considerations: There are no specific anesthetic implications.

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1. Phang JM, Chien-an AH, Valle D. Disorders of proline and hydroxyproline metabolism. In: Scriver CR, Beaudet AL, Sly WS, et al., eds. *The metabolic and molecular bases of inherited disease*. Vol. II, 8th ed. New York: McGraw-Hill, 2001:1820-1838.

2. Kim SZ, Varvogli L, Waisbren S, et al. Hydroxyprolinemia: comparison of a patient and her unaffected twin sister. *J Pediatr* 1997;130:437-441.

Hyperekplexia (hyperexplexia)

See Stiff baby syndrome

Hyperglycerolemia

See Glycerol kinase deficiency

Hyperglycinemia (nonketotic)

See Nonketotic hyperglycinemia

Hyperhydroxyprolinemia

See Hydroxyprolinemia

Hyperimmunoglobulin D syndrome

See Mevalonic aciduria

Hyperimmunoglobulin E syndrome

See Job syndrome

Hyperkalemic periodic paralysis

See Familial periodic paralysis

Hyperlysinemia

See Familial hyperlysinemia

Hyperornithinemia with gyrate atrophy of the choroid and retina

See Ornithine delta-aminotransferase deficiency

Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome

See HHH syndrome

Hyperoxaluria

See Oxalosis

Hyperprolinemia type I

Synonym: Proline oxidase (dehydrogenase) deficiency

MIM #: 239500

This autosomal recessive disorder of proline metabolism is due to deficient activity of proline oxidase, also known as proline dehydrogenase. This enzyme catalyzes the first step in proline catabolism, the conversion of proline to pyrroline-5-carboxylate. The enzyme is tightly bound to the inner mitochondrial membrane. The proline oxidase gene is located on chromosome 22, immediately adjacent to, or very close to, the region involved in the DiGeorge syndrome (see earlier). A case of hyperprolinemia type I has been described in a patient with DiGeorge syndrome.

Initially, patients with this syndrome were reported to have various associated clinical findings. However, this was likely due to ascertainment bias since these patients came to medical attention because they had other medical

problems. Patients who have been identified prospectively (through neonatal screening programs) have ranged from having no clinical manifestations to having a variety of neurologic abnormalities.

Neuromuscular: May have intellectual disability, psychiatric problems, stereotypical behaviors, hyperactivity. May have hypotonia, seizures.

Other: Hyperprolinemia, prolinuria.

Miscellaneous: This gene is a homologue of the "*sluggish-A*" gene in *Drosophila*. It has been suggested that at least some mutations in this gene might be a risk factor for the development of schizophrenia.

Anesthetic Considerations: In the absence of neurologic abnormalities, there are no specific anesthetic considerations associated with this disorder.

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1. Clelland CL, Read LL, Baraldi AN, et al. Evidence for association of hyperprolinemia with schizophrenia and a measure of clinical outcome. *Schizophr Res* 2011;131:139-145.

2. Guilmatre A, Legallic S, Steel G. Type I hyperprolinemia: genotype/phenotype correlations. *Hum Mutat* 2010;31:961-965.

3. Di Rosa G, Pustorino G, Spano M, et al. Type I hyperprolinemia and proline dehydrogenase (PRODH) mutations in four Italian children with epilepsy and mental retardation. *Psych Genet* 2008;18:40-42.

Hyperprolinemia type II

MIM #: 239510

This autosomal recessive disorder is due to deficient activity of delta-1-pyrroline-5-carboxylic acid dehydrogenase. This mitochondrial matrix enzyme catalyzes a terminal step in proline catabolism, the conversion of glutamate-gamma-semialdehyde to glutamate, with the production of NADH. Patients may have secondary vitamin B_6 deficiency due to deactivation of pyridoxal phosphate (the active form of vitamin B_6) by delta-1-pyrroline-5-carboxylic acid.

Although early reports listed clinical manifestations of this disease, these were likely due to ascertainment bias because patients were identified only after coming to medical attention for other problems. Prospectively identified patients (through neonatal screening programs) have exhibited variable neurologic involvement, with neonatal seizures being the most consistent finding. It has been hypothesized that excess proline can contribute to the multifactorial pathogenesis of these seizures because proline is known to have neuromodulatory properties.

Neuromuscular: Neonatal seizures. May have intellectual disability. May have behavioral problems.

Other: Hyperprolinemia, hyperprolinuria. Secondary vitamin B_6 deficiency.

Miscellaneous: Hyperprolinemic mice have learning deficits.

Anesthetic Considerations: Chronic use of anticonvulsant medications can alter the metabolism of some

anesthetic drugs.

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1. Mitsubuchi H, Nakamura K, Matsumoto S, et al. Inborn errors of proline metabolism. *J Nutr* 2008;138:S2016-2020.

2. Farrant RD, Walker V, Mills GA, et al. Pyridoxal phosphate deactivation by pyrroline-5-carboxylic acid. Increased risk of vitamin B6 deficiency and seizures in hyperprolinemia type II. *J Biol Chem* 2001;276:15107-15116.

Hyperprostaglandin E syndrome

See Bartter syndrome

Hypertelorism-hypospadias syndrome

Synonym: G syndrome; Opitz syndrome; Opitz-Frias syndrome; Opitz G/BBB syndrome; Telecanthus-hypospadias syndrome

MIM #: 145410, 300000

This syndrome is distinguished by hypertelorism and hypospadias. There is a predominance of affected male patients, which suggests X-linked inheritance or autosomal dominant inheritance with partial sex limitation. In fact, genetic heterogeneity has been established, with an X-linked form that maps to the short arm of the X chromosome and an autosomal dominant form that maps to the long arm of chromosome 22. There are no significant phenotypic differences between the two forms. The X chromosome gene has been identified as *MID 1* (midline 1). Its protein product has been termed midin and associates itself with microtubules. Boys are usually more severely affected than girls. This is a disorder of midline development.

HEENT/Airway: Hypertelorism, telecanthus. Prominent occiput, posterior scalp defects. Slight slanting of palpebral fissures, epicanthal folds (in X-linked form only), strabismus. Protruding and posteriorly rotated ears. Broad nasal bridge, anteverted nares. Short lingual frenulum. High-arched palate. Cleft lip or palate (in X-linked form only). Bifid uvula. Micrognathia.

Can have hypoplastic epiglottis, laryngotracheal cleft or hypoplasia/malformation of the larynx. Can have high carina in the most severely affected patients. Can have tracheoesophageal fistula, which is more common and more severe in boys.

Chest: Stridor with a weak cry. Rare pulmonary alveolar and vascular hypoplasia. Esophageal abnormalities can result in recurrent aspiration.

Cardiovascular: Can have congenital cardiac defect, especially coarctation of the aorta and atrial septal defects.

Neuromuscular: Can have mild intellectual disability. Hypotonia. Can have agenesis of the corpus callosum, hypoplasia of the cerebellar vermis, enlarged cisterna magna, cortical atrophy.

GI/GU: Dysphagia and swallowing difficulties, achalasia, hiatal hernia. Imperforate anus. Hypospadias,

cryptorchidism, bifid scrotum, splayed labia majora. Can have renal anomalies.

Other: Increased incidence of monozygotic twinning.

Miscellaneous: Opitz called this "G syndrome," using the initials of the family in which he first described this syndrome. In the mouse, several exons of the homologous gene are located on the X chromosome, while some are located on both the X and Y chromosomes.

Anesthetic Considerations: Micrognathia and laryngeal anomalies may make direct laryngoscopy and tracheal intubation difficult. Laryngeal hypoplasia can limit the size of endotracheal tube that may be passed. Inadvertent endobronchial intubation is more likely in patients with a high carina. Because of dysphagia and swallowing difficulties, these patients are at risk for perioperative aspiration. Patients may have limited pulmonary reserve secondary to recurrent aspiration or pulmonary hypoplasia. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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1. Fontanella B, Russolillo G, Meroni G. *MID1* mutations in patients with X-linked Optiz G/BBB syndrome. *Hum Mutat* 2008;29:584-594.

2. So J, Suckow V, Kijas Z, et al. Mild phenotypes in a series of patients with Opitz GBBB syndrome with MID1 mutations. *Am J Med Genet A* 2005;132:1-7.

3. Arcand P, Abela A, Al-Ammar A, et al. Laryngeal manifestations in Opitz BBB/G syndrome. *J Otolaryngol* 2000;29:179-182.

4. Robin NH, Opitz JM, Muenke M. Opitz G/BBB syndrome: clinical comparisons of families linked to Xp22 and 22q, and a review of the literature. *Am J Med Genet* 1996;62:305-317.

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Hypochondroplasia

MIM #: 146000

This autosomal dominant disorder is often confused with achondroplasia. Like achondroplasia, this syndrome involves short stature and caudal narrowing of the spinal canal. Unlike achondroplasia, there are no significant craniofacial abnormalities, very infrequent cervical spinal cord abnormalities, and only mild abnormalities of the hands. Most cases of hypochondroplasia are caused by mutations in the gene for fibroblast growth factor receptor-3 (*FGFR3*), the same gene associated with achondroplasia. Thus, in many instances, the two disorders are allelic. However, some patients with hypochondroplasia have no known mutation in *FGFR3*, and thus are not allelic with achondroplasia.

HEENT/Airway: Macrocephaly, brachycephaly. Mild frontal bossing. Ptosis, esotropia, cataracts.

Neuromuscular: Caudal narrowing of the spinal canal. May have learning disabilities.

Orthopedic: Short stature. Lumbar lordosis. Narrow vertebral interpedicular distance. Proportionately short limbs. Limited elbow extension. Short hands and feet, without trident hand. May have brachydactyly, polydactyly. Marked bowing of the legs, which may improve with age. Fibulae relatively longer than the tibiae—may cause inversion of the feet. Small ilia.

Other: May have acanthosis nigricans.

Anesthetic Considerations: There are no specific concerns about the airway or the stability of the cervical spine, as there are with achondroplasia. Regional anesthesia may be technically difficult secondary to spinal and limb abnormalities. As in achondroplasia, cesarean section is often preferable in hypochondroplastic women because of lumbar lordosis and relatively small ilia.

Bibliography:

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2. Song SH, Balce GC, Agashe MV, et al. New proposed clinico-radiologic and molecular criteria in hypochondroplasia: FGFR 3 gene mutations are not the only cause of hypochondroplasia. *Am J Med Genet A* 2012;158:2456-2462.

Hypoglossia-hypodactyly syndrome

See Oromandibular-limb hypogenesis

Hypohidrotic ectodermal dysplasia, autosomal dominant type

See Rapp-Hodgkin ectodermal dysplasia

Hypokalemic periodic paralysis

See Familial periodic paralysis

Hypomelanosis of Ito

Synonym: Incontinentia pigmenti achromians

MIM #: 300337

Hypomelanosis of Ito is a disorder which involves areas of skin hypopigmentation that form a characteristic whorl or streak pattern along the lines of Blaschko on the trunk or limbs. The characteristic skin lesions have multiple etiologies but may be a nonspecific marker for chromosomal mosaicism. Hypomelanosis of Ito may be associated with craniofacial, limb, or neurologic anomalies. The skin lesions are somewhat like a negative of the hyperpigmented lesions in classic incontinentia pigmenti (see later) and do not undergo evolutionary changes as in incontinentia pigmenti.

HEENT/Airway: Macrocephaly. Hypertelorism. Epicanthal folds, strabismus, abnormal retinal pigmentation. Abnormal ears. Cleft lip/palate. Dental dysplasia and irregularities.

Neuromuscular: Can have intellectual disability, seizures, hypotonia, gray matter heterotopia, cerebral atrophy.

Orthopedic: Short stature. Kyphoscoliosis/lordosis. Syndactyly, polydactyly, clinodactyly, ectrodactyly, triphalangeal thumb. Genu valgum.

Other: Areas of skin hypopigmentation form a characteristic whorl or streak pattern on the trunk or limbs. Alopecia. Hypertrichosis.

Anesthetic Considerations: Careful preoperative examination of the teeth is indicated. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs.

Bibliography:

1. Assogba K, Ferlazzo E, Striano P, et al. Heterogeneous seizure manifestations in hypomelanosis of Ito: report of four new cases and review of the literature. *Neurol Sci* 2010;31:9-16.

2. Taibjee SM, Bennett DC, Moss C. Abnormal pigmentation in hypomelanosis of Ito and pigmentary mosaicism: the role of pigmentary genes. *Br J Dermatol* 2004;151:269-282.

Hypoparathyroidism-Retardation-Dysmorphism syndrome

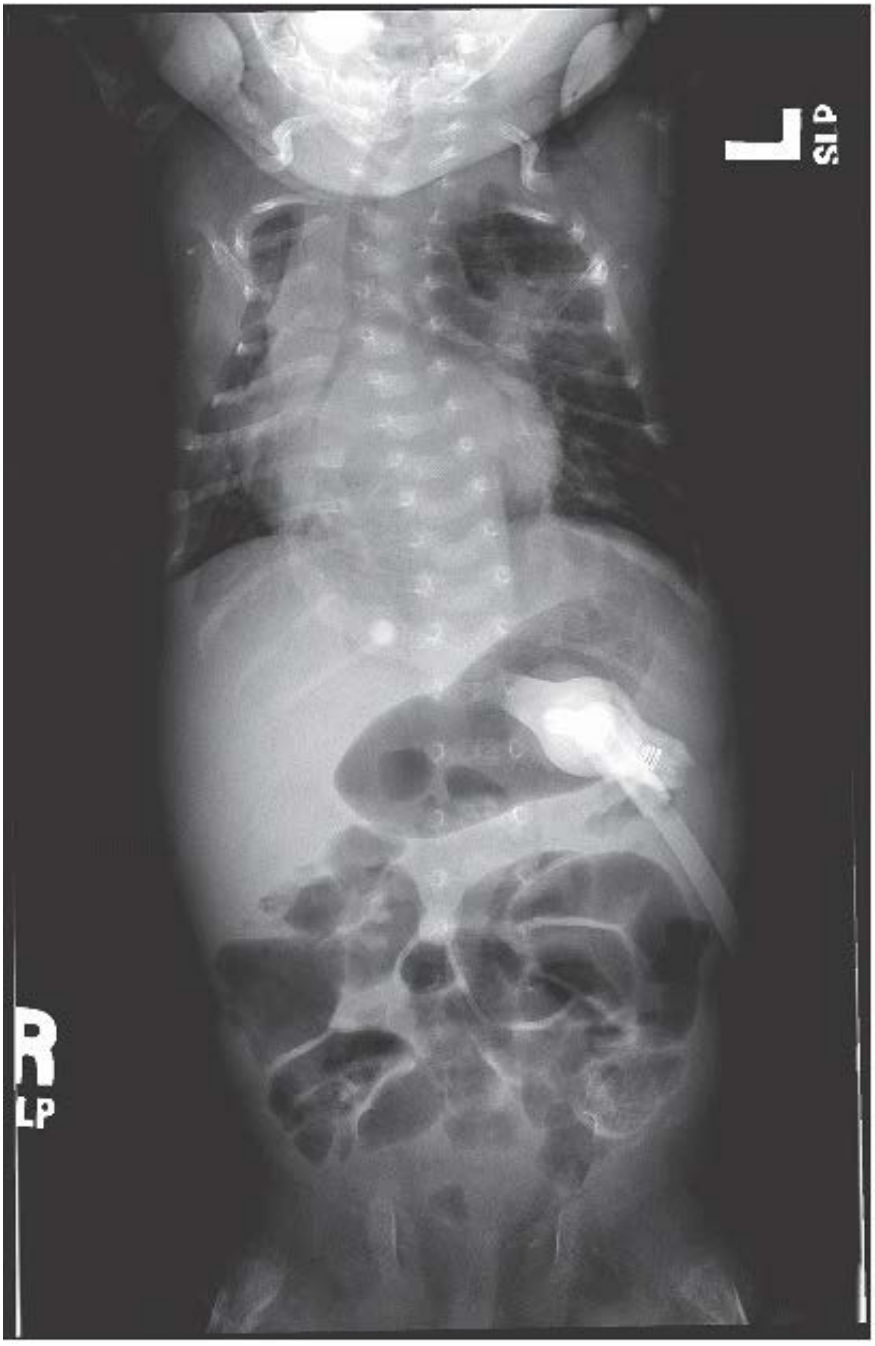
See Sanjad-Sakati syndrome

Hypophosphatasia

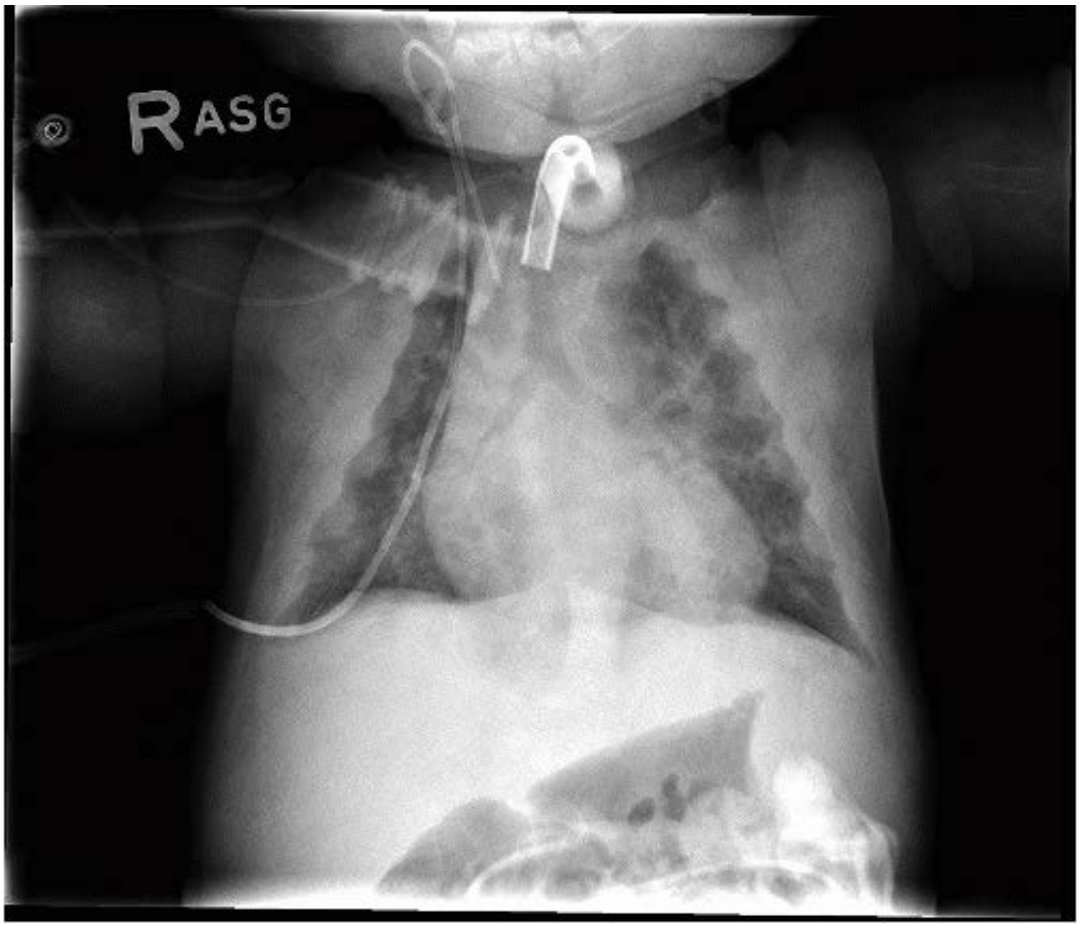
MIM #: 241500, 241510, 146300

This usually autosomal recessive disorder is characterized by a severe deficiency of skeletal mineralization. The syndrome is called “hypophosphatasia” because there is deficient alkaline phosphatase activity in serum, tissues, and organs. There is wide variability in the clinical expression of this syndrome, with severe infantile and milder childhood onset or adult onset diseases. Some patients are asymptomatic, whereas others suffer from recurrent fractures, and severely affected patients die *in utero*. Clinically, this syndrome often resembles rickets. However, traditional therapy for rickets (vitamin D) must be avoided in these patients because they have normal levels of vitamin D. Excessive vitamin D exacerbates the hypercalcemia and hypercalciuria seen with this syndrome. Some patients can present solely with dental abnormalities. The disorder is due to a

defect in the *ALPL* gene (alkaline phosphatase, liver/bone/kidney type), and many specific mutations have been described, mostly missense mutations. Recently, an enzyme replacement therapy has been trialed in severely affected infants, resulting in improvement in radiographic disease and enhancement of pulmonary and physical function.



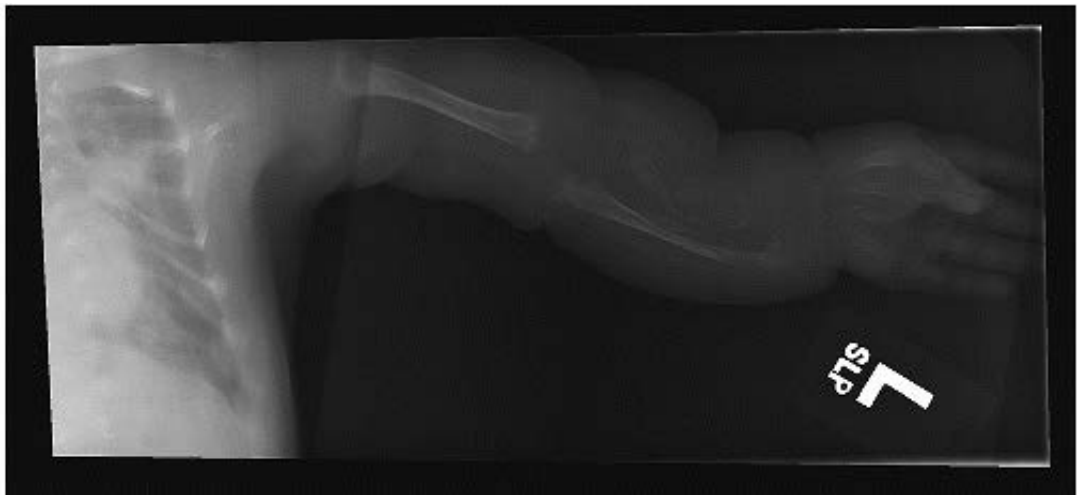
Hypophosphatasia. FIG. 1. Chest radiograph at 6 months of age. (Courtesy of Dr. Jill Simmons, Department of Pediatrics, Vanderbilt University.)



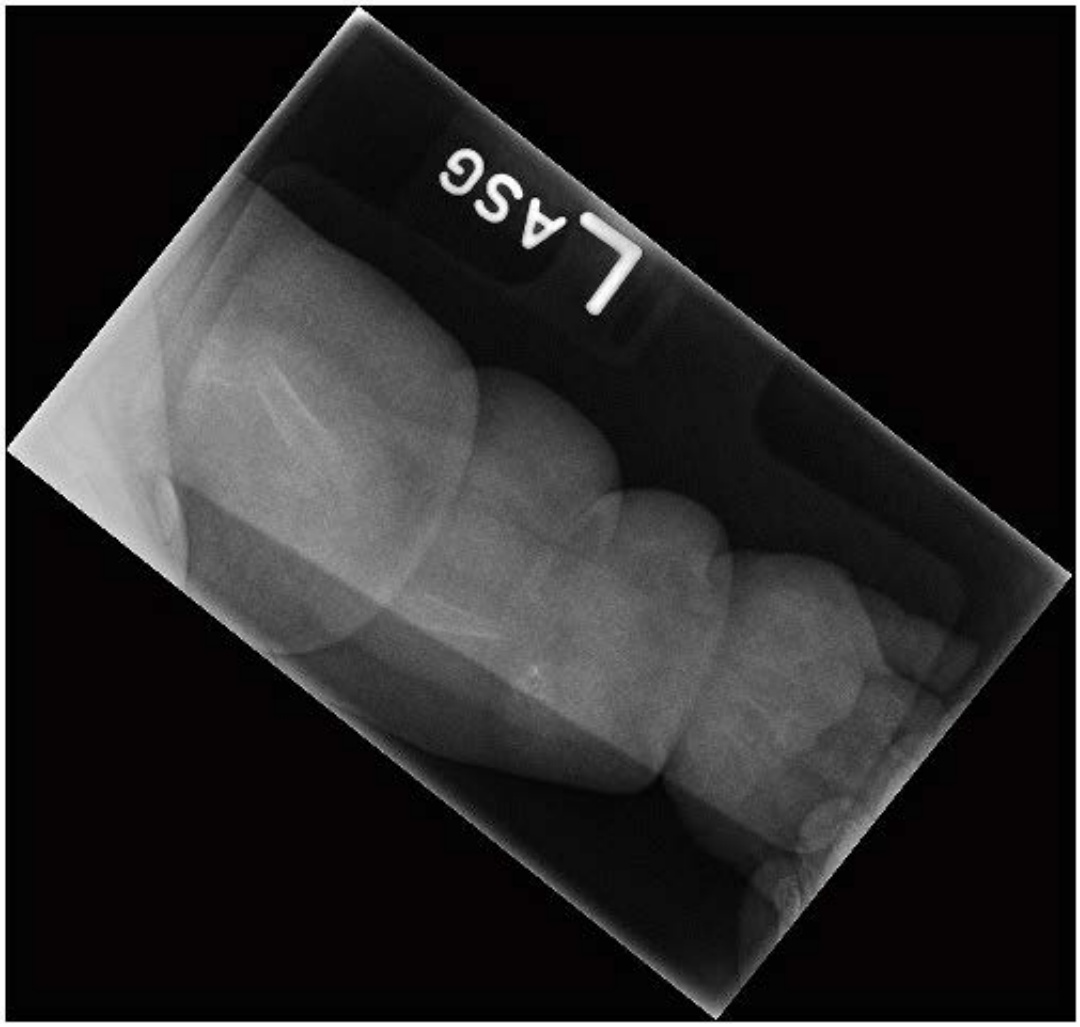
Hypophosphatasia. FIG. 2. Chest radiograph at 20 months of age. Compare and note extraordinary osteopenia. (Courtesy of Dr. Jill Simmons, Department of Pediatrics, Vanderbilt University.)

HEENT/Airway: Underossified cranial bones give the appearance of widely separated sutures in severely affected neonates. Can have brachycephaly. Can have mild hypertelorism, proptosis, blue sclerae. Aplasia or hypoplasia of dental cementum with premature loss of deciduous teeth. Early loss of adult teeth in milder, adult form.

Chest: Respiratory insufficiency from rachitic disease of the chest. Recurrent pneumonia. Harrison's groove (a classic finding in rickets)—a horizontal depression at the attachment point of the anterior diaphragm to the chest wall. “Rachitic rosary” at costochondral junctions.



Hypophosphatasia. FIG. 3. Left arm radiograph at 6 months of age. (Courtesy of Dr. Jill Simmons, Department of Pediatrics, Vanderbilt University.)



Hypophosphatasia. FIG. 4. Left arm radiograph at 20 months of age. Compare and note marked osteopenia. (Courtesy of Dr. Jill Simmons, Department of Pediatrics, Vanderbilt University.)

Neuromuscular: Hypotonia. Children with infantile onset have functional craniosynostosis due to defective ossification, which can cause elevated intracranial pressure, papilledema. Seizures, periodic apnea in severe cases. Can have muscle weakness, particularly of the thighs.

Orthopedic: Short stature. In the most severe form, there is almost complete lack of skeletal mineralization at birth with short, deformed limbs and abnormal long bone spurs. Rachitic changes of wrist and knees. Scoliosis. Bowed legs, waddling gait. Poorly healing fractures. Osteomalacia, stress fractures, and pseudofractures in adults. Adults can have arthritis from deposition of calcium phosphate crystals.

GI/GU: Extramedullary hepatic hematopoiesis. Nephrocalcinosis, renal stones.

Other: Anemia, possibly secondary to marrow cavity encroachment by osteoid. Can have symptomatic hypercalciuria, with or without hypercalcemia. Can have increased incidence of primary hyperparathyroidism.

Anesthetic Considerations: There is premature loss of deciduous teeth in children and permanent teeth in adults, so dental abnormalities should be documented preoperatively. Care must be taken

during laryngoscopy to avoid damage to fragile teeth. Patients must be adequately hydrated perioperatively to minimize the risk of hypercalciuric stone formation. Patients should be positioned and padded carefully, although the bones are not as fragile as they are in osteogenesis imperfecta. Precautions to avoid further increases in intracranial pressure must be taken in patients with increased intracranial pressure. Severely affected infants need close observation of their postoperative respiratory status.

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1. Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev* 2013;10:S380-388.

2. Whyte MP, Greenberg CR, Salman NJ, et al. Enzyme replacement therapy in life-threatening hypophosphatasia. *N Engl J Med* 2012;366:904-913.

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

I

I-cell disease

Synonym: Mucolipidosis II

MIM #: 252500

This autosomal recessive disease is related to the mucopolysaccharidoses. Before the biochemistry of the mucolipidoses was understood, it was recognized that these patients had features of both the mucopolysaccharidoses and the sphingolipidoses; hence the name “mucolipidosis.” “I cell” stands for “inclusion cell” and refers to the abnormal inclusions found in the cytoplasm of fibroblasts in this disease. This syndrome is characterized by abnormal lysosomal enzyme transport in cells of mesenchymal origin, resulting in enzymes being released into the extracellular stroma rather than being stored in lysozymes. The deficient enzyme is *N*-acetylglucosamine-1-phosphotransferase (*GNPTAB*), which is also deficient in pseudo-Hurler syndrome or mucolipidosis III (see later). This enzyme catalyzes the formation of mannose 6-phosphate, required for targeting lysosomal hydrolases to the lysosome. The phenotype resembles Hurler syndrome (see earlier), but with earlier onset. The presence of gingival hypertrophy in I-cell disease also differentiates the two. Death is often by 5 to 8 years of age, but some can survive into adolescence.

HEENT/Airway: Coarse facies. Corneal opacities. Puffy eyelids. Hearing loss. Anteverted nostrils. The base of the tongue, epiglottis, larynx, and tracheal wall can be thickened. Hyperplastic gums. The adenoids and tonsils can be involved and enlarged. The jaw and neck can be stiff. Short neck. May have obstructive sleep apnea.

Chest: Thoracic deformities, which may lead to restrictive lung disease. Recurrent respiratory infections. May have pulmonary fibrosis.

Cardiovascular: The valves can be thickened because of numerous vacuolated fibroblasts. Aortic insufficiency. May have hypertrophic cardiomyopathy.

Neuromuscular: Severely retarded psychomotor development. Hypotonia.

Orthopedic: Kyphoscoliosis, lumbar gibbus deformity, anterior beaking of vertebral bodies, congenital hip dislocation. Carpal tunnel syndrome, claw hand. Stiff joints. Intrauterine fractures. Congenital dislocation of the hip. Growth failure.

GI/GU: Abdominal distension with hepatomegaly. Inguinal hernias, diastasis recti, umbilical hernia. Constipation alternating with diarrhea.

Other: Hydrops fetalis in the most severely affected.

Anesthetic Considerations: The anesthetic implications are similar to those of the mucopolysaccharidoses, such as Hunter and Hurler syndromes (see earlier). When meeting the patient before surgery, recall that he or she may have hearing loss. Direct laryngoscopy and tracheal intubation may be very difficult, and may become more

difficult as the patient ages. It may be difficult to maintain a patent airway with a mask, even with an oral airway. The laryngeal mask airway (LMA) has been used successfully, but it has also failed to provide an adequate airway (3). If the patient's tracheal wall is thickened, an endotracheal tube that is smaller than predicted may be required. Patients must be carefully positioned and padded secondary to stiff joints. Postoperative respiratory complications are common, and the presence of obstructive sleep apnea may increase the risk of respiratory complications. Close monitoring should continue into the postoperative period, and opioids should be used with care. Patients with cardiac disease should receive an appropriately tailored anesthetic.

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Ichthyosis

(Includes collodion membranes)

Ichthyosis. Typical lamellar scales. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

MIM #: Many

"Ichthyosis" is a general term used to describe any skin disorder that results in dry, scaly (fishlike) skin. Skin involvement may vary from mild to severe. Most cases of ichthyosis are congenital, but ichthyosis can also occur secondary to chronic diseases such as hypothyroidism, renal insufficiency, malabsorption, or lymphoma. The pathogenesis of ichthyosis involves overproduction of keratin, excessive retention of keratin in the stratum corneum layer, or the production of abnormal keratin. The congenital ichthyoses can be divided into four major forms and a fifth form that is exceedingly rare.

1. **Ichthyosis vulgaris** (also called **ichthyosis simplex**) is the mildest and most common form of ichthyosis. It is inherited in an autosomal dominant fashion, and is noted for sparing of the flexural surfaces. It is usually not present at birth and is first noted in childhood. It involves large, lamellar scales, and sometimes smaller white scales. This form tends to improve with age.
2. **Sex-linked ichthyosis** is inherited in an X-linked recessive fashion and is therefore seen primarily in male patients. It is first noted in infancy (usually by age 3 months). Some infants have a collodion-like (parchment-like) membrane at birth. The palms and soles, central face, and flexural areas are spared. It involves large, brownish scales, which is why it is also known as **ichthyosis nigricans.** Corneal opacities develop in some patients. This form remains stable or worsens with age.
3. **Lamellar ichthyosis** is much more rare, and is inherited in an autosomal recessive fashion. It presents at birth or in early infancy. At birth, most patients have a **collodion membrane** (a parchment-like membrane with

cracking), the so-called “collodion baby.” The collodion membrane fissures and desquamates over several weeks. Sheetlike layers are shed, leaving residual redness and hyperkeratosis. This form of ichthyosis involves large, quadrangular, gray-brown scales. The scales are adherent centrally, and the edges are raised, such that they resemble armor plates. The scales are more common in the flexural areas, palms, and soles. The cheeks are often spared. The nails may be involved. Ectropion develops in some patients. This form remains stable or worsens with age.

4. **Keratinopathic ichthyosis** (formerly epidermal hyperkeratosis or bullous ichthyosis) is inherited in an autosomal dominant fashion. It involves thick, gray-brown, verruciform scales, particularly in the flexural and intertriginous areas. The palms and soles are involved. Bullae appear shortly after birth and are replaced by hyperkeratosis by the age of 3 months. This form remains stable or worsens with age.

5. The most dramatic form of congenital ichthyosis is the exceedingly rare **harlequin fetus**, in which the child is covered by thick plates of stratum corneum separated by deep fissures at birth. The skin is hard and thick, with the feel of bark. The skin restricts respiratory movements. The joints are contractured. All infants die in the neonatal period, usually in the first week. Death is a consequence of hypoventilation and pneumonia, or sepsis stemming from cutaneous infection. The name is derived from the deep purple fissures that divide the thickened gray or yellow skin into geometric plaques, giving the appearance of a harlequin's costume.

Anesthetic Considerations: Treatment of ichthyosis is aimed at reducing or softening the scale by the application of lubricants or keratinolytic agents. The oily base in these agents prevents adhesives from sticking to the skin. Perioperatively, noninvasive monitors, tubes, and catheters may need to be sewn or tied into place. Peripheral intravenous access may be difficult. In severe ichthyosis, temperature regulation is impaired. Patients with severe disease may have protein and electrolyte losses and dehydration, and are at risk for the development of sepsis. The collodion baby has severe restrictive lung disease and may be difficult to intubate secondary to limited mouth opening and facial distortion.

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3. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Soreze 2009. *J Am Acad Dermatol* 2010;63:607-641.

Idiopathic basal ganglia calcification

See Fahr disease

Immotile cilia syndrome

See Kartagener syndrome

Incontinentia pigmenti

Synonym: Bloch-Sulzberger syndrome

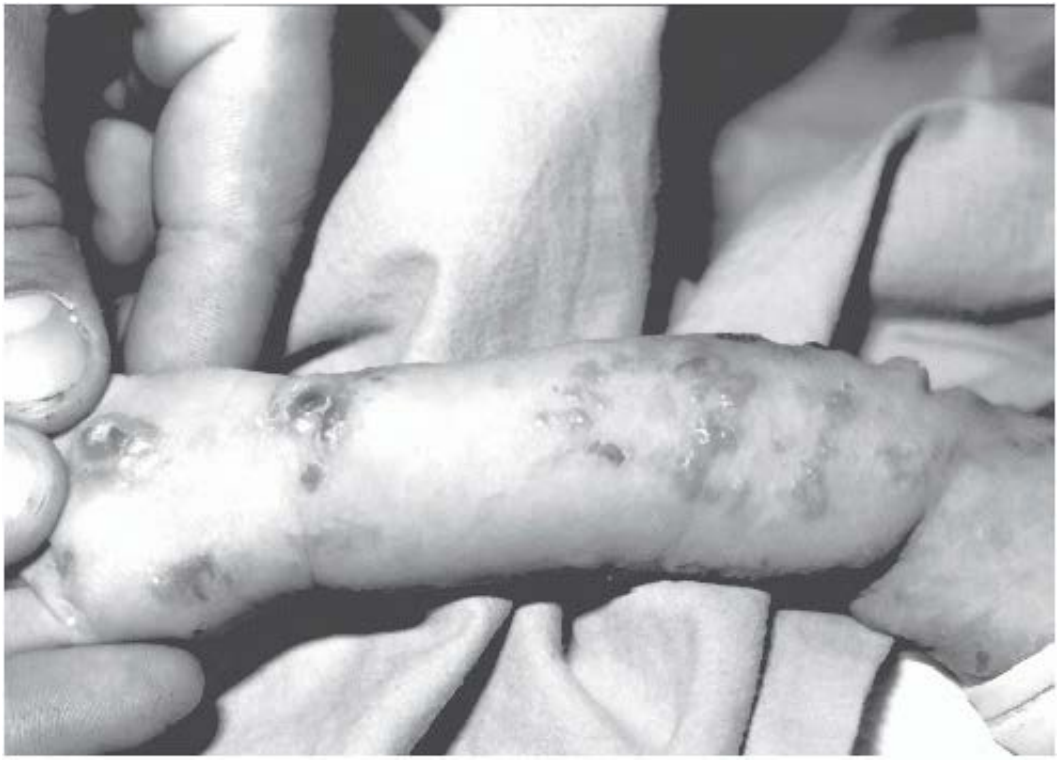
MIM #: 308300

This X-linked dominant disease is usually lethal in hemizygous males. The major findings in incontinentia pigmenti are characteristic skin changes, eye anomalies, and neurologic abnormalities. The disorder is due to mutations in the gene *IKK-gamma*, also known as *NEMO*, the NF-kappa-B essential modulator gene. In females, cells expressing the mutated gene are selectively eliminated around the time of birth, so that X-inactivation is not random.

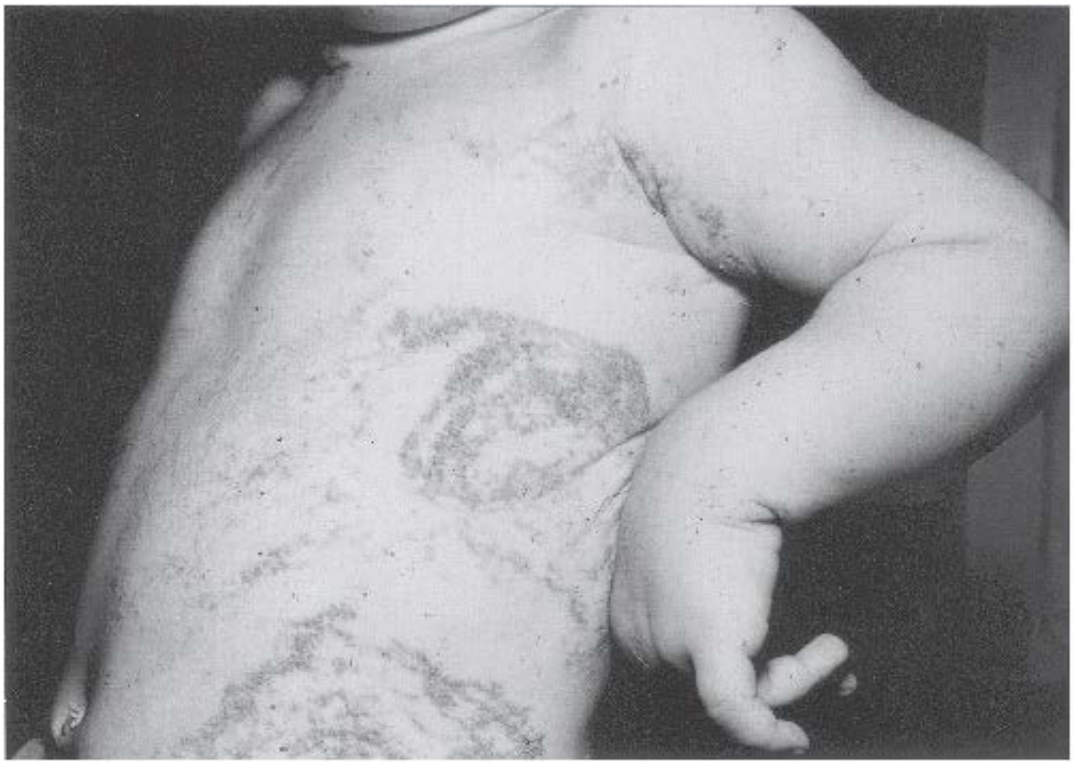
HEENT/Airway: Microcephaly. Strabismus, cataracts, optic atrophy, uveitis, keratitis, retinal vascular and pigmentary abnormalities, retinal detachment. Delayed dentition with pointed and absent teeth.

Chest: Occasional unilateral breast aplasia or hypoplasia.

Neuromuscular: Intellectual disability. Spasticity, hemiparesis, seizures. Dilated ventricles. Hypoplasia of the corpus callosum and/or cerebellum. Neonates may have encephalopathy.



Incontinentia pigmenti. FIG. 1. Relatively early skin lesions of incontinentia pigmenti. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)



Incontinentia pigmenti. FIG. 2. Relatively later skin lesions of incontinentia pigmenti. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Orthopedic: Short stature. May have scoliosis. Mild dystrophy of the nails.

Other: The hallmark finding is so-called autochthonous tattooing of the skin in a swirl pattern (resembling the pattern in a marble cake). The skin is initially erythematous with vesicles and pustules, followed by papules, verrucous lesions with hyperkeratosis, hyperpigmentation, and, finally, pallor, atrophy, and scarring. The hyperpigmentation typically fades by adulthood. The pigmented swirl lesions can also occur in areas not obviously affected by the inflammatory changes. Spotty alopecia. Can have abnormal nails.

Miscellaneous: The name is derived from the early belief that the basal layer of epidermis was “incontinent” of melanin. The progression of the skin lesions has been interpreted as representing the gradual replacement of cells containing an abnormal gene on the X chromosome with cells containing a normal gene on the X chromosome (the Lyon hypothesis). X-linked dominance with lethality in male hemizygotes is supported by the presence of this disease in a male patient with Klinefelter syndrome (XXY).

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Recall that patients may have visual impairment. Chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs. Succinylcholine may be contraindicated in patients with hemiparesis or spasticity because of the risk of hyperkalemia. Patients with vesicular or pustular skin lesions should be carefully positioned and well padded perioperatively.

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Incontinentia pigmenti achromians

See Hypomelanosis of Ito

Infantile cortical hyperostosis

See Caffey disease

Infantile Refsum disease

Note: This is distinct from Refsum disease

MIM #: 601539

Infantile Refsum disease is an autosomal recessive peroxisomal biogenesis disorder due to an abnormality in the genes peroxin-1 (*PEX1*), peroxin-2 (*PEX2*), or peroxin-26 (*PEX26*). Patients are unable to transport proteins into peroxisomes appropriately. Peroxisomal function is deficient, and peroxisomes may be absent. This leads to an accumulation of phytanic acid as in Refsum disease (see later) but also to an accumulation of very-long-chain fatty acids, dihydroxycholestanoic and trihydroxycholestanoic acids, and pipecolic acid. There are genetic and biochemical similarities among infantile Refsum disease, neonatal leukodystrophy (see earlier, adrenoleukodystrophy), and Zellweger syndrome (see later). These three disorders may represent a continuum of peroxisome biogenesis disorders, with Zellweger syndrome being the most severe, neonatal adrenoleukodystrophy intermediate, and infantile Refsum disease being the least severe. Patients with infantile Refsum disease may reach adulthood.

HEENT/Airway: High forehead, flattened facies. Retinitis pigmentosa. Sensorineural hearing loss.

Neuromuscular: Intellectual disability, language delay. Hypotonia, seizures. May develop spasticity.

Orthopedic: Skeletal changes with osteoporosis.

GI/GU: Hepatomegaly, protracted diarrhea. Renal cysts. May have impaired adrenal cortical function.

Other: Episodic bleeding.

Anesthetic Considerations: Keep in mind that patients will likely have impaired vision and/or hearing. Patients may have electrolyte imbalances secondary to chronic diarrhea. Avoid protracted fasting. Patients require careful perioperative positioning and padding secondary to osteoporosis and hypotonia. Propofol should be used with caution in patients with peroxisomal disorders as they may be at higher risk for developing propofol infusion

syndrome. Adrenal response to stress may be inadequate, and patients may require perioperative stress doses of steroids. Chronic use of anticonvulsant medications alters the metabolism of some anesthetic drugs.

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Isovaleric Acidemia

Synonym: Isovaleryl-CoA dehydrogenase deficiency

MIM #: 243500

This autosomal recessive disease is due to a defect in the enzyme isovaleryl-CoA dehydrogenase. Isovaleryl-CoA dehydrogenase catalyzes a step in the catabolism of leucine. Patients present either in the neonatal period with an episode of severe metabolic acidosis, often fatal, or later in infancy with a chronic intermittent metabolic acidosis. Both forms have the same biochemical defect, and this difference may be nothing more than an indication of the period of imposed metabolic stress since neonates who survive an episode at birth can go on to have the chronic intermittent form. Episodes of the chronic intermittent form are associated with intercurrent infection or increased dietary protein. Patients often self-select a protein-restricted diet. Chronic therapy with glycine and carnitine may be helpful. These work by enhancing the excretion of the major abnormal metabolite, isovaleryl-CoA, as the nontoxic isovaleryl-glycine and isovaleryl carnitine. Isovaleryl carnitine is excreted in the urine at a rate greater than the body's ability to synthesize carnitine, so these patients may have low carnitine levels.

Neuromuscular: Psychomotor development is usually normal, but some have mild or occasionally severe intellectual disability. Episodes of lethargy may progress to coma, hypothermia, or seizures. Rare strokes.

GI/GU: Episodic severe vomiting, episodic pancreatitis, diarrhea, hepatomegaly.

Other: Episodes of metabolic acidosis, with hyperammonemia and mild ketosis. Hypocalcemia. Occasional hyperglycemia. There is an odor of sweaty feet from elevated isovaleric acid levels, particularly during acute episodes. Hypoplastic bone marrow. Thrombocytopenia, neutropenia with acute episodes. May have associated carnitine deficiency.

Miscellaneous: Isovaleric acidemia was the first inborn error of metabolism to be diagnosed by gas chromatography-mass spectrometry of metabolites. Chronically, it is treated with a protein-restricted diet, carnitine, and glycine. Acutely, it is treated with the provision of glucose and protein restriction.

Anesthetic Considerations: Patients must receive adequate perioperative glucose to minimize protein catabolism. Protein-restricted diets should be continued perioperatively. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load and trigger an acute decompensation.

Regional anesthesia is contraindicated in patients with significant thrombocytopenia. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity and a lowered arrhythmia threshold. A case of intraoperative arrhythmia thought to be associated with bupivacaine toxicity has been reported (2). Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

Figure: See **Appendix D**

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Isovaleryl-CoA dehydrogenase deficiency

See Isovaleric acidemia

Ivemark syndrome

See Asplenia or Polysplenia

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

J

Jackson-Lawler syndrome

See Pachyonychia congenita syndrome

Jacobsen syndrome

See 11q syndrome

Jadassohn-Lewandowski syndrome

See Pachyonychia congenita syndrome

Jansen-type metaphyseal dysplasia

See Metaphyseal chondrodysplasia, Jansen type

Jansky-Bielschowsky disease

Synonym: Late infantile neuronal ceroid lipofuscinosis. (Includes Batten disease)

MIM #: 204500

This autosomal recessive lysosomal disorder is marked by profound central nervous system degeneration. It is one of multiple, perhaps 13, neuronal ceroid lipofuscinoses. Of the lipofuscinoses, there are four major subtypes: Santavuori-Haltia (CLN1, not discussed in this text), Jansky-Bielschowsky disease (CLN2), Spielmeyer-Vogt disease (CLN3) (see later), and Kuf's disease (CLN4, not discussed in this text). Spielmeyer-Vogt disease (CLN3) has also been called Batten disease, but **Batten disease** is now more commonly used to encompass all forms of neuronal ceroid lipofuscinosis. These neurodegenerative disorders are marked by the accumulation of autofluorescent pigment in the brain and other tissues. Jansky-Bielschowsky disease is late infantile neuronal ceroid lipofuscinosis and is due to mutations in the gene *TPP1* (*CLN2*), which encodes a lysosomal peptidase. This form of lipofuscinosis presents at 2 to 4 years of age, and death occurs at 10 to 15 years of age. Major problems include seizures, myoclonus, intellectual disability, and ataxia.

HEENT/Airway: Progressive visual loss leading to blindness, retinal degeneration, absent electroretinogram.

Neuromuscular: Drug-resistant grand mal and myoclonic seizures. Intellectual disability, developmental regression, ataxia, cerebral atrophy. Autofluorescent lipopigment in neurons and extraneuronal cells.

Other: Autonomic dysregulation, including abnormal thermal regulation.

Anesthetic Considerations: Severe intellectual disability may complicate preoperative management. Patients may be bedridden with muscle atrophy, so succinylcholine should be avoided, and volatile anesthetics alone may provide adequately relaxed muscles. Perioperative hypothermia can result from abnormal thermal regulation (1,3). Seizures can be difficult to control and can occur perioperatively. Chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs.

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Jarcho-Levin syndrome

Synonym: Spondylocostal dysostosis; spondylothoracic dysplasia

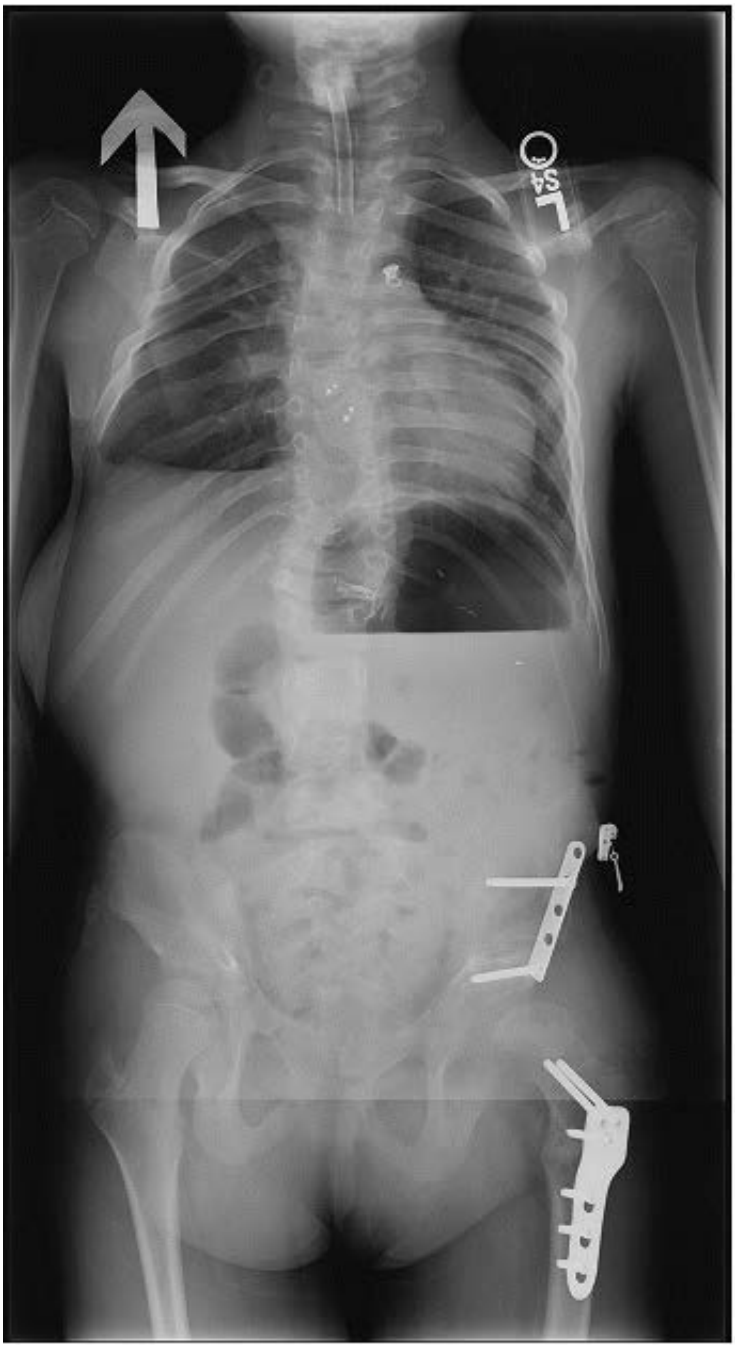
MIM #: 277300

This autosomal recessive form of dwarfism is distinguished by a short trunk with a short, malformed thoracic cage. It can be due to abnormalities in the gene *DLL3*, but the disorder is genetically heterogeneous, so abnormalities in many other genes can lead to the same phenotype. The disorder is apparently one of inappropriate segmentation.

HEENT/Airway: Wide forehead, prominent occiput, low posterior hairline. Upslanting palpebral fissures. Wide nasal bridge, anteverted nares. Can have cleft palate. Short neck, with limited mobility.

Chest: Short thoracic cage with an increased anteroposterior diameter and ribs that fan out, giving the thorax a crablike appearance on radiography. Rib anomalies, including absent ribs, hemivertebrae, posterior rib fusion. Pectus carinatum. Pulmonary hypoplasia in the most severely affected. Intrathoracic tracheal abnormalities may contribute to respiratory insufficiency.

Cardiovascular: Can have congenital heart disease.



Jarcho-Levin syndrome. An 8-year-old girl admitted for a femoral osteotomy, done with general anesthesia and a lumbar epidural. Note the tracheostomy (not ventilator dependent) and devices closing an atrial septal defect and a patent ductus arteriosus. Her severe kyphosis is not fully appreciated on this anteroposterior view.

Neuromuscular: Can have meningomyelocele.

Orthopedic: Short-trunk dwarfism—extremities are normal in length. Multiple thoracic vertebral defects, including hemivertebrae, vertebral fusions. Kyphoscoliosis, lordosis.

GI/GU: Protuberant abdomen. Can have cryptorchidism, hypospadias, ureteral or urethral obstruction.

Miscellaneous: Abnormalities in *DLL3* in mice results in the "pudgy" phenotype. Jarcho and Levin misidentified the first cases as Klippel-Feil syndrome.

Anesthetic Considerations: Patients have severe restrictive lung disease secondary to limited thoracic volume, limited chest excursion, and recurrent infection. Many patients die in infancy secondary to respiratory insufficiency. Direct laryngoscopy and tracheal intubation can be difficult because of the short neck with limited extension. Neuraxial anesthesia/analgesia may be technically challenging secondary to vertebral abnormalities, but is not otherwise contraindicated.

Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Jervell and Lange-Nielsen syndrome

Included in Long QT syndrome

Jeune syndrome

Synonym: Asphyxiating thoracic dystrophy; Thoracic-pelvic-phalangeal dystrophy

MIM #: 208500

This autosomal recessive disorder is characterized by severe thoracic hypoplasia and deformity, short limbs, and hypoplastic iliac wings. Death in infancy is common. In long-term survivors, chronic renal failure is common. Although there are several similar syndromes, Jeune syndrome is perhaps the best known of the short-rib thoracic dysplasia (SRTD) syndromes.

HEENT/Airway: Can have progressive retinal degeneration. Occasional cleft lip or palate.

Chest: Severe deformity of the thoracic cage prevents adequate respiratory excursion in the neonate. In the most severe cases, there is also pulmonary hypoplasia. Persistent pulmonary hypertension has been reported in some neonates. Early infant death is common, secondary to asphyxia or pneumonia. Chest radiographs show a typical, very narrow thorax with short horizontal ribs. Survivors usually exhibit progressive growth of the thoracic cage. Attempts at surgical expansion of the thoracic cage have met with variable success.

Cardiovascular: Cor pulmonale secondary to restrictive lung disease or chronic hypoxemia. Myocardial failure has

been reported in older patients.

Neuromuscular: Rare intellectual disability. Rare mild congenital hydrocephalus.

Orthopedic: Short stature. Short limbs, especially marked in the hands. Occasional polydactyly. Hypoplastic iliac wings.

GI/GU: Occasional direct hyperbilirubinemia. Hepatic cirrhosis has been observed in some children, and portal hypertension has been described requiring transplantation. Occasional pancreatic fibrosis or cysts. Intestinal malabsorption has been reported. Cystic renal disease or renal fibrosis can lead to chronic renal failure by late infancy or early childhood in those patients who have survived the neonatal period.

Miscellaneous: Expandable titanium rib prostheses have been proposed for these children, and there is evidence of rib growth and ossification, which is not ultimately dependent on the prosthetic ribs.

Anesthetic Considerations: Most patients have severe respiratory insufficiency. If not already hypoxemic at rest, patients will likely desaturate with agitation secondary to asynchronous rib and abdominal motion superimposed on small lung volumes. Intraoperatively, peak airway pressures must be maintained as low as possible to avoid barotrauma and the effects of high airway pressures on pulmonary arterial blood flow. After thoracoplasty, most infants require long-term mechanical ventilation. Cor pulmonale is not uncommon in these patients and must be anticipated. Renal disease has implications for perioperative fluid management and the choice of anesthetic drugs. Hepatic insufficiency may affect the binding or metabolism of some anesthetic agents. Neuraxial anesthesia/analgesia may be technically challenging secondary to thoracic abnormalities, but is not otherwise contraindicated. It is thought that modern neonatal care will improve mortality.

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Job syndrome

Synonym: Hyperimmunoglobulin E syndrome

MIM #: 147060, 243700

This syndrome leads to overproduction of immunoglobulin E (IgE) and deficient neutrophil and monocyte chemotaxis, resulting in recurrent skin and sinopulmonary infections. There is an autosomal recessive and an autosomal dominant form. The gene responsible for the recessive form is the *DOCK8* gene located on the short arm of chromosome 9. The gene responsible for the dominant form is the *STAT3* gene located on the long

arm of chromosome 17. Inability to produce interleukin-17 may be the underlying cause of susceptibility to infection in these patients.

HEENT: May have craniosynostosis. Facial asymmetry, prominent forehead, deep-set eyes, broad nasal bridge with wide fleshy tip, and thickened ears. Full lower lip. Rough facial skin with prominent pores. Mild prognathism. Failure or delayed shedding of primary teeth due to deficient root resorption. May have mucocutaneous candidiasis.

Chest: Recurrent bacterial infections of the sinopulmonary tract, usually due to *Staphylococcus aureus*. Patients present frequently for abscess drainage. There is a very high incidence of empyema. Large pneumatoceles can form.

Neuromuscular: Strokes and lymphocytic encephalitis. A variety of central nervous system problems in the recessive type.

Orthopedic: May have scoliosis. Hyperextensible joints, bone fractures with minimal trauma in the dominant type.

Other: Eczema is common. Patients often have red hair. Serum IgE levels are at least 10 times normal. Eosinophilia. Neutrophil and monocyte chemotaxis is deficient. Recurrent bacterial infections of the skin. Abscesses may form, which are often quite large. Bacteremia or deep infections of viscera or the central nervous system are uncommon. The recessive type has been associated with small vessel vasculitis.

Miscellaneous: "So went Satan forth from the presence of the Lord, and smote Job with sore boils from the sole of his foot until his crown" (Job II,7).

Anesthetic Considerations: Attention to good aseptic technique and appropriate antibiotic prophylaxis is imperative. Sinopulmonary disease is common, and lung function may not be optimal perioperatively. Pneumatoceles are also common, so vigorous positive pressure ventilation and nitrous oxide should be avoided. Placing an epidural or spinal needle through chronically infected skin may increase the infectious risk of epidural or spinal anesthesia. Because abscesses in this syndrome do not elicit a local inflammatory response, an epidural abscess, should it form, would not become apparent until it has caused neurologic compromise. Patients must be carefully positioned because of joint hyperextensibility. A single case of prolonged effect of succinylcholine in a patient with normal plasma cholinesterase activity has been reported (5).

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Johanson-Blizzard syndrome

MIM #: 243800

This autosomal recessive disease affects a variety of organ systems, which characteristically includes nasal alar hypoplasia (beaked nose), dental and scalp defects, sensorineural hearing loss, hypothyroidism, pancreatic exocrine insufficiency, postnatal growth retardation, and imperforate anus. The disorder is due to abnormalities in the gene *UBR1*, involved in the degradation of damaged proteins or those with a short half-life.

HEENT/Airway: Microcephaly. High forehead. Lateral hairline can extend onto the forehead. Midline scalp defects (aplasia cutis congenita). Can have strabismus. Missing eyelashes and eyebrows. Nasolacrimal duct-cutaneous fistulae or aplasia. Low-set ears. Sensorineural hearing loss. Hypoplasia or aplasia of the alae nasi with beaked nose. Hypoplastic deciduous and absent permanent teeth. Can have micrognathia.

Cardiovascular: May have congenital heart disease.

Neuromuscular: Intelligence can be normal but can have mild intellectual disability. Can have hypopituitarism.

Orthopedic: Postnatal growth retardation. Clinodactyly. Simian crease.

GI/GU: Malabsorption. Anorectal anomalies, including imperforate anus. Can have malrotation. Can have exocrine pancreatic insufficiency. Urogenital abnormalities, including double vagina, double uterus, and rectovaginal fistula. Cryptorchidism. Abnormalities of renal pelvis with hydronephrosis.

Other: Hypothyroidism, hypopituitarism, pancreatic exocrine insufficiency. Deficiency of fat-soluble vitamins due to pancreatic insufficiency. Can have diabetes.

A patient with insulin resistance has been reported. Alopecia. Sparse blond hair. Can have failure to thrive. Can have situs inversus.

Miscellaneous: Robert Blizzard was the Chairman of the Department of Pediatrics at the University of Virginia.

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Airway management can be challenging due to micrognathia and abnormal facies. Obtaining a proper mask fit may be difficult. Patients are at risk for postoperative airway obstruction (2). Nasolacrimal duct abnormalities may lead to accelerated drying of the cornea under general anesthesia. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Hypothyroidism, when present, could result in delayed gastric emptying, alterations in drug metabolism, and impaired temperature regulation. Recall when meeting the patient before surgery that they may have hearing loss. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Joseph disease

Synonym: Machado-Joseph disease; spinocerebellar ataxia type 3

MIM #: 109150

This autosomal dominant neurologic disease often does not become apparent until adulthood. It is characterized by loss of neurons and gliosis in a variety of locations, including the substantia nigra, the nuclei of the vestibular and cranial nerves, and the anterior horns. Clinically, patients present with ataxia, dystonia, spasticity, and nystagmus. There may also be peripheral nerve involvement. The responsible gene, *ATXN3* (or *MJD1*), is located on chromosome 14. The gene product, ataxin-3, may be a component of the ubiquitin proteasome system and play a role in transcriptional regulation. The defect involves repeats of the trinucleotide sequence CAG, and the number of repeats is related to the disease severity and age at onset. It has been suggested that this repeat may be responsible for inducing apoptosis, or programmed cell death.

HEENT/Airway: Bulging eyes, limited eye movement, nystagmus, external ophthalmoplegia. May develop dysarthria.

Chest: Dysfunction of respiratory control mechanisms. May develop restrictive pulmonary disease.

Neuromuscular: Parkinson-like features. Loss of leg reflexes, ataxia, dystonia, cerebellar tremors, Babinski sign, spasticity. May have autonomic dysfunction. Facial and lingual fasciculations, other muscle fasciculations. Muscle cramps. Muscle atrophy. Can develop dementia. Can have peripheral nerve involvement.

GI/GU: Dysphagia.

Other: Diabetes mellitus. Chronic pain, usually back and lower extremities.

Miscellaneous: This disease is named for the family in which it was first described. Although that family was from the Azores, the syndrome has subsequently been described in other populations, including the Japanese, possibly because of the early Portuguese influence in Japan. This disease has also been reported in a Yemenite Jewish family. Interestingly, the family's name was Yoseph.

Nucleic acid base triplet repeats are also apparently the etiology of other diseases, including Friedreich ataxia, fragile X syndrome, and spinocerebellar ataxia type 1.

Anesthetic Considerations: Diabetes mellitus is common, and patients should be evaluated preoperatively for evidence of diabetes. Swallowing difficulties can increase the risk of perioperative aspiration. Because of their bulging eyes, patients must receive meticulous perioperative eye care to avoid corneal injury. Patients may have respiratory control abnormalities and pulmonary dysfunction. Autonomic dysfunction may also complicate perioperative management. Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers

may exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects. Succinylcholine is contraindicated in patients with significant muscle atrophy, secondary to the risk of hyperkalemia. Although use of regional anesthesia is controversial in these patients with preexisting neurologic disease (2), neuraxial anesthesia has been used successfully (5,6). Patients may have chronic pain concerns.

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Joubert syndrome

Synonym: Joubert-Boltshauser syndrome

MIM #: 213300

This usually autosomal recessive disorder is similar to Dandy-Walker malformation because there is agenesis of the cerebellar vermis. It can be differentiated from Dandy-Walker malformation on computed tomography scan by the presence of normal cerebellar hemispheres in Joubert syndrome and the presence of cerebellar hypoplasia in Dandy-Walker malformation. Joubert syndrome can also be distinguished on magnetic resonance imaging by the presence of the “molar tooth sign,” a consequence of dysplasia of the isthmic segment of the brainstem. Joubert syndrome is genetically heterogeneous, and the phenotype is variable.

HEENT/Airway: Jerky eye movements. Oculomotor apraxia. Often associated with congenital retinal blindness. Chorioretinal and optic nerve colobomas. Low-set ears. Upturned nose. Can be associated with high-arched palate, large protruding tongue, and micrognathia. Uncommon tumors of the tongue. Can have laryngomalacia. Can have short neck.

Chest: Infants often present with episodic panting. Can have dysregulated breathing with periods of hyperpnea and apnea, which may improve with age.

Neuromuscular: Agenesis or hypoplasia of the cerebellar vermis with cystic malformation of the brainstem. Other brainstem malformations. Ataxia, tremor, hypotonia, global developmental delay, central apnea. Occipital meningoencephalocele. Behavioral abnormalities such as hyperactivity, aggressiveness, and self-mutilation.

GI/GU: Can have hepatic fibrosis. Can have renal cysts, renal dysplasia, renal failure.

Miscellaneous: Marie Joubert was only a resident when she first described this syndrome.

Anesthetic Considerations: When meeting the patient before surgery, be sensitive to the possibility that he or she is likely to have visual loss. Patients are very sensitive to the respiratory depressant effects of opioids and anesthetic agents. Postoperatively, patients should be observed closely for adequacy of ventilation. Episodic panting is common, so postoperative hyperventilation can be central and not necessarily indicative of pain. Renal disease can affect perioperative fluid management and the use of renally excreted drugs.

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Joubert-Boltshauser syndrome

See Joubert syndrome

Juvenile hyaline fibromatosis

MIM #: 228600

This autosomal recessive disorder results in deposition of hyaline material in a variety of tissues, leading to fibromatosis. The disorder is due to abnormalities in the gene *CMG2* (*ANTXR2*), which encodes capillary morphogenesis protein-2. The name *ANTXR2* is indicative of the fact that the gene product is an anthrax toxin receptor.

HEENT/Airway: Gingival fibromatosis and hypertrophy. There can be deposits at the commissures of the lips, and mouth opening can be limited.

Chest: There can be tracheal deposits.

Cardiovascular: There can be deposits in the heart.

Neuromuscular: Normal intelligence.

Orthopedic: Painful joint contractures. Osteolytic and osteoclastic long bone lesions, osteolysis of the terminal digits. Nodules of the finger tips.

GI/GU: Perianal granulomas.

Other: Multiple, large, slow-growing subcutaneous nodules, primarily on the head and neck and on the hands, which are often the presenting sign. There is a high recurrence rate after wide surgical excision. The nodules frequently become infected, usually with a strain of *Staphylococcus*. Serious infections can lead to death. Thyroid and adrenal deposits have been described. Sclerodermaform and atrophic skin changes.

Miscellaneous: When first described in 1873 and 1903, it was described as familial “molluscum fibrosum.”

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation can be exceedingly difficult secondary to gingival, oral and tracheal involvement, as well as contractures of the temporomandibular joint and cervical spine. Oral disease worsens as the patient ages. Patients might require a smaller than expected endotracheal tube if sized for age. A laryngeal mask has been used successfully (5). A single patient has been described who had succinylcholine resistance despite normal plasma cholinesterase activity and normal neuromuscular function (4). Response to nondepolarizing muscle relaxants is apparently normal. Patients must be carefully positioned and padded perioperatively secondary to painful joint contractures.

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Juvenile macular degeneration

See Stargardt disease

Juvenile spinal muscle atrophy

See Kugelberg-Welander disease

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

K

Kabuki syndrome

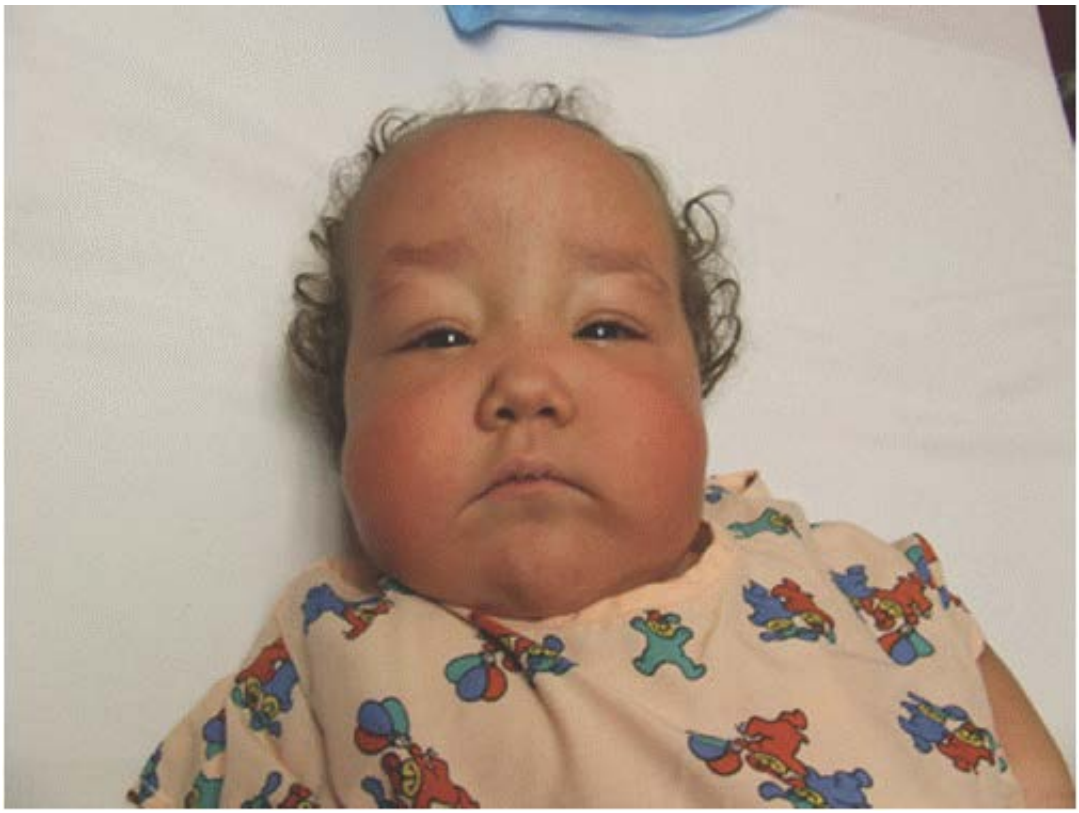
MIM #: 147920

This probably autosomal dominant syndrome is recognized by characteristic facial features that include long palpebral fissures and eversion of the lower eyelids. Most cases of Kabuki syndrome, but not all, are caused by mutations of the gene *MLL2* on chromosome 12. A related Kabuki syndrome-2 is caused by mutations in the gene *KDM6A*. There can be variable clinical findings in affected families.

HEENT/Airway: Long palpebral fissures, eversion of the lateral part of the lower eyelids, arched eyebrows, ptosis, strabismus, epicanthal folds, coloboma. Prominent ears, recurrent otitis media. Conductive or sensorineural hearing impairment. Short nasal septum, depressed nasal tip. Broad philtrum. Abnormal dentition. Cleft palate.

Chest: Bronchomalacia has been reported. Rib anomalies. Can have pectus excavatum. Can have diaphragmatic eventration or hernia. Early thelarche in girls.

Cardiovascular: Cardiac defects are common, most commonly coarctation of the aorta, atrial septal defect, and ventricular septal defect. Right bundle branch block can also be seen.



Kabuki syndrome. This 13-month-old boy has the superficial facial features of a Japanese Kabuki actor. He was hypertonic with a seizure disorder and had a patent ductus arteriosus and a ventricular septal defect, both of which closed spontaneously. He also had a difficult airway.

Neuromuscular: Mild to moderate intellectual disabilities. Hypotonia. Can have seizures. Abnormalities in the hypopituitary-pituitary axis are uncommon.

Orthopedic: Short stature. Short digits, brachydactyly, cutaneous syndactyly. Dermatoglyphic abnormalities, nail hypoplasia. Scoliosis, vertebral anomalies. Hyperextensible joints. Dislocated hips.

GI/GU: Can have biliary atresia or cholangitis. Can have umbilical hernia, inguinal hernias, imperforate anus. Can have cryptorchidism, renal anomalies. Can have uteropelvic junction obstruction.

Other: Café au lait spots. Can be obese. Can be hirsute. Can have congenital hypothyroidism. Can have increased susceptibility to infections, probably based on an abnormal immunoglobulin response.

Miscellaneous: Called Kabuki syndrome because of the similarity in facial appearance between affected people and the makeup of actors in Kabuki, a traditional Japanese theatrical form.

Anesthetic Considerations: Dental anomalies should be documented preoperatively. Patients with hyperextensible joints need to be positioned carefully. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Possible renal impairment or chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs.

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Kallmann syndrome

MIM #: 308700, 147950, 244200

The clinical hallmarks of this syndrome are hypogonadotropic hypogonadism, midline intracranial anomalies, and anosmia (inability to smell). X-linked (*KAL1* gene), autosomal dominant [fibroblast growth factor receptor-1 (FGFR1) gene], and autosomal recessive (*KAL3* gene) transmission have all been reported as well as involvement of other genes (*GNRHR*, *NELF*, and *GPR54*), which may act alone or in consort to cause deficiency of gonadotropin-releasing hormone (GnRH). The product of the X-linked *KAL1* gene, termed anosmin-1, is synthesized by neural cells, and is involved in the migration of gonadotropin-releasing hormone neurons and olfactory neurons to the hypothalamus. Patients can have findings of other X-linked disorders, as the syndrome can be related to X chromosome deletions. A small number of men can have sustained reversal of hypogonadotropic hypogonadism after discontinuation of hormone treatment.

HEENT/Airway: Hypotelorism. Sensorineural hearing loss. Anosmia; female carriers of the X-linked form have partial or complete anosmia. Choanal atresia. High-arched palate; cleft lip or palate.

Chest: Gynecomastia.

Cardiovascular: Rarely can be associated with congenital cardiac defects.

Neuromuscular: Can have intellectual disabilities. Agenesis of the olfactory lobes. Other midline intracranial anomalies. Mirror movements of the hands (bimanual synkinesia), cerebellar ataxia.

Orthopedic: Rarely can be associated with short stature. Pes cavus.

GI/GU: Hypogonadism, due to a deficiency of hypothalamic gonadotropin-releasing hormone. Becomes apparent with the failure to develop secondary sex characteristics at puberty. Cryptorchidism. Can have unilateral or bilateral renal agenesis.

Miscellaneous: Kallmann, a German psychiatrist and geneticist, opposed Nazi racial doctrines, which led to him being banned from publishing in the medical literature and from speaking at medical meetings. He left for the United States in 1936.

Anesthetic Considerations: When meeting the patient before surgery, recall that he or she may have hearing loss.

Endocrinologic dysfunction appears to be limited to gonadotropin. The presence of choanal atresia precludes a nasal airway, nasal intubation, or a nasogastric tube.

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Kanner syndrome

See Autism spectrum disorder

Kanzaki disease

Included in Schindler disease

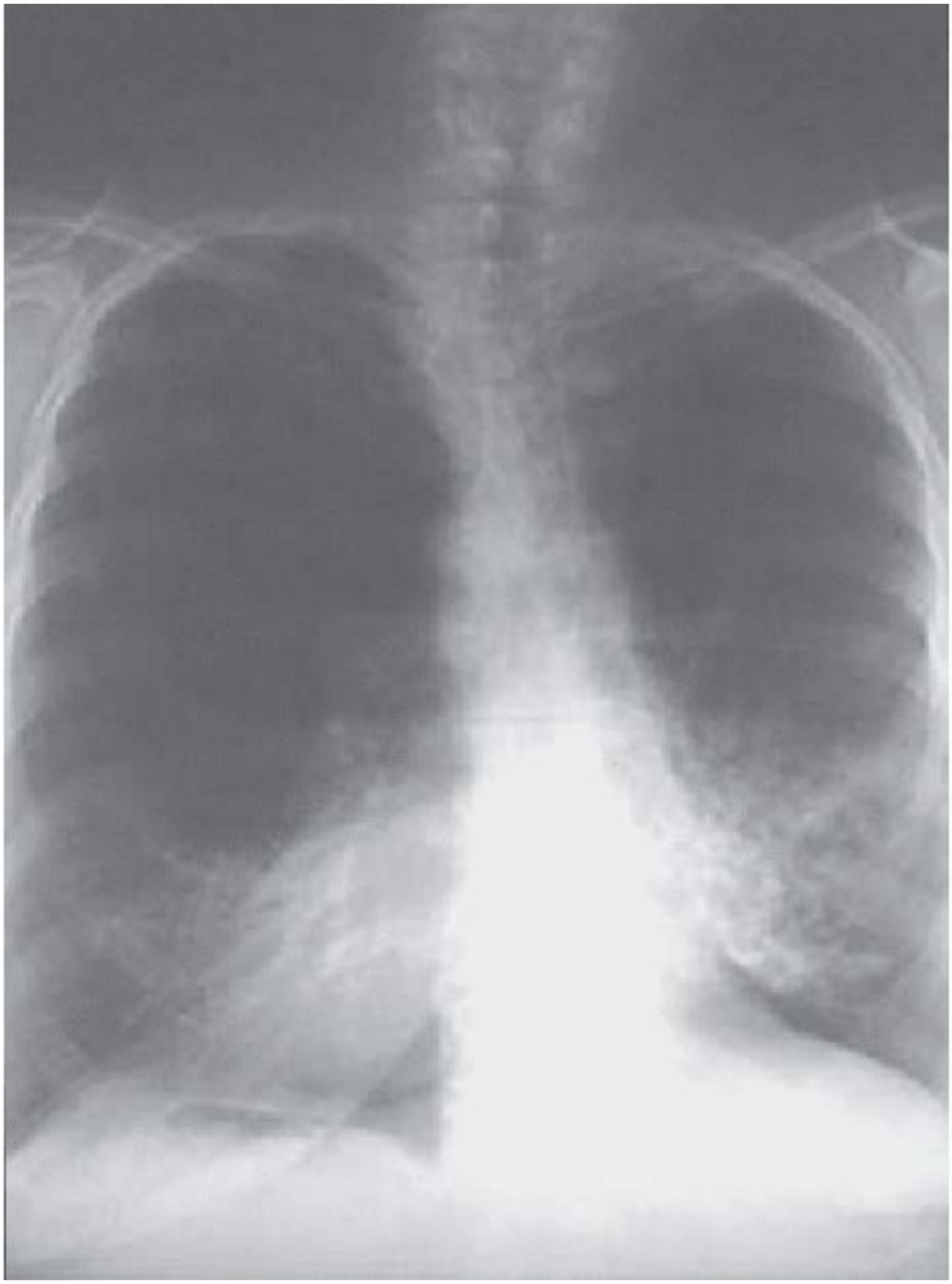
Kartagener syndrome

Synonym: Immotile cilia syndrome

MIM #: 244400

This autosomal recessive syndrome is characterized by situs inversus, chronic sinusitis, bronchiectasis, and male sterility. Kartagener syndrome is a form of primary ciliary dyskinesia. The disorder is genetically diverse, and the underlying defect is an absence of ciliary dynein arms, which renders cilia immotile. Immotile cilia cause functional failure of the respiratory epithelium, leading to chronic sinusitis, chronic respiratory tract infection, and bronchiectasis. Immotile cilia also cause male sterility because sperm are rendered immobile. Immotile cilia in embryonic epithelial tissues may be the cause of situs inversus. The disorder is caused by mutations in the gene *DNAI1*. Numerous other genes, however, can also result in ciliary dyskinesia. Diagnosis can be made by examining nasal cilia obtained by brushing.

HEENT/Airway: Can have corneal abnormalities. Frontal sinus may not develop; poor aeration of mastoid cells. Rhinitis, nasal polyps, chronic sinusitis. Olfactory incompetence. Chronic otitis media. Conductive hearing loss can develop.



Kartagener syndrome. This adult man with Kartagener syndrome has situs inversus (note the heart, stomach bubble, and liver on the “incorrect” side and note the vertical angle of the left mainstem bronchus) and bronchiectasis. (Courtesy of Dr. David Jones, Thoracic Service, Memorial Sloan-Kettering Cancer Center.)

Chest: Chronic cough with thick, tenacious sputum. Chronic respiratory tract infections, bronchiectasis, particularly of the dependent lung. Bronchiectasis can necessitate partial lung resection. May have reactive airway disease.

Cardiovascular: Dextrocardia as part of situs inversus. However, there is not a significantly increased incidence of cardiac septation defects as is seen in isolated dextrocardia. The electrocardiogram with complete situs inversus is a mirror image of normal. Chronic bronchiectasis can result in cor pulmonale.

Neuromuscular: Chronic headaches (the ependyma of the brain is ciliated epithelium). Can have communicating hydrocephalus. Can have a history of depression, schizophrenia.

GI/GU: Can have asplenia. Male sterility. Women may have decreased fertility but are not necessarily infertile.

Other: Situs inversus. May have low levels of IgA and abnormal neutrophil chemotaxis but no increased incidence of infections other than respiratory tract infections. It has been suggested, though, that these ciliated respiratory epithelial cells do not secrete nitric oxide on exposure to bacteria, and preliminary results suggest that exhaled nitric oxide might serve as a diagnostic tool.

Miscellaneous: Manes Kartagener was born in Austria but practiced in Geneva. He reported the syndrome 29 years after Siewert. In affected families, approximately one-half of the affected individuals have situs inversus. Normal ciliary motion is required for the establishment of normal embryonic asymmetry, so without it laterality is random. Despite immotile spermatozoa, *in vitro* fertilization procedures are possible if sperm are placed within or adjacent to the egg.

Anesthetic Considerations: Patients have thick, tenacious sputum. Profound hypoxemia with difficult ventilation has been reported after induction of anesthesia and tracheal intubation. Humidification of inspiratory gases is beneficial. Good perioperative chest physiotherapy is necessary. The increased incidence of nasal polyps, sinusitis, and otitis media is a relative contraindication for nasotracheal intubation. Anticholinergics decrease the volume of pulmonary secretions but not their chemical consistency—they are not thicker. Thus, anticholinergics are not contraindicated.

In the presence of situs inversus, an endotracheal tube placed too deeply will likely enter the left mainstem bronchus rather than the right mainstem bronchus. A left-sided, double-lumen endobronchial tube may occlude the proximal takeoff of the left upper lobe bronchus. The origin of the upper lobe bronchus is more distal in the right lung. A left-sided tube can be rotated to the right and placed in the right mainstem bronchus and vice versa for a right-sided tube. Cannulation of the left internal jugular vein is analogous to cannulation of the right internal jugular vein in normal patients. The electrocardiogram is a mirror image of normal, and leads should be placed accordingly. Defibrillator paddles should be placed in a mirror-image fashion over the right chest. Parturients should have right, rather than left, uterine displacement.

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Kasabach-Merritt syndrome

MIM #: 141000

This syndrome occurs when apparent capillary hemangiomas cause platelet trapping and a consumptive coagulopathy. Development of this syndrome is typically associated with rapid enlargement of the apparent hemangioma. Although this syndrome has been described somewhat generically with hemangiomas, the histology

of the lesions is not that of true hemangiomas (2), and the lesions are better described as kaposiform hemangioendotheliomas. About 50% are present at birth, and unlike infantile hemangiomas have a predilection for the proximal extremities and trunk. Coagulopathy at birth has been reported. Involvement of the head and face is rare. The tumor tends to be very difficult to treat medically, surgically, or by interventional radiologic techniques. The etiology of the disorder is currently unknown.

Cardiovascular: High-output cardiac failure, worsened by anemia.

Orthopedic: Can infiltrate muscle and bone.

GI/GU: Retroperitoneal hemangiomas with possible direct visceral spread. Spontaneous splenic rupture has occurred.

Other: Microangiopathic hemolytic anemia with thrombocytopenia. Full-blown disseminated intravascular coagulation with hemorrhage may develop. Coagulopathy in adults is due to stasis, which initiates the generation of thrombin and local clot formation, but the platelet count is minimally depressed (50 to 150,000/mm^3). Children with kaposiform hemangioendothelioma have platelet counts in the range of 3 to 60,000/mm^3 due to platelet trapping within the tumor. There can also be red cell sequestration within the tumor. The peripheral blood smear does not show microangiopathic hemolytic changes. Severe hemorrhage is uncommon, and chronic low platelet levels are generally well tolerated. Tumors can regress with time.

Anesthetic Considerations: Assess platelet count and tests of coagulation preoperatively. Surgical resection can result in large amounts of blood loss. Transarterial embolization has been used successfully. Patients may need perioperative red blood cell, platelet, or fresh frozen plasma transfusions. Recombinant activated factor VII has been suggested if needed. Transfused platelets have a shortened half-life of 1 to 24 hours due to consumption within the tumor. Tumor size can increase after platelet transfusion. Patients may have been treated with vincristine, ticlopidine, steroids, or interferon-α. Patients on chronic steroids will require perioperative stress dosing. Drugs that inhibit platelet function should be avoided. Tumors can uncommonly involve the spine. These should be excluded radiographically prior to epidural or subarachnoid anesthesia.

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Kaufman-McKusick syndrome

See McKusick-Kaufman syndrome

Kearns-Sayre syndrome

Synonym: Ophthalmoplegia plus

MIM #: 530000

This sporadically occurring, but occasionally familial, mitochondrial myopathy is characterized by progressive external ophthalmoplegia, pigmented retinal degeneration, and atrioventricular conduction defects. Onset is before 20 years of age, usually in the preteen years. Light microscopy of the muscle often shows “ragged red” fibers, which represent abnormal, enlarged mitochondria and excess lipid. A deletion in the mitochondrial genome has been documented in many, but not all, patients, and the disorder can be due

to abnormalities in mitochondrial leucine tRNA. The deletion in the mitochondrial genome tends to be found in muscle and central nervous system tissue. The spectrum of disease is determined by the relative amounts and distribution of mutant versus regular mitochondrial DNA. The same deletion, but with different organ distribution, is found in Pearson syndrome (see later).

HEENT/Airway: Abnormal retinal pigmentation associated with external ophthalmoplegia, ptosis, progressive visual loss. Sensorineural hearing loss. Weakness can involve the pharyngeal muscles.

Chest: There can be a depressed respiratory drive.

Cardiovascular: Heart block (second- or third-degree atrioventricular block, bundle branch block, or fascicular block) usually in the third decade of life, often presenting as Stokes-Adams attacks or sudden death. Often starts with left anterior fascicular block, but progression to complete heart block can be rapid. Prolonged QT with potential development of *torsade de pointes*. Congestive cardiomyopathy can develop.

Neuromuscular: Can have cerebellar dysfunction with ataxia. Can have cranial nerve involvement. Can have weakness of bulbar and limb girdle muscles. Myopathy with proximal limb weakness. Seizures, dementia.

GI/GU: Fanconi syndrome (see earlier) can develop.

Orthopedic: Short stature. Kyphoscoliosis or scoliosis. Pes cavus.

Other: Hirsutism. Decreased 17-ketosteroid and 11-hydroxycorticoid excretion. Can have multiple endocrinopathies. A variety of defects in the respiratory chain and oxidative phosphorylation result in elevated serum lactate during exercise. Hyperglycemia and fatal hyperosmolar coma have been reported after steroid therapy.

Anesthetic Considerations: Stress, such as seen with surgery or infection, can increase the demand for adenosine triphosphate production to levels above which the patient can produce. Acidosis should be corrected preoperatively if possible. Patients with excessive lactic acidemia should not receive Ringer's lactate. Bulbar involvement and weakness of the pharyngeal muscles increase the perioperative aspiration risk. Postoperative clinical deterioration has been reported (5). Postoperative mechanical ventilation might be required.

Second- or third-degree atrioventricular block, bundle branch block, or fascicular block are common. Baseline EKG should be evaluated for conduction defects. Sudden third-degree block can occur and a temporary pacemaker should be available. An indwelling pacemaker should be interrogated if not done recently. Patients can have a cardiomyopathy.

Patients with Kearns-Sayre syndrome may be particularly sensitive to induction agents. It is reasonable to avoid succinylcholine in patients with a significant myopathy because of the risk of an exaggerated hyperkalemic response. Patients with mitochondrial myopathies may be more sensitive to mivacurium (6), curare (11), rocuronium (4), atracurium (4), and succinylcholine, although one report did not find increased sensitivity to succinylcholine or pancuronium (12). Nondepolarizing neuromuscular blockers should be given incrementally and with appropriate monitoring, if required at all. Opioids or other drugs inhibiting respiratory drive should be used with caution because increased central responsiveness has been suggested. There is no relationship between the mitochondrial myopathies and malignant hyperthermia. Because of its mitochondrial depressant effects, it may be

judicious to avoid anything more than short-term use of propofol in these patients for fear of triggering the propofol infusion syndrome.

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Kelley-Seegmiller syndrome

Included in Lesch-Nyhan syndrome

Kenny syndrome

Synonym: Kenny-Caffey syndrome

MIM #: 127000, 244460

Both autosomal dominant and autosomal recessive forms of this syndrome exist. The autosomal recessive form is due to mutations in the gene *TBCE*, which encodes tubulin-specific chaperone E. Chaperones are a group of proteins that aid in proper protein folding. This syndrome is distinguished by osteosclerosis and proportional dwarfism (prenatal and postnatal). It occurs mostly in Middle Eastern populations. Sanjad-Sakati syndrome (see later) is also due to mutations in this gene but lacks the osteosclerosis. It is similarly found primarily in Middle Eastern populations.

HEENT/Airway: Macrocephaly, delayed closure of the anterior fontanelle, absence of the diploic space of the skull. Dysmorphic ("birdlike") facies. Ophthalmologic abnormalities with hypertelorism, hyperopia, microphthalmia, corneal and retinal calcifications, papilledema, glaucoma, and cataracts. Mandibular hypoplasia. Dental caries and dental anomalies.

Chest: Long thin clavicles and ribs. There is a single case report of the Mounier-Kuhn syndrome (tracheobronchomegaly and communicating paratracheal cysts) in an adult patient with Kenny syndrome.

Neuromuscular: Normal intelligence. Hypocalcemic seizures. Calcification of the basal ganglia.

GI/GU: May have microorchidism and reduced fertility.

Orthopedic: Proportional dwarfism of prenatal onset. Delayed bone age, cortical thickening of the tubular bones (osteosclerosis).

Other: Episodic hypocalcemia, which can be symptomatic, presumably due to transient hypoparathyroidism. Hypophosphatemia, low calcitonin levels. Anemia.

Miscellaneous: First described by Kenny. Caffey, a famous name in pediatric radiology, described the radiologic features a year later.

Anesthetic Considerations: Serum calcium, phosphorus, and hematocrit should be evaluated and may need to be corrected preoperatively. Avoid increased intraocular pressure if glaucoma is present. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. Mandibular hypoplasia may make direct laryngoscopy and tracheal intubation difficult. A laryngeal mask has been used successfully (1).

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Kenny-Caffey syndrome

See Kenny syndrome

Ketotic hyperglycinemia

See Propionic acidemia

KID syndrome

See Senter syndrome

King syndrome

Synonym: King-Denborough syndrome

MIM #: 145600

This genetically heterogeneous syndrome is characterized by Noonan-like features (see Noonan syndrome, later), congenital myopathy, and susceptibility to malignant hyperthermia. Unlike true Noonan syndrome, there is no increased incidence of congenital heart disease, webbed neck, or intellectual disabilities. Most reported cases are sporadic, but an autosomal dominant mode of inheritance is possible. It has been suggested that King syndrome represents a phenotype that can result from several different slowly progressive congenital myopathies (7,8) and may simply be a synonym for malignant hyperthermia susceptibility (see later). A variety of mutations in the gene *RYR1* encoding the ryanodine receptor have been reported in patients with this syndrome.

HEENT/Airway: Unusual facies, suggestive of Noonan syndrome—ptosis, strabismus, low-set ears, malar hypoplasia, cleft or high-arched palate, crowded teeth. No hypertelorism or epicanthal folds as seen in Noonan syndrome. May have mild micrognathia. No webbed neck as seen in Noonan syndrome.

Chest: Pectus carinatum or excavatum. May have thoracic kyphoscoliosis. May have restrictive lung disease. Progressive myopathy may lead to respiratory failure. May have diaphragmatic eventration.

Cardiovascular: No cardiac defects characteristic of Noonan syndrome. One report of dilated ventricles, aorta, and pulmonary artery.

Neuromuscular: Congenital myopathy, which is slowly progressive. May have mild intellectual disabilities. May have tethered spinal cord.

Orthopedic: Short stature. May have kyphoscoliosis, lumbar lordosis. Shoulder and patellar dislocation. Pes cavus.

GI/GU: Cryptorchidism.

Other: Susceptible to the development of malignant hyperthermia. May have elevated creatine kinase. No coagulation abnormalities as seen in Noonan syndrome. Fatal rhabdomyolysis after a viral infection has been reported.

Anesthetic Considerations: Patients are susceptible to the development of malignant hyperthermia and must receive a nontriggering general anesthetic, neuraxial block, or peripheral nerve block. (For more information, see malignant hyperthermia susceptibility, later). Succinylcholine is contraindicated in these patients with slowly progressive myopathy because of the risk of an exaggerated hyperkalemic response. Patients with advanced

myopathy are at risk for perioperative respiratory compromise. Epidural analgesia has been utilized successfully for labor.

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King-Denborough syndrome

See King syndrome

Kinky hair syndrome

See Menkes kinky hair syndrome

Kleeblattschaedel

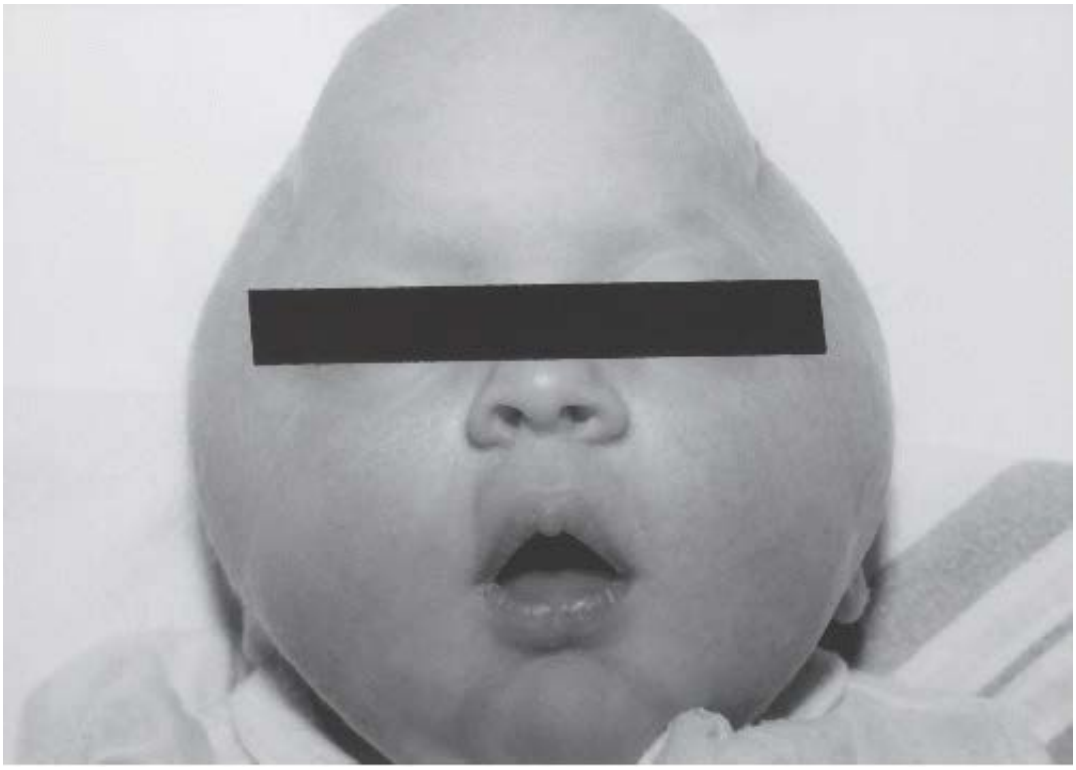
Synonym: Cloverleaf skull. (Includes scaphocephaly, dolichocephaly, brachycephaly, plagiocephaly, acrocephaly, turricephaly, trigonocephaly, and bathrocephaly)

MIM #: 148800

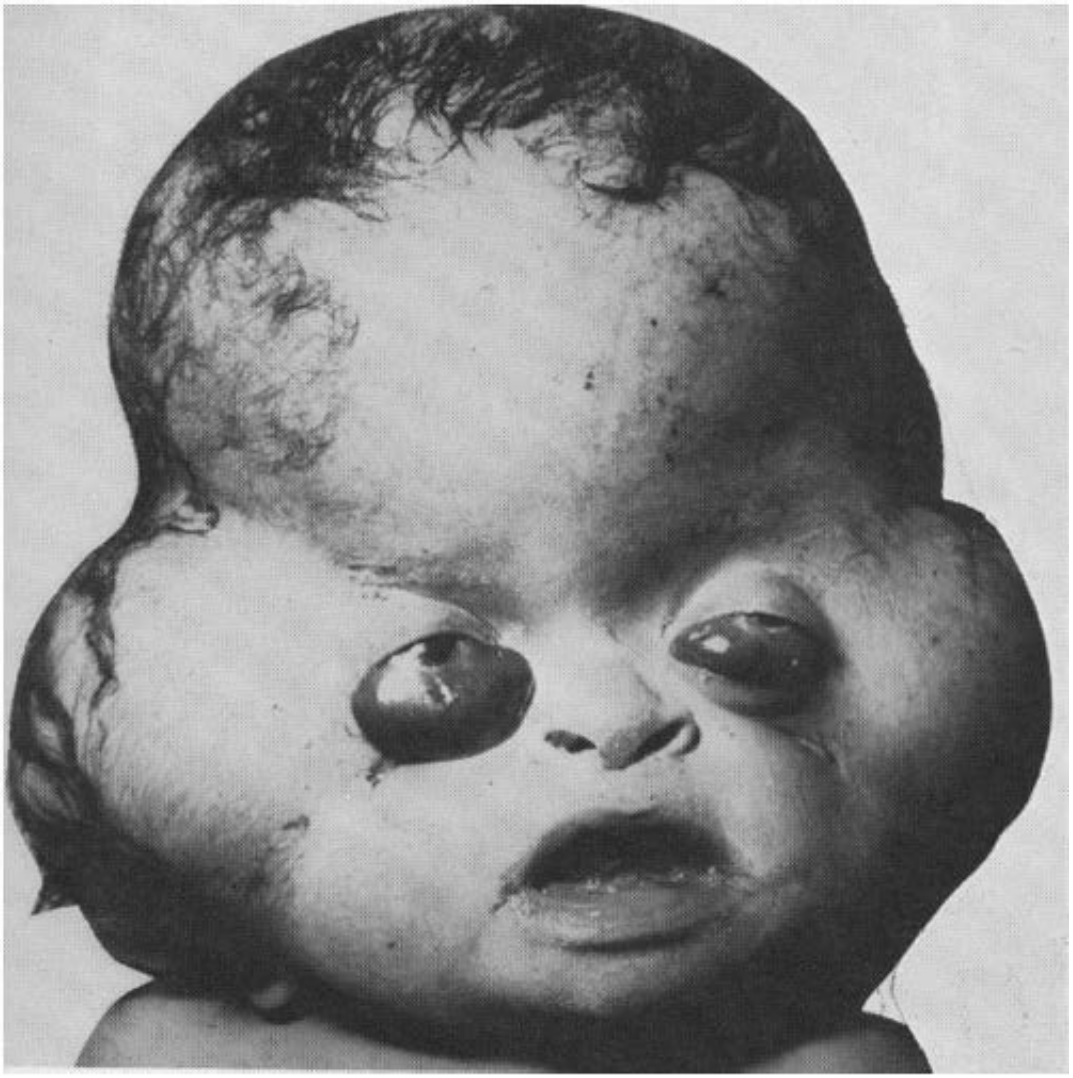
This deformity of the skull can occur in isolation or as part of a larger dysmorphic complex such as Carpenter, Crouzon, or Pfeiffer syndrome. It is due to congenital craniosynostosis (the premature closure of a skull suture) of multiple cranial sutures combined with hydrocephalus and results in a pattern of vertical and inferolateral skull growth, resulting in a cloverleaf-shaped (trilobular) skull. Although a single family with apparent autosomal dominant transmission has been described, the entity appears to be sporadic. Children require extensive craniofacial surgery and may require multiple surgeries.

There are many patterns of craniosynostosis. All of the craniosynostoses can occur in isolation or as part of a syndrome complex. Sagittal synostosis prevents lateral skull growth, resulting in **scaphocephaly** (boat-shaped cranium) or **dolichocephaly** (long, narrow cranium). This can be seen in association with Marfan syndrome, Russell-Silver syndrome, and trisomy 18. Coronal synostosis prevents anteroposterior skull growth, resulting in **brachycephaly** (broad cranium). This can be seen in association with Down syndrome

and Zellweger syndrome. Unilateral coronal synostosis results in **plagiocephaly** (slanted cranium). Coronal and lambdoid synostosis results in **acrocephaly** or **turricephaly**, where the cranium is pointed or tower shaped. This pattern is seen with the acrocephalosyndactyly syndromes. Metopic synostosis results in **trigonocephaly** (triangular cranium). Trigonocephaly can be associated with some of the chromosomal deletion syndromes and with C syndrome. Excessive bone formation at the lambdoid suture causes a steplike posterior projection of the skull, called **bathrocephaly** (step cranium).



Kleeblattschaedel. FIG. 1. An infant with kleeblattschaedel deformity of the skull. (Courtesy of Dr. K. Lin and the Craniofacial Anomalies Clinic, University of Virginia Health System.)



Kleeblattschaedel. FIG. 2. A second infant with somewhat more severe disease, although the similarities are apparent. (Courtesy of Dr. Robert Holzman, Boston Children's Hospital.)

HEENT/Airway: Craniosynostosis of the coronal and lambdoid sutures results in cloverleaf (trilobular) skull. Can have severe exophthalmos. Can have other facial anomalies.

Neuromuscular: Hydrocephalus. Otherwise, there is rarely an abnormality of the central nervous system.

Orthopedic: Ankylosis of the elbow. Can have long bone anomalies.

Anesthetic Considerations: Precautions against increased intracranial pressure need to be taken in patients with significant hydrocephalus. Patients with exophthalmos need meticulous perioperative eye care to avoid corneal abrasions. Patients with associated syndromes may have anesthetic implications specific to that syndrome. Surgical correction may entail excessive blood loss.

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Klein-Waardenburg syndrome

Included in Waardenburg syndrome

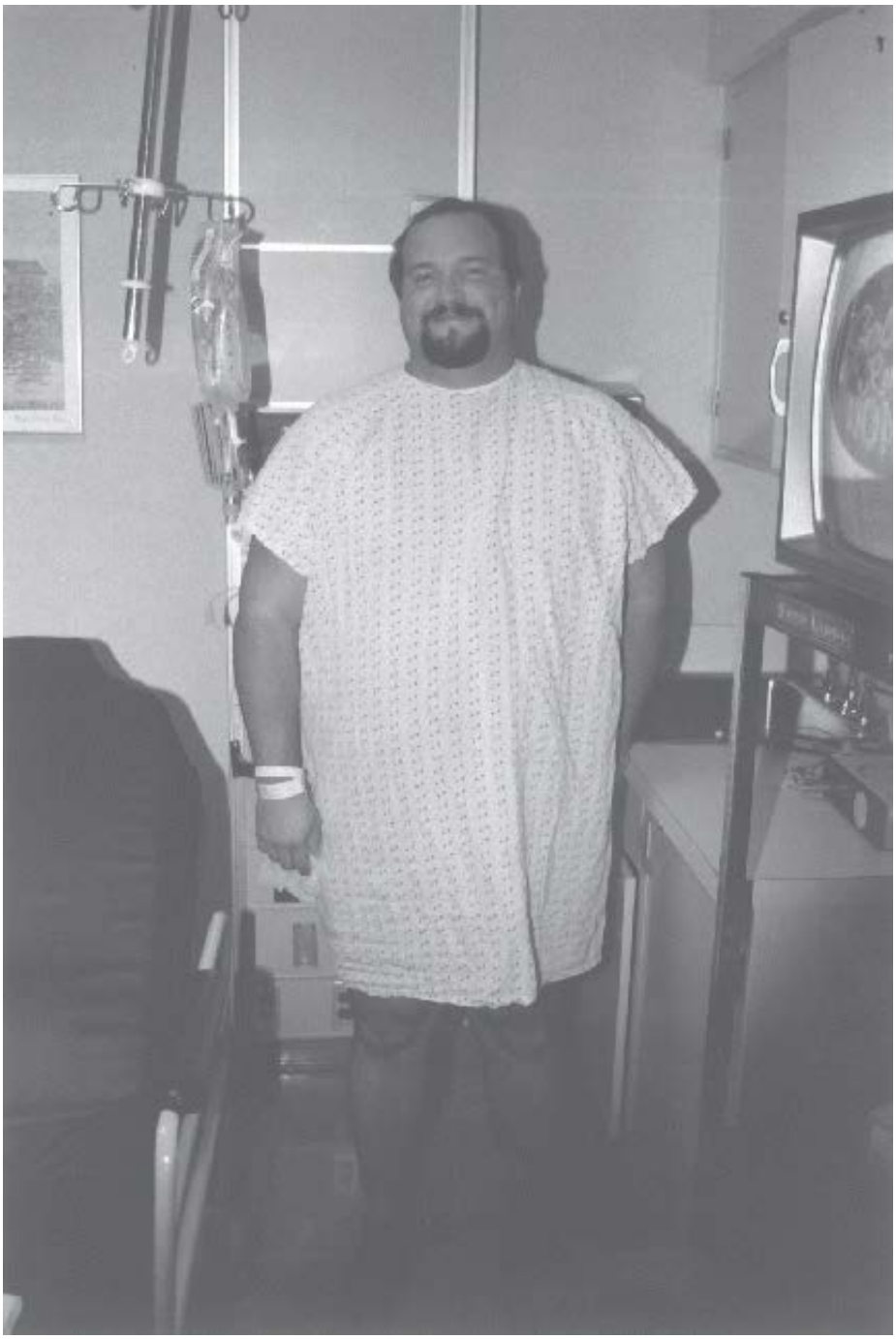
Klinefelter syndrome

Synonym: XXY syndrome. (Includes XXXY, XXXXY, and XXYY syndromes)

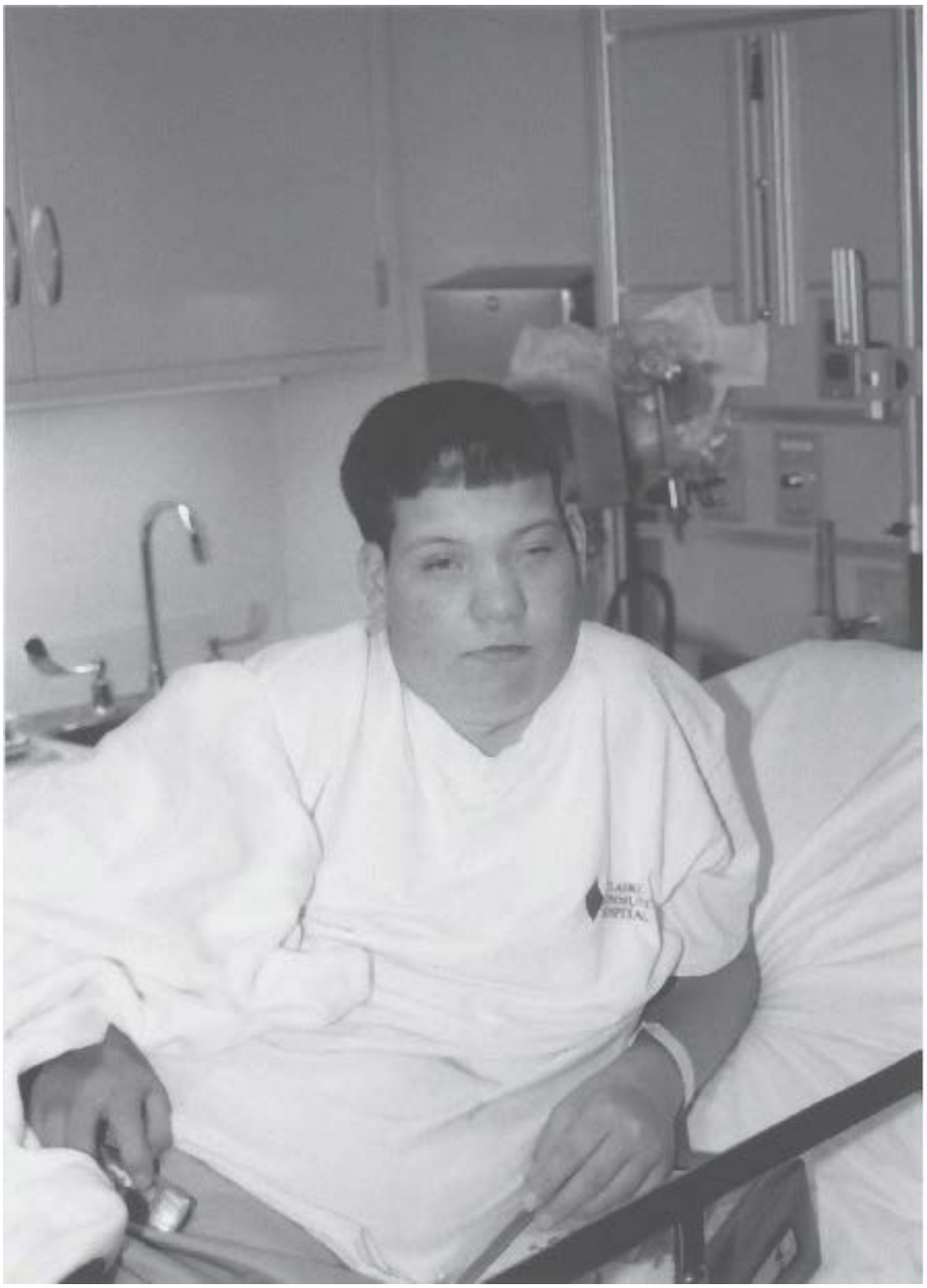
MIM #: None

Klinefelter syndrome is an anomaly of the sex chromosomes in which the patient has a 47, XXY karyotype. Klinefelter syndrome is the most common cause of male hypogonadism and infertility. Affected individuals are also often mildly intellectually impaired and

may exhibit behavioral problems. There is significant phenotypic variability. Karyotypes **XXXY**, **XXXXY**, and **XXYY** exhibit features of Klinefelter syndrome to varying degrees, and so are included here. XXXY, XXXXY, and XXYY patients are more likely to be intellectually impaired than XXY patients. XXXY patients can also have growth deficiency, radioulnar synostosis at the elbow, and congenital heart disease.



Klinefelter syndrome. FIG. 1. This married 36-year-old man receives chronic testosterone injections. He has had liposuction for gynecomastia and later developed breast cancer.



Klinefelter syndrome. FIG. 2. This teenager with XXXXY syndrome became physically violent in the preoperative holding area and refused oral premedication. After a long talk with him, induction of anesthesia was uneventful.

Chest: Chronic bronchitis is relatively common.

Cardiovascular: XXXY patients can have congenital heart disease.

Neuromuscular: Most have mild intellectual disabilities (especially the XXXY, XXXXY, and XXYY variants). Verbal performance is usually close to or within the normal range. Patients frequently exhibit behavioral problems,

including aggressive behavior, poor judgment, and boastfulness. Can have an intention tremor.

Orthopedic: Relatively tall, slim stature, with long extremities (from androgen deficiency). Osteoporosis. Scoliosis can develop during adolescence. Clinodactyly. XXXY patients can be short and have radioulnar synostosis at the elbow. XXXXY boys have a high incidence of musculoskeletal abnormalities.

GI/GU: Hypogenitalism and hypogonadism (small penis and testes, inadequate testosterone production, inadequate virilization) appear at the time of puberty. Testicular failure results in elevated gonadotropin levels. Infertility. Can have cryptorchidism, hypospadias. Infertility due to sclerosed seminiferous tubules.

Other: Gynecomastia. Extragonadal malignant germ cell tumors, and increased incidence of breast cancer. Increased risk for development of diabetes mellitus. Can have autoimmune diseases. Despite the relatively benign clinical implications, approximately half of all cases are lost prenatally. Sparse body hair.

Anesthetic Considerations: Behavioral problems may make the smooth induction of anesthesia difficult. Patients may require a lot of preoperative effort and attention, and may benefit from premedication. Older patients may have diabetes mellitus. Some patients may have limited spine mobility from scoliosis.

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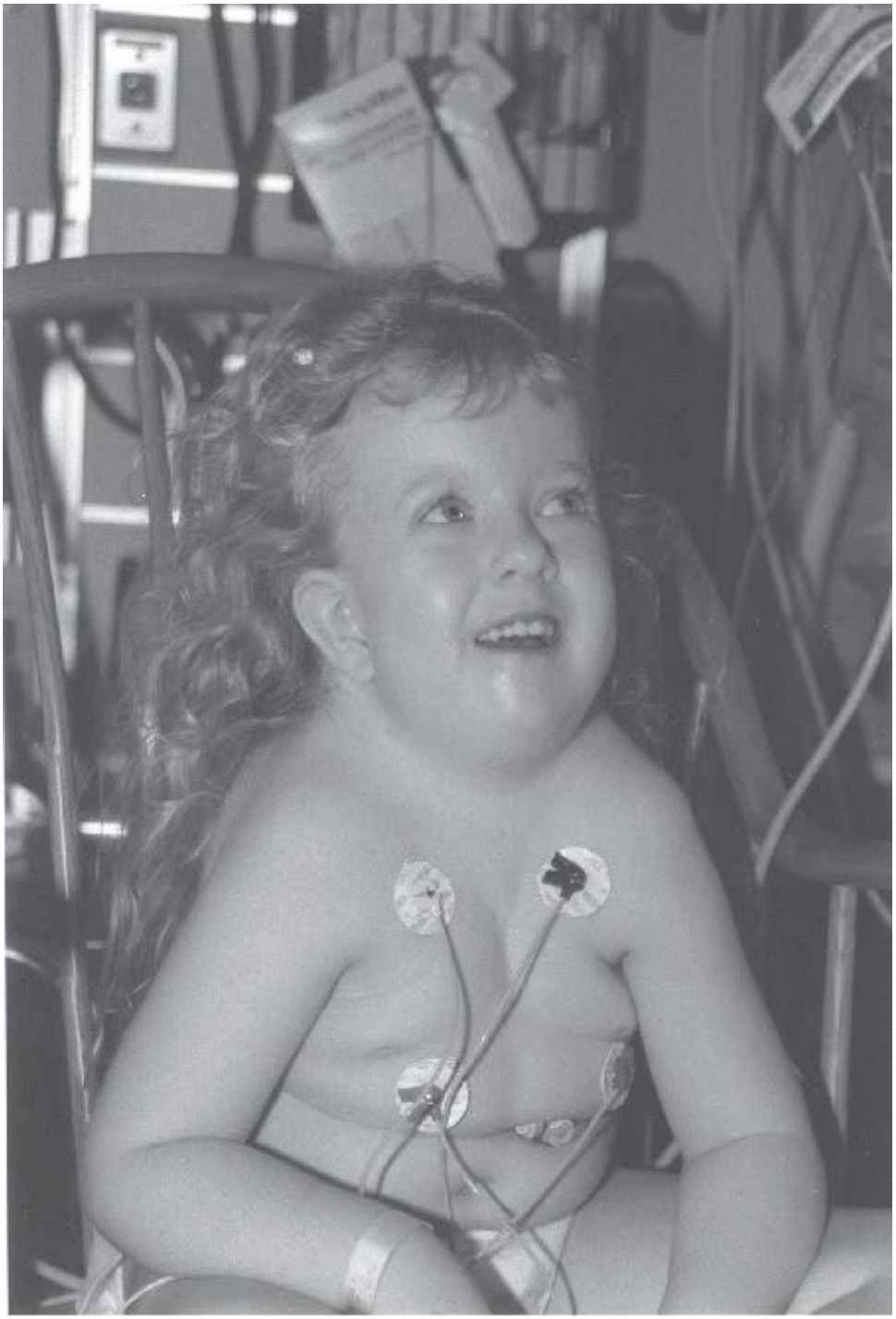
Klippel-Feil sequence

MIM #: 118100

This sometimes autosomal dominant but usually sporadically occurring disorder is characterized by a short neck, a low posterior hairline, and limited mobility of the cervical spine. It has been suggested that Klippel-Feil sequence, Moebius sequence, and Poland sequence (see later for both), all of which can occur in various combinations in the same patient, might represent anomalies from the intrauterine disruption of the subclavian or vertebral arteries, or one of their branches. Therefore, some advocate calling these the subclavian artery supply disruption syndromes. It has also been suggested that this is a defect of embryonic postotic neural crest cells. Mutations in several genes can result in the syndrome, most commonly in the gene *GDF6*. Three (or four) types have been described depending on the location and extent of spinal fusions and the presence or absence of sacral agenesis.



Klippel-Feil sequence. This young girl with Klippel-Feil sequence required home oxygen for obstructive sleep apnea and required a tonsillectomy. She has profound sensorineural hearing loss and absent neck flexion or extension. At age 4 years, laryngoscopy and intubation were reported as only moderately difficult.

HEENT/Airway: Skull malformations can occur. May have facial asymmetry. Low posterior hairline. Can have sensorineural or conductive hearing loss. Can have cleft lip. Can have primary and permanent oligodontia. Can have micrognathia. Short, webbed neck. Torticollis. Malformed laryngeal cartilage with voice abnormalities can

occur.

Chest: Thoracic outlet syndrome has been reported.

Cardiovascular: Can have a congenital cardiac anomaly, particularly ventricular septal defect.

Neuromuscular: Hypermobility (though less common than limited mobility) of the upper cervical spine can be associated with neurologic impairment. Neurologic sequelae include paraplegia, hemiplegia, cranial or cervical nerve palsies. Syncope has been induced by sudden neck rotation. Can be associated with neural tube defects or sacral agenesis. May have posterior fossa dermoid cysts. A child with vertebral artery dissection has been reported.

Orthopedic: Limited mobility of the cervical spine secondary to vertebral fusion, hemivertebrae, or other vertebral defects. Atlantooccipital fusion. Increased susceptibility to cervical osteoarthritis and trauma. Scoliosis. May have winged scapulae (Sprengel deformity). Can have thoracic or lumbar vertebral anomalies. Can have sacral agenesis. It is thought that patients with hypermobility of the upper cervical spine are at risk for neurologic sequelae, whereas those with limited mobility in the lower cervical spine are more at risk for development of degenerative disease (8).

GI/GU: Genitourinary or renal anomalies.

Miscellaneous: Maurice Klippel was described in his obituary as a “philosopher, poet, historian, and one of the most prominent masters of French medicine.” His report apparently followed the first description of the syndrome by 169 years.

Anesthetic Considerations: A short neck and limited mobility of the cervical spine makes laryngoscopy and intubation extremely difficult. Since cervical fusion is progressive, a previous uncomplicated tracheal intubation does not assure repeated easy success (5). An unstable cervical spine raises the possibility of neurologic insult with head manipulation and positioning. Consider preoperative lateral flexion-extension radiographs of the cervical spine to identify patients with cervical spine instability. The laryngeal mask airway (LMA) has been used successfully (4) as have the newer fiberoptic laryngoscopes. However, these can still exert significant force on the cervical spine, and one failure has been reported in an adult. Strongly consider fiberoptic intubation as an alternative to direct laryngoscopy because it requires significantly less head manipulation, an awake intubation in cooperative older children and adults, or following an inhalation induction with maintenance of spontaneous ventilation in others. Access to the central veins via the neck veins or subclavian veins may be problematic. High lumbar or thoracic epidural access should not be exceptionally problematic (6). Although an attractive option, lumbar epidural or subarachnoid anesthesia may be difficult in the face of scoliosis. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Klippel-Trenaunay syndrome

See Klippel-Trenaunay-Weber syndrome

Klippel-Trenaunay-Weber syndrome

Synonym: Klippel-Trenaunay syndrome

MIM #: 149000

This syndrome involves asymmetric extremity hypertrophy and various vascular abnormalities, including varicose veins, hemangiomas, arteriovenous fistulae, and phlebectasia. The syndrome occurs sporadically. At least some cases are due to mutations in the gene *VG5Q*, which encodes an angiogenic factor. Clinically, this syndrome often resembles Sturge-Weber syndrome (see later).

HEENT/Airway: Asymmetric facial hypertrophy. Can have microcephaly or macrocephaly. Glaucoma, cataracts, Marcus Gunn pupil.

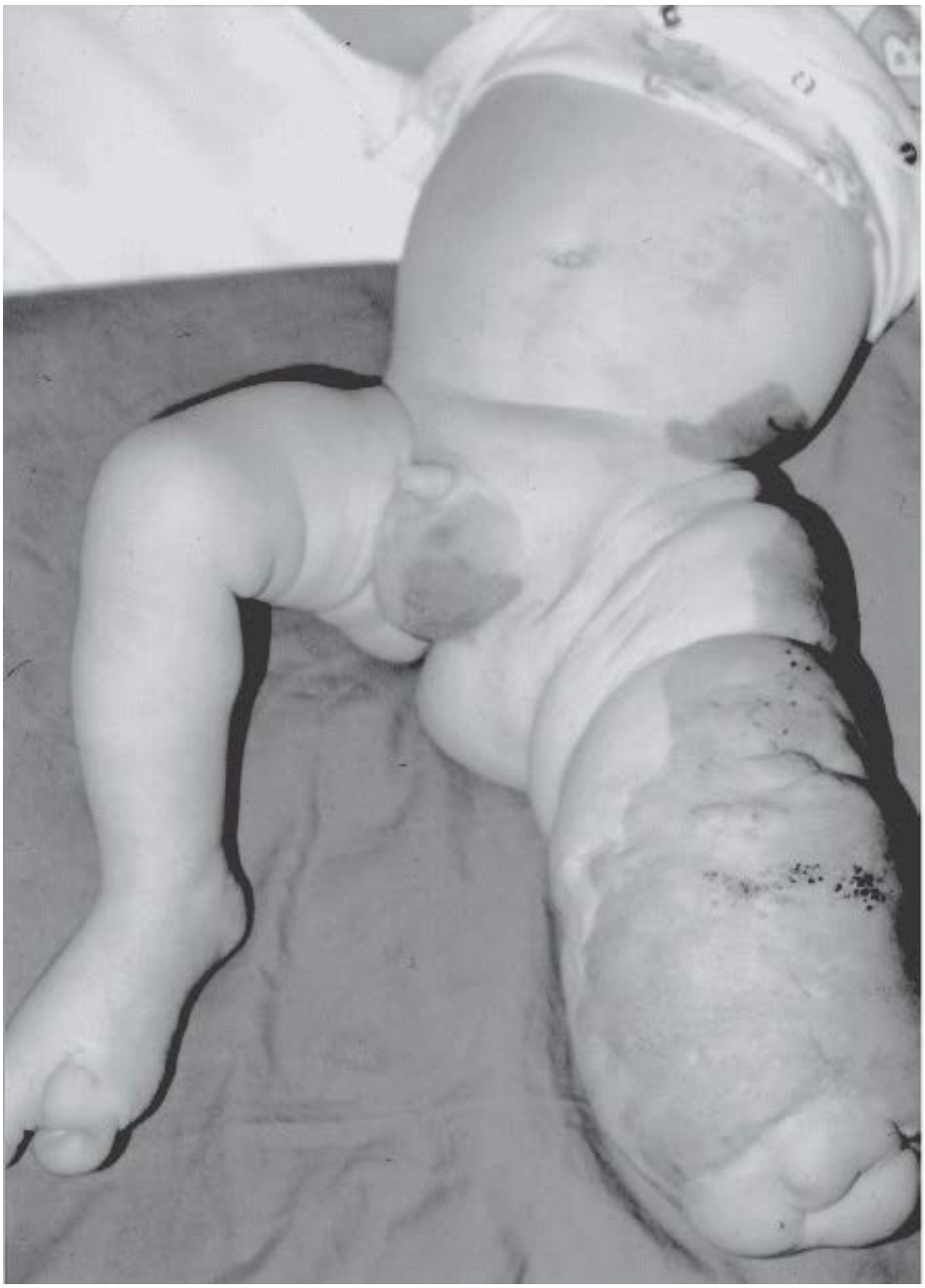
Chest: Pectus excavatum. Intrathoracic hematomas, pleural hemangiomas. Risk of pulmonary thromboembolism from the deep venous malformations.

Cardiovascular: Rarely, large arteriovenous fistulae lead to high-output congestive heart failure. Postural hypotension can occur with filling of a massively dilated venous bed. Inferior vena cava may be absent.

Neuromuscular: Epidural hemangiomas, which can bleed. Spinal cord arteriovenous malformations, which can rupture. Bleeding can be spontaneous. Intracranial hemangiomas or calcifications. Patients with facial hemangiomas can have seizures or intellectual disabilities. Otherwise, intelligence is normal. Central nervous system and cutaneous manifestations often occur in the same dermatome.

Orthopedic: Asymmetric extremity hypertrophy— can be bony and soft tissue hypertrophy or massive enlargement from vascular lesions. The latter may require amputation. Bone hypertrophy appears postnatally. The most

common site for involvement is the leg. Digits can be large or small, and there can be polydactyly. Can have kyphoscoliosis. Arthritis may develop.



Klippel-Trenaunay-Weber syndrome. Severely involved lower extremity in a young child with Klippel-Trenaunay-Weber syndrome. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

GI/GU: Visceral or pelvic hemangiomas. Rupture of hemangiomas can cause gastrointestinal or urinary tract bleeding or menorrhagia. Massive splenomegaly has been reported.

Other: Vascular abnormalities occur most commonly in the legs, buttocks, and abdomen. Vascular abnormalities are also usually asymmetric. Increased risk of chronic disseminated intravascular coagulation (Kasabach-Merritt syndrome, see earlier). Consumptive coagulopathy has been treated with rivaroxaban. Thrombophlebitis. Recurrent cellulitis in about one-quarter of patients. Cutis marmorata. Embolization of problematic varicosities can improve symptoms.

Miscellaneous: Weber described the occurrence of arteriovenous fistulae with this syndrome, and sometimes the name Klippel-Trenaunay-Weber syndrome is used when arteriovenous fistulae are a feature of the syndrome, whereas Klippel-Trenaunay syndrome is used when arteriovenous fistulae are not present.

Maurice Klippel was described in his obituary as a “philosopher, poet, historian, and one of the most prominent masters of French medicine.” F. Parkes Weber was a British physician who had an interest in rare disorders and uncommon syndromes. Weber's father came from Germany to Britain (where he became physician to Queen Victoria), and Weber continued to pronounce his last name with the “W” pronounced as the Germanic “V.” He had an encyclopedic knowledge of rare disorders. It is said that when, at a meeting of the Royal Society of Medicine, he first announced that he had not heard of a certain syndrome, such cheers and applause broke out from the audience that the meeting had to be abandoned. He wrote a total of 1200 medical papers.

Anesthetic Considerations: Expanding hemangiomas can result in Kasabach-Merritt syndrome (see earlier), with thrombocytopenia and consumptive coagulopathy. Surgical injury to hemangiomas or fistulae can result in excessive intraoperative bleeding and may not be completely controlled by a tourniquet. Bleeding can occur with abdominal as well as orthopedic surgery. Blood for intraoperative transfusion should be available. These vessels also have abnormal autoregulation, so perioperative blood pressure must be conscientiously controlled, and coughing, straining, or vomiting should be avoided if possible. Defasciculation prior to succinylcholine administration and deep extubation would seem appropriate in these patients. Similarly, straining and a Valsalva during the second stage of a vaginal delivery is a time of higher risk. Postoperative pulmonary embolism can occur.

Because of the risk of bleeding from epidural hemangiomas and spinal cord arteriovenous malformations, regional anesthesia is relatively contraindicated. However, it has been undertaken after magnetic resonance imaging evaluation of the lumbosacral spine and back. Consumptive coagulopathy should be excluded prior to attempting regional techniques. One patient experienced severe pain in an affected leg coincident with the onset of the sympathectomy following epidural anesthesia, which resolved with the onset of the sensory blockade (4).

Although potentially possible (2), difficult laryngoscopy and intubation have not generally been a problem (1). Limb involvement can limit peripheral venous access. Excessive venous pulsations can result in erroneously low pulse oximetry readings if the probe is placed on an affected limb. Peripheral nerve stimulators should not be placed on an involved extremity. Cardiac function should be evaluated preoperatively for evidence of high-output failure. Excision of veins for coronary artery bypass grafting should be avoided in favor of arterial conduits if at all possible. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Kniest dysplasia

See Kniest syndrome

Kniest syndrome

Synonym: Kniest dysplasia; metatropic dysplasia, type II; pseudometatrophic dysplasia

MIM #: 156550

This autosomal dominant disorder is characterized by progressive short trunk dwarfism, short limbs, flat facies, and limited joint mobility. The clinical features are similar to metatropic dwarfism (see later), except that inheritance is autosomal dominant. Kniest syndrome is caused by a mutation in the *COL2A1* gene, which leads to abnormal type II collagen. Abnormal type II collagen leads to soft cartilage that has a “Swiss cheese” appearance on microscopic examination, secondary to multiple lacunae. Mutations in the *COL2A1* gene are also responsible for achondrogenesis, spondyloepiphyseal dysplasia congenita, and Stickler syndrome.

HEENT/Airway: Macrocephaly. Flat facies. Prominent eyes, myopia, cataracts, vitreoretinal degeneration, retinal detachment. Flat nasal bridge. Cleft palate. Recurrent otitis media related to cleft palate can cause hearing loss. Can have micrognathia. Tracheomalacia.

Chest: Increased anteroposterior diameter of the chest.

Neuromuscular: Intelligence is normal.

Orthopedic: Short stature. Short trunk secondary to marked lumbar lordosis and kyphoscoliosis. Atlantooccipital instability. Short limbs. Limited joint mobility. Flexion contractures of major joints. Premature arthritis. Small pelvis.

GI/GU: Umbilical hernia, inguinal hernias.

Miscellaneous: Described by Kniest when he was a chief resident in pediatrics.

Anesthetic Considerations: Recall that despite the child-size stature, patients have intelligence that is normal for their chronologic age. Tracheomalacia may be severe enough to cause perioperative respiratory distress. Patients must be carefully positioned and padded secondary to limited joint mobility. There are as of yet no reports of cervical spine injury during laryngoscopy in patients with atlantooccipital instability.

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Kohlmeier-Degos disease

See Malignant atrophic papulosis

Kok disease

See Stiff-baby syndrome

Kostmann disease

MIM #: 202700

This autosomal recessive neonatal immune deficiency syndrome is marked by neutropenia. This is a genetically heterogeneous disorder. In about two-thirds of patients, the disorder is due to mutations in the neutrophil elastase gene (*ELANE*). Cyclic neutropenia (see earlier) is an allelic disorder. Another common defect is in the gene *HAX1*, which encodes the mitochondrial protein HAX-1. The bone marrow shows normal granulocyte precursors, and the disease is thought to be due to arrested neutrophil development. Death often occurs during infancy. Treatment is with granulocyte colony-stimulating factor (G-CSF) or bone marrow transplantation. Myelodysplastic syndrome or acute myelogenous leukemia can develop and might be associated with chronic G-CSF.

HEENT/Airway: Otitis media. Periodontal disease. Oral ulcers.

Chest: Upper and lower respiratory tract infections. Pneumonia.

Orthopedic: Bone pain and atypical fractures maybe related to G-CSF.

GI/GU: Mild hepatosplenomegaly. Neonatal omphalitis.

Other: Overwhelming (and fatal) bacterial infections develop during infancy. There can also be eosinophilia and thrombocytosis. Increased risk for acute monocytic leukemia and myelodysplasia.

Anesthetic Considerations: Meticulous aseptic technique and appropriate perioperative antibiotics are imperative.

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Kozlowski spondylometaphyseal dysplasia

See Spondylometaphyseal dysplasia

Krabbe disease

Synonym: Cerebroside lipidosis; galactocerebrosidase deficiency; globoid cell leukodystrophy

MIM #: 245200

All of the leukodystrophies involve defective formation of myelin. This autosomal recessive leukodystrophy is caused by a deficiency of galactocerebrosidase (galactosylceramidase). Galactocerebrosidase splits galactocerebroside into ceramide and galactose. Galactocerebroside is a sphingoglycolipid containing sphingosine, fatty acid, and galactose and is found almost entirely within the myelin sheath. This disease is characterized by loss of myelin and oligodendroglia. It is thought that the accumulation of psychosine, also a metabolic substrate for this enzyme, is responsible for the destruction of the oligodendroglia by inducing apoptosis. Globoid cells (mesodermal macrophages containing undigested galactocerebroside) are seen in the white matter. Because myelination begins just before birth in humans, patients often exhibit a relatively normal neonatal course, which is then followed by deterioration. Most become symptomatic within the first 6 months (infantile type). This disease

is typically devastating and fatal in the first 2 years. However, improved diagnostic techniques have identified older patients with milder disease, and there is a subset of patients with juvenile- and even adult-onset disease, which tend to have less severity and slower progression. Neonatal screening will also identify patients who will have late onset of symptoms. There is no specific therapy. Bone marrow or banked umbilical cord stem cell transplantation has recently been shown to reverse or prevent the central nervous system deterioration, as microglia are derived from hematopoietic stem cells. Survival is markedly improved if transplantation occurs when patients are still asymptomatic, and the outcome of stem cell transplantation has not been effective in symptomatic patients with infantile onset. Intravenous enzyme replacement therapy has been ineffective in delivering adequate amounts of enzyme to the brain. MicroRNA has been suggested as a possible therapeutic approach to down-regulate the toxic exposure of overexpressed gene in hematopoietic cells transfected with a viral vector carrying the normal gene. Overexpression is not problematic in later, differentiated cells.

The other leukodystrophies include adrenoleukodystrophy, metachromatic leukodystrophy, Canavan disease, Pelizaeus-Merzbacher disease, and Alexander disease.

HEENT/Airway: Blindness, slow pupillary reflexes. Protruding ears, hearing loss. Copious oral secretions.

Chest: Respiratory failure eventually develops in most patients.

Neuromuscular: Profound intellectual and motor deterioration. Early hypertonicity. Prominent pyramidal tract

signs. Hemiplegia. Severe demyelination. Peripheral neuropathy. Seizures, choreoathetosis. Irritability, hypersensitivity to external stimuli, and hypertonicity progressing to weakness, hypotonia, and flaccidity. Eventual decerebration, which can on occasion persist for several years.

GI/GU: Increased incidence of gastroesophageal reflux. Recurrent vomiting and feeding difficulty.

Other: Episodic fever.

Miscellaneous: Knud Krabbe was an exceptional Danish neurologist. He spoke Greek by the age of 3 years, and he published his first scientific paper at age 10.

Anesthetic Considerations: Patients are at increased risk for perioperative aspiration because of copious secretions, poor airway tone, and gastroesophageal reflux. Consideration should be given to anticholinergic premedication to dry oral secretions. Careful perioperative positioning and padding is important in these patients with poor nutrition. Chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs, requiring more frequent dosing. Anticonvulsant medications should be continued through the perioperative period. A parenteral form of anticonvulsant medication may need to be substituted while patients are unable to take oral medications. Phenothiazines, butyrophenones, and other dopaminergic blockers should be avoided because they can exacerbate movement disorders. Ondansetron may be an appropriate antiemetic because it does not have antidopaminergic effects. Increased risk from succinylcholine has not been reported, but it is not unreasonable to avoid it in patients with profound muscle disease. Because of copious oral secretions and airway hypotonia, patients should be observed closely for postoperative ventilatory adequacy.

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Kugelberg-Welander disease

Synonym: Spinal muscular atrophy III; juvenile spinal muscle atrophy

MIM #: 253400, 158600

This usually autosomal recessive disease of the anterior horn cells involves a defect in the gene *SMN1* (survival of motor neuron 1), which appears to have a role in RNA processing. This is the same gene that is responsible for spinal muscular atrophy types I, II, and IV (see later), of which type I, acute Werdnig-Hoffman disease, is the most severe form. The four forms are allelic. An autosomal dominant form of Kugelberg-Welander disease has also been described. This lower motor neuron disease usually has its onset in childhood, with expected survival into adulthood. In fact, life expectancy is normal. Boys are often more severely affected than their female siblings. Kugelberg-Welander disease may initially be misdiagnosed as limb-girdle muscular dystrophy (see later) because muscle weakness and atrophy often begin with the proximal limb muscles.

Chest: Pulmonary function is generally normal but decreased pulmonary function with recurrent respiratory infections. Sleep-disordered breathing.

Cardiovascular: Atrial tachyarrhythmias and atrioventricular block have been occasionally reported in adults.

Neuromuscular: Lower motor neuron disease without sensory loss. Muscle weakness and atrophy beginning with the proximal limb muscles, especially the hip girdle. Later, muscle weakness involves the distal musculature. Onset of weakness can be asymmetric. There can be pseudohypertrophy of the calf muscles (appearing hypertrophied in comparison to the atrophied thigh muscles). Facial and bulbar involvement is rare. The electromyogram shows evidence of denervation and reinnervation, with fibrillations, fasciculations, and large-amplitude polyphasic potentials.

Orthopedic: Kyphoscoliosis and contractures late in the disease.

GI/GU: Can have gastrointestinal reflux.

Miscellaneous: In 1964, Lisa Welander became the first female professor of neurology in Sweden.

Anesthetic Considerations: Succinylcholine is contraindicated in this disease of lower motor neurons because of the risk of exaggerated hyperkalemia. Nondepolarizing muscle relaxants should be used sparingly, if at all, and titrated to effect. Some patients will have gastroesophageal reflux. Patients may require protracted postoperative ventilation. Kyphoscoliosis may make regional techniques difficult, although they are not contraindicated. There is an increased requirement for cesarean section due to weak abdominal wall musculature.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

L

Lacrimoauriculodentodigital syndrome

See Levy-Hollister syndrome

LADD syndrome

See Levy-Hollister syndrome

Landouzy-Dejerine disease

See Facioscapulohumeral muscular dystrophy

Langer mesomelic dysplasia

MIM #: 249700

This syndrome is distinguished by mesomelic dwarfism, aplastic or severely hypoplastic fibulae, and mandibular hypoplasia. This syndrome is the homozygous form of the autosomal dominant disorder known as Leri-Weill dyschondrosteosis (see later). Both are due to a deletion or mutation in the genes *SHOX* or *SHOXY*, and parents with Leri-Weill dyschondrosteosis can have children with Langer mesomelic dysplasia. Although the genes are located on the X chromosome, it is said to be pseudoautosomal (analogous segments of chromosome on both the X and Y chromosomes). Langer mesomelic dysplasia is associated with more severe involvement of the forearms and lower legs and more striking mesomelic dwarfism than is the autosomal dominant form. The homozygous form also has the additional feature of mandibular hypoplasia.

HEENT/Airway: Hypoplastic mandible.

Neuromuscular: Normal intelligence.

Orthopedic: Mesomelic dwarfism. Hypoplastic and bowed radius. Aplastic or severely hypoplastic ulna. Aplastic or severely hypoplastic fibulae. Hypoplastic and bowed tibia. No other skeletal abnormalities.

Anesthetic Considerations: Remember that despite the significant orthopedic disability, patients are of normal intelligence. Direct laryngoscopy and tracheal intubation may be more difficult secondary to mandibular hypoplasia. Severe mesomelic dwarfism makes peripheral intravenous access more difficult.

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Langer-Giedion syndrome

Synonym: Trichorhinophalangeal syndrome, type II

MIM #: 150230

This usually sporadic syndrome is characterized by intellectual disabilities, multiple bony exostoses, cone-shaped epiphyses, characteristic facies with a bulbous nose, and redundant skin in infancy. The facies of Langer-Giedion syndrome resemble those of trichorhinophalangeal syndrome, type I, but the Langer-Giedion syndrome also involves intellectual disabilities, multiple exostoses, and redundant skin. Different-sized deletions on the long arm of chromosome 8 are responsible for both the Langer-Giedion syndrome and the trichorhinophalangeal syndrome, type I. The Langer-Giedion syndrome involves deletion of a greater amount of genetic material, involving functional loss of the genes *TRPS1* and *EXT1*. Rare patients will have *TRPS1* unaffected. Growth hormone has been used selectively but has not shown routine success.

HEENT/Airway: Microcephaly. Deep-set eyes, heavy eyebrows, exotropia, coloboma. Large, protruding ears. Hearing loss. Bulbous nose with broad nasal bridge. Long, prominent philtrum, thin upper lip. Abnormal dentition. Micrognathia. A single patient has been reported with subglottic stenosis (1).

Chest: Recurrent upper respiratory tract infections.

Cardiovascular: May have congenital cardiac defects.

Neuromuscular: Variable intellectual disabilities. Speech delay. Hypotonia in infancy. Electroencephalographic abnormalities or seizures may develop.

Orthopedic: Mild growth deficiency. Multiple bony exostoses, particularly of the long bones. Single report of a large cervical exostotic osteochondroma causing cord compression and quadriparesis. Multiple exostoses affect bone growth and increase the risk of fracture. Cone-shaped epiphyses. Syndactyly. Hypoplastic nails. Winged scapulae. Hyperextensible joints. Vertebral defects. Scoliosis.

GI/GU: May have umbilical hernia, inguinal hernias. May have cryptorchidism, cloacal anomalies. May have ureteral reflux.

Other: Loose, redundant skin in infancy. Fine, sparse scalp hair. Maculopapular nevi on the head, neck, upper trunk, and limbs. May have hypochromic anemia.

Anesthetic Considerations: Consider obtaining a preoperative hematocrit because of the possibility of hypochromic anemia. Recurrent upper respiratory tract infections are common and may lead to cancellation of elective cases. Direct laryngoscopy and endotracheal intubation may be difficult secondary to micrognathia, particularly in infancy. Abnormal dentition may be more easily injured during laryngoscopy. Redundant skin may make intravenous access more difficult. Care must be taken during laryngoscopy, and patients must be carefully positioned and padded perioperatively secondary to hyperextensible joints and the increased risk of bony fracture. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Langer-Saldino achondrogenesis

Included in Achondrogenesis

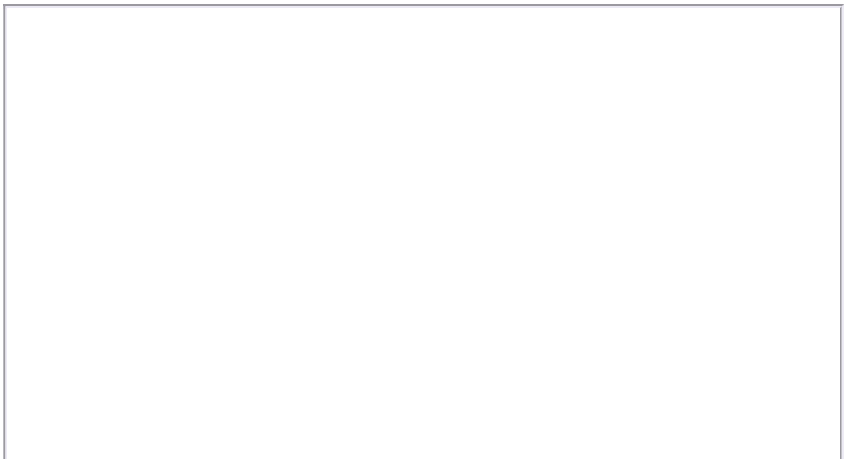
Langerhans cell histiocytosis

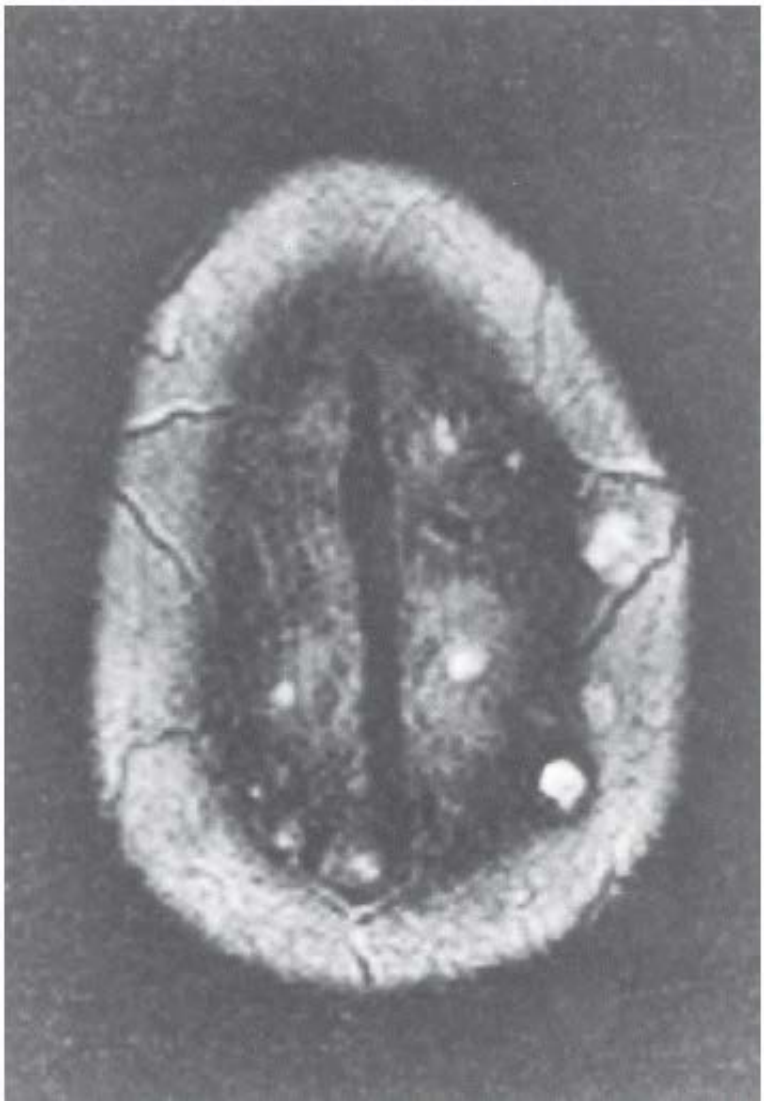
Previously called histiocytosis X. (Includes eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease)

MIM #: 604856

This term includes three entities that were previously included under the designation “Histiocytosis X.” In increasing order of severity, these entities are **eosinophilic granuloma, Hand-Schüller-Christian disease**, and **Letterer-Siwe disease.** They are all caused by a proliferation of a specific type of histiocyte, the Langerhans cell. These are not malignant diseases but rather manifestations of immune dysregulation. The proliferation of these normal cells affects the function of a variety of organs. It is suggested that the disease be characterized specifically by the degree and number of organ systems involved, rather than by the names used previously. Originally, **eosinophilic granuloma** referred to solitary, circumscribed, nonprogressive skull lesions, sometimes associated with eosinophilia.

Hand-Schüller-Christian disease referred to a triad of exophthalmos, bony defects, and diabetes insipidus. **Letterer-Siwe disease** referred to acute disseminated histiocytosis with cutaneous, mucosal, and bony lesions.





Langerhans cell histiocytosis. FIG. 1. Intracranial lesions.

HEENT/Airway: Solitary or multiple circumscribed skull lesions. Orbital lesions may cause proptosis. Hearing loss may develop. Lesions of the mastoid or petrous portion of the temporal bone can lead to chronic ear drainage that mimics chronic draining otitis media. Lesions of the mandible and maxilla can cause displacement, loosening, or loss of teeth.

Chest: Pulmonary involvement with cough, dyspnea, cyanosis, and pleural effusions. Infiltrative nodules, interstitial pneumonitis. Lung cysts, which can rupture and cause a pneumothorax. Respiratory failure in severe cases.

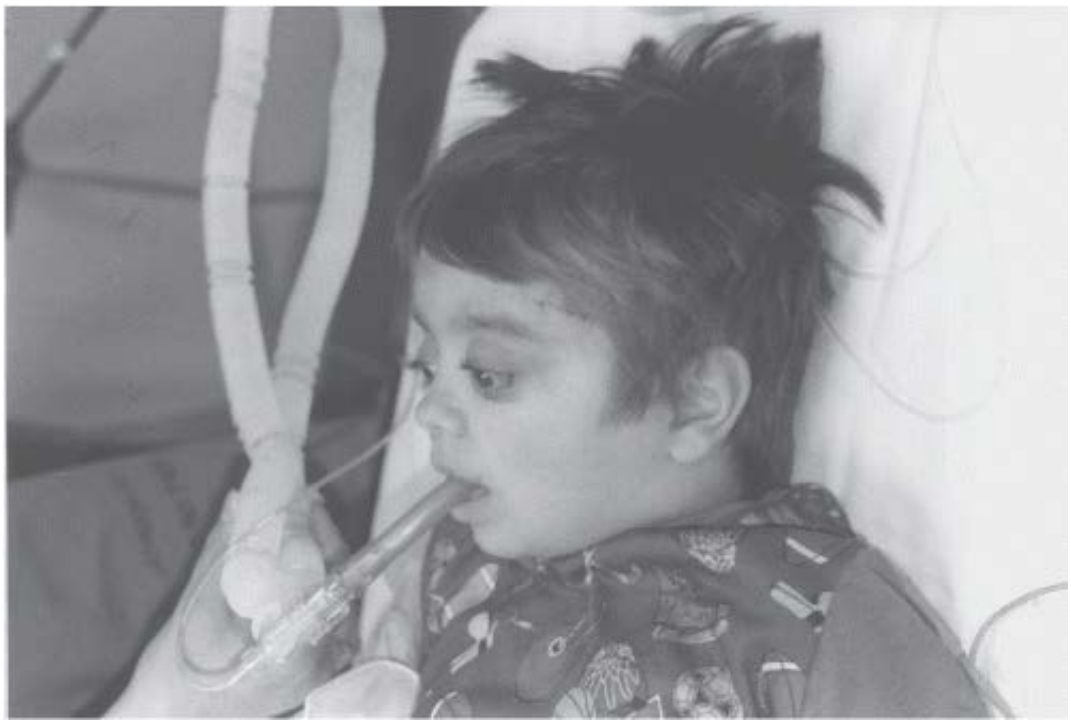
Cardiovascular: Involvement of pericardial fat can result in constrictive pericarditis.

Neuromuscular: Lesions at the base of the skull place pressure on the pituitary, sometimes leading to hypopituitarism. Myalgias. Degenerative CNS lesions.

Orthopedic: Growth retardation. Lesions in a variety of bones, including the femur, pelvis, and vertebral bodies,

with pathologic fractures. Arthralgias.

GI/GU: Hepatic dysfunction with hypoalbuminemia, hyperbilirubinemia, hepatosplenomegaly, and ascites. Pancreatic infiltration. Abdominal pain from mesenteric involvement. Retroperitoneal involvement may affect adrenal function.



Langerhans cell histiocytosis. FIG. 2. This 6-year-old with Langerhans cell histiocytosis has exophthalmos, diabetes insipidus, skull lesions, splenomegaly, and a scaly rash. She also has seizures and temperature instability from hypothalamic involvement.

Other: Lymphadenopathy. Skin rash, which looks like seborrheic dermatitis ("cradle cap"—greasy, scaly, and crusted), and may be tender. Pancytopenia with decreased absolute neutrophil count. Recurrent fever. Infiltration of the thyroid may cause hypothyroidism. May have hypopituitarism—diabetes insipidus, hyperprolactinemia, hypogonadism, panhypopituitarism.

Miscellaneous: The Langerhans cell was described by Paul Langerhans when he was a medical student (1868). Because of its dendritic character, he thought it was part of the nervous system.

Artur Schüller escaped from Vienna in 1938 shortly before the Nazis arrived. His two sons were not so lucky, and ultimately died in concentration camps.

Anesthetic Considerations: Patients should be evaluated preoperatively for evidence of hypopituitarism. Patients who are on steroids should receive perioperative stress doses of steroids. Patients may have pancytopenia, and the hematocrit and the platelet count should be evaluated preoperatively. Dental abnormalities, including the presence of loose teeth, should be evaluated and documented preoperatively. Massive cervical and mediastinal adenopathy has been reported. Low airway pressures or spontaneous ventilation should be maintained

intraoperatively in patients known to have lung cysts. Hepatic dysfunction may affect the binding and metabolism of certain anesthetic drugs. Edema secondary to hypoalbuminemia may make vascular access challenging. Recurrent fevers may be mistaken for postoperative infection.

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Laron dwarfism

MIM #: 262500, 245590

This autosomal recessive dwarfing disorder, due to a mutation in the gene encoding the growth hormone receptor (type I disease), or a defect in the postreceptor signaling mechanism that at least in some instances is due to a mutation in the *STAT5B* gene (type II disease), is associated with immunodeficiency. Failure of feedback results in elevated growth hormone levels. Patients with this disorder are resistant to the effects of growth hormone. Treatment with insulin-like growth factor-1 (IGF1) has been used experimentally.

HEENT/Airway: Small face. Occasional blue sclerae. High-pitched voice. Delayed dentition.

Neuromuscular: Intelligence is usually normal.

Orthopedic: Proportionate short stature. More pronounced decrement in body size than in head size, resulting in childlike body proportions in adults. Advanced bone age for age and height. Limited extension of the elbow. Degenerative hip disease. Can develop Legg-Calvé-Perthes disease (see later).

Other: Possible fasting hypoglycemia. Growth hormone resistance. Failure to generate somatomedin in response to growth hormone. Delayed menses. Growth hormone abnormalities may actually allow longer survival.

Anesthetic Considerations: Recall that despite their short stature, patients have intelligence that is normal for their chronologic age, and they must be treated in an age-appropriate manner. Prolonged fasting should be avoided due to risk of hypoglycemia. Patients might require a smaller than expected endotracheal tube if sized for age. Careful perioperative positioning and padding is important in these patients with limitations in joint extension.

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Larsen syndrome

MIM #: 150250, 245600

This dysmorphic syndrome is both genetically and phenotypically variable. It is characterized by flat facies and multiple large joint dislocations. Both autosomal dominant and autosomal recessive inheritance have been documented. Autosomal dominant Larsen syndrome is caused by a mutation in the gene *FLNB*, which encodes filamin. Recessive disease is due to mutations in the gene *B3GAT3*, which codes a glucuronyltransferase protein.

HEENT/Airway: Flat facies with prominent forehead. Hypertelorism. Cataracts. Conductive or sensorineural hearing loss. Depressed nasal bridge. Cleft palate. Mobile, in-folding arytenoid cartilage. Subglottic stenosis. Laryngomalacia, tracheomalacia.

Chest: Tracheomalacia, bronchomalacia. May have restrictive lung disease or chronic respiratory infections secondary to thoracic kyphoscoliosis. May have pectus excavatum. Rare pulmonary hypoplasia.

Cardiovascular: A variety of cardiac defects have been reported, including atrial septal defect, ventricular septal defect, mitral valve prolapse, aortic dilatation, and aortic valvular insufficiency.

Neuromuscular: Cervical spine instability or cervical kyphosis may cause symptomatic spinal cord impingement. Hydrocephalus. May have developmental delay.

Orthopedic: Short stature. Joint hyperlaxity and multiple joint dislocations, particularly at the elbows, wrists, hips, and knees. Long, cylindrical fingers, spatulate thumbs, hypoplastic fingernails. Short terminal phalanges cause pseudoclubbing. Accessory carpal bones. Vertebral anomalies, including segmentation defects, hypoplastic vertebrae, wedged vertebrae, spina bifida. Abnormal cervical vertebrae may lead to cervical spine instability. Kyphoscoliosis, including cervical, which can fatally impinge the spinal cord. Osteoarthritis. Clubfoot deformity. Double ossification center of the calcaneus—may be diagnostic for this syndrome.

GI/GU: May have cryptorchidism.

Other: May have poor wound healing.

Anesthetic Considerations: Patients should be evaluated preoperatively for cervical spine instability. Care should be taken during positioning for laryngoscopy secondary to the potential for cervical subluxation. Laryngoscopy should be performed with axial traction due to the possibility of an unstable cervical spine. Complications associated with intubation can be minimized or avoided with the use of a laryngeal mask airway (LMA), if otherwise appropriate (2). Prior cervical fusion may make intubation difficult. Spinal cord myelopathy from

impingement on the cervical cord may produce distal muscle disuse atrophy and a risk of hyperkalemia with succinylcholine administration.

The larynx may be difficult to visualize because of mobile, in-folding arytenoid cartilages. Patients with subglottic stenosis may require a smaller-than-expected endotracheal tube. Tracheomalacia or subglottic stenosis may be so severe as to warrant a tracheostomy. However, abnormalities of the trachea may extend beyond the tracheostomy tube and continue to cause symptoms. Postextubation airway problems due to laryngotracheomalacia are possible.

Patients with restrictive lung disease may be at increased risk for postoperative pulmonary complications. Rarely, patients have pulmonary hypoplasia, which is usually lethal in the neonatal period. Patients with hydrocephalus may have elevated intracranial pressure, and measures should be taken to avoid further increases in intracranial pressure. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Laryngo-onycho-cutaneous syndrome

Synonym: LOGIC syndrome

MIM #: 245660

This autosomal recessive disease results in ulcerations and granuloma formation in a variety of epidermal tissues, particularly the larynx, the nails, and the skin. It is due to a mutation in the gene *LAMA3*, located on the long arm of chromosome 18, leading to defects in the lamina lucida of the basal membrane of the skin. It is classified as a subtype of junctional epidermolysis bullosa. In somewhat of a stretch for an acronym, it has been suggested that this syndrome be called LOGIC syndrome, for **L**aryngeal and **O**cular **G**ranulation **I**n **C**hildren from the Indian Subcontinent, because it has been described exclusively in Punjabi populations. Onset is within weeks of birth. If the child survives, remission can occur in the second decade.

HEENT/Airway: Skin lesions of the face. Conjunctival scarring. Blisters that heal with scarring may occur in the mouth. Deformed teeth with hypoplastic enamel. Vocal cord thickening with or without nodules, hoarse, weak cry

and voice. Laryngeal obstruction can be fatal.

Other: The skin and mucosal surfaces are sensitive to trauma. There are dystrophic changes of the nails with chronic bleeding, crusted lesions that heal with scarring and loss of nails. There is a risk of intercurrent infection.

Miscellaneous: The 2:1 male-to-female ratio has been ascribed to the increased willingness of poor families in the areas in which this was first described to take male children in for medical treatment.

Anesthetic Considerations: Lesions on the vocal cords may cause significant airway obstruction. Spontaneous ventilation without the use of muscle relaxants has been recommended when laryngeal lesions are present (3). Dental abnormalities should be documented before surgery. The skin and mucosal surfaces are sensitive to trauma, so these patients must be carefully positioned and padded.

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Late infantile neuronal ceroid lipofuscinosis

See Jansky-Bielschowsky disease

Laurence-Moon syndrome

MIM #: 245800

This autosomal recessive disorder is similar to, but possibly distinct from, that described by Bardet and Biedl (see earlier, Bardet-Biedl syndrome). It is characterized by intellectual disabilities, retinal dystrophy,

hypogenitalism, and spastic paraplegia. Unlike the patients described by Bardet and Biedl, the patients described by Laurence and Moon had spastic paraplegia and did not have obesity or polydactyly. The two syndromes have sometimes been recognized as distinct and have sometimes not. Thus, the literature contains many references to both the Laurence-Moon-Biedl syndrome and the Laurence-Moon-Biedl-Bardet syndrome (or other permutations).

HEENT/Airway: Pigmentary retinopathy, with visual loss (a “retinal ciliopathy”). Strabismus. Night blindness, cataracts. May have bifid epiglottis. May have dental abnormalities.

Neuromuscular: Intellectual disabilities, behavioral problems. Spastic paraplegia.

Orthopedic: No polydactyly.

GI/GU: Hypogenitalism, hypogonadism without apparent structural or functional pituitary abnormality. Male infertility. Female amenorrhea. Renal disease.

Other: No obesity. May have speech disorder.

Miscellaneous: Laurence was a British ophthalmologist and Moon was his student. Moon later practiced in Philadelphia.

Anesthetic Considerations: Intellectual disabilities, behavioral problems, and speech disorders may make the smooth induction of anesthesia a challenge. Succinylcholine may be contraindicated in patients with severe spastic paraplegia, secondary to the risk of hyperkalemia.

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LCAD deficiency

See Long-chain acyl-CoA dehydrogenase deficiency

Leber congenital amaurosis

Synonym: Congenital absence of the rods and cones

Note: This disorder is distinct from Leber hereditary optic neuropathy (see later).

MIM #: 204000, 204100

Autosomal recessive defects in multiple genes can produce this heterogeneous disorder. Type I disease is due to a defect in the gene encoding retinal guanylyl cyclase (*GUCY2D*), with at least six different loci described. It may be that some of these cases are also caused by a defect in the gene for guanylyl cyclase-activating proteins, which are required for the activation of retinal guanylyl cyclase. Heterozygous mutations in this gene can cause the disorder cone-rod dystrophy-6. Type II disease is due to a defect in the gene encoding retinal pigment epithelium (*RPE65*). It is sometimes termed “congenital absence of the rods and cones.” To date, mutations in 16 distinct genes have resulted in the identification of 16 separate disorders (LCA 1 to 16). Leber congenital amaurosis can be separated into three general types: aplasia of photoreceptors, early degeneration with cell death of receptors, or dysfunction of receptors with normal anatomy. It is suggested that some patients have a peroxisome disorder. There has been preliminary success with gene therapy in very early trials (2).

HEENT/Airway: Early vision loss with nystagmus, photophobia. Pigmentary retinopathy that may resemble retinitis pigmentosa. Keratoconus. Infants may poke at their eyes (the digitoocular sign of Franceschetti). May have hearing loss.

Neuromuscular: May have intellectual disabilities, neuropsychiatric problems, seizures, hypoplastic cerebellar vermis.

Orthopedic: Growth retardation.

GI/GU: Hepatomegaly.

Miscellaneous: This disease may be due to a defect in one of two distinct genes. Thus, a family has been reported in which both parents had the disease, but who had normal children, because each parent had a defect in a different gene.

Theodor von Leber pronounced his name “Layber” and was the founder of scientific ophthalmology. He had wanted to be a chemist but was told by Professor Bunsen that there were already too many chemists, so he chose medicine as an alternative.

Anesthetic Considerations: Infants with photophobia may be extremely sensitive to the bright lights in operating rooms. Efforts should be made to minimize their discomfort. Additional oral explanations are clearly needed for patients with limited sight.

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Leber hereditary optic atrophy

See Leber hereditary optic neuropathy

Leber hereditary optic neuropathy

Synonym: Leber hereditary optic atrophy

Note: This disorder is distinct from Leber congenital amaurosis (see earlier).

MIM #: 535000

This disease is due to an abnormality in mitochondrial DNA. Clinical findings are typically limited to optic nerve disease with visual loss, although at least one form results in a spectrum of findings. At least 18 separate missense mutations in mitochondrial DNA can result in this syndrome. However, three mutations are responsible for over 90% of the cases. Although the onset is usually in adulthood, this disorder has been diagnosed as early as 1 year of age. Once begun, deterioration in vision progresses rapidly. It is likely that the defect(s) occur in the respiratory chain, particularly in complex I, III, or IV (see earlier, complex I, III, or IV deficiency). The disease can manifest a latent

phase, acute phase, and a chronic phase. It may be confused with multiple sclerosis. As a mitochondrial DNA defect, this disorder is maternally transmitted. There appears to be increased clinical severity in male patients with the disease.

HEENT/Airway: Subacute, painless loss of central vision with a central scotoma. Vascular changes in the fundus, with peripapillary telangiectasis, microangiopathy, disk pseudopapilledema, and vascular tortuosity. The degree of visual loss is variable and in part depends on the specific mutation.

Cardiovascular: Conduction defects, including Wolff-Parkinson-White and Lown-Ganong-Levine syndromes, and long QT syndrome (see later for all) have been reported in one family.

Neuromuscular: Headaches. Posterior column and corticospinal tract involvement with tremor, ataxia, dystonia, sensory neuropathy, and extrapyramidal rigidity. Rarely seizures, cerebral edema. Depression.

Other: Lactic acidosis. Death in childhood.

Miscellaneous: Theodor von Leber pronounced his name “Layber,” and was the founder of scientific ophthalmology. He had wanted to be a chemist, but was told by Professor Bunsen that there were already too many chemists, so he chose medicine as an alternative.

Anesthetic Considerations: There are no recent reports of anesthesia for patients with this disease. It might seem reasonable, however, given the clinical experience with other mitochondrial diseases, to avoid succinylcholine. Adequate perioperative glucose should be ensured to minimize the need for anaerobic metabolism. Some patients with mitochondrial diseases have been shown to have abnormal respiratory drive (7), so opioids and other respiratory depressants should be used with care. A baseline electrocardiogram should exclude cardiac conduction abnormalities. Cyanide can inhibit the electron transport chain. It has been suggested that there may be an inability adequately to handle cyanide in this (and related) diseases, and for this reason, nitroprusside should be used with caution or avoided (8). Because of its mitochondrial depressant effects, it may be judicious to avoid anything more than short-term use of propofol in these patients for fear of triggering the propofol infusion syndrome.

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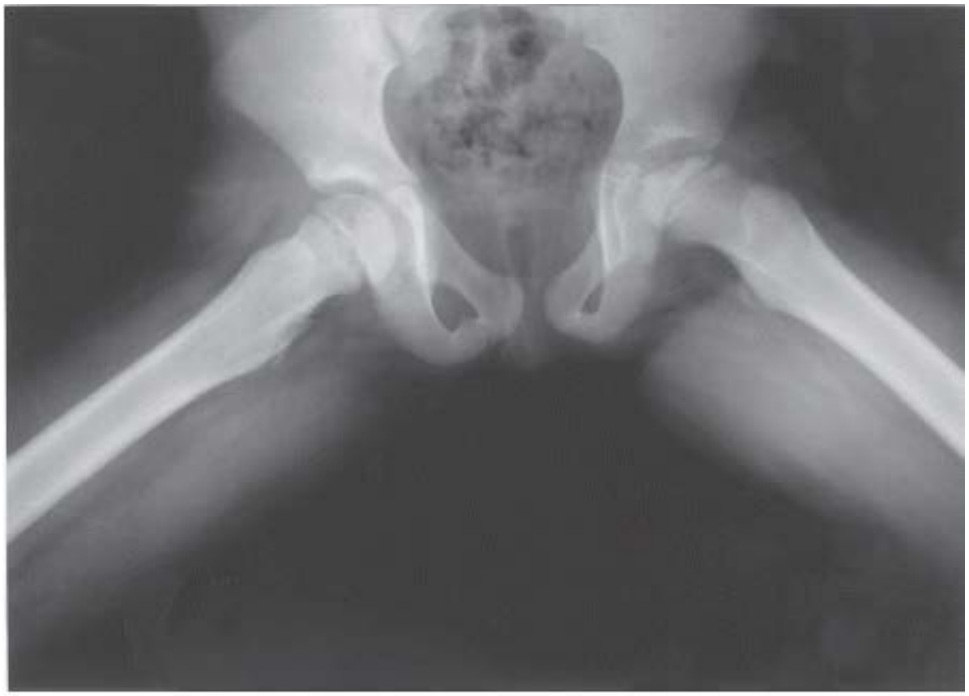
Legg-Calvé-Perthes disease

MIM #: 150600

This disorder is fairly common and is characterized by ischemic or avascular necrosis and resorption of the proximal femoral epiphysis. It has also been called coxa plana. Although apparently autosomal dominant cases have been reported, most cases are sporadic. The onset is during childhood, and boys are affected four times as often as girls, although in familial cases, the sex

ratio approximates 1:1. Approximately 15% of cases are bilateral. Treatment consists of bracing or surgical osteotomy. The cause is unknown, although it has been suggested that it may be related to thrombophilia or hypofibrinolysis (which can be familial). It has also been suggested that low levels of protein C or S, which render the patient hyperthrombotic, could increase the risk of development of the disease, and there is an increased incidence in individuals with factor V Leiden (see earlier).



Legg-Calvé-Perthes disease. Note the avascular necrosis of the head of the left femur.

Orthopedic: Avascular necrosis of the proximal femoral epiphysis. Short stature. Patients limp, but often have minimal pain.

Miscellaneous: This disease was not fully differentiated from the much more common tuberculous bone and joint disease until after the development of radiography. Calvé described this disease after examining the radiographs of 500 children purported to have tuberculosis of the hip joints. Ten of the children turned out to have avascular necrosis of the proximal femoral epiphysis.

During the German campaign in China in the early 1900s, the German army surgeon Georg Perthes experimented with the (then) new technology of radiography by taking radiographs of the feet of Chinese women, which had been bound in the traditional manner.

Anesthetic Considerations: There are no specific anesthetic considerations.

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Leigh disease

MIM #: 256000, 266150

This clinically heterogeneous disease is characterized by gray matter degeneration and focal brainstem necrosis. Multiple defects in the mitochondrial genome have been identified, including complexes I, II, III, IV, and V. The disease has been linked primarily to deficiencies of mitochondrial complexes but has also been associated with other abnormalities such as pyruvate carboxylase deficiency. It appears that defects in a variety of genes involved in energy metabolism, in particular the mitochondrial genes, can cause this clinical phenotype. Brain MRI findings are typical for a mitochondrial disorder. The clinical course of Leigh disease is marked by remissions and acute exacerbations. Patients may be receiving dichloroacetate, thiamine, and riboflavin. Rapamycin has shown preliminary success in a mouse model.

HEENT/Airway: External ophthalmoplegia, abnormal eye movements, sluggish pupils, optic atrophy, blindness. Hearing loss.

Chest: Wheezing, gasping, aspiration pneumonia. Cheyne-Stokes respirations, hypoventilation, central apnea, respiratory failure. Can have recurrent aspiration. Respiratory status may be acutely worsened by surgery, general anesthesia, or intercurrent illness.

Cardiovascular: Hypertrophic cardiomyopathy.

Neuromuscular: Gray matter degeneration and focal brainstem necrosis. Symmetric lesions are often found in the walls of the third ventricle, basal ganglia, brainstem, cerebellum, and spinal cord with cortical sparing. Variable clinical manifestations include developmental delay, hypotonia, seizures, weakness, tremor, ataxia, absent deep tendon reflexes, and a Babinski sign. Emotional lability.

Orthopedic: Growth retardation. Can develop scoliosis.

Other: Increased CSF and blood lactate, impaired gluconeogenesis. Hypothermia.

Miscellaneous: Denis Leigh pronounced his name “Lee” not “Lay.”

Anesthetic Considerations: Stress, as with surgery or infection, can increase demands for adenosine triphosphate production to levels above which the patient can produce. Elective surgery should be postponed for fever or other intercurrent illness. Acidosis should be

corrected preoperatively, and patients with excessive lactic acidemia should not receive lactated Ringer's solution. Prolonged preoperative fasting should be avoided, adequate glucose should be supplied perioperatively, and blood glucose appropriately monitored. These patients warrant close postoperative observation because they may have abnormal responses to hypoxia and hypercarbia, in addition to muscle weakness. Postoperative clinical deterioration has been reported (8), and one patient's MRI was consistent with activation of her underlying disease. Patients may be at increased risk for aspiration. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

Although barbiturates and volatile anesthetics can inhibit mitochondrial respiration, induction of anesthesia with thiopental has been used without complication. Because of its mitochondrial depressant effects, it may be judicious to avoid anything more than short-term use of propofol in these patients for fear of triggering the propofol infusion syndrome. Succinylcholine should be used with caution in patients with evidence of a myopathy because of the risk of exaggerated hyperkalemia. There is a report of a single patient with an unspecified mitochondrial myopathy who exhibited increased sensitivity to rocuronium and atracurium (7). Although there are no clinical reports, it is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. There is a report of three patients in whom general anesthesia precipitated respiratory failure, leading to death (11). All three had preoperative respiratory findings. In one, the diagnosis of Leigh disease had not yet been made. Acute respiratory compromise has also been reported in two children after receiving chloral hydrate for a radiologic procedure (12). Both had had apnea and gagging before the procedure. Many children with mitochondrial diseases have abnormal respiratory control (4,5,13), suggesting that opioids and other respiratory depressants be used with care. Patients may have difficulty maintaining body temperature. Patients with hypertrophic cardiomyopathy should receive an appropriately tailored anesthetic. It has been suggested that postoperative pain management in patients with Leigh disease can be difficult, and parenteral or oral clonazepam has been used successfully.

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Lennox-Gastaut syndrome

MIM #: None

Lennox-Gastaut syndrome is a severe seizure disorder of childhood. The seizures are difficult to control, and the syndrome is often associated with developmental and intellectual disabilities. Peak onset is from 3 to 5 years of age. Half of those surviving to adulthood are neurologically devastated. It is not apparently genetically

transmitted, and there is no one single known etiologic process or causative event.

Neuromuscular: Early childhood seizures of multiple types [tonic, tonic-clonic, atonic, akinetic (drop attacks), myoclonic, and absence]. These seizures are often preceded by infantile spasms ("salaam seizures"). The electroencephalogram is abnormal and diagnostic (spike and dome). Intellectual and motor function, which may have been normal before the onset of seizures, deteriorate. The seizures may be refractory to common anticonvulsant medications, and most patients are on multiple medications. The anticonvulsant drugs rufinamide, lamotrigine, topiramate, and felbamate have been shown to have activity, but none have been shown to have major efficacy. Patients may be on a ketogenic diet. Clobazam, a benzodiazepine available in Europe has been used to treat the drop attack component. Severe behavioral disorders and personality disorders are almost always present. Possible development of psychosis.

Miscellaneous: Salaam seizures, which usually carry a poor prognosis, are so named because during the seizure, the child's arms come up to the head, which is flexed downward along with the trunk, mimicking a "salaam" gesture.

Lennox-Gastaut syndrome was featured in *The Spirit Catches You and You Fall Down*, written by journalist Anne Fadiman and published in 1997. This is the (true) story of the tremendous medical and cultural clashes that occurred between American medical providers and a Hmong family whose youngest child had Lennox-Gastaut syndrome.

Anesthetic Considerations: Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. The anticonvulsant medication felbamate has been associated with the development of aplastic anemia and acute liver failure.

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Lenz-Majewski hyperostosis syndrome

MIM #: 151050

This sporadic disorder is characterized by short stature, hyperostosis, symphalangism, and skin hypoplasia. It is associated with increased paternal age. Those affected die in infancy or childhood and have been described as

looking somewhat like patients with progeria. The disorder is caused by a gain-of-function mutation in the gene *PTDSS1* that encodes phosphatidylserine synthase 1.

HEENT/Airway: Macrocephaly, prominent forehead. Progressive sclerosis of facial bones. Late closure of large fontanelles. Sparse hair in infancy. Prominent scalp veins. Hypertelorism, nasolacrimal duct obstruction. Large ears. Can have sensorineural hearing loss. Choanal stenosis or atresia, which may cause respiratory insufficiency. Dysplastic dental enamel. May have facial palsy. May have cleft palate. May have micrognathia. Small tongue.

Chest: Broad, thick ribs and clavicles cause thoracic immobility. Recurrent pneumonia is common.

Neuromuscular: Intellectual disabilities. May have cerebral atrophy. May have agenesis of the corpus callosum. May have hydrocephalus.

Orthopedic: Short stature. Hyperostosis of the skull and diaphyses. Humeral-radial synostosis. Delayed bone age. Proximal symphalangism. Hypoplastic or absent middle phalanges. Cutaneous syndactyly. Hyperextensible joints. May have flexion contractures at the elbows and knees.

GI/GU: Inguinal hernias. Anteriorly displaced anus. Cryptorchidism, hypospadias.

Other: Intrauterine growth retardation, failure to thrive. Cutis laxa in infancy, sparse hair in infancy. Skin becomes hypoplastic with prominent cutaneous veins.

Anesthetic Considerations: Choanal stenosis or atresia may cause respiratory insufficiency, and precludes the use of a nasal airway or a nasogastric tube. Recurrent pneumonia may cause chronic lung disease and places patients at increased risk for postoperative respiratory complications. Patients must be carefully positioned and padded because of hyperextensible joints, flexion contractures at the elbows and knees, and hypoplastic skin. Thin skin and failure to thrive suggest that efforts to maintain perioperative body temperature are important.

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LEOPARD syndrome

Synonym: Multiple lentigines syndrome

MIM #: 151100

This autosomal dominant syndrome consists of **L**entigines (multiple), **E**lectrocardiographic conduction abnormalities, **O**cular hypertelorism, **P**ulmonic stenosis, **A**bnormal genitalia, **R**etardation of growth, and **D**eafness. Lentigines are large freckles. LEOPARD syndrome is thought to be due to a primary abnormality in neural crest cells. There is marked variability in the clinical expression of this syndrome. Some patients may even fail to exhibit the characteristic lentigines. LEOPARD syndrome can be caused by a mutation in the gene *PTPN11*, which encodes a protein-tyrosine phosphatase. Mutations in this gene are also responsible for approximately one-half of cases of Noonan syndrome (see later); thus, these two syndromes are allelic. There is also a type 2 disease (gene *RAF1*) and

a type 3 disease (gene *BRAF*).

HEENT/Airway: Hypertelorism. Protruding ears. Sensorineural deafness. May have dental abnormalities. May have cleft palate, prognathism. Tooth abnormalities. May have short neck.

Chest: Pectus excavatum or carinatum. Restrictive lung disease with pulmonary arterial hypertension from scoliosis has been reported.

Cardiovascular: Cardiac conduction abnormalities, with variable types of conduction block. Abnormal P waves. Pulmonic stenosis—the pulmonic valve may be dysplastic. Hypertrophic obstructive cardiomyopathy, which has also been reported to involve the right ventricle. Subaortic stenosis, mitral valve involvement, and a left atrial myxoma have also been reported.

Neuromuscular: May have intellectual disabilities.

Orthopedic: Growth deficiency. Winged scapulae. May have kyphoscoliosis.

GI/GU: Cryptorchidism, hypospadias. May have renal agenesis or hypoplasia. Delayed puberty.

Other: Multiple lentigines of the skin, particularly on the neck and trunk. Can also have café au lait spots. The number of lentigines can increase with age. Lentigines are macules similar to freckles, but unlike freckles are not restricted to sun-exposed areas. They are dark brown to black and round to oval.

Miscellaneous: The multiple spotting of the skin by lentigines led Gorlin to formulate the mnemonic LEOPARD syndrome as an aid to recalling the features of the multiple lentigines syndrome.

Anesthetic Considerations: Provisions should be made for communication with patients who are deaf. Baseline renal function should be assessed. Patients warrant a preoperative cardiac evaluation. Given the incidence of obstructive cardiomyopathy, which can be asymptomatic, preoperative screening echocardiography could be considered. Cardiac conduction abnormalities are also common. Patients with heart disease should receive an appropriately tailored anesthetic.

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Leprechaunism

Synonym: Donohue syndrome

MIM #: 246200

This autosomal recessive disorder is characterized by severe growth deficiency, hyperplasia of the islets of Langerhans, and a deficiency of subcutaneous fat. There is usually severe failure to thrive, recurrent infection, and death during infancy. The syndrome is caused by a mutation of the insulin receptor gene (*INSR*). Abnormal insulin receptors result in severe insulin resistance, islet cell hyperplasia, hyperinsulinemia, hyperglycemia, and growth deficiency. Death in infancy is common.

HEENT/Airway: Elfin-like facies with prominent eyes, large ears, wide nostrils, and thick lips. Gingival hyperplasia. High-arched palate.

Chest: Breast hyperplasia in females.

Cardiovascular: May have hypertrophic obstructive cardiomyopathy.

Neuromuscular: Intellectual disability and motor retardation.

Orthopedic: Intrauterine and postnatal growth deficiency with marked deficiency of subcutaneous fat and muscle wasting. Relatively large hands and feet. Delayed osseous maturation.

GI/GU: Relatively large abdomen. Can have hepatic fibrosis. Can have umbilical or inguinal hernia. Large penis or clitoris. Cystic ovaries.

Other: Multiple endocrinologic abnormalities, including hyperplasia of the islets of Langerhans, Leydig cell hyperplasia, hyperinsulinemia, hyperglycemia, resistance to endogenous growth hormone, and precocious puberty. Postprandial hypoglycemia. Hirsutism. Hyperkeratosis. Hypertrichosis. Nail dysplasia. Wrinkled, loose skin. Acanthosis nigricans. Limited fat and muscle mass. Decreased lymphatic tissue including tonsils.

Miscellaneous: Originally called “dysendocrinism” by Donohue; it was later renamed “leprechaunism” (because of the elfin-like facies) by Donohue and Uchida.

Anesthetic Considerations: Patients may have a variety of endocrinologic abnormalities. Although usually hyperglycemic secondary to lack of response to insulin, patients may become hypoglycemic during a fast. Perioperative glucose monitoring is essential. Patients with hypertrophic obstructive cardiomyopathy should receive an appropriately tailored anesthetic.

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Leri-Weill dyschondrosteosis

Synonym: Dyschondrosteosis

MIM #: 127300

This autosomal dominant syndrome is distinguished by mesomelic dwarfism, short and bowed forearms, and radial

deviation of the hands secondary to shortening of the distal radius. Patients may also have short lower extremities. The homozygous form of this disorder is known as Langer mesomelic dysplasia (see earlier). This disorder is usually caused by mutations in the genes *SHOX* (short stature homeobox) or *SHOXY* or in a downstream regulatory domain. This gene is located on the X chromosome but is said to be pseudoautosomal (analogous segments of chromosome on both the X and Y chromosomes). There is a female-to-male ratio of 4:1, and female patients are more severely affected. There is a recent report of a Leri-Weill dyschondrosteosis phenotype associated with a pseudoautosomal deletion that does not involve the *SHOX* gene. Growth hormone has been used.

HEENT/Airway: High-arched palate.

Neuromuscular: Normal intelligence.

Orthopedic: Mesomelic dwarfism, with variable short stature. Short forearms. Bowed radius. Dorsal dislocation of distal ulna. Radial deviation of the hands at the wrist (Madelung deformity) secondary to shortening of the distal radius. May have partial dislocation of the ulna at the wrist or elbow, with limitation of joint mobility at the wrist or elbow. May have short lower extremities, with tibiofibular disproportion as well as hip and pelvic abnormalities. Scoliosis.

Anesthetic Considerations: Patients should be addressed in a manner appropriate to their chronologic age and not their height age. Radial arterial access might be difficult. Positioning may be complicated by restricted elbow and wrist movement.

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Lesch-Nyhan syndrome

(Includes Kelley-Seegmiller syndrome)

MIM #: 300322

Lesch-Nyhan syndrome is an X-linked recessive disease caused by a mutation in the gene *HPRT*, which encodes hypoxanthine phosphoribosyltransferase. This enzyme is involved in the salvage of the purines hypoxanthine and guanine, allowing their reuse. Absence of this ability results in hyperuricemia. There are a variety of different mutations in the gene for this enzyme that may result in the clinical syndrome. Some patients may have a partial deficit in enzyme activity and manifest less than the full syndrome (>8% activity results in the **Kelley-Seegmiller syndrome**, which lacks the neurologic manifestations, but patients remain hyperuricemic). The hallmark clinical findings are developmental delay, motor abnormalities, and self-mutilation. CNS findings are due predominantly to abnormal dopaminergic signaling. Heterozygote females will have mild disease.

HEENT/Airway: May have sequelae of perioral self-mutilation. Dysarthria.

Chest: Risk of recurrent aspiration from athetoid dysphagia.

Neuromuscular: Intellectual disabilities. Dysarthria makes intelligence testing difficult, and patients may have less impairment than immediately obvious. Developmental delay followed by pyramidal and extrapyramidal tract signs. Early hypotonia followed by

development of hypertonia and spasticity. Cerebellar ataxia in some. Choreoathetosis, spasticity, dystonia, opisthotonos. Self-mutilatory behavior, with head banging as a common manifestation. Other behavior problems, including aggression and compulsive behaviors.

Lesch-Nyhan syndrome. This 21-year-old man with Lesch-Nyhan syndrome could recognize when he had an uncontrollable self-mutilating urge, and his parents would give him chloral hydrate. Although not well seen here, his lips have been extensively chewed. Note the bandage on his finger, and that his hands are tied to the wheelchair as a restraint.

Orthopedic: Gouty arthritis. Self-mutilation of fingers and hands.

GI/GU: Can have vomiting. Hyperuricemia with renal stones. Orange crystals in urine and on diapers. Hyperuricemia (but not neurologic findings) can be controlled by inhibition of xanthine oxidase (e.g., with allopurinol). Urinary tract infections. Testicular atrophy.

Other: There is diminished monoamine oxidase activity. There is diminished adrenergic response to stress. Megaloblastic anemia. Abnormal B-cell lymphocyte proliferation or function. Overwhelming infection may be a cause of death.

Miscellaneous: Lesch was only a medical student (at Johns Hopkins) when he and Nyhan described this disease in 1964.

Anesthetic Considerations: Behavioral problems may make pre- and postoperative care challenging. Spastic musculoskeletal malformations may make intravenous access and positioning difficult. Dystonia likely raises the risk of aspiration. Although there are multiple metabolic abnormalities, routine anesthetic techniques have been used successfully. Patients have tolerated propofol sedation for noninvasive radiologic procedures, despite the fact that propofol may increase urinary uric acid excretion (4). This may be a consideration for prolonged cases using propofol for anesthesia or sedation. Abnormal monoamine oxidase activity and abnormal adrenergic pressor responses suggest that exogenous catecholamines should be used with care.

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Letterer-Siwe disease

Included in Langerhans cell histiocytosis

Levy-Hollister syndrome

Synonym: Lacrimoauriculodentodigital syndrome; LADD syndrome

MIM #: 149730

This autosomal dominant syndrome is characterized by lacrimal gland and duct abnormalities, external ear anomalies, dental hypoplasia, and digital anomalies. There is wide variability in clinical expression. Most patients have persistent dry mouth secondary to decreased salivation and are prone to the development of severe dental caries. The disorder can be due to mutations in several genes encoding fibroblast growth factor receptors (*FGFR2* and *FGFR3*) or an FGFR ligand encoded by *FGF10*.

HEENT/Airway: Broad forehead. Nasolacrimal duct obstruction, hypoplasia or aplasia of lacrimal glands. A patient with a giant dacryocystocele has been reported. Chronic dacryocystitis, corneal abrasions. Small, simple, cup-shaped ears. Conductive or sensorineural hearing loss. May have cleft lip/palate. Dental hypoplasia, peg-shaped incisors, enamel dysplasia, delayed eruption of primary teeth. Severe dental caries often develop. Parotid gland hypoplasia or aplasia. Oral candidiasis.

Chest: Rare pulmonary vascular and alveolar malformations. Rare unilateral diaphragmatic nerve palsy.

Cardiovascular: May have QT prolongation.

Orthopedic: Digital anomalies, including digitalization of the thumb, duplication of the distal phalanx of the thumb, triphalangeal thumb, digital bone and soft tissue hypoplasia, thenar muscle hypoplasia, polydactyly, syndactyly, clinodactyly. May have shortening of radius and ulna, or absent radius.

GI/GU: May have hypospadias, cystic ovarian disease. May have renal disease.

Anesthetic Considerations: Patients have absent or decreased tear production and are prone to chronic dacryocystitis. Meticulous perioperative eye care is imperative to avoid exacerbation of symptoms and corneal abrasions. Dental abnormalities should be documented preoperatively. Patients with severe dental caries may be at risk for intraoperative tooth loss. Recall that patients may have hearing loss. Hypoplasia or absence of the radius may make intravenous or intra-arterial access more difficult. At least one patient has been noted to have QT prolongation (2).

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Liddle syndrome

Synonym: Pseudohyperaldosteronism (pseudoaldosteronism)

MIM #: 177200

Liddle syndrome is an autosomal dominant cause of heritable hypertension that is caused by a defect in the beta or gamma subunit of the epithelial sodium channel *SCNN1*, preventing binding of a regulatory protein and preventing normal degradation of the channel, leading to constitutive activation of the epithelial sodium channel in the collecting tubule luminal membrane with unregulated sodium resorption in the distal renal tubule. Patients are hypertensive and have a hypokalemic metabolic alkalosis that is not secondary to hyperaldosteronism. The metabolic defects are completely reversible with renal transplantation.

Cardiovascular: Hypertension.

GI/GU: Late renal failure secondary to chronic hypertension.

Other: Hypokalemic metabolic alkalosis, hypoaldosteronism, decreased serum renin and angiotensin.

Miscellaneous: Dr. Grant Liddle was the Chair of Medicine at Vanderbilt University. Pseudohyperaldosteronism can also be caused by excessive licorice ingestion.

Anesthetic Considerations: Patients are likely to be hypertensive. Serum electrolytes, particularly potassium and bicarbonate, should be evaluated preoperatively. Spironolactone is ineffective in correcting the metabolic alterations, but amiloride or triamterene with dietary sodium restriction is helpful. Inadvertent perioperative hypocapnia will worsen preexisting alkalosis.

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Li-Fraumeni syndrome

MIM #: 151623

Originally described as an autosomal dominant cause of childhood sarcomas, this syndrome is also responsible for an excess of a variety of other cancers, including breast cancer, brain tumors, leukemia, and adrenocortical carcinoma. It can occur secondary to a mutation in the tumor suppressor gene *TP53*, which encodes the p53 protein. Two additional forms are due to mutations in the genes *CHEK2* and *LFS3*. Evidence suggests a role for p53 in regulating mitochondrial bioenergy homeostasis (1). The p53 protein is undetectable or present in very low

levels in resting cells but is present in a wide variety of proliferating or transformed cells. It has structural and functional similarities to the *MYC* family of oncogenes. Patients may have multiple primary tumors. More than 50% of patients will have cancer by age 30 years, and 90% by age 70 years. Gene replacement therapy with p53 has been proposed.

Other: The long list of tumors for which these patients are at risk includes rhabdomyosarcoma, soft tissue sarcomas, breast cancer, brain tumors, osteosarcoma, leukemia, adrenocortical carcinoma, lymphocytic or histiocytic lymphoma, lung adenocarcinoma, melanoma, gonadal germ cell tumors, prostate carcinoma, and pancreatic carcinoma.

Anesthetic Considerations: The anesthetic management is specific to the particular tumor present, the type and amount of chemotherapy the patient has received, and the proposed surgery.

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Limb-girdle muscular dystrophy

MIM #: 159000, 253600

Limb-girdle muscular dystrophy can be inherited in an autosomal dominant fashion (type 1) or in an autosomal recessive fashion (type 2), each with subtypes. The autosomal dominant types are less common and more typically have symptomatic onset in adulthood.

Approximately 25 subtypes have been described, with varying age of onset, severity, and disease progression. A variety of muscle-related proteins can be defective in this disorder. All of these result in abnormalities in dystroglycan function, which links the cytoskeleton and the extracellular matrix. Secondary dystrophinopathies involve abnormal glycosylation of α-dystroglycan. Limb-girdle muscular dystrophy is marked by muscle weakness, particularly in the pelvis and legs. There have been preliminary attempts at treatment with gene therapy.

HEENT/Airway: Nasal speech. Late facial weakness.

Chest: Respiratory muscle weakness can lead to recurrent respiratory tract infections. Scoliosis can cause restrictive lung disease.

Cardiovascular: Atrioventricular conduction disorders, symptomatic bradyarrhythmias. Dilated cardiomyopathy is uncommon.

Neuromuscular: Myopathy with muscle weakness, legs often weaker than arms. In type 2 disease, muscle weakness is first evident in the pelvis or, less frequently, the shoulder girdle. Serum creatine kinase is usually

moderately or markedly increased but can be normal. Intellectual disabilities can be associated with some types.

Orthopedic: Scoliosis. Late joint contractures. Pseudohypertrophy of the calves.

Anesthetic Considerations: Cardiac conduction disorders are common, and the baseline cardiac rhythm should be determined. Patients are at increased risk for development of perioperative respiratory complications, secondary to respiratory muscle weakness. Succinylcholine is contraindicated in patients with a myopathy because of the risk of an exaggerated hyperkalemic response. Malignant hyperthermia is not associated with this disease. Rhabdomyolysis and hyperkalemia associated with volatile anesthetic use has been reported in patients with other types of muscular dystrophy, making an anesthetic technique devoid of volatile agents appealing.

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Linear sebaceous nevus syndrome

See Nevus sebaceus of Jadassohn

Lipofuscinosis

See Jansky-Bielschowsky disease and Spielmeyer-Vogt disease

Lip pit-cleft lip syndrome

See van der Woude syndrome

Lipodystrophy

Synonym: Berardinelli-Seip syndrome; Berardinelli lipodystrophy; Seip syndrome. (Includes Seip-Lawrence

syndrome)

MIM #: 269700, 608594

This autosomal recessive disease is one of generalized lipodystrophy and insulin-resistant diabetes mellitus. There is an inability to store energy as fat, and patients have elevated basal metabolic rates. There is genetic heterogeneity. Mutations in the *AGAPAT2* gene cause type 1 lipodystrophy, and mutations in the gene encoding seipin cause type 2 lipodystrophy. It is proposed that seipin plays a role in adipocyte differentiation. Berardinelli-Seip syndrome is used to describe the inherited form and **Seip-Lawrence syndrome** an acquired form.

HEENT/Airway: Triangular facies. Corneal opacities. May have macroglossia. May have tonsil and adenoid hypertrophy. Can have large mandible.

Cardiovascular: Atherosclerotic cardiovascular disease, hypertrophic cardiomyopathy. Onset of ischemic cardiac disease can begin in adolescence. Peripheral pulmonic stenosis has been reported.

Neuromuscular: Diabetic neuropathy. Muscular hypertrophy. Mild to moderate intellectual disabilities with type 2 disease.

Orthopedic: Advanced bone age. Long bone sclerosis or angiomatosis. Postpubertal cystic lesions of appendicular bones. Large hands and feet.

GI/GU: Hepatomegaly, steatosis, cirrhosis, portal hypertension. May develop pancreatitis. Can have umbilical hernia. Diabetic nephropathy. Polycystic ovaries. Sexual precocity, but delayed puberty has been reported. Decreased female fertility. Can have hypertrophy of female external genitalia.

Other: Near complete lack of adipose tissue. Hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, insulin-resistant nonketotic diabetes mellitus. Acanthosis nigricans. Abnormal hypothalamic or pituitary function. Hyperpigmentation. Hypertrichosis with curly scalp hair. Can have exaggerated appetite.

Anesthetic Considerations: Patients with diabetes may have an autonomic neuropathy. Significantly diminished body fat may make perioperative temperature maintenance difficult. Serum glucose levels should be followed perioperatively, and adequate glucose should be supplied to avoid hypoglycemia. Hepatic failure may affect the binding and metabolism of some anesthetic drugs, and cirrhosis can cause esophageal varices. Hyperkeratosis can make intravenous access more difficult. Patients with cardiac disease should receive an appropriately tailored anesthetic. A single case of delayed emergence has been reported (1), in which case desflurane would seem the most appropriate volatile anesthetic to use in these patients.

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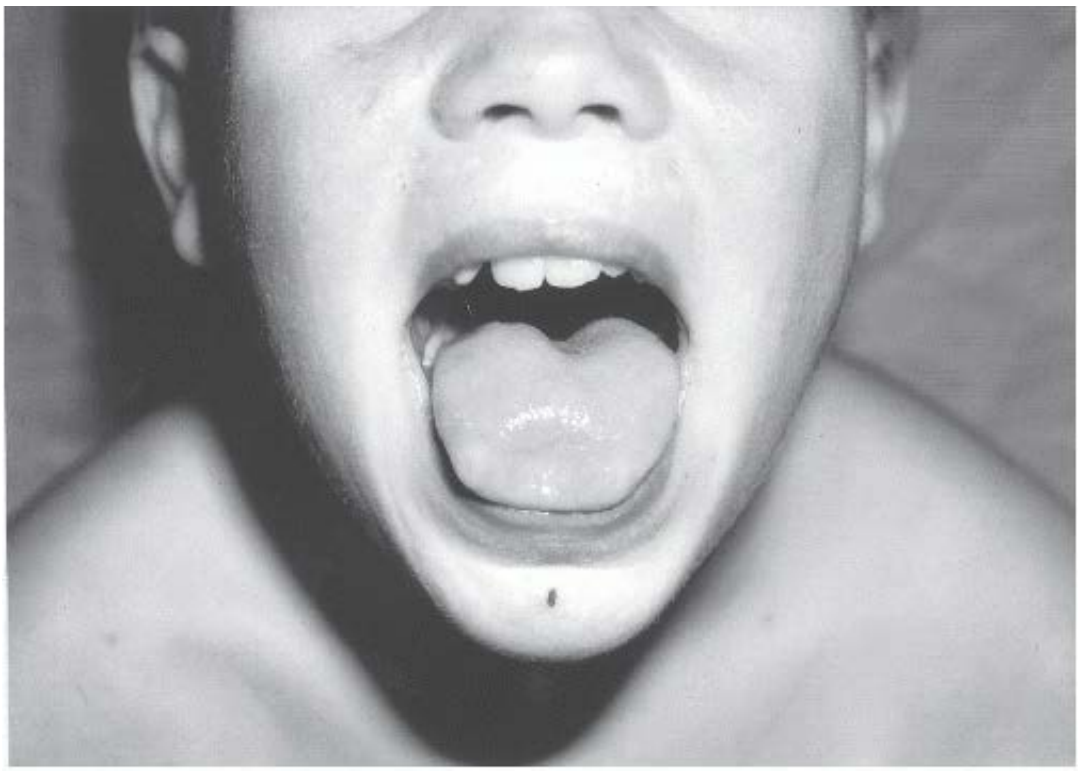
Lipoid proteinosis

Synonym: Urbach-Wiethe disease

MIM #: 247100

Lipoid proteinosis is an autosomal recessive disease involving the skin and blood vessels. The primary manifestations are early hoarseness and an unusual skin rash. This disorder is caused by a mutation in the *ECM1* gene, coding extracellular matrix protein 1. Clinical manifestations are heterogeneous.

HEENT/Airway: Skin lesions resembling acne, particularly along the borders of the eyelids. Drusen-like lesions of the fundus. Itchy eyes. An immobile, woody tongue from infiltration of the tongue and frenulum may cause problems with swallowing and mouth opening. Hoarseness at an early age is the most common finding. Laryngeal mucosal involvement causes decreased mucous production. There is progressive narrowing of the upper respiratory tract.



Lipoid proteinosis. The tongue of this patient with lipoid proteinosis has limited mobility. This is its maximal protrusion.

Cardiovascular: There is deposition of hyaline material in arterial and capillary vessel walls.

Neuromuscular: Intracranial calcifications and possibly seizures. Memory impairment. Paranoia and rage attacks have been reported.

Other: There is deposition of hyaline material in the skin. There may be hyperkeratosis and scarring in areas of

skin trauma. May have patchy alopecia.

Miscellaneous: Involvement of the amygdala in Urbach-Wiethe patients has confirmed the important role of the intact amygdala in threat vigilance, for example, scary faces, snakes, or spiders.

Anesthetic Considerations: Behavioral problems may make preoperative care challenging. Limitations in mouth opening and infiltration of the soft tissues of the tongue and larynx may make laryngoscopy and tracheal intubation difficult. Because of laryngeal involvement, patients may require a smaller-than-expected endotracheal tube. An impaired gag reflex may increase the risk of aspiration associated with laryngoscopy. Antisialagogues are best avoided because of the secretory defect of the larynx. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs.

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Lipoprotein lipase deficiency

MIM #: 238600

This autosomal recessive disease is usually caused by abnormalities in the gene encoding the enzyme lipoprotein lipase (LPL). There are multiple alleles. The disease can also be the result of a deficiency in the activator of lipoprotein lipase, apolipoprotein C-II. Patients exhibit massive chylomicronemia and hyperlipidemia on a normal diet. This resolves after several days of a fat-free diet. The disease is marked by xanthomas and recurrent abdominal pain. Gene therapy has been used in preliminary studies, but with only transient results. Treatment with orlistat (Xenical), an antiobesity drug used to block the absorption of dietary fats, has also proven to be of some use in preliminary studies.

HEENT/Airway: Lipemia retinalis.

Cardiovascular: Do not generally develop premature atherosclerotic peripheral vascular or coronary artery disease.

GI/GU: Attacks of abdominal pain, nausea, and vomiting. Pancreatitis. Hepatosplenomegaly, bile duct stenosis, jaundice. Use of birth control pills has been associated with the development of pancreatitis.

Other: Eruptive xanthomas. Hypercholesterolemia, hyperlipidemia. Can have mild hemolysis. Cardiac glucose uptake is increased in these hearts with limited fatty acids derived from lipoprotein lipase-mediated hydrolysis of triglycerides.

Anesthetic Considerations: Episodes of abdominal pain may mimic a “surgical abdomen.”

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Lissencephaly syndrome

See Miller-Dieker syndrome

Liver glycogen phosphorylase deficiency

See Hers disease

Loeys-Dietz syndrome

Synonym: Furlong syndrome

MIM #: 609192 ,608967, 610168, 613795, 603109

This connective tissue disorder, somewhat similar to Marfan syndrome, is an autosomal dominant disorder due to mutations in the genes encoding transforming growth factor beta receptor 1 (*TGFBR1*, type 1A and 2A disease) or 2 (*TGFBR2*, type 1B and 2B disease). The disorder is marked by aortic aneurysms (particularly of the aortic root) that can occur in childhood, arterial tortuosity particularly of the head and neck vessels, bifid uvula, and hypertelorism. Aortic aneurysms and dissections presenting in childhood can be life threatening. Patients with type 1 disease (both 1A and 1B) have craniofacial findings. Those with type 2 disease (2A and 2B) do not, aside from the bifid uvula. Types 1A and 1B are clinically indistinguishable, as are types 2A and 2B. In general, onset of disease is earlier with type 1 disease, and patients have a greater risk of aortic disruption. Both types are associated with earlier aortic disruption than are other connective tissue diseases such as vascular Ehlers-Danlos or Marfan syndrome. This disease is also clinically similar to Shprintzen-Goldberg syndrome (see later), but Loeys-Dietz syndrome is associated with normal intelligence. Additionally, there is a type 3 disease, associated with early-onset arthritis (mutations in the gene *SMAD3*), and a type 4 disease (also due to mutations in *TGFBR2*).

HEENT/Airway: Can have craniosynostosis. Hypertelorism. Can have malar hypoplasia. Can have blue sclerae, downward slanting palpebral fissures. Broad or bifid uvula. Rarely cleft palate. Can have retrognathia or micrognathia.

Chest: Can have pectus excavatum or carinatum.

Cardiovascular: Aortic aneurysms, particularly of the root and ascending aorta. Tortuous head and neck arteries. Can have bicuspid aortic valve. Patent ductus arteriosus. Pulmonary artery aneurysm that can potentially cause airway impingement. May have descending aortic or cerebral aneurysms. Spontaneous coronary artery dissection has been reported. Peripheral arterial aneurysms can occur.

Neuromuscular: Can have tortuous intracranial vessels.

Orthopedic: Can have unstable vertebral subluxations. Arachnodactyly, camptodactyly, clubfoot deformity, scoliosis, joint laxity.

GI/GU: Can have inguinal hernias. Can have abdominal wall hernias.

Other: Easy bruising and abnormal scarring. Translucent skin. High rate of pregnancy complications.

Miscellaneous: Loeys and Dietz recommend surgical repair when the aortic diameter is greater than 99th percentile for age. Aortic anomalies are congenital and have been described *in utero*. The risk for aortic disruption occurs at a smaller aortic diameter than is typical for Marfan syndrome. Intracranial aneurysms can be amenable to endovascular repair. It has been proposed that the 18th dynasty pharaoh Akhenaten and his family (16th to 11th century BCE) had Loeys-Dietz syndrome.

Anesthetic Considerations: Patients may be on chronic beta-blocker therapy, which should be continued perioperatively. Direct laryngoscopy may be difficult in patients with micrognathia. The possibility of an unstable cervical spine should also be considered. Hemodynamics need to be particularly well controlled perioperatively to avoid excessive aortic wall tension.

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LOGIC syndrome

See Laryngo-onycho-cutaneous syndrome

Long-chain acyl-CoA dehydrogenase deficiency

Synonym: Hydroxyacyl-CoA dehydrogenase deficiency; Hydroxydicarboxylic acidemia; LCAD deficiency

MIM #: 201475

This autosomal recessive disease involves defects in the gene for long-chain acyl-CoA dehydrogenase (LCAD), which plays a role in the first step of mitochondrial oxidation of fatty acids. This defect prevents the use of adipose or dietary long-chain (C8-18) fatty acids for energy production or hepatic ketone formation. Short- and medium-chain fatty acids are metabolized normally. LCAD activity is found in mitochondrial trifunctional protein (see later, mitochondrial trifunctional protein deficiency). Defects in LCAD can be isolated or found in association with

defects in the two other LCAD proteins, enoyl-CoA hydratase, and 3-ketoacyl-CoA thiolase. A patient with LCAD deficiency has been reported with hypoparathyroidism, a characteristic of mitochondrial trifunctional protein deficiency. The primary clinical manifestation of this disease is hypoglycemia. Three clinical types have been described, a clinically severe type with onset in the first few days of life that has a high incidence of cardiomyopathy and death, a milder type with onset by age 4 years, and an “adult” type with onset after age 13 years. The intermediate type has less cardiac involvement, and the adult-onset type is limited to muscle involvement with no cardiac disease.

Fatty acids are oxidized in mitochondria. After mobilization from adipose tissue, they are taken up by the liver and other tissues and converted to acyl-CoA esters in the cytoplasm. They enter mitochondria as carnitine esters and become reesterified as acyl-CoA esters. Beta-oxidation results in the liberation of electrons. As beta-oxidation proceeds, the acyl chain is gradually shortened, and this first step in the oxidation process is catalyzed by acyl-CoA dehydrogenases with differing, but overlapping, chain-length specificities. These are very-long-chain, long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases. Symptoms can become more pronounced with fasting or infection.

Although the classic presenting finding is hypoketonemic hypoglycemia with fasting or a mild illness, presenting signs are often nonspecific, making rapid diagnosis problematic. Activation of the LCAD gene and related genes are under the control of PPAR (the peroxisome proliferator-activated receptor) signaling pathway, and pharmacologic methods to activate PPAR, as with fibrates and other PPAR activators, have been investigated as a therapeutic modality. Patients will be on a very low-fat, high-carbohydrate diet.

HEENT/Airway: Retinopathy.

Chest: Can have recurrent pneumonia secondary to hypotonia. Can have recurrent aspiration.

Cardiovascular: Cardiomegaly and possibly cardiomyopathy. Cardiorespiratory arrest.

Neuromuscular: Hypotonia. Recurrent muscle cramps with elevated serum creatinine kinase levels. Peripheral neuropathy. Myopathy. Muscle pain, muscle stiffness, or rhabdomyolysis with exercise in older patients.

GI/GU: Hepatomegaly. Liver disease with cholestasis.

Other: Fasting hypoglycemia without ketonemia. Lactic acidemia during episodes of metabolic decompensation. There is secondary carnitine deficiency

of unclear etiology. A patient with hypoparathyroidism has been described.

Miscellaneous: Presence of this abnormality in a fetus can cause acute fatty liver of pregnancy or HELLP syndrome in the mother. Presumably, abnormal fetal metabolites overwhelm the ability of the heterozygote mother's mitochondria to oxidize them. A family was investigated for infanticide because three infants died as neonates but in retrospect had LCAD.

Anesthetic Considerations: The patient's cardiac status should be evaluated before surgery for the presence of a cardiomyopathy. Serum glucose levels should be monitored perioperatively, and adequate glucose should be supplied. Extensive perioperative fasting should be avoided. Patients with lactic acidemia should not receive lactated Ringer's solution. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

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Long QT syndrome

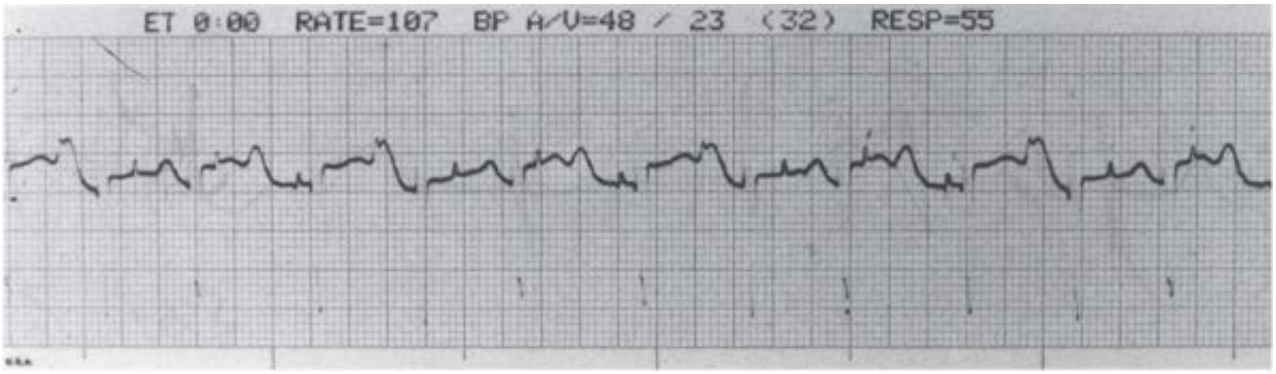
Synonym: Prolonged QT syndrome. [Includes Jervell-Lange-Nielsen syndrome, Romano-Ward syndrome, Andersen (Andersen-Tawil) syndrome, and Timothy syndrome]

MIM #: 192500 and 220400 (LQTS 1), 152427 (LQTS 2), 603830 (LQTS 3), 600919 (LQTS 4), 176261 (LQTS 5), 603796 (LQTS 6), 170390 (LQTS 7), 601005 (LQTS 8), 604001 (LQTS 9), 611819 (LQTS 10), 611820 (LQTS 11), 612955 (LQTS 12)

Long QT syndrome is a cardiac disorder that leads to an increase in cardiac arrhythmogenicity. The QT interval is determined by a balance of ion flows through several sodium and calcium channels (inward depolarizing currents) and outward repolarizing currents (via several potassium channels). Mutations in several genes encoding the cardiac ion channels lead to a prolongation of ventricular repolarization, often evidenced by a prolonged QT interval on the electrocardiogram. However, up to 40% of patients with long QT syndrome do not manifest a prolonged QT interval on the electrocardiogram and remain undiagnosed until they become symptomatic. While superficially similar, there is some phenotypic variation among the different channelopathies. Phenotype does not always follow genotype, and the clinical presentation is affected by what specific part of the channel is abnormal (pore regions are worse) and how much of the function of the channel is left intact. Long QT syndrome can present as syncope, seizures, or sudden death. Patients are predisposed to develop polymorphic ventricular tachycardia (*torsade de pointes*), which results in syncope or seizure-like activity if it ceases spontaneously, or sudden death if it degenerates into ventricular fibrillation. Triggers include physical activity, anxiety, and stress—and therefore include surgery and anesthesia. In 1957, **Jervell and Lange-Nielsen** described an autosomal recessive form of long QT syndrome associated with congenital nerve deafness (found in LQTS 1 and 5), and later **Romano and Ward** independently described a much more common autosomal dominant form of LQTS 1 that is not associated with deafness. Children with Jervell-Lange-Nielsen syndrome are at high risk for cardiac events in the first year of life and more than 90% will have an event during childhood. Heterozygotes with Jervell-Lange-Nielsen syndrome have a prolonged QT interval without deafness. Congenital long QT syndrome is due to one of several mutations in a variety of genes: long QT syndrome 1 (LQTS 1), accounting for approximately 42% to 54% of patients, is due to a loss-of-function mutation of the *KCNQ1* gene, which encodes part of the cardiac slow delayed rectifier potassium

channel (I_{Ks}), which is also found in the inner ear; long QT syndrome 2 (LQTS 2), accounting for approximately 35% to 45% of patients, is due to a loss-of-function mutation of the *HERG* gene (also known as *KCNH2*), which encodes the channel carrying the rapid delayed rectifier current (I_{Kr}); long QT syndrome 3 (LQTS 3), which accounts for approximately 5% of patients, is due to a gain-of-function mutation of the *SCN5A* gene, which encodes the sodium channel and which is also responsible for Brugada syndrome (see earlier); long QT syndrome 4 (LQTS 4) is due to a defect in the ankyrin-B gene, whose gene product localizes ion channels appropriately; long QT syndrome 5 (LQTS 5), which is generally a milder disease accounting for approximately 3% of patients, has been ascribed to the gene *KCNE1*, which encodes the ß subunit of I_{Ks}, a potassium channel subunit that regulates both *KCNQ1* and *HERG*, and can cause both clinical syndromes; long QT syndrome 6 (LQTS 6), accounting for about 2% of patients, is due

to a mutation in the gene *KCNE2*, another regulatory gene involved with the rapid delayed rectifier I_{Kr} (with *HERG*) and with the slow rectifier I_{Ks} (with *KCNQ1*); long QT syndrome 7 (**Andersen syndrome**, LQTS 7), which is due to abnormalities in the gene *KCNJ2*, coding for the inward rectifier potassium current; and long QT syndrome 8 (**Timothy syndrome**, LQTS 8), which is due to a mutation in the gene *CACNA1C*, which encodes the L-type calcium current, $Ca_V1.2$, reducing inactivation of the calcium channel during the plateau phase of the cardiac action potential. There is a high incidence of death in young childhood with Timothy syndrome with acute arrhythmias precipitated by infections, severe illness, or anesthesia. Long QT syndrome 9 (LQTS 9) is caused by mutations in *CAV3*, encoding caveolin-3, a component of the dystrophin glycoprotein complex and which modifies the sodium channel. There is nonexertional syncope and cardiac arrest during sleep. Long QT syndrome 10 (LQTS 10) is similar to LQTS 3 and has been reported in only a single Mexican family. It is due to a mutation in the gene *SCN4B*, which encodes a ß subunit of the sodium channel. Presumably treatment with sodium channel blockers would be helpful. Two additional rare syndromes are LQTS 11 and LQTS 12 about which little is known clinically.



Long QT syndrome. This electrocardiogram is from a newborn boy in whom an arrhythmia was noticed. In addition to prolongation of the QT interval, there is also 4:3 Wenckebach second degree block. His mother and maternal grandmother had been treated for a “seizure disorder” with anticonvulsants, and both died suddenly (the mother shortly before the diagnosis was made in her infant).

LQTS 7, also known as **Andersen syndrome**, is very rare and produces a skeletal and a cardiac muscle phenotype. It has several distinctive dysmorphic features, including hypertelorism, ptosis, low-set ears, cleft palate, and micrognathia.

Common precipitating events are stress, pain, diving or swimming (LQTS 1), or sudden noises (LQTS 2), but events with LQTS 3 and LQTS 9 typically occur with sleep. Exercise prolongs the QT in LQTS 4 causing syncope or sudden death. Although LQTS 1 and 2 are autosomal disorders, the mutated alleles are transmitted to daughters more often than to sons.

It is proposed that the critical factor is not QT prolongation, but rather heterogeneity of the QT interval (described as dispersion of repolarization) that predisposes to the development of *torsade de pointes*. Quite a few drugs that can prolong the QT interval do not have an effect on dispersion, rendering blanket statements about the risk of specific drugs complicated. Pentobarbital, for example, increases QTc but decreases dispersion.

High risk factors for malignant arrhythmias include QTc > 500 msec, T-wave alternans, boys less than 10 years old with LQTS 1 and with 2:1 AV block, and homozygous or compound heterozygous disorders (e.g., Jervell-Lange-Nielsen). In adolescents, those with a syncopal event are at high risk for recurrent cardiac events in the next 2 years. In adults, high risk factors include female gender (except for LQTS 3), QTc ≥ 550 msec, LQTS 2, frequent cardiac events when younger than 18 years, and the 9 postpartum months. In general, the incidence of events decreases with aging in males and increases in females. Finally, QTc ≥ 500 msec while on beta-blocker treatment is a risk factor. The incidence is lower but the lethality higher, with LQTS 3, and risk is not determined by the QTc duration.

The age of onset of symptoms in long QT syndrome varies by genotype, ranging from infancy to adulthood, but in most cases occurs sometime during childhood or adolescence. The clinical consequences of cardiac events also vary by genotype. The risk of cardiac events is highest in patients with LQTS 1 and LQTS 2, whereas the highest percentage of lethal cardiac events occurs in patients with LQTS 3.

The binding site for the proarrhythmic local anesthetic drugs is the *HERG* potassium channel. *KCNQ1*/*KCNE1* channel complexes that generate the slowly activating delayed rectifier current (I_{Ks}) are unaffected. It is suggested that certain mutations will increase the risk of LQTS patients to the arrhythmogenic effects of local anesthetics (10).

HEENT/Airway: Congenital nerve deafness with Jervell-Lange-Nielsen syndrome. Low-set ears, hypertelorism, and hypoplastic mandible with Andersen

syndrome. Persistent primary teeth and oligodontia with Andersen syndrome.

Cardiovascular: Prolonged QTc interval (QT interval corrected for heart rate), usually defined as greater than 440 msec. Can cause sudden death due to ventricular tachyarrhythmia, classically *torsade de pointes*. Untreated symptomatic patients have a 5% to 20% annual risk of a syncopal episode and an approximate 10-year survival rate of 50%. If treated, the 10-year mortality can be reduced to 3% to 4%. Therapies have included beta antagonists, cardiac pacing, and left stellate ganglion ablation (see below). Current therapy includes beta-blockers and an implantable defibrillator with pacing capability (to counteract the bradycardic effects of beta-blockade). The effect of beta-blockers is indirect, through the autonomic nervous system. By themselves, they actually increase the QT interval. The incidence of syncopal episodes decreases with age. Patients with Andersen syndrome may have associated congenital cardiac defects and a particularly high incidence of sudden death. Patients with Timothy syndrome can have associated congenital cardiac defects and bradycardia with conduction block and T-wave alternans. T-wave abnormalities can occur: broad based (LQTS 1), low amplitude and notched (LQTS 2), late appearing (LQTS 3), and mild prolongation but with prominent U waves (LQTS 7). T-wave alternans can be a precursor to a malignant ventricular arrhythmia. Patients with LQTS 4 often have bradycardia and require a

pacemaker.

Neuromuscular: Potassium-sensitive periodic paralysis (hypo-, normo-, or hyperkalemic, but usually hypokalemic) in Andersen syndrome. May have learning disability in Andersen syndrome. Autism spectrum disorder in Andersen syndrome and Timothy syndrome.

Orthopedic: Syndactyly, short stature, scoliosis, and clinodactyly with Andersen syndrome. Syndactyly with Timothy syndrome.

Other: The postpartum period is associated with a significantly increased risk of cardiac events, particularly with LQTS 2. Timothy syndrome patients can have intermittent hypoglycemia and immunodeficiency.

Miscellaneous: The first reported case of long QT syndrome may have been that of a deaf girl in 1856 who reportedly died suddenly while being admonished at school. Jervell was one person, and Lange-Nielsen was another. *HERG*, the gene involved in LQTS 2, is the human homologue of the *ether-a-go-go* gene, a potassium channel gene originally described in *Drosophila*, which was so named because it results in abnormal movements on exposure to ether.

Anesthetic Considerations: When presented with a patient with known LQTS, it is strongly suggested that preoperative consultation with a cardiologist be obtained.

Patients with long QT syndrome are at risk for developing ventricular tachyarrhythmias perioperatively, particularly *torsade de pointes*. An intraoperative arrhythmia can be the first manifestation of disease. Unfortunately, there is no definitive perioperative standard of care for these patients. Beta-blockade therapy can reduce, but not eliminate, the risk of malignant tachyarrhythmias. Beta-blockers will not shorten the resting QTc. Beta-blockade is most successful in LQTS 1 and 5, less so in LQTS 2 and 6, and may be contraindicated in LQTS 3 as it causes bradycardia. LQTS 3 patients will benefit from sodium channel blockers such as flecainide or mexiletine, but they may increase the risk of sudden death in the related Brugada syndrome. Cardiac medications should be continued perioperatively. Most patients will be receiving beta-blockade therapy, and the adequacy of beta-blockade should be evaluated. Hypocalcemia, hypomagnesemia, and hypokalemia can all prolong the QT interval and should be corrected prior to surgery and averted perioperatively. Pretreatment with magnesium, even in normomagnesemic patients, has been suggested. A left stellate ganglion block with local anesthetic has been experimented with in the past to shorten the QT interval and decrease the risk of ventricular tachyarrhythmias perioperatively. Unfortunately, this approach has not proven beneficial in most patients and is now reserved for patients refractory to all other interventions. Implanted defibrillators should have the defibrillator function disabled immediately prior to surgery, with the concurrent placement of cutaneous defibrillator pads. An external defibrillator and appropriate resuscitation drugs should always be available. Patients should have continuous electrocardiographic monitoring throughout surgery and well into the recovery period, possibly for a full 24 hours after the completion of surgery (16). Adequate premedication and good control of postoperative pain are important. Maintenance of a quiet environment perioperatively is also important, as auditory stimuli can trigger tachyarrhythmias.

Light anesthesia, hypoxemia, hypocarbia, and hypercarbia should be avoided. Hypothermia prolongs the QT interval and should be avoided. Periods of brief stimulation, such as laryngoscopy and tracheal intubation or extubation, can be covered with the addition of a short-acting beta-blocker or opioid. The Valsalva maneuver can increase the QT interval and should be avoided. Surgical infiltration of local anesthetic with epinephrine has resulted in intraoperative *torsade de pointes* (27). Consider using local anesthesia without epinephrine when performing local and regional blocks (12). Extubation should be considered while the patient is still deeply anesthetized, or, if done at a lighter plane, after additional beta-blockade, because ventricular

fibrillation has developed during emergence. Placement of a central venous catheter could be considered, as it

would facilitate transvenous pacing should that become necessary, but is not typical care. Drugs that can prolong the QT interval should be avoided and include the phenothiazines and erythromycin. The list of drugs that have been shown to potentially lengthen the QT interval continues to grow and includes many drugs encountered in everyday anesthetic practice, such as lidocaine, ondansetron, droperidol, chlorpromazine, haloperidol, and tamoxifen. The QT is also prolonged by class Ia (e.g., quinidine, procainamide), class II (e.g., sotalol), and class III (e.g., amiodarone) antiarrhythmics. An updated list of the many medications that can prolong the QT interval can be found at www.crediblemeds.org.

Arrhythmias in children with LQTS have been reported immediately following the administration of ondansetron with (3) or without (5) temporally related reversal of neuromuscular blockade during emergence from anesthesia. There are additional reports implicating reversal of neuromuscular blockade (20). Ventricular fibrillation has also been reported during the maintenance phase of anesthesia (4).

Because of the sensitization of the myocardium to catecholamines by halothane, other volatile anesthetics have been suggested as better choices. Halothane, isoflurane, and sevoflurane have all been shown to prolong the QT interval in healthy humans, which may or may not be predictive of their effect in patients with long QT syndrome as the risk appears to be related to QT dispersion rather than strictly to the QT interval. All these volatile agents have a record of use in both eventful and uneventful anesthetics in patients with long QT syndrome. Experience with desflurane has not yet been reported. Isoflurane has shortened the QT interval in patients with long QT syndrome, and thiopental has had no effect (28). However, an opposing study arrived at the conclusion that halothane shortened the QT interval in normal patients, whereas isoflurane prolonged it (25). Sevoflurane has been shown to prolong the QT interval in a patient with long QT syndrome; however, ventricular arrhythmias did not occur except during periods of intense stimulation and increased sympathetic tone (22). In another patient with long QT syndrome, sevoflurane precipitated *torsade de pointes* intraoperatively, which resolved when the anesthetic was changed to propofol. Because of its sympathomimetic properties, ketamine should be avoided in patients with long QT syndrome. Propofol causes less QT prolongation than does thiopentone in normal humans. Propofol has also been shown to reverse sevoflurane-induced QT prolongation (19). Succinylcholine and the nondepolarizing muscle relaxants have been used without complications, even though succinylcholine prolongs the QTc. Because of the tachycardia associated with pancuronium, other nondepolarizing muscle relaxants have been suggested as better choices. Midazolam has no effect on the QTc (16). Opioids have been used in patients with long QT syndrome without adverse effects. Spinal and epidural anesthesia have been used successfully for Cesarean section.

Treatment of perioperative *torsade de pointes* includes electrical cardioversion if the patient is hemodynamically compromised. Even normomagnesemic patients should receive magnesium (30 to 50 mg/kg loading dose, followed by 0.3 to 1 mg/kg/h—in adults 2 gm load then 2 to 4 mg/minute) and monitoring of serum levels. Other treatment options include correction of any electrolyte abnormalities (particularly potassium, magnesium, and calcium), beta-blockade, nicorandil for LQTS 2 (21), and increasing the heart rate (which decreases the QT interval). The heart rate may be increased using atrial pacing (overdrive pacing) or intravenous isoproterenol. Amiodarone can prolong repolarization and predisposes to *torsade de pointes*, so is best avoided.

Patients with Andersen syndrome (LQTS 7) have dysmorphic facial features, which may lead to difficulty with intubation. In patients with Andersen syndrome, succinylcholine should be avoided because of the risk of a hyperkalemic response (13).

There is a case report of recurrent arrhythmias with prolonged use of arm tourniquets in a child with Timothy syndrome (LQTS 8) that resolved with deflation. It was proposed that sympathetic stimulation from ischemic pain was not adequately controlled by axillary plexus blocks (9).

Pregnancy is a particularly high-risk period. The postpartum period is the period of highest risk. Ten percent of

affected women will have their first episode in the postpartum period. Oxytocin will transiently increase the QT interval (1 to 3 minutes) but has been used without complication.

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Louis-Bar syndrome

See Ataxia-telangiectasia

Lowe syndrome

Synonym: Oculocerebrorenal syndrome

MIM #: 309000

The hallmarks of this X-linked disorder are hydrophthalmia, cataracts, intellectual disabilities, vitamin D-resistant rickets, aminoaciduria, and reduced ammonia production by the kidney. This syndrome is caused by a defect in the *OCRL1* gene. The gene product is a lipid phosphatase that controls levels of a critical cellular metabolite, phosphatidylinositol 4,5-bisphosphate-5-phosphatase, which is localized in a trans-Golgi network involved in actin polymerization. Actin is required for formation and maintenance of tight junctions in the eye and proximal renal tubule. A few cases have been documented in females. Mutations in this gene are also responsible for Dent disease (not discussed in this text).

HEENT/Airway: Frontal bossing. Hydrophthalmia, cataracts in infancy, lens opacities, corneal scarring, enophthalmos, nystagmus, glaucoma. Female carriers can have fine lens opacities and posterior cataracts. Dental cysts, enamel hypoplasia. Can have retrognathism.

Neuromuscular: Mild to moderate intellectual disabilities. Hypotonia, intention tremor. Behavioral problems including stereotypical behavior, stubbornness, and temper tantrums. Seizures.

Orthopedic: Vitamin D-resistant rickets. Scoliosis, kyphosis, platyspondyly. Genu valgum. Hypermobile joints. Osteomalacia. Subcutaneous nodules on the fingers and flexion contractures of the digits. Short stature.

GI/GU: Cryptorchidism. Renal failure, renal tubular acidosis, aminoaciduria, proteinuria, carnitine wasting, phosphaturia with hypophosphatemia. Can develop Fanconi syndrome (see earlier).

Other: Failure to thrive.

Anesthetic Considerations: Serum electrolytes, phosphate level, ionized calcium level, and acid-base status should be evaluated preoperatively. Patients may be receiving chronic bicarbonate therapy. Chronic stable hypokalemia is usually well tolerated, but the risk of perioperative arrhythmia exists. Hyperventilation and hyperglycemia can both further decrease blood potassium levels and should be avoided. If acidotic, patients may be more sensitive to opioids as more opioid will exist in the nonionized state, facilitating penetration into the brain. Renal dysfunction has implications for the titration of perioperative fluids and for the choice of anesthetic drugs. Rachitic extremities must be carefully positioned and padded. Patients can have elevated intraocular

pressure, and positions or interventions that further elevate intraocular pressure should be avoided if possible. Patients with glaucoma can be receiving chronic beta-blocker eye drops. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Lown-Ganong-Levine syndrome

MIM #: 108950

This electrophysiologic syndrome is closely related to Wolff-Parkinson-White syndrome (WPW, see later). In WPW, Kent fibers bypass the atrioventricular (AV) node to enter the ventricular myocardium directly, accounting for the short PR interval (the normal AV nodal delay is bypassed) and the initial slow upstroke of the QRS, because of the initial cell-to-cell transmission of the electrical impulse, until the normally conducted impulse finally gets through the AV node and depolarizes the ventricles rapidly by way of the His-Purkinje system. In Lown-Ganong-Levine syndrome, James fibers, which are analogous to Kent fibers, bypass the AV node but insert into the His bundle. As a consequence, the PR interval is short, but there is no delta wave because the sequence of ventricular depolarization is normal. The presence of James fibers sets up a potential reentry circuit with the possibility of development of paroxysmal supraventricular tachycardia, just as in WPW.

Cardiovascular: Risk of atrial tachyarrhythmias (paroxysmal tachycardia). Rate-related bundle branch block can confuse the diagnosis. Has been reported in association with left ventricular noncompaction.

Miscellaneous: Dr. Bernard Lown developed the first direct current defibrillator. In 1985, he shared the Nobel Peace Prize on behalf of the International Physicians for the Prevention of Nuclear War, which he cofounded. He also cofounded Physicians for Social Responsibility.

Anesthetic Considerations: Episodes of reentrant tachycardia may be induced by sympathetic stimulation, and so good preoperative sedation would seem reasonable. Drugs used to terminate tachycardia (adenosine or beta-blockers) may exacerbate reactive airway disease. $Beta_2$ agonists such as albuterol should not induce arrhythmias.

Perioperative increases in vagal tone, such as from drugs or gagging, may inhibit normal antegrade conduction through the AV node and unmask conduction down the bypass tract with preexcitation (short PR interval) suddenly visible.

Verapamil and digoxin (without quinidine) are contraindicated for the treatment of atrial flutter or fibrillation in these patients because they may accelerate the rate of conduction through the bypass tract and induce ventricular fibrillation. Concurrent verapamil and propranolol (and possibly other combinations of calcium channel and beta-blockers) may cause significant bradycardia. Chronic therapy with amiodarone may cause hypothyroidism or pulmonary fibrosis.

Isoflurane has been used without apparent problems during electrophysiologic mapping or radiofrequency catheter ablation in patients with the related Wolff-Parkinson-White syndrome (see later). Propofol has also been used without incident.

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Lymphedema-distichiasis syndrome

Synonym: Distichiasis-lymphedema syndrome

MIM #: 153400

This autosomal dominant syndrome is characterized by an extra row of eyelashes and generalized lymphedema. There is marked variability of expression with this syndrome. The syndrome is due to abnormalities in the forkhead family transcription factor gene *FOXC2*. This gene is a regulator of adipocyte metabolism. There are several other allelic syndromes with lymphedema being a common factor. It has been suggested that the defect is due to aberrant lymphatic vessel valve formation and an abnormal interaction between the lymphatic endothelial cells and pericytes.

HEENT/Airway: Distichiasis—a double row of eyelashes. The supernumerary lashes arise from the meibomian glands and are usually turned inward, causing corneal irritation. Occasional ptosis, microphthalmia, strabismus, epicanthal folds. May have photophobia. Occasional cleft palate, bifid uvula, micrognathia. Webbed neck.

Cardiovascular: May have a variety of congenital cardiac defects, including defects of the conduction system. Varicose veins.

Neuromuscular: Spinal extradural arachnoid cysts (SEDACs) are common.

Orthopedic: Vertebral anomalies. Occasional scoliosis/kyphosis or short stature.

Other: Lymphedema, most pronounced in the lower extremities, is usually apparent by the end of puberty. Varicose veins. One family has been reported in which affected members also had renal disease and diabetes.

Miscellaneous: Actress Elizabeth Taylor had distichiasis, which in her case was cosmetically enriching and apparently did not lead to chronic corneal irritation.

Anesthetic Considerations: Micrognathia, if present, may make laryngoscopy and tracheal intubation more difficult. Peripheral intravenous access may be difficult secondary to lymphedema. The liberal use of eye ointment is indicated, particularly in patients who already have some degree of corneal irritation. Epidural cysts may cause secondary neurologic impairment, which should be well documented before undertaking neuraxial anesthesia/analgesia. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Lysinuric protein intolerance

Synonym: Dibasic aminoaciduria type 2

MIM #: 222700

This autosomal recessive disease is the result of a disorder in the transport of lysine as well as the other cationic amino acids arginine and ornithine. It is due to a mutation in the gene *SLC7A7*, which encodes an amino acid transporter. Urinary clearance and excretion of these amino acids is increased, and intestinal absorption is decreased. The intestinal defect has been localized to the antiluminal epithelial surface. The effects on lysine are most pronounced. Symptoms usually develop when infants stop breast-feeding. Patients learn to avoid a high-protein diet. Treatment is by protein restriction and oral citrulline supplementation. **Dibasic aminoaciduria type 1** is a phenotypically related autosomal dominant disorder [not discussed in this text (*MIM #*: 222690)].

Chest: Interstitial pneumonitis, which is of unclear origin and may be severe or even fatal. Patients may have dyspnea, cough, and rarely hemoptysis or pulmonary hemorrhage. Histologically, the process looks like alveolar proteinosis.

Neuromuscular: Episodes of stupor and asterixis. Coma with high-protein diets. Most patients have normal intelligence, but there may be mild to moderate intellectual disability. Hypotonia. Weakness. Force feeding a high-protein diet has resulted in an isoelectric electroencephalogram.

Orthopedic: Short stature. Osteopenia with bone fragility.

GI/GU: Diarrhea, malabsorption. Episodes of nausea and vomiting. Hepatosplenomegaly, cirrhosis. Immune complex glomerulopathy, renal failure.

Other: Protein intolerance, failure to thrive, hyperammonemia (from insufficient ornithine to support ornithine transcarbamylase), low blood urea nitrogen. May be pancytopenic. May be hypertriglyceridemic. Sparse hair. Loose skin. Centripetal obesity. Pregnancies at high risk (hemorrhage and toxemia), but infants of mothers with the disease are unaffected. May exhibit intermittent hemophagocytic lymphohistiocytosis— defined as fever, hepatosplenomegaly, hypofibrinogenemia, hypertriglyceridemia, and pancytopenia, with hemophagocytosis occurring in bone marrow, spleen, or lymph nodes. Abnormal macrophage function, related to arginine transport.

Miscellaneous: Patients have been misdiagnosed as having celiac disease. Some findings are due to arginine deficiency, such as endothelial dysfunction from impaired nitric oxide production. Whole lung lavage has been proposed for treatment of the apparent pulmonary alveolar proteinosis. A child has been reported who received a lung transplant for pulmonary alveolar proteinosis, which then recurred 18 months later in the transplanted lung. The interstitial pneumonitis may be steroid responsive. May have impaired nitric oxide production, and thrombocytopenia with elevated antithrombin III levels.

Anesthetic Considerations: The patient's pulmonary and renal function should be evaluated carefully preoperatively. Blood urea nitrogen may be a poor indicator of renal function. Patients may be pancytopenic, so hematologic and coagulation status should be assessed preoperatively. A low-protein diet should be continued perioperatively. Patients with interstitial pneumonitis may be taking steroids and require perioperative stress doses of steroids. Postoperative ventilation may be necessary in patients with severe lung disease. Patients with severe osteopenia should be carefully positioned and padded.

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Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

M

Machado-Joseph disease

See Joseph disease

MADD

See Glutaric acidemia type II

Maffucci syndrome

Included in Ollier disease

Majewski-type short rib-polydactyly syndrome

See Short rib-polydactyly syndrome

Malignant atrophic papulosis

Synonym: Degos disease, Kohlmeier-Degos disease

MIM #: 602248

This multisystem vasculitis of small and mediumsized arteries affects primarily the skin, gastrointestinal tract and central nervous system. The etiology of this disease is not known, although familial cases have been reported. Boys are more frequently affected than are girls, with a ratio of 3:1. The disease is sometimes limited to the skin. Systemic involvement can have onset weeks to months after skin manifestations and can indicate severe and even fatal disease.

HEENT/Airway: Avascular patches on the conjunctivae, although other ocular components can be affected. May have avascular involvement of sclerae, choroid, retina, or optic nerve.

Chest: Pleuritis with pleural effusions.

Cardiovascular: Constrictive pericarditis. Myocardial infarctions have been reported.

Neuromuscular: Central nervous system infarcts or hemorrhage.

GI/GU: Gastrointestinal lesions may result in bowel infarction and perforation.

Other: Skin lesions are marked by a wedge-shaped area of necrosis extending from the epidermis through the dermis. There are multiple atrophic skin papules with an atrophic white center surrounded by a telangiectatic border. In one report, they were misdiagnosed in an infant as cigarette burns.

Anesthetic Considerations: Pleural and pericardial disease should be excluded preoperatively if possible. Patients may require emergent surgery for bowel perforation and can be quite ill at the time of surgery. Meticulous perioperative eye protection is indicated in these patients. Patients may be on corticosteroids or antimetabolite drugs, which have had preliminary use in the treatment of the disease.

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Malignant hyperthermia susceptibility

MIM #: 145600

Malignant hyperthermia (MH) is a potentially lethal disorder of skeletal muscle. In humans, susceptibility to malignant hyperthermia is inherited in an autosomal dominant fashion. Malignant hyperthermia manifests as a hypermetabolic response to volatile inhalational anesthetic agents and/or succinylcholine and uncommonly to exertion or heat stress. It is characterized by increased oxygen consumption, increased carbon dioxide production, and rhabdomyolysis. In one large perioperative series, almost all patients were exposed to volatile anesthetics, and the incidence was similar whether or not there was exposure to succinylcholine (3). Clinical signs of

the hypermetabolic state include elevated end-tidal carbon dioxide, tachypnea, tachycardia, acidosis, hyperkalemia, muscle rigidity, myoglobinuria, and hyperpyrexia (usually a late finding). Onset of signs can immediately follow the induction of anesthesia or can occur hours later, and can even present postoperatively (usually in the postanesthesia care unit). Signs may appear later with isoflurane or desflurane than with sevoflurane. Interestingly, the reaction does not always occur in susceptible individuals despite exposure to known triggering agents. In one series from the North American Registry, 51% had two or more unremarkable anesthetic exposures prior to developing a malignant hyperthermia episode (3). Rarely, an episode of malignant hyperthermia can occur in susceptible individuals in the absence of anesthetic or succinylcholine exposure. Children appear to be at greater risk for developing malignant hyperthermia than adults, and boys more so than girls, for unclear reasons.

Malignant hyperthermia is caused by an abnormal elevation of intracellular calcium secondary to an increase in the release of calcium from the sarcoplasmic reticulum. This increased release of calcium is usually due to a mutation in the gene encoding for the ryanodine receptor (*RYR1*), which is embedded in the sarcoplasmic reticulum and is responsible for regulating calcium transport. Rarely, mutations in the gene encoding DHPR, the dihydropyridine receptor on the T tubule that interacts with the ryanodine receptor, can also be responsible for MH. MH has also been ascribed to a specific mutation in the gene *CACNA1S*, encoding the α-1 subunit of the skeletal muscle L-type calcium channel ($Ca_V1.1$). There are at least 30 different mutations of *RYR1* associated with malignant hyperthermia susceptibility, and some patients with the disease cannot be mapped to any of the known genetic variants. Patients with **multiminicore disease** (not discussed in this text), **central core disease** (CCD), or **King-Denborough syndrome** (see earlier for both) are likely to be malignant hyperthermia susceptible. It appears that although the pathophysiology of central core disease and malignant hyperthermia involves mutations in *RYR1*, the mechanisms of altered calcium release differ. Various mutations can be associated with the phenotype of MH, CCD, or both. It may be that the phenotype depends on the leak rate of the RYR1 channel and whether calcium is depleted excessively and cannot support adequate contractility, resulting in weakness. An association between malignant hyperthermia susceptibility and multiple other syndromes has frequently been proposed. The weak, verging on absent, support for these has recently been reviewed (4).

The caffeine-halothane contracture test has been the gold standard for diagnosing malignant hyperthermia susceptibility for several decades. This test involves extracting a piece of skeletal muscle from the patient's thigh, exposing it *in vitro* to the ryanodine receptor agonists halothane and caffeine, and measuring the degree of muscle contraction. Muscle tissue from patients susceptible to malignant hyperthermia typically shows an excessive degree of contraction. There are differences in the sensitivity of this test—sevoflurane, for example, does not reliably detect malignant hyperthermia sensitivity in this *in vitro* test. Development of a genetic screen for malignant hyperthermia susceptibility has been the focus of considerable research. The number of *RYR1* mutations associated with malignant hyperthermia susceptibility has made genetic testing for this disorder challenging. In some families, a specific mutation can be found to correlate with malignant hyperthermia susceptibility, and in those families, a genetic test can be used in place of the muscle biopsy. If the same mutation is found, then the patient is considered to be susceptible to malignant hyperthermia. If the mutation is not identified, malignant hyperthermia susceptibility CANNOT be ruled out. Not all patients with malignant hyperthermia will have the disorder associated with a known mutation. Of the several hundred identified mutations in *RYR1*, only a few more than 30 have been determined to be causative.

Initially, the mortality rate associated with malignant hyperthermia was 70%, but with the advent of dantrolene and advances in supportive care, the mortality rate is now less than 5% in developed countries.

HEENT/Airway: Masseter spasm can be the presenting sign of muscle rigidity.

Chest: Respiratory acidosis. Can develop pulmonary edema.

Neuromuscular: Generalized muscle rigidity.

GI/GU: Cola-colored urine. Can develop renal dysfunction.

Other: Metabolic acidosis is less frequent than is respiratory acidosis.

Miscellaneous: Malignant hyperthermia was first described in 1962 by Denborough and Lovell who identified a family in Australia in which 10 of 38 people who had undergone a general anesthetic had died. A case of fatal recrudescence 10 hours after a successful 24-hour course of dantrolene has been reported. The mechanism of dantrolene is not known. There is evidence that it works via modification of other calcium entry systems and not specifically via the RYR1 channel.

Anesthetic Considerations: Patients known to be susceptible to malignant hyperthermia must receive a nontriggering general anesthetic, a neuraxial block or a peripheral nerve block. If an anesthetic machine is used, it should either be “MH dedicated” or adequately flushed with oxygen. The duration of flushing required depends on the model of anesthesia machine—with some of the newer anesthesia workstations requiring greater than 60 minutes of flushing. Alternatively, placement of a commercially available charcoal filter on the inspiratory limb of the anesthesia circuit will reduce anesthetic gas concentration to very low (trace) levels. Prophylactic dantrolene administration is not indicated. Liquid crystal skin temperature probes have not proven to correlate adequately with core temperature probes.

The treatment of malignant hyperthermia includes immediate discontinuation of triggering agents; hyperventilation with 100% oxygen; administration of dantrolene in doses of 2.5 mg/kg, repeated up to 10 mg/kg; active cooling; and appropriate treatment of hyperkalemia (hyperventilation, bicarbonate, calcium, glucose and insulin, epinephrine). Calcium channel blockers should not be used with dantrolene, as this may exacerbate hyperkalemia. Patients should be monitored closely for 48 to 72 hours after the initiation of treatment, being especially vigilant for adequate urine output, the development of myoglobinuria or renal failure, or the development of a coagulopathy. Relapse can occur in 25% of patients within 24 hours of the initial administration of dantrolene, so dantrolene should be continued in the postoperative period (1 mg/kg intravenously or orally every 6 hours until the patient's vital signs have stabilized in the normal range).

The Malignant Hyperthermia Association of the United States (MHAUS) established a hotline that can be accessed for medical consultation 24 hours a day 7 days a week by calling 1 (800) MHHYPER [1 (800) 644-9737] in the United States or (315) 464-7079 from outside of the United States. Or visit the MHAUS Web site at www.mhaus.org.

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Malpuech syndrome

Synonym: 3MC syndrome, Carnevale syndrome, Mingarelli syndrome, Michels syndrome

MIM #: 248340, 257920, 265050

The term 3MC syndrome is currently used to describe what were previously known as four separate autosomal recessive disorders: Malpuech, Mingarelli, Michels, and Carnevale syndromes. They are predominantly disorders of facial dysmorphism. The 3MC syndrome is due to mutations in the gene *MASP1*. There is also a 3MC syndrome-2, which is due to mutations in the gene *COLEC11*, and a 3MC syndrome-3, which is what had been referred to as Malpuech syndrome.

HEENT/Airway: Craniosynostosis. Malar hypoplasia. Hypertelorism, blepharophimosis, blepharoptosis, and high-arched eyebrows. Rarely anterior chamber defects. Hearing loss. Cleft lip and palate. Micrognathia has been reported. Prominent teeth. There may be natal teeth, and these are lost soon after birth.

Cardiovascular: May have cardiac defects.

Neuromuscular: Cognitive impairment.

Orthopedic: Radioulnar synostosis. Thoracolumbar scoliosis. Rare caudal appendage.

GI/GU: Rare umbilical hernia or diastasis recti. Can have genital and bladder anomalies including ectopic testis, micropenis, bifid scrotum, and hypospadias.

Other: Postnatal growth retardation.

Anesthetic Considerations: Mandibular hypoplasia, micrognathia, and prominent teeth can make laryngoscopy and intubation challenging. Spinal malformations may make spinal or caudal blocks more difficult to place.

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Mandibulofacial dysostosis

See Treacher Collins syndrome

Mannosidosis

Synonym: Alpha-mannosidosis

Note: Beta-mannosidosis (*MIM #:* 248510), not discussed here, is less common and more severe.

MIM #: 248500

This autosomal recessive progressive lysosomal storage disease is due to a mutation in the gene *MAN2B1*, encoding lysosomal alpha-mannosidase. Three types have been described: Type 1 is the mildest with onset after age 10 years, without skeletal involvement, and slowly progressive. Type 2 has onset before age 10 years, has skeletal abnormalities, and is slowly progressive with ataxia developing by age 20 to 30 years. Type 3 is the most severe form with onset in early infancy, skeletal abnormalities, and early death from central nervous system disease or myopathy. Most patients fall in type 2. This replaces an earlier nosology where type I was the more severe and type II the less. As a lysosomal storage disease, the phenotype resembles that of Hurler syndrome. There is deposition of mannoside-rich oligosaccharides in many tissues. The clinical spectrum varies widely.

HEENT/Airway: Large head with thick calvarium. Coarse features. Frontal bossing. Low anterior hairline. Thick eyebrows. Spoke-like lens opacification. Retinal detachments in adults. Nystagmus in adults. Flat nose. Macroglossia, widely spaced teeth, gingival hypertrophy. Prognathism. Sensorineural deafness. Large ears.

Chest: Recurrent respiratory tract infections. Pectus carinatum. Thick ribs.

Neuromuscular: Ataxia. Hypotonia. Muscle pain. Intellectual disabilities. Dilated cerebral ventricles. Corticospinal and spinocerebellar tract disease in legs in adults. Hyperreflexia. Extensor plantar response. Cerebellar atrophy in adults.

Orthopedic: Lumbar gibbus, big hands and feet, dysostosis multiplex, and bowed femurs. Spondylosis. Spondylolisthesis of L5 on S1. Abnormal vertebral bodies.

GI/GU: Mild hepatosplenomegaly. Recurrent vomiting. May have inguinal hernia.

Other: Tall stature. Pancytopenia, storage cells in marrow. Vacuolated lymphocytes. Immunoglobulin deficiency. Susceptibility to infections, particularly respiratory tract, middle ear, and gastrointestinal tract. Antiplatelet and antineutrophil antibodies. Low haptoglobin. Growth retardation in severe cases. Hypertrichosis.

Miscellaneous: Alpha-mannosidosis has been described in cattle, cats, and guinea pigs. Both hematopoietic stem cell and bone marrow transplantation have ameliorated the disease in humans, and recombinant enzyme replacement has been preliminarily evaluated (2).

Anesthetic Considerations: Since these patients are phenotypically similar to patients with Hurler syndrome, it might be expected that similar concerns would apply. These include difficult face mask fit, and difficult laryngoscopy and intubation that can worsen with age. However, a recent series showed no difficulty with mask ventilation, placement of a laryngeal mask, or orotracheal intubation (2), although this might have been reflective of a lower severity population.

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Maple syrup urine disease

MIM #: 248600

This is an autosomal recessive disease whose well-known name is derived from the odor imparted to the urine by the increased concentration of a metabolite, the keto acid of isoleucine (alpha-keto-beta-methylvaleric acid). Maple syrup urine disease can be caused by defects in genes encoding the mitochondrial multienzyme complex, branched-chain alpha-keto acid dehydrogenase (*BCKDHA* and *BCKDHB*), and the gene encoding dihydrolipoamide dehydrogenase (*DBT*). Mutations can cause defects in the E1-alpha (type IA) or E1-beta subunit (type IB) or the E2 subunit (type II) portions of the enzyme. Mutations in an additional gene result in an overlapping, more severe phenotype called DLD deficiency, also known as maple syrup urine disease 3. Branched-chain alpha-keto acid dehydrogenase is required for the catabolism of the neutral branched-chain amino acids leucine, isoleucine, and valine. Routine neonatal screening has improved the clinical outcome because early diagnosis allows for early dietary modification. Today, it is rare to come across an untreated, and therefore clinically unmodified, patient.

A variety of clinical subtypes, varying in the timing of onset and severity of symptoms, have been described. The “classic” type (type IA) presents at several days of age and is severe, with death occurring, if untreated, by several months of age. Other subtypes are “intermediate”; “intermittent,” with symptomatic episodes triggered by stress (surgery included), intercurrent illness, or acute increases in dietary protein, as is typical of many metabolic diseases; and a “thiamine-responsive” form. The final subtype is “E3 deficient.” The severity of the disease depends on the amount of residual enzyme activity. Peritoneal dialysis or hemodialysis can remove the offending amino acids in an acute decompensation. Liver transplantation has been used successfully. It can rapidly control the metabolic abnormality. Already existing brain injury can be arrested but not reversed.

HEENT/Airway: Ptosis and ophthalmoplegia if untreated.

Neuromuscular: In the classic form, lethargy and poor feeding rapidly progress to seizures, apnea, and coma. Severe psychomotor developmental delay if untreated. Intermittent subtypes may have intermittent ataxia, irritability, and progressive lethargy. Cerebral edema has been described in older patients. Patients with an intermittent type are usually normal between episodes.

GI/GU: Episodic pancreatitis. Emesis.

Other: Hypoglycemia if untreated. Life-threatening metabolic decompensation with acidosis. Ketosis. Failure to thrive.

Miscellaneous: This syndrome was first described by Menkes (of Menkes kinky hair syndrome). The abnormal, sweet smell may not be present in the urine for the first few months. It is first noticed in the cerumen, probably because of the lipophilic nature of the involved organic acids. It is particularly common in an inbred Old Order Mennonite population in Lancaster County, PA. An animal model exists in a subtype of the accordion phenotype of zebrafish larvae.

A case of pseudo-maple syrup urine disease has been reported in a young infant given herbal tea made from fenugreek seeds with a resultant abnormal odor similar to that of maple syrup urine. Evaluation showed the presence of sotolone, responsible for the peculiar smell in maple syrup urine disease, in both the seeds and the child's urine.

Anesthetic Considerations: Patients can become hypoglycemic, so prolonged perioperative fasting should be avoided, glucose-containing intravenous fluids should be used, and serum glucose levels should be monitored. Additional caloric sources should include intravenous fat emulsion to minimize the glucose load. Patients should receive calories adequate to prevent catabolism. The patient's special low-protein diet should be reinstituted postoperatively as soon as is practicable. High levels of keto acids can result in metabolic acidosis. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load and trigger acute decompensation. Patients should be observed closely postoperatively for evidence of symptomatic worsening.

Overhydration may exacerbate cerebral edema. It has been suggested that hypertonic glucose may exacerbate this condition because of increases in CO_2 production and norepinephrine secretion.

Figure: See **Appendix D**

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Marden-Walker syndrome

MIM #: 248700

This autosomal recessive disorder is characterized by blepharophimosis, immobile facies, micrognathia, multiple joint contractures, and intellectual disabilities. Many patients die in infancy. The responsible gene and gene product are not known.

HEENT/Airway: Microcephaly. Large anterior fontanelle. Immobile facies. Blepharophimosis, strabismus. Small mouth. High-arched palate or cleft palate. Micrognathia. May have short frenulum. May have short neck.

Chest: Pectus excavatum or carinatum. Rare pulmonary hypoplasia. Rare absent clavicle.

Cardiovascular: May have congenital cardiac defect.

Neuromuscular: Severe intellectual disabilities. Aggressive behavior and hyperactivity in patients as they approach puberty. Hypotonia. May have electroencephalographic abnormalities, seizures. May have

agenesis of the corpus callosum, Dandy-Walker malformation, hydrocephalus. May have hypoplastic cerebellum, inferior vermis, or brainstem.

Orthopedic: Severe pre- and postnatal growth deficiency. Multiple joint contractures. Kyphoscoliosis. Camptodactyly and arachnodactyly. Clubfoot deformity.

GI/GU: Inguinal hernias, pyloric stenosis. Cryptorchidism, hypospadias, micropenis. Rare renal hypoplasia or cystic disease.

Other: Zollinger-Ellison syndrome has been reported. May have pilonidal sinus. Bleeding dyscrasia, lax skin, and impaired wound healing were reported in one child.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia and short neck. Patients are at risk for perioperative aspiration. Patients must be carefully positioned and padded perioperatively because of multiple joint contractures, and intravenous access could be potentially more difficult. Patients with hydrocephalus may have elevated intracranial pressure, and perioperative measures should be taken to avoid further elevations in pressure. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Abnormal clavicles may make placement of a subclavian intravenous cannula or an infraclavicular block difficult.

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Marfan syndrome

MIM #: 154700

This autosomal dominant disease has widespread manifestations in both skeletal and connective tissues. A significant minority of cases are due to new mutations. Prominent characteristics include a tall, asthenic build; joint laxity, arachnodactyly; mitral valve prolapse; aortic dissection; optic lens dislocation; and scoliosis. There is a high degree of penetrance but incomplete expressivity, so there is much individual variation. The disease is due to a defect in the gene fibrillin-1 (*FBN1*). Fibrillin is the major element of extracellular microfibrils in both elastic and nonelastic connective tissues. Fibrillin can bind the transforming growth factor TGF-ß. Lung disease in Marfan syndrome is a developmental abnormality due to excess active TGF-ß. Similarly, mitral and aortic disease progression in mice, and aortic disease children, can be limited by long-term use of the angiotensin II receptor blockers losartan or irbesartan, which antagonize TGF-ß (4). This therapy was more effective than was beta blockade in mice (not evaluated in children). Loeys-Dietz syndrome (see earlier), a disease with an overlapping phenotype, is due to mutations in genes encoding TGF-ß.

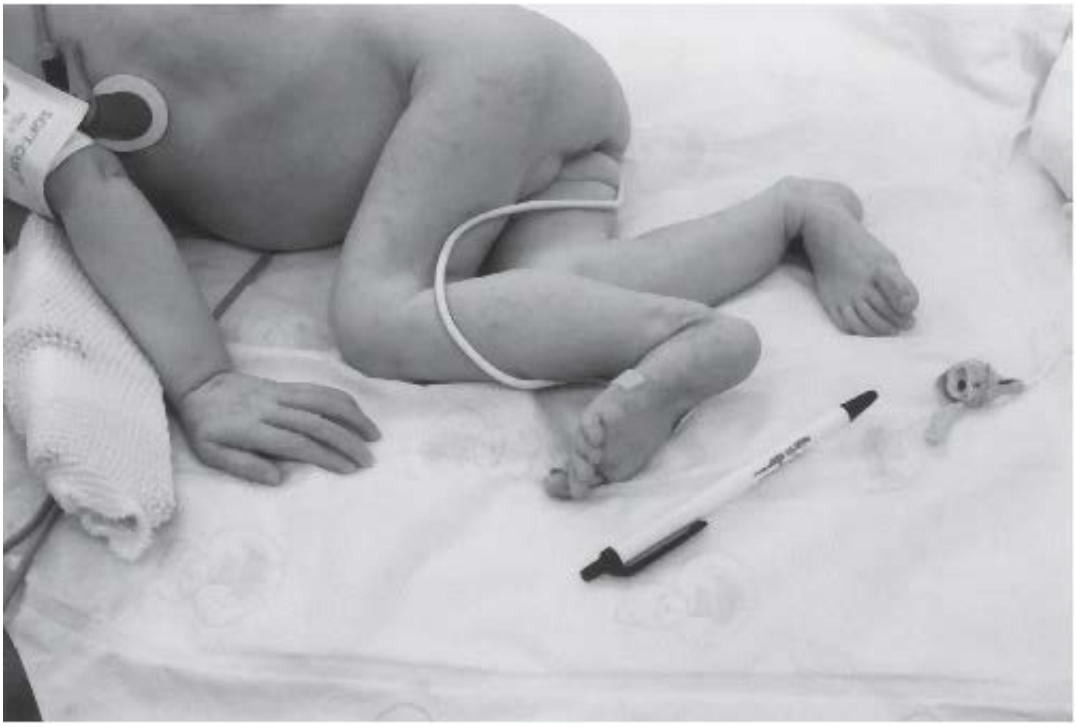
Marfan syndrome. FIG. 1. This 6′ 7″ (201 cm) 27-year-old man was seen the day before surgery for repair of a detached retina and is pictured with his mother. Six months previously, he had had a dislocated lens repaired. His father (6′ 8″), also with Marfan syndrome, died at 25 years of age from an aortic dissection. At the time this patient was seen in the preoperative evaluation center, he was noted to have new T-wave inversions that were not present 6 months previously. Echocardiography showed that he had mitral valve prolapse with insufficiency and a slightly dilated ascending aorta. Three years later, he required urgent surgery for an aortic dissection.

When presenting in infancy, the disorder is more severe and is also associated with lax skin, severe scoliosis,

flexion contractures, micrognathia, muscle hypoplasia, and poor fat over joints.

HEENT/Airway: Dolichocephaly. Long, narrow facies with a high-arched palate and crowded teeth.

Lens dislocation is very common and can result in cataract formation. The globe is elongated, and patients tend to be myopic and have increased risk of retinal detachment. Risk of glaucoma, even at a young age. Rare tracheomalacia.



Marfan syndrome. FIG. 2. Long fingers and toes are already apparent in this 6-month-old with Marfan syndrome.

Chest: Pectus excavatum, less commonly pectus carinatum. Even patients without scoliosis or other spine deformities can have lower-than-predicted forced vital capacity, presumably due to earlier airway closure from inadequate small airway elastic tissue. Emphysema and bronchogenic cysts can develop. Pulmonary blebs with spontaneous pneumothoraces are relatively common. Obstructive sleep apnea (possibly secondary to pharyngeal laxity).

Cardiovascular: Aortic or pulmonary artery dilatation, aortic dissection, aortic insufficiency. Mitral prolapse with insufficiency. The most common type of aortic dissection is DeBakey type 2 (ascending aorta proximal to the innominate artery). The histologic change in the aorta is cystic medial necrosis. Elective root replacement has much lower operative mortality than does emergent repair of aortic dissection. Valvar and vascular findings can be present at birth. Echocardiography can demonstrate mitral valve prolapse in over 80% of patients.

In coronary arteries, including those supplying the sinus and atrioventricular nodes, medial necrosis can develop that can progress to luminal narrowing.

Marfan disease can present in the neonatal period, and neonates, if they experience major problems, tend to have mitral insufficiency rather than aortic insufficiency as the primary manifestation.

Neuromuscular: Widened lumbosacral canal. Spinal arachnoid cysts or dural ectasia (widened lumbosacral dural sac) is common, and while it can occur at any level, it is most commonly at L5-S1.

Orthopedic: Tall with an arm span greater than the height. Winged scapula. Ulnar deviation of the metacarpophalangeal joints and arachnodactyly (long fingers). Recurrent dislocations due to joint laxity. Scoliosis, sometimes at multiple locations along the spine. (Thoracic scoliosis is almost always convex to the right.) Kyphosis. Congenital contractures. Flat feet. Atlantoaxial instability has been reported.

GI/GU: Increased incidence of inguinal, umbilical, and femoral hernias.

Other: Skin striae.

Miscellaneous: It has been suggested that the 5-year-old girl described by Marfan in 1896 actually had contractural arachnodactyly [Beals contractural arachnodactyly (see earlier), which is due to a defect in the gene *fibrillin-2*]. Achard may have reported the first true case of Marfan syndrome in 1902. The aneurysms of the ascending aorta were first described by Helen Taussig (and coauthors). Marfan syndrome is phenotypically similar to homocystinuria. Interestingly, the optic lens dislocates down in homocystinuria and up in Marfan syndrome.

Bernard J. A. Marfan held the first chair in pediatrics in Paris, early in the 20th century. Although he did not use the term “arachnodactyly” in his 1896 report (Achard did in a report 6 years later), the term probably is derived from Marfan's use of the phrase *pattes d'araignee* (“spider legs”) in his original report.

Abraham Lincoln and Nicolò Paganini are hypothesized to have had Marfan syndrome.

Anesthetic Considerations: Preoperative echocardiography should be obtained, or recent studies reviewed, to exclude cardiac or aortic pathology. Patients may be on beta-blocker therapy, which should be continued perioperatively. Hypertension should be avoided in these patients who are at risk for aortic dissection. Supplementation of induction agents with opioid to further blunt the hemodynamic effects of laryngoscopy and intubation has been encouraged. Patients can require additional intraoperative antihypertensive medications such as nicardipine. A patient has been reported who had acute, intraoperative coronary artery obstruction (presumably not a coronary air embolus) (12).

These patients are at increased risk for pneumothoraces, which must be kept in mind when using positive-pressure ventilation. Mid-tracheal obstruction has been reported after Harrington rod placement (16) and secondary to unexpected tracheomalacia after the induction of general anesthesia (9). The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

Patients must be carefully positioned to avoid joint dislocations secondary to joint laxity. Atlantoaxial instability has been reported. Although there is the possibility of temporomandibular joint dysfunction, this has not been reported to cause difficulty with laryngoscopy. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

These patients may require larger-than-normal doses of spinal or epidural anesthetics because of their increased length. In addition, inadequate spread of spinal anesthesia has been reported, presumably due to increased cerebrospinal fluid volume due to dural ectasia. Both regional and general anesthesia, including remifentanil/propofol, have been used successfully in parturients (1,10,11,13,14,15). Given the variabilities in effect due to dural ectasias, it has been suggested that a combined spinal epidural technique (CSE) be used rather than a simple subarachnoid block, to allow augmentation if required. Combined cesarean section/aortic dissection

repair has been reported and was complicated by excessive uterine bleeding requiring hysterectomy (3). There are currently no data supporting vaginal versus cesarean delivery and general versus neuraxial anesthesia for cesarean deliveries.

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Marinesco-Sjögren syndrome

MIM #: 248800

This is an autosomal recessive disorder whose primary manifestations are cerebellar ataxia, congenital cataracts, and psychomotor retardation. This disorder is caused by a mutation in the gene *SIL1*, which encodes a nucleotide exchange factor for the heat shock protein 70 (HSP70) chaperone HSPA5. Hypergonadotropic hypogonadism is often associated with Marinesco-Sjögren syndrome. The two genes may be linked, or this may be a further manifestation of Marinesco-Sjögren syndrome.

HEENT/Airway: Microcephaly, congenital cataracts, nystagmus, strabismus. Dysarthria.

Chest: Pectus carinatum.

Neuromuscular: Psychomotor retardation. Cerebellar cortical atrophy with vacuolated Purkinje cells. Cerebellar ataxia, spasticity. Hypotonia, progressive muscle weakness and atrophy, myopathy.

Orthopedic: Short stature. Kyphosis, scoliosis, contractures. Short metacarpals and metatarsals. Coxa valga, cubitus valgus, pes planus.

GI/GU: Hypergonadotropic hypogonadism.

Miscellaneous: An early name for this disorder was “hereditary oligophrenic cerebellolental degeneration.” The syndrome was first described in the Hungarian literature a quarter century before Marinesco's report.

Anesthetic Considerations: Succinylcholine should be avoided in patients with significant myopathy secondary to the risk of exaggerated hyperkalemia. Kyphoscoliosis and contractures may complicate perioperative positioning. Severe muscle weakness combined with severe kyphoscoliosis increases the risk of postoperative pulmonary complications, and patients should be monitored closely in the postanesthesia care unit.

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Maroteaux-Lamy syndrome

Synonym: Mucopolysaccharidosis VI

MIM #: 253200

This autosomal recessive mucopolysaccharidosis is due to a defect in the gene for the lysosomal enzyme arylsulfatase B. It is characterized by prominent bone and eye findings with usually normal intelligence. There are mild, intermediate, and severe forms. Enzyme replacement therapy is available with galsulfase.

HEENT/Airway: The face is usually mildly involved, but some may have the coarse facies characteristic of Hurler syndrome. Macrocephaly. Corneal clouding. Glaucoma. Recurrent middle ear infections. Macroglossia and upper airway obstruction from mucopolysaccharide accumulation. Short neck. Jaw arthrosclerosis.

Chest: Pectus carinatum. A deformed chest may be present at birth. Recurrent upper respiratory tract infections. Sleep apnea. Patients with a mucopolysaccharidosis are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Aortic valve calcification, with possible mitral involvement. Heart failure is the most common cause of death, usually in the second or third decade of life.

Neuromuscular: Intelligence is usually normal. Spinal compression from dural thickening is common, particularly in adults with milder disease. Compression is usually cervical and its onset may be insidious. Communicating hydrocephalus has occurred with cervical vertebral compression or from thickening of the arachnoid villi.

Orthopedic: Growth can be normal for the first few years and then essentially stops. Skeletal changes are similar to those of Hurler syndrome (see earlier). There is hypoplasia of the hip acetabulae and small, flared iliac wings. There is hypoplasia of the L1-L2 vertebral bodies and prominent lumbar kyphosis. There is proximal femoral dysplasia and irregular diaphyseal distention of the tubular bones. Storage of polysaccharide in ligaments causes contractures of joints. Restriction in mobility of the hips, knees, and elbows results in these children assuming a crouched stance. Involvement of the wrists and hands causes carpal tunnel syndrome or a claw hand. Can have scoliosis, atlantoaxial dislocation.

Maroteaux-Lamy syndrome. This 23-year-old woman with Maroteaux-Lamy syndrome is pictured with her 26-year-old sister who also has the syndrome. The patient could not be intubated orally, and nasal intubation was extremely difficult. Her sister, who has had a cervical spine fusion in the past, has required an emergency tracheostomy. Six years after this photo was taken, the older sister developed symptomatic mitral disease (stenosis and insufficiency) and aortic stenosis and required cardiac surgery.

GI/GU: Umbilical and inguinal hernias. Hepatosplenomegaly with hypersplenism.

Other: "Tight" skin with mild hirsutism. Anemia and thrombocytopenia secondary to hypersplenism. Inclusions seen in white blood cells. Enzyme replacement therapy has not affected the degree of cardiac valve dysfunction in one series and a child was reported in whom cervical myelopathy developed while receiving enzyme replacement therapy.

Anesthetic Considerations: Laryngoscopy and tracheal intubation may be extremely difficult. When positioning for laryngoscopy, the possibility of an unstable cervical spine should be considered. Intubation can become increasingly difficult with age. An oropharyngeal airway may worsen airway obstruction by pushing down a long, high epiglottis over the larynx. A nasopharyngeal airway may help, but on occasion, advancement is difficult because of mucopolysaccharide deposits. The laryngeal mask airway has been used successfully in patients with mucopolysaccharidoses (4). Patients should be closely observed postoperatively for the development of airway obstruction. There may be postoperative respiratory compromise, and postobstructive pulmonary edema has been reported (3).

A thorough preoperative cardiac evaluation is indicated because heart failure is the most common cause of death. The hematocrit and platelet count should be evaluated preoperatively in patients with a history of hypersplenism. Severe contractures may make vascular access more difficult to obtain. Patients must be carefully positioned and padded secondary to contractures.

Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Marshall syndrome

MIM #: 154780

This autosomal dominant syndrome involves cataracts, sensorineural deafness, and a very small nose. It is caused by a mutation in the gene *COL11A1*, which is located on the short arm of chromosome 1 and encodes collagen-type XI. There is wide variability in clinical expression. There is significant clinical overlap with Stickler syndrome (see later) and there has been discussion as to whether these represent two distinct disorders (1).

HEENT/Airway: Thick calvarium, absent frontal sinuses, flat midface. Shallow orbit with prominent eyes, hypertelorism. Cataracts, lens dislocation, myopia, esotropia, glaucoma, retinal detachment. Sensorineural deafness. Short nose with flat nasal bridge, upturned tip, and anteverted nares. Prominent upper incisors. May

have dental dysplasia. May have cleft palate. Pierre Robin anomaly has been reported occasionally.

Neuromuscular: May have intellectual disability. Falx, tentorial, and meningeal calcifications.

Orthopedic: Short stature. Vertebral epiphyseal abnormalities of a wide variety and varying degree.

Other: May have ectodermal dysplasia with sparse hair. Deficient sweating can result in hyperthermia.

Anesthetic Considerations: When talking with patients, remember that they may have sensorineural hearing loss. Pierre Robin anomaly can make laryngoscopy and intubation difficult. Dental abnormalities should be documented preoperatively. Patients should be carefully positioned and padded perioperatively secondary to ectodermal dysplasia. Deficient sweating can result in hyperthermia. Patients can be on topical treatment for glaucoma that can on occasion have systemic effects. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Marshall-Smith syndrome

MIM #: 602535

This autosomal recessive disorder is due to mutations in the gene *NFIX*, which encodes nuclear factor I, a ubiquitously expressed protein that stimulates gene transcription. Sotos syndrome-2 (see later) is also caused by mutations in this gene. The most marked feature of Marshall-Smith syndrome is accelerated growth and maturation. One affected person reportedly had a wrist bone age of 3 to 4 years by the age of 4 weeks. Most patients die before the age of 2 years.

HEENT/Airway: Prominent forehead. Shallow orbits with prominent eyes, bluish sclerae. Synophrys. May have abnormal ears, hearing loss. Upturned nose, flat nasal bridge, midface hypoplasia. Hypoplastic mandibular ramus with micrognathia. Dental anomalies. May have choanal atresia or stenosis, rudimentary epiglottis, abnormal larynx, laryngomalacia.

Chest: Tracheomalacia. Short sternum. Pneumonia, atelectasis, and aspiration are common. Patients with severe lung disease may have pulmonary hypertension. Childhood death from pulmonary infections is common. Can have obstructive sleep apnea.

Cardiovascular: May develop pulmonary arterial hypertension secondary to chronic airway obstruction.

Neuromuscular: Intellectual disabilities, developmental delay. Hypotonia. May have cerebral atrophy, absent

corpus callosum. Severe spinal stenosis at the craniocervical junction may cause dysfunction of the lower medulla, leading to apnea.

Orthopedic: Markedly accelerated skeletal maturation and linear growth. Thin long bones. Broad proximal and middle phalanges with narrow distal phalanges. May have craniocervical instability with atlantoaxial subluxation. Scoliosis. Platyspondyly. May have sacrococcygeal hypersegmentation. May have osteopenia and/or bony fragility.

GI/GU: Umbilical hernia. Occasional omphalocele.

Other: Failure to thrive in terms of weight. Hypertrichosis. May have immunologic defects.

Anesthetic Considerations: Patients should be evaluated preoperatively for evidence of craniocervical instability. Dental abnormalities should be documented preoperatively. Laryngoscopy and endotracheal intubation are likely to be extremely difficult due to abnormal pharyngeal anatomy. Patients may have perioperative respiratory distress secondary to choanal atresia or stenosis, abnormal larynx, or laryngomalacia. Difficult mask ventilation following thiopentone that became impossible after the administration of succinylcholine has been reported. Ketamine with spontaneous ventilation was used successfully for a later laryngoscopy (4). These authors and others suggest that intubation be performed without the use of muscle relaxants. Fiberoptic intubation via a laryngeal mask airway in a spontaneously breathing child has been done successfully (2). Prolonged use of a nasopharyngeal airway to maintain airway patency and for use during induction of an inhalational anesthetic has been reported (5). The presence of choanal atresia would preclude the use of a nasal airway or a nasogastric tube. Patients are at risk for perioperative aspiration. Patients are at risk for perioperative apnea, particularly if there is dysfunction of the lower medulla. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Patients with significant lung disease may have pulmonary hypertension. Abnormal sacrococcygeal anatomy might make caudal anesthesia technically difficult. Patients with osteopenia and/or bony fragility require careful perioperative handling and positioning and padding.

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Martin-Bell syndrome

See Fragile X syndrome

MASA syndrome

Synonym: X-linked hydrocephalus syndrome, Spastic paraplegia-1

MIM #: 303350

This syndrome of hydrocephalus associated with aqueductal stenosis is inherited in an X-linked recessive fashion. The acronym MASA stands for **M**ental retardation, **A**phasia, **S**huffling gait (from lower limb spasticity), and **A**dducted thumbs. Female carriers may have mild intellectual disabilities or minimally adducted thumbs. This syndrome is caused by a mutation in the gene for the neural L 1 cell adhesion molecule (*L1CAM*) that is required for proper nervous system development.

HEENT/Airway: Macrocephaly. May have facial asymmetry. May have strabismus.

Neuromuscular: Hydrocephalus associated with aqueductal stenosis is present *in utero* and may be severe enough to necessitate delivery by cesarean section. Can have agenesis of the corpus callosum. Intellectual disabilities. Aphasia. Shuffling gait secondary to spasticity of the lower extremities. May have spastic paraplegia. Hyperactive deep tendon reflexes in the lower extremities.

Orthopedic: Adducted thumbs (thumb flexed over the palms) secondary to hypoplastic or absent extensor pollicis longus or brevis muscles. Small stature. Rounded shoulders with internally rotated arms. Lumbar lordosis. Can have clubfoot deformity.

Anesthetic Considerations: Precautions against increases in intracranial pressure are needed in patients with severe hydrocephalus. Succinylcholine may be contraindicated in patients with spastic paraplegia because of the risk of exaggerated hyperkalemia.

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Maternal phenylketonuria syndrome

Synonym: Maternal PKU syndrome, Fetal hyperphenylalaninemia syndrome

MIM #: None

This syndrome is due to the teratogenic effects of elevated serum phenylalanine levels in women with phenylketonuria (PKU). The affected offspring exhibits microcephaly, intellectual disabilities, growth deficiency, and a variety of structural defects. Elevated levels of phenylalanine in the first trimester cause abnormalities of organogenesis. The syndrome can be prevented if good metabolic control can be obtained by 8 to 10 weeks' gestation. Thereafter, elevated levels of phenylalanine cause abnormalities of myelination and organ maturation. These children are not at risk for having phenylketonuria unless their fathers also have a PKU gene. Treatment is with a phenylalanine-restricted diet during pregnancy. Sapropterin dihydrochloride, a synthetic preparation of the dihydrochloride salt of tetrahydrobiopterin, has been approved for use during pregnancy, although outcome data are currently limited (2).

HEENT/Airway: Microcephaly. Round facies. Epicanthal folds, short palpebral fissures, strabismus. Small, upturned nose. Long, simple philtrum with thin upper lip. May have cleft lip or palate. Mandibular hypoplasia.

Cardiovascular: May have congenital heart disease, particularly ventricular septal defect and tetralogy of Fallot or other conotruncal anomalies.

Neuromuscular: Intellectual disabilities, which are not progressive because newborns are able to regulate their phenylalanine levels. Hypertonicity. May exhibit hyperactivity.

Orthopedic: Intrauterine and postnatal growth retardation. May have cervical and sacral spine anomalies. Pigeon-toed gait.

GI/GU: May have esophageal atresia.

Miscellaneous: Adverse effects on the fetus can be correlated with maternal serum levels of phenylalanine, and timely and adequate dietary restriction of phenylalanine during pregnancy will provide protection to the fetus during organ development and will maximize the offspring's intellectual potential. On the other hand, low maternal phenylalanine levels during gestation have been correlated with intrauterine growth retardation. Gastrostomy feeding has been offered to help pregnant women who cannot tolerate adequate oral feeding during pregnancy.

Anesthetic Considerations: Intellectual disability or hyperactivity may make the smooth induction of anesthesia a challenge. Direct laryngoscopy and tracheal intubation may be difficult secondary to mandibular hypoplasia. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Mayer-Rokitansky-Kuster syndrome

See Rokitansky-Kuster-Hauser syndrome

Mayer-Rokitansky-Kuster-Hauser syndrome

See Rokitansky-Kuster-Hauser syndrome

May-Hegglin anomaly

Included in Fechtner syndrome

MCAD deficiency

See Medium-chain acyl-CoA dehydrogenase deficiency

McArdle syndrome

Synonym: Glycogen storage disease type V; Muscle phosphorylase deficiency

MIM #: 232600

This autosomal recessive glycogen storage disease is due to the absence of muscle phosphorylase, which results in an inability to liberate glucose from glycogen in muscle, with consequent accumulation of glycogen and the development of a myopathy. Over 130 specific mutations have been described. Muscle phosphorylase is a major muscle protein, accounting for 5% of all muscle protein. Without the enzyme, muscle derives energy from blood glucose and free fatty acids. This is a relatively benign disease—the metabolic findings are analogous to those of marathon runners who have depleted their glycogen reserves. For unclear reasons, young children are usually asymptomatic and most patients are diagnosed as adolescents or young adults. Boys are more frequently affected, which has been suggested by some to reflect the fact that boys are required to exercise their muscles more and so are more likely to become symptomatic. Symptoms disappear rapidly with rest. Patients require no specific therapy. A rare severe infantile form and a late-onset form have been described. A patient has been described who

suddenly developed symptoms at age 60 years. Patients may have low pyridoxine (vitamin B_6) levels as this vitamin is bound to muscle phosphorylase, but symptomatic pyridoxine deficiency has not been reported. However, one patient has been reported whose symptoms and muscle biopsy improved with pyridoxine supplementation.

Cardiovascular: The heart is usually unaffected, although rare incidences of conduction block have been reported.

Neuromuscular: Muscle pain and easy fatigability. Stiffness, pain, or cramps with moderate exertion. Symptoms disappear rapidly with rest. In some patients, a "second wind" can develop, presumably from increased blood flow to the muscle, delivering fatty acids that can be used as an energy source, and also possibly due to the recruitment of more motor units. Muscle wasting can occur in older patients with fatty replacement, particularly in the upper extremities. Patients can usually perform moderate exercise, on level ground, for prolonged periods. Laboratory studies (forearm ischemic exercise or cycle ergometry) will show a lack of increased lactate.

GI/GU: The liver is normal. Many patients have myoglobinuria after intense exercise. Rarely, this has caused renal impairment. Uterine muscle is apparently normal.

Other: Hypoglycemia is not a typical feature. There is a fall in serum lactate levels with exercise. Blood creatine kinase levels are elevated at rest and may be significantly elevated after exercise. Glucose or glucagon may provide temporary improvement in symptoms.

Miscellaneous: This was the first hereditary myopathy shown to be due to an enzyme defect. The first patient described by McArdle was 30 years of age at the time. This real, but mild, disease has resulted in some patients being accused of malingering. A ketogenic diet has been suggested to be effective as it supplies an alternative fuel source to muscle.

Anesthetic Considerations: Because glycogen cannot be used as an energy source for muscle, patients should receive perioperative infusions of glucose. Oral sucrose has been suggested to improve exercise tolerance and limit rhabdomyolysis and by extension to improve perioperative muscle strength, although further analysis casts doubt on this claim (3). Succinylcholine may be contraindicated in patients with a myopathy because of the risk of exaggerated hyperkalemia. Patients may be overly sensitive to nondepolarizing muscle relaxants, and a nerve stimulator should be used. Postoperative shivering should be avoided. Because muscle destruction is thought to be secondary to repeated ischemic episodes, prolonged use of tourniquets, as for a Bier block or to minimize blood loss in extremity surgery, should be limited. Muscle destruction may be associated with rhabdomyolysis, myoglobinuria, and acute renal failure. Although several patients have had a positive *in vitro* contracture test, there have been no reports of malignant hyperthermia in the literature. The heart is usually unaffected, although rare incidences of conduction block have been reported.

Figure: See **Appendix E**

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McCune-Albright syndrome

Synonym: Osteitis fibrosa cystica; Polyostotic fibrous dysplasia; Albright syndrome

Note: This is a distinct entity from Albright hereditary osteodystrophy (see later, Pseudohypoparathyroidism).

MIM #: 174800

This is a disease with a classical triad of irregularly shaped café au lait spots, precocious puberty, and fibrous dysplasia of bone. It occurs in both sexes and may be associated with excessive hormone production by other glands. The disease is caused by mosaic somatic mutations (i.e., not in germ cells) in the gene *GNAS1* (encoding guanine nucleotide-binding protein, alpha-stimulating polypeptide). This protein, commonly abbreviated $G_{s\alpha}$, is the stimulatory G protein and is involved in numerous adenylyl cyclase-mediated intracellular functions. Inheritance may be autosomal dominant lethal, with viability occurring only when the genetic defect occurs in the mosaic state. Affected tissues have gsp mutations, which encode substitutions on the arginine finger of the protein, which is that portion that engages the G protein-coupled receptor. The genetic defect here apparently makes this protein constitutively active (i.e., always active). Receptors affected include ACTH, thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Similar changes have been found in some hormone-secreting pituitary tumors and thyroid tumors. Because the mutation is not present in areas of normal skin, this likely represents mosaicism from postzygotic somatic cell mutation, with the percent of cells affected varying from organ to organ. As such, there tends to be variation from patient to patient.

HEENT/Airway: May have fibrous dysplasia of skull and facial bones. Blindness and deafness from bony impingement on cranial foramina. Multinodular goiter.

Chest: Rarely, involvement of ribs can produce profound restrictive lung disease from poor chest wall compliance.

Cardiovascular: Increased incidence of arrhythmias and sudden death in infancy. Involved ribs can rarely impinge on thoracic venous drainage.

Neuromuscular: Skull base bone lesions can compress cranial nerves.

Orthopedic: Bony lesions tend to be asymmetric. Fibrous dysplasia of multiple bones. Involvement is typically asymmetric. Can have hypophosphatemic osteomalacia (rickets). Pathologic fractures, bone deformity, pseudarthroses. Shepherd's crook deformity of the femur is characteristic. There may be malignant transformation of bone lesions.

McCune-Albright syndrome. "Coast of Maine" skin lesion in McCune-Albright syndrome.

GI/GU: Gastrointestinal polyps have been reported. Testicular microlithiasis. Renal tubule phosphate wasting from inadequate reabsorption. Menstruation occurs in the first months of life, and spermatogenesis has been reported by age 6 years. Normal ovarian and uterine function can be restored by removing the abnormal, hyperfunctioning ovary.

Other: Asymmetric, irregularly shaped café au lait spots. These typically are predominantly on one side and stop abruptly at the midline and are due to mimicking of the normal effects of melanocyte-stimulating hormone. The nape of the neck is a common location. Endocrine hyperfunction in a variety of glands may result in precocious puberty, thyrotoxicosis, pituitary gigantism or acromegaly, or Cushing syndrome from hyperadrenalism. Signs of precocious puberty can become apparent in infancy. Cushing syndrome can also become apparent in infancy. Gynecomastia. Hypophosphatemia. Rapid progression of bone lesions during pregnancy has been reported. Interestingly, osteogenic cells from these lesions manifested estrogen and progesterone receptors. Increased activity of the FOS oncogene in bone lesions has been reported.

Miscellaneous: Skin lesions are described as "coast of Maine" for their irregular border (the smoother, but

superficially similar, lesions of neurofibromatosis are termed “coast of California”).

Donovan McCune was a pediatrician at Columbia University. Fuller Albright, the Boston physician, is the father figure of endocrinology. This is the same Albright of Albright hereditary osteodystrophy. He also described vitamin D-resistant rickets (once known as Albright-Butler-Bloomberg system). Albright suffered from early-onset Parkinson's disease. In 1946, Albright lamented that Parkinson's disease “does not

belong to my special medical interests, or else I am certain I would have solved it long ago.”

Anesthetic Considerations: Cushingoid patients with a buffalo hump may be difficult to position for intubation. Cushingoid patients may have fragile veins. Excessive growth hormone may result in a larger-than-normal larynx and the need for a somewhat larger-than-normal endotracheal tube. The larynx may be difficult to visualize in patients with acromegaly. Bone fragility requires careful patient positioning. Maxillary and mandibular disease can grossly disfigure the airway, making laryngoscopy and intubation challenging (2). Tracheomalacia can result from a long-standing large goiter. Preexisting hyperthyroidism should be corrected as should electrolyte abnormalities with Cushing syndrome. Thoracic involvement with restricted venous drainage requiring surgery necessitates intravenous access in the lower extremities (3).

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McKusick-Kaufman syndrome

Synonym: Kaufman-McKusick syndrome

MIM #: 236700

The hallmarks of this syndrome are hydrometrocolpos and postaxial polydactyly. It is caused by a mutation in the *MKKS* gene located on the short arm of chromosome 20, which encodes a protein that is similar to members of the chaperonin family, which aid in protein folding. Mutations in the same gene can also cause one form of Bardet-Biedl syndrome (see earlier). There is also some clinical overlap with Pallister-Hall syndrome (see later).

HEENT/Airway: May have complete tracheal ring. May have tracheomalacia.

Chest: A large pelvic mass may extend cephalad enough to displace the diaphragm.

Cardiovascular: May have congenital heart disease.

Orthopedic: Postaxial polydactyly.

GI/GU: May have Hirschsprung disease. May have imperforate anus. Hydrometrocolpos beginning in the fetus due to a transverse vaginal membrane or vaginal atresia. Hypospadias, prominent scrotal raphe, and micropenis in males. Undescended testes. The large pelvic mass can obstruct the urinary tract resulting in hydroureter or hydronephrosis.

Other: Can develop fetal hydrops due to caval compression and lymphatic obstruction from the pelvic mass.

Miscellaneous: Because of diagnostic overlap in infancy, children should be evaluated later for possible development of additional manifestations of Bardet-Biedl syndrome.

Anesthetic Considerations: Mechanical ventilation is probably preferred to spontaneous ventilation in young infants with large masses. Nitrous oxide will increase bowel distension, potentially further displacing the diaphragm and decreasing functional residual capacity. Baseline renal function should be evaluated in the presence of hydronephrosis. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Meadow syndrome

See Münchausen syndrome by proxy

Meckel syndrome

See Meckel-Gruber syndrome

Meckel-Gruber syndrome

Synonym: Meckel syndrome; Dysencephalia splanchnocystica

MIM #: 249000

This autosomal recessive syndrome includes occipital encephalocele, polydactyly, polycystic kidney disease, and bile duct anomalies. Patients usually die in the perinatal period. Renal failure is a contributing factor in most deaths. It is due to mutations in the gene *MKS1*, which encodes part of the flagellar apparatus body proteome, and is thus due to primary ciliary dysfunction during embryogenesis. Thus, it is one of the "ciliopathies." This section covers type I disease. There are a total of 10 types, each due to mutations in different genes.

HEENT/Airway: Microcephaly, sloping forehead. Microphthalmia, coloboma of the iris. Hypertelorism or hypotelorism. External ear anomalies. Low-set ears. Cleft lip or palate. May have neonatal teeth. Micrognathia. Large tongue. Short neck, sometimes with webbing. May have cleft epiglottis.

Chest: May have pulmonary hypoplasia.

Cardiovascular: Congenital cardiac defects include atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, and pulmonary stenosis.

Neuromuscular: Occipital encephalocele. Holoprosencephaly. Anencephaly. Cortical hypoplasia. Agenesis of the corpus callosum. Hydrocephalus. Seizures. May have Arnold-Chiari malformation. May have Dandy-Walker malformation. Absent optic nerve, olfactory tracts.

Orthopedic: Polydactyly, usually postaxial. Syndactyly, clinodactyly. Clubfoot deformity. May have simian crease, bowed limbs.

GI/GU: Bile duct anomalies, including bile duct proliferation, bile duct dilatation, and portal fibrosis. May have hepatic fibrosis. May have omphalocele, intestinal malrotation, imperforate anus. May have accessory spleens or asplenia, adrenal hypoplasia. Polycystic kidney disease. Cryptorchidism. Ureteral or urethral anomalies. May have small or ambiguous genitalia.

Miscellaneous: The oldest account of this syndrome may date to 1684, with the description of "a monstrous child" whose features are suggestive of Meckel-Gruber syndrome. Meckel's detailed description of the syndrome appeared in 1822. The disorder occurs with a relatively high frequency in Tatars, Finns, and Indians in Gujarati.

Johann F. Meckel was an early 19th-century German physician who was a founder of the field of embryology. He is actually Johann Friedreich Meckel the Younger. Johann Friedreich the Elder, his grandfather, was a professor of anatomy and surgical obstetrics. Meckel the Younger also described Meckel's diverticulum.

Anesthetic Considerations: Laryngoscopy and tracheal intubation may be difficult secondary to micrognathia, a short neck, and an encephalocele. Patients may have neonatal teeth (teeth present at birth), which can easily be dislodged during laryngoscopy. Renal disease has implications for the titration of perioperative fluids and for the choice of perioperative medications, avoiding or adjusting the dose of renally excreted drugs. Careful perioperative positioning is required secondary to the presence of an occipital encephalocele. Patients with hydrocephalus may have elevated intracranial pressure, and precautions should be taken to avoid further elevations in pressure. Chronic use of anticonvulsant medications alters the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Median cleft face syndrome

Synonym: Frontonasal dysplasia sequence

MIM #: 136760

This syndrome involves a primary defect in midline facial development that results in midline facial clefting. The clinical severity is highly variable. This syndrome may be due to errors in early fetal development and may on occasion not be genetically based. The incidence increases with increasing parental age. Also known as frontonasal dysplasia, three genetic types have been delineated. Frontonasal dysplasia 1 is an autosomal recessive disorder due to mutations in the aristaless-like homeobox-3 gene (*ALX3*). Frontonasal dysplasias 2 and 3 are due to mutations in the genes *ALX4* and *ALX1*, respectively. Frontonasal dysplasia can also occur as one feature of a multiple malformation syndrome.

HEENT/Airway: May have anterior cranium bifidum occultum (midline bony defect in frontal bone). Widow's peak. Marked hypertelorism. Lateral displacement of the inner canthi. May have optic anomalies. May have ptosis, coloboma. May have preauricular

skin tag, low-set ears, conductive hearing loss. Broad nasal root with variable clefting of the nose—from an abnormality confined to the tip to widely separated nares. May have notching of the alae nasi. May have maxillary hypoplasia. May have hypoplastic frontal sinuses. May have cleft lip or anterior cleft palate.

Cardiovascular: Has been associated with tetralogy of Fallot.

Neuromuscular: Intelligence is usually normal but is diminished in a small percent. Can have agenesis of the corpus callosum. Can have anterior basal encephalocele.

Orthopedic: May have brachydactyly, clinodactyly, camptodactyly.

Other: Can have frontal cutaneous lipoma.

Anesthetic Considerations: There exists the possibility of a difficult airway. Patients with tetralogy of Fallot

require an appropriately tailored anesthetic.

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Medium-chain acyl-CoA dehydrogenase deficiency

Synonym: MCAD deficiency (MCADD)

MIM #: 201450

This autosomal recessive disorder of the gene encoding medium-chain acyl-CoA dehydrogenase (MCAD) presents with an intermittent Reye syndrome-like picture. MCAD is one of several acyl-CoA dehydrogenases, which are mitochondrial enzymes that are required for beta-oxidation of fatty acids. Deficiencies in any of the acyl-CoA dehydrogenases will cause clinical symptoms. MCAD deficiency is the most common of these. It occurs most commonly in Northern Europeans. Symptomatic episodes are often precipitated by fasting or intercurrent viral infections. Compound heterozygotes (carrying two different mutations) often have a more benign course. The disease typically presents at 3 to 36 months of age, but presentation, and even death, can occur in the first few days of life. Symptoms in patients with milder disease may be overlooked and the diagnosis not made until later in life (1,2).

Fatty acids are oxidized in mitochondria. After mobilization from adipose tissue, they are taken up by the liver and other tissues and converted to acyl-CoA esters in the cytoplasm. They enter mitochondria as carnitine esters and become reesterified as acyl-CoA esters. Beta-oxidation results in the liberation of electrons. As beta-oxidation proceeds, the acyl chain is gradually shortened, and this first step in the oxidation process is catalyzed by acyl-CoA dehydrogenases with differing, but overlapping, chain-length specificities. These are very-long-chain, long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases.

Cardiovascular: Fatal ventricular tachyarrhythmias during acute events can occur, even in neonates.

Neuromuscular: Seizures, hypotonia, lethargy, and coma during acute episodes.

GI/GU: Peripheral lobular fatty changes, hepatomegaly. Emesis during acute episodes.

Other: Intermittent hypoketotic hypoglycemia, hyperammonemia, metabolic acidosis, impaired ketogenesis with hypoketotic hypoglycemia, secondary carnitine deficiency. Carnitine therapy is not uniformly beneficial. In fact, treatment with carnitine may be ineffective and possibly dangerous. Newborn screening is available.

Anesthetic Considerations: Prolonged perioperative fasting should be avoided. Serum glucose levels should be monitored, and patients will likely need perioperative glucose supplementation. Patients may be at risk for ventricular tachyarrhythmias. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with

intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

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MELAS syndrome

MIM #: 540000

MELAS syndrome is a genetically heterogeneous mitochondrial disease, related to Kearns-Sayre syndrome, Leigh disease, MERRF (myoclonic epilepsy with ragged red fibers), and others. MELAS stands for **M**itochondrial myopathy, **E**ncephalopathy, **L**actic **A**cidosis, and **S**trokelike episodes. The most common symptoms are sudden onset headache, vomiting, and seizures. It is caused by a deficiency in oxidative phosphorylation in the mitochondria. Many patients have deficiency in NADH-cytochrome c reductase (complex I). The disease has been ascribed to a mutation of the mitochondrial transfer RNA (*leu-UUR*) gene in most cases. Because this is a mitochondrial disease, transmission is maternal. Because of the varying distribution of mitochondria, in most cases, there is only a single family member with the disease, but other family members can have single features of the syndrome. For example, a lower mutation load can result in maternally inherited deafness and diabetes, while a higher mutation load will manifest a more complete MELAS phenotype. Onset is late in childhood and the diagnosis can sometimes first be made in adulthood (2). There is an overlapping phenotype with MERRF syndrome (see later). Treatment with coenzyme Q10 is helpful. MELAS syndrome is in the differential diagnosis of most strokes in childhood. A deficiency of nitric oxide, based on several factors, has been suggested, and arginine and citrulline supplementation have been suggested, but not yet systemically evaluated.

HEENT/Airway: Cataracts, cortical blindness, pigmentary retinopathy, and ophthalmoplegia. Progressive sensorineural hearing loss.

Chest: Respiratory failure is the most common cause of death.

Cardiovascular: Cardiomyopathy, Wolff-Parkinson-White syndrome (see later), atrioventricular block.

Neuromuscular: Diffuse spongy degeneration and focal encephalomalacia with focal infarcts, cortical or cerebellar atrophy, or basal ganglia calcification on computed tomography scan. Recurrent headache. Strokelike episodes, including sudden onset of hemiparesis, hemianopsia, or cortical blindness. Strokes are very focal, asymmetric and do not follow a specific vascular territory. Seizures. Headaches. Dementia. Myoclonus, peripheral neuropathy. Myopathy, with muscle weakness and poor exercise tolerance. Reduced muscle mass. Muscle biopsies show “ragged red” fibers, which represent a proliferation of mitochondria.

Orthopedic: Short stature.

GI/GU: Episodic vomiting. Chronic intestinal pseudo-obstruction has been reported. Nephropathy.

Other: Elevated baseline serum lactate. Metabolic (lactic) acidosis, worse with fasting. Postoperative hyponatremia and hyperkalemia. Defects in electron transport chain complexes I and IV. Thin habitus, hirsutism, purpura. Diabetes mellitus. Absence of cytochrome c reductase (complex I).

Miscellaneous: It has been suggested that Charles Darwin may have suffered from MELAS syndrome.

Anesthetic Considerations: Patients who are blind and deaf benefit from the presence of a family member or translator during induction of anesthesia. A baseline electrocardiogram should be obtained to evaluate for cardiac conduction abnormalities (Wolff-Parkinson-White syndrome, AV block), and an echocardiogram may be indicated to screen for cardiomyopathy. There may be excessive perioperative heat loss in these very thin patients, particularly as the mitochondrial respiratory chain is responsible for thermogenesis. Protracted preoperative fasts should be avoided and adequate perioperative glucose should be ensured to minimize the need for anaerobic metabolism and to prevent a catabolic state. Lactate metabolism is impaired, implying Ringer's lactate should be avoided (2), but it has been utilized without additional acidosis, though the authors concluded it would be wise to avoid it (1). Intraoperative and postoperative serum lactate should be monitored and compared to preoperative baseline values. Severe lactic acidosis can be treated with dichloroacetate (50 mg/kg intravenously) over 30 minutes, which stimulates pyruvate dehydrogenase. This enzyme converts lactate to pyruvate. Postoperative hyponatremia and hypokalemia have been seen in a large percentage of patients in one series (1). It is not known if this represents adrenal insufficiency. Patients with diabetes mellitus need to be monitored and treated appropriately. It is unclear if episodic emesis correlates with gastroesophageal reflux and intraoperative aspiration risk (4).

Patients with mitochondrial myopathies may be more sensitive to mivacurium (8), curare, rocuronium (6), atracurium (6), and succinylcholine (10), although one report did not find increased sensitivity to succinylcholine or pancuronium (11), and there is even one report of resistance to cisatracurium (3). Metabolism of these drugs can also be affected by the use of certain antiepileptic medications. That said, a recent small series that included patients anesthetized prior to their diagnosis showed no unusual drug reactions with a variety of neuromuscular blocking drugs, including succinylcholine (1). However, it would seem that muscle

relaxation should be used judiciously and with appropriate monitoring of neural blockade. Although use of succinylcholine has been reported, the use of this drug in a myopathic patient is probably best avoided if possible because of the risk of exaggerated hyperkalemia. Some patients with mitochondrial disease may have abnormal respiratory control (9), suggesting that opioids and other respiratory depressants be used with care, although excessive respiratory depression specifically from sedatives and opioids has not been reported in this syndrome. Similarly, preoperative sedation should be administered with care, if at all. Treatment with anticonvulsant medications may alter the metabolism of some anesthetic drugs. Although there are abnormalities in mitochondrial respiration, particularly complex I, there have been no reports of propofol infusion syndrome, although all reported anesthesia cases have used propofol only for relatively short periods of time.

A relationship between the mitochondrial myopathies and malignant hyperthermia has been suggested in the past but there seems to be no evidence for this. Spinal anesthesia has been used successfully. Treatment with anticoagulants and antiplatelet drugs is probably not helpful in preventing strokes.

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Melkersson syndrome

See Melkersson-Rosenthal syndrome

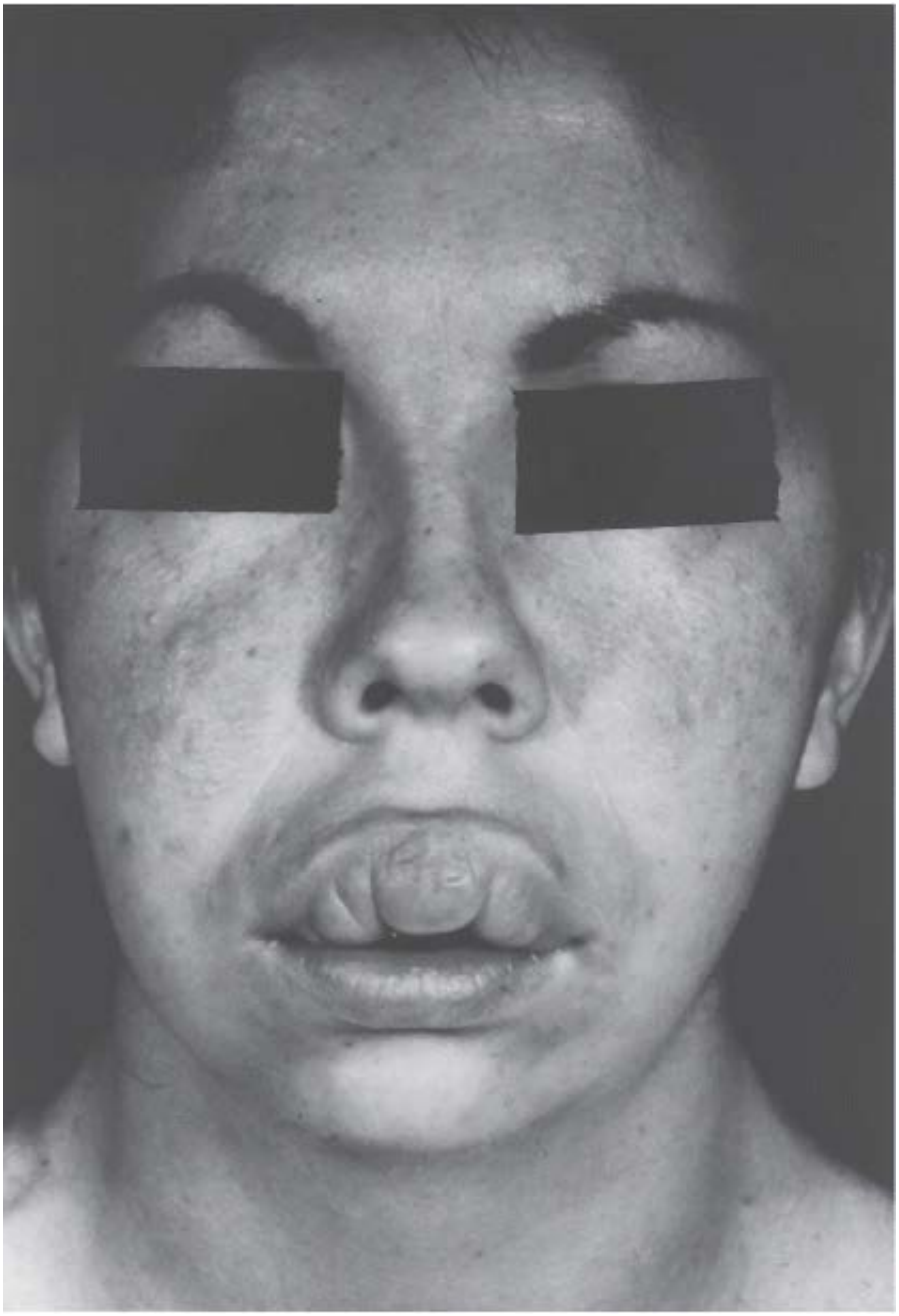
Melkersson-Rosenthal syndrome

Synonym: Melkersson syndrome

MIM #: 155900

This autosomal dominant syndrome results in episodic swelling of the face and relapsing peripheral facial palsy. With time, the episodes take longer to resolve and there is eventually chronic facial weakness and swollen, disfigured lips. The responsible gene has not been identified, but is thought to be on chromosome 9. There is no effective therapy. Anti-inflammatory drugs have been used.

HEENT/Airway: Chronic facial swelling, which may be limited to the lips. Relapsing peripheral facial palsy, clinically identical to Bell's palsy, from involvement of the facial nerve. There may be uveitis and visual disturbances during exacerbations. May have reduced lacrimation and salivation. May have eyelid edema. Fissured (“scrotal”) tongue. There may be swelling, erythema, or painful erosions of the gingiva, buccal mucosa, palate, or tongue. There may be noncaseating granulomas in the edematous tissue.



Melkersson-Rosenthal syndrome. FIG. 1. Chronic swelling of the lips in a patient with Melkersson-Rosenthal syndrome. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Melkersson-Rosenthal syndrome. FIG. 2. Fissured tongue of a patient with Melkersson-Rosenthal syndrome. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Chest: Acute episodes may be accompanied by exacerbations of asthma.

Neuromuscular: Recurrent facial nerve palsy. Exacerbations may be accompanied by migraines.

Other: Exacerbations may be accompanied by fever.

Anesthetic Considerations: Significant oral and laryngeal swelling during acute exacerbations may compromise laryngoscopy and tracheal intubation (4) and can cause postextubation airway difficulty. Patients may require endotracheal intubation until the episode of swelling resolves.

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Melnick-Fraser syndrome

Synonym: BOR syndrome; Branchiootorenal syndrome

MIM #: 113650

This autosomal dominant syndrome has as its main features branchial arch abnormalities, hearing loss, and renal disease. The disorder is predominantly due to a mutation in the gene *EYA1*. This gene is the human homologue of the *Drosophila* gene "eyes absent." Some are due to abnormalities in the gene *SIX1*, also homologous to a gene in *Drosophila*. The role of this gene and its gene product are not known, but it is expressed in all areas of the developing inner ear and in the metanephric cells of the early developing kidney. There is variability in expression of this syndrome, so any patient in whom hearing loss develops in childhood should be carefully examined for evidence of branchial arch abnormalities and renal disease. Often, the syndrome is not diagnosed until after the onset of hearing loss.

Melnick-Fraser syndrome. This 4-year-old girl is about to have surgical repair of her stenosed left nasolacrimal duct. She was hearing impaired and used hearing aids. In addition, she had cup-shaped ears, a preauricular pit, a small branchial arch cyst, and small kidneys with normal renal function. At age 15 years, she had placement of a cochlear implant. At that time, her kidneys were small with renal function at the lower range of normal. Her mother also has the syndrome and has also required treatment of nasolacrimal

duct stenosis.

HEENT/Airway: Can have facial nerve paralysis. May have microphthalmia. Lacrimal duct hypoplasia or atresia. Branchial arch abnormalities, including preauricular pits and branchial fistulas or cysts. Hearing loss may be conductive, sensorineural, or mixed. May have cholesteatoma. Cup-shaped external ear. Microtia. Middle or inner ear abnormalities, particularly cochlear hypoplasia. Lacrimal duct stenosis. Occasional deep overbite, cleft palate. High-arched palate. Bifid uvula.

GI/GU: Renal dysplasia. A small percentage have renal agenesis or renal failure. Anomalies of the renal collecting system.

Anesthetic Considerations: Intraoperative bradycardia requiring pharmacologic intervention has been reported in two siblings during sevoflurane anesthesia (1). Recognize that some patients with this syndrome are profoundly deaf. A severe overbite may make

laryngoscopy more difficult. Renal disease has implications for the titration of perioperative fluid and the choice of perioperative drugs.

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Melnick-Needles syndrome

MIM #: 309350

This X-linked dominant syndrome is distinguished by a small face with exophthalmos, bowing of the extremities, and ribbon-like ribs. It is caused by mutations in the gene encoding filamin A (*FLNA*). Filamin A crosslinks actin filaments and aids in anchoring membrane proteins. There is some clinical heterogeneity. Most of those affected are female, and there is evidence of greater severity and early lethality in male patients. Approximately half the cases are thought to be due to new mutations. This is one of four otopalatodigital syndromes caused by mutations in this gene. The others are frontometaphyseal dysplasia (see earlier) and otopalatodigital syndrome—types I and II (see later). These four syndromes constitute a clinical spectrum. Melnick-Needles is the most severe.

HEENT/Airway: Small face, prominent forehead, late-closing fontanelles, delayed paranasal sinus development, sclerosis of the skull base. Hirsute forehead, full cheeks. Exophthalmos, hypertelorism, downslanting palpebral fissures, glaucoma. Large ears. May have recurrent otitis media. Broad nasal bridge and tip, anteverted nares. Delayed sinus development. Malaligned teeth, gingival hypertrophy, delayed tooth eruption. May have high-arched palate or cleft palate. Micrognathia. May have hoarse voice.

Chest: Small thoracic cage with irregular, ribbon-like ribs. Short clavicles with narrow shoulders. Pectus excavatum. Recurrent respiratory tract infections are common. Patients with severe lung disease may have pulmonary hypertension. Sleep apnea in a teenager has been treated with nasal CPAP.

Cardiovascular: May have mitral or tricuspid valve prolapse. May have ventricular noncompaction cardiomyopathy.

Neuromuscular: May have hypotonia, motor delay.

Orthopedic: May have short stature. Short upper limbs. Bowing of the humerus, radius, ulna, and tibia. May have abnormal gait secondary to bowing. Metaphyseal flaring of long bones. Iliac flaring. Short distal phalanges with cone-shaped epiphyses. Clubfoot deformity. Kyphoscoliosis. May have dislocated hip, osteoarthritis of back and hip.

GI/GU: May have ureteral obstruction and hydronephrosis. Males may have omphalocele.

Other: Small pelvis in affected women may necessitate delivery by cesarean section. Males may have lax skin.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult in patients with significant micrognathia. There is an increased risk of postoperative respiratory complications in these patients with small thoracic cages and irregular, ribbon-like ribs. Patients with severe lung disease may have pulmonary hypertension. Short clavicles may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Menkes kinky hair syndrome

Synonym: Kinky hair syndrome

MIM #: 309400

This X-linked recessive disorder is due to an abnormality in the gene encoding copper-transporting adenosine triphosphatase, alpha polypeptide (*ATP7A*). It is somewhat similar to the genetic defect in Wilson disease (see later) in that both have the characteristics of a copper-transporting adenosine triphosphatase. The Wilson disease gene product is involved with the export of copper out of cells, whereas the Menkes kinky hair syndrome gene

product is involved with the transport of copper into cells. Abnormal copper transport results in low serum levels of copper and ceruloplasmin. A variety of enzymes requiring copper as a cofactor are affected, including tyrosinase, monoamine oxidase, lysyl oxidase, and cytochrome c oxidase.

The manifestations of this disorder are due to deficiencies in these enzymes. The syndrome derives its name from the characteristic kinky hair of patients with this syndrome. Patients also have progressive cerebral deterioration and seizures, with death usually occurring by age 3 years. Female carriers may have subtle manifestations of the disorder. Copper supplementation will not reverse the disease progression; however, early neonatal supplementation with copper-histidine has proven beneficial, particularly with the uncommon child whose mutation allows for some residual activity (4). X-linked Ehlers-Danlos syndrome (Ehlers-Danlos type IX; see earlier), also known as the occipital horn syndrome, is caused by a mutation in the same gene.

HEENT/Airway: May have microcephaly or brachycephaly. Frontal bossing. Wormian bones. Fat cheeks. Abnormal eyebrows.

Cardiovascular: Vascular elongation and tortuosity, aneurysms, capillary fragility secondary to lysyl oxidase deficiency.

Neuromuscular: Progressive cerebral and cerebellar degeneration, beginning at age 1 to 2 months. Focal gliosis. Hypertonia. Seizures, often difficult to control. Developmental delay. Eventual decerebration. Can have spontaneous intracerebral hemorrhage. May have occipital horns (wedge-shaped calcifications within the tendinous insertions of the trapezius and sternocleido-mastoid muscles to the occipital bone).

Orthopedic: Intrauterine growth retardation. Short stature. Skeletal demineralization due to ascorbate oxidase deficiency (similar to lesions of scurvy). May have pathologic fractures. Metaphyseal widening with spurs. Lax joints.

GI/GU: May have gastroesophageal reflux. May have gastric polyps and gastrointestinal bleeding. Small testes. Bladder and ureter diverticulae.

Other: Depigmentation of the hair and skin secondary to tyrosinase deficiency, kinky hair secondary to monoamine oxidase deficiency, abnormal collagen function secondary to lysyl oxidase deficiency, and hypothermia secondary to cytochrome c oxidase deficiency. Hair is sparse, stubby, and depigmented. Microscopically, hair shafts are of varying diameter, are twisted, and have regularly spaced shaft fractures.

Miscellaneous: John Menkes was also the first to describe maple syrup urine disease.

Anesthetic Considerations: A child was reported in whom bulky pharyngeal tissue, hypotonic pharyngeal muscles, and possibly abnormal neural control of oropharyngeal muscles conspired to cause airway obstruction and difficult laryngoscopy and tracheal intubation (5). Patients may have gastroesophageal reflux and are at increased risk for aspiration. Capillary fragility might increase the risk of intraoperative bleeding, but this has not been documented. Capillary fragility and tortuosity can make venous cannulation challenging (3) and is a relative contraindication to regional techniques. Repeat dental damage with laryngoscopy has been reported (2). Careful perioperative positioning and padding is important in these patients who have lax joints and are at risk for pathologic fractures. Patients are prone to the development of perioperative hypothermia. Anticonvulsant drugs should be continued perioperatively and alternatives given parenterally if required. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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MERRF syndrome

MIM #: 545000

Myoclonus **E**pilepsy with **R**agged **R**ed **F**ibers is due to a defect in one or more mitochondrial genes with onset in the neonatal period. It is related to Kearns-Sayre syndrome, Leigh disease, MELAS syndrome, and others. Eighty percent to ninety percent of cases are due to a defect in the gene encoding mitochondrial lysine tRNA. A specific mutation in mitochondrial DNA causes multiple deficiencies in the complexes of the respiratory chain, particularly complexes I and IV (see earlier). This syndrome is associated with “ragged red” fibers in muscle biopsy specimens, which represent a proliferation of mitochondria and excess lipid. The clinical spectrum depends on the relative amounts of normal and abnormal mitochondria. For example, there is a case with the typical genetic defect with a normal muscle biopsy. There can be phenotypic overlap with MELAS syndrome (see earlier) (1).

HEENT/Airway: Optic atrophy. Sensorineural hearing loss.

Neuromuscular: Myoclonic epilepsy, ataxia, spasticity, intention tremor. Myopathy with muscle weakness. Isolated muscle pain has been reported as the presenting complaint. Degenerative changes in the cerebrum, cerebellum, and spinal cord.

GI/GU: Chronic intestinal pseudo-obstruction has been reported.

Other: Elevated serum pyruvate or lactate. Elevated serum alanine. Abnormalities in respiratory chain complexes I and IV.

Anesthetic Considerations: Be sensitive to the fact that patients may have hearing loss. Stress, such as seen with surgery or infection, may increase demands for adenosine triphosphate production to levels above that which the patient can produce. Acidosis should be corrected preoperatively, and patients with excessive lactic acidemia should not receive Ringer's lactate. Severe lactic acidosis can be treated with dichloroacetate (50 mg/kg intravenously) over 30 minutes, which stimulates pyruvate dehydrogenase. This enzyme converts lactate to

pyruvate.

Ringer's lactate has been used successfully in stable patients with the related MELAS syndrome (see earlier), although even those authors suggested it might best be avoided. Protracted preoperative fasting should be avoided, and glucose-containing intravenous fluids begun preoperatively when feeding stops and continued into the postoperative period. Postoperative clinical deterioration in patients with a mitochondrial myopathy has been reported (7).

Patients with mitochondrial myopathies may be more sensitive to succinylcholine, curare (10), mivacurium (8), rocuronium, and atracurium (6), although one report did not find increased sensitivity to succinylcholine or pancuronium (11). The use of succinylcholine may be best avoided in this myopathy, secondary to the risk of exaggerated hyperkalemia. Because propofol can inhibit respiratory chain complex I, large doses are probably best avoided, although there are no specific reports for this syndrome. Some patients with mitochondrial disease have abnormal control of respiration, suggesting that opioids and other respiratory depressants be used with care. Chronic use of anticonvulsant medication affects the metabolism of some anesthetic drugs. A relationship between the mitochondrial myopathies and malignant hyperthermia has been suggested in the past, but there seems to be no evidence for this.

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Metachromatic leukodystrophy

MIM #: 250100

Metachromatic leukodystrophy is an autosomal recessive disease due to the absence of arylsulfatase A, the lysosomal enzyme responsible for the degradation of sulfatide, an important constituent of myelin. There is accumulation of sulfatide (galactosyl and, to a lesser extent, lactosyl) in both neural and nonneural tissues, which can be identified as metachromatic granules. Metachromatic leukodystrophy is the most common of the leukodystrophies. Infantile, juvenile, and adult forms have been described, which are allelic disorders. The initial signs of the adult form are often psychiatric. Metachromatic leukodystrophy can less commonly be due to the absence of saposin B or a multiple sulfatase deficiency, disorders that combine phenotypic features of the mucopolysaccharidoses with metachromatic leukodystrophy. Umbilical cord and hematopoietic stem cell transplantation have been used with preliminary success to stabilize the disease, with earlier use more successful. There has also been preliminary success using a modified HIV virus to insert the missing gene.

The other leukodystrophies include adrenoleukodystrophy, Canavan disease, Krabbe disease, Pelizaeus-Merzbacher disease, and Alexander disease.

HEENT/Airway: Optic atrophy. Copious oral secretions.

Neuromuscular: There is regression of neurologic development with loss of motor skills, gait disturbances, ataxia, hypotonia, Babinski sign, seizures,

choreoathetosis. Torsion spasms of the neck, spine, and limbs. There is a loss of deep tendon reflexes. Eventual spastic quadriparesis. Loss of intellectual milestones. The adult form may include dysarthria, dementia, and psychotic thought processes.

GI/GU: Increased incidence of gastroesophageal reflux. Megacolon. Gallbladder dysfunction. Cholecystitis. Gallbladder polyps and gastric and duodenal polyps have been reported. Sulfatide deposition can also be seen in the kidney, but without renal dysfunction. Urinary incontinence.

Other: Associated with intermittent fever and abdominal pain.

Miscellaneous: Metachromatic staining of the central nervous system was first described by Alzheimer. Sulfatides received their name because they are sulfur containing.

Anesthetic Considerations: Patients are at risk for perioperative aspiration secondary to poor airway tone, copious oral secretions, and an increased incidence of gastroesophageal reflux. Consideration should be given to anticholinergic premedication to dry oral secretions. Careful perioperative positioning and padding is important in

these patients with poor nutrition. Hypertonia resolves with the administration of muscle relaxants. Phenothiazines, butyrophenones, and other dopaminergic blockers should be avoided because they may exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects. Anticonvulsant medications should be continued perioperatively and may alter the metabolism of some anesthetic drugs. Exaggerated hyperkalemia from succinylcholine use has not been reported, but it is reasonable to avoid succinylcholine in patients with chronic disabling disease involving muscle disuse. Airway hypotonia and copious oral secretions increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

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Metaphyseal chondrodysplasia, Jansen type

Synonym: Metaphyseal dysplasia, Jansen type

MIM #: 156400

There are many types of metaphyseal chondrodysplasia—see also McKusick type (cartilage-hair hypoplasia syndrome), Pyle type, Schmid type, Shwachman syndrome, and Spahr type [not included in this text (*MIM #:* 250400)]. The Jansen type of metaphyseal chondrodysplasia is inherited in an autosomal dominant fashion, with most cases representing fresh mutations. It is characterized by severe postnatal short stature and significant joint dysfunction. It is caused by a mutation in the parathyroid hormone-1 receptor resulting in constitutive activity of the cAMP signaling pathway.

HEENT/Airway: Cranial bone sclerosis particularly with aging and wide cranial sutures. Small face, prominent eyes, and supraorbital ridge. Hypertelorism. May have hearing loss. High-arched palate. Micrognathia. May have choanal stenosis or atresia.

Chest: Small thorax. Thoracic kyphoscoliosis. Abnormal ribs, with a tendency to fracture.

Neuromuscular: Intelligence is normal.

Orthopedic: Severe short stature. Enlarged, dysfunctional joints with flexion contractures, particularly at knees and hips. Short distal phalanges. Irregular and disorganized metaphyses, with normal-appearing epiphyses. Short, bowed limbs. Waddling gait. Evidence of increased bone resorption without sufficient compensatory bone formation.

GI/GU: May have nephrocalcinosis.

Other: Hypercalcemia, hypercalciuria.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia. Choanal stenosis, if present, may preclude the use of a nasal airway or a nasogastric tube. There is an increased risk of perioperative respiratory complications because of the thoracic cage abnormalities. Asphyxiating thoracic dysplasia, as in Jeune syndrome (see earlier), has been described. Patients must be carefully positioned and padded secondary to severe joint dysfunction. Patients are hypercalcemic. Adequate urine output should be maintained secondary to hypercalciuria.

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Metaphyseal chondrodysplasia, McKusick type

See Cartilage-hair hypoplasia syndrome

Metaphyseal chondrodysplasia, Schmid type

Synonym: Metaphyseal dysplasia, Schmid type

MIM #: 156500

There are many types of metaphyseal chondrodysplasia—see also Jansen type, McKusick type (cartilage-hair hypoplasia syndrome), Pyle type, Shwachman syndrome, and Spahr type [not included in this text (*MIM #:* 250400)]. The Schmid type of metaphyseal chondrodysplasia is a short-limb dwarfism inherited in an autosomal dominant fashion with variable expression. It is characterized by moderate short stature, bowed legs, and a waddling gait. The orthopedic abnormalities tend to improve over time. Schmid-type metaphyseal chondrodysplasia is caused by a mutation in the gene for type X collagen (*COL10A1*). Collagen X is limited to the growth plate, explaining the metaphyseal location. It plays a role in endochondral calcification.

Chest: Lower rib cage mildly flared anteriorly.

Neuromuscular: Intelligence is normal.

Orthopedic: Moderate short stature. Bowed legs. Enlarged capital femoral epiphyses. Coxa vara. Waddling gait. Irregular metaphyses, with normal-appearing epiphyses. Metaphyseal cupping of the proximal phalanges and metacarpals. No vertebral abnormalities.

Anesthetic Considerations: Patients must be carefully positioned and padded secondary to orthopedic abnormalities.

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Metaphyseal dysplasia, Jansen type

See Metaphyseal chondrodysplasia, Jansen type

Metaphyseal dysplasia, McKusick type

See Cartilage-hair hypoplasia syndrome

Metaphyseal dysplasia, Pyle type

See Pyle metaphyseal dysplasia

Metaphyseal dysplasia, Schmid type

See Metaphyseal chondrodysplasia, Schmid type

Metatropic dwarfism

Synonym: Metatropic dysplasia, type I

MIM #: 156530

This autosomal dominant disorder is characterized by progressive short-trunk dwarfism, short limbs, small thorax, odontoid hypoplasia, and metaphyseal flaring. Findings are present at birth. It is due to mutations in the gene *TRPV4*, which encodes a cation channel that mediates calcium entry into epithelial cells. Mutations in this gene are also responsible for spondylometaphyseal dysplasia, Kozlowski type (see later), as well as other disease states. Many features of this disorder are similar to Kniest syndrome (also known as metatropic dysplasia, type II; see earlier).

HEENT/Airway: Macrocephaly. Short neck. May have precocious calcification of the cricoid and hyoid bones. May have overgrowth of cartilage in the trachea.

Chest: Small thorax with short ribs, thoracic kyphoscoliosis. Short ribs. May have severe restrictive lung disease with respiratory failure. May have sleep apnea.

Neuromuscular: May have cervical cord compression secondary to atlantoaxial instability. May have ventriculomegaly.

Orthopedic: Short-trunk dwarfism develops secondary to progressive and severe kyphoscoliosis. Can have arthrogryposis or joint contractures. Hyperplastic femoral trochanters. Short fingers. Odontoid hypoplasia with atlantoaxial instability may lead to cord compression, quadriplegia, and death. Platyspondyly. Short limbs with metaphyseal flaring (long bones appear dumbbell shaped). Large joints with limited joint

mobility, particularly at knees and hips. Small pelvis. Long coccyx resembling a short tail.

Other: Small pelvis in affected women may necessitate delivery by cesarean section. Can have fetal akinesia.

Miscellaneous: "Metatropic" is derived from the Greek for "different shape," referring to the changing body proportions with age as the kyphoscoliosis progresses. These patients may be misdiagnosed with achondroplasia at birth and Morquio syndrome when older.

Anesthetic Considerations: Patients may have atlantoaxial instability. Direct laryngoscopy may be difficult because of the short neck, particularly if there is limited neck mobility secondary to C1-C2 fusion done for atlantoaxial instability. Neck flexion may occlude the airway. Patients might require a smaller-than-expected endotracheal tube if sized for age. Patients must be carefully positioned and padded secondary to limited joint mobility. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

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Metatropic dysplasia, type I

See Metatropic dwarfism

Metatropic dysplasia, type II

See Kniest syndrome

Methemoglobinemia

Synonym: Congenital methemoglobinemia

MIM #: 250800, 250790

Methemoglobin is hemoglobin in which the iron has not been reduced from its ferric (Fe^{3+}) state to its ferrous (Fe^{2+}) state. Methemoglobin cannot bind molecular oxygen. Methemoglobin in low levels (<1% of total hemoglobin) is normally formed in the red blood cells. There is an intracellular mechanism responsible for maintaining normal levels of reduced hemoglobin, which is normally well in excess of the rate of hemoglobin oxidation. The classic reductase is located solely in red blood cells. A more severe and even lethal disease is caused by a generalized reductase deficiency, which has major neurologic manifestations and intellectual disabilities.

Methemoglobinemia results from one of three mechanisms. First, the normal cellular mechanisms can be overwhelmed by exogenous agents. This is particularly easy to do in infants, whose red blood cells have approximately one-half the methemoglobin reducing capability of adult red blood cells. For example, there was a case report of carrot juice inducing methemoglobinemia in an infant. Second, there can be a structurally abnormal hemoglobin. These are designated as the hemoglobins M (with the location of the place of discovery following as a subscript). The amino acid substitutions in the hemoglobins M form a covalent link with iron, stabilizing it in the oxidized (Fe^{3+}) state. These are transmitted in an autosomal dominant fashion. Defects in the alpha chain present with cyanosis from birth. Cyanosis develops at several months of age in patients with defects in the beta chain, coincident with the postnatal shift to synthesis of this chain. Third, there can be a defect in the cell's ability to reduce red blood cell iron, either NADH-dependent hemoglobin reductase (methemoglobin reductase, cytochrome b5 reductase) or cytochrome b5 itself. These are transmitted in an autosomal recessive fashion. Cytochrome b5 is required as a cofactor for functioning of methemoglobin reductase.

Cyanosis develops at methemoglobin levels greater than 10% to 20%; headaches, fatigue, weakness, tachycardia, and dizziness at levels from about 30% to 40%; dyspnea and lethargy at about 40% to 50%; acidosis, hypoxia, seizures, and coma at levels of about 50% to 60%; and death at levels over about 70%.

HEENT/Airway: Microcephaly and nystagmus in the generalized reductase defect only. Conjunctival cyanosis is present in patients with methemoglobinemia, but not in patients with cyanosis from poor oxygenation of blood. Apparently, the conjunctival sac allows oxygenation of red blood cells from the air, which would not make any difference in patients with methemoglobinemia.

Neuromuscular: Variable intellectual disabilities, opisthotonos, attacks of athetosis, and hypertonia in the generalized reductase defect only.

Other: Blood with over approximately 10% methemoglobin turns dark red or brownish on standing or

on shaking with air. Methemoglobin is detectable by cooximeters.

Miscellaneous: A variety of compounds can cause methemoglobin formation either directly or indirectly. Endogenous intracellular compounds that can produce methemoglobin include molecular oxygen, hydrogen peroxide, and several free radicals. Toxic exogenous compounds include (but are not limited to) benzocaine, prilocaine, chloral hydrate, nitrites (which can be found in well water), nitrates, hydrazines, primaquine, chloroquine, sulfonamide, metoclopramide, dapsone, phenacetin, and acetanilide.

The defect is common in both Navajo and Athabascan Indians. Interestingly, the languages of both of these groups are also similar, suggesting a common origin. One case report noted that their patient was from the area in India where the Hindu god Krishna was born. Krishna was said to have dark bluish skin (4).

Anesthetic Considerations: The color of these infants is not really the same as that of patients with cyanosis. It is more of a slate-grayish color, somewhat like that seen with venous suffusion. Arterial PO_2 is otherwise appropriate

for the FiO_2. Patients breathing supplemental oxygen are cyanotic appearing but have a high arterial PO_2.

Benzocaine, prilocaine (in EMLA cream, a eutectic mixture of local anesthetics), nitroglycerin, sulfonamides, and chloral hydrate can produce methemoglobin and should be avoided if possible in these patients. Exogenous agents in sufficient quantities can induce methemoglobinemia even in normal patients (patients without congenital methemoglobinemia), as, for instance, with the overuse of benzocaine when topicalizing the airway (10,11).

Pulse oximeters (and oximetric pulmonary arterial catheters) do not reliably reflect hemoglobin oxygen saturation in the presence of methemoglobin (12). Methemoglobin increases light absorbance at both wavelengths used by pulse oximeters to calculate oxygen saturation. The large increase in absorbance in both the numerator and denominator of the formula used to calculate oxygen saturation forces the ratio toward 1. At a ratio of 1, the oxygen saturation is calculated as 85%. Thus, methemoglobinemia forces a saturation approaching 85% independent of the PO_2 or true hemoglobin oxygen saturation.

The rate of methemoglobin reduction can be accelerated by a variety of agents, including methylene blue and ascorbic acid. The dose of methylene blue is 1 to 2 mg/kg intravenously (it comes as a 1%, or 10 mg/mL, solution) or 2 mg/kg orally per day (100 to 300 mg in adults). It has been used prophylactically prior to surgery. Methylene blue does not work in patients with one of the hemoglobinopathies or in patients who are also glucose-6-phosphate dehydrogenase deficient. Excessive methylene blue can itself result in hemolysis. Oral ascorbic acid (500 to 1000 mg/day in an adult) also lowers methemoglobin levels, but has certain long-term side effects. Oral riboflavin (20 to 60 mg/day in adults) is also said to help.

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Methylene tetrahydrofolate reductase deficiency

See 5,10-methylene tetrahydrofolate reductase deficiency

Methylmalonic acidemia

Synonym: Methylmalonic aciduria; Methylmalonyl-coenzyme A mutase deficiency

MIM #: 251000, 251100

This autosomal recessive and genetically heterogeneous disorder is caused by defects in the activity of one of several enzymes, resulting in methylmalonic acidemia. Severe metabolic acidosis, ketosis, and hyperammonemia can develop at times of increased protein catabolism. There can be a defect in methylmalonyl-coenzyme A mutase, a defect in adenosylcobalamin synthesis causing impaired mutase function (and that may respond to

pharmacologic doses of cyanocobalamin or adenosylcobalamin), or a defect in the function of both adenosylcobalamin synthesis and methylcobalamin-dependent N5-methyltetrahydrofolate methyltransferase. The latter causes methylmalonic acidemia and homocystinuria. In addition, there may be multiple alleles for each of these. Mutations in methylmalonyl-coenzyme A mutase are referred to as mut^0 if the protein structure is affected or mut^- if the amount of enzyme is reduced. Methylmalonyl-coenzyme A mutase converts propionyl-CoA to succinyl-CoA. In its absence, its substrate is converted to methylmalonyl-CoA. Methylmalonyl-coenzyme A also requires a B_{12}-dependent coenzyme (adenosylcobalamin) as a cofactor. Deficiency of adenosylcobalamin is always associated with abnormalities of propionyl-CoA metabolism, with resultant propionic acidemia and carnitine deficiency. Treatment includes a nonpropionate-producing amino acid diet with adequate carbohydrates and lipids as energy sources, continuous nighttime gastric feeding, L-carnitine supplementation to increase renal excretion of propionyl groups via propionyl-carnitine, and supplemental vitamin B_{12} (in B_{12} responsive types). Liver transplantation has been proposed but has been ineffective, as continued synthesis of propionyl-CoA within the central nervous system leads to accumulation of methylmalonate in the brain. Hemodialysis is useful in the acute

management of catabolic crises. Untreated, the mean age at death is 1.5 to 2 years.

Cardiovascular: May have cardiomyopathy.

Neuromuscular: Lethargy, hypotonia, dystonia, seizures. Can have strokes. Occasional intellectual disabilities. Rare progression to coma. Patients do not have the neurologic findings of cobalamin deficiency.

Orthopedic: Growth retardation. Osteoporosis with pathologic fractures.

GI/GU: Recurrent vomiting. Episodic pancreatitis. Hepatomegaly. May have small kidneys, interstitial nephritis, and renal insufficiency.

Other: Failure to thrive, hypoglycemia, metabolic acidosis, ketosis, and hyperammonemia. Neutropenia, thrombocytopenia. Patients do not have the hematologic findings of cobalamin deficiency.

Miscellaneous: Patients may be receiving chronic oral citrate or bicarbonate to maintain a normal pH and supplemental cobalamin. It has been suggested that therapy with intramuscular cyanocobalamin alone is inadequate for patients with methylmalonic acidemia and homocystinuria, and patients should be treated with hydroxocobalamin.

Anesthetic Considerations: All preoperative medications related to the disease should be continued perioperatively. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Prolonged fasting must be avoided perioperatively. Abnormal diet in the days after surgery can result in an exacerbation of acidosis (4). Intravenous fluids and dextrose should be used generously perioperatively to avoid hypovolemia and protein catabolism. An orogastric tube and throat packs should be placed for surgery with the potential for oral or intestinal bleeding, because blood in the GI tract provides a protein load that may trigger acute decompensation. The platelet count should be evaluated preoperatively to screen for thrombocytopenia. Intraoperative arterial blood gas tensions and measurements of electrolytes, glucose, and ammonia may be warranted to detect acidosis or hyperammonemia. It has been suggested that muscle relaxants metabolized by ester hydrolysis be avoided as they can be metabolized to methylmalonic acid. Acute preoperative hemodialysis has been used. Nitrous oxide inhibits vitamin B_{12}-dependent coenzymes, including adenosylcobalamin, and probably should be avoided in these patients (2). Patients must be carefully positioned and padded secondary to osteoporosis. Postoperative metronidazole has been used to diminish production of propionate by gut flora, a major source of propionate. Patients with cardiomyopathy should receive an appropriately tailored anesthetic.

Figure: See **Appendix D**.

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Methylmalonic aciduria

See Methylmalonic acidemia

Methylmalonyl-coenzyme A mutase deficiency

See Methylmalonic acidemia

Mevalonic aciduria

Synonym: Mevalonate kinase deficiency; Hyperimmunoglobulin D syndrome

MIM #: 610377

This autosomal recessive autoinflammatory disorder was the first described defect in cholesterol metabolism. As such, it is not surprising that it affects multiple organ systems. The disorder is marked by psychomotor retardation, cerebellar ataxia, recurrent inflammatory febrile episodes, and early childhood death. Because of the lack of feedback inhibition, massive amounts of mevalonate can be synthesized and lost in the urine. Other typical manifestations of metabolic disease, such as hypoglycemia, metabolic acidosis, or lactic acidosis, are absent here. The disease is allelic to hypergammaglobulinemia D and periodic fever syndrome (*MIM #:* 260920), which is typically not associated with dysmorphic features or neurologic findings. The difference in phenotype between the two allelic syndromes depends on the residual enzyme activity, with mevalonate kinase deficiency having the least activity and therefore the most severe disease. During febrile episodes, a variety of proinflammatory cytokines are elevated.

In addition to leading to the steroid biosynthesis pathway (via cholesterol; see Appendix A) and to the formation of bile acids, mevalonate is also a precursor to a variety of other important compounds, including coenzyme Q10, isopentenylated RNAs (involved in protein synthesis), prenylated proteins (which are involved in intracellular signal transduction), and others.

Mevalonic acid is synthesized by a reaction catalyzed by HMG-CoA reductase. This is the enzyme inhibited by the statin drugs. However, due to upregulation of HMG-CoA reductase and the low-density lipoprotein (LDL) cholesterol receptor, levels of cholesterol and subsequent biosynthetic products are normal. Levels of coenzyme Q10 are reduced, however, suggesting that important intermediates are preferentially converted to cholesterol.

There is no good treatment for mevalonic aciduria, and supplementation of cholesterol or coenzyme Q10 has not proven helpful. Corticosteroids can lessen the severity of attacks, but not prevent them. Preliminary data on the use of statins have demonstrated some clinical deterioration but also a decrease in the incidence and severity of attacks. Similarly, tumor necrosis factor α antagonists (TNF-α antagonists, e.g., etanercept) have been used with variable success. Bone marrow transplantation has been of benefit, but long-term outcome is unknown.

HEENT/Airway: Microcephaly, dolichocephaly, wide and irregular fontanelles, triangular facies. Downward slanting palpebral fissures, blue sclerae, nystagmus. Can have cataracts. Low-set ears.

Neuromuscular: Psychomotor retardation. Hypotonia. Progressive ataxia. Cerebral and cerebellar ataxia. Agenesis of cerebellar vermis. Progressive myopathy.

GI/GU: Fluctuating hepatosplenomegaly, likely from extramedullary hematopoiesis. Vomiting. Diarrhea.

Orthopedic: Arthralgias.

Other: Short stature, failure to thrive. Anemia. Leukocytosis. Thrombocytopenia. Early childhood onset of recurrent febrile crises associated with lymphadenopathy, hepatosplenomegaly, vomiting, diarrhea, arthralgias, and skin rash.

Anesthetic Considerations: The hematocrit and platelet count should be evaluated preoperatively. Episodic emesis during a febrile crisis may increase the risk of perioperative aspiration. Patients may be taking steroids and should receive stress doses of steroids perioperatively. Fever may not (or may) be indicative of infection.

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Mevalonate kinase deficiency

See Mevalonic aciduria

Michels syndrome

See Malpuech syndrome

Microphthalmia-linear skin defects syndrome

Synonym: MIDAS syndrome

MIM #: 309801

This X-linked syndrome involves microphthalmia, sclerocornea, and focal linear dermal hypoplasia. The mnemonic MIDAS stands for **MI**crophthalmia, **D**ermal **A**plasia, and **S**clerocornea. Patients have

severe visual impairment. All affected individuals are female, suggesting lethality in males. MIDAS syndrome is due to mutations in the gene *HCCS*. This gene shares homology with genes encoding holocytochrome c-type synthetases, enzymes that catalyze the addition of a heme group onto c-type cytochromes in mitochondria. It has been proposed that MIDAS syndrome and Aicardi syndrome (see earlier) are due to the same gene or genes, and

different patterns of X-inactivation result in the phenotypic variation among them.

HEENT/Airway: Can have microcephaly. Microphthalmia. Sclerocornea. May also have anterior chamber defects, cataracts, iris coloboma, pigmentary retinopathy, glaucoma. Midface hypoplasia. External ear deformity. Can have hearing loss.

Chest: Diaphragmatic hernia has been reported. May have costovertebral anomalies.

Cardiovascular: May have cardiomyopathy, cardiac conduction abnormality or arrhythmias, atrial septal defect, ventricular septal defect, overriding aorta.

Neuromuscular: May have agenesis of the corpus callosum, absence of the septum pellucidum. May have seizures. May have mild to severe intellectual disabilities.

Orthopedic: Mild short stature.

GI/GU: May have anomalies of external or internal genitalia.

Other: Focal dermal hypoplasia or aplasia, usually linear, particularly affecting the head and neck that heal with hyperpigmentation but without scarring. Rarely, there may be herniation of adipose tissue through the defect.

Anesthetic Considerations: Patients must be carefully positioned and padded secondary to focal dermal hypoplasia. Patients may have cardiac conduction abnormalities. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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MIDAS syndrome

See Microphthalmia-linear skin defects syndrome

Miller syndrome

Synonym: Postaxial acrofacial dysostosis syndrome

MIM #: 263750

This autosomal recessive syndrome consists of craniofacial abnormalities somewhat similar to those of the Treacher Collins syndrome, plus postaxial upper and lower limb defects. It is due to abnormalities in the gene *DHODH*. The gene encodes dihydroorotate dehydrogenase, which catalyzes a step in the synthesis of pyrimidines.

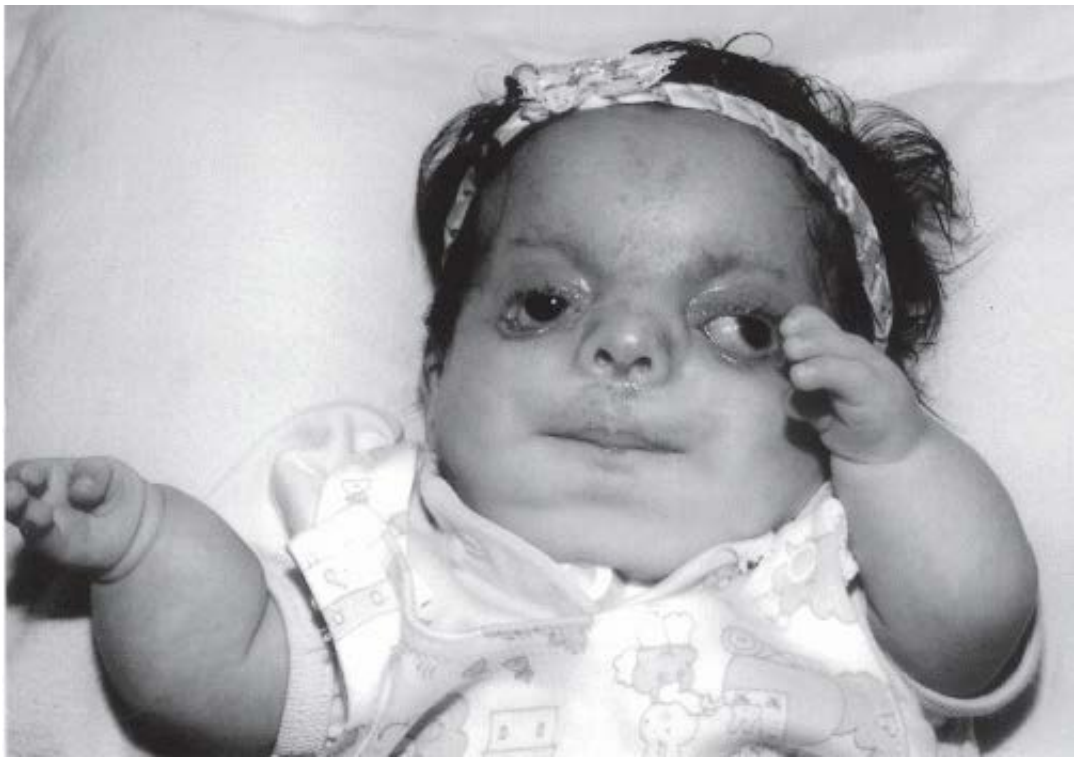
HEENT/Airway: Malar hypoplasia. Absent superior orbital ridges, downslanting palpebral fissures, eyelid coloboma,

and lower lid ectropion. Hypoplastic, low-set, cup-shaped ears. May have conductive hearing loss. Cleft lip or palate. Micrognathia. May have choanal atresia. Lid ectropion and facial asymmetry may progress over time. Micrognathia may improve over time.

Chest: May have pectus excavatum. May have rib anomalies. May have absent hemidiaphragm.

Cardiovascular: Congenital cardiac defects include atrial septal defects, ventricular septal defects, and patent ductus arteriosus.

Neuromuscular: Intelligence is usually normal.



Miller syndrome. FIG. 1. This young girl has Miller syndrome. She was reported in the paper by Stevenson et al. Note tracheostomy, coloboma, absent fifth fingers, short forearms, and micrognathia.

Miller syndrome. FIG. 2. The young girl in Photo 1 at age 16.

Orthopedic: Postaxial upper and lower limb defects, including absent fifth digit of all four limbs. Can have absence of third and fourth toes as well. Forearm shortening, secondary to ulnar or radial hypoplasia. Syndactyly. Congenital hip dislocation.

GI/GU: May have pyloric stenosis, malrotation, volvulus. Cryptorchidism. May have renal anomaly.

Other: Accessory nipples.

Miscellaneous: Previously known as Genee-Wiedemann syndrome. Nager syndrome (see later) also has Treacher Collins-like facies, but is distinguishable from Miller syndrome because it involves preaxial rather than postaxial upper limb defects. The findings are similar to those of fetal methotrexate exposure. Methotrexate also inhibits purine biosynthesis. A similar phenotype (due to abnormal pyrimidine biosynthesis) was described by the famous American geneticist Thomas Hunt Morgan in *Drosophila* in 1910.

Anesthetic Considerations: Malar hypoplasia may result in a poor mask fit. Direct laryngoscopy and tracheal intubation can be extremely difficult. Choanal atresia, if present, precludes the use of a nasal airway or nasogastric tube. Peripheral intravenous access may be difficult secondary to limb defects. Radial anomalies may make placement of a radial arterial catheter more difficult. The eyelids may not completely cover the eyes, which then need additional perioperative protection.

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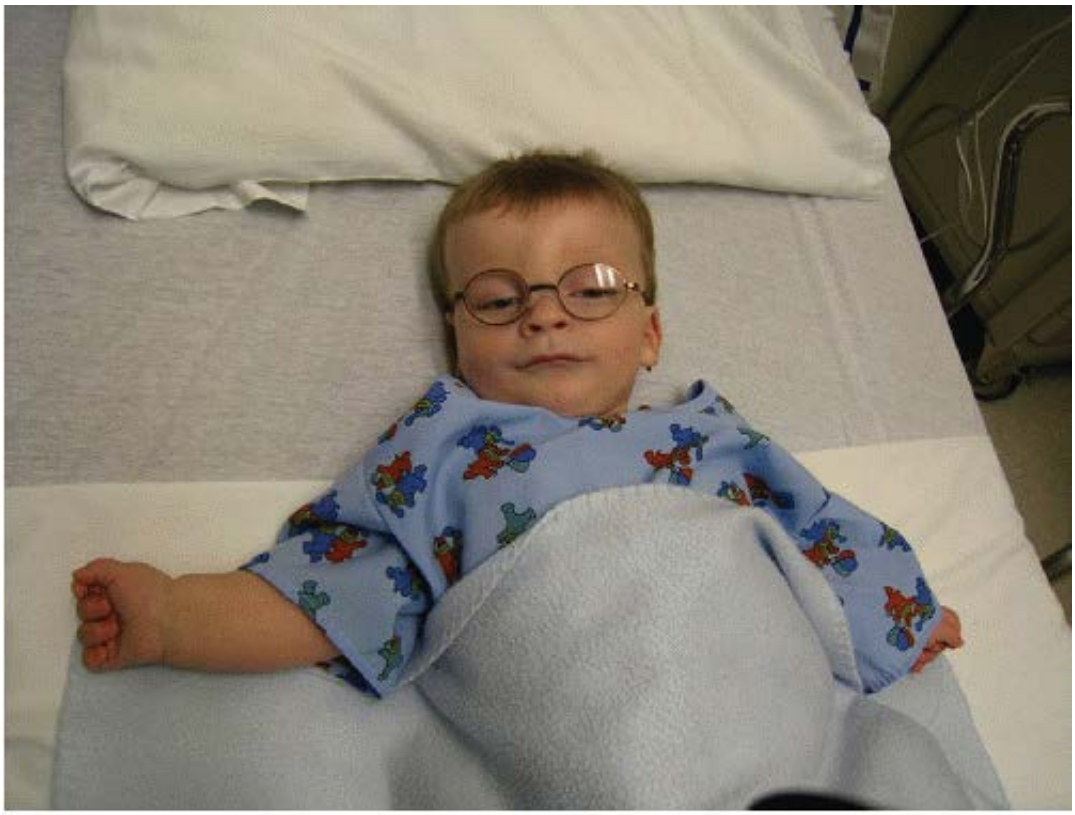
Miller-Dieker syndrome

Synonym: Lissencephaly syndrome

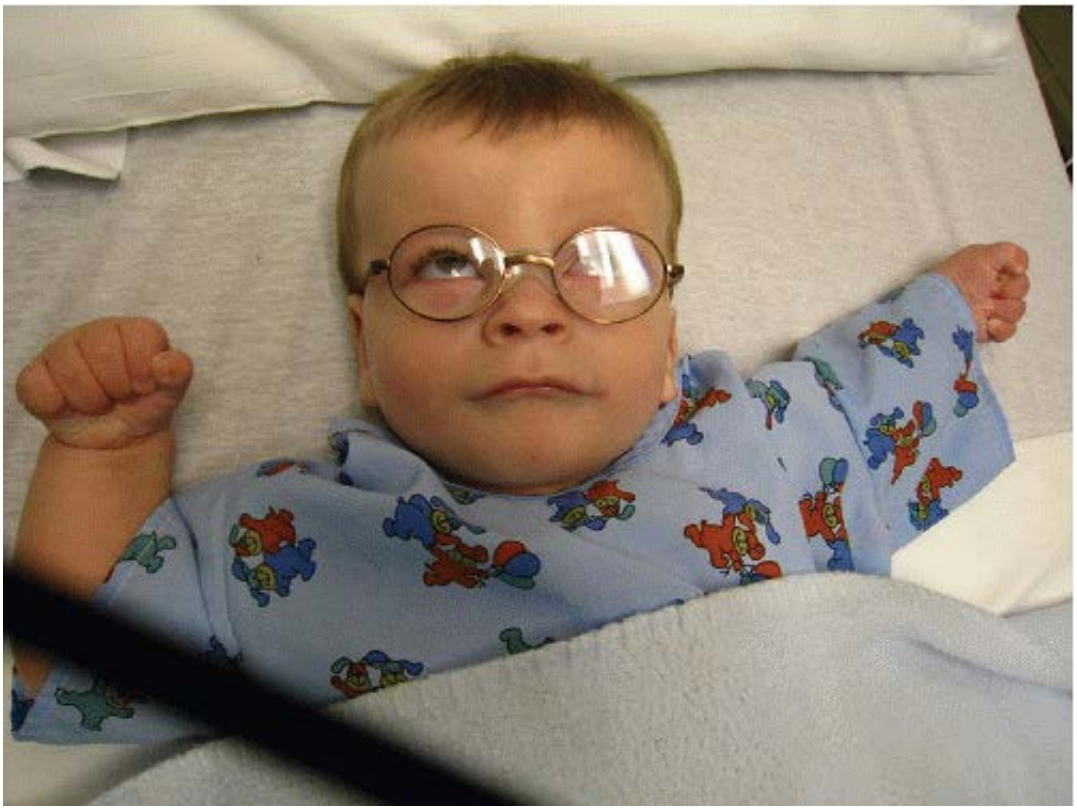
MIM #: 247200

This autosomal dominant disorder is a contiguous gene deletion syndrome of genes located on the short arm of chromosome 17. Death often occurs in early childhood. A defect in the gene *L1S1* (now called *PAFAH1B1*) is responsible for the lissencephaly. Defects in contiguous genes such as *YWHAE* cause the other features of Miller-Dieker syndrome, such as microcephaly, bitemporal narrowing, short nose with anteverted nares, micrognathia, and agenesis of the corpus callosum. There is evidence that the *L1S1* gene product is the human homologue of a subunit of bovine

brain platelet-activating factor acetylhydrolase, which inactivates platelet-activating factor in the bovine brain. The exact role of the *L1S1* gene product is not known, but it may be involved in a signal transduction pathway that is crucial for cerebral development.



Miller-Dieker syndrome. FIG. 1. A young boy with Miller-Dieker syndrome.



Miller-Dieker syndrome. FIG. 2. The boy in Photo 1 in the midst of a seizure.

HEENT/Airway: Microcephaly, prominent forehead, bitemporal narrowing. Midline forehead furrowing, especially noticeable when crying. Hypertelorism. Upslanted palpebral fissures, ptosis. Low-set and/or posteriorly rotated ears. Short nose with anteverted nares. Prominent philtrum. Thin, protuberant upper lip. Micrognathia. May have cleft palate.

Chest: Recurrent aspiration pneumonia.

Cardiovascular: May have a cardiac defect such as atrial septal defect, ventricular septal defect, tetralogy of Fallot, pulmonic stenosis.

Neuromuscular: Lissencephaly—smooth brain surface (absent gyri) with incomplete development of the brain. Thickened cortex. Wide sylvian fissure apparent on computed tomography scan. Large ventricles. Absent corpus callosum. Midline calcifications. Severe intellectual disabilities and severe developmental delay. Initial hypotonia progresses to opisthotonos, spasticity, and decorticate and decerebrate posturing. Seizures. Occasional lipomeningocele with tethered cord.

Orthopedic: Transverse palmar crease. Clinodactyly, polydactyly. May have growth deficiency.

GI/GU: Dysphagia and gastroesophageal reflux are common. Cryptorchidism. Pilonidal sinus. May have omphalocele. May have renal dysplasia.

Other: Polyhydramnios. Failure to thrive.

Miscellaneous: Dr. James Q. Miller was a respected and well-liked neurologist at the University of Virginia.

Anesthetic Considerations: Severe intellectual disabilities and severe developmental delay may make the smooth induction of anesthesia a challenge. Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia. Gastroesophageal reflux is common, and patients are at increased risk for perioperative aspiration. Patients with recurrent aspiration pneumonia have chronic lung disease and are more likely to experience postoperative respiratory complications. Chronic use of anticonvulsant medications alters the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Mingarelli syndrome

See Malpuech syndrome

Mitochondrial acetoacetyl-CoA thiolase deficiency

See Beta-ketothiolase deficiency

Mitochondrial disorders

MIM #: Many

Mitochondrial disorders, also called mitochondrial cytopathies, have become increasingly commonly identified as causes of encephalomyopathy. Any structural or functional mitochondrial abnormality can disrupt the cellular machinery for energy production (ATP generation); however, abnormalities in the oxidative phosphorylation pathway are the most common cause of significant mitochondrial dysfunction. Tissues that are highly dependent on oxidative metabolism are most likely to be affected by mitochondrial dysfunction, hence the disproportionate impact of mitochondrial disorders on the brain and skeletal muscles. However,

because mitochondria exist in all tissues, mitochondrial disorders are multisystemic disorders. Systemic manifestations include developmental delay, hypotonia, ataxia, cardiomyopathy, conduction abnormalities, ophthalmoplegia, dysphagia, gastroesophageal reflux, apnea, and respiratory failure. Metabolic derangements are also common, with elevated serum lactate being almost universal. Organs and tissues can become glucose dependent, and therefore, hypoglycemia is also common. Fasting, surgical stress, and infection can trigger metabolic decompensation.

Mitochondrial disorders exhibit enormous phenotypic variability, even when the underlying genetic defects are equivalent. This is likely due to the vagaries of mitochondrial genetics (as distinct from Mendelian genetics) and the distribution of abnormal mitochondria among cell lines. Classification of mitochondrial disorders is evolving. Deficiencies of the electron transport chain protein complexes (see complex I deficiency, complex II deficiency, complex III deficiency, complex IV deficiency, or complex V deficiency) have been described. Most of these electron transport chain proteins, as well as the proteins required for proper assembly and function of the

respiratory chain, are encoded by nuclear DNA (nDNA). Alternatively, mutations or deletions in mitochondrial DNA (mtDNA) can also cause mitochondrial disorders, many of which have constellations of symptoms that are consistent enough to be delineated into clinically useful syndromes (see Kearns-Sayre syndrome, Leber hereditary optic neuropathy, Leigh disease, MELAS, MERRF, MNGIE, NARP). Disorders of mitochondria can also play a role in the development of neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Currently, there is no proven therapy for any of the mitochondrial disorders, and treatment is primarily focused on supportive measures.

HEENT/Airway: Ophthalmoplegia, pigmentary retinopathy, optic atrophy. Ptosis. Sensorineural hearing loss.

Cardiovascular: Cardiomyopathy, cardiac conduction defects.

Neuromuscular: Ataxia, seizures. Muscle weakness, dystonia. Psychomotor regression. Peripheral neuropathy.

GI/GU: Fanconi syndrome.

Other: Lactic acidosis, hypoglycemia.

Anesthetic Considerations: See also the specific mitochondrial disorders as delineated above. Baseline neuromuscular function should be delineated. The overall perioperative goal is to minimize metabolic stress, given the already impaired aerobic metabolism. Fasting should be minimized. Maintenance intravenous fluid should contain glucose and should not contain lactate. Serum glucose and electrolytes should be monitored perioperatively. Normothermia should be maintained to avoid metabolic stress and the increased metabolic rate associated with shivering. Patients with significant dysphagia are at increased risk for perioperative aspiration. Patients may not respond normally to anesthetic agents. Barbiturates, propofol, and volatile anesthetics all inhibit mitochondrial respiration. There are some reports of excessive anesthetic sensitivity and prolonged anesthetic effects with each of these drugs, but there are also many reports of uneventful use of these anesthetics in patients with mitochondrial disorders. Because it impairs mitochondrial ß-oxidation, it may be judicious to avoid anything more than short-term use of propofol in these patients for fear of triggering the propofol infusion syndrome. Chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs. Patients with advanced neuromuscular disease are at risk for hyperkalemia with the use of succinylcholine. Both sensitivity and normal response to the nondepolarizing neuromuscular blockers have been reported. Local anesthetics disrupt oxidative phosphorylation, so regional and local techniques should be undertaken with care, although there are many reports of successful use of both. Opioid medications should be used cautiously, as patients may have an impaired respiratory response to hypercarbia and hypoxemia. Respiratory function is frequently compromised at baseline, and patients are at risk for perioperative respiratory complications. Patients may have cardiomyopathy or cardiac conduction disorders. Despite the myriad perioperative concerns, many patients with mitochondrial disorders have undergone uneventful anesthetics using a variety of anesthetic techniques, primarily for minor procedures (2,3). Although there is a case report of a patient with a positive malignant hyperthermia susceptibility *in vitro* test whose muscle biopsy was also consistent with the diagnosis of a mitochondrial myopathy (7), the risk of malignant hyperthermia in a patient with mitochondrial disease is likely not to be elevated above baseline.

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Mitochondrial trifunctional protein deficiency

MIM #: 609015

This protein catalyzes three steps in the beta-oxidation of fatty acids in mitochondria. The three enzyme activities are enoyl-CoA hydratase, 3-ketoacyl-CoA thiolase, and long-chain acyl-CoA dehydrogenase (LCAD—see Long-chain acyl-CoA dehydrogenase deficiency, earlier). There may be defects in either the alpha or the beta subunits of the protein, with differing limitations in enzyme action. The α-subunit contains the hydratase and LCAD activity, and the ß-subunit contains the thiolase activity. In general, the clinical picture is worse than that of isolated LCAD deficiency. The disorder is inherited in an autosomal recessive fashion. Three phenotypes have been described: A

neonatal onset type can present as sudden infant death, an infantile onset type can present as a Reye-like syndrome, and an adolescent onset type presents more insidiously with skeletal myopathy and cardiomyopathy. Mortality is often due to cardiac disease.

HEENT/Airway: Retinopathy with vision loss is uncommon.

Cardiovascular: Cardiomyopathy, arrhythmias.

Neuromuscular: Decreased level of consciousness. Delayed psychomotor development. Skeletal myopathy. Can have rhabdomyolysis. Hypotonia. Can have peripheral neuropathy.

GI/GU: Reye-like syndrome with abnormal liver function tests, recurrent myoglobinuria.

Other: Sudden unexplained death. Recurrent hypoketotic hypoglycemia with lactic acidosis. Older patients may exhibit recurrent myoglobinuria. Hypocalcemia sometimes with hypoparathyroidism has been described. Failure to thrive. Can have lactic acidosis.

Miscellaneous: Presence of this abnormality in a fetus can cause acute fatty liver of pregnancy or HELLP syndrome in the mother. Presumably, abnormal fetal metabolites overwhelm the ability of the heterozygote mother's mitochondria to oxidize them. Can have hydrops fetalis. A low-fat diet with medium-chain triglyceride supplementation is used to prevent progression of retinopathy.

Anesthetic Considerations: Patients should be evaluated preoperatively for evidence of cardiomyopathy. Preoperative fasting should be kept to a minimum and patients may require a glucose infusion perioperatively secondary to their predisposition to hypoglycemia. Succinylcholine may be contraindicated in patients with skeletal myopathy because of the risk of hyperkalemia. A single child with this syndrome has been reported with evidence of a significant myopathy who developed rhabdomyolysis (creatine kinase from 15000 to 50000) during a general anesthetic where succinylcholine was not used.

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pregnant women. *N Engl J Med* 1999;340:1723-1731.

Möbius sequence

See Moebius sequence

MOCOD

See Molybdenum cofactor deficiency

Moebius sequence

MIM #: 157900

This usually sporadically occurring syndrome is characterized by masklike facies with congenital sixth and seventh cranial nerve palsies. Other cranial nerves also can be involved. The pathogenesis of Moebius sequence is related to absence, hypoplasia, or destruction of the

cranial nerve nuclei, a peripheral nerve abnormality, or a myopathy. It has been suggested that Klippel-Feil sequence, Moebius sequence, and Poland sequence, all of which can occur in various combinations in the same patient, may represent anomalies from an *in utero* disruption of the fetal subclavian or vertebral arteries. Moebius sequence, it appears, is usually the result of a focal *in utero* hypoxic/ischemic insult. However, Moebius sequence can be familial, and a gene responsible for at least some cases of Moebius sequence maps to the long arm of chromosome 13. In addition, Moebius syndrome has been reported as a complication of maternal use of misoprostol as an unsuccessful abortifacient (6). Plastic surgery has been offered to these children so that they are able to smile.

HEENT/Airway: Masklike facies secondary to facial nerve palsy, usually but not always bilateral. Abducens palsy. Strabismus, ptosis, epicanthal folds. Prominent ears, which may be low set. May have hearing loss. Flat nose. May have cleft lip or palate. Microstomia, tethered tongue with unilateral paresis. Palatal weakness with nasal speech. Micrognathia.

Chest: Weak swallow and poor cough result in recurrent aspiration. Patients may have idiopathic tachypnea. May have recurrent aspiration.

Cardiovascular: May have a congenital cardiac defect.

Neuromuscular: Intelligence is usually normal but is mildly abnormal in a small minority. Cranial nerve palsies, especially cranial nerves VI and VII. May have other central nervous system anomalies. Peripheral neuropathy and autonomic dysfunction have been reported. Patients may have central hypoventilation.

Orthopedic: Frequently have clubfoot deformity. May have limb reduction defects, syndactyly, digital contractures. May have arthrogryposis. May have cervical spine anomalies.

GI/GU: Swallowing/feeding difficulties. Hypoplastic male external genitalia.

Other: Has been associated with hypogonadotropic hypogonadism.

Miscellaneous: Paul Moebius was a German neurologist in private practice. He gave up his teaching post after being told that he would not receive a professorial appointment. Moebius also described ophthalmic migraine.

Anesthetic Considerations: Direct laryngoscopy and intubation of the trachea may be difficult secondary to oral/palatal abnormalities and micrognathia (3). A gum elastic bougie, Bellhouse laryngoscope (Belscope), and laryngeal mask have all been used successfully (7). Copious secretions and difficulty in swallowing can compromise the airway, and an antisialagogue may be helpful. Swallowing difficulties and a poor cough increase the risk of perioperative aspiration. Patients may have anomalies of the cervical spine, which should be assessed preoperatively.

Peripheral vascular access may be difficult secondary to extremity deficits. Patients may have a peripheral neuropathy, which must be taken into account before undertaking regional anesthesia. Facial (seventh) nerve palsy may result in an inability to close the eyes. The eyes must be protected perioperatively to avoid corneal abrasions. In addition, monitoring neuromuscular blockade through the facial nerve may be inaccurate. Recurrent apneic episodes have been described, suggesting that patients should be monitored closely postoperatively, particularly when opioids are given. Patients with congenital heart disease should receive an appropriately tailored anesthetic. The inability to express a full spectrum of facial emotions can make the assessment of pain difficult in preverbal children.

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Mohr syndrome

Synonym: Oral-facial-digital syndrome, type II

MIM #: 252100

This autosomal recessive syndrome is characterized by conductive hearing loss, minor midline clefts (tongue, lip, palate), and partial reduplication of the big toe. The gene and gene product are not known. It is suggested that there is a spectrum with this syndrome and Majewski-type short rib-polydactyly syndrome (see short rib-polydactyly syndrome, later).

HEENT/Airway: Cranium may contain wormian bones. Maxillary hypoplasia. Hypertelorism and

telecanthus. Conductive hearing loss secondary to defect of the incus. Flat nasal bridge, broad nasal tip. Can have bifid tip of the nose. Partial midline cleft lip, may have cleft palate. Midline cleft tongue. Lobulate tongue. Papilliform protuberances on tongue. Hyperplastic frenulum, may have multiple frenula. Mild mandibular hypoplasia. Absent central incisor.

Chest: Tachypnea is common. May have pectus excavatum.

Cardiovascular: May have endocardial cushion defect.

Neuromuscular: Intelligence is usually normal. May have hydrocephalus, arachnoid cysts, hypotonia, seizures, apnea, Dandy-Walker abnormality, cerebellar atrophy.

Orthopedic: Mild short stature. Partial reduplication of the big toe. Short hands. Postaxial (hands) or preaxial (feet) polydactyly, clinodactyly, or brachydactyly. Flared metaphyses. May have scoliosis.

GI/GU: May have hypoplastic genitalia.

Miscellaneous: Otto Mohr was a distinguished Norwegian geneticist. He was the first to recognize the effects of radiation on chromosomes and also described the genetic basis of phenylketonuria. He was dismissed by the Nazis during the occupation of Norway in 1940 because of his opposition to their policy of eugenics and was incarcerated in a concentration camp. After the war, he became the president of the University of Oslo. He also authored several books on Norwegian painters and poets.

Anesthetic Considerations: The mild mandibular hypoplasia is not likely to affect the ease of direct laryngoscopy. Dysgenesis of the corpus callosum can delay recovery from general anesthetics.

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Molybdenum cofactor deficiency

Synonym: MOCOD; Combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase

MIM #: 252150

This autosomal recessive syndrome is caused by a mutation at one of two steps in the formation of molybdenum cofactor. This cofactor is required for the functioning of three enzymes: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. The disorder is due to a mutation in one of four genes: *MOCS1*, *MOCS2*, *MOCS3*, or *GPHN*. Findings are related to those caused by deficiencies in these enzymes and the accumulation of toxic metabolites. Sulfite oxidase converts sulfite (a metabolite of methionine and cysteine) to sulfate. Symptoms are identical to those with isolated sulfite oxidase deficiency. Xanthine dehydrogenase catalyzes the hydroxylation of xanthine and hypoxanthine to uric acid. Aldehyde oxidase hydroxylates hypoxanthine into xanthine. The most common presentation of molybdenum cofactor deficiency is intractable seizures in the neonatal period. The prognosis is very poor and the disorder is usually fatal in infancy or early childhood.

HEENT/Airway: Can have acquired microcephaly. Narrow bifrontal diameter. Deep-set eyes. Dislocated lens. Lack of light response.

Neuromuscular: Profound intellectual disabilities, treatment-resistant seizures, spastic tetraparesis, brain atrophy, encephalopathy. Myoclonus. Opisthotonos. Dystonia has been reported as the presenting finding, aside from lens dislocation, in a young adult. Axial hypotonia with peripheral hypertonia. Milder disease can present later, with loss of milestones. CNS volume loss has resulted in a malformation resembling Dandy-Walker malformation.

GI/GU: Feeding difficulties. May have hypertrophic pyloric stenosis. Urinary xanthine stones.

Other: May have absent serum homocysteine.

Miscellaneous: The easy bedside test, now a strip test, for detecting urinary sulfite was originally developed to determine the sulfite level in wine. Careful what you drink. It has been suggested that the prevalence of *MOCS2* disease in European port cities might be due to “distribution” by a merchant sailor.

Anesthetic Considerations: Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Perioperative fluid administration must be adequate to maintain a diuresis and prevent further concentration of xanthine in the urine. Xanthine is more soluble at an alkaline pH. However, symptomatic xanthinuria has not been a problem in these young children with limited life expectancy. Methylxanthines such as theophylline and caffeine are not metabolized by xanthine oxidase and are not contraindicated. S-Sulfocysteine, a sulfite metabolite, is similar to several excitatory amino acids such as

glutamate. It is possible that some characteristics of the disease are due to excessive activity at NMDA receptors. This could account for the treatment-resistant seizures and suggests a possible anesthetic benefit for ketamine, an NMDA antagonist.

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Morquio syndrome

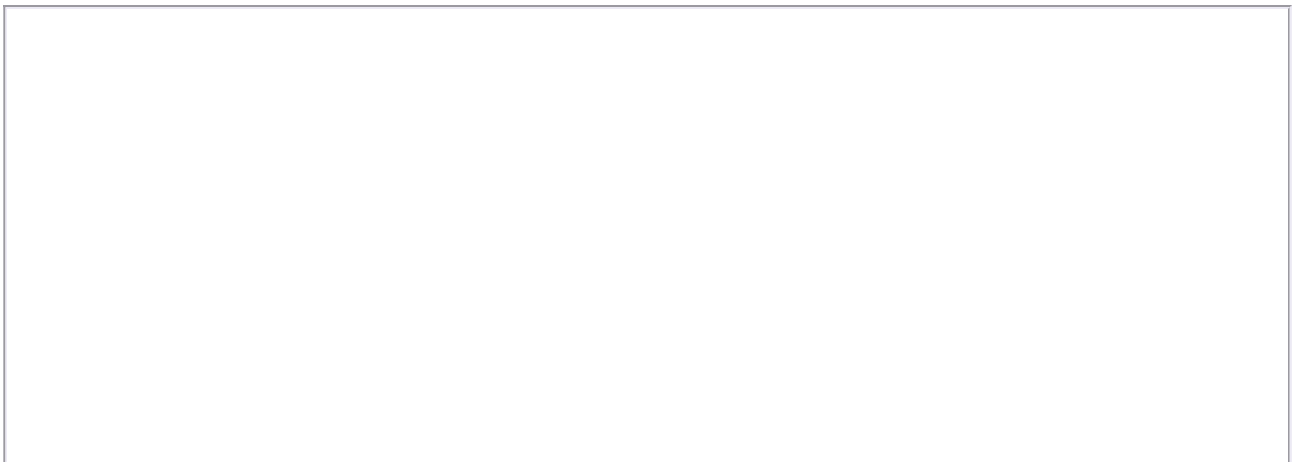
Synonym: Morquio-Brailsford syndrome, Mucopolysaccharidosis IV

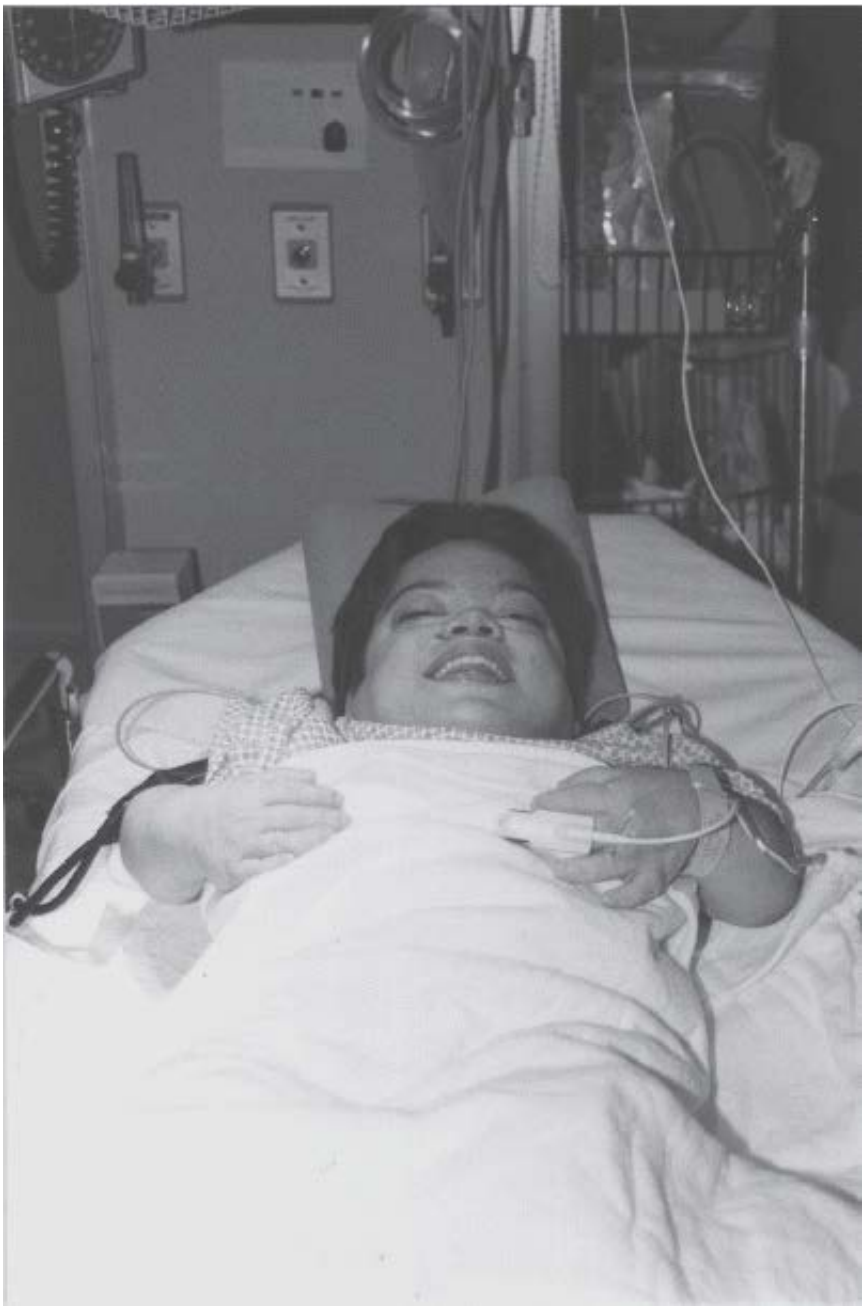
MIM #: 253000, 253010

This autosomal recessive lysosomal storage mucopolysaccharidosis occurs in two types, types A and B. The lysosomal enzyme defect does not allow degradation of keratin sulfate in cartilage, which then accumulates along with chondroitin-6-sulfate. Type A is due to an abnormality in the gene encoding *N*-acetylgalactosamine-6-sulfate sulfatase (galactose-6-sulfatase), and type B is due to an abnormality in the gene encoding beta-galactosidase, which is specific for keratin sulfate. Clinically, the two forms are similar. The major findings are skeletal. There is some phenotypic variability that might be due to allelic variations.

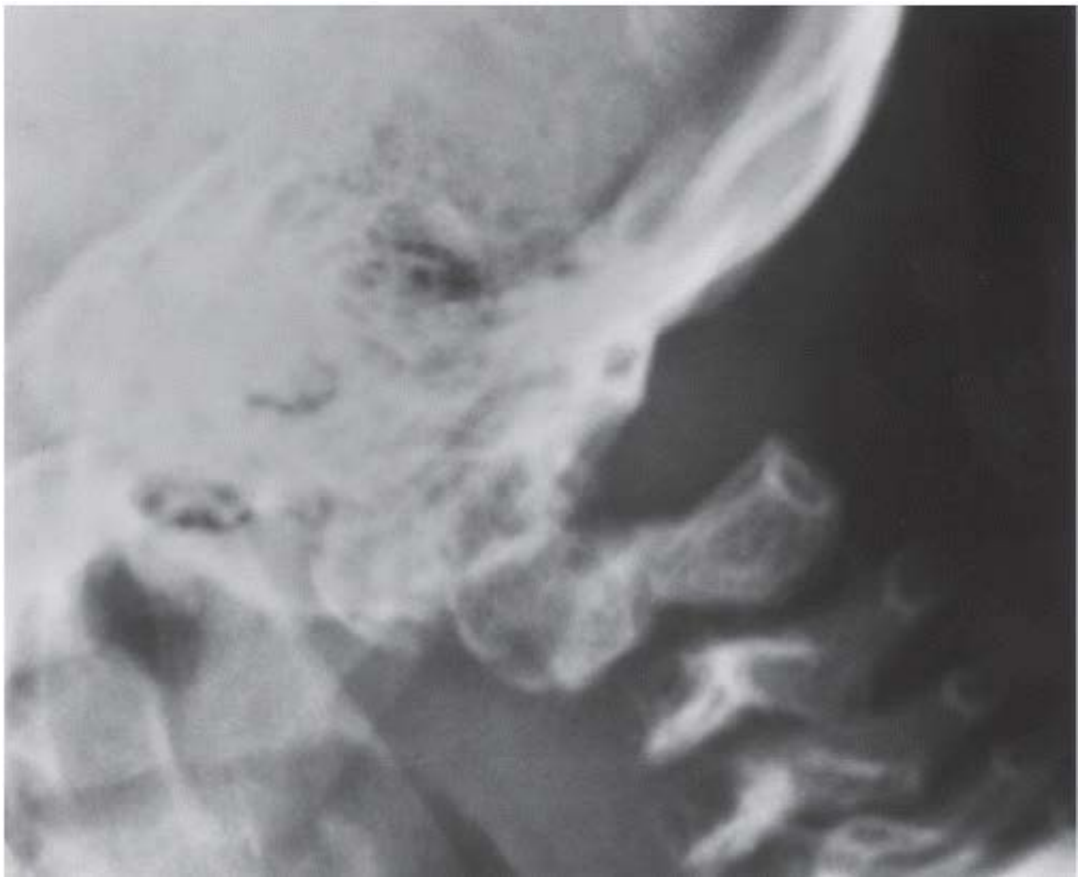
HEENT/Airway: Dense calvarium. There may be mild coarsening of the facial features. Mild corneal clouding. Progressive sensorineural or mixed hearing loss. Short, anteverted nose. Broad mouth with redundant pharyngeal mucosa. Hypertrophied tonsils, adenoids, nasal mucosa, and tongue. Enamel hypoplasia with pitting (type A only). The maxillary anterior teeth are widely spaced. Short neck with limited movement due to keratin sulfate accumulation. May have limited mouth opening due to temporomandibular joint involvement. The epiglottis can be stiff. Vocal cord paralysis has been reported.

Chest: Pectus carinatum, rib flaring. Restrictive lung disease from kyphoscoliosis. The trachea may be narrowed from deposition in the tracheal rings. May have obstructive sleep apnea. Frequent upper respiratory infections. The most common cause of death has been respiratory insufficiency from spine and chest deformity. Patients with mucopolysaccharidoses are susceptible to pulmonary hemorrhage after bone marrow transplantation.

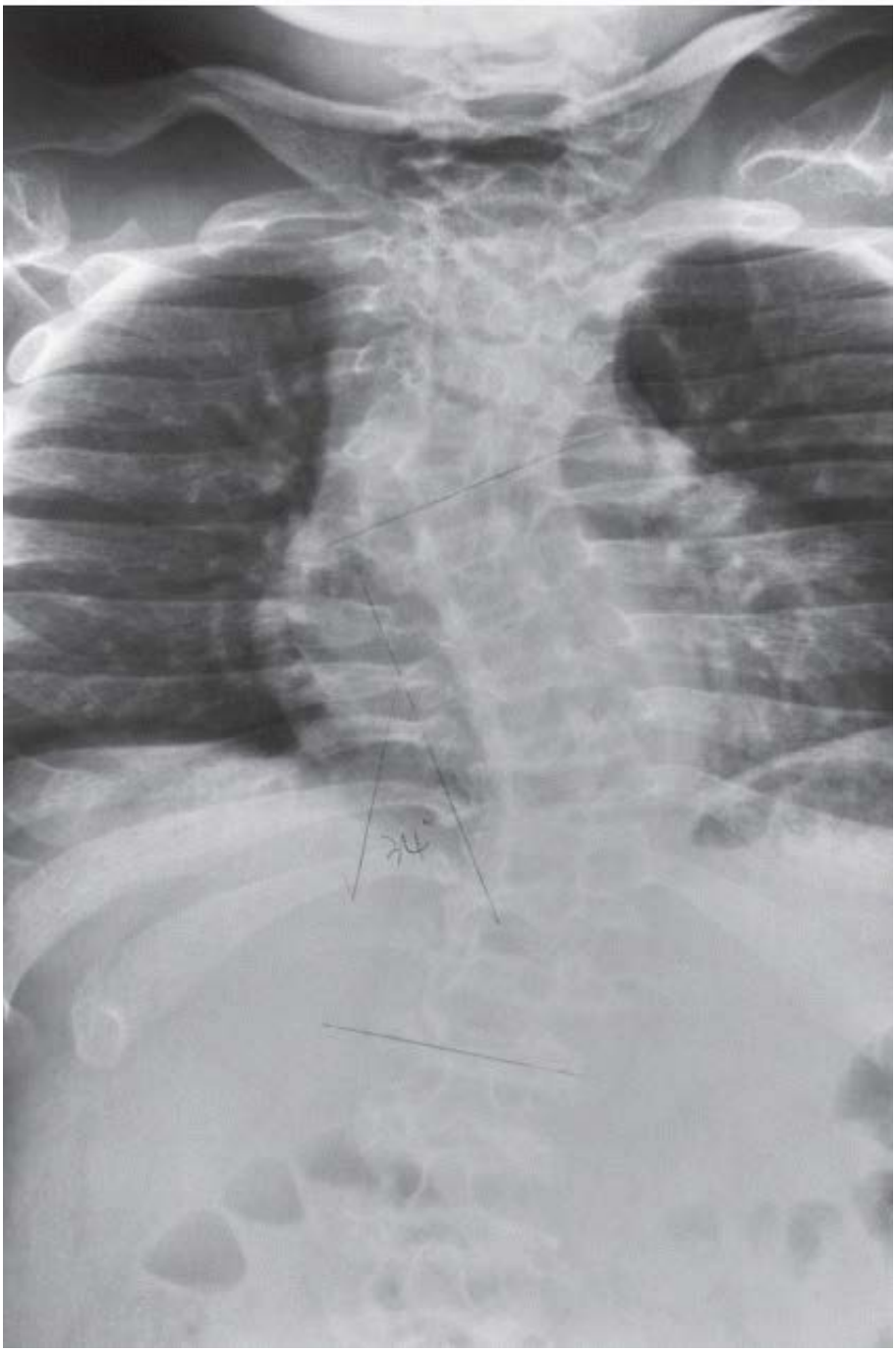




Morquio syndrome. FIG. 1. A pleasant and intelligent 20-year-old young woman with Morquio syndrome.



Morquio syndrome. FIG. 2. The same patient at age 5 years, showing anterior dislocation of C1 on C2. She later had surgical fusion of her cervical spine.



Morquio syndrome. FIG. 3. The same patient at age 13 years showing severe scoliosis.

Cardiovascular: Mitral and aortic valve involvement—aortic insufficiency is relatively common later in the disease. Pulmonary hypertension may develop secondary to lung disease. Keratin sulfate infiltration resulted in failure of a pulmonary valve autograft years after the surgery. Although there can be infiltration of coronary arteries, ischemic heart disease has not been reported.

Neuromuscular: Normal intelligence. Atlantoaxial instability with subsequent myelopathy. Most require posterior cervical fusion.

Orthopedic: Short stature due to shortening of the trunk and neck. Shortening of the long bones with short, stubby hands. Flattening of the vertebral bodies (platyspondyly). High incidence of cervical spine instability with severe odontoid hypoplasia and atlantoaxial subluxation with risk of paraplegia. Coxa vara. Genu valgum. Joint laxity and instability. Kyphoscoliosis, lumbar lordosis.

GI/GU: Mild hepatomegaly.

Miscellaneous: This disorder was described separately in the same year (1929) by Morquio and Brailsford, a British radiologist. It has in the past been known as Morquio-Brailsford syndrome. Morquio was professor of pediatrics at the University of Montevideo (Uruguay). Conveniently, the chair was established by his family, and he was the second holder of the chair. Previously, Osler had misdiagnosed the disorder as cretinism (congenital hypothyroidism).

Anesthetic Considerations: These patients have a high incidence of cervical spine instability, particularly odontoid hypoplasia with atlantoaxial subluxation. Intraoperative injury resulting in quadriparesis has occurred. The cervical spine should be evaluated preoperatively, and precautions should be taken to avoid compression of the cervical spinal cord during positioning or laryngoscopy. Direct laryngoscopy and tracheal intubation are often difficult, and become more difficult with age. This is made more problematic by the presence of an unstable cervical spine. Neck flexion may occlude the airway. The laryngeal mask airway has been used successfully in patients with mucopolysaccharidoses, as has fiberoptic intubation, although these may be becoming displaced as a first technique of choice by the video laryngoscope (3). Success can be augmented by grasping the tongue and manually displacing the tongue anteriorly. Evoked potential monitoring during laryngoscopy in high-risk patients has been suggested (3). Patients may require an endotracheal tube that is smaller than predicted. Postoperative airway compromise of a variety of types has been reported. Tonsillectomy and adenoidectomy will not reliably relieve upper airway obstruction. Emergent tracheostomy would be expected to be exceedingly difficult due to the chest abnormality, short neck, limited neck mobility, unstable neck, and/or abnormal trachea. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

Patients must be carefully positioned perioperatively secondary to joint laxity and instability. Although meningeal involvement has been noted, and scoliosis can occur, a (continuous) spinal technique has been used as well as caudal and lumbar epidural analgesia. Needless to say, care must be taken in positioning for a spinal or epidural block in the face of a potentially unstable cervical spine. Pectus carinatum may make sternotomy more difficult. A short trachea and moving to a prone position increases the risk of endobronchial placement of an endotracheal tube and fiberoptic confirmation has been suggested.

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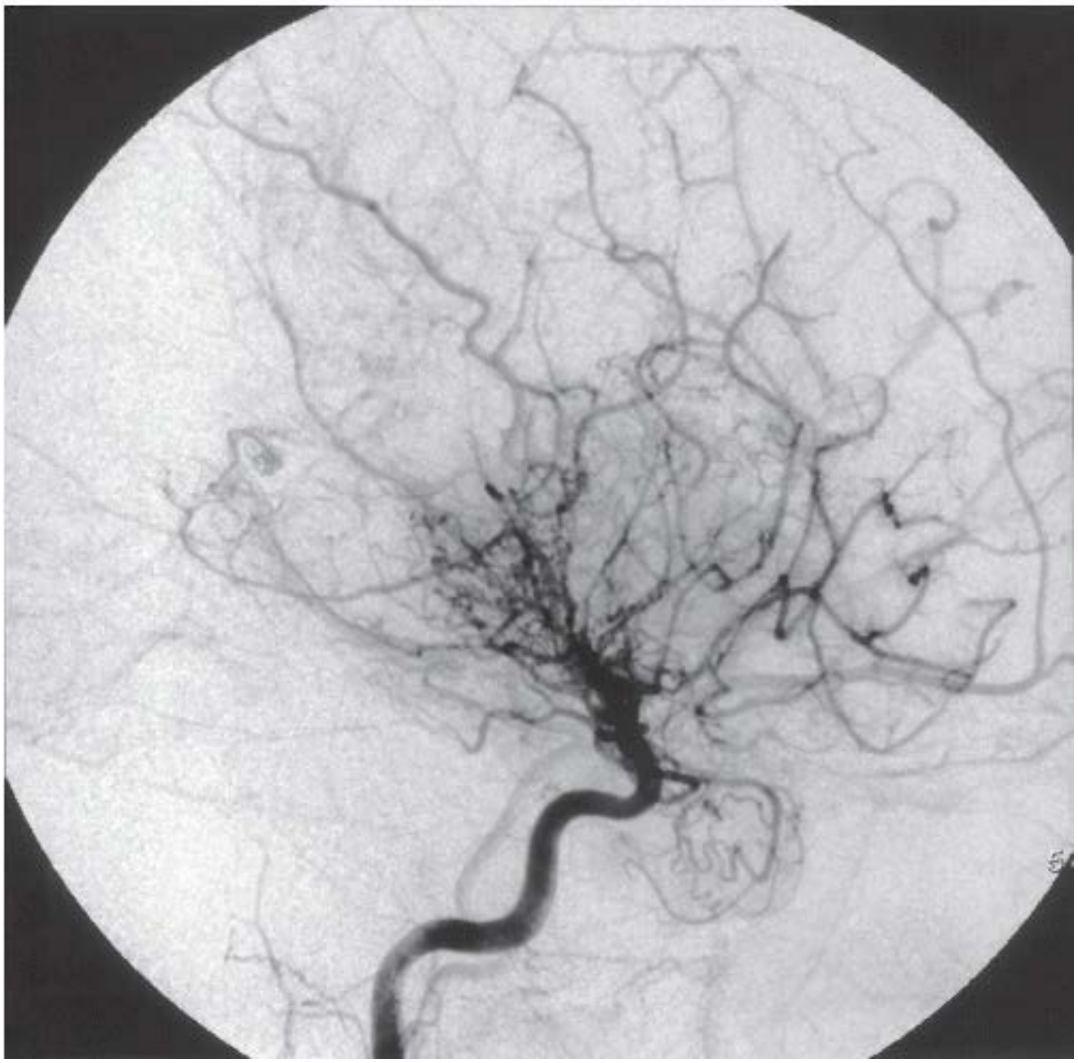
Morquio-Brailsford syndrome

See Morquio syndrome

Moyamoya syndrome

MIM #: 252350

Moyamoya syndrome involves progressive occlusion of the intracranial portion of the carotid artery, the middle cerebral artery, and the anterior and posterior communicating arteries with the subsequent development of profuse collateral flow at various levels (leptomeningeal, basal ganglia, and transdural). The telangiectatic collateral vessels produce a characteristic pattern on cerebral angiography (see figure). Cerebral blood flow is severely compromised in these patients, leading to cerebral ischemia. Children usually present before the age of 5 years with signs of ischemic disease: headache, new-onset seizures, transient ischemic attacks, and/or hemiplegia. Frequent transient ischemic attacks and strokes lead to progressive loss of neurologic function. Unilateral disease often progresses to bilateral involvement. A high incidence of moyamoya disease is found in Asia, predominantly in Japan. The disorder occurs more frequently in females. Surgical revascularization procedures designed to enhance cerebral flow have met with variable results. These revascularization procedures are either direct, by anastomosing an external carotid artery branch to a cortical artery, or indirect, by placing vascularized tissue directly on the brain.



Moyamoya syndrome. Cerebral angiogram demonstrating the fine “puff of smoke” pattern.

Susceptibility to moyamoya syndrome exhibits genetic heterogeneity. Four autosomal recessive types have been described with mapping to chromosomes 3p (*MYMY1*), 8q (*MYMY3*), 10q (*ACTA2*), and 17q (*RNF213*). There is an additional X-linked recessive type (*MYMY4*) associated with short stature, hypogonadotropic hypogonadism, and facial dysmorphism. There is an increased familial incidence, on the same order as congenital heart disease. There are over 50 cases of moyamoya syndrome associated with neurofibromatosis (see later), a disease that has also been mapped to chromosome 17q.

Moyamoya syndrome refers to the genetic form of this disorder. Moyamoya disease has been used to refer to acquired occlusion of the vessels in the circle of Willis and describes a characteristic pattern of reaction to intracerebral vascular injury. About 15% of all cases are familial. Adults with moyamoya disease can present with subarachnoid hemorrhage. Hemorrhage, in both adults and children, can be intraventricular, intraparenchymal, or subarachnoid.

HEENT/Airway: Morning glory disk anomaly (see later, Papillorenal syndrome) of the optic disc with retinovascular changes.

Neuromuscular: Migraine-like headaches, seizures, cerebrovascular ischemia—transient ischemic attacks

and strokes. Recurrent transient paralysis or hemiplegia. Choreiform movements from basal ganglia involvement (may resolve after revascularization surgery). Progressive loss of neurologic function. In children, the most common findings are dysphagia, dysarthria, and hemiparesis. Adults most commonly manifest the sequelae of intracranial hemorrhage, strokes, and migraine-like headaches.

Miscellaneous: Moyamoya is a Japanese word that means “something hazy, like a puff of cigarette smoke drifting in the air,” often shortened to “puff of smoke,” which is descriptive of the netlike image of blood vessels seen on cerebral angiogram.

Anesthetic Considerations: Preoperatively, the patient's neurologic history and current status should be assessed. Cerebral blood flow is severely compromised in these patients, and anesthetic management is tailored to minimize the risk of perioperative stroke. Affected cerebral vessels and collaterals are already maximally dilated, and cerebrovascular responses to changes in arterial gas tensions and systemic blood pressure can result in further ischemia. Cerebral vasodilators have been shown to lead to intracerebral steal. Cerebral blood flow and oxygen delivery must be maximized, which means that it is imperative to avoid hypoxemia, hypo- (vasoconstriction) or hypercapnia (steal), cerebral vasoconstriction, hypovolemia, hypotension, anemia, and increases in blood viscosity. Attention should be given to minimizing cerebral metabolic rate for oxygen. Inhalational anesthesia with isoflurane has been advocated for these patients because of the favorable cerebral blood flow/cerebral metabolic rate ratio. TIVA techniques have also been used successfully and avoid some intracranial vascular effects of the volatile anesthetics (5,8). Because of the risk of hyperkalemia in patients with a history of stroke, succinylcholine should be used with caution. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Anticoagulants are sometimes used in these patients as are calcium channel blockers. The first may need to be temporarily discontinued perioperatively, and the latter continued.

Despite careful perioperative management, new neurologic deficits postoperatively are not uncommon, particularly after cerebral revascularization surgery. Hypocapnea secondary to crying has been implicated in the development of cerebral ischemia, so it would seem that adequate postoperative sedation and analgesia are critical. Patients should continue to receive postoperative fluids at about 1.25 to 1.5 times maintenance.

Elective cesarean section has been advocated in the parturient to avoid increases in intracranial pressure with bearing down and hyperventilatory hypocapnea, which can lead to cerebral vasoconstriction. General anesthesia

has been suggested as the anesthetic of choice since decreased systemic blood pressure after regional anesthesia may lead to decreased cerebral perfusion (20), although regional techniques have also been used successfully (11,18).

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MTHFR deficiency

See 5,10-methylene tetrahydrofolate reductase deficiency

Muckle-Wells syndrome

See Urticaria-deafness-amyloidosis syndrome

Mucolipidosis I

See Sialidosis

Mucolipidosis II

See I-cell disease

Mucolipidosis III

See Pseudo-Hurler syndrome

Mucolipidosis IV

MIM #: 252650

This autosomal recessive lysosomal storage disease results in deposits in almost every tissue in the body. It is caused by a mutation in the gene encoding mucolipin-1 (*MCOLN1*) located on the short arm of chromosome 19. The defect causes a problem in lysosomal transport resulting in the intracellular accumulation of multiple lysosomal substrates. A wide variety of gangliosides, phospholipids, and mucopolysaccharides are accumulated in the deposits. Primary manifestations include intellectual disabilities, developmental delay, and eye defects.

Before the biochemistry of the mucolipidoses was understood, it was recognized that these patients had features of both the mucopolysaccharidoses and the sphingolipidoses, hence the name “mucolipidosis.”

HEENT/Airway: Microcephaly. Normal facies. Corneal clouding from early infancy, retinal degeneration, decreased vision, myopia, puffy eyelids, strabismus, photophobia.

Neuromuscular: Psychomotor retardation, which is not progressive. Some patients may have improvement in language and motor skills with time, although most will have persistent severe intellectual disability. Hypotonia. Pyramidal tract sign.

GI/GU: May have achlorhydria (low or absent gastric acid). No organomegaly.

Miscellaneous: Eighty percent of patients diagnosed with mucolipidosis IV are of Ashkenazi Jewish ancestry. Geneologic studies of the involved families (currently residing all over the world) indicate that the mucolipidosis IV mutation originated as recently as the 18th or 19th century in the region of northern Poland or Lithuania.

Anesthetic Considerations: Patients may have decreased vision, and patients with photophobia may be extremely sensitive to the bright lights in operating rooms. Difficulty with direct laryngoscopy and tracheal intubation has not been reported with mucolipidosis IV, although it has been reported with mucolipidosis II, or I-cell disease (see earlier) (3). If the patient's tracheal wall is thickened by deposits, an endotracheal tube that is smaller than predicted may be required.

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Mucopolysaccharidosis I H

See Hurler syndrome

Mucopolysaccharidosis I H/S

See Hurler-Scheie syndrome

Mucopolysaccharidosis I S

See Scheie syndrome

Mucopolysaccharidosis II

See Hunter syndrome

Mucopolysaccharidosis III

See Sanfilippo syndrome

Mucopolysaccharidosis IV

See Morquio syndrome

Mucopolysaccharidosis VI

See Maroteaux-Lamy syndrome

Mucopolysaccharidosis VII

See Sly syndrome

Mucoviscidosis

See Cystic fibrosis

Mulibrey nanism syndrome

Synonym: Perheentupa syndrome

MIM #: 253250

This autosomal recessive disorder is distinguished by short stature and pericardial constriction. The mnemonic MULIBREY stands for the organs that may be involved: **MU**scle, **LI**ver, **BR**ain, and **EY**es. Nanism is derived from the Greek for dwarf. The syndrome is caused by a mutation in the gene *TRIM37*, which encodes a peroxisomal protein. Most patients diagnosed with Mulibrey nanism have been Finnish.

HEENT/Airway: Dolichocephaly. Long, shallow sella turcica, hypoplastic frontal or sphenoid sinuses. Triangular facies, frontal bossing. Abnormal retinal pigmentation with clusters of yellowish dots in the fundus. Dental anomalies, including crowded, hypoplastic teeth. Small tongue. High-pitched voice.

Cardiovascular: During infancy or childhood, a thick, adherent pericardium develops that leads to pericardial constriction and elevated central venous pressure. Many will need a pericardiectomy. Myocardial involvement (including myocardial hypertrophy and myocardial fibrosis) may lead to heart failure. Death from cardiac causes is not uncommon.

Neuromuscular: Muscular hypotonia. Hypoplastic corpus callosum. Large ventricles. Normal intelligence.

Orthopedic: Short stature. Cystic fibrous dysplasia, especially of the tibia.

GI/GU: Hepatomegaly secondary to pericardial constriction. Can have ascites. Post menarchal ovarian failure. Fibrothecoma (ovarian stromal tumor). Infertility in men and women.

Other: Prenatal growth retardation. Nevus flammeus. Incomplete breast development. May have immunoglobulin deficiency. Neonatal hypoglycemia and pituitary insufficiency. It appears that there is an increased incidence of a variety of benign and malignant tumors.

Anesthetic Considerations: Patients may have visual abnormalities. Dental abnormalities should be documented preoperatively. Patients may have pericardial constriction with elevated central venous pressures and liver congestion. Significant hepatic congestion can sometimes cause a bleeding dyscrasia. Myocardial involvement may contribute to congestive heart failure. Succinylcholine should be used with caution in patients with significant muscle involvement because of the risk of exaggerated hyperkalemia.

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Multiminicore disease

See under Malignant hyperthermia susceptibility

Multiple acyl-CoA dehydrogenase deficiency

See Glutaric acidemia II

Multiple carboxylase deficiency

See Biotinidase deficiency; Holocarboxylase synthetase deficiency

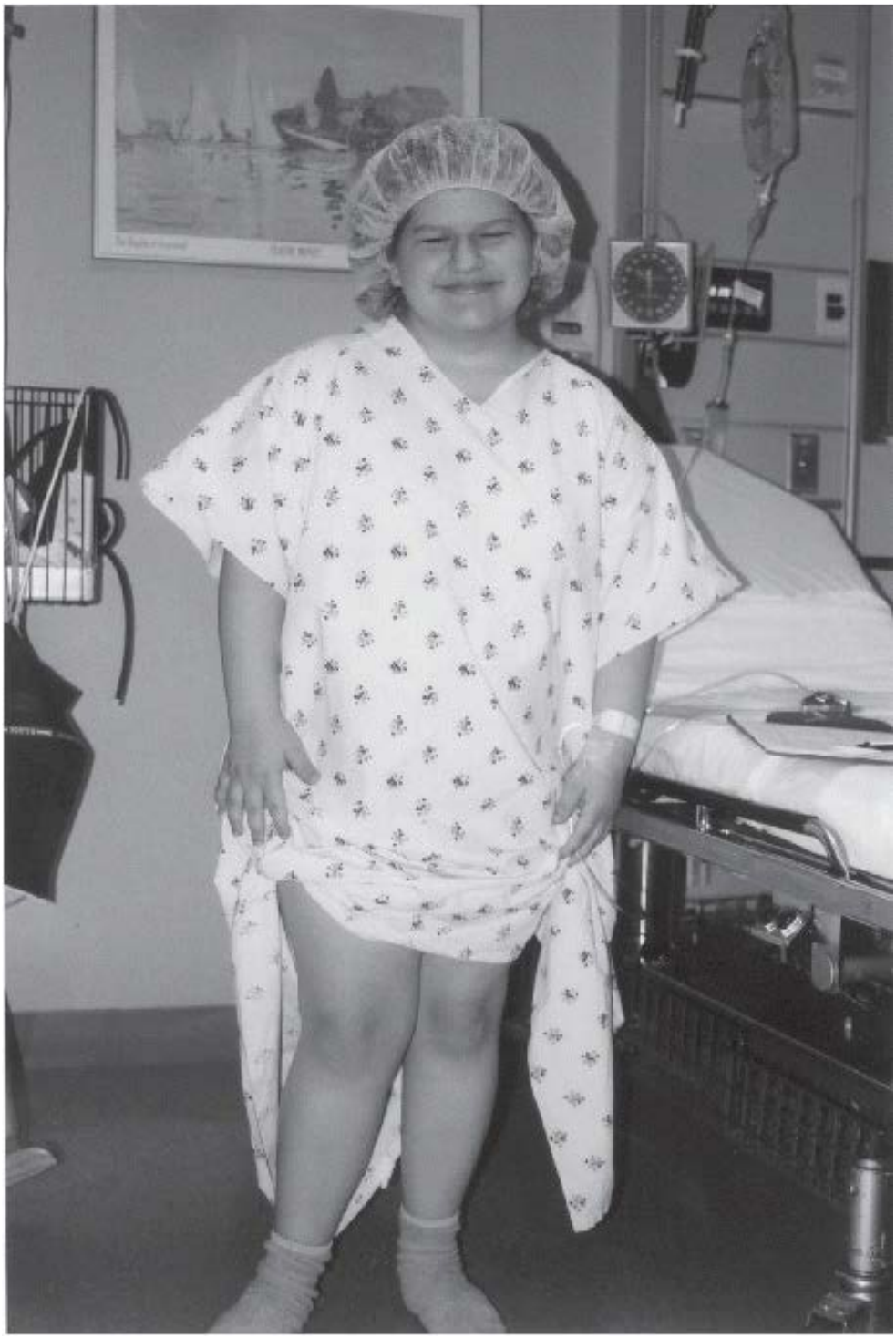
Multiple epiphyseal dysplasia

(Includes Fairbank and Ribbing types of multiple epiphyseal dysplasia)

MIM #: 132400, 226900

This usually autosomal dominant short-limb dwarfing syndrome is characterized by short stature, pain and stiffness in the hips and knees, and small, irregular epiphyses. There is extensive phenotypic variability. Six distinct types have been described, but multiple epiphyseal dysplasia has been broadly subdivided into a more severe **Fairbank type** and a less severe **Ribbing type**. The six types and the responsible genes are EDM1 (*COMP*, encoding collagen oligomeric matrix protein—mutations in this gene also cause pseudoachondroplasia, a more severe disorder; see later), EDM2 (*COL9A2*), EDM3 (*COL9A3*), EDM4 (*DTDST*), EDM5 (*MATN3*), and EDM6 (*COLA1*).

There is certainly genetic heterogeneity with this syndrome, even within types. Some patients have no identifiable mutations.



Multiple epiphyseal dysplasia. This 15-year-old with multiple epiphyseal dysplasia is only 4′ 10″ (127 cm) tall. Her mother is similarly short. She has short stubby fingers and involvement of multiple upper and lower extremity joints.

HEENT/Airway: May have a round face.

Neuromuscular: Intelligence is normal.

Orthopedic: Short stature. Small, irregular epiphyses. Progressive joint pain and stiffness, especially of the hips and knees. Severe premature osteoarthritis, which may require joint replacement. May also have back pain. Short, stubby fingers. Brachydactyly. Hyperextensible fingers. May have symmetric shoulder involvement. Platyspondyly. Short femoral neck. Avascular necrosis of the femoral head. Patellar dislocation. Genu valga. Abnormalities of the distal tibia. Waddling gait. Clubfoot deformity.

Anesthetic Considerations: Patients must be carefully positioned and padded secondary to pain and stiffness in the hips, knees, and back. Older patients may have artificial joints secondary to premature osteoarthritis.

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Multiple exostoses syndrome

Synonym: Diaphyseal aclasis

MIM #: 133700, 133701, 600209

This autosomal dominant syndrome is characterized by bony outgrowths of the cancellous bone between the diaphysis and epiphysis that ultimately result in deformities of the extremities. The exostoses appear and expand during childhood and adolescence, but do not expand further during adulthood, after epiphyseal plate closure. Multiple exostoses syndrome is genetically heterogeneous. Multiple exostoses type I is due to mutations in the gene *EXT1* that encodes exostosin-1. Type II disease is due to mutations in the gene *EXT2* encoding the protein exostosin-2. Type III has been mapped to chromosome 19. *EXT1* and *2* form a complex that catalyzes the polymerization of heparin sulfate, essential in the regulation of chondrocyte differentiation, ossification, and apoptosis. *EXT1* has a putative tumor suppressor function. Multiple exostoses can also occur in the Langer-Giedion syndrome (see earlier).

HEENT/Airway: The cranium is usually not involved.

Neuromuscular: Compression of the spinal cord by exostoses has been reported. Compression of peripheral nerves by exostoses has been reported, particularly the peroneal nerve.

Orthopedic: Mild short stature. Multiple diaphyseal bony outgrowths, usually capped by cartilage, especially at the ends of long bones, but can involve the shaft. Involved bone can be short or bowed. Deformity of the legs, forearms, and hands is most common. The knee is frequently involved. Coxa vara. Overriding toes. Metacarpals can be short. Ribs, vertebrae, and scapulae may be involved. May have enchondromas. Rare chondrosarcoma, osteosarcoma (0.5% to 2%).

Miscellaneous: Very common in the Chamorro people of Guam (1 in 1000).

Anesthetic Considerations: The exostoses may compress peripheral nerves, causing a peripheral neuropathy. A

complete neurologic examination should be performed before performing regional anesthesia. Patients need to be carefully positioned and padded secondary to deformities of the extremities.

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Multiple lentigines syndrome

See LEOPARD syndrome

Multiple pterygium syndrome

Synonym: Escobar syndrome; Pterygium syndrome

MIM #: 265000

This autosomal recessive disorder is characterized by multiple pterygia, camptodactyly, syndactyly, cleft palate, and severe micrognathia. It is due to abnormalities in the gene *CHRNG* that encodes the gamma subunit of the acetylcholine receptor. It can be considered a fetal akinesia deformation sequence. There is an allelic lethal type multiple pterygium syndrome (*MIM #:* 253290).

HEENT/Airway: Flat, long, and expressionless face. Hypertelorism, ptosis, inner canthal folds. Low-set ears. May have conductive hearing loss. Cannot open mouth widely, ankyloglossia (adhesion of the tongue to the palate), syngnathia (intraoral webbing). High-arched palate, cleft palate. Severe micrognathia. Webbing of the neck.

Chest: Severe kyphoscoliosis may lead to restrictive lung disease and problems such as dyspnea and recurrent pneumonia. Fused ribs.

Cardiovascular: May have a cardiac defect.

Neuromuscular: Normal intelligence. May have hypotonia, muscular atrophy.

Orthopedic: Pterygia (webbing of the skin) across multiple joints—usually progressive and may lead to fixed contractures of the joints. Camptodactyly, syndactyly. Clubfeet, rocker-bottom feet. Small stature. Scoliosis, kyphosis. Vertebral fusion, usually cervical. Dislocated hip.

GI/GU: Cryptorchidism, hypospadias. Hypoplastic or aplastic labia majora. May have diaphragmatic hernia.

Anesthetic Considerations: Oral, mandibular, and neck involvement limit mouth opening, position the tongue

posteriorly, limit neck extension, and severely limit direct visualization of the larynx. The laryngeal mask airway has been used successfully (4,5,6) and intubation can be done via the laryngeal mask if required. Worsening rotation and flexion of the neck may make airway management more difficult as the patient ages.

Patients may have restrictive lung disease. Morbidity from respiratory disease is reportedly high. Patients must be carefully positioned and padded secondary to pterygia and possible fixed joint contractures. Severe scoliosis, kyphosis, or vertebral fusion makes neuraxial anesthesia technically difficult, although it has been possible (3). One poorly documented case, not in the anesthesia literature, suggested an association with malignant hyperthermia, but this is very unlikely (7).

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Multiple synostoses syndrome

Synonym: Facioaudiosymphalangism syndrome

MIM #: 186500

This autosomal dominant syndrome consists of multiple synostoses, particularly of the digits (symphalangism) and carpal and tarsal bones. The synostoses are progressive. There are several types. Type 1 is due to a mutation in the gene encoding noggin (*NOG*), which is important to fetal limb growth and development. Type 2 is due to abnormalities in the gene encoding growth/differentiation factor-5, and type 3 is due to abnormalities in the gene

encoding fibroblast growth factor 9. There is marked variability in clinical expression. There are several other allelic disorders of *NOG* that have as characteristics symphalangism and/or stapes ankylosis and/or tarsal abnormalities.

HEENT/Airway: Narrow face. Strabismus. External ear anomalies, conductive hearing loss due to osteosclerosis. Hypoplastic alae nasi, hypoplastic nasal septum.

Broad tubular-shaped nose. Short philtrum, thin upper lip. May have Klippel-Feil sequence (see earlier).

Chest: Pectus excavatum. Short sternum.

Neuromuscular: May have intellectual disabilities. May have stenosis of the cervical spinal canal.

Orthopedic: Multiple and progressive synostoses, involving digits (symphalangism), elbows, carpal bones, and tarsal bones. Hypoplasia of distal digits, nails. Cutaneous syndactyly, clinodactyly, brachydactyly. Absence of skin creases over proximal and distal interphalangeal joints. May have subluxation of the radial head. Cubitus valgus. May have calcaneonavicular synostosis. Limited joint mobility at the shoulder, elbow, hip. Ankylosis of joints is progressive and progresses from ulnar to radial and proximal to distal. Short feet. May have vertebral anomalies. A single case of a novel *NOG* mutation resulted in growth acceleration.

Anesthetic Considerations: Positioning may be difficult due to limited joint mobility. Vascular access may be more difficult than usual. In some, cervical fusion can begin in childhood. Limited neck mobility could make laryngoscopy and intubation difficult.

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Multisynostotic osteodysgenesis

See Antley-Bixler syndrome

Münchausen syndrome by proxy

Synonym: Meadow syndrome

MIM #: None

Münchausen syndrome by proxy is an entity in the pediatric population that is analogous to Münchausen syndrome in the adult population. In Münchausen syndrome by proxy, parents or guardians report or create factitious medical problems in their children to gain medical attention. This type of child endangerment can be extremely difficult to diagnose. Children of both sexes and all ages are at risk, although it is most common in infants and young children. In most cases, the responsible parent is the mother. These parents often have some rudimentary medical training, appear to be extremely conscientious caregivers, and tend to form intense personal bonds with the medical personnel who are involved with their child's care. There are many ways in which Münchausen syndrome by proxy

can present, the most common being vomiting, diarrhea, fever, bleeding (hematemesis, hematuria), seizures, and apnea. Münchausen syndrome by proxy should be considered in any patient who has repeated serious illnesses of unknown etiology, whose siblings have had a similar history, whose symptoms occur only in the presence of the parent, whose illness takes an atypical course, or whose illness fails to respond to the usual therapy. Least physical harm is done to the child if the parent merely fabricates the symptoms in the child, although these children are at risk for unnecessary diagnostic tests, many of which are invasive. More harm is done if the parent actually produces the symptoms in the child. This can be accomplished in a multitude of ways, most commonly through poisoning, suffocation, exsanguination, introduction of exogenous blood into the GI tract or bladder, or inoculation with bacteria. The mortality rate from this syndrome may be as high as 10%. A new twist is “Münchausen syndrome by internet” wherein well individuals fake illness on, for example, online support groups.

Miscellaneous: Born in Germany in 1720, Baron Hieronymus Carl Friedrich Freiherr von Münchhausen was notorious for his fictitious accounts of travel, adventure, and achievement. In the 1950s, his name became associated with the syndrome in which adults fabricate medical illness to gain medical attention. In 1977, Roy Meadow coined the phrase “Münchausen syndrome by proxy” in an article in the Lancet to describe how children could be victimized by this disorder. Meadow became an expert on the sudden infant death syndrome (SIDS) and was knighted in 1998 for “services to child health.” However, in 2005, the British General Medical Council found Meadow guilty of “serious professional misconduct” for his expert testimony (which was subsequently found to be erroneous) in the trials of three women who were initially convicted (but now exonerated) of murdering their infant children.

Anesthetic Considerations: Occasionally, anesthesiologists or surgeons are in a position to suspect Münchausen syndrome by proxy, as when a child is repeatedly referred for diagnostic tests that are always normal. When such a diagnosis is suspected, the patient's primary care physician must be consulted. Extreme care must be taken in dealing with the parents, particularly in the perioperative setting (4). The management and treatment of Münchausen syndrome by proxy is difficult and lengthy and involves multiple health care professionals as well as child protective services.

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MURCS association

MIM #: 601076

This sporadically occurring disorder involves **MU**llerian duct aplasia, **R**enal aplasia, and **C**ervicothoracic **S**omite dysplasia.

HEENT/Airway: May have facial asymmetry. May have external ear defects, hearing loss. May have cleft lip or palate, micrognathia.

Cardiovascular: A patient has been reported with tetralogy of Fallot.

Neuromuscular: Occipital encephalocele. Rare cerebellar cyst.

Orthopedic: Short stature. Cervicothoracic vertebral defects, including partial to complete cervical fusion. May have rib anomalies, winged scapula, absent radius, duplicated thumb.

GI/GU: Mullerian duct aplasia—absence of the proximal vagina and hypoplasia or absence of the uterus (the Rokitansky-Kuster-Hauser syndrome, see later). Renal aplasia. May have anal atresia.

Anesthetic Considerations: Micrognathia is usually mild and is unlikely to interfere with the ease of direct laryngoscopy and intubation. Cervicothoracic vertebral defects, particularly cervical spine fusion, may make visualization of the larynx by direct laryngoscopy more difficult. Renal insufficiency affects perioperative fluid management and the choice of anesthetic drugs.

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Muscle-eye-brain disease

[Includes muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies); Walker-Warburg syndrome]

MIM #: 253280

This autosomal recessive disorder affects the eyes, muscle, and brain. It is caused by a mutation in O-mannose beta-1,2-N-acetylglucosaminyltransferase (*POMGNT1*), which is important in the synthesis of O-mannosyl glycan. This enzyme is involved with the glycosylation of alpha-dystroglycan, one of the proteins in the complex that links dystrophin to the cell membrane. An allelic disorder, **Walker-Warburg syndrome** (*MIM #:* 236670), is one type of limb-girdle muscular dystrophy. Originally, the two disorders were described separately, but they have recently been coalesced within the single (but far more unwieldy) name of **muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies)** (*MIM #:* 253280, 236670). Walker-Warburg syndrome tended to have more severe findings. Death in infancy is possible in severe cases.

HEENT/Airway: Glaucoma, cataracts, retinal hypoplasia, retinal detachment, congenital myopia, strabismus, nystagmus, centrally regulated abnormal eye movements, blindness. Microphthalmia. Hyperplastic vitreous causing

retrolental mass. Microtia, absent external auditory canals. Cleft lip or palate. Temporomandibular joint contractures may limit mouth opening. Can have mild micrognathia.

Neuromuscular: All have muscular dystrophy. Severe intellectual disabilities, seizures, myoclonic jerks. Surface abnormalities of the brain and cerebellum (lissencephaly, agyria, pachygyria, polymicrogyria, thickened cortex, hypoplastic or absent corpus callosum or septum pellucidum). Absence of cortical lamination. Aqueductal stenosis. Cerebellar malformations. Dandy-Walker malformation. Hypotonia, weakness, and congenital muscular dystrophy with elevated creatine kinase levels. Creatine kinase levels do not correlate with the clinical severity—they tend to be highest in infancy and decline with age.

Orthopedic: Joint contractures may be present at birth.

Other: Hypothermia, suggesting abnormal hypothalamic function, has been reported (2). Intrauterine growth retardation.

Anesthetic Considerations: Temporomandibular joint contractures may limit mouth opening and make direct laryngoscopy difficult (4). Contractures can make perioperative positioning difficult. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients can have elevated intracranial or intraocular pressure, in which case

precautions should be taken to avoid further elevations in pressure. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. Perioperative temperature regulation may be abnormal. Rhabdomyolysis and elevations of creatine kinase with the administration of succinylcholine have been reported, and succinylcholine is contraindicated in this myopathic disease (4,5). Renal function should be evaluated preoperatively. Seizures, poor airway control, and swallowing difficulties make close observation for postoperative respiratory complications important.

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Muscle phosphofructokinase deficiency

See Glycogen storage disease type VII

Muscle phosphorylase deficiency

See McArdle syndrome

Muscular dystrophy

See the specific type of muscular dystrophy: Becker muscular dystrophy, Duchenne muscular dystrophy, Emery-Dreifuss muscular dystrophy, Facioscapulohumeral muscular dystrophy, and Limb-girdle muscular dystrophy.

Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies)

See Muscle-eye-brain disease

Myositis ossificans progressiva

See Fibrodysplasia ossificans progressiva syndrome

Myotonia congenita

Synonym: Thomsen disease, Thomsen-type myotonia congenita

MIM #: 160800

Myotonia congenita is one of the myotonic syndromes. The most common of the myotonic syndromes is myotonic dystrophy (see later). Myotonia congenita is an autosomal dominant form of myotonia that is due to a mutation in the *CLCN1* (skeletal muscle chloride channel) gene. The myotonia is related to lack of normal chloride influx during repolarization, impairing the ability of the skeletal muscle voltage-gated chloride channels to maintain normal muscle excitability. Myotonia congenita presents in childhood without further progression and is associated with normal life expectancy without significant handicap. In general, no specific therapy beyond warming up with continued light exercise is needed. Becker disease, also called Becker-type myotonia congenita (see earlier), is an autosomal recessive disorder involving different mutations in the same gene, which presents at several years of age into adolescence.

HEENT/Airway: Blepharospasm (myotonia of the eyelids) may be symptomatic.

Cardiovascular: No cardiac involvement.

Neuromuscular: The hallmark finding, myotonia, refers to delayed relaxation of contracted muscle. Examples include the inability to release a handshake (“action myotonia”), or the sustained contraction with direct tapping or stimulation of a tendon reflex (“percussion myotonia”—best elicited by tapping the thenar eminence or finger extensors). In myotonia congenita, unlike myotonic dystrophy, myotonia is worse after rest and improves after exercise (the “warm-up phenomenon”). In myotonia congenita (but not myotonic dystrophy), myotonia is worse with cold. All muscle groups are affected. There may be muscle hypertrophy.

Miscellaneous: First described by Dr. A. J. T. Thomsen, a Danish physician practicing in Germany, in himself and his family. In 1876, when he was 61 years old, his youngest son, who was affected by the disease, was accused of

trying to avoid military service. Thomsen reacted by writing his definitive account, in which he could trace the disease back to his maternal great-grandmother.

Anesthetic Considerations: Anesthetic or surgical manipulations can induce myotonic contractions, as can cold and shivering. Even pain from the intravenous

injection of propofol can cause myotonic contractions. These patients can have abnormal drug reactions.

Neither regional anesthesia nor muscle relaxants prevent or reverse myotonic contractions. Drugs that have been used to attenuate the contractions are quinine, procainamide, phenytoin, volatile anesthetics, and steroids. When all else fails, direct infiltration of the muscle with a local anesthetic has been recommended. Succinylcholine can induce sustained contraction of chest wall muscles, making positive-pressure ventilation difficult even in the intubated patient (see figure, myotonic dystrophy, later). A case has been reported of a 32-year-old woman who displayed profound generalized muscle spasms that precluded mouth opening and adequate ventilation following succinylcholine administration as the first significant manifestation of her disease (5). Response to nondepolarizing muscle relaxants is normal in myotonia congenita, but nondepolarizing muscle relaxants will not counteract myotonic contractions that have already been provoked. Anticholinesterase drugs used to reverse nondepolarizing muscle relaxants can precipitate myotonia, and the use of shorter-acting muscle relaxants that do not require reversal has been suggested. An association with susceptibility to malignant hyperthermia has been suggested in the past but a clear relationship is not likely and in fact doubtful (1). The muscle rigidity that routinely follows succinylcholine administration in patients with myotonia may confuse the question of malignant hyperthermia susceptibility.

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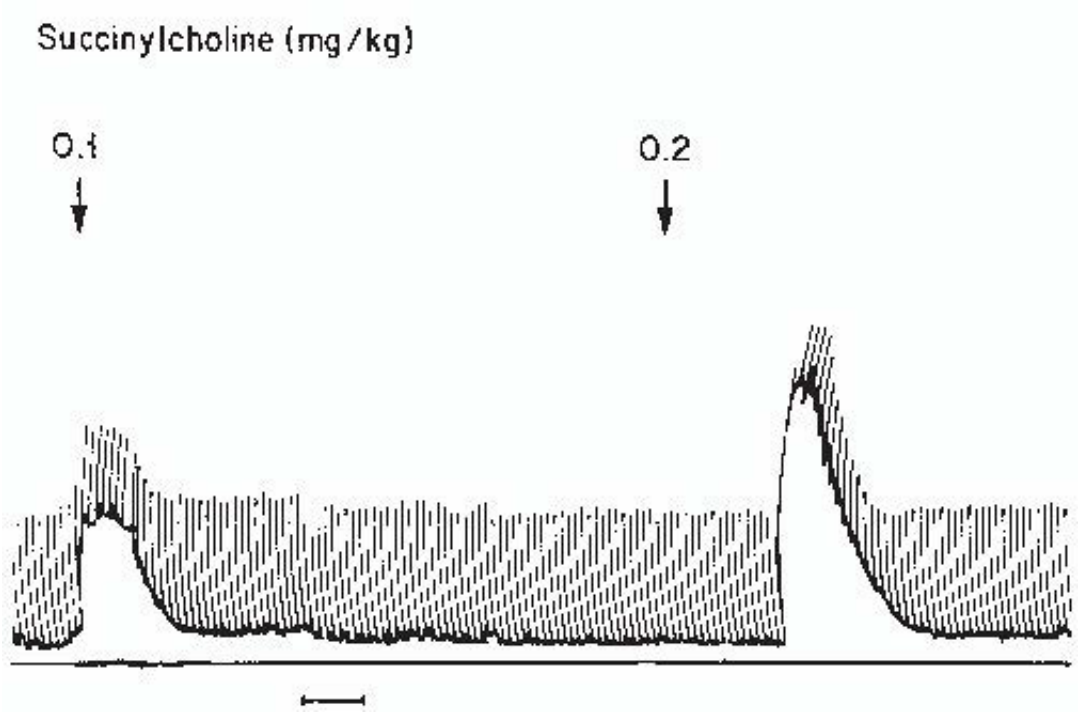
Myotonic dystrophy

Synonym: Steinert disease (Includes congenital myotonic dystrophy)

MIM #: 160900, 602668

Myotonic dystrophy is the most common of the myotonic syndromes. Unlike the other myotonias, myotonic dystrophy is a multisystem disease. And, unlike most of the other myotonias, it is associated with dystrophy of the muscles. Children who are symptomatic from infancy typically have more severe disease in adulthood than do those whose symptoms do not appear until later in childhood or adulthood. Patients who have been symptomatic since infancy are often considered to have a clinically distinguishable disease, referred to as **congenital myotonic dystrophy** (*MIM #:* 160900).



Myotonic dystrophy. The evoked thumb adductor response to succinylcholine in a myotonic patient. The upward shift in the baseline tension represents the contracture. (From Mitchell MM, Ali HN, Savarese JJ. Myotonia and neuromuscular blocking agents. *Anesthesiology* 1978;49:44-48, with permission.)

Myotonic dystrophy is inherited in an autosomal dominant fashion, and there are two genetic subtypes. The molecular defect in myotonic dystrophy-1 is amplification of a GCT nucleotide triplet upstream from the gene for

the protein myotonic dystrophy protein kinase. This kinase normally limits the intracellular sodium current. Dysfunction of the protein kinase results in a larger sodium current and altered muscle excitability. This is potentially the etiology of sudden (presumably tachyarrhythmic) death. Interestingly, although it is autosomal dominant, longer GCT repeats, and therefore worse disease, are inherited from the mother. Each successive generation inheriting the disease has an increased number of GCT triplets and therefore more severe disease. Myotonic dystrophy-2, with a similar but milder phenotype, is due to an expansion of a CCGT repeat in *ZNF9*, encoding the zinc finger protein-9.

The pathogenic mechanism is complicated, however. The expanded repeats are transcribed into RNA. These abnormal RNAs fold into an unusual hairpin shape and accumulate within nuclei, disrupting the regulation of alternative splicing of messenger RNA. Alternative splicing is a mechanism whereby pre-mRNAs from several genes produce mRNAs that encode different but related proteins, thus explaining the multiorgan

findings. For example, in myotonic dystrophy, several developmentally regulated splicing events do not switch from an embryonic to an adult form, leaving embryonic isoforms unable to meet adult requirements, expressed in the adult. Muscle hyperexcitability and insulin resistance, for example, are related to retention of the embryonic splicing pattern of the muscle-specific chloride channel and the insulin receptor.

Newborns with symptomatic myotonic dystrophy may be mechanical ventilator dependent. Prolonged neonatal mechanical ventilation has previously been thought to be uniformly fatal, but two survivors have been reported. The incidence of sudden death in individuals with adult onset disease is over 20%.

HEENT/Airway: Premature frontal baldness, muscle wasting leading to hollowed cheeks, and temporal fossae. Facial weakness leads to an “expressionless” face. Extraocular muscle involvement is a consistent finding. Cataracts are common. Neonates with congenital myotonic dystrophy can have facial diplegia with a tentshaped mouth.

Chest: Bulbar weakness may lead to recurrent aspiration pneumonia. Involvement of the diaphragm and intercostal muscles may lead to a poor cough and alveolar hypoventilation. Patients may have central or obstructive sleep apnea. Neonates with congenital myotonic dystrophy may have profound weakness of respiratory muscles, requiring mechanical ventilation.

Cardiovascular: Cardiac symptoms may be the presenting feature. Ninety percent of patients have conduction abnormalities; first-degree heart block and intraventricular conduction delays are the most common. Patients may have left axis deviation and ST-T wave changes. Sudden death has been associated with the development of third-degree block, but also occurs in the presence of a functioning pacemaker, suggesting ventricular tachyarrhythmia. Inducible sustained ventricular tachycardia (in the electrophysiology laboratory) is due to bundle branch reentry, which should be ablatable. The only risk factors for sudden death are a severe EKG abnormality and a diagnosis of atrial tachyarrhythmia (5). Cardiac enlargement and interstitial fatty infiltration and fibrosis can occur. Impaired ventricular function is usually a late finding. There is an increased incidence of mitral valve prolapse. There is little correlation between the severity of the cardiac disease and the severity of the muscle disease.

Neuromuscular: The hallmark finding, myotonia, refers to delayed relaxation of contracted muscle. Examples include the inability to release a handshake (“action myotonia”), or the sustained contraction with direct tapping or stimulation of a tendon reflex (“percussion myotonia”—best elicited by tapping the thenar eminence or finger extensors). Facial, neck, and distal musculature is primarily involved, with preservation of limb-girdle strength until late in the disease. In myotonic dystrophy, unlike myotonia congenita, myotonia is worse after exercise. In some apparently unaffected siblings, myotonia can be detected only electromyographically. When made audible, the electromyogram sounds somewhat like being buzzed by a propeller-driven dive bomber. There may be mild intellectual disability. Expressionless facies can be interpreted as “dull,” increasing misperception of mild

intellectual disability. Patients with congenital myotonic dystrophy are hypotonic at birth. Muscle tone and strength then improve over the first years of life, but there is inexorable progression of the disease to the adult form during the first decade. Patients exhibit muscle wasting.

Orthopedic: Clubfoot deformity is common in young children with symptomatic disease. Neonates with congenital myotonic dystrophy may present with arthrogryposis.

GI/GU: Dysphagia, reduced peristalsis. Neonates with congenital myotonic dystrophy can have such poor sucking and swallowing that they require feeding through a nasogastric tube. Intestinal pseudo-obstruction and spontaneous pneumoperitoneum have been reported. Increased incidence of gallstones due to abnormal gallbladder tone. Gonadal atrophy or ovarian failure with infertility may occur.

Other: Associated with premature labor, uterine atony, and postpartum hemorrhage. Pregnancy may exacerbate muscle symptoms. May have abnormal insulin response to glucose. May have increased incidence of colloid goiters. Muscle stiffness and pain in type 2 disease (milder phenotype) have on occasion resulted in a misdiagnosis of fibromyalgia.

Miscellaneous: The incidence of this disease is particularly high in Québec.

Anesthetic Considerations: "The production of muscle relaxation in a myotonic patient is one of the most difficult problems facing the anesthesiologist" (15). Anesthetic or surgical manipulations can induce myotonic contractions, as can cold and shivering. The patient's body temperature should be maintained as close to normal as possible for this reason. Even pain from the intravenous injection of propofol can cause myotonic contractions.

Neither regional anesthesia nor muscle relaxants prevent or reverse myotonic contractions. Drugs that have been used in the past to attenuate the contractions are

quinine, procainamide, phenytoin, volatile anesthetics, and steroids. When all else fails, direct infiltration of the muscle with a local anesthetic has been recommended. Succinylcholine can induce sustained contraction of the chest wall muscles, making positive-pressure ventilation difficult even in the intubated patient (see figure). Succinylcholine may even cause tonic contractions in infants with congenital myotonic dystrophy in whom clinically apparent myotonia has not yet developed. Because of dystrophic muscle changes, it is possible that in advanced cases, succinylcholine might result in an exaggerated hyperkalemic response—another reason to avoid the drug. This disease is not associated with malignant hyperthermia.

Tracheal intubation can often be performed after an intravenous induction followed by administration of a volatile anesthetic, without the use of muscle relaxants. Responses to nondepolarizing muscle relaxants have generally been reported as normal, although sensitivity to rocuronium (1) and vecuronium (8) has been described. Anticholinesterase drugs used to reverse nondepolarizing muscle relaxants may precipitate myotonia, although that assertion has recently been challenged (2), and the use of shorter-acting muscle relaxants that do not require reversal has been suggested. Sugammadex has been used to reverse residual rocuronium neuromuscular blockade (1).

In one study, the only independent risk factors for adverse perioperative events in children were the muscular impairment rating scale (a measure of the extent of muscle weakness) and the use of muscle relaxant without reversal (4). The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

A baseline EKG should be examined because 90% of patients have conduction abnormalities, usually first-degree heart block or intraventricular conduction delays. Patients may have ST-T wave changes that can be mistaken for ischemia. The development of third-degree heart block has been associated with asystole. Patients may be at risk for ventricular tachyarrhythmias (9). Ventricular function usually remains normal until late in the disease.

Patients may have abnormal insulin response, and blood sugar should be monitored. Patients may have abnormal drug reactions. They appear more likely to experience apnea after the administration of a wide variety of intravenous anesthetics, including propofol, benzodiazepines, opioids, and barbiturates, although an uneventful primary propofol technique has been reported. Preoperative sedation must be carefully titrated in a monitored setting. Patients also need to be observed closely postoperatively for signs of respiratory depression. There is a report of a patient experiencing severe respiratory depression after a small dose of epidural morphine (21). The antiarrhythmic mexiletine has been shown to decrease myotonia.

These patients often have dysphagia and reduced peristalsis and thus are at increased risk for perioperative aspiration (7,10). Weakness and atrophy of the respiratory muscles may cause postoperative respiratory complications in neonates as well as in adults. Even without significant respiratory muscle weakness, patients may have an inadequate cough, which predisposes to postoperative pulmonary complications. Although epidural anesthesia has been used successfully (18), associated shivering may precipitate myotonic contractions. Uterine atony may cause excessive postpartum hemorrhage.

A relatively small review of myotonic dystrophy type 2 suggests adverse perioperative events may be less common than in type 1 (3). The patients in this series tolerated succinylcholine administration as well as reversal of nondepolarizing neuromuscular blockade with neostigmine.

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Note: Although we have endeavored to include essentially all papers in the English language anesthesia literature relevant to specific syndromes, there are too many dealing with anesthesia and myotonic dystrophy to make that practical and we have had to be selective.

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Myotubular myopathy

Synonym: Centronuclear myopathy

MIM #: 310400

This usually X-linked myopathy is due to mutations in the gene for myotubularin. Myotubularin is required for muscle cell differentiation. Histologically, one sees a large number of centrally located nuclei in the myocytes, hence the synonym “centronuclear myopathy.” This disease is usually fatal in infancy secondary to respiratory insufficiency. Prolonged survival often requires mechanical ventilation. Several families with X-linked disease with survival into adulthood have been reported. There are also autosomal recessive and dominant forms of this disease. Some reserve the term “myotubular myopathy” to refer to the X-linked form and use “centronuclear myopathy” for the autosomal forms. The autosomal recessive form (*MIM #:* 255200) usually has an earlier onset than does the autosomal dominant form. The autosomal recessive form is slowly progressive and most patients are wheelchair bound or deceased by the second or third decade of life. It is due to abnormalities in the gene encoding amphiphysin-2. The autosomal dominant form (*MIM #:* 160150) is usually manifest by the third decade, and the progression is slower than with either the X-linked or autosomal recessive forms. It is due to mutations in the gene encoding dynamin-2, a GTPase. An additional syndrome, myotubular myopathy with abnormal genital development (*MIM #:* 300219), likely represents a contiguous gene syndrome to the X-linked form.

The other congenital myopathies are central core disease (see earlier), minicore myopathy (not covered in this text), and nemaline rod myopathy (see later).

HEENT/Airway: Large head circumference. Elongated, myopathic facies. External ophthalmoplegia. Ptosis. Myopia. Can have high-arched palate. Micrognathia in the X-linked form. Malocclusion.

Chest: Neonatal respiratory distress. Respiratory failure from restrictive disease. Atrophic or thin diaphragm.

Neuromuscular: Profound hypotonia. Areflexia. Can develop seizures. Intellectual development is usually normal. May have swallowing difficulties. Rare hydrocephalus.

Orthopedic: Scoliosis. Contractures. Long thin digits. Clubfeet. Can have advanced bone age.

GI/GU: Pyloric stenosis. Liver dysfunction. Gallstones. Hepatic bleeding has been reported. Renal stones or nephrocalcinosis. Cryptorchidism.

Other: Increased birth length. Polyhydramnios. Serum creatine kinase levels are usually normal or only mildly elevated. Can have vitamin K-dependent bleeding dyscrasia.

Miscellaneous: The name myotubular myopathy derives from the histologic similarity of these diseased muscles to fetal myotubes.

Anesthetic Considerations: Patients with swallowing difficulties are at increased risk for perioperative aspiration. Bleeding tests (prothrombin time) should be evaluated preoperatively and may require preoperative vitamin K administration. Succinylcholine should be avoided in this myopathy due to the risk of an excessive hyperkalemic response. Response to nondepolarizing muscle relaxants is probably normal, but they may not be required in this disease of markedly diminished muscle tone. Patients are at risk for perioperative respiratory failure. Continuous spinal anesthesia (a failed combined spinal/epidural) has been reported. In view of a suspected case of malignant hyperthermia and the similarity of this disease to central core disease, it has been suggested that malignant hyperthermia precautions be observed (4,8).

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

N

N-Acetylglutamate synthetase deficiency

Synonym: NAGS deficiency

MIM #: 237310

This autosomal recessive disorder is closely related to the urea cycle defects. The urea cycle degrades amino acids to urea, and defects in the urea cycle can lead to hyperammonemia. Symptoms of this disorder can be triggered by stress such as surgery or infection or episodes of protein catabolism such as the involution of the postpartum uterus. Both early-onset and later-onset disease occur. Absent enzyme activity leads to early-onset disease, which presents in the neonatal period with neurologic deterioration leading to coma and death. Later-onset disease, where there is some residual enzyme activity, is marked by recurrent Reye-like episodes. Liver transplantation is curative.

N-Acetylglutamate, an activator of carbamoyl phosphate synthetase, is synthesized in the liver by mitochondrial *N*-acetylglutamate synthetase (NAGS). Without *N*-acetylglutamate, carbamoyl phosphate synthetase cannot be activated. Carbamoyl phosphate synthetase 1 deficiency (see earlier) is one of the urea cycle defects, and the symptoms of NAGS deficiency are identical. Pharmacologic therapy, using parenteral phenylacetate and benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors.

Neuromuscular: Hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and is characterized by lethargy, agitation, and confusion with eventual coma and cerebral edema. Between acute episodes, mental status is normal, but there may be developmental delay or intellectual disability. Possible increased intracranial pressure during an acute decompensation.

Other: Episodes of hyperammonemia begin with anorexia and lethargy. Vomiting and headaches may be prominent.

Anesthetic Considerations: Acute metabolic encephalopathy can develop perioperatively. Acute metabolic encephalopathy may be associated with cerebral edema and increased intracranial pressure. Patients should maintain high carbohydrate intake (and low protein intake) perioperatively. Intravenous fluids and dextrose should be used generously perioperatively to avoid hypovolemia and protein catabolism. Throat packs or an orogastric tube should be placed for any surgery with the potential for oral or intestinal bleeding, because blood in the GI tract provides a protein load that may lead to the development of hyperammonemia. Acute hyperammonemic crises can be treated, in addition to high-caloric intravenous fluids, with *N*-carbamoyl-L-glutamate and hemofiltration. Other acute treatments include l-arginine and sodium benzoate.

Figure: See **Appendix C**

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NADH-coenzyme Q reductase deficiency

See Complex I deficiency

NADH-ubiquinone oxidoreductase

See Complex I deficiency

Nager acrofacial dysostosis syndrome

See Nager syndrome

Nager syndrome

Synonym: Nager acrofacial dysostosis syndrome

MIM #: 154400

This autosomal dominant mandibulofacial dysostosis syndrome is distinguished by conductive hearing loss, radial limb hypoplasia, and craniofacial abnormalities that are similar to those of the Treacher Collins syndrome. It is one of the acrofacial disorders. It is due to mutations in the gene *SF3B4*, which encodes splicing factor 3B, subunit 4.

HEENT/Airway: Characteristic facies with absent zygomatic arches and hypoplastic malar region. Down-slanting palpebral fissures, absent lower eyelashes, lower lid coloboma. Low-set, posteriorly rotated ears. Atresia of the external auditory canal, conductive hearing loss. Choanal atresia. Small mouth. Cleft palate, soft palate agenesis, velopharyngeal insufficiency. Micrognathia. Hypoplasia of the larynx or epiglottis.

Chest: Neonates may experience respiratory distress secondary to micrognathia and palatal anomalies.

Cardiovascular: Rare congenital cardiac defect.

Neuromuscular: Intelligence is usually normal. May have hydrocephalus, agenesis of the corpus callosum, polymicrogyria.

Orthopedic: Short stature. Hypoplastic or aplastic radius. Radioulnar synostosis. Limited elbow extension. Hypoplastic or aplastic thumbs. Occasional syndactyly, clinodactyly, or camptodactyly. Shortened humerus. May have clubfoot deformity. Dislocated hips. May have cervical vertebral anomalies, scoliosis.

GI/GU: May have Hirschsprung disease (see earlier). May have genitourinary anomalies.

Miscellaneous: Mandibular hypoplasia is often worse than in Treacher Collins syndrome. Miller syndrome (see earlier) also has Treacher Collins-like facies but is distinguishable from Nager syndrome because it involves postaxial rather than preaxial (radial) upper limb defects. In 2005, Gobbel and colleagues identified Nager syndrome in a fetus found in the Meckel Anatomical Collection at the University of Halle, Germany. The specimen dates to 1812 and is currently the oldest known example of Nager syndrome.

Anesthetic Considerations: Small mouth, micrognathia, and hypoplasia of the larynx make direct laryngoscopy and tracheal intubation very difficult or impossible. Urgent tracheostomy or retrograde intubation techniques have been required. Passage of an endotracheal tube through a laryngeal mask airway (LMA) has also been reported (3). The mouth may be small enough to prevent adequate surgical exposure to repair a palatal cleft (7). Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Peripheral vascular access may be difficult to obtain secondary to limb deformities. Radial anomalies may make placement of a radial arterial catheter more difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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NAGS deficiency

See *N*-Acetylglutamate synthetase deficiency

Nail-patella syndrome

Synonym: Hereditary onychoosteodysplasia

MIM #: 161200

This autosomal dominant disorder is characterized by nail dysplasia, patellar hypoplasia, and dysplasia of other mesenchymal tissues. It is caused by a mutation in the gene for LIM-homeodomain protein (*LMX1B*). The nail-patella gene locus and the ABO blood group locus are closely linked on the long arm of chromosome 9.

HEENT/Airway: Cloverleaf pigmentation of the inner margin of the iris. Open angle glaucoma. May have ptosis, microcornea, cataracts. Sensorineural hearing loss. May have weakened teeth. May have cleft lip or palate.

***Chest*:** Hypoplastic first ribs. Malformed sternum.

Neuromuscular: May have intellectual disability, spina bifida. May have muscular aplasia. Can have episodic numbness and paresthesias and decreased sensation to pain and cold in extremities.

Occasional psychosis. Increased incidence of attention deficit hyperactivity disorder (ADHD) and major depression.

Orthopedic: Short stature. Dysplastic nails. Hypoplastic or absent patella. Limited joint mobility, especially at the elbows. May have antecubital pterygia and restricted range of motion at the elbow. Joint dislocations, especially in the head of the radius and the patella. Posterior iliac spurs (“horns”). Valgus deformity of femoral neck. Clubfoot deformity. Premature osteoarthritis. May have scoliosis or increased lumbar lordosis. May have spina bifida occulta. Chronic back pain.

GI/GU: Can have chronic constipation. Nephropathy similar to glomerulonephritis, with proteinuria, hematuria, or casts. Renal insufficiency may develop by the late teens.

Other: May have polyarteritis-like vasculitis. May have peripheral neuropathy and vasomotor instability (1).

Anesthetic Considerations: Patients with renal insufficiency need careful titration of perioperative fluids and judicious use of renally excreted drugs. Proteinuria may lead to significant hypoalbuminemia. Weak teeth may be more easily injured during laryngoscopy. Patients must be carefully positioned, with attention to their limited joint mobility and tendency toward joint dislocation. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. Glaucoma eye drops can potentially have systemic effects. For example, acetazolamide can affect serum electrolytes. Avoid hypotension and anemia in order to maximize retinal perfusion in patients with glaucoma.

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NARP syndrome

MIM #: 551500

This disorder is characterized by sensory **N**europathy, **A**taxia, and **R**etinitis **P**igmentosa. It is due to a specific point mutation in the segment of mitochondrial DNA encoding subunit 6 of mitochondrial adenosine triphosphatase. This is a component of complex V of the respiratory chain (see earlier). The clinical severity generally parallels the relative amount of the mutant DNA, which may be unevenly distributed in the different tissues. Different mutations in this gene can result in Leigh disease or Leber hereditary optic neuropathy (see earlier for both). Based on *in vitro* work, it has been proposed that supplementation with alpha-ketoglutarate/aspartate to increase substrate level phosphorylation might protect cells lacking this enzyme.

HEENT/Airway: Retinitis pigmentosa with eventual blindness.

Neuromuscular: Sensory neuropathy, developmental delay, seizures, ataxia, dementia. Neurogenic muscle weakness without myopathy. Ragged red muscle fibers on biopsy. Some reinnervation of muscle may occur.

Anesthetic Considerations: When meeting the patient before surgery, recall that he or she may have loss of vision. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Although not reported, the small amount of denervation with collateral reinnervation described suggests that succinylcholine should be avoided. It is reasonable to avoid the use of nitroprusside because cyanide can inhibit the electron transport chain. Although barbiturates and volatile anesthetics can inhibit mitochondrial respiration, induction of anesthesia with thiopental has been used without any complications in the related Leigh disease (see earlier). Because of its mitochondrial depressant effects, it may be judicious to avoid anything more than short-term use of propofol in these patients for fear of triggering the propofol infusion syndrome.

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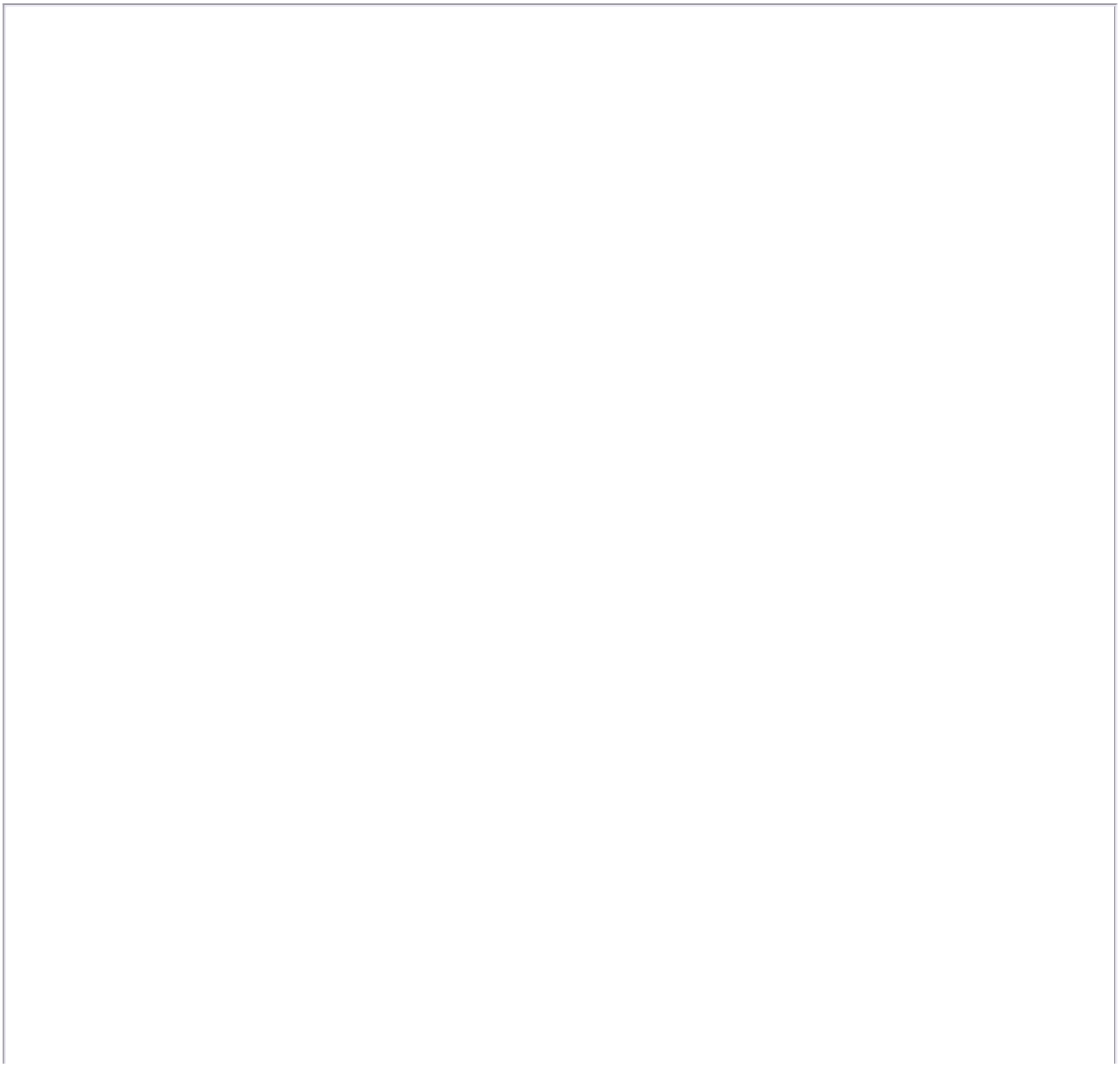
Nemaline rod myopathy

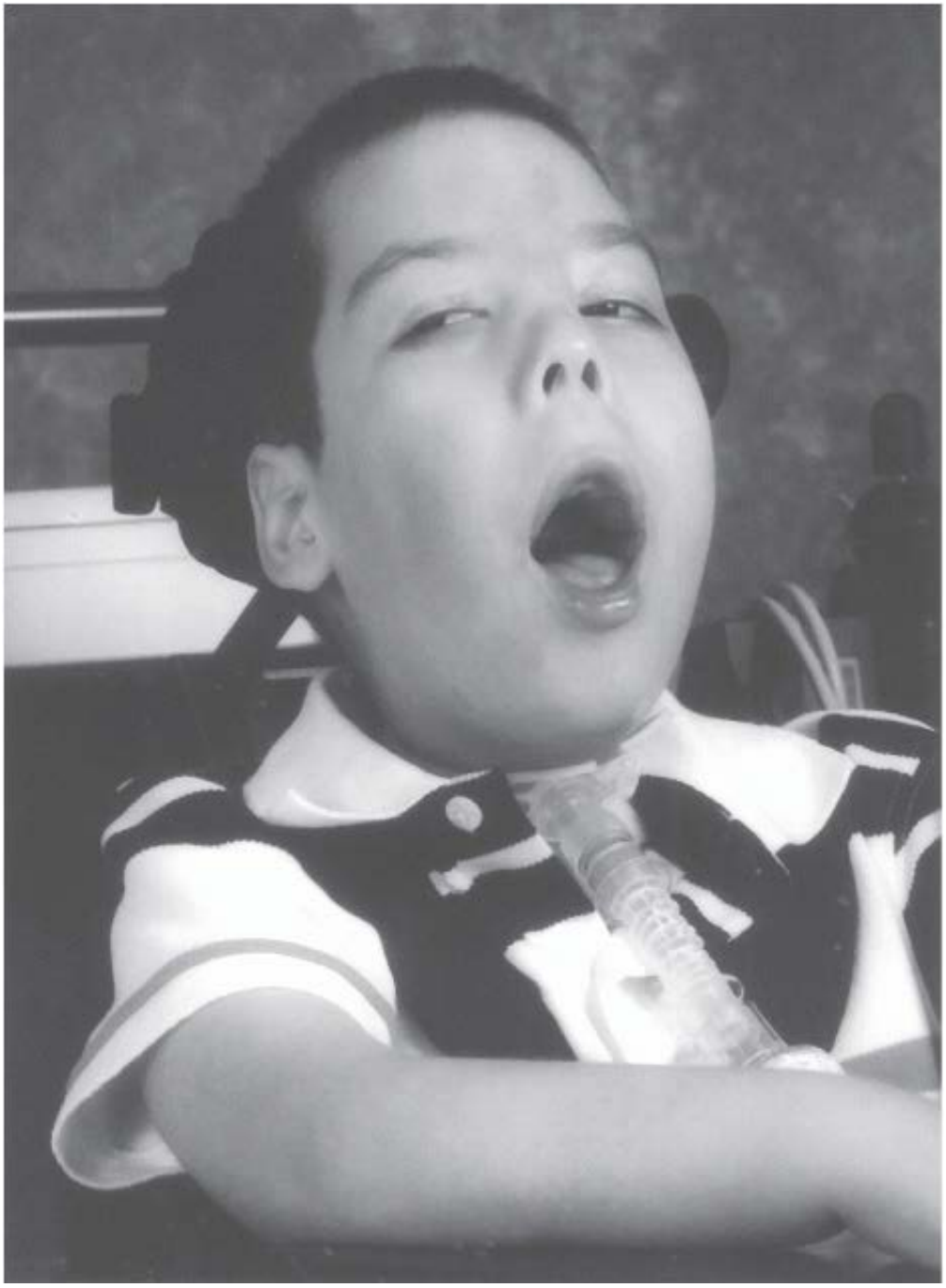
MIM #: 161800, 256030, 609284, and Others

This congenital myopathy is related to central core disease (see earlier) and the mitochondrial myopathies. It is

inherited autosomally and displays clinical and genetic heterogeneity. There are several types, which are clinically indistinguishable from each other. Type 1, which is autosomal dominant, is due to a defect in the gene for tropomyosin-3. Type 2, which is autosomal recessive, is due to a mutation in the gene encoding nebulin, another muscle protein. Type 3, which is apparently inherited in an autosomal dominant

fashion, is caused by a mutation in the alpha-actin-1 gene. Type 4 is due to mutations in the beta-tropomyosin gene. Type 5 (known as Amish nemaline myopathy) is caused by a mutation in the troponin T1 gene. Type 6 is caused by a mutation in the gene *KBTBD13*. Type 7 is due to a mutation in the gene encoding cofilin-2. Six of these seven genes encode components of skeletal muscle sarcomeric thin filaments. In all forms, type I muscle fibers exhibit subsarcolemmal rodlike structures, which are presumably derived from Z-disk material. Some patients can have moderate, nonprogressive disease, and there can be clinical variability within a family. Presumably the clinical heterogeneity is due to the differing effects of different mutations within the genes. At its most severe, profound hypotonia can be life threatening in the neonatal period. There is also an adult-onset disease, which appears to not be heritable and may reflect a different disease entity.





Nemaline rod myopathy. This young boy with nemaline rod myopathy has obvious myopathic facies and requires mechanical ventilation.

The other congenital myopathies are central core disease (see earlier), minicore myopathy (not covered in this text), and myotubular myopathy (see earlier).

HEENT/Airway: The face is long with a high-arched palate. Malocclusion and micrognathia or prognathism are common. Can have retrognathia.

Chest: There can be involvement of the diaphragm and the intercostal muscles. Restrictive disease from kyphoscoliosis. Death is usually from respiratory failure. Pectus excavatum.

Cardiovascular: Although several children with congenital heart disease have been reported (5), it is not clear if this represents a part of the pathologic process or a chance occurrence. A small number of patients who have developed a cardiomyopathy have been reported.

Neuromuscular: Hypotonia, weak cry, and poor suck in infancy. Delayed motor development. Truncal and proximal limbs are typically involved as in most myopathies, but distal limb, pharyngeal, and facial muscles can also become involved. Bulbar muscle weakness. Muscle weakness is slowly progressive, if at all, and most patients can ambulate. Intelligence is usually normal.

Orthopedic: Kyphosis, scoliosis. Exaggerated lordosis. Congenital hip dislocation, pes cavus. Can develop joint contractures. Arthrogryposis in severe cases.

GI/GU: Poor swallowing.

Other: Serum creatine kinase levels are usually normal. Sudden progression of the severity of the disease in late middle age has been reported.

Miscellaneous: "Nema" is the Greek word for thread—descriptive of the subsarcolemmal rodlike structures that are seen histopathologically in this disease.

Anesthetic Considerations: The narrow face, micrognathia, and malocclusion may make direct laryngoscopy and tracheal intubation difficult. Preoperative pulmonary function testing may be used to evaluate the patient's pulmonary status at baseline. Patients should be evaluated for congenital heart disease and/or cardiomyopathy preoperatively. Patients may be at increased risk for aspiration. Patients are at risk for postoperative respiratory complications. Severely affected patients may require postoperative ventilation. Postoperative pain with splinting may further impair pulmonary function. Successful spinal anesthesia in a neonate has been reported (3), but loss of intercostal muscle activity with a high level of anesthesia could be problematic.

The use of succinylcholine has been reported in a single case. There was delayed onset of relaxation and no excessive potassium release (6), although its routine use would seem ill advised. Muscle relaxation is often not necessary in patients with significant muscle weakness and in fact may be a poor choice in patients with poor muscular reserve.

Malignant hyperthermia has not been described in patients with nemaline rod myopathy, and the risk is considered to be low (1). However, occasional patients will also have additional evidence of cores on histologic examination making a firm conclusion impossible at this time, as central core disease does present a malignant hyperthermia risk.

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Neonatal adrenoleukodystrophy

Included in Adrenoleukodystrophy

Neonatal progeroid syndrome

Synonym: Wiedemann-Rautenstrauch syndrome

MIM #: 264090

Children with this autosomal recessive disorder present with progeroid features at birth (see Progeria, later). The responsible gene and gene product are not known. Most patients die in infancy; however, survival into the second decade has been reported. Unlike phenotypically similar diseases, the lipodystrophy is not generalized, but tends to primarily affect the head, the distal extremities, and the paravertebral and lateral gluteal areas.

HEENT/Airway: Sparse hair. Pseudohydrocephalus (due to frontal and parietal bossing), macrocephaly, persistent anterior fontanelle, prominent scalp veins. Triangular face. Entropion. Nystagmus. Sparse eyelashes and eyebrows. Progressive beaking of nose. Dysphagia. High-pitched voice. May have neonatal teeth. Protruding chin. Can have micrognathia.

Chest: Gynecomastia.

Cardiovascular: May have congenital cardiac defects.

Neuromuscular: Mild to moderate psychomotor developmental delay. Tremor. Ataxia. Poor muscle development.

Orthopedic: Short stature. Osteopenia. Long slender bones. May develop scoliosis in adolescence. Vertebral body hypoplasia. May have reduced joint mobility. Large hands and feet with long fingers and toes. Hypoplastic nails.

GI/GU: Paradoxical accumulation of fat around the anogenital area, the buttocks, and the flanks (although it is unclear if this represents areas of normal fat contrasted to nearby areas of lipodystrophy). Urinary reflux. Delayed onset of puberty. Cryptorchidism.

Other: Prenatal growth deficiency, areas of lipodystrophy with absence of subcutaneous fat. Sparse scalp hair, eyebrows, eyelashes. May have hyperinsulinemia and possibly insulin resistance. May have variable endocrine abnormalities.

Anesthetic Considerations: Unlike progeria, premature atherosclerotic cardiovascular disease has not been

reported. Lack of subcutaneous fat may make a good mask fit difficult. Neonatal teeth (teeth present at birth) may be loose, and can be lost during laryngoscopy. Lack of subcutaneous fat may lead to perioperative hypothermia. Positioning may be difficult with restricted joint mobility. A case of propofol infusion syndrome after six hours of propofol use has been reported. Presumably this is related to abnormal lipid metabolism, although this patient had received propofol uneventfully before (1).

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Netherton syndrome

MIM #: 256500

This autosomal recessive disorder is caused my mutations in the gene *SPINK5*, which encodes a serine protease inhibitor. The hallmarks are so-called bamboo hair (trichorrhexis invaginata), an ichthyosiform rash (see Ichthyosis, earlier) and atopic disease. It mostly occurs in females. The most severely affected infants are born with collodion membrane, failure to thrive, and hypernatremic dehydration. In general though, patients have a normal life span.

HEENT/Airway: Sparse eyebrows. Brittle, sparse scalp hair.

Chest: Asthma.

Neuromuscular: Can have developmental delay. Can have seizures or spastic diplegia.

GI/GU: Villous atrophy. May require nutritional support due to higher metabolic demand.

Other: Failure to thrive. Generalized erythroderma, ichthyosis, urticaria. At risk for hypernatremic dehydration. Recurrent infections. Angioedema. Elevated IgE, atopic disease.

Anesthetic Considerations: Extreme care must be taken when applying dressings, tourniquets, blood pressure cuffs, and the like, which should be well padded against the skin. Temperature, intravascular volume, and electrolytes need to be followed closely due to the skin abnormality. Excessive transdermal losses are to be expected. Salicylates can be a component of topical treatments, and systemic absorption can affect platelet function. There is an increased risk of perioperative infection.

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Neu-Laxova syndrome

MIM #: 256520

This autosomal recessive, early lethal syndrome is distinguished by microcephaly, characteristic facies with exophthalmos, lissencephaly, and syndactyly. Patients are stillborn or die in the neonatal period. The responsible gene and gene product are not currently known.

HEENT/Airway: Absent scalp hair. Microcephaly, sloping forehead. Characteristic canine facies with hypertelorism and exophthalmos. Absent eyelids and eyelashes, cataracts. Large ears. Flat nose. Round mouth with large lips. May have cleft lip or palate. Micrognathia. Short neck.

Cardiovascular: May have patent ductus arteriosus, patent foramen ovale, atrial septal defect, ventricular septal defect, transposition of the great vessels.

Neuromuscular: Lissencephaly. Agenesis of the corpus callosum, absent olfactory bulbs, cortical hypoplasia, anencephaly, spina bifida, Dandy-Walker malformation, choroid plexus cysts. Muscular atrophy.

Orthopedic: Short limbs. Syndactyly. Calcaneovalgus. Joint contractures, pterygia. Poorly mineralized bones. Adipose hypertrophy. Marked subcutaneous edema.

GI/GU: Abnormal external genitalia, including cryptorchidism. Bifid uterus. May have renal agenesis.

Other: Thin skin with ichthyosis. Abnormal placenta. Intrauterine growth deficiency.

Anesthetic Considerations: This disorder is lethal early on, and there is rarely an indication for surgery. Intubation (also not indicated) may be difficult secondary to micrognathia, short neck, and marked edema. Subcutaneous edema may make vascular access problematic. Positioning could be difficult with joint contractures.

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Neurocutaneous melanosis

MIM #: 249400

This degenerative disorder is distinguished by skin and meningeal pigmentation and central nervous system deterioration. Melanosis of the skin is apparent at birth. Central nervous system function may be normal at birth, but deterioration usually results in death during early childhood. Neural or cutaneous malignancies eventually occur in most patients. The pathogenesis is assumed to be related to a developmental aberration in the neural crest cells that ultimately form the skin and meninges.

Neuromuscular: Meninges are thick and pigmented, with focal accumulations of melanotic cells. The brain and spinal cord are involved. There is progressive deterioration of central nervous system function because of progressive pigmentation and thickening of the meninges. Intellectual disabilities develop, as well as seizures, cranial nerve palsies, spinal cord compression, and psychosis. Hydrocephalus occurs secondary to blockage of cisternal pathways or obliteration of the arachnoid villi. There may be increased intracranial pressure. May have Dandy-Walker malformation. Meningeal melanomas eventually occur in most patients.

GI/GU: May have Meckel's diverticulum. May have urinary tract anomalies, including ureteral malformations,

unilateral renal cysts, and renal agenesis. Metastatic spread to the peritoneum through ventriculoperitoneal shunts has been reported.

Other: Large, pigmented nevus, usually on the trunk, or numerous smaller nevi are apparent at birth. Cutaneous nevi can become malignant, and leptomeningeal melanoma can occur.

Anesthetic Considerations: Patients with hydrocephalus and increased intracranial pressure warrant precautions to avoid further elevations in intracranial pressure. Patients may have symptomatic spinal cord compression. Patients with renal disease will need fluid and medications titrated carefully perioperatively. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. It is potentially possible to implant melanocytes into the meninges by passing a spinal or epidural needle through a pigmented lesion.

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Neurodegeneration with brain iron accumulation

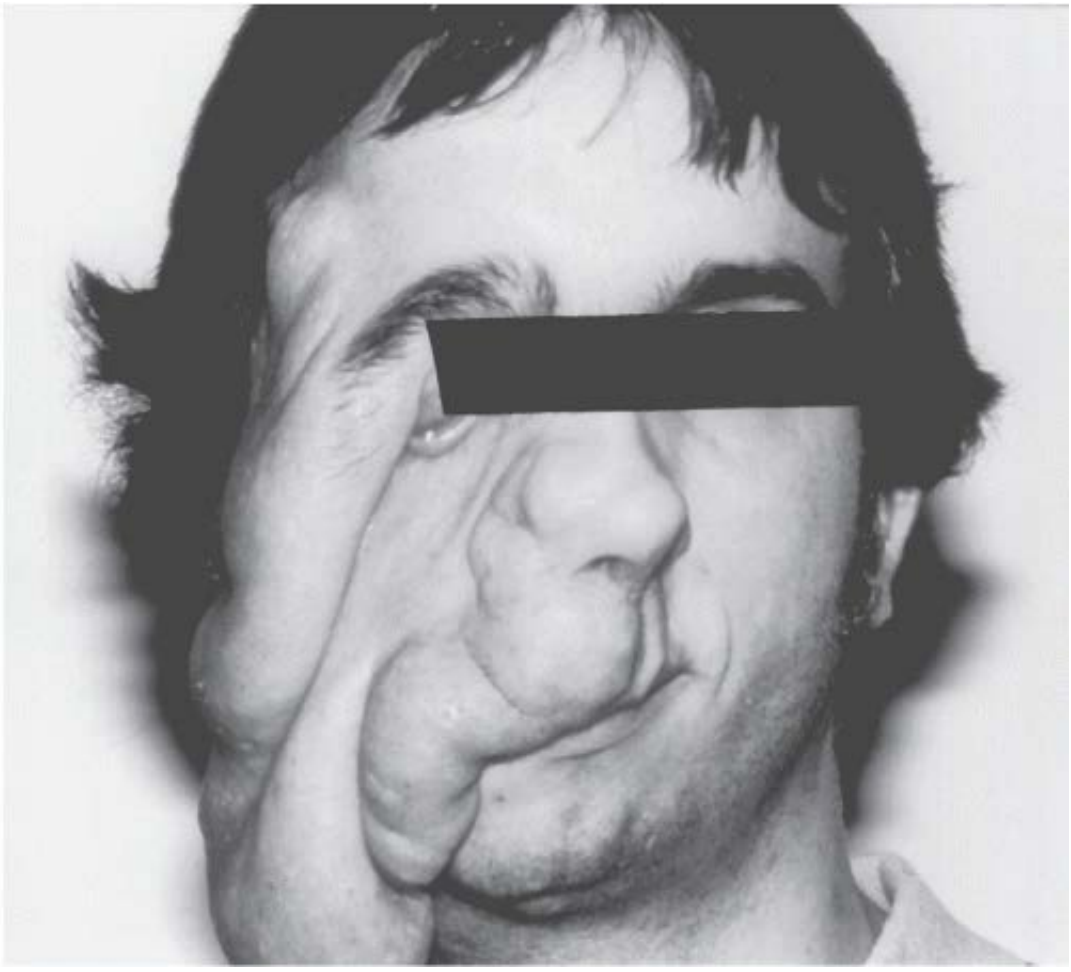
See Hallervorden-Spatz disease

Neurofibromatosis

Synonym: von Recklinghausen disease

MIM #: 162200, 101000

There are at least two types of neurofibromatosis (NF). NF-1 is the classic von Recklinghausen neurofibromatosis and is seen in 85% of patients with neurofibromatosis. It is inherited in an autosomal dominant fashion, with a relatively high incidence of new mutations and significant clinical variability. Sporadic cases may arise from paternal germ cell mutations. NF-1 is characterized by cutaneous café au lait spots, peripheral and central nervous system neurofibromas, osseous abnormalities, and certain other benign and malignant tumors, particularly of the central nervous system. Pheochromocytomas may develop in adult patients. The gene responsible for NF-1 is located on the long arm of chromosome 17, and the gene product is called neurofibromin. Neurofibromin influences guanine nucleotide metabolism and the function of the ras oncoprotein. Presumably, its effect on a tumor suppressor gene modulates the development of the wide range of tumors that can be found in NF-1. Neurofibromas are benign Schwann cell tumors. There are a variety of types of these. Only the plexiform type has the ability to transform into a malignant peripheral nerve sheath tumor.



Neurofibromatosis. Severe cutaneous involvement with neurofibromatosis in a young man (Courtesy of Dr. K. Lin and the Craniofacial Anomalies Clinic, University of Virginia Health System).

NF-2 (“central neurofibromatosis”), also an autosomal dominant disorder, lacks the peripheral and cutaneous manifestations of NF-1. It is characterized by bilateral schwannomas of the eighth cranial nerve, meningiomas of the brain, and schwannomas of the dorsal roots of the spinal cord. NF-2 is linked to a gene on chromosome 22, clearly distinct from the gene that causes NF-1. The NF-2 gene product, called neurofibromin-2 or merlin, may have a tumor suppressor function. Some patients with neurofibromatosis have manifestations of Noonan syndrome (see later).

The expression of this disease is highly variable. Included in the following are the possible features of NF-1.

HEENT/Airway: Macrocephaly. Dysplasia of the sphenoid wing. Hypertelorism. Lisch nodules (iris hamartomas) in older children, optic glioma possibly causing blindness, choroid hamartomas, glaucoma, cataracts. Sphenoid wing dysplasia may cause pulsating exophthalmos. Acoustic neuromas or bony deformity of the acoustic meatus may cause deafness. Airway obstruction

from pharyngeal neurofibromas has been reported but is rare. There can be laryngeal involvement, typically of the arytenoids and aryepiglottic folds. Large parapharyngeal tumors can also impinge upon the airway.

Chest: Restrictive lung disease from kyphoscoliosis. Pulmonary fibrosis with pulmonary hypertension in adulthood. Pectus excavatum. Large posterior mediastinal masses can compress the trachea and bronchi.

Cardiovascular: An arterial vasculopathy affects typically the abdominal aorta or its branches, resulting in renovascular hypertension. The vasculopathy has also been reported to affect the limb vasculature, causing limb hypoplasia (12). Hypertension secondary to pheochromocytoma may be intermittent or persistent. Death due to aneurysm rupture has been reported.

Neuromuscular: Neurofibromas of the cranial nerves, spinal cord, nerve roots, or peripheral nerves. Nodular plexiform neurofibromas may grow along the spinal columns, eventually eroding the spine and compressing the cord. Increased incidence of meningiomas, gliomas, and ependymomas. Pituitary or hypothalamic dysfunction. May have intellectual disabilities, developmental delay, learning disabilities. May have seizures. May have carotid intracranial aneurysms. Many patients will have unidentified bright spots on MRI scans, particularly of the basal ganglia, cerebellum, and brainstem. It is not known what these represent, but they are not tumors.

Orthopedic: Kyphoscoliosis (usually cervical and upper thoracic). An overlying hair whorl may precede the development of kyphoscoliosis (Riccardi sign). Cervical spine stiffness. Massive leg overgrowth, thinning of long bone cortex. Tibial pseudarthrosis is fairly specific to NF-1. Short stature. Pathologic fractures.

Other: The classic skin finding is café au lait spots. Commonly, there is freckling in intertriginous regions, such as the axillae and inguinal area. Systemic arterial hypertension can be due to renal artery stenosis, pheochromocytoma, or catecholamine-secreting nodular plexiform neuroblastomas.

Pruritus may be associated with a rapidly growing neurofibroma. There are four types of neurofibromas:

1. Cutaneous—the most common
2. Subcutaneous—may be tender
3. Nodular plexiform—clusters of neurofibromas along proximal nerve roots and major nerves. These are noninfiltrating.
4. Diffuse plexiform—may have overlying hyperpigmentation. Infiltration of surrounding tissue can cause disfigurement. These have the potential for malignant degeneration.

The list of tumors that can develop is long and includes meningioma, optic or other glioma, ependymoma, acoustic

neuroma, hypothalamic tumors, schwannoma, neurofibrosarcoma, parathyroid adenoma, rhabdomyosarcoma, duodenal carcinoid, somatostatinoma, and pheochromocytoma. Although only 0.1% to 6% of patients with NF-1 will develop pheochromocytoma, up to 25% of patients with pheochromocytoma will have NF-1. Neurofibromatosis has also been associated with moyamoya syndrome (see earlier).

Can develop endocrinopathies, including central precocious puberty or growth hormone deficiency. Pregnancy can initiate or exacerbate the growth of neurofibromas and is associated with the development of pheochromocytoma. Pregnancy can also see worsening hypertension, and cesarean section is more likely than in the general population due to complications of bony abnormalities, pheochromocytoma, or spinal cord neurofibromas.

Miscellaneous: This is one of the phakomatoses or neurocutaneous disorders. Other phakomatoses include Sturge-Weber syndrome, tuberous sclerosis, von Hippel-Lindau syndrome, and nevus sebaceus syndrome of Jadassohn. “Phakos” is Greek for a lentil or lens-shaped spot.

Friedrich von Recklinghausen was a German pathologist at the turn of the last century. He was an assistant to Virchow. The first clear description of the disorder was by Robert W. Smith of the University of Dublin 33 years before von Recklinghausen's description in 1882. von Recklinghausen was the first to appreciate that the tumors had a neural origin.

It is now widely believed that Joseph Merrick (the “Elephant Man”) probably had Proteus syndrome (see later) and not neurofibromatosis, as has been suggested in the past.

Anesthetic Considerations: Mask ventilation or tracheal intubation may be difficult because of neck stiffness, facial bone deformities, macroglossia, or tumors of the tongue or larynx (4,11). A patient was reported in whom a large neurofibroma at the base of the tongue caused airway obstruction, requiring an emergent tracheostomy after the induction of anesthesia (16). Atlantoaxial dislocation has been reported, but is rare. Kyphoscoliosis may make supine positioning difficult. There can be mediastinal masses. Severe spinal deformity may cause restrictive lung disease. Hypertension is common in these patients and has a variety of potential causes. Baseline hypertension should be evaluated preoperatively. If acute and unexpected intraoperative hypertension occurs, the possibility of a pheochromocytoma should be considered.

Increased sensitivity to succinylcholine and nondepolarizing muscle relaxants has been reported in the past, but current thought is that these patients respond normally to neuromuscular blockers (9,14). Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

Because of the high incidence of cord involvement, spinal or epidural techniques should be used only when neuroimaging has shown that there are no nearby cord lesions (6,8). Similarly, ultrasound imaging can be used to localize neurofibromas prior to peripheral nerve block (1).

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Neuronal ceroid lipofuscinosis

See Jansky-Bielschowsky disease and Spielmeyer-Vogt disease

Nevoid basal cell carcinoma syndrome

See Basal cell nevus syndrome

Nevus sebaceus of Jadassohn

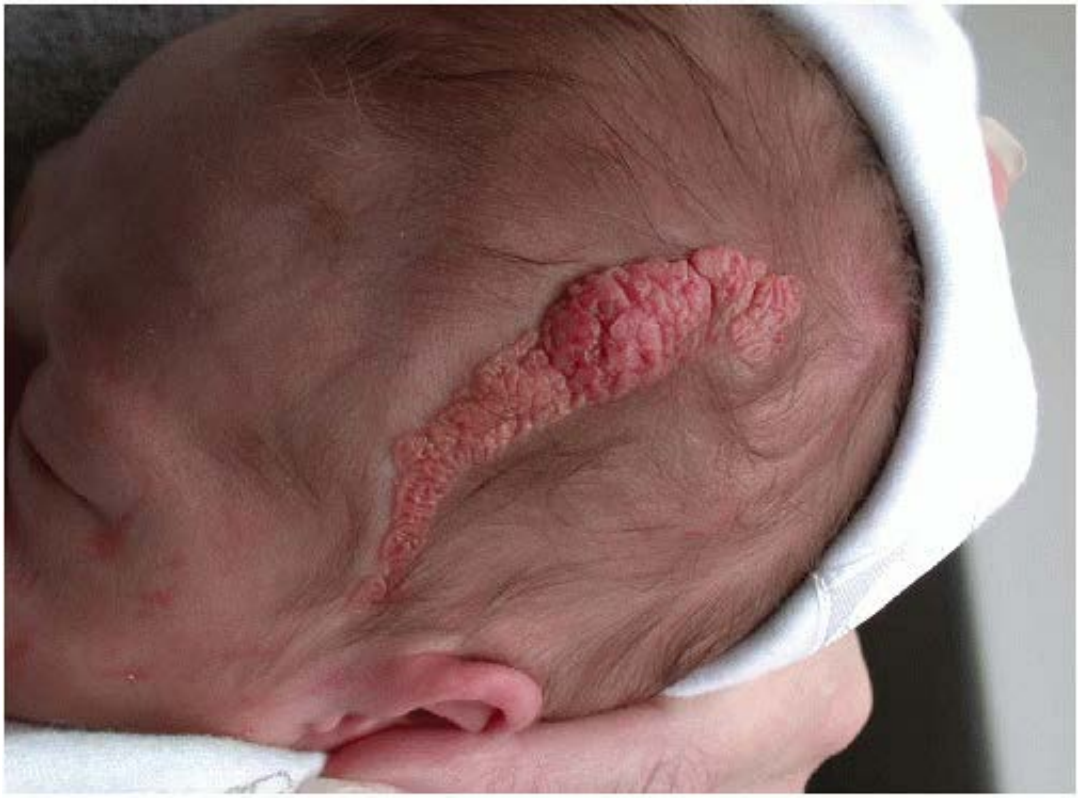
Synonym: Linear sebaceous nevus syndrome; Epidermal nevus syndrome; Sebaceous nevus syndrome, Schimmelpenning-Feuerstein-Mims syndrome

MIM #: 163200

This neurocutaneous syndrome involves midfacial linear sebaceous nevi, seizures, and intellectual disabilities. Some patients manifest sebaceous nevi without any neurologic signs. It is caused by postzygotic somatic mutation in either the gene *HRAS* or the gene *KRAS*, both of which are oncogenes. Since it occurs postzygotically, there is somatic mosaicism. The nevi follow the lines of Blaschko and have alopecia within the lesion. Skin cancers can develop within these lesions.

HEENT/Airway: May have cranial asymmetry with hemimegalencephaly, facial asymmetry. Sphenoid abnormalities, abnormalities of the sella turcica. May have esotropia, colobomas of the eyes and eyelids, cleft palate, dental abnormalities (pigmented malformed teeth).

Cardiovascular: Congenital cardiac lesions include patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, hypoplastic left heart. May have cardiac arrhythmias. May have hypoplasia of the pulmonary artery.



Nevus sebaceus of Jadassohn. A linear nevus on the scalp of an infant. (Courtesy of Dr. Ilona Frieden, Department of Dermatology, University of California, San Francisco.)

Neuromuscular: Seizures, which are often difficult to control. Variable intellectual disabilities. May have cortical hypoplasia, arachnoid cysts, hydrocephalus, hemiparesis, cranial nerve palsies, cortical blindness, intracerebral calcifications. May have cerebral hamartomas. Linear sebaceous nevi are more likely to be associated with underlying central nervous system disorders.

Orthopedic: Short stature. May have scoliosis, kyphosis. Abnormalities of the ulna, radial head, humerus, or fibula. May have polydactyly, syndactyly. Osteopenia.

GI/GU: May have cryptorchidism. May have hypoplasia of the renal artery, renal hamartomas, horseshoe kidney.

Other: Linear sebaceous nevi, especially in the midfacial region. Usually present at birth as raised, yellow, waxy lesions and may have periods of rapid growth. Over time, the lesions become hyperpigmented, hyperkeratotic, and verrucous. Malignant basal cell carcinoma may develop—there is an approximately 15% to 20% risk of malignant degeneration of the lesions.

Vitamin D-resistant rickets occasionally develops, which is responsive to calcitriol and phosphorus or removal of the lesions. This form of rickets is a variant of tumor-induced osteomalacia.

Miscellaneous: This is one of the phakomatoses or neurocutaneous disorders. Other phakomatoses include neurofibromatosis, Sturge-Weber syndrome, tuberous sclerosis, and von Hippel-Lindau syndrome. “Phakos” is Greek for a lentil or lens-shaped spot.

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Asymmetric head and face may lead to difficult mask fit and/or difficult tracheal intubation (1). Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Niemann-Pick disease

MIM #: 257200, 607616, 257220, 607625

Niemann-Pick disease is actually a group of diseases, the sphingomyelin-cholesterol lipidoses. Clinical manifestations are due to lipid storage—predominantly in the reticuloendothelial system, brain, and viscera. Large foam cells are found in the marrow and reticuloendothelial system.

These disorders are inherited in an autosomal recessive fashion and have been classified into types. Type A (classic infantile form) and type B (visceral form) are due to a mutations in the gene sphingomyelin phosphodiesterase-1 (which encodes acid sphingomyelinase), with subsequent accumulation of sphingomyelin and cholesterol. Patients with type A disease, which is associated with mutations that result in non-catalytic enzyme, often die within the first few years of life. The allelic type B is associated with residual levels of enzyme activity and is compatible with survival to adulthood. Type C1 (subacute or juvenile form) and type D (the Nova Scotia type) are due to mutations in the *NPC1* gene. Type C2 is due to mutations in the gene *NPC2*. The exact function of the gene products of these is currently unknown. Type C involves abnormalities in the intracellular transport of cholesterol with the accumulation of unesterified cholesterol in lysosomes and endosomes. Type C has broad phenotypic variation. Several other types (types E and F) have also been described. Type A has the most prominent neurologic findings. In type B disease, sphingomyelin accumulates predominantly in the viscera and reticuloendothelial system. An alternative nomenclature combines types A and B as type I and types C and D as type II.

Niemann-Pick disease is sometimes treated with miglustat, an inhibitor of glycosphingolipid synthesis. This agent is a reversible inhibitor of glucosylceramide synthase, which catalyzes the first step in the biosynthesis of most glycosphingolipids. Successful bone marrow and hematopoietic stem cell transplantation has been reported in type B disease.

HEENT/Airway: Corneal opacification with brownish discoloration of the anterior lens capsule. Approximately one-half have a cherry-red spot in the macular area. Supranuclear gaze palsy (especially type C). Can have loss of hearing.

Chest: Restrictive lung disease. Alveolar infiltration can cause a diffusion defect. May develop cor pulmonale. Can have recurrent aspiration. Lung disease tends to be primary in type C2 and secondary, due to neurologic impairment, aspiration, and muscle weakness, in type C1.

Neuromuscular: The classic disease, type A, has rapidly progressive central nervous system degeneration after approximately one year of age. Psychomotor delay and regression, seizures, behavioral changes, myoclonus, ataxia. Can have cataplexy. Athetosis late. Type C has dystonia.

GI/GU: Hepatosplenomegaly, vomiting, feeding difficulties, diarrhea. May develop cirrhosis with esophageal varices. Can develop ascites. Possible hypersplenism.

Other: Lipid-filled foam cells in the marrow, spleen, adrenals, brain, lymph nodes, and lung. Yellow-brown discoloration of the skin. Failure to thrive, recurrent fever. Anemia and thrombocytopenia late in the disease course. Type C disease can have conjugated hyperbilirubinemia in neonates.

Miscellaneous: Niemann first described this disease, and thought it was a fulminant form of Gaucher disease. Thirteen years later, Pick, a pathologist, recognized this disease as a distinct entity. Despite having served with distinction in the German army during WWI, Pick was removed to the Theresienstadt concentration camp during WWII, where he died in 1944 at the age of 76 years.

Anesthetic Considerations: The combination of cognitive impairment, dysarthria, and hearing impairment may make communicating with the patient difficult. Patients usually accommodate a normal-sized endotracheal tube, rather than a tube that is smaller than predicted, as is the case in the closely related Gaucher disease. With advanced disease, patients may have anemia or thrombocytopenia. Moderate difficulty with intubation has been reported (4). Dysphagia increases the risk of perioperative aspiration. Despite the aspiration risk, most (but not all) children will tolerate procedural sedation without the need to instrument the airway (1). Patients with pulmonary disease and/or recurrent aspiration are at increased risk for perioperative respiratory complications, and close monitoring should continue into the postoperative period. In the presence of significant hepatosplenomegaly, cardiopulmonary reserve may be excessively impaired by muscle relaxation and placement in the supine position. Abnormal splanchnic perfusion and diminished hepatic function can prolong the metabolism of hepatically metabolized drugs. Consider the possibility of esophageal varices prior to passing gastric and similar tubes. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Preoperative anticonvulsant medications should to be continued perioperatively.

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Nonketotic hyperglycinemia

Synonym: Glycine encephalopathy; Hyperglycinemia (nonketotic)

MIM #: 605899

This autosomal recessive disease involves a defect in the glycine cleavage enzyme system, a four-protein mitochondrial enzyme complex that metabolizes glycine to CO_2, ammonia, and hydroxymethyl tetrahydrofolic acid. The four proteins are known as P, H, T, and L. Defects, which lead to nonketotic hyperglycinemia, can arise in any of these four proteins. Glycine, an inhibitory neurotransmitter, is responsible for the clinical manifestations of this syndrome. Dextromethorphan and sodium benzoate have been used to treat this disease and have resulted in transient improvement. Dextromethorphan is an antagonist of the glutamate NMDA receptor, of which glycine is an activator. Sodium benzoate complexes with glycine to form hippuric acid, which is excreted in the urine. Classically, the disease presents in the neonatal period with significant neurologic impairment and death in infancy, but there is variability in expression, and some patients are only mildly affected. In addition, there is a transient neonatal form that resolves after several weeks.

HEENT/Airway: Microcephaly.

Chest: Persistent hiccups. Prone to respiratory failure, and may become ventilator dependent.

Cardiovascular: May develop pulmonary hypertension. In one small series, treatment with pulmonary vasodilators was associated with fatal pulmonary edema (1).

Neuromuscular: Lethargy, weak cry, hypotonia, areflexia, and episodic myoclonic jerks in the newborn period, progressing to coma and apnea. May have hydrocephalus. Survivors have profound intellectual disabilities, myoclonus, opisthotonos, hypertonicity, minimal cerebral development, and intractable seizures. Abnormal electroencephalogram (EEG) with burst suppression or hypsarrhythmia pattern. May have absent corpus callosum.

Other: Nonketotic hyperglycinemia. Glycine is the only abnormally accumulated chemical, and glycine levels can be very high, particularly in the central nervous system. Episodes of lethargy, coma, and increased seizures can be due to both hyperglycinemia from underdosing benzoate and toxicity from overdosing. Treatment with valproate has worsened the condition.

Miscellaneous: This disorder is common in Finland.

Anesthetic Considerations: Ketamine is an NMDA receptor antagonist and has been used to cause transient improvement in the EEG and clinical findings in patients with nonketotic hyperglycinemia (2,6). Although these changes were not permanent, it suggests that ketamine might have a role in anesthetizing these patients.

Benzodiazepines have proven particularly useful in treatment of seizures in these patients because they compete for glycine receptors in the central nervous system.

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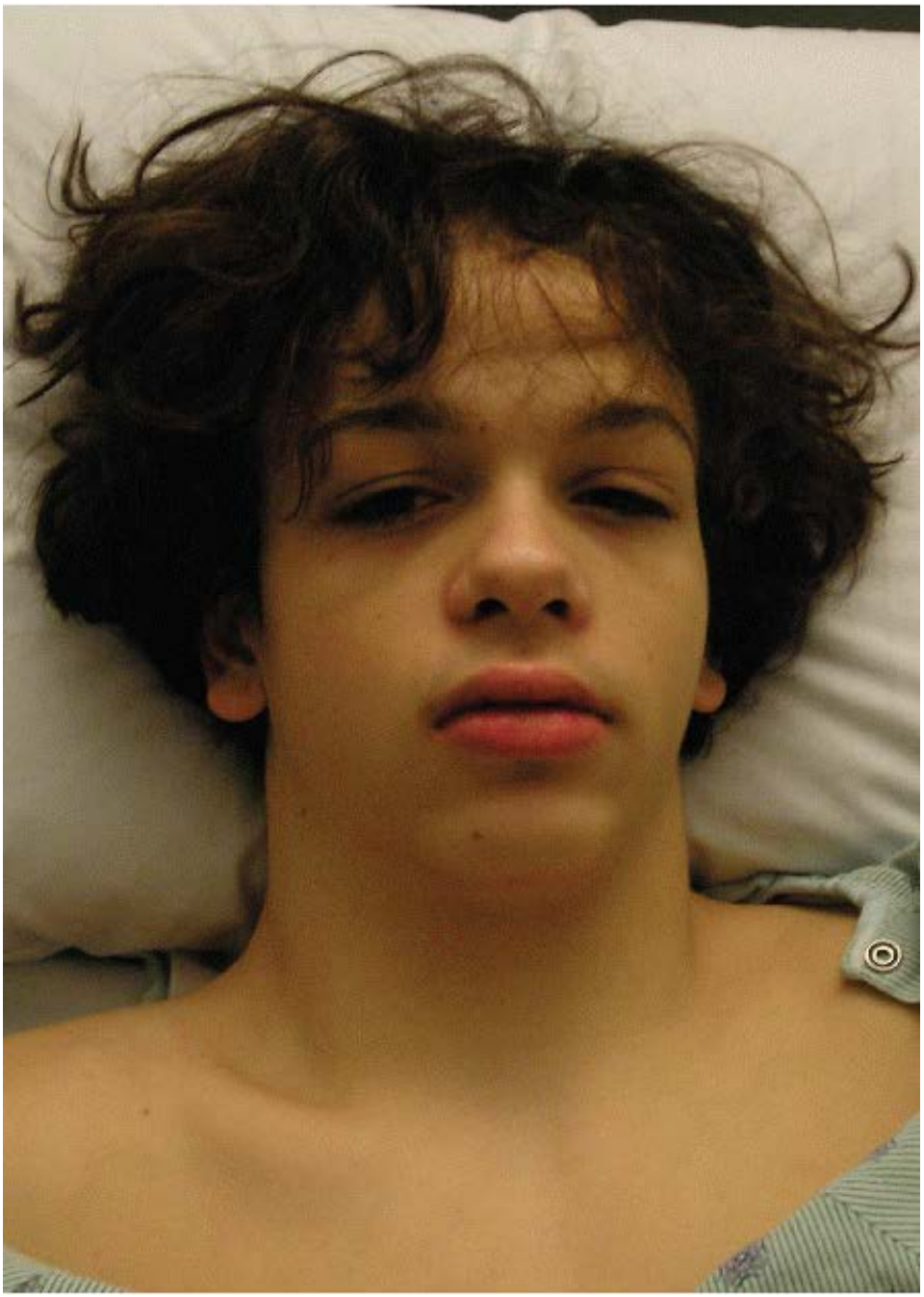
Noonan syndrome

MIM #: 163950

This usually sporadic, but sometimes autosomal dominant, disorder is noted for its superficial similarities to Turner syndrome. People with Noonan syndrome exhibit short stature, characteristic facies, a webbed neck, pectus excavatum, cryptorchidism, pulmonic stenosis, and occasionally hearing loss and/or a bleeding diathesis. Unlike Turner syndrome, patients with Noonan syndrome can be male or female. There is wide genotypic and phenotypic variability. About half the patients have familial disease (for an example, see later, under *Miscellaneous*), due to mutations in the gene *PTPN11*, which encodes the protein tyrosine phosphatase. LEOPARD syndrome (see earlier) is also caused by mutations in this gene, and these two syndromes are allelic. Some patients with neurofibromatosis (see earlier) have manifestations of Noonan syndrome.



Noonan syndrome. This 14-year-old boy has a Turner phenotype (note the “webbed” neck). He has a history of coarctation of the aorta and aortic stenosis.

HEENT/Airway: Triangular facies. Low posterior hairline. Hypertelorism. High-arched eyebrows, downward-slanting palpebral fissures, epicanthal folds, ptosis, myopia, strabismus, nystagmus. Low-set ears with thickened helix. May have sensorineural hearing loss. Flattened midface, depressed nasal bridge. Wide mouth, full upper lip. High-arched palate. Dental malocclusion. Micrognathia. Short or webbed neck. May have posterior cervical cystic hygroma. Distinctive facial characteristics usually become less marked with age.

Chest: Sternal deformities with shield chest and widely spaced nipples. Pectus excavatum or carinatum. May have thoracic kyphoscoliosis. Chest deformities may lead to decreased functional residual capacity or restrictive lung disease. Rare chylothorax.

Cardiovascular: Unlike Turner syndrome, which is associated with left-sided cardiac lesions, patients with Noonan syndrome commonly have pulmonic stenosis. The valve is often dysplastic or thickened. There may be an associated septal defect. Patients often have hypertrophic obstructive cardiomyopathy [HOCM; also called idiopathic hypertrophic subaortic stenosis (IHSS)], which is sometimes nonobstructive and

asymptomatic. Alternatively, patients may have generalized left ventricular hypertrophy. Patent ductus arteriosus, aortic stenosis, and coarctation of the aorta have also been reported.

Neuromuscular: May have intellectual disabilities, which are usually mild. A relatively narrow spinal canal contains a normal-sized spinal cord. May have Arnold-Chiari malformation. May have cerebral arteriovenous malformation.

Orthopedic: Short stature. Cubitus valgus. Abnormal vertebrae. May have spina bifida occulta. May have kyphoscoliosis, lumbar lordosis. May have winged scapulae. Can develop multiple giant cell lesions of the jaw or other bony or soft tissues (called pigmented villonodular synovitis when affects joints).

GI/GU: May have hepatosplenomegaly. Infants may have poor feeding, gastric dysmotility, and gastroesophageal reflux. Cryptorchidism and decreased fertility in male patients. Male patients without cryptorchidism may be fertile. Female patients may have delayed menarche but are fertile. May have renal dysfunction.

Other: May have coagulation or platelet defects, including abnormalities in the intrinsic pathway, isolated factor XI deficiency, von Willebrand disease, and thrombocytopenia. May have lymphatic vessel dysplasia. Juvenile myelomonocytic leukemia has been found in several patients. May have subcutaneous edema, particularly of the hands and feet.

Miscellaneous: In 1980, Cole (16) pointed out that the blacksmith who posed for Ivan Le Lorraine Albright's painting, *Among Those Left*, appears to have had Noonan syndrome. His short stature, facial features, low-set ears, and probable pectus deformity are highly suggestive. Interestingly, the blacksmith's great-grandson also had the characteristic features of Noonan syndrome, including pulmonic stenosis. Ivan Le Lorraine Albright, best known for *The Picture of Dorian Gray*, was also a medical illustrator. In this instance, he was unaware of his contribution to the medical literature. Although the eponym is for Dr. Jacqueline Noonan, a pediatric cardiologist, the syndrome was first described in 1883 by Kobylinski, a Russian medical student.

Anesthetic Considerations: Short or webbed neck, micrognathia, and dental malocclusion may make tracheal intubation very difficult. These problems usually become less marked with age. Peripheral intravenous access may be difficult if there is significant subcutaneous edema. Chest deformities may lead to decreased functional residual capacity or restrictive lung disease. The presence of a bleeding diathesis may increase the amount of perioperative bleeding. Renal impairment may affect the metabolism of renally excreted drugs.

Patients with congenital heart disease should receive an appropriately tailored anesthetic. A decrease in peripheral vascular resistance, hypovolemia, or increased contractility should be avoided if HOCM (IHHS) is present. If HOCM (IHHS) is present, subarachnoid blocks are probably best avoided, and epidural blocks should be activated slowly. Intravenous hydration, halothane, and beta-adrenergic blockade are useful in patients with HOCM (IHHS).

Regional and general anesthesia have been used for labor analgesia or cesarean section in parturients with Noonan syndrome (1,4,8,9,14), although it must be kept in mind that there may be clotting abnormalities. Kyphoscoliosis, exaggerated lumbar lordosis, vertebral anomalies including spina bifida occulta, and a relatively narrow spinal canal with a normal-sized spinal cord make identifying the epidural and subarachnoid spaces more difficult.

Because of the spinal deformities, insertion of an epidural catheter may be difficult, and spread of subarachnoid anesthetic may be unpredictable.

There is a report of a patient with Noonan syndrome who developed malignant hyperthermia on induction of anesthesia (6). In older reports in the nonanesthesia literature, the patients described also had myopathies and are probably more legitimately classified as having had King syndrome (see earlier), which is clearly associated with malignant hyperthermia susceptibility. A relationship between Noonan syndrome and malignant hyperthermia remains extremely unlikely (3).

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

O

OAT deficiency

See Ornithine delta-aminotransferase deficiency

Oculoauriculovertebral syndrome

See Goldenhar syndrome

Oculocerebrocutaneous syndrome

See Delleman syndrome

Oculocerebrorenal syndrome

See Lowe syndrome

Oculodentodigital syndrome

Synonym: Oculodentoosseous dysplasia; ODOD

MIM #: 164200, 257850

This dysmorphic syndrome involves the eyes, nose, teeth, and bones. The most frequent manifestations are microphthalmia, small nose, enamel dysplasia, and camptodactyly. This syndrome is usually inherited in an autosomal dominant fashion. The responsible gene encodes connexin 43, a gap junction protein. There is a more rare and more severe autosomal recessive form, due to mutations in the gene *GJA1*. Half of cases are associated with advanced paternal age.

HEENT/Airway: Osteosclerosis of the skull. Microphthalmia, microcornea, short palpebral fissures, epicanthal folds. May have glaucoma, usually open angle, which develops late. May have iris dysplasia. May have conductive hearing loss. Long, thin nose with hypoplastic alae nasi and small anteverted nostrils. May have high-arched palate, cleft lip or palate. Dental enamel hypoplasia or dysplasia. May have premature tooth loss. May have either mandibular overgrowth or micrognathia.

Neuromuscular: Intelligence is usually normal. May have abnormal white matter, calcification of the basal ganglia, dilated ventricles. May have dysarthria, ataxia, hyperactive reflexes, spastic paraparesis or quadriparesis, seizures. May have neurogenic bladder. Spinal cord compression from an enlarged C1 vertebra has been reported. Spastic paraplegia has been the presenting finding in an adult.

Orthopedic: Camptodactyly of fifth fingers. Syndactyly of fourth and fifth fingers and third and fourth toes. Hypoplastic or missing phalanges. There is a generalized problem with bone modeling. Broad clavicles, ribs, long

bones. May have polydactyly. May have cubitus valgus, hip dislocation. May have yellow-orange hyperkeratosis of palms and soles.

Other: Sparse, fine hair. Low serum calcium in some patients.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to either mandibular overgrowth or micrognathia. The small nose with small nares may make nasotracheal intubation difficult. Dental abnormalities should be documented preoperatively. Dysplastic teeth are at risk for damage or loss during laryngoscopy. Clavicular abnormalities may alter the anatomic landmarks for the insertion of a subclavian venous catheter and could make placement of an infraclavicular block more difficult. Patients with paraparesis or quadriparesis may be at risk for hyperkalemia after the administration of succinylcholine. Patients should be evaluated for the presence of open-angle glaucoma. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Oculodentoosseous dysplasia

See Oculodentodigital syndrome

ODOD

See Oculodentodigital syndrome

OEIS complex

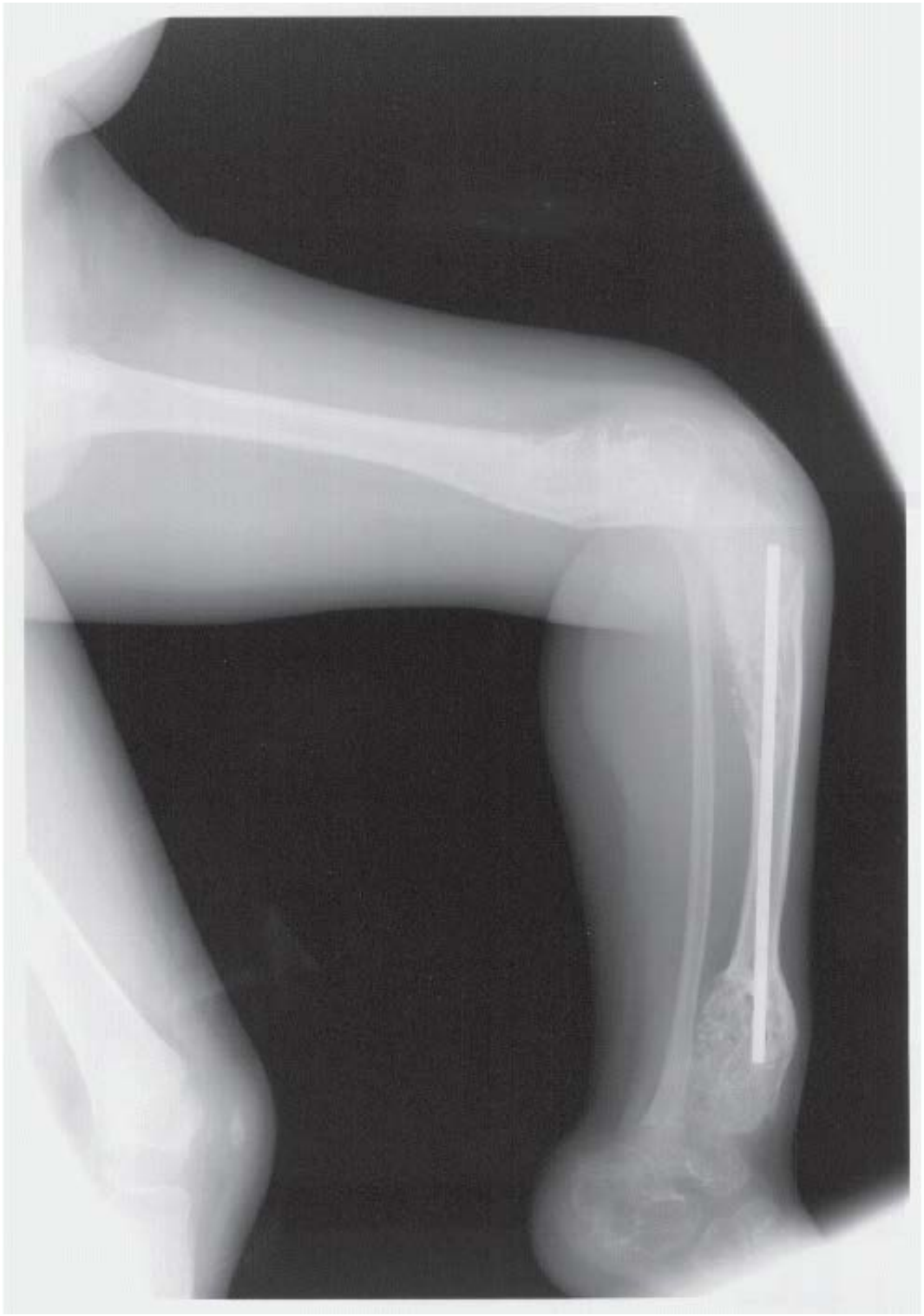
See Exstrophy of the cloaca sequence

Oligohydramnios sequence

See Potter syndrome

Ollier disease

Synonym: Osteochondromatosis syndrome (Includes Maffucci syndrome)



Ollier disease. FIG. 1. Note enchondroma of distal femur and distal tibia.

MIM #: 166000

This sporadically occurring syndrome involves asymmetric enchondromas with associated asymmetric growth deficiency. When hemangiomas [hemangiomata (and enchondromata) if you are a purist] are also present, the condition is known as **Maffucci syndrome** (*MIM #:* 614569).

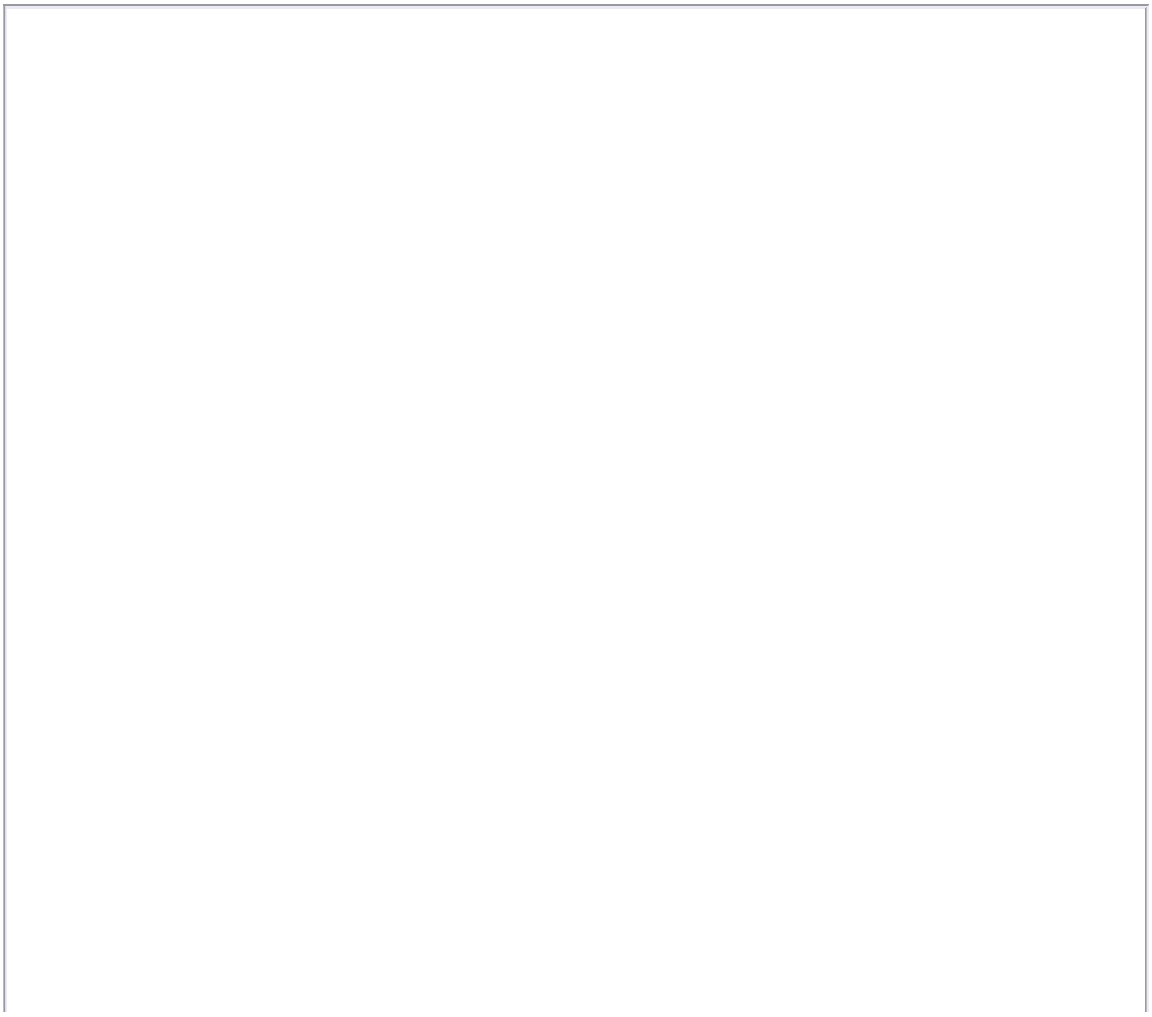
HEENT/Airway: Hemangiomas can involve the head and neck, the pharynx, and the airway.

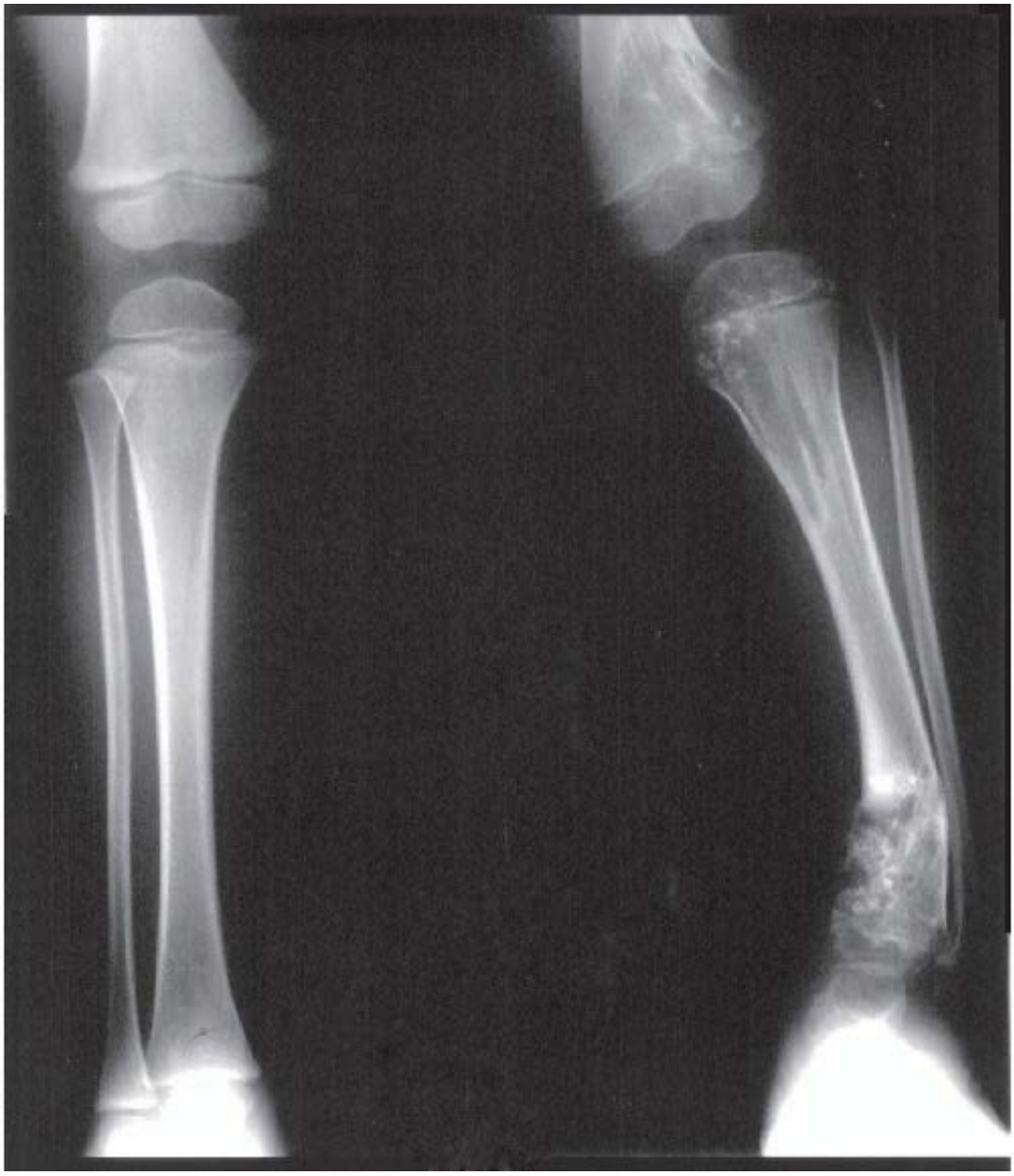
Neuromuscular: A variety of intracranial malignancies have been reported. Hemangiomas can be located within the cervical spine. Both can impinge on neural tissue causing deficits. Pituitary tumors have been reported.

Orthopedic: Asymmetric long bone enchondromas (benign cartilaginous tumors). Limited growth of the affected bones results in asymmetric extremities. Long bones can become bowed and the spine scoliotic. Enchondromas can also develop in the bones of the hands, feet, and pelvis. Fractures related to enchondromas are common. There is a major lifelong risk of malignant transformation of enchondromas (into chondrosarcoma), probably greater than 40%. Hemangiomas can involve the spine.

GI/GU: Maffucci syndrome may have associated splenomegaly and may develop low-grade splenic

angiosarcoma. Hemangiomas in the GI tract can cause bleeding. Ovarian juvenile granulosa cell tumor causing precocious pseudopuberty has been reported.





Ollier disease. FIG. 2. Note asymmetric involvement.

Other: The Maffucci syndrome involves hemangiomas located in the subcutaneous fat and dermis adjacent to the enchondromas. Hemangiomas are usually cavernous but can also be capillary or phlebectasia. Thrombosis of the dilated blood vessels with phlebolith formation frequently occurs. Consumptive coagulopathy can occur, but the etiology (splenic vs. hemangiomas) is not clear. Hemangiomas can undergo malignant transformation to hemangiosarcoma, lymphangiosarcoma, or hemangioendothelioma.

Miscellaneous: On the same day that the president of France, Marie François Sadi Carnot, made Ollier commander of the Légion d'Honneur (June 24, 1894), Carnot was stabbed to death by an Italian anarchist. Although Ollier was summoned to aid the president, there was nothing he could do to save him.

Anesthetic Considerations: Hemangiomas can be located in many sites, including the oropharynx and trachea (5).

Patients must be carefully positioned and padded perioperatively because of the risk of pathologic fractures related to enchondromas. The potential presence of (asymptomatic) perimedullary hemangiomas needs to be excluded if neuraxial block is being considered. The use of sequential venous compression devices over affected extremities during prolonged surgery might be considered to avoid stasis. Surgical disruption of hemangiomas can result in significant blood loss.

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Omodysplasia

MIM #: 164745, 258315

There appear to be two forms of this rhizomelic dwarfing disease, an autosomal dominant form and an autosomal recessive form. Common to the two forms are characteristic facies, growth defects of the distal humerus, and deformities of the elbows. In the autosomal dominant form, findings are restricted to the upper extremities. The gene and gene product of the autosomal dominant form are not known. Findings are more generalized in the autosomal recessive form, with severe dwarfism. This form is due to mutations in the gene *GPC6*, which encodes a heparin sulfate proteoglycan.

HEENT/Airway: Frontal bossing. Midline hemangiomas, short nose, depressed nasal bridge, long philtrum. May have short neck with short thyromental distance, large tongue, or hypoplastic mandible.

Cardiovascular: Can have congenital heart disease.

Neuromuscular: May have intellectual disabilities.

Orthopedic: Micromelic dwarfism. Short humerus with characteristic hypoplastic distal humerus. Radioulnar diastasis. Hypoplastic, everted humeral condyle. Clubbed proximal femurs. Limited extension of elbows and knees. Anterolateral radial head dislocation.

GI/GU: May have cryptorchidism or umbilical hernia.

Miscellaneous: "Omo" comes from the Greek for shoulder and is used to indicate a connection with the shoulder or scapula.

Anesthetic Considerations: Mandibular and neck findings may make laryngoscopy and intubation difficult. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Ondine's curse

Synonym: Central hypoventilation syndrome (Includes Haddad syndrome)

MIM #: 209880

This syndrome involves the failure of autonomic control of ventilation, particularly during sleep, which leads to complications of hypoventilation and chronic carbon dioxide retention. The syndrome may be genetic (congenital) or secondary to central nervous system

injury. In congenital cases, the abnormal respiratory drive usually becomes apparent in the neonatal period. Inheritance is autosomal recessive or autosomal dominant with reduced penetrance. There is also a strong association with Hirschsprung disease (see earlier), which has been referred to as **Haddad syndrome** or as Ondine-Hirschsprung disease. In congenital cases, there is rarely an intracranial anatomic defect to account for the disorder. It is thought that the disorder could be secondary to a problem with migration of neural crest cells. There is also a smaller association with other disorders of neural crest cells, including neuroblastoma and ganglioneuroma. A mutation in the *PHOX2B* gene (polyalanine expansion) has been most frequently associated with congenital central hypoventilation syndrome, but mutations in several other genes have been implicated as well, including *RET*, *GDNF*, *EDN3*, *BDNF*, and *ASCL1*. There can be significant clinical variability within families. The disease has presented as prolonged postoperative apnea as the initial finding (4).

HEENT/Airway: May have distinctive facial features such as downward-slanting palpebral fissures, low-set, posteriorly rotated ears, small nose, and triangular mouth. May have abnormalities of the eye including strabismus. Loss of upper airway patency with onset of central apnea.

Chest: The ventilatory response to carbon dioxide is blunted. Oxygen supplementation may exacerbate hypoventilation if the ventilatory drive depends on hypoxia. There has been some success with diaphragmatic

pacing.

Cardiovascular: Pulmonary arterial hypertension, cor pulmonale. Pulmonary arterial hypertension may be improved with supplemental oxygen. Autonomic control of the heart rate can also be defective.

Neuromuscular: Central autonomic ventilatory failure, particularly during sleep, resulting in apnea and hypoventilation. Hypoventilation may improve during REM sleep. Patients are somnolent and lethargic. Arcuate nucleus may be absent. Many have mild to moderate developmental delay. May have seizures. May have hypotonia.

GI/GU: Up to 50% of patients with Ondine's curse will also have Hirschsprung disease (see earlier). Esophageal motility is reduced.

Other: Erythrocytosis, in response to ventilatory failure. Inappropriate secretion of antidiuretic hormone with hyponatremic seizures has been reported. May be associated with neuroblastoma and ganglioneuroma. Both intermittent hyperglycemia and hypoglycemia, manifestations of autonomic dysfunction, have been reported in two small series.

Miscellaneous: The legend of Ondine dates from 15th-century Germany. Undine, the spirit of water, would acquire a soul, and mortality, on marrying a mortal. Her husband was cursed by the King of the Ondines for being unfaithful and from thence forward had to command actively every bodily function: “One moment of inattention and I shall forget to hear, to breathe” (12). Although the disease entity had been described earlier, the sobriquet of “Ondine's curse” is from Severinghaus and Mitchell.

Anesthetic Considerations: Patients frequently have had a tracheostomy placed for nighttime positive-pressure ventilation. Hypoventilation is exacerbated by anesthesia. The ventilatory response to carbon dioxide is blunted, and perioperative supplemental oxygen may cause apnea. Patients usually require positive-pressure controlled ventilation during general anesthesia. It is convenient to have the patient's home ventilator available for use in the postanesthesia care unit. Patients should not receive opioid or other premedication unless they will be carefully monitored. The use of short-acting anesthetics of all classes would seem appropriate. Extubation should be delayed until patients are completely awake, and the patient should be observed closely for adequate ventilation after general anesthesia. Regional anesthesia would seem advantageous, if appropriate.

Patients have decreased esophageal motility and are therefore at risk for perioperative aspiration. Anticonvulsant medications need to be continued (or a parenteral form substituted) and may alter the metabolism of some anesthetic drugs, requiring more frequent dosing. Inappropriate secretion of antidiuretic hormone with hyponatremic seizures has been reported at least twice.

In patients with significant pulmonary arterial hypertension, cor pulmonale and cardiac failure may have developed. Recall that autonomic control of heart rate may also be impaired (8). Complete heart block after induction with propofol has been reported (9).

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Ophthalmoplegia plus

See Kearns-Sayre syndrome

Opitz syndrome

See Hypertelorism-hypospadias syndrome

Opitz-Frias syndrome

See Hypertelorism-hypospadias syndrome

Opitz G/BBB syndrome

See Hypertelorism-hypospadias syndrome

Opitz-Kaveggia syndrome

See FG syndrome

Opitz trigonocephaly syndrome

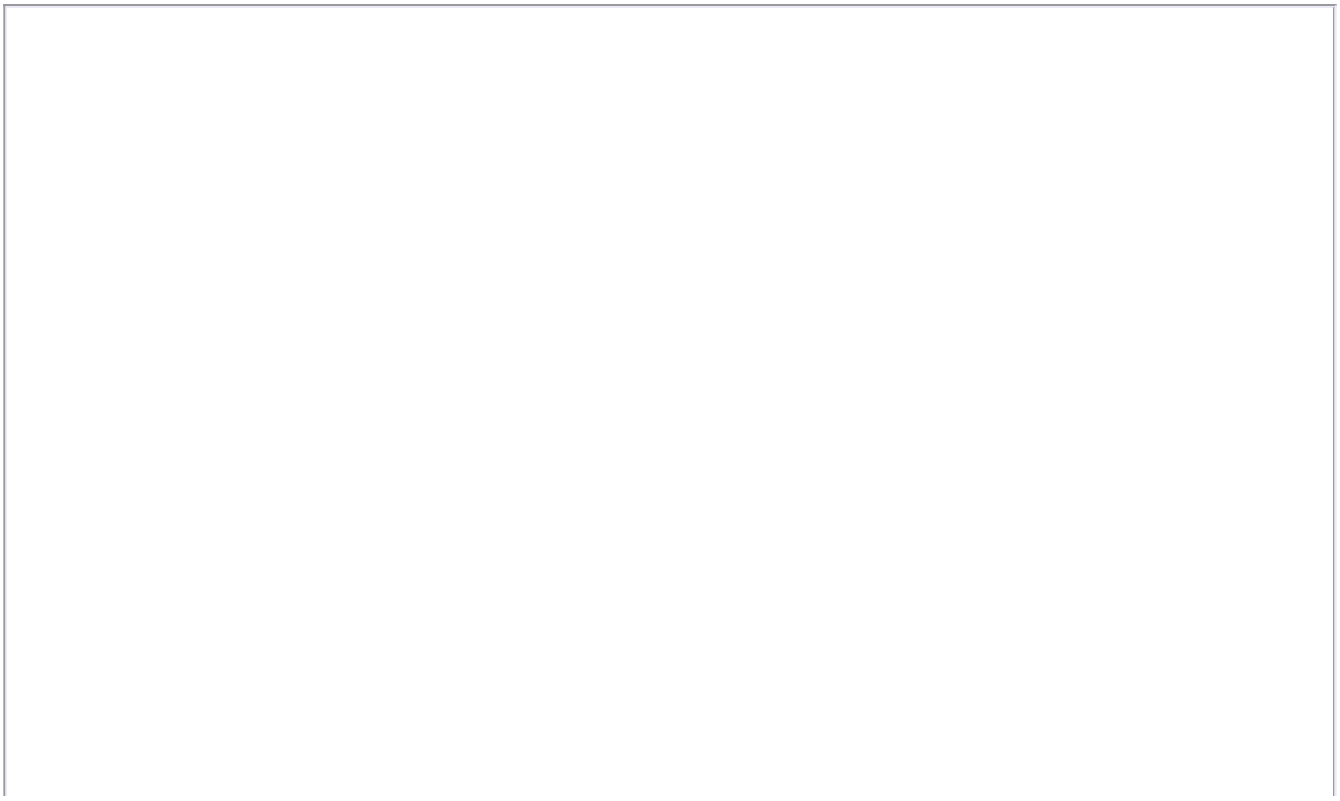
See C syndrome

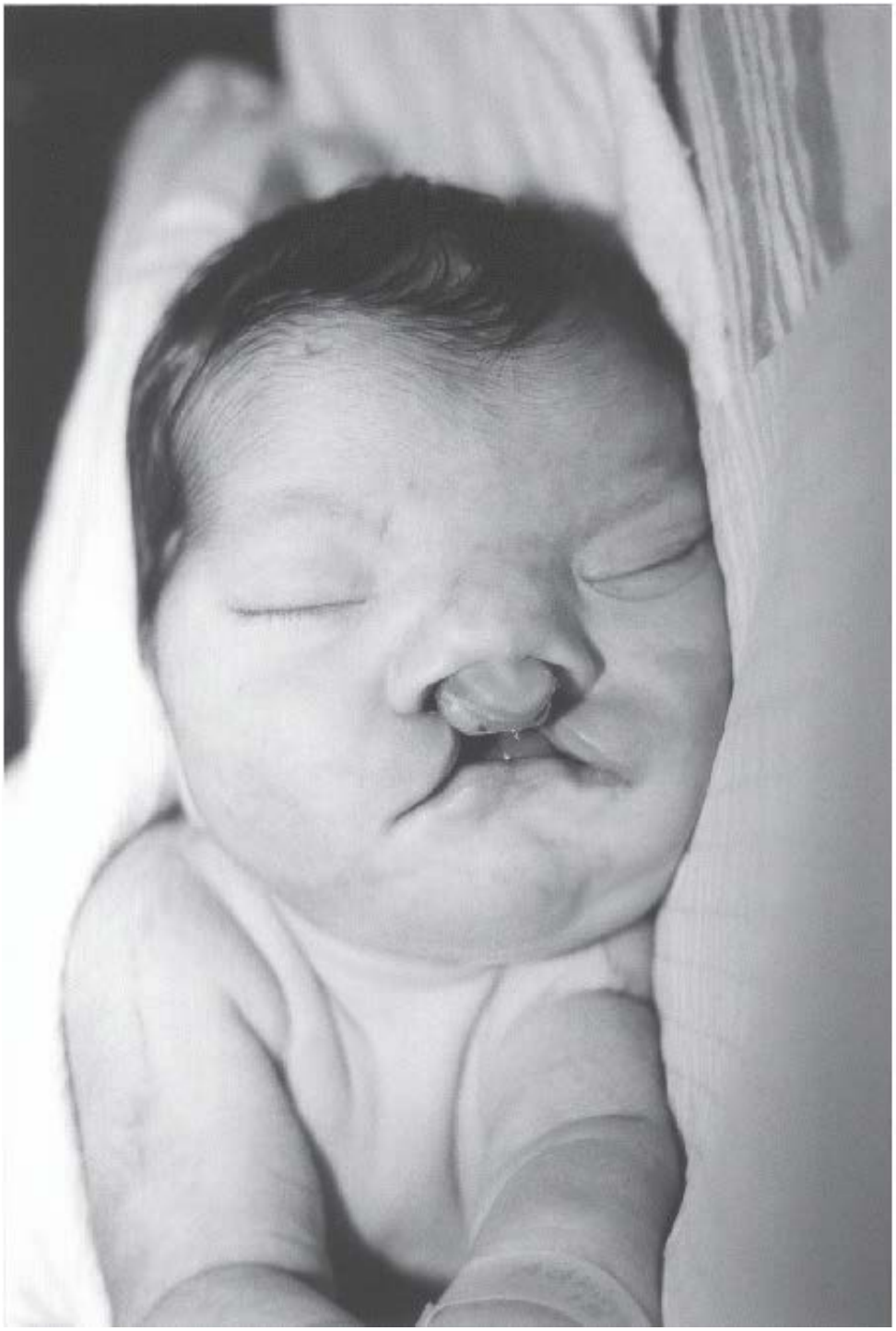
Oral-facial-digital syndrome, type I

(Includes oral-facial-digital syndromes, types III to XI)

MIM #: 311200

This X-linked dominant syndrome is characterized by oral frenula, oral clefts, hypoplastic alae nasi, and asymmetric shortening of the digits. Neurologic manifestations occur in up to 40% of patients. Most patients are female, suggesting X-linked dominant inheritance with lethality in boys. It is considered a ciliopathy as the responsible gene (*OFD1*, also known as *CXORF5*) encodes a centrosomal protein localized to the basal bodies at the origin of primary cilia. Mutations in this same gene can also cause one form of Joubert syndrome, X-linked Joubert syndrome (see earlier), and Simpson-Golabi-Behmel syndrome type 2 (see later).





Oral-facial-digital syndrome, type I. FIG. 1. An infant with oral-facial-digital syndrome type I showing cleft and widely spaced eyes.

There are at least eleven different oral-facial-digital syndromes with overlapping phenotypes. Oral-facial-digital syndrome type II is also known as Mohr syndrome (see earlier). The other nine types have only subtle clinical distinctions. They are listed here for completeness:

Type III (Sugarman syndrome)

MIM #: 258850

Autosomal recessive inheritance

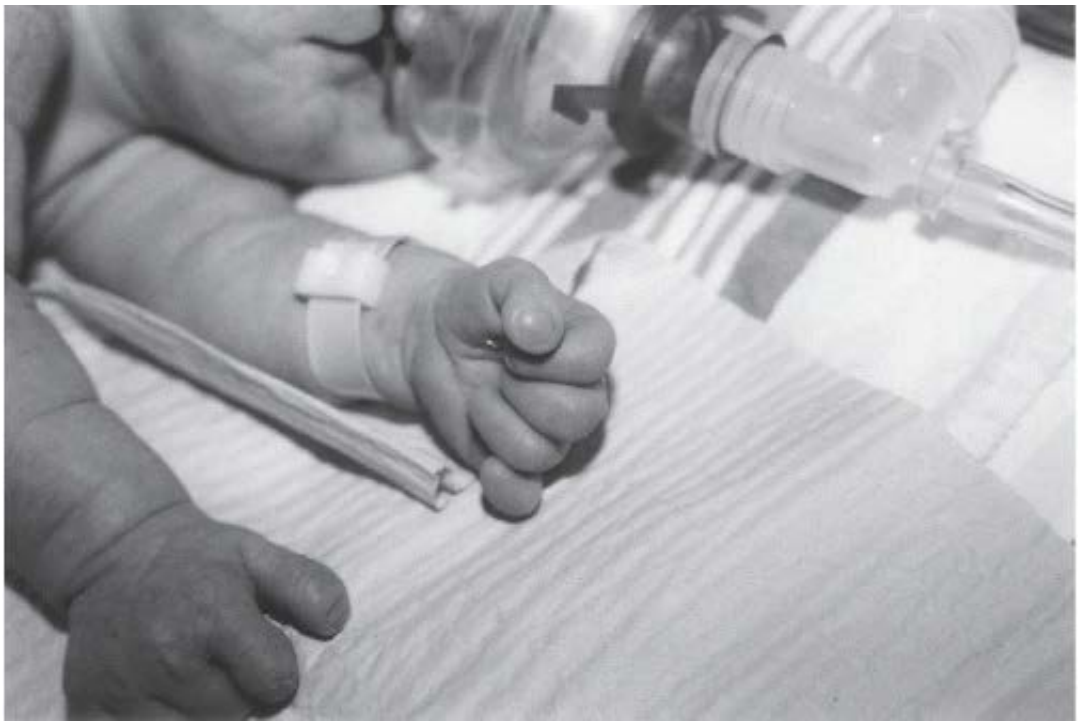
Intellectual disabilities, “metronome” eye movements

Type IV (Baraitser-Burn syndrome)

MIM #: 258860

Autosomal recessive inheritance

Tibial dysplasia, postaxial polydactyly, porencephaly



Oral-facial-digital syndrome, type I. FIG. 2. Short fingers with broad, hypoplastic nails.

Type V (Thurston syndrome)

MIM #: 174300

Autosomal recessive inheritance

Median cleft lip, postaxial polydactyly

Type VI (Varadi-Papp syndrome)

MIM #: 277170

Autosomal recessive inheritance

Metacarpal abnormalities, preaxial (toes) and postaxial (fingers) polydactyly, cerebellar abnormalities

Type VII (Whelan syndrome)

MIM #: 608518

X-linked dominant or autosomal dominant inheritance

Facial asymmetry, hydronephrosis

Type VIII

MIM #: 300484

X-linked recessive inheritance

Hypoplastic epiglottis and arytenoids

Type IX

MIM #: 258865

Autosomal or X-linked recessive inheritance

Retinal abnormalities

Type X

MIM #: 165590

Autosomal dominant

Fibular aplasia, radial shortening, tarsal coalescence

Type XI (Gabrielli syndrome)

MIM #: 612913

Inheritance pattern unknown

Odontoid hypoplasia, fused C2-C3 posterior arches, partial atlantooccipital synostosis

HEENT/Airway: Inner canthi are displaced laterally. Hypoplastic alae nasi. Midline cleft lip. Midline cleft tongue. Cleft alveolar ridge. Cleft palate. Papilliform protuberances on tongue. Tongue hamartoma. Hyperplastic frenulum. May have multiple oral frenula. Abnormal dentition, including missing lateral incisors, dental caries, enamel hypoplasia, supernumerary teeth. May have choanal atresia. May have mandibular hypoplasia. Rudimentary epiglottis.

Chest: Ciliary hypokinesia can result in recurrent respiratory infections.

Cardiovascular: Congenital heart disease is rare.

Neuromuscular: May have intellectual disabilities. May have agenesis of the corpus callosum, seizures, hydrocephalus. Heterotopic gray matter.

Orthopedic: Asymmetric shortening of the digits. Syndactyly, clinodactyly, or brachydactyly of the hands. Unilateral postaxial polydactyly of the feet. Irregular mineralization of the bones of the hands and feet.

GI/GU: Fibrocystic liver and pancreas. Polycystic kidney disease can develop. The incidence of renal failure increases with aging in adulthood. Ovarian cysts.

Other: Facial milia (a common benign rash) in infancy. Sparse hair. May have spotty alopecia.

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Carious teeth may be more easily dislodged during laryngoscopy. Small mandible and cervical spine abnormalities (type XI) could make laryngoscopy difficult. Choanal atresia may cause respiratory distress in neonates, and precludes the use of nasotracheal and nasogastric tubes. Patients with polycystic kidney disease may have renal insufficiency or failure, which affects fluid management and the choice of anesthetic agents.

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Oral-facial-digital syndrome, type II

See Mohr syndrome

Oral-facial-digital syndromes, types III-XI

Included in oral-facial-digital syndrome, type I

Ornithine carbamoyltransferase deficiency

See Ornithine transcarbamylase deficiency

Ornithine delta-aminotransferase deficiency

Synonym: OAT deficiency; Hyperornithinemia with gyrate atrophy of the choroid and retina

MIM #: 258870

This autosomal recessive disease is due to diminished activity of ornithine delta-aminotransferase, a mitochondrial enzyme involved both in ornithine synthesis and degradation. The hallmark is characteristic gyrate atrophy of the choroid and retina. This enzyme is pyridoxine dependent, and pyridoxine may be therapeutic in some patients.

There are multiple alleles that can cause this disease.

HEENT/Airway: Progressive retinal atrophy with myopia. The retinal lesions begin as small circular areas and gradually enlarge, coalesce, and extend to the posterior pole of the fundus. Decreased peripheral vision progressing to decreased night vision, and complete blindness by adulthood. Posterior subcapsular cataracts beginning in adolescence.

Neuromuscular: Normal intelligence. Tubular aggregates may be found in type 2 (fast-twitch) muscle fibers of skeletal muscle, but there is no documentable myopathy, although a few have mild proximal weakness. There is eventual atrophy of type 2 muscle fibers, but this occurs later than the eye changes. Electroencephalographic abnormalities without increased incidence of seizures. White matter degeneration.

Other: Hyperornithinemia. There may be a dibasic aminoaciduria. There is no associated hyperammonemia, at rest, after fasting, or with stress. Elevated ornithine levels inhibit the synthesis of creatine, and creatine phosphate deficiency is a concern. However, creatine supplementation has not been found to be helpful.

Anesthetic Considerations: There are no specific anesthetic considerations other than an awareness of the visual loss.

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Ornithine transcarbamylase deficiency

Synonym: Ornithine carbamoyltransferase deficiency

MIM #: 311250

This urea cycle defect is a partially dominant X-linked disorder, the only urea cycle defect that is not autosomal recessive. It is a potential cause of hyperammonemia. The urea cycle degrades amino acids to urea. Symptoms can be triggered by stress, such as surgery or infection, or episodes of protein catabolism, such as involution of the postpartum uterus. The clinical picture in heterozygous females is variable, from asymptomatic to severely affected, due to random X chromosome inactivation. Heterozygous, asymptomatic women are

at risk for hyperammonemic coma, particularly during the puerperium. The clinical picture of deterioration is reminiscent of Reye syndrome. Patients may be relatively asymptomatic and may spontaneously avoid protein-rich foods. Chronic treatment includes a low-protein diet and supplemental dietary arginine. Liver transplantation is curative. Onset of signs is usually within the first days of life, but delayed onset has been described and adults have presented with fatal perioperative cerebral edema. The variation in presentation is likely due to the number of different mutations that have been described.

Ornithine transcarbamylase deficiency. This 6½-year-old boy weighed 9 kg and had suffered a femur fracture from a minor fall. He also had profound developmental delay and hand contractures. He came to the operating room with sodium phenylacetate, sodium benzoate, and arginine infusions.

The clinical presentations of the urea cycle defects carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, and argininosuccinic acid lyase deficiencies are essentially identical. Pharmacologic therapy, using parenteral phenylacetate and sodium benzoate or oral phenylbutyrate, is aimed at scavenging ammonia by creating alternative pathways to excrete nitrogen precursors.

Neuromuscular: Chronic findings include episodic lethargy, irritability, and ataxia. Developmental delay. Seizures. Hyperammonemic encephalopathy is clinically similar to hepatic encephalopathy and proceeds through stages of lethargy and agitation to coma with cerebral edema. Sodium valproate can precipitate acute hyperammonemia.

GI/GU: Episodic vomiting. Hepatic synthetic function is normal, although there may be elevations in serum transaminases, both during and between episodes of hyperammonemia. Hepatic failure can be precipitated by sodium valproate. Recurrent pancreatitis has been reported.

Other: Failure to thrive. Respiratory alkalosis. Acrodermatitis. Episodes of hyperammonemia begin with anorexia and lethargy and may progress through agitation, irritability, and confusion. Vomiting and headaches may be prominent. Untreated, central nervous system deterioration ensues with worsening encephalopathy and eventually coma and death with cerebral edema. Diminished nitric oxide synthesis (derived from arginine, produced only in the urea cycle).

Miscellaneous: One boy was described who was very difficult with a “volcanic temper” and who became unconscious at age 14 years after a high-protein meal. After the diagnosis was made, he was treated with dietary modifications and became so improved that he was accepted to medical school (albeit a few years later). Hemodialysis and/or N-carbamylglutamate can be used to reduce ammonia levels acutely in emergent situations. A defect in this gene causes the “sparse fur” mouse.

Anesthetic Considerations: Patients should not fast preoperatively for more than a few hours. Patients should maintain a high carbohydrate intake (and low protein intake) perioperatively. Dehydration and catabolism are particularly detrimental. Intravenous glucose alone does not prevent the accumulation of amino acids but will minimize protein catabolism. In patients with intercurrent hyperammonemia, the perioperative maintenance intravenous solution should ideally contain sodium benzoate (0.25 g/kg/d), sodium phenylacetate (0.25 g/kg/d), and 10% arginine hydrochloride (0.21 g/kg/d). If patients have not already been on therapy, these should follow a loading dose (24 hours of drug). These drugs optimize alternate pathways (nonurea cycle) for waste nitrogen removal. This intravenous solution may result in potassium wasting, so serum potassium levels should be followed and potassium chloride added to the maintenance intravenous fluids as needed. Ammonia scavenging drugs have a high sodium content, so serum electrolytes need to be followed closely. An argument could be made for limiting other intravenous sodium sources, such as from isotonic intravenous fluid, but that remains unsettled. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load and trigger an acute exacerbation.

Acute metabolic encephalopathy can present after anesthesia and surgery. Acute metabolic encephalopathy may be associated with cerebral edema and increased intracranial pressure. Postoperative nausea and vomiting could represent an early sign of metabolic decompensation. Serum pH and ammonia levels should be followed throughout the perioperative period, and consideration should be given to postoperative observation in a pediatric intensive care unit. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Seizures should not be treated with sodium valproate, as this may precipitate acute hyperammonemia. Patients who are in stable condition (with mild disease) seem to tolerate minor surgical procedures well (2,4,5).

Figure: See **Appendix C**

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Oromandibular-limb hypogenesis

Synonym: Aglossia-adactyly syndrome; Hypoglossia-hypodactyly syndrome; Hanhart syndrome

MIM #: 103300

This sporadically occurring syndrome is characterized by hypoglossia, distal limb defects, and micrognathia. It has been hypothesized that the oromandibular-limb hypogenesis sequence is a consequence of fetal vascular disruption. The distal regions are most often affected, giving rise to tongue, distal limb, and mandibular abnormalities. In support of this hypothesis is the finding that fetal disturbance by chorionic villus sampling or uterine curettage during early pregnancy has been associated with an increased risk for development of this syndrome. Several subtypes have been described.

HEENT/Airway: Small mouth with hypoglossia or aglossia. May have epicanthal folds, hypodontia, cleft palate, aberrant attachment of the tongue. Absence of lower incisors. Micrognathia, retrognathia.

Neuromuscular: Intelligence is usually normal. May have Moebius sequence (see earlier) or isolated cranial nerve palsies, thought also to be secondary to *in utero* vascular disruption.

Orthopedic: Variable distal limb defects, particularly hypoplastic phalanges, adactyly, syndactyly.

GI/GU: May have “apple peel” bowel, thought to be due to disruption of the superior mesenteric artery *in utero*. One report of gastroschisis. May have splenogonadal fusion.

Miscellaneous: This syndrome was probably represented in a series of illustrations from 16th-century England. This is the oldest known report of oromandibular-limb hypogenesis.

Anesthetic Considerations: Microstomia and micrognathia may make tracheal intubation difficult, although the small or absent tongue may facilitate direct laryngoscopy and tracheal intubation (2). Dental abnormalities should be documented preoperatively. In the absence of a tongue, patients may have difficulty swallowing, and excess oral secretions may result. An antisialagogue may be indicated. Patients with facial (seventh cranial) nerve palsy may be unable to close their eyelids. The eyes must be protected perioperatively to avoid corneal abrasions.

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Orotic aciduria

MIM #: 258900, 258920

The classic autosomal recessive disease (orotic aciduria I) involves diminished activity of two enzymes, orotidine-5′-pyrophosphorylase and orotidine-5′-phosphate-decarboxylase. These enzymes catalyze the two final steps in pyrimidine synthesis, the conversion of orotic acid to uridine monophosphate. It seems that both enzyme activities reside on the same gene, that encoding UMP synthase (uridine monophosphate synthetase). Orotic aciduria II is thought to be due to inadequate orotodine-5′-phosphate-decarboxylase activity only, although that claim has been called into question. A putative third type is distinguished by the absence of the typical megaloblastic anemia. Orotic aciduria can also result from urea cycle defects, essential amino acid deficiency, Reye syndrome, and parenteral nutrition. The major clinical findings are megaloblastic anemia and complications from orotic acid crystal formation in the urine. Symptoms resolve after treatment with uridine.

Cardiovascular: There may be an increased incidence of congenital heart disease.

Neuromuscular: Psychomotor retardation, sluggishness.

GI/GU: Urinary obstruction from orotic acid crystals in the urine has been reported. This has occurred at the renal, ureteral, and urethral levels.

Other: Failure to thrive. Megaloblastic anemia unresponsive to vitamin B_{12} or folate, hypochromic microcytic anemia unresponsive to iron or pyridoxine. There may be a predisposition to severe infections with abnormal T-cell function, but the *in vitro* effects are variable and most patients do not have excessive problems with infectious diseases. Sparse, short hair.

Miscellaneous: When it is left standing, fine, needle-shaped crystals form in the urine. This disorder has also occurred in Japanese black cattle.

Anesthetic Considerations: A hematocrit should be obtained preoperatively. Perioperative fluid administration should be sufficient to maintain a reasonable diuresis to avoid increasing the concentration of urinary crystals, which may lead to urinary obstruction.

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Osgood-Schlatter disease

This is a fairly common, benign disorder involving pain and tenderness of the tibial tubercle in the preteen and early teenage years. Inflammation of the tibial tubercle at the point of insertion of the patellar tendon may be due to tiny stress fractures of the apophysis. Symptoms are exacerbated by vigorous running and jumping. Patients may need to limit vigorous exercise to control symptoms. The disease is usually self-limited and resolves with maturation and closure of the tibial growth plate. Occasionally, surgical treatment is indicated to ameliorate a painful ossicle.

Orthopedic: Swelling and point tenderness over the tibial tubercle. Radiographs of the knee are usually normal. May have increased external tibial torsion. Rarely, there is permanent prominence of the tibial tubercle as a sequela.

Anesthetic Considerations: There are no specific anesthetic implications. Patients may be on chronic anti-inflammatory drugs. Surgical treatment can sometimes be done under local anesthesia (1).

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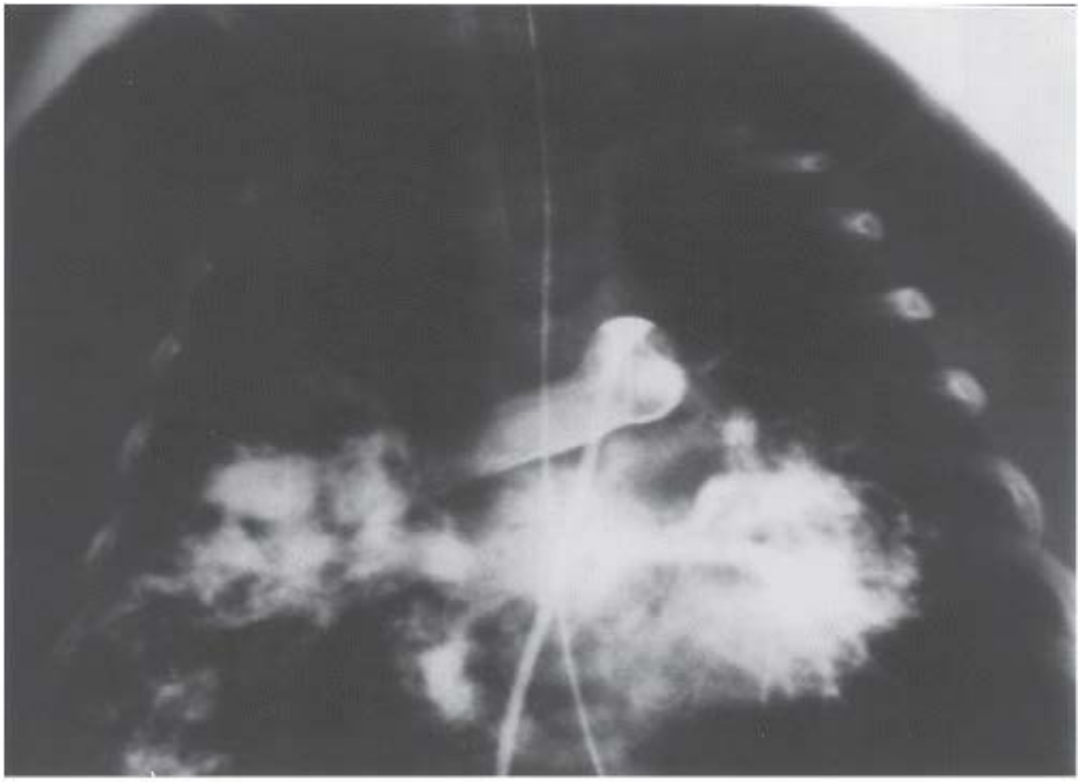
Osler-Weber-Rendu syndrome

Synonym: Hereditary hemorrhagic telangiectasia

MIM #: 187300

This autosomal dominant, highly penetrant vasculopathy is marked by multiple telangiectases of the skin, mucosa, and viscera. These telangiectases are prone to recurrent bleeding. Recurrent epistaxis is the most common type of bleeding, and hemorrhage may be significant. There may also be gastrointestinal, pulmonary, or intracerebral bleeding. Thirty percent of affected individuals require hospitalization for control of bleeding. Blood vessels in the telangiectatic areas have dilated, histologically abnormal vessel walls and are likely to form aneurysms or arteriovenous fistulae. Type 1 is due to mutations in the gene *ENG*, encoding endoglin [a transforming growth factor-beta (TGF-ß)-binding protein], and type 2 disease is due to abnormalities in the gene encoding activin-receptor-like kinase (*ALK1*). Mutations in the gene *ALK1* can also be responsible for familial primary pulmonary arterial hypertension. Both *ENG* and *ALK1* encode receptor proteins in the TGF-ß superfamily. Additional genes that encode components of the TGF-ß signaling pathway have also been invoked in the etiology of the syndrome. Arteriovenous malformations often can be successfully treated with transcatheter embolization. Pulmonary malformations greater than 3 cm can be coiled by interventional radiologists.



Osler-Weber-Rendu syndrome. Pulmonary arteriogram of a 4-day-old cyanotic infant showing massive left-sided and large right-sided pulmonary arteriovenous fistulae. Early drainage to the pulmonary veins and left atrium can be appreciated. This infant's systemic oxygen saturation was 56% while breathing 100% oxygen. His mother required a partial lung resection during pregnancy for worsening cyanosis, and his maternal grandfather died of a nosebleed.

HEENT/Airway: Telangiectases of the face, lips, tongue, nasopharynx, and conjunctiva. Can have retinal vascular malformations. Recurrent epistaxis (very common).

Chest: Pulmonary telangiectases are common. May have pulmonary bleeding. Pulmonary arteriovenous fistulae can cause significant systemic arterial desaturation from intrapulmonary right-to-left shunting.

Hypoxemia may worsen during pregnancy. Pulmonary arterial hypertension.

Cardiovascular: Pulmonary arteriovenous fistulae increase the risk of paradoxical emboli. Large shunts through hepatic or pulmonary arteriovenous fistulae have resulted in high-output congestive heart failure. Recurrent hemopericardium and hemothorax have also been reported.

Neuromuscular: Neurologic complications most frequently result from pulmonary arteriovenous fistulae with paradoxical emboli or brain abscess formation. Other causes of neurologic complications include vascular malformations (arteriovenous fistulae or aneurysms) of the brain or spinal cord, bleeding from intracerebral telangiectases, or hypoxemic injury secondary to pulmonary arteriovenous fistulae. The incidence of spinal arteriovenous malformations is approximately 1% to 2%. Increased incidence of migraine headaches.

Orthopedic: Fingertip and nail bed telangiectases. Clubbing (pulmonary hypertrophic osteoarthropathy) with chronic cyanosis.

GI/GU: Gastrointestinal, hepatic, and bladder telangiectases. Gastrointestinal bleeding. Hepatic arteriovenous fistulae; most are asymptomatic. May develop hepatic cirrhosis. Liver transplantation has on occasion been required.

Other: Pregnant patients are more likely to bleed. Patients may be anemic from repeated hemorrhage. Patients may be taking oral iron or oral estrogen, which has been found to improve the integrity of the telangiectatic vessel walls. Increased tissue plasminogen activator in abnormal endothelium can impair thrombus formation when bleeding begins. Patients with severe recurrent epistaxis may be receiving intranasal tranexamic acid. Other drugs which have shown preliminary benefit include bevacizumab, an anti-VEGF antibody, and thalidomide. Arteriovenous malformations can serve as a nidus for endocarditis.

Miscellaneous: This disorder was differentiated from hemophilia by Rendu in 1896 and further described by Osler in 1901, who emphasized the familial nature. Weber expanded the clinical description in 1907. The term “hereditary hemorrhagic telangiectasia” was introduced in 1909 by Hanes, a medical student, but the triple eponym is still more commonly used when referring to this syndrome. There is an increased incidence in African Caribbean inhabitants of Bonaire and Curaçao. For students of Greek-inspired grammar, the individual lesion is a telangiectasis, the plural is telangiectases, and the process is telangiectasia.

Osler was the leading international medical figure of his time. He was a Canadian who was appointed to the chair of medicine at the University of Pennsylvania and then became one of the founding figures at the Johns Hopkins University School of Medicine, serving as the first professor of medicine there. He became Regius Professor at Oxford 16 years later and was made a baronet in 1911. Osler married Grace Gross, a great-granddaughter of Paul Revere of American Revolution fame, and they named their son Revere in honor of his great-great-grandfather.

F. Parkes Weber was a British physician who had an interest in rare disorders and uncommon syndromes. Weber's father came from Germany to Britain (where he became physician to Queen Victoria), and Weber continued to pronounce his last name with the “W” pronounced as the Germanic “V.” He had an encyclopedic knowledge of rare disorders. It is said that when, at a meeting of the Royal Society of Medicine, he first announced that he had not heard of a certain syndrome, such cheers and applause broke out from the audience that the meeting had to be abandoned. He wrote a total of 1200 medical papers.

Henri Rendu was a prominent French physician, who also held a doctorate in geology. He served as a surgeon to the army in the Franco-Prussian war. He published over 100 medical articles.

Anesthetic Considerations: Nasal intubation, nasal trumpets, and nasogastric tubes are contraindicated because of the likelihood of nasopharyngeal telangiectases and the consequent risk of bleeding. Care must be taken to avoid trauma to oral telangiectases during laryngoscopy. Consider lubricating the laryngoscope and endotracheal tube. Consider downsizing the endotracheal tube. Adhesive tape should be avoided on lips that have telangiectases. Consider deep extubation to avoid localized pharyngeal trauma with emergence. Bleeding may be severe enough that transfusion is required (1). Consider prophylactic antifibrinolytic. Abnormal vessels will not respond normally to vasoconstrictors (e.g., phenylephrine).

Intravenous catheters need to be kept free of air bubbles because of the risk of right-to-left shunting through pulmonary arteriovenous fistulae. Because these fistulae tend to be in the lower lobes, postural changes in the degree of shunting often result in increased oxygen saturation in the supine position versus the upright position, and saturations can improve from an enlarged gravid uterus compressing the lower lobes when the pregnant patient is supine. Large rapid hemodynamic shifts can be of concern in the presence of intracranial arteriovenous malformations.

anesthesia, and complications from neuraxial anesthesia have been reported.

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Osteitis fibrosa cystica

See McCune-Albright syndrome

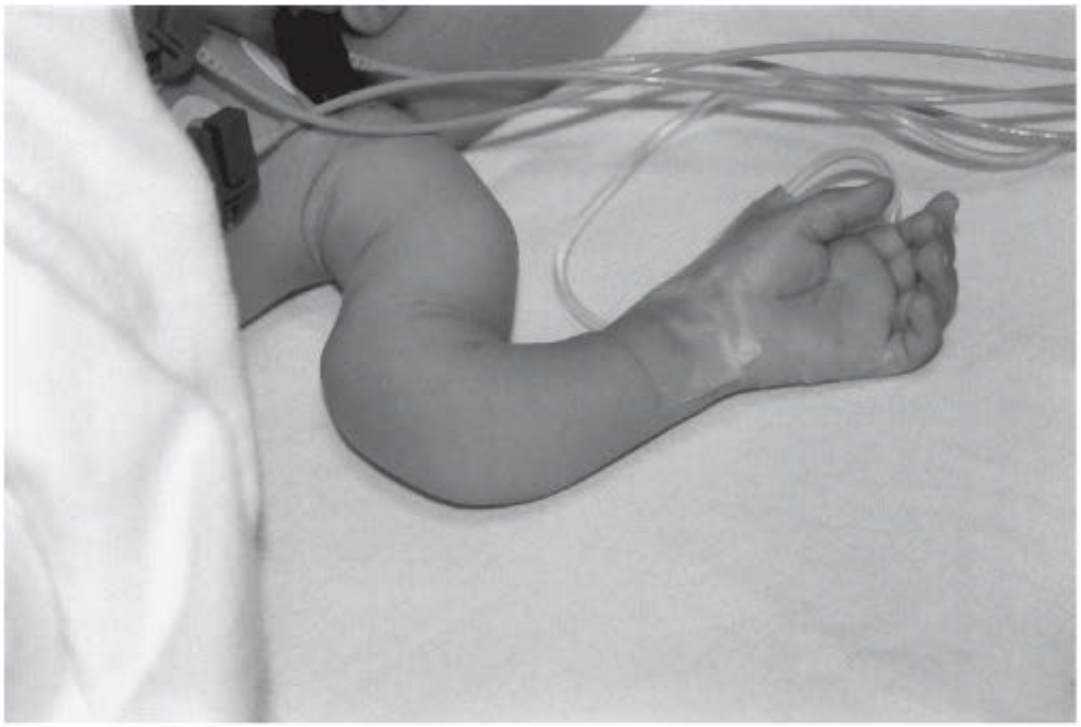
Osteochondromatosis syndrome

See Ollier disease

Osteogenesis imperfecta

MIM #: 166200, 166210, 259420, 166220

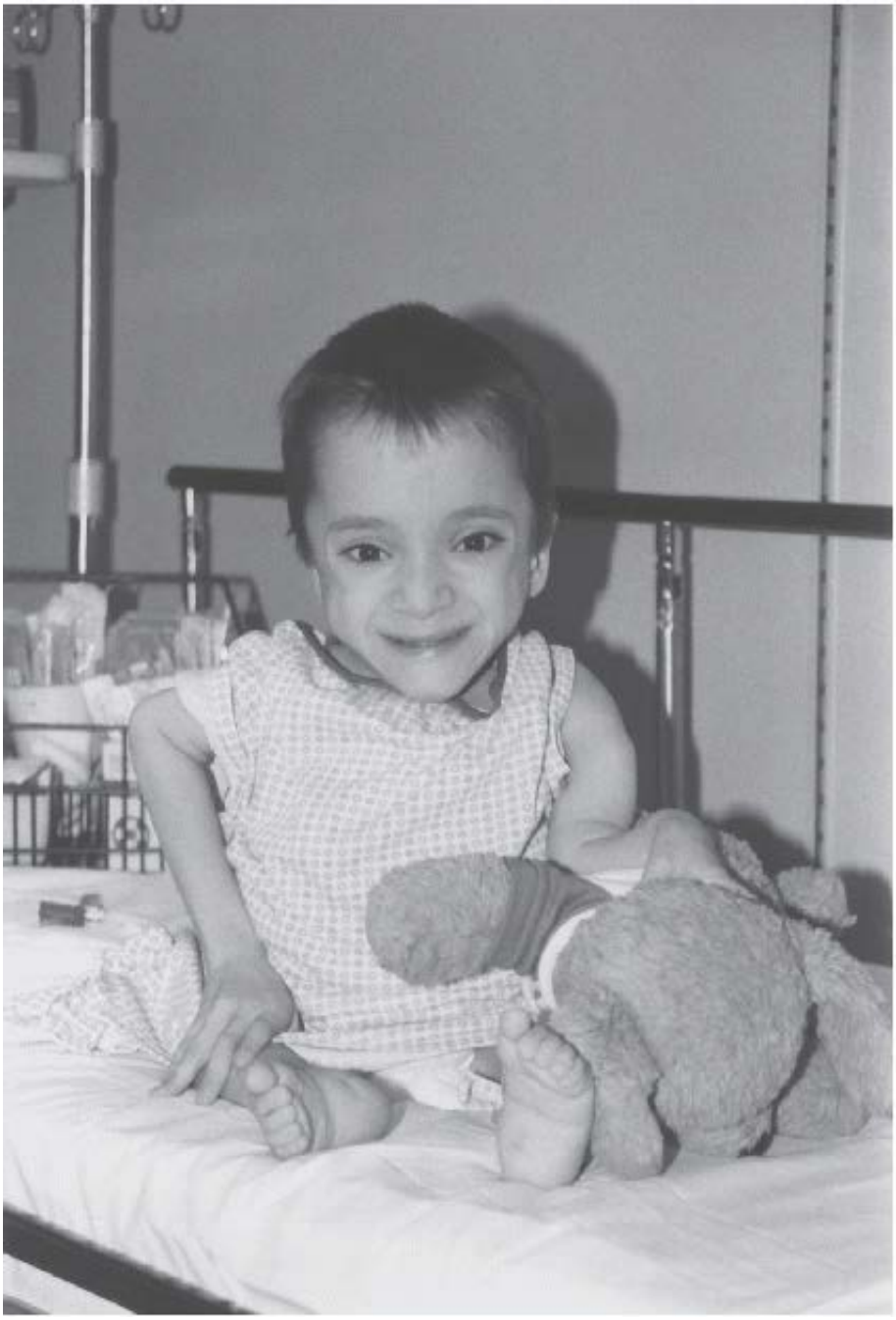
Osteogenesis imperfecta (OI) is a disorder in which the bones are extremely fragile and can be fractured easily, even with only minor trauma. Four types of osteogenesis imperfecta have been delineated. The genetic abnormality in these types of osteogenesis imperfecta is a mutation in one or both of the genes for type 1 collagen, *COL1A1 or COL1A2*. Bisphosphonates have been used in preliminary studies in children with severe disease, and mutant gene inactivation using mesenchymal stem cells has been proposed. Although 4 clinical types are widely accepted, a total of 15 types, involving abnormalities in over 30 genes, has been described.



Osteogenesis imperfecta. FIG. 1. The arm of a young child with osteogenesis imperfecta type III. It has already been deformed by multiple fractures.

Type I OI, the most common and fortunately the mildest form, is inherited in an autosomal dominant fashion and is characterized by blue sclerae, fragile bones, hyperextensible joints, progressive conductive

hearing loss, and dentinogenesis imperfecta. There is variability in expression, but most patients have fractures during childhood, but not as neonates. The incidence of fractures remains stable through puberty and then decreases in adulthood with a resurgence in postmenopausal women and men over 60.



Osteogenesis imperfecta. FIG. 2. This 28-inch tall (71 cm), 8-year-old boy weighs 8 kg. He has osteogenesis imperfecta type III.

Type II OI is lethal either *in utero* or in the perinatal period. It is characterized by blue sclerae; growth retardation; short, bent limbs with multiple fractures; and severe thoracic cage abnormalities. If not stillborn, most patients die in the neonatal period of respiratory insufficiency. Inheritance may be autosomal recessive or autosomal dominant lethal.

Type III OI is inherited in an autosomal dominant fashion and is characterized by blue sclerae at birth that thereafter normalize, multiple fractures, and progressive bony deformities. Patients usually die in childhood or adolescence as a consequence of cardiorespiratory complications. A rare autosomal recessive form of type III OI has been described.

Type IV OI is inherited in an autosomal dominant fashion and is characterized by bony fragility and multiple fractures without the scleral, audiologic, and dental abnormalities of type I OI. As in type I OI, there is improvement after puberty, and fractures are uncommon in adults.

HEENT/Airway: *Type I OI:* Can have wormian bones. Blue sclerae. Progressive conductive hearing loss—40% of adults need a hearing aid. Tinnitus and/or vertigo in adulthood. May have dentinogenesis imperfecta—hypoplasia of dentin resulting in translucent yellow teeth, which are prone to the development of caries.

Type II OI: Poorly mineralized, soft skull with large fontanelles, and wormian bones. Blue sclerae. Apparent hypotelorism, shallow orbits. Low nasal bridge, small, beaked nose. No deafness.

Type III OI: Macrocephaly with frontal bossing and triangular facies. Poorly mineralized skull with wormian bones. Large anterior fontanelle. Blue sclerae in infancy become progressively less blue with age. Hearing loss is rare. Dentinogenesis imperfecta. Micrognathia.

Type IV OI: Wormian bones. Normal sclerae (may be bluish during infancy). Hearing loss from osteosclerosis. Rare dentinogenesis imperfecta.

Chest: *Type I OI:* Severe kyphoscoliosis can lead to restrictive lung disease and respiratory compromise.

Type II OI: Severe thoracic cage abnormalities cause fatal respiratory insufficiency. Beaded ribs.

Type III OI: Severe kyphoscoliosis can lead to restrictive lung disease and respiratory compromise. Thin ribs.

Cardiovascular: *Type I OI:* May have aortic root dilation, aortic insufficiency, mitral valve prolapse. Rare pulmonary hypertension and cor pulmonale from severe kyphoscoliosis.

Type III OI: Rare cor pulmonale from severe kyphoscoliosis.

Neuromuscular: *Type II OI:* Hypotonia, variable hydrocephalus.

Orthopedic: *Type I OI:* Near normal stature. Osteopenia. Fractures heal rapidly, with evidence of good callus formation and generally without deformity. However, deformities of the limbs secondary to fractures occur—particularly bowing of the femurs and tibias. Metatarsus varus, flat feet. Mildly hyperextensible joints. Progressive kyphoscoliosis.

Type II OI: Fractures at birth. Short, thick long bones with multiple fractures and callus formation. The limbs, particularly the lower extremities, are bent. Flattened vertebrae.

Type III OI: Short limb dwarfism apparent at birth. Short stature. Osteopenia. Can have *in utero* fractures. Multiple fractures and progressive deformities of the limbs and the spine with kyphosis and scoliosis.

Type IV OI: Short stature. Fractures can occur *in utero*, during delivery or in the neonatal period. Incidence decreases and then increases with ambulation, decreasing with puberty and increasing after menopause. Varying degree of multiple fractures, bony deformities. Bowing of the lower limbs. Kyphosis. Scoliosis. Vertebral abnormalities.

GI/GU: *Type I OI:* May have inguinal hernias.

Type II OI: May have inguinal hernias.

Other: *Type I OI:* Thin, easily bruised skin. May have functional platelet abnormality, which is usually not clinically significant, but which has been shown to cause increased bleeding after cardiac and other surgery. This can occur in the face of normal tests of coagulation and is thought to be due to capillary strength and the effects of the abnormal collagen on platelet-endothelial interaction. May have hyperthyroidism.

Type II OI: Very thin skin. Can have fetal hydrops.

Anesthetic Considerations: Significant perioperative morbidity results from the extreme bony fragility. Hyperextension of the neck may result in a fracture. The mandible may be fractured during laryngoscopy. Succinylcholine-induced fasciculations may cause fractures. In particular, positioning the patient for surgery may result in a fracture. Even inflation of the blood pressure cuff has resulted in fractures, and in severe cases of osteogenesis imperfecta, the anesthesiologist may decide not to use a blood pressure cuff. Alternatively, an arterial catheter may be used.

The larynx can be difficult to visualize secondary to distortion from thoracic kyphoscoliosis or decreased

neck mobility. The laryngeal mask airway (LMA) and the intubating LMA have both been used successfully (4,10,11), as have awake fiberoptic and fiberoptic laryngoscope techniques. Patients with dentinogenesis imperfecta are at increased risk for perioperative tooth loss. These patients should have their dental abnormalities documented preoperatively. Consideration should be given to using a mouth guard to protect the teeth. Some patients with type I OI may have excessive bleeding secondary to friable tissues and platelet dysfunction, and desmopressin (DDAVP) was utilized successfully in one patient (5). Cesarean section is often required due to cephalopelvic disproportion or a fetus with OI. Regional anesthesia, including spinal or combined spinal and epidural, has been reported for cesarean section. Spinal anesthesia has been used in an adult with type IV OI (6), and caudal anesthesia has also been used successfully (14). However, bear in mind that the full implications of the coagulopathy associated with this disease have not been delineated. Given the short stature associated with severe disease, epidural dosing should be incremental. Patients with cardiac disease should receive an appropriately tailored anesthetic. There is a risk of bisphosphonate-associated osteonecrosis of the jaws after dental surgery.

Several patients have reportedly experienced a perioperative hypermetabolic state with fever (4,18,19). It is generally thought that this does not represent malignant hyperthermia (13). It may be related to high levels of thyroid hormone. One patient has developed lactic acidosis during total intravenous anesthesia using propofol (8).

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Osteopetrosis

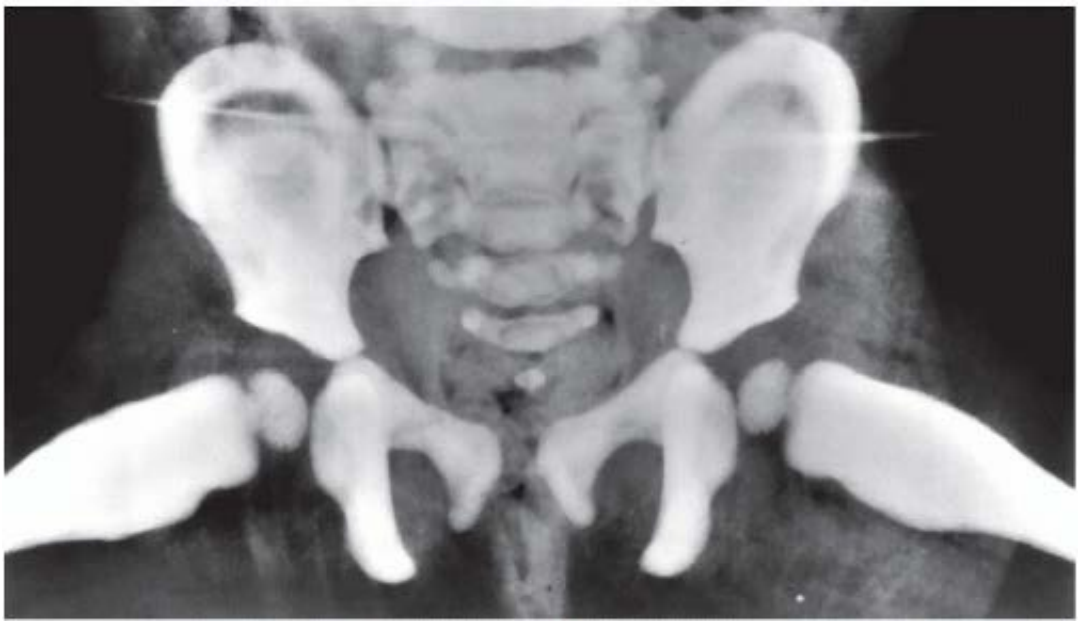
Synonym: Albers-Schönberg disease

MIM #: 166600, 259700, 259710, 607634

This disease of bone occurs in autosomal dominant and autosomal recessive forms, and more than a dozen genetically distinct subtypes have been described. Osteopetrosis results from defective osteoclastic resorption of immature bone. The autosomal dominant form is much more common and is more benign, with an expected normal life span. It can be caused by mutations in a variety of genes, including *LRP5* and *CLCN7*. Cardinal features are bony fragility and bony overgrowth, dental abscesses, and osteomyelitis, particularly of the mandible. Bone resorption requires acidification of the subosteoclastic resorption lacuna. The autosomal recessive form, although less common, is much more debilitating and uniformly lethal before adolescence. It is also caused by mutations in a variety of genes, including *TCIRG1* and *TNFSF11*. In addition to bony fragility and overgrowth, the recessive form involves secondary pancytopenia, cranial nerve compression, and visual impairment. The prognosis is poorest in patients with early onset of hematologic and ocular defects. Death is usually a result of anemia, bleeding, or overwhelming infection. Steroids, high-dose calcitriol, or interferon gamma therapy may be beneficial. Bone marrow and hematopoietic stem cell transplantation is being offered as a potentially curative therapy for this disorder (1) because it leads to restoration of osteoclast function. The autosomal recessive form is described here in detail.

HEENT/Airway: Macrocephaly. Frontal bossing. Bone growth leading to proptosis may cause extraocular

muscle paralysis or dysfunction of the optic nerve, leading to blindness. Retinal degeneration in autosomal dominant disease. Chronic nasal stuffiness. Obtuse mandibular angle may develop. Mandibular osteomyelitis. Teeth erupt late, are distorted, and are prone to early decay and loss. Dental abscesses. High-arched palate. Obstructive sleep apnea.



Osteopetrosis. FIG. 1. Osteopetrosis. Pelvic radiograph showing markedly increased bone density (Courtesy of the Division of Pediatric Radiology, University of Virginia Health System).

Neuromuscular: Bone growth causing compression of the cranial nerves may lead to deafness, vestibular nerve palsy, or other cranial nerve dysfunction. Increased intracranial pressure from bone growth into the cranial space. Intellectual disability is common.

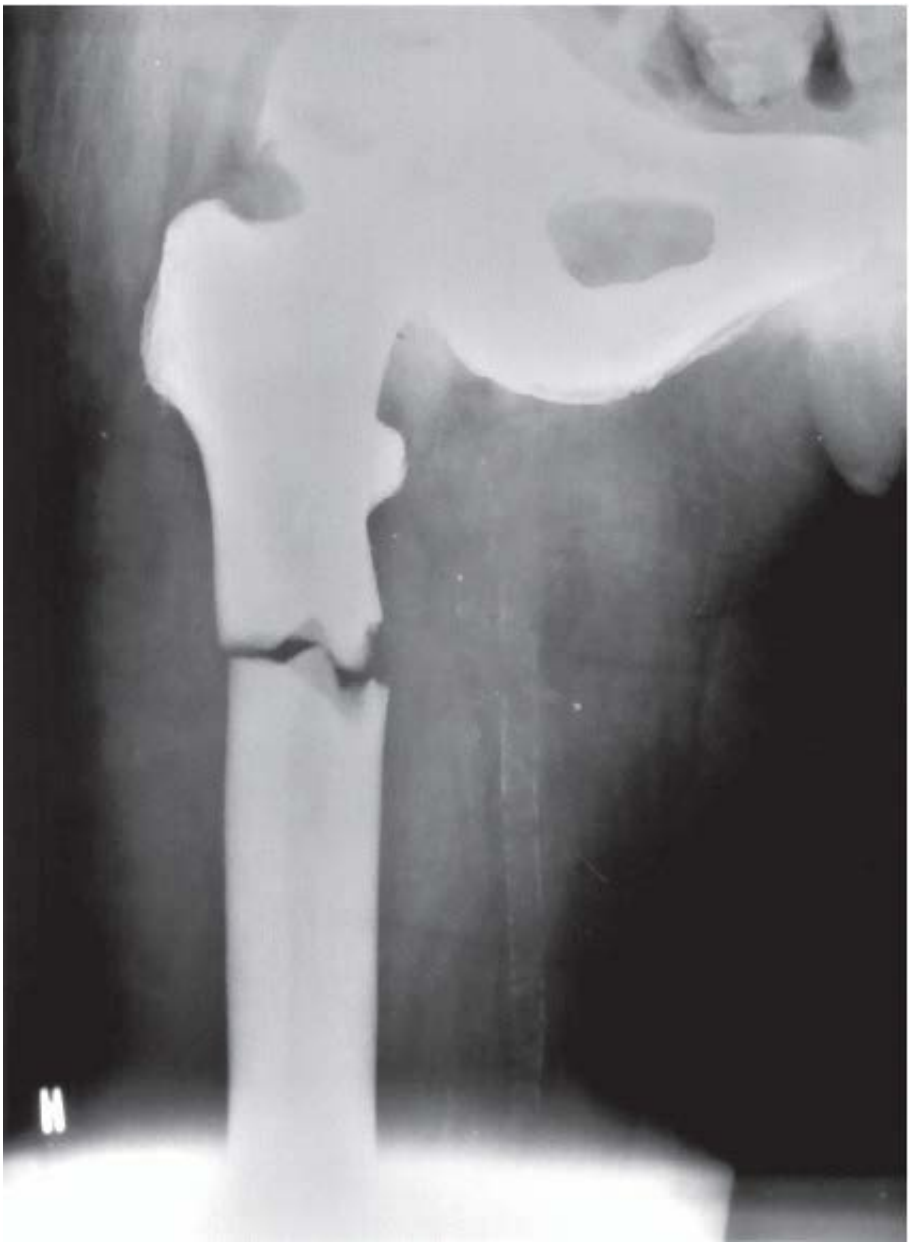
Orthopedic: Bone is thick, dense, and fragile. Pathologic fractures are common, including cervical vertebrae. Upper and lower end-plate sclerosis of vertebral bodies has been referred to as “sandwich vertebrae” or “rugger jersey spine” on radiographs. Osteomyelitis. May have carpal tunnel syndrome.

Patients with autosomal dominant disease have bone pain, osteoarthritis of the hip, and osteomyelitis—particularly of the jaw.

GI/GU: Hepatosplenomegaly secondary to compensatory extramedullary hematopoiesis.

Other: Recessive disease can result in fetal demise. Bone growth causes bone marrow obliteration and leads to secondary pancytopenia. Serum calcium levels may be low, and serum phosphorus and alkaline phosphatase may be elevated.

Miscellaneous: Despite the hyphenated eponym, Heinrich Albers-Schönberg was one person. He was a German radiologist at the turn of the last century. In 1904, Albers-Schönberg received the Grand Prize at the world fair in St. Louis because of the quality of his diagnostic X-rays. In a not uncommon scenario for the early radiologists, he contracted radiation-induced tumors. He eventually required amputations and lost the use of both arms. He requested that the results of his autopsy (at age 56 years) be published for the use of others.



Osteopetrosis. FIG. 2. Pathologic fracture through dense bone (Courtesy of the Division of Pediatric Radiology, University of Virginia Health System).

Anesthetic Considerations: The hematocrit and platelet count should be evaluated preoperatively. Care must be taken in positioning the patient because bones are fragile and prone to fracture. Limited mandibular joint movement may make oral intubation difficult (1), and bony encroachment on the nasal turbinates may preclude nasal intubation (3). Airway complications related to a restricted oropharynx and nasopharynx are not uncommon (1) and are likely related to the increased incidence of obstructive sleep apnea. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Periodontal attachment is poor, leading to risk of tooth loss. Hypercapnia should be avoided in the presence of increased intracranial pressure. Hypocalcemic seizures or tetany may occur. Patients may have abnormal white cell and macrophage function, so are at risk for infection. Patients may be taking

steroids and should receive stress doses of steroids perioperatively. Postoperative mortality is increased in these children (5).

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Otopalatodigital syndrome, type I

Synonym: Taybi syndrome

MIM #: 311300

This X-linked disorder is characterized by hearing loss, cleft palate, and broad thumbs and great toes with short nails. Female carriers have mild clinical expression. Like otopalatodigital syndrome, type II (see later), it is caused by a mutation in the gene encoding filamin A (*FLNA*), an actin-binding protein. There are four otopalatodigital syndromes caused by mutations in *FLNA*. The other three are frontometaphyseal dysplasia (see earlier); otopalatodigital syndrome, type II (see later); and Melnick-Needles syndrome (see earlier), and the four syndromes constitute a phenotypic spectrum. Note that this syndrome is distinct from the more widely known Rubinstein-Taybi syndrome.

HEENT/Airway: Thickened base of skull and frontal bone with frontal bossing, delayed closure of anterior fontanelle. Occipital prominence. Absent frontal and sphenoid sinuses. Facial bone hypoplasia. Hypertelorism. Conductive hearing loss. Broad nasal root, small nose. Small mouth, missing teeth, impacted teeth, small tonsils. Cleft palate. Can have micrognathia. Tracheomalacia has been reported in two families.

Chest: Pectus excavatum.

Neuromuscular: Mild intellectual disability. Delayed speech.

Orthopedic: Small stature. Broad thumbs and great toes. Large gap between first and second toes. Other digits may also be broad. Short nails. Second ossification center at the base of both the second metacarpal and

metatarsal. Clinodactyly. Limited elbow extension, dislocation of the radial head (“nursemaid's elbow”). Bowed tibia. Small iliac crests. May have dislocated hips, limited knee flexion. May have scoliosis.

Anesthetic Considerations: Recall that most patients have significant hearing loss. Dental abnormalities should be documented preoperatively. Small mouth, micrognathia, and/or cleft palate could make laryngoscopy difficult. Postoperative respiratory arrest (occurring 5 hours after surgery) was reported in a child and was thought to be secondary to brainstem compression from the thickened skull base (3).

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Otopalatodigital syndrome, type II

Synonym: Cranioorofacial digital syndrome

MIM #: 304120

This X-linked syndrome is characterized by hearing loss, cranial and facial abnormalities, cleft palate, digital abnormalities, and bowing of the long bones. The manifestations in male patients are much more severe than in otopalatodigital syndrome, type I, an allelic disorder. Most male patients are stillborn or die in infancy secondary to respiratory failure. Female carriers have only mild manifestations of the syndrome. Like otopalatodigital syndrome, type I (see earlier), it is caused by a mutation in the gene encoding filamin A (*FLNA*). There are four otopalatodigital syndromes caused by mutations in *FLNA*. The other three are frontometaphyseal dysplasia (see earlier), otopalatodigital syndrome I (see earlier), and Melnick-Needles syndrome (see earlier), and the four syndromes constitute a phenotypic spectrum.

HEENT/Airway: Microcephaly. Prominent forehead, wide sutures, late closure of anterior fontanelle. Flat midface. Hypertelorism, downward-slanting palpebral fissures. Abnormal, low-set ears. Conductive hearing loss. Flat nasal bridge. Very small mouth. May have dental abnormalities. Cleft palate. Severe micrognathia.

Chest: Pectus excavatum. Small thorax with irregular clavicles and ribs. Respiratory insufficiency commonly develops.

Neuromuscular: May have intellectual disabilities. May have cerebellar hypoplasia, hydrocephalus. Arnold-Chiari and Dandy-Walker malformations have been reported.

Orthopedic: Growth deficiency. Short, broad thumbs and great toes. Flexed, overlapping fingers. Hypoplastic phalanges. Abnormal proximal phalangeal epiphyses. Postaxial polydactyly, syndactyly, clinodactyly,

brachydactyly. Short first metacarpal, extra bone in the capitate-hamate complex. Bowed radius, ulna, femur, tibia. Hypoplastic fibula. Subluxation at elbows, wrists, and knees. Small iliac crests. Hip dislocation. Rocker-bottom feet. May have abnormalities of the cervical spine, flattened vertebrae.

GI/GU: May have omphalocele. May have cryptorchidism, hypospadias, hydronephrosis, hydroureter.

Anesthetic Considerations: Most patients have severe restrictive lung disease and are at risk for perioperative respiratory failure. Clavicular anomalies may make placement of a subclavian venous catheter and an infraclavicular block more difficult. Direct laryngoscopy and tracheal intubation are difficult secondary to the very small mouth and very severe micrognathia. Recall that most patients have significant hearing loss. Dental abnormalities should be documented preoperatively. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities, which predispose to renal insufficiency.

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Oxalosis

Synonym: Hyperoxaluria

MIM #: 259900, 260000, 613616

There are three separate autosomal recessive disorders that can present with excessive production and excretion of oxalic acid. Type I disease, by far the more common, is due to an abnormality in the enzyme alanine-glyoxylate aminotransferase (AGXT or AGT), which should be present in liver peroxisomes. There may be three abnormalities: no AGXT protein in hepatocytes, inactive AGXT protein in peroxisomes, and AGXT protein misdirected to mitochondria instead of peroxisomes. In the absence of adequate peroxisomal AGXT, glyoxylate is not metabolized to less toxic metabolites but is instead converted to oxalate and glycolate. Oxalate is renally excreted, and excessive amounts of oxalate lead to the formation of calcium oxalate crystals in the urine and deposition in various tissues. Type II disease is due to a defect in hydroxypyruvate metabolism due to a lack of glyoxylate reductase-hydroxypyruvate reductase (GPHPR), which results in its conversion to l-glyceric acid with eventual formation of oxalate. Type II is the least clinically severe type. Type III disease is due to mutations in the hepatic-specific mitochondrial gene 4-hydroxy-2-oxoglutarate aldolase (*HOGA*). Other causes of hyperoxaluria include ingestion of ethylene glycol or ascorbic acid, pyridoxine deficiency (a cofactor for the enzyme AGXT), resection or disease of the terminal ileum, or other fat malabsorption. It is thought that excessive fatty acids compete with oxalate for intestinal calcium, leaving oxalate to form salts more soluble than calcium oxalate, with increased absorption.

Treatment of oxalosis includes chronic diuresis with a diuretic, administration of magnesium and phosphates (limiting calcium oxalate stone formation) and ascorbic acid, and avoidance of oxalate-rich foods. Oxalate is found in high concentrations in leafy plants such as spinach and rhubarb, in cocoa, and in tea. Its high concentrations in some ornamental plants have led them to be classified as toxic. Pyridoxine has helped a few patients with type I disease. Dialysis does not remove oxalate adequately, and patients on dialysis have extrarenal oxalate deposits. Combined hepatic and renal transplantation (or isolated hepatic transplantation if done early) is curative. Liver cell transplantation as a bridging technique has been used in an infant for whom hepatic transplantation was not feasible.

HEENT/Airway: There may be deposits of calcium oxalate crystals in the retina with visual loss. There can be root resorption with loose teeth.

Cardiovascular: Arrhythmias, particularly complete atrioventricular block (oxalate crystals have been seen near the conduction system) and peripheral vascular insufficiency from oxalate deposits. An infiltrative cardiomyopathy can also occur.

Orthopedic: Short stature (possibly secondary to renal tubular acidosis). There may be oxalate crystal deposition in the joints and in bone. Crystal deposits in bones can lead to fractures.

GI/GU: Recurrent abdominal pain. Hematuria, urolithiasis, nephrocalcinosis, renal insufficiency, renal tubular acidosis. May rarely present as renal failure (without lithiasis) in infancy. Calcium oxalate stones are radiopaque. The natural history of the disease is progression to renal failure and death. The disease rapidly recurs in transplanted kidneys.

Other: There may be oxalate deposits in the skin. There can be distal peripheral arterial insufficiency (occlusion, claudication, Reynaud's phenomenon,

livedo reticularis, acrocyanosis, gangrene). Bone marrow oxalate deposition has resulted in variable bone marrow failure.

Miscellaneous: Although the presence of oxalate stones in the urine has been recognized for over 200 years, the disease was formally described only in 1925.

Anesthetic Considerations: Teeth can be abnormally loose. Patients receiving chronic diuretic therapy may have electrolyte abnormalities, and serum electrolytes should be evaluated preoperatively as indicated. A baseline electrocardiogram should be obtained to evaluate cardiac conduction abnormalities. Prolonged preoperative fasting should be avoided, and a brisk diuresis should be maintained. Patients with renal tubular acidosis should have alkali therapy maintained perioperatively. Renal failure has implications for the titration of perioperative fluids and the choice of perioperative medications. Careful positioning may be needed in patients with disabling bone involvement. A single patient who developed hepatitis two days after a sevoflurane anesthetic has been reported, but no link to oxalosis could be identified or theorized (4).

Hyperoxaluria and nephrocalcinosis have been reported after the administration of methoxyflurane, without subsequent renal failure. This is presumably due to secondary hyperoxalosis from metabolism of methoxyflurane to oxalate, rather than a genetic disease.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

P

Pachydermoperiostosis syndrome

Synonym: Touraine-Solente-Golé syndrome

MIM #: 167100, 614441

This usually autosomal dominant disorder is distinguished by thick, coarse skin (pachyderma); clubbing of the fingers (hypertrophic osteoarthropathy); and thickening of the periosteum. There is wide variability in expression, but the disease is consistently more severe in male patients. The disorder can be diagnosed in childhood, but is usually diagnosed in adolescence, when it becomes clinically more apparent. The disorder progresses over a decade or two and then stabilizes. The responsible gene and gene product are unknown. A more rare autosomal recessive type has been suggested, which may be caused by mutations in the prostaglandin transporter gene *SLCO2A1*. Three clinical forms have been described: one with both periostosis and pachyderma, a second without pachyderma, and a third with pachyderma and minimal skeletal changes.

HEENT/Airway: Acromegalic facial features. Ptosis may develop. May have periodontal abnormalities.

Orthopedic: Clubbing of the fingers. Thickening of the periosteum, especially of the distal extremities. Joint, muscle, and bone pain. Kyphosis. Can have myelofibrosis with marrow failure.

GI/GU: May have gastrointestinal tract polyps.

Other: Progressive coarsening and thickening of the skin, particularly over the face (pachyderma). Hyperhidrosis. Peripheral vascular stasis.

Anesthetic Considerations: Note that clubbing of the fingers is secondary to periostosis and is not in this case reflective of any cardiopulmonary disease. Skin changes might make vascular access more difficult. Abnormal fingernails may make obtaining a pulse oximetry signal difficult. Patients with acromegaly may have excessive pharyngeal soft tissue, thickened vocal cords, and an enlarged tongue and epiglottis, all of which may make laryngoscopy and tracheal intubation difficult. Mandibular enlargement increases the lip-to-vocal cord distance. Hypertrophy of the turbinates may make passage of a nasogastric or nasotracheal tube difficult or impossible. A good mask fit may be difficult in patients with pronounced acromegalic features. There is significant clinical variability, and it is unclear if the acromegalic features in this syndrome can be severe enough routinely to affect airway management.

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Pachyonychia congenita syndrome

Synonym: Jackson-Lawler syndrome; Jadassohn-Lewandowski syndrome

MIM #: 167200, 167210

This autosomal dominant syndrome of ectodermal dysplasia is characterized by hypertrophic nails, hyperkeratosis, hyperhidrosis, and palmar and plantar bullae. There are two forms of this syndrome, a more common form (type 1, the Jadassohn-Lewandowski type) that includes oral leukokeratosis and a rarer form (type 2, the Jackson and Lawler type) that includes epidermal cysts and natal teeth but no oral leukokeratosis. The two forms of this syndrome are caused by mutations in the keratin 16 or 6A genes (type 1), or the keratin 17 or 6B genes (type 2).

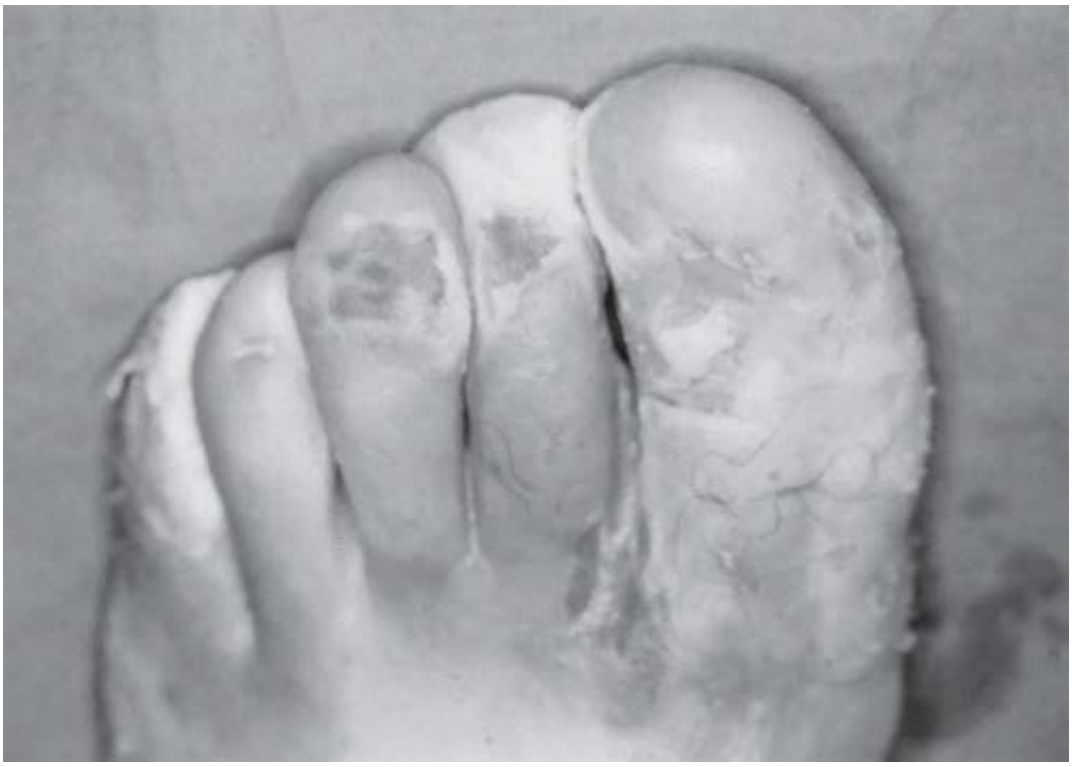
HEENT/Airway: Leukokeratosis of the oral membranes occurs in the more common form of pachyonychia congenita syndrome. Dental abnormalities, including neonatal teeth, malformed teeth, early eruption of primary teeth, and caries. May have cataracts. Excessive ear wax production. May have recurrent oral candidiasis. May have hoarseness secondary to laryngeal leukokeratosis.

Chest: Laryngeal leukokeratosis may result in recurrent upper respiratory tract irritation and infection. Severe laryngeal involvement has required tracheostomy.

Neuromuscular: May have intellectual disability.

Orthopedic: Arthritis may develop in large joints.

GI/GU: May have intestinal diverticulae.



Pachyonychia congenita syndrome. Typical changes of the toes. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Other: Hyperkeratosis of the palms, soles, knees, and elbows. Hyperhidrosis. Palmar and plantar bullae. Hypertrophic nails become thick, discolored, and misshapen. Recurrent cutaneous candidiasis may exacerbate the nail dystrophy. Nails often eventually need to be surgically removed. Keratosis pilaris. Epidermal cysts on the face, neck, and upper chest in the rarer form of pachyonychia congenita syndrome. Verrucous lesions on the elbows, knees, and lower legs. May have sparse, dry hair. Painful oral and nipple lesions during breast-feeding.

Anesthetic Considerations: Patients may have significant oral, laryngeal, or tracheal leukokeratosis, which may interfere with visualization of the larynx or cause respiratory compromise. Although laryngeal involvement can occur, there are no reports of difficult laryngoscopy/intubation. Dental abnormalities should be documented preoperatively. Abnormal or carious teeth are susceptible to damage during laryngoscopy.

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Palizaeus-Merzbacher disease

See Pelizaeus-Merzbacher disease

Pallister-Hall syndrome

MIM #: 146510

This autosomal dominant disorder consists of hypothalamic hamartoblastoma, panhypopituitarism, anal defects, and postaxial polydactyly. Most patients die in infancy or early childhood. If treated adequately with replacement therapy, some patients may reach adulthood. Replacement therapy consists of l-thyroxine, growth hormone, and corticosteroids. This disorder is due to frameshift mutations in the gene *GLI3*, an oncogene that maps to the short arm of chromosome 7. Although the disorder is fully penetrant, it is variably expressed—so the degree of involvement can vary. Many spontaneous cases have been reported. Some hamartomas have been surgically resected.

HEENT/Airway: Bathrocephaly. Midline capillary hemangioma. Flattened midface. May have downward-slanting palpebral fissures, ptosis, microphthalmia.

Abnormal external ear. Flat nasal bridge, short nose, anteverted nares. May have choanal atresia. Microglossia, multiple oral frenula. May have cleft lip, palate, or uvula. Micrognathia. Can have natal teeth. Bifid, hypoplastic, or absent epiglottis in greater than 50%. Laryngeal cleft. May have posterior subglottic web. Dysplastic tracheal cartilage. May have cricoid stenosis.

Chest: Hypoplastic or absent lung. May have abnormal lung lobation. May have rib anomalies.

Cardiovascular: Congenital cardiac defects include patent ductus arteriosus, ventricular septal defects, endocardial cushion defects, mitral and aortic valve defects, and coarctation of the aorta.

Neuromuscular: Intelligence usually normal but may have mild intellectual disability. Hypothalamic hamartoblastoma, which replaces the normal hypothalamus. Pituitary aplasia/dysplasia leading to panhypopituitarism. May have occipital encephalocele, holoprosencephaly, polymicrogyria, Dandy-Walker malformation. May have seizures.

Orthopedic: Postaxial or central polydactyly. Oligodactyly, syndactyly, brachydactyly, camptodactyly. Nail dysplasia. Short limbs. May have vertebral abnormalities. May have congenital hip dislocation. May have radial dislocation.

GI/GU: Anal defects, including imperforate anus, rectal atresia. May have Hirschsprung's disease. Hypoplasia of the adrenal glands. May have hypoplasia of the pancreas. May have hypospadias, micropenis. Vaginal atresia. Renal agenesis or dysplasia.

Other: Hypoplasia of the thyroid gland. May have hypoparathyroidism. May have precocious puberty.

Miscellaneous: Philip Pallister was trained as a general practitioner. Part of his role as a rural practitioner was caring for patients at the local state hospital, which led to his interest in genetics.

Anesthetic Considerations: Micrognathia and epiglottic anomalies may make direct laryngoscopy and tracheal intubation more difficult. Patients with abnormal tracheal cartilage or a posterior subglottic web may require a

smaller-than-expected endotracheal tube. Choanal atresia, if present, precludes the use of a nasal airway or a nasogastric tube. Patients with lung hypoplasia or abnormal lung lobation are at increased risk for postoperative respiratory complications.

Patients will likely be on steroid replacement therapy, and require perioperative stress doses of steroids as well as postoperative continuation of steroids. The presence of renal disease has implications for fluid therapy and the choice of anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs.

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Pallister-Killian syndrome

MIM #: 601803

This syndrome is due to mosaicism for tetrasomy of chromosome 12p. There is a mosaic supernumerary isochromosome 12p. The phenotype can be somewhat variable.

HEENT/Airway: Prominent forehead. Coarse facial features develop. At birth, sparse temporofrontal balding with abundant hair on the top of the head is reminiscent of a “mohawk.” Sparse eyebrows and eyelashes. Hypertelorism, ptosis, strabismus, epicanthal folds, cataracts, exophthalmos. Deafness. Large ears. Stenotic external auditory canals. Short anteverted nose. Micrognathia in infancy changing to prognathism and macroglossia in adulthood. Cupid-bow lip, macroglossia, protruding lower lip, cleft palate, bifid uvula. Delayed dental eruption. Short webbed neck.

Chest: Pulmonary hypoplasia. Congenital diaphragmatic hernia. Accessory nipples.

Cardiovascular: Congenital cardiac defects, pericardial agenesis, hypertrophic cardiomyopathy.

Neuromuscular: Profound intellectual disabilities, seizures. Hypotonic when newborn, hypertonic with aging.

Orthopedic: Kyphoscoliosis. Sacral appendage. Congenital hip dislocation. Hypermobile joints. Contractures with age. Mesomelic/rhizomelic limb shortening. Broad hands, clinodactyly of the fifth finger. Short fingers and toes, hypoplasia of distal digits. Postaxial polydactyly. Transverse (simian) palmar crease.

GI/GU: Umbilical hernia, omphalocele. Malrotation of the gut. Anal atresia, imperforate anus, anal stenosis. Cystic or dysplastic kidneys. Urogenital cloaca. Inguinal hernia. Cryptorchidism, hypospadias, small scrotum. Hypoplastic labia majora, absent upper vagina or uterus.

Other: Obesity. Hypo- and hyperpigmented hair streaks.

Miscellaneous: Philip Pallister was trained as a general practitioner. Part of his role as a rural practitioner was caring for patients at the local state hospital, which led to his interest in genetics.

Anesthetic Considerations: Macroglossia and micrognathia may make laryngoscopy and tracheal intubation more difficult, but have not been reported in the literature. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs. Patients with cardiac disease require an appropriately tailored anesthetic. Contractures may make positioning challenging.

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Pantothenate kinase-associated neurodegeneration (PKAN)

See Hallervorden-Spatz disease

Papillon-Lefèvre syndrome

MIM #: 245000

This autosomal recessive disorder, which maps to the long arm of chromosome 11, is characterized by hyperkeratosis of the palms and soles and periodontal disease. It is caused by a mutation in the gene for cathepsin C (*CTSC*), which is a lysosomal protease. The disease is treated with retinoids, which appear successfully to preserve adult teeth. Mutations in this gene can also cause Haim-Munk syndrome (not covered in this text).

HEENT/Airway: Eyelid cysts. Periodontal disease with premature loss of primary and adult teeth. Early eruption of adult teeth.

Neuromuscular: Calcification of the choroid and dura mater.

Orthopedic: Fragile nails. May have osteoporosis.

GI/GU: May develop pyogenic liver abscess.

Other: Hyperkeratosis of the palms and soles. Hypotrichosis. Depressed neutrophil chemotaxis.

Anesthetic Considerations: Dental abnormalities should be documented preoperatively. Patients may have loose teeth at an age when it is not expected. Care must be taken to avoid dental damage during laryngoscopy. Some cases can affect the dorsum of the hands and feet with poor healing, so intravenous access should be avoided in those sites.

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Papillorenal syndrome

MIM #: 120330

This autosomal dominant disorder involves primarily optic and renal abnormalities. The primary eye finding is an optic nerve coloboma termed morning glory anomaly, which refers specifically to a retinal finding that resembles a morning glory flower. The syndrome may represent abnormal regression of embryonic mesoderm of the optic disc. Papillorenal syndrome is due to a mutation in the *PAX2* gene. There is phenotypic variability.

HEENT/Airway: Morning glory anomaly—funnel-shaped, excavated optic disc with surrounding pigmentary changes. May have myopia, exotropia, retinal vascular abnormalities, and retinal detachment. May have high-frequency sensorineural hearing loss. May have midline defects including cleft lip and palate and hypertelorism.

Neuromuscular: May have basal myelomeningocele as part of midline defects. May have agenesis of the

corpus callosum. May have Arnold-Chiari malformation. May have seizures.

GI/GU: Vesicoureteral reflux. Congenital renal hypoplasia. Renal cysts. Congenital and progressive renal insufficiency often requiring transplantation.

Other: Morning glory anomaly has been found with the CHARGE association and moyamoya syndrome (see earlier).

Anesthetic Considerations: There is a single report of difficult intubation and difficulty in seating a laryngeal mask (3). Patients with renal insufficiency require careful titration of perioperative fluids and careful dosing of renally excreted medications. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs.

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Paramyotonia congenita

Synonym: Eulenburg disease

MIM #: 168300

This autosomal dominant syndrome is due to a mutation in the gene encoding the alpha subunit of the type IV sodium channel (*SCN4A*) on the long arm of chromosome 17. As such, it is allelic with hyperkalemic and hypokalemic periodic paralysis (see earlier), and the phenotypes of the disorders overlap. Abnormal inactivation of the mutant channels allows additional sodium to enter the cells. Cells remain excitable during the delayed inactivation. The hallmarks of this autosomal dominant disease are myotonia (failure of timely muscle relaxation), which is exaggerated by cold, intermittent flaccidity; lability of serum potassium; and lack of histologic muscle changes. The disease is manifest in infancy or early childhood, is nonprogressive, and does not affect life expectancy. The phenotype is variable.

HEENT: Neonatal stridor was the presenting sign in one child, and recurrent stridor persisted for several years.

Cardiovascular: There are no myopathic or arrhythmogenic implications.

Neuromuscular: Cold-sensitive myotonia, predominantly of the face, neck, and hands. Grip myotonia. May have percussion myotonia. Myotonia increases with exercise (“paradoxical myotonia”), unlike other myotonic disorders. Myotonia is also precipitated by rest after exercise. Often will develop weakness on muscle warming or after cooling. May have episodic weakness unrelated to myotonia. May have paresis. May have transient neonatal hypotonia.

Other: Hypokalemia and hyperkalemia have been reported. Cold-induced abortion has been reported.

Miscellaneous: Exacerbation by cold means that eating ice cream (even the low-fat kind) can be dangerous to these patients. Unlike myotonia congenita, stiffness and weakness are exacerbated by activity, thus the term para(doxical) myotonia.

Anesthetic Considerations: Patients need to be kept warm, utilizing warm operating rooms, warmed surgical prep solutions, warmed intravenous fluids, and external warming devices as appropriate. Propofol may be the anesthetic agent of choice (4). Succinylcholine should be avoided as it can induce myotonia (see myotonic dystrophy figure). Nondepolarizing muscle relaxants have been used without complication. Anticholinesterases may aggravate the myotonia (2). There have been no untoward effects of local anesthetics. There appears to be no intrinsic reason for preoperative potassium manipulation. Postoperative hypokalemia has been observed (7). A case of cardiac surgery utilizing moderate hypothermia (and adequate rewarming) resulted in no sequelae. Respiratory status must be monitored carefully perioperatively, as there is the potential for respiratory insufficiency during an episode of flaccid paresis.

In the event of a myotonic crisis, serum potassium should be measured emergently. Drugs that have been used include type I antiarrhythmics (e.g., quinidine, procainamide, propafenone, mexiletine, and tocainide). Other drugs that have been tried include epinephrine, acetazolamide, albuterol, and calcium gluconate.

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Parenti-Fraccaro achondrogenesis

Included in Achondrogenesis

Parry-Romberg disease

See Romberg disease

Patau syndrome

See Trisomy 13

Pearson syndrome

MIM #: 557000

This is a syndrome of sideroblastic anemia, vacuolization of marrow precursors, and exocrine pancreatic dysfunction. The disorder is due to deletions and duplications of several mitochondrial DNA genes. The clinical variations in the manifestations of the syndrome are thought to reflect the tissue distribution and relative proportion of the abnormal DNA. The clinically similar Shwachman syndrome (see later) also involves anemia and exocrine pancreatic dysfunction. Shwachman syndrome additionally involves pancytopenia (particularly neutropenia), immunologic abnormalities, and metaphyseal chondrodysplasia. Pancreatic dysfunction is associated with pancreatic fatty infiltration in Shwachman syndrome and with pancreatic fibrosis in Pearson syndrome. Patients have been reported with Pearson syndrome who later acquired Kearns-Sayre syndrome or Leigh disease, other diseases of mitochondria (see earlier for both). Pearson syndrome can be fatal in infancy.

Cardiovascular: May develop heart block. May develop left ventricular failure.

Neuromuscular: Can have mitochondrial encephalopathy.

GI/GU: Pancreatic exocrine dysfunction with pancreatic fibrosis. Splenic atrophy. Fanconi syndrome (see earlier). May have renal cysts. May have metabolic acidosis.

Other: Low birth weight, failure to thrive. Sideroblastic anemia. Normal marrow cellularity with vacuolization of marrow precursors. Insulin-dependent diabetes that may present in infancy; metabolic lactic acidosis, which may be chronic. Adrenal insufficiency has been reported. A case has been reported with fibrosis of the thyroid.

Anesthetic Considerations: The hematocrit should be evaluated preoperatively. Patients may have insulin-dependent diabetes. A child with adrenal insufficiency has been reported. Patients may have Fanconi syndrome, so consideration should be given to evaluating renal function and electrolyte status preoperatively. In the presence of Fanconi syndrome, urine output may not adequately reflect intravascular volume. Patients may acquire Kearns-Sayre syndrome or Leigh disease (see earlier for anesthetic considerations with each of these).

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Pelizaeus-Merzbacher disease

Synonym: Palizaeus-Merzbacher disease

MIM #: 312080

This is an X-linked recessive leukodystrophy with onset in infancy. There is significant genetic and clinical heterogeneity. The disease is due to an abnormality in the gene for proteolipid protein, or lipophilin, a major constituent of myelin. Three types have been described: the classic type with onset in infancy and death by young adulthood, the connatal type that is fatal by early childhood, and the transitional type, which is intermediate. Stem cell transplantation and gene therapy are being explored as possible treatment options. Spastic paraplegia type 2, not discussed in this text, is an allelic disorder and is less severe.

The other leukodystrophies include adrenoleukodystrophy, metachromatic leukodystrophy, Krabbe disease, Canavan disease, and Alexander disease (see earlier for all).

HEENT/Airway: Microcephaly. Head shaking and rotatory nystagmus. May have hearing impairment.

Copious oral secretions, poor airway tone, tracheomalacia, and neonatal stridor.

Chest: Can have respiratory failure with pulmonary complications.

Neuromuscular: Slowly progressive psychomotor retardation with eventual dementia. Neonatal hypotonia. Severe hypotonia. Seizures. Choreoathetosis, ataxia, spasticity, pyramidal signs, Parkinsonian symptoms. The neuropathologic findings include diffuse demyelination with interspersed areas of normal myelin, the “tigroid appearance.” Magnetic resonance imaging scans show multiple areas of hyperintensity in the periventricular and subcortical white matter areas. Myelination of peripheral nerves and electrophysiologic studies of peripheral nerves are normal.

Orthopedic: Poor growth.

GI/GU: Increased incidence of gastroesophageal reflux.

Miscellaneous: The analogous defect of Pelizaeus-Merzbacher disease in mice is the “jimpy” defect, and Pelizaeus-Merzbacher disease seems similar or identical to “paralytic tremor” in chinchillas.

Anesthetic Considerations: Copious secretions and airway hypotonia make close perioperative observation of respiratory adequacy important. Consideration should be given to anticholinergic premedication to dry oral secretions. Patients are at increased risk for perioperative aspiration because of poor airway tone, copious oral secretions, and an increased incidence of gastroesophageal reflux. Patients should be carefully positioned and padded perioperatively secondary to their poor nutritional status. The risk of excessive potassium release with

succinylcholine is unknown, but is theoretically possible in bedridden patients with atrophic muscles. Anticonvulsant medications need to be continued perioperatively (or a parenteral form substituted) and may alter the metabolism of some anesthetic drugs, requiring more frequent dosing.

Phenothiazines, butyrophenones, and other dopaminergic blockers may exacerbate movement disorders. Metoclopramide may cause extrapyramidal effects and should be avoided if possible. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects.

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Pena-Shokeir syndrome, type I

See Fetal akinesia/hypokinesia sequence

Pena-Shokeir syndrome, type II

See Cerebrooculofacioskeletal syndrome

Pendred syndrome

MIM #: 274600

This autosomal recessive syndrome is characterized by congenital deafness and abnormal organification of thyroid hormone. It is caused by a mutation in the *SLC26A4* gene, located on the long arm of chromosome 7. The gene product, termed “pendrin,” is a chloride-, bicarbonate-, and iodide-specific transporter, which is responsible for iodide efflux in the thyroid gland. Mutations in this gene can also cause autosomal recessive deafness type 4 (*DFNB4*, not covered in this text).

HEENT/Airway: Congenital neurosensory deafness, sometimes associated with cochlear malformation and vestibular dysfunction. Widened vestibular aqueduct. Goiter.

Neuromuscular: Intellectual disabilities have been reported.

Other: Defect in thyroid hormone organification with compensated (euthyroid) hypothyroidism, but can be symptomatically hypothyroid if severe. Exaggerated response to thyroid-releasing hormone. Because of the very abnormal appearance of the thyroid on histologic study, an incorrect diagnosis of thyroid cancer may be made.

However, thyroid carcinoma may develop.

Miscellaneous: Described by Pendred in 1896, it took exactly 100 years to map the gene to the long arm of chromosome 7.

Anesthetic Considerations: Preoperative thyroid studies should be obtained, and patients should be euthyroid before elective surgery is undertaken. Airway evaluation in the face of a large goiter. Be sensitive to the fact that patients may have hearing loss and vestibular dysfunction.

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Penta X syndrome

Synonym: XXXXX syndrome

MIM #: None

This chromosomal syndrome consists primarily of intellectual disabilities, growth retardation, small hands, and patent ductus arteriosus. This syndrome is due to five copies of the X chromosome. Of interest, the X chromosomes are of maternal origin.

HEENT/Airway: Microcephaly, low posterior hairline. Upward-slanting palpebral fissures, hypertelorism, epicanthal folds, iris colobomas, optic nerve hypoplasia. Low nasal bridge. Malocclusion. Premature loss of deciduous teeth. May have cleft palate, macroglossia, micrognathia.

Cardiovascular: Patent ductus arteriosus or other congenital cardiac defects.

Neuromuscular: Moderate to severe intellectual disabilities. Seizures. Hypotonia. May have hydrocephalus.

Orthopedic: Short stature. Small hands with clinodactyly of fifth fingers. Excessively lax joints with risk of dislocations of multiple joints, including shoulder, elbow, hips, knees, wrists, and fingers. Clubfoot deformity.

GI/GU: Occasional renal dysplasia, horseshoe kidney. May have ovarian agenesis.

Other: Small for gestational age, failure to thrive.

Anesthetic Considerations: Difficult intubation has not been reported, but may be a concern given the incidence of macroglossia and micrognathia. Deciduous teeth may be prematurely loose, particularly the anterior teeth. Baseline renal function should be established. Patients must be carefully positioned secondary to joint laxity.

Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications can alter the metabolism of some anesthetic drugs, requiring more frequent dosing.

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Pentalogy of Cantrell

Synonym: Thoracoabdominal syndrome; Cantrell's pentalogy

MIM #: 313850

This likely X-linked disorder involves failure of midline fusion and includes defects in the (a) abdominal wall, (b) sternum, (c) diaphragm, (d) pericardium, and (e) heart. Infants often require a multistaged surgical repair.

HEENT/Airway: Hydrocephalus or anencephaly. Cystic hygroma. Cleft lip or palate.

Chest: Failure of sternal fusion. Diaphragmatic hernia, hypoplastic lungs.

Cardiovascular: Ectopia cordis (heart protrudes through an open sternum) with a variety of congenital cardiac defects, including ventricular septal defect, atrial septal defect, tetralogy of Fallot, and left ventricular diverticulum. Absent pericardium.

GI/GU: Omphalocele. Hypospadias. Renal agenesis.

Anesthetic Considerations: Infants may be quite ill with multiorgan involvement. Anesthetic management depends on the specific anatomic anomalies and their severity. Displacement of intra-abdominal organs can interfere with fetal ultrasound, and associated intracardiac defects could be missed. Surgeons must be particularly careful not to place undue pressure on the abdomen or chest by resting on a draped patient. Closure of an omphalocele has resulted in dislocation of abdominal contents through an anterior diaphragmatic hernia, with acute cardiopulmonary deterioration. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Perheentupa syndrome

See Mulibrey nanism syndrome

Periodic paralysis

See Familial periodic paralysis

Perlman syndrome

MIM #: 267000

This autosomal recessive disorder is due to mutations in the gene *DIS3L2*, which encodes an exonuclease. The disorder is an overgrowth syndrome phenotypically similar to Beckwith-Wiedemann syndrome (see earlier). It is often fatal in the neonatal period.

HEENT/Airway: Macrocephaly. Full, round face. Epicanthal folds. Upswept anterior scalp hair. Low-set ears. Flat and broad nose. Micrognathia. Anteverted upper lip, open mouth.

Chest: Diaphragmatic hernia. Can have pulmonary hypoplasia.

Cardiovascular: Interrupted aortic arch has been reported.

Neuromuscular: Developmental delay. Agenesis of the corpus callosum.

GI/GU: Hypoplasia of abdominal muscles, visceromegaly, hypertrophy of islets of Langerhans. Renal failure. Nephromegaly. Hydronephrosis. Cryptorchidism. Renal hamartomas. There is a high incidence of Wilms tumor, which is often bilateral.

Other: Fetal ascites without hydrops. Large for gestational age. Hypoglycemia.

Anesthetic Considerations: Hypoglycemia is a major concern. Micrognathia has been reported, but is usually mild. Visceromegaly can increase the risk of aspiration on induction of general anesthesia. The major cause of death is respiratory insufficiency from visceromegaly.

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Peters Plus syndrome

MIM #: 261540

Peters anomaly (corneal clouding and adhesions between the iris and lens) is a defect in the embryonic development of the anterior chamber of the eye. It can occur in isolation or with many genetic and nongenetic syndromes. Peters plus syndrome is an autosomal recessive disorder of Peters anomaly, short limb dwarfism, and intellectual disabilities. It is due to mutations in the gene *B3GALTL*, the beta-1,3-galactosyltransferase-like gene.

HEENT/Airway: Microcephaly and less commonly macrocephaly. Premature closure of fontanelles. Round face, hypertelorism, corneal clouding, anterior lens adhesions, lens opacity, glaucoma, iris or retinal coloboma, decreased vision. Prominent ears. Narrowed external auditory canals with hearing loss. “Cupidbow” thin upper lip, smooth philtrum, short frenulum. Absent upper lateral incisors. Mild micrognathia. Cleft lip and/or palate. Broad neck.

Chest: Occasional pectus excavatum.

Cardiovascular: A variety of acyanotic cardiac defects.

Neuromuscular: Intellectual disabilities ranging from mild to severe. Occasional dilated lateral ventricles, seizures, spastic diplegia. Agenesis of the corpus callosum has been reported.

Orthopedic: Short-limb dwarfism, primarily rhizomelic. Limited range of motion of the elbows, with hypermobility of other joints. Broad, short hands and feet, fifth finger clinodactyly.

GI/GU: Hydronephrosis, duplication of kidneys, cryptorchidism. Occasional hypospadias, or hypoplastic labia majora and clitoris. Rudimentary vagina and uterus.

Other: Prenatal onset of growth deficiency. May have growth hormone deficiency.

Miscellaneous: Similar findings have been reported in snow leopards.

Anesthetic Considerations: Although there may be mild micrognathia, difficult laryngoscopy and tracheal intubation have not been reported. Recall that patients

are likely to have visual impairment. Patients should be carefully positioned secondary to joint hypermobility. Consider preoperative evaluation of renal function in patients with a history of renal abnormalities, which

predispose to renal insufficiency. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Petty syndrome

MIM #: 612289

This syndrome was originally described as a type of progeria, but it is currently not considered so because patients appear aged at birth rather than aging prematurely. The etiology is not currently known. It has been suggested that it represents a laminopathy, related to abnormalities in the lamin A gene (*LMNA*).

HEENT/Airway: Large anterior fontanelle. Thin calvarium. Scalp vascular malformation. Coronal synostosis. Midface hypoplasia. Prominent eyebrows. Small ears.

Neuromuscular: Normal development, but can have intraparenchymal brain hemorrhage.

Orthopedic: Hypoplastic nails and distal phalanges.

GI/GU: Umbilical hernia. Small bowel can be thin walled. Genital hypoplasia/cryptorchidism.

Other: Prenatal and postnatal growth retardation. Lipodystrophy, diminished subcutaneous fat. Fragile, wrinkled skin. Scant hair.

Anesthetic Considerations: A case of gastric perforation in a neonate from placement of a nasogastric tube has been reported. Lack of adipose tissue from lipodystrophy will require attention to temperature maintenance, and fragile skin will require extra care when placing cutaneous monitors.

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Peutz-Jeghers syndrome

MIM #: 175200

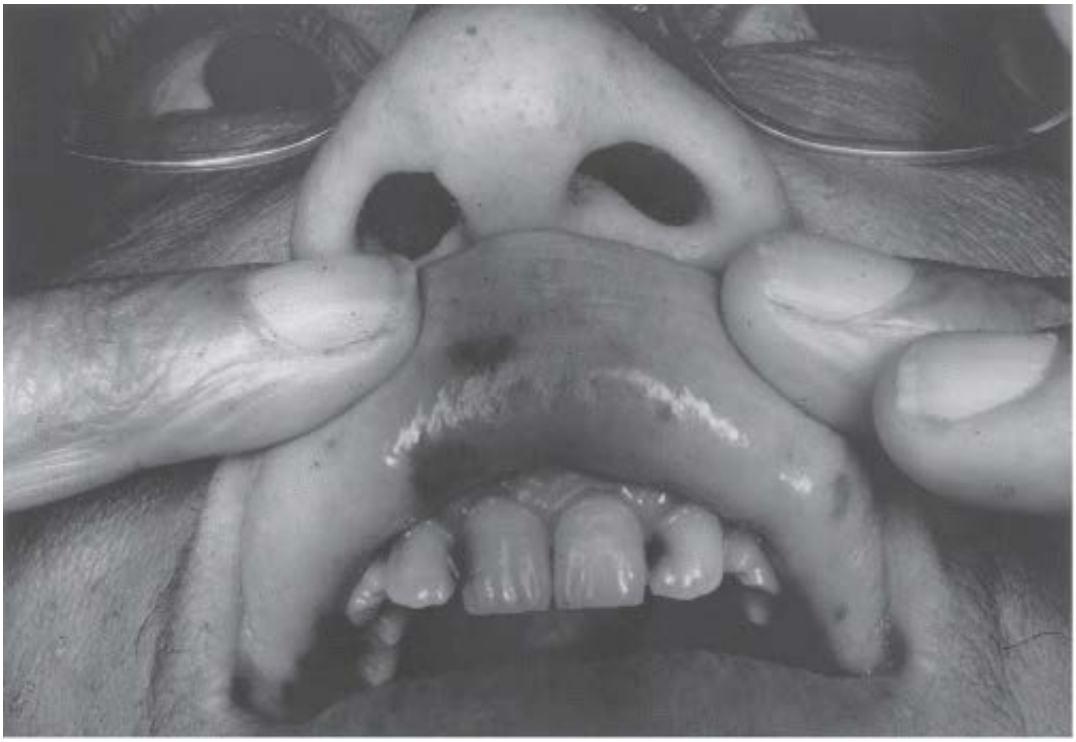
This autosomal dominant disease is characterized by intestinal polyposis and melanin spots on the oral mucosa, lips, and digits. Cutaneous spots fade with age, but the oral spots persist. Malignant degeneration of the intestinal polyps can occur, and there is a high incidence of both intestinal and extraintestinal cancers. This syndrome is due to a mutation in the gene for serine/threonine kinase 11, *STK11*, located on the short arm of chromosome 19. This gene may act as a tumor suppressor gene.

HEENT/Airway: Melanin spots on the oral mucosa and lips. Nasal polyps.

Chest: Bronchial polyps.

Orthopedic: Melanin spots on the digits. These are actually classified as lentigines. Lentigines are macules similar to freckles but, unlike freckles, are not restricted to sun-exposed areas. They are dark brown to black and round to oval.

GI/GU: Multiple intestinal polyps (hamartomas), from stomach to rectum, but particularly jejunal. Rare malignant degeneration of intestinal polyps. Intussusception, gastrointestinal bleeding, rectal prolapse (all secondary to polyps). May have esophageal polyps, as well as polyps of the kidney, ureter, and bladder. Increased incidence of gonadal tumors (ovarian and testicular), and increased incidence of pancreatic cancer. Ovarian cysts.



Peutz-Jeghers syndrome. Typical melanin spots of the lips. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Other: Pigmented macules can develop in preexisting psoriatic lesions that are in otherwise atypical locations. Can have prepubertal gynecomastia. Increased incidence of breast cancer.

Miscellaneous: In 1895 Connor described twins with darkly pigmented spots on their lips and oral mucosa, likely the first description in the literature of the Peutz-Jeghers syndrome. The paper by Peutz (1921, in Dutch) came 28 years before that of Jeghers. Bruwer introduced the eponym Peutz-Jeghers syndrome in 1954. During his career, Jeghers kept an extensive collection of medical articles, systematically filed and annotated, which is currently accessible as the Jeghers Medical Index (www.jeghers.com).

Anesthetic Considerations: The possibility of nasal polyps should be appreciated before passing nasal tubes or catheters. Similarly, caution should be taken in endotracheal suctioning because of the possibility of bronchial polyps. Patients can be anemic from gastrointestinal bleeding.

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Pfeiffer syndrome

Synonym: Acrocephalosyndactyly type V

MIM #: 101600

This autosomal dominant syndrome is marked by craniosynostosis, mild syndactyly, and broad thumbs and great toes. Although most cases are due to mutations in the genes encoding fibroblast growth factor receptors 1 or 2 (*FGFR1* or *FGFR2*), some cases cannot be ascribed to either. Different mutations in *FGFR2* are also responsible for Antley-Bixler, Apert, Beare-Stevenson, and Crouzon syndromes (see earlier).

Three clinical subtypes have been described. Type 1 is an autosomal dominant disorder, whereas types 2 and 3 have occurred sporadically. The classic syndrome is type 1. Types 2 and 3 have more severe involvement. Type 2 involves the typical hand and foot anomalies as well as Kleeblattschaedel (cloverleaf skull; see earlier), severe proptosis, complete tracheal rings, and ankylosis of the elbows. Patients with type 2 have had diminished life expectancy. Type 3 is similar to type 2 but without cloverleaf skull. Ocular proptosis in type 3 is also severe. Various visceral malformations have been found in association with type 3.

HEENT/Airway: Brachycephaly with coronal and possibly also sagittal craniosynostosis. Maxillary hypoplasia. Kleeblattschaedel anomaly (cloverleaf skull) (type 2). Hypertelorism, shallow orbits with proptosis (types 2 and 3). Can have atresia of external auditory canal. Conductive hearing loss. Small nose with flat bridge. Rare choanal

atresia. There has been a report of a cartilaginous trachea and a calcified trachea and also laryngomalacia, tracheomalacia, and bronchomalacia. Obstructive sleep apnea.

Cardiovascular: A low incidence of a variety of congenital cardiac malformations has been reported.

Neuromuscular: Intelligence is usually normal; occasional intellectual disability. May have seizures, hydrocephalus, and Arnold-Chiari malformation (particularly in type 2). May have increased intracranial pressure if craniosynostosis is severe. Types 2 and 3 have a higher incidence of CNS abnormalities.

Orthopedic: Broad thumbs and great toes. Polysyndactyly. Radiosynostosis at elbow. Occasional fifth finger clinodactyly, radiohumeral synostosis of the elbow. Vertebral fusion, usually upper cervical spine.

GI/GU: A variety of intestinal defects have been reported, including prune belly syndrome (see later), malrotation, and duplication.

Anesthetic Considerations: It has not been reported, but it has been suggested that these children may have a difficult airway (4). Certainly, upper cervical vertebral fusion could limit mobility and make laryngoscopy and tracheal intubation more difficult. Placement of a maxillary distraction device may increase the difficulty of tracheal intubation (3). Tracheal abnormalities may lead to tracheal stenosis. Choanal atresia, if present, precludes the use of a nasal airway or placement of a nasogastric tube. The eyes must be carefully protected perioperatively secondary to proptosis. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Patients may have elevated intracranial pressure, in which case precautions should be taken to avoid further elevations in pressure. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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PHACE association

MIM #: 606519

Because it occurs almost exclusively in females, this neurocutaneous disorder may be X-linked dominant with lethality in males. It may also occur sporadically. PHACE stands for **P**osterior fossa brain malformations, **H**emangiomas of the face, **A**rterial anomalies, **C**ardiac anomalies, and **E**ye abnormalities. The association has been referred to as PHACES when ventral defects, such as **S**ternal clefting or **S**upraumbilical raphe, are also present.

HEENT/Airway: Facial hemangiomas—usually large and/or complex and often in the distribution of the V1 dermatome. Ocular anomalies include congenital cataracts, choroidal hemangiomas, cryptophthalmos, exophthalmos, microphthalmos, colobomas, optic atrophy, esotropia, optic nerve hypoplasia, and congenital glaucoma. These are ipsilateral to the hemangioma. May have micrognathia. Subglottic hemangioma. Airway hemangiomas can also be located in other pharyngeal structures such as the epiglottis. May have lingual thyroid.

Chest: May have sternal clefting.

Cardiovascular: Coarctation of the aorta or other cardiac anomalies. Arterial anomalies, such as aberrant arterial origins, stenosis, atresia and aneurysms— including one report of aortic aneurysm that ruptured with minor trauma. Aneurysms and anomalous branching of the carotids. Aortic arch/subclavian anomalies. Can develop renovascular hypertension.

Neuromuscular: Cerebral vascular malformations— particularly aneurysm formation and the presence of anomalous branches of the internal carotid artery. At risk for ischemic strokes. Structural malformations of the brain, most commonly a Dandy-Walker malformation. May have agenesis of the corpus callosum. Cerebellar and posterior fossa malformations. Neurologic sequelae include seizures, developmental delay, and contralateral hemiparesis. May have Horner syndrome.

GI/GU: May have supraumbilical raphe.

Other: Hemangiomas occur in locations other than the face in 30% of cases. May have congenital hypothyroidism.

Anesthetic Considerations: Be sensitive to the fact that patients may have some loss of vision. Subglottic or pharyngeal hemangiomas might bleed with instrumentation or intubation of the airway. May have a lingual thyroid. Patients with aortic or cerebral aneurysms warrant tight control of blood pressure. Given the carotid and cerebrovascular involvement, monitoring cerebral oximetry bilaterally is worth considering. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Patients may be on propranolol for hemangioma control, and this should not be stopped acutely perioperatively. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Phenylketonuria

Synonym: PKU. [Includes Tetrahydrobiopterin (BH4) deficiency]

MIM #: 261600, 261630

This autosomal recessive disease is due to a defect in phenylalanine hydroxylase. This enzyme converts phenylalanine to tyrosine. There are multiple alleles, and some patients have defects that allow partial enzyme activity. These patients may have only moderately elevated levels of phenylalanine, not high enough to warrant treatment. Approximately 1% to 2% of patients with phenylketonuria do not have a defect in phenylalanine hydroxylase, but instead have a defect in the gene coding for the cofactor **tetrahydrobiopterin (BH4)** or for the cofactor's regeneration (dihydropteridine reductase deficiency). This cofactor is also needed for hydroxylation of tryptophan and tyrosine in the central nervous system, and limited BH4 causes decreased

synthesis of the neurotransmitters serotonin and the catecholamines.

Treatment is by dietary restriction of phenylalanine, an essential amino acid. Commercial infant formulas are available. Patients with tetrahydrobiopterin-responsive phenylketonuria will also be treated with sapropterin (a synthetic tetrahydrobiopterin). The artificial sweetener aspartame is hydrolyzed in the intestinal lumen to phenylalanine and aspartic acid. It needs to be studiously avoided by patients with phenylketonuria. Phenylalanine hydroxylase is resident in the liver. Interestingly, liver transplantation in a boy with coincident end-stage liver disease also cured his phenylketonuria.

It is recommended that the restricted diet be continued until at least adolescence for boys and longer for girls. Elevated phenylalanine levels have been shown to be toxic to the fetus (see **Maternal phenylketonuria syndrome**, earlier). Fetal effects are proportional to maternal phenylalanine levels, and toxicity to the fetus is preventable with strict maternal dietary control at the time of conception and for the duration of pregnancy. Reasons not to stop the special diet in women of childbearing age include the following: (a) pregnancy may be unexpected, and (b) the diet is so unpleasant that once people are off of it, it is hard to get them back on.

HEENT/Airway: Blue eyes. Rare keratomalacia if untreated.

Neuromuscular: If untreated, will have severe psychomotor retardation, poor head growth, seizures, increased deep tendon reflexes, abnormal gait, and sitting posture. Slightly lower than average IQ in treated patients. Brain calcifications if untreated. Patients with the biopterin-deficient variant may have a Parkinson-like progressive deterioration and often die young, even with good dietary phenylalanine control. There is evidence of abnormal brain myelin on magnetic resonance imaging, even without neurologic symptoms.

Orthopedic: Osteopenia.

GI/GU: If untreated, will have episodes of vomiting (some have been misdiagnosed as having pyloric stenosis during the neonatal period).

Other: Pale, dry skin. Treated patients compliant with a protein-restricted diet may have vitamin B_{12} deficiency and megaloblastic anemia if they fail to take adequate vitamin supplementation.

If untreated, patients will have a mousy, pungent odor. Patients usually have less pigmentation than the rest of the family, including lighter hair ("dilute" pigmentation), although it will have been normal at birth. Indolent, often perirectal, eczema-like or scleroderma-like skin rash.

Miscellaneous: Old names for this disease included "imbecillitas phenylpyruvica" and "phenylpyruvic oligophrenia." This disease is an important historical paradigm for inborn errors of metabolism and the first for which widespread testing of newborns was offered (the Guthrie test). The two children in whom it was first described were brought for medical attention because the pungent, musty odor they exuded induced asthma in their father. The odor is caused by an oxidation product of phenylalanine, phenylacetic acid.

It has been suggested that the heterozygous state may offer selective protection against the mycotoxin ochratoxin A. This toxin can be found in moldy stored grains and foods. Interestingly, the Celtic and Scandinavian regions, which have had repeated famines during which moldy foods were frequently eaten, also have a particularly high incidence of phenylketonuria.

Anesthetic Considerations: The special phenylalanine-restricted diet must be maintained perioperatively. Proconvulsant anesthetic agents should be avoided. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Protracted fasting could result in a catabolic state with increased tissue catabolism and elevated phenylalanine levels. There is a single case report of a patient who developed paraparesis after an anesthetic, which included nitrous oxide (6). By inactivating the B_{12}-dependent enzyme methionine synthase, nitrous oxide is a known cause of myeloneuropathy. The authors postulated that their patient was vitamin B_{12} deficient and that the further effect of nitrous oxide led to his neurologic symptoms. Avoidance of nitrous oxide in patients with phenylketonuria, particularly if they are known or suspected to be vitamin B_{12} deficient, seems reasonable.

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Phosphoenolpyruvate carboxykinase deficiency

MIM #: 261680, 261650

This autosomal recessive disease is a cause of lactic acidemia in childhood. Phosphoenolpyruvate carboxykinase is important in the conversion of pyruvate

to glucose. It is the rate-limiting step in renal and hepatic gluconeogenesis. Pyruvate is converted to oxaloacetate and then by this enzyme to phosphoenolpyruvate, which is then converted to glucose. There are two genes implicated in the pathogenesis of this syndrome: one coding for enzyme, which resides in the cytosol (*PCK1*), and the other coding for enzyme, which resides in mitochondria (*PCK2*). Symptoms in patients with the mitochondrial enzyme defect tend to be more persistent, whereas activity of the cytosolic enzyme is influenced by insulin, glucocorticoids, diet, cyclic adenosine monophosphate, and thyroid hormone to maintain appropriate glucose production.

HEENT/Airway: Optic nerve atrophy.

Cardiovascular: Can have fatty infiltration of the heart.

Neuromuscular: Hypotonia. Developmental delay. Can have seizures.

GI/GU: Hepatomegaly, fatty liver, rarely hepatic failure. Fatty kidney.

Other: Lactic acidemia. Impaired gluconeogenesis, hypoglycemia. Failure to thrive.

Anesthetic Considerations: Serum glucose levels should be monitored perioperatively. Prolonged perioperative fasting should be avoided. Adequate perioperative glucose intake must be ensured. Lactated Ringer's solution is best avoided in patients with persistent lactic acidemia.

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Phosphofructokinase deficiency

See Glycogen storage disease VII

Phosphoglycerate kinase deficiency

MIM #: 172270, 311800

The X-linked abnormality (PGK 1) is characterized by hemolytic anemia and neurologic manifestations in boys and occasional hemolytic anemia in girls. Phosphoglycerate kinase is an important enzyme in glycolysis, as it catalyzes the interconversion of 3-phosphoglycerate and 1,3-diphosphoglycerate, with the production of adenosine

triphosphate. There are multiple variants of this disorder, with differing levels of enzyme activity. In addition, it is thought that the variable involvement of red blood cells, muscle, and nervous system may in part be due to organ-specific isozymes that are secondary to organ-specific posttranslational modifications. Bypass of the phosphoglycerate kinase enzyme in the Embden-Meyerhof pathway by triose results in its diversion to form 2,3-diphosphoglycerate (2,3-DPG) in red blood cells. Phosphoglycerate kinase may also be secreted by tumor cells and participate in tumor-associated angiogenesis, which is necessary for tumor expansion and metastasis. A second, autosomal recessive, form of this enzyme defect (PGK 2*)* is localized to spermatozoa.

Neuromuscular: Behavioral problems, emotional lability, impaired speech, variable intellectual disabilities, seizures, extrapyramidal tract disease, weakness after exercise. Hemiplegia or coma during exacerbations of hemolysis. It may be associated with juvenile Parkinson's disease. Recovery from exacerbations is rapid. Some variants are associated with myopathic symptoms and rhabdomyolysis without hemolysis.

GI/GU: Postexercise nausea and anorexia. Occasional hemoglobinuria. May develop renal failure.

Other: Chronic hemolytic anemia with spherocytosis, and occasional hemolytic crises. 2,3-DPG levels are elevated.

Anesthetic Considerations: The hematocrit should be evaluated preoperatively. Ensuring adequate perioperative glucose would seem reasonable. Brisk diuresis should be maintained perioperatively if there is hemoglobinuria. Fluids and medications should be titrated carefully in patients with renal failure. Elevated 2,3-DPG levels might be expected to have mild effects on the correlation of oxygen saturation and pO_2, with lower saturation for the same pO_2 because of a right-ward shift in the oxyhemoglobin dissociation curve. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Given the possible myopathic symptoms and rhabdomyolysis, succinylcholine should be used with care. Phenothiazines, butyrophenones, and other dopaminergic blockers may exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects.

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Phosphohexose isomerase deficiency

See Glucose phosphate isomerase deficiency

Phosphorylase kinase deficiency

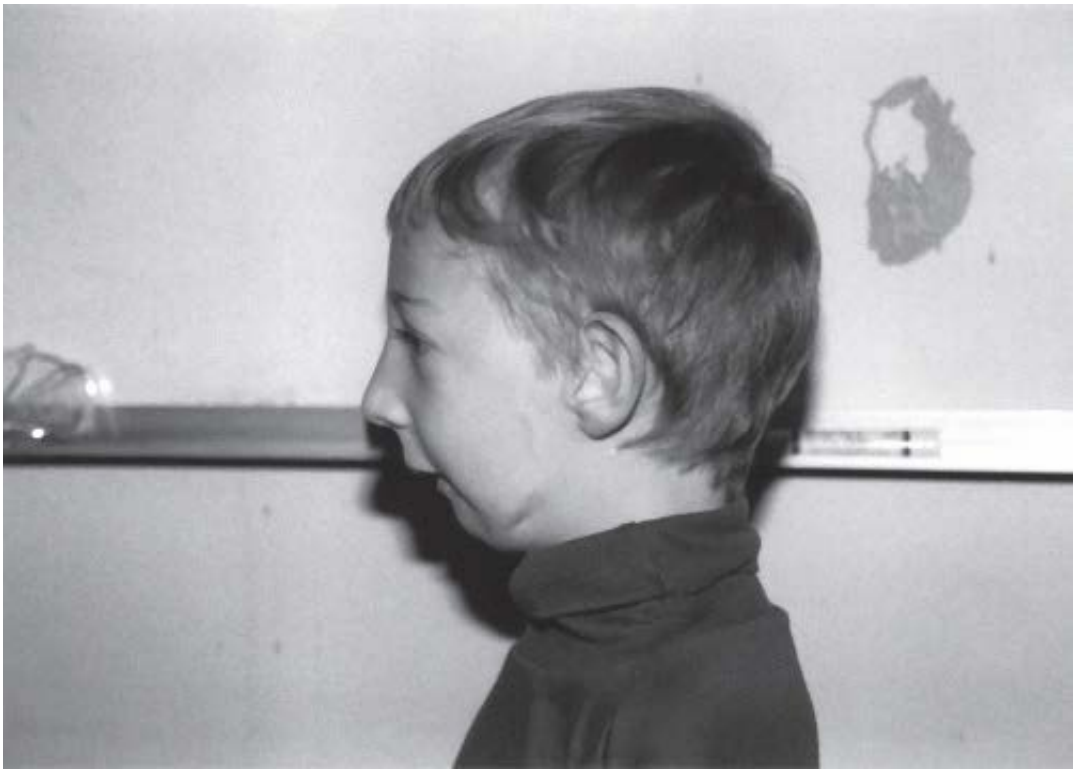
See Glycogen storage disease IX

Pierre Robin sequence

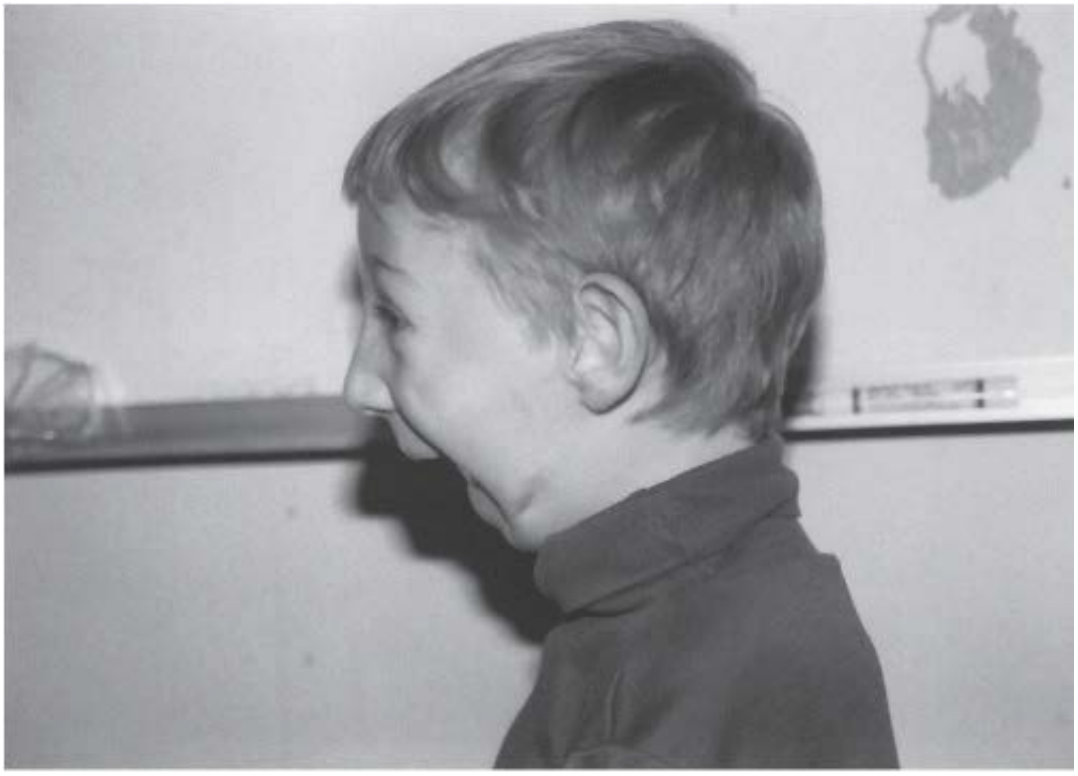
Synonym: Pierre Robin syndrome; Robin sequence

MIM #: 261800

This syndrome of micrognathia, glossoptosis, and a cleft soft palate is a well-known cause of difficult intubations in children. The mandible may demonstrate significant catch-up growth with aging. The etiologic defect is probably early mandibular hypoplasia *in utero*, placing the tongue posteriorly, which keeps the palatal shelves (which normally must grow over the tongue) from closing in the midline, causing a cleft. The rounded contour of the cleft differs from the usual inverted “V” shape of most palatal clefts. Neonates may require prone positioning, a nasopharyngeal airway, suturing of the tongue to the lip, or even urgent tracheostomy to preserve an airway. As an isolated finding in an otherwise healthy infant, the prognosis is good if the neonatal airway problems can be managed. Pierre Robin syndrome can occur, however, as a component of many multiple-malformation syndromes. Pierre Robin “syndrome” is more properly referred to as a “sequence.”



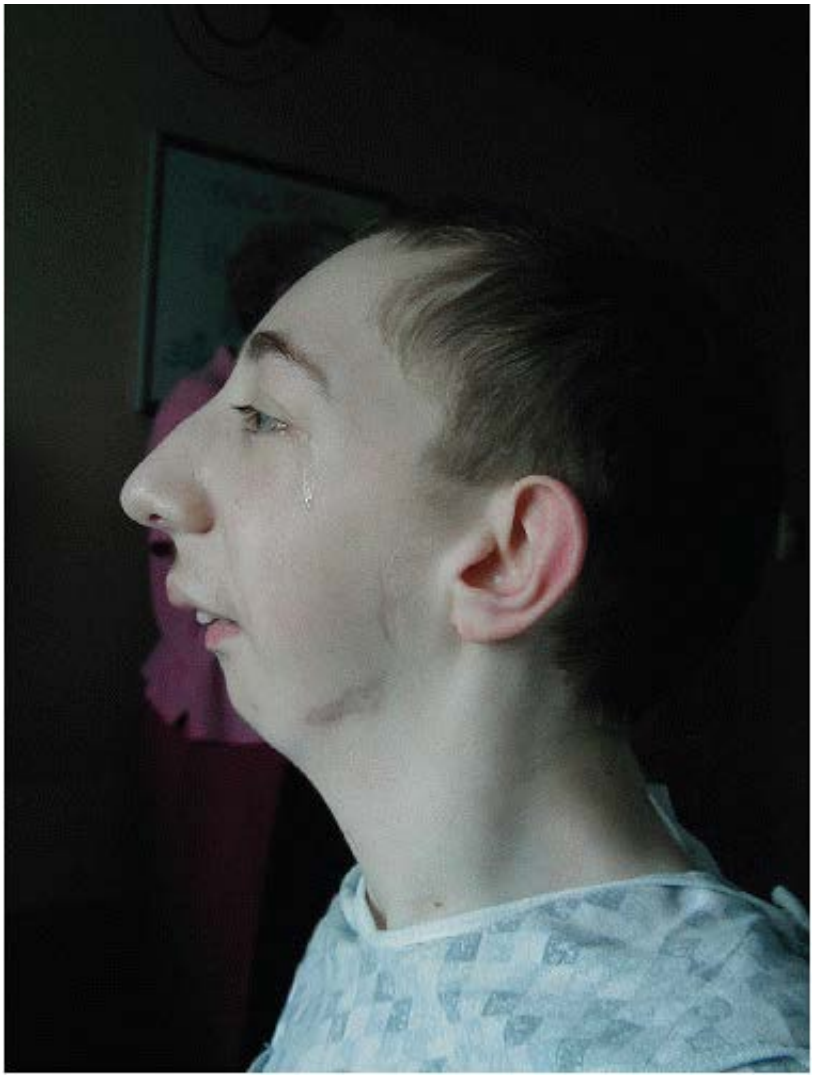
Pierre Robin syndrome. FIG. 1. A 4-year-old boy with Pierre Robin syndrome. He has already had mandibular augmentation surgery, but still has a very small mandible. Orotracheal intubation by a senior pediatric anesthesiologist had been impossible during a prior surgery, and he required fiberoptic intubation, which was reportedly very difficult. For his current surgery (tympanostomy tubes, resection of frenulum, and dental surgery), a laryngeal mask airway was easily placed. The dentist worked around the airway, and the anesthesia was uncomplicated and uneventful.



Pierre Robin syndrome. FIG. 2. Patient from Figure 1, laughing.

HEENT/Airway: Severe micrognathia. Glossoptosis. Cleft soft palate. Obstructive apnea. Airway obstruction usually improves with age.

Chest: Hypoxia from airway obstruction.



Pierre Robin syndrome. FIG. 3. The same boy at 14 years of age during admission for scoliosis repair. Despite mandibular advancement surgery (scar visible), he still required fiberoptic intubation via a laryngeal mask airway, although the pharynx would only accommodate a size 2½ LMA, which was very difficult to place in his restrictive pharyngeal space. Despite the tear, he was smiling when this photo was taken.

Cardiovascular: Cor pulmonale can develop with severe chronic airway obstruction. May have vagal hyperactivity.

Neuromuscular: Patients may have brainstem dysfunction, with periods of central apnea.

GI/GU: Feeding difficulties are common secondary to anatomic abnormalities and also possibly to swallowing problems due to brainstem dysfunction.

Miscellaneous: Pierre Robin (one person) was the leading French dental surgeon of his day. He was not, however, the first to describe his eponymous syndrome. That honor goes to St. Hilaire 101 years before.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation can be extremely difficult. A variety of alternative airway management techniques have been suggested, including the laryngeal mask airway (LMA)

(17,18,19,20,23,24), which can be placed in infants while awake, several models of video laryngoscopes (8), intubation through a laryngeal mask airway (13), fiberoptic intubation through a laryngeal mask airway (12,14), digitally assisted intubation (22), fiberoptic nasal intubation (25), nasal fiberoptically guided oral intubation (2), retrograde tracheal intubation (27), laryngoscopy with the Bullard laryngoscope, blind nasal intubation in the prone position with hyperextension of the neck (26), utilization of the paraglossal approach with a gum elastic bougie (4), or even utilization of the cleft to convert to a nasal intubation (3). Intervening procedures, such as cleft palate repair, may make a once-uncomplicated laryngoscopy difficult in the future by altering visualization of the larynx. Laryngoscopy may be easier after mandibular distraction surgery, but the incidence of difficult laryngoscopy does not approach zero.

Neonates may require prone positioning, a nasopharyngeal airway, suturing of the tongue to the lip, or even urgent tracheostomy to preserve the airway. Spontaneous ventilation may be improved by placing the patient prone so the tongue does not fall posteriorly into the pharynx. Patients should be closely observed postoperatively for evidence of airway obstruction (6). Consider scheduled postoperative ICU admission for severely affected airways.

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Pierre Robin syndrome

See Pierre Robin sequence

Pitt-Rogers-Danks syndrome

See 4p-syndrome

PKU

See Phenylketonuria

Plott syndrome

MIM #: 308850

This autosomal dominant or X-linked recessive disorder is one of congenital bilateral laryngeal abductor paralysis and intellectual disabilities. There is also sixth nerve palsy and possible visual or auditory impairment. The laryngeal motor defect is thought to be due to abnormal formation of the medullary nucleus ambiguus. Nonfunctioning of the posterior cricoarytenoid, the only cord abductor, results in a midline, adducted position of the vocal cords at rest, with complete adduction with crying. The other clinical manifestations are thought to be due to developmental abnormalities of other cranial nerve nuclei, particularly IX, X, and XII. It is unclear if the intellectual disability is a primary event or is a sequela of episodes of perinatal asphyxia. A gene for the autosomal dominant disorder has been localized to the long arm of chromosome 6.

HEENT/Airway: Possible blank facies. Possible abnormal vision and hearing. Sixth nerve palsy. High-arched palate. Micrognathia. Bilateral congenital laryngeal abductor paralysis with neonatal stridor at rest that may be severe

enough to cause asphyxia.

Neuromuscular: Intellectual and motor delay.

Anesthetic Considerations: Intellectual disabilities may make the gentle induction of anesthesia more difficult. Difficult laryngoscopy and tracheal intubation have not been reported. Patients are at risk for the development of postanesthesia stridor. One child has had severe bouts of postanesthesia coughing (2).

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Poikiloderma congenitale syndrome

See Rothmund-Thomson syndrome

Poland sequence

MIM #: 173800

This disorder involves unilateral hypoplasia or aplasia of the chest wall muscles, hypoplasia of the chest wall structures, and ipsilateral syndactyly. It has been suggested that Klippel-Feil sequence, Moebius sequence, and Poland sequence, all of which can occur in various combinations in the same patient, be grouped together and that they represent anomalies from fetal disruption of the subclavian artery, the vertebral artery, or one of their branches around the 6th week of development. Therefore, some advocate calling these the “subclavian artery supply disruption syndromes.” Poland sequence is sporadic, although rare familial instances have occurred. It is three times as common in boys as in girls, and three-fourths of cases are right sided.

HEENT/Airway: Flat facies from involvement of cranial nerves XI and XII has been reported.

Chest: Unilateral hypoplasia or aplasia of the pectoralis major muscle, nipple, and areola. Rib defects. Breast aplasia in girls.

Cardiovascular: Occasional dextrocardia in left-sided Poland sequence, but one case with right-sided disease has been reported. Dextrocardia apparently requires partial agenesis of at least two ribs.

Neuromuscular: Unilateral hypoplasia or aplasia of pectoralis minor, the sternal head of the pectoralis major, latissimus dorsi, and serratus anterior.

Orthopedic: Ipsilateral hypoplasia of distal limbs with varying degrees of syndactyly, brachydactyly, oligodactyly, and, rarely, a more severe limb reduction defect. Occasional hemivertebrae or winged scapulae.

GI/GU: Occasional renal anomaly.

Other: Patchy absence of axillary hair. Rare situs inversus.

Miscellaneous: Poland's account (1841) was based on George Elt, a deceased convict he dissected while he (Poland) was still a medical student.

Anesthetic Considerations: Patients with significant chest wall muscle abnormalities may be at increased risk for perioperative respiratory complications, including paradoxical respirations while under general anesthesia. Peripheral vascular access may be limited in patients with significant limb abnormalities.

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Polyostotic fibrous dysplasia

See McCune-Albright syndrome

Polysplenia

Synonym: Ivemark syndrome; Heterotaxy syndrome

MIM #: 208530

Polysplenia, and the related syndrome of asplenia (see earlier), are often thought of as disorders of laterality: patients with asplenia are bilaterally right sided (i.e., they have two copies of right-sided structures, and they lack normal left-sided structures, the spleen being one), and patients who are polysplenic are bilaterally left sided (left isomerism). Thus, they often have neither situs solitus nor sites inversus, but are said to have situs ambiguus. However, true bilateral left sidedness is not found in all patients and in even less in those who present as adults, who typically would not have complex congenital cardiac disease. Multiple genes are known to be involved in the development of normal human laterality. Heterotaxy is the general term for abnormal embryonic development of normal left-right asymmetry. The responsible gene or genes have not yet been identified, although several mutations have been identified in patients with polysplenia. Although most cases are sporadic, there is an increased incidence of congenital heart defects in close family members. Some patients may have this disorder and be asymptomatic. Hearts defects with polysplenia tend to be more amenable to two ventricle repairs than with the related asplenia syndrome, which more often requires Fontan-like single-ventricle repairs.

Chest: There are two left lungs [bilobed with the bronchial-arterial relationship of the left lung (a hyparterial bronchus below the pulmonary artery)].

Cardiovascular: Patients with polysplenia have a wider variety of cardiac defects than patients with asplenia, and they have a somewhat lower incidence of pulmonary stenosis or atresia. Patients with polysplenia have two left atria (“left atrial isomerism”). Thus, there is no true sinoatrial node. There is absence of the inferior vena caval connection to the right atrium, with azygos continuation to the superior vena cava and independent entry of the hepatic veins to the atria. Because there are two left atria, there may well be abnormal pulmonary venous return, often to the right side of the atria. May have atrioventricular canal defect. May have absent coronary sinus. The conduction system is variable. Can have congenital extrahepatic portosystemic shunts (such as splenorenal), with development of hepatopulmonary syndrome (3). Cardiopulmonary anatomy is reviewed in references (1,2,4).

Neuromuscular: May have agenesis of the corpus callosum.

GI/GU: There may be multiple small spleens, all located to the left of the spine. There is laterality to the “tacking down” of the fetal GI tract in normal fetuses (which is why the appendix fairly reliably ends up in the right lower quadrant). In this disease of abnormal laterality, there may be malrotation of the gut, which can present with volvulus. There are two left lobes to the liver and often no gallbladder, also a right-sided structure. May have extrahepatic biliary atresia. May have horseshoe adrenal gland. Can have annular or semiannular pancreas. Agenesis of the dorsal pancreas has been described. Splenic torsion has been described.

Miscellaneous: From a semantic point of view, it is unfortunate that the genes *LEFTY A* and *LEFTY B* have been cleared of having a role in the causation of this syndrome.

Anesthetic Considerations: Specific anesthetic management varies with the individual cardiac defect. Vascular abnormalities might affect cannulation techniques for cardiopulmonary bypass. Patients having cardiac surgery may develop conduction abnormalities. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Although not reported, presumably there would be no relative advantage to using a left-sided, double-lumen endobronchial tube, because both lungs have the anatomy of a left lung. Patients may be referred for a prophylactic Ladd procedure for asymptomatic malrotation.

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Pompe disease

Synonym: Glycogen storage disease type II; Acid maltase deficiency; Alpha-1,4-glucosidase deficiency

MIM #: 232300

This autosomal recessive glycogen storage disease, due to the absence of lysosomal acid maltase (alpha-1, 4-glucosidase), results in glycogen deposition in a wide variety of organs, including the heart, skeletal muscle, smooth muscle, brain, spinal cord, kidney, liver, spleen, and tongue. In the other glycogen storage diseases, glycogen is stored diffusely in the cytoplasm. In Pompe disease, it is stored in the lysosomes. There are multiple alleles. Disease presenting in infancy is often fatal in the 1st year of life, from respiratory failure or cardiomyopathy. A high-protein, low-carbohydrate diet has been found to be beneficial in several adults with the disease. Recombinant α-glucosidase is available and is of particular utility in infants, but has also provided improved exercise tolerance and pulmonary function in older patients. The subsequent reduction in ventricular mass likely reduces anesthetic risk. Unfortunately, antibodies to the replacement enzyme can occur.

The infantile form, classic Pompe disease, is marked by hypotonia and cardiomegaly. In the juvenile and adult forms, skeletal muscle involvement is predominant with minimal cardiac involvement. The classic disease is

described here.

HEENT/Airway: The large tongue and muscle weakness can cause significant airway obstruction. Oropharyngeal dysphagia has been reported in late-onset patients.

Chest: Decreased cough and poorly coordinated swallowing increase the risk of aspiration. Massive cardiomegaly can compress the bronchi, causing atelectasis. Respiratory insufficiency from muscle weakness can be severe even in the milder adult-onset type.

Cardiovascular: Cardiomegaly is prominent. Ventricular hypertrophy. Cardiomyopathy with congestive heart failure usually develops by 2 to 3 months of age. The electrocardiogram typically shows left ventricular hypertrophy, a wide QRS complex, a short PR interval, and T-wave inversion. There can be hypertrophy of the ventricular septum sufficient to cause outflow obstruction.

There does not appear to be cardiac involvement in the adult form.

Neuromuscular: Normal intellectual development. Hypotonia, progressive muscle weakness.

GI/GU: Feeding difficulty in neonates. There can be hepatomegaly, but not to the massive degree seen with von Gierke disease. Hepatic function is normal. There is no hepatic enlargement in the adult form.

Other: There is no hypoglycemia.

Miscellaneous: Johannes Pompe, a Dutch pathologist, was killed by the Nazis shortly before the liberation of The Netherlands. He had maintained a clandestine radio in his laboratory and was executed for blowing up a strategic rail line.

Anesthetic Considerations: Macroglossia may compromise the airway during induction of anesthesia and may also complicate laryngoscopy. Succinylcholine should be used with caution in this muscle disease because of the risk of exaggerated hyperkalemia. A regional technique with ketamine sedation has been used successfully in infants who have required a muscle biopsy (7) but would be relatively contraindicated with obstructive cardiomyopathy. A patient who developed *torsade de pointes* with a ketamine induction has been reported (1). Patients with muscle weakness, including diaphragmatic weakness, are at risk for perioperative respiratory compromise (10). Hypotonic infants may require no muscle relaxants, which will simplify postoperative management. Patients may require postoperative mechanical ventilation. Neuraxial anesthesia could be appropriate in adults who do not have cardiac disease (4,5), and caudal blocks have been used in infants (2).

Anesthetics with myocardial depressant effects should be avoided in most cases, and cardiac arrest with a sevoflurane induction (with or without propofol) has been reported (3,6,7) as has arrest with halothane (12). The specific cardiac lesion must be delineated because the optimal anesthetic technique for cardiomyopathy with poor ventricular function is at odds with the optimal anesthetic technique for

obstructive cardiomyopathy. Ejection fraction can be overestimated in the presence of profound myocardial hypertrophy leading to unwarranted reassurance. Higher ventricular filling pressures are required by hypertrophied hearts and are required in the face of dynamic left ventricular outflow obstruction, and systemic vascular resistance needs to be maintained in order to assure adequate coronary perfusion in the face of higher left ventricular diastolic pressure. Anesthetic agents, which decrease systemic vascular resistance, should be used sparingly if at all.

Figure: See **Appendix E**

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Popliteal pterygium syndrome

Synonym: Faciogenitopopliteal syndrome

MIM #: 119500

This autosomal dominant disorder is characterized by lower lip mucous cysts, cleft lip or palate, genital anomalies, and popliteal pterygia (webs). There is marked variability in expression. The disorder is allelic with van der Woude syndrome (see later), as both are due to defects in the gene encoding interferon regulatory factor 6. In mildly affected patients, this syndrome is easily confused with van der Woude syndrome.

HEENT/Airway: Ankyloblepharon filiforme adnatum (webbing between the eyelids). Occasional conductive hearing loss. Lower lip mucous cysts. Cleft lip or palate. May have intraoral webbing (syngnathia). Syngnathia can vary from a few thin connections to bony fusion.

Chest: Short sternum. May have bifid ribs.

Neuromuscular: Normal intelligence.

Orthopedic: Popliteal webs, which can extend from the ischial tuberosity to the heel. Can also have muscle or other lower extremity anomaly, such that repair of webs does not completely restore lower extremity function. Syndactyly of toes and fingers. Dysplastic nails.

GI/GU: Genital anomalies, including hypoplastic labia majora, bifid scrotum, and cryptorchidism. May have hypoplastic vagina and uterus. Genital anomalies may be secondary to intercrural pterygia. May have inguinal hernias.

Miscellaneous: Single-nucleotide polymorphisms in interferon regulatory factor 6 are thought to be a major contributor to the development of cleft lip with or without cleft palate.

Anesthetic Considerations: Mouth opening and access to the larynx may be severely limited by intraoral webbing, which connects the mandibular and maxillary alveolar ridges. In addition, the tongue may be displaced posteriorly. Division of oral bands can be done with no anesthesia if the bands are small enough. Awake intubation of neonates has been suggested for the potentially difficult airway (5) and nasal fiberoptic intubation, and optical stylets have also been used (1,2). Intubation via an LMA has been reported, but would require adequate mouth opening. The lower extremities must be carefully positioned because the sciatic nerve and the popliteal artery are often contained within the popliteal web.

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Porphyria

MIM #: 176000, 176090, 176100, 176200, 121300, 125270, 263700

The several porphyrias are associated with defects in heme synthesis and the overproduction of heme precursors (see **Appendix F**). There is great clinical heterogeneity. The porphyrias can be separated into the erythropoietic or hepatic porphyrias, depending on the major site of heme precursor overproduction. In all forms, environmental factors can alter the clinical expression. Decreased heme concentration stimulates the regulatory enzyme ALA synthetase (delta-aminolevulinic acid synthetase), which stimulates porphyrins produced proximal to the enzymatic block. Acute attacks are manifest by abdominal pain, autonomic instability, electrolyte disturbances, and neuropsychiatric changes. Most attacks occur between puberty and menopause. Attacks range from mild to fatal. Factors that have triggered attacks include starvation, infection, pregnancy, estrogens, exposure to sunlight, and drugs (see Table 4), including barbiturates, sulfonamides, oral contraceptives, anticonvulsants, and alcohol. Barbiturates trigger a crisis by

stimulating the cytochrome P450 system, incorporating more heme into new cytochromes, decreasing heme levels, and thereby decreasing negative feedback on ALA synthetase activity. Latent carriers, such as prepubertal children of porphyric families, can have acute attacks on exposure to porphyrinogenic drugs. The mortality rate with an acute attack is approximately 10%, usually secondary to infection, respiratory failure, or arrhythmia. More than 50% of pregnant women with porphyria experience an attack during pregnancy, with the mortality rate reported to be as high as 42%.

TABLE 4. Anesthetic drugs and porphyria

Drug class	Likely safe	Likely unsafe	Unclear
Intravenous anesthetics	Midazolam Lorazepam Propofol	Barbiturates Etomidate Chlordiazepoxide Flunitrazepam Nitrazepam	Diazepam Ketamine
Inhalational	Nitrous oxide	Enflurane (based on animal	Sevoflurane

anesthetics	Halothane Isoflurane Desflurane	data)	
Muscle relaxants	Succinylcholine Vecuronium d-Tubocurarine Pancuronium Rocuronium Atracurium *cis*-Atracurium		
Premedications	Scopolamine Benzodiazepines Atropine Droperidol Promethazine Chloral hydrate Diphenhydramine Cimetidine		
Opioids	Morphine Fentanyl Alfentanil Remifentanil Meperidine Naloxone	Pentazocine	Sufentanil
Anticholinesterases	Neostigmine		
Local anesthetics	Bupivacaine Lidocaine Procaine	Mepivacaine	Prilocaine
Cardiovascular	Atropine Epinephrine ß-Blockers Labetalol Guanethidine Reserpine α-Blockers Furosemide	Alpha-methyldopa Hydralazine Phenoxybenzamine Nifedipine	Amiodarone

Other	Glucose loading Anticonvulsants Metoclopramide Diclofenac Haloperidol	Oral contraceptives Griseofulvin Cimetidine	Ranitidine

Modified partially from Jensen NF, Fiddler DS, Striepe V. Anesthetic considerations in porphyrias. *Anesth Analg* 1995;80:591-599; Harrison GG, Meissner PN, Hift RJ. Anaesthesia for the porphyric patient. *Anaesthesia* 1993;48:417-421; and James MFM, Hift RJ. Porphyrias. *Br J Anaesth* 2000;85:143-153.

The erythropoietic porphyrias include congenital erythropoietic porphyria (CEP), erythropoietic protoporphyria (EPP), and hepatoerythropoietic porphyria (HEP). CEP is an uncommon autosomal recessive disorder of uroporphyrinogen III cosynthetase. EPP is an autosomal dominant disorder due to deficient activity of ferrochelatase, and the clinical findings are similar to those of CEP, with the exception of milder skin findings. EPP is the most common of the erythropoietic porphyrias. HEP is a rare autosomal recessive disorder due to decreased activity of uroporphyrinogen decarboxylase. Clinical findings are similar to CEP.

The hepatic porphyrias include the more widely known variants, acute intermittent porphyria (AIP), porphyria cutanea tarda (PCT), hereditary coproporphyria (HC), and variegate porphyria (VP). AIP is an autosomal dominant disorder due to diminished activity of uroporphyrinogen I synthase (PBG deaminase). It is one of the more common porphyrias and has variable clinical manifestations, depending on environmental factors, such as drug exposure. Patients are usually asymptomatic between episodes of clinical attacks. PCT is also relatively common. It is autosomal dominant and may occur sporadically. PCT is due to decreased activity of uroporphyrinogen decarboxylase. There is incomplete penetrance, and not all carriers of the gene have symptoms. Acute attacks, as with AIP, do not occur. HC is an autosomal dominant disorder due to diminished activity of coproporphyrinogen oxidase. There is variable expression of the disease, which is similar to, but milder than, AIP. VP is an autosomal dominant disorder due to a defect in the gene for protoporphyrinogen oxidase. This enzyme, located on the inner membrane of mitochondria, catalyzes the conversion of protoporphyrinogen IX to protoporphyrin IX.

Acute attacks are found with AIP, HC, and VP and also with aminolevulinic acid dehydratase deficiency (the very uncommon plumboporphyria). PCT and the erythropoietic porphyrias CEP and EPP are not associated with drug-induced crises.

HEENT/Airway: *CEP:* Deformation of the nose, ears, eyelids, and corneas from secondary skin infections. Reddish-brown teeth.

HEP: Discoloration of teeth.

Chest: *AIP:* Chest or back pain with attacks. Respiratory failure from neuropathy, which may be fatal.

Cardiovascular: *AIP:* Tachycardia or hypertension with an attack.

VP: Hypertension during attacks.

Neuromuscular: *AIP:* Muscle weakness, sensory disturbances, or psychiatric disturbances (disorientation, hallucinations, paranoia, anxiety, depression) with attacks. There may also be a neuropathy (motor > sensory) that can include cranial nerve and bulbar dysfunction during an acute attack and which may predict impending

respiratory failure from paralysis. The neuropathy can also involve the hypothalamus and the splanchnic nerves. There may be neuronal damage and axonal degeneration followed by demyelination. There may be residual weakness after a severe attack, which may take several months for full recovery. Twenty percent of patients in crisis have seizures during the crisis.

HC: Similar to, but milder than, AIP.

VP: Similar to AIP

Orthopedic: *CEP and HEP:* Deformation of the digits from secondary skin infections, pathologic fractures.

AIP: Bone pain with attacks.

GI/GU: *CEP and HEP:* Hemolytic anemia with hypersplenism, cirrhosis. Reddish-brown urinary staining of diaper in infants.

EPP: Protoporphyrin-containing biliary stones, cirrhosis, hepatic failure.

AIP: Abdominal pain, vomiting, ileus, and constipation during episodic attacks. Urinary dysfunction (retention or incontinence) with attacks. The urine turns reddish brown ("port wine") on standing. Some women have attacks related to the menstrual cycle.

PCT: Hepatic involvement common by adulthood. Cirrhosis, focal necrosis, hepatoma.

VP: Minimal hepatic involvement.

Other: *CEP and HEP:* Severe cutaneous photosensitivity (to light with a wavelength of approximately photosensitivity 400 nM) with formation of bullae and subsequent scarring and hyperpigmentation. Friable skin and hypertrichosis.

EPP: Similar, but less severe. Scarring and hyperkeratosis, if present, are mild.

AIP: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

PCT: Cutaneous photosensitivity with bullae, scarring, hyperpigmentation, friable skin, hypertrichosis, lichenification.

HC: Similar to PCT.

VP: Similar to PCT. Attacks of VP result in hyperpigmentation and hypertrichosis.

Miscellaneous: Hematin (used to treat acute attacks of porphyria) was the first drug approved under the Orphan Drug Act.

Plumboporphyria derives its name from the increased levels of ALA analogues in the urine, similar to that found in lead poisoning. Lead levels in plumboporphyria are, however, normal.

Variegate porphyria is particularly common in South Africans of Afrikaans descent, where its arrival can be traced back to a single Dutch settler (or his wife, who was one of the orphan girls sent to South Africa to provide wives for the early Dutch settlers).

The malady of George III of England has been suggested to be porphyria (and hotly debated). Although the symptoms of George suggest AIP, the skin and other manifestations of his family suggest the variegate type. In addition, it has recently been suggested that his condition was exacerbated by high levels of arsenic, delivered in arsenic containing medications (4).

Anesthetic Considerations: Abdominal findings may lead to the misdiagnosis of a surgical abdomen during an acute attack of AIP. Dehydration, fever, infection, stress (including surgery), and endogenous steroids can all induce ALA synthetase (the initial and rate-limiting step in heme synthesis). Psychological stress has been reported to precipitate crises, so good premedication is indicated in patients with porphyria. Scarring from phototoxicity around the nose, mouth, and neck could result in a challenging airway. Care needs to be taken perioperatively to avoid causing inadvertent skin infections from skin trauma. Lighting should be as dim as practical or an appropriate light filter used for patients with photosensitivity (an acrylate filter to filter out wavelengths <530 nM). Even the light from an endoscope or a pulse oximeter can cause burns in patients with erythropoietic porphyria from photoactivation of protoporphyrin deposits in skin. Maintenance of adequate hemoglobin levels will minimize heme synthesis and minimize protoporphyrin levels.

Ketamine has been implicated in porphyrinogenesis (16), although it has also been used uneventfully on multiple occasions. There are many reports of the successful use of propofol in patients with porphyria (3,13,15,22). However, an asymptomatic increase in porphyrinogenesis has been described in one patient who was given propofol (20). Also, a prolonged alteration in consciousness with transient neurologic symptoms and elevated porphyrins was described in a patient who received propofol who did not have a prior diagnosis of porphyria (14). However, in this patient, the diagnosis of porphyria remains unproven (12). Despite its contraindication in patients with porphyrias, barbiturates have been given during latent phases without causing clinical manifestations, making interpretation of claims for the safety of other agents difficult if they were also administered during latent phases of the disease. In fact, it is rare for any anesthetic drug to cause symptoms in latent disease. Morphine or other opioids can be used for pain, but may worsen constipation or urinary retention during an acute attack.

Because cold can induce stress and increased steroid synthesis, minimal hypothermia (32°C) has been suggested for cardiac surgery (17), although others have allowed patient temperatures of less than 30°C (24). One of these patients had postoperative biochemical evidence of an acute crisis.

Treatment of an acute episode includes hematin 1 to 4 mg/kg/d (possible side effects include renal failure, thrombophlebitis, and coagulopathy) or hemoperfusion to remove porphyrin precursors. Oral or intravenous carbohydrate or glucose loading may be helpful during an acute attack. Electrolytes, including magnesium, should be measured and repleted appropriately. Hypovolemia and autonomic neuropathy during an acute attack may be an indication for invasive blood pressure monitoring. A crisis may occur up to 5 days postoperatively.

Not surprisingly, regional anesthesia has been used successfully (23,25); however, regional techniques during an acute attack may cloud neuropathic changes, and mental status changes and cooperation may be a problem. Hypovolemia and autonomic instability during an acute attack increase the risk of hemodynamic instability associated with the sympathectomy of major regional techniques. Although theoretical differences exist, there does not appear to be any advantage or disadvantage with any specific local anesthetic.

It is likely that single, acute exposures to potent inducers, such as short-term exposure to anesthetic drugs, are tolerated in the stable patient, but can be problematic in the patient in whom a crisis has already developed. Exposure to multiple inducers is likely significantly worse than exposure to a single inducing drug. There are a variety of resources available on the Web regarding the most current information about the risk of specific drugs. The information about safety profiles keeps changing and, due to limited information, might differ from site to site. Just some of the available sites are:

www.porphyria-europe.com/

www.porphyriafoundation.com/about-porphyria/types-of-porphyria/AIP (United States, Europe, and South Africa)

www.wmic.wales.nhs.uk/porphyria_info.php#why

http://porphbook.tripod.com/2.html (Helpful as it lists the potentially dangerous drug only)

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Postaxial acrofacial dysostosis syndrome

See Miller syndrome

Potter syndrome

Synonym: Oligohydramnios sequence

MIM #: None

When Potter described this dysmorphic syndrome, she described it in association with bilateral renal agenesis. However, it has become clear that it is due to the *in utero* fetal effects of oligohydramnios. The etiology of the oligohydramnios is unimportant. For example, decreased amniotic fluid production, as with renal agenesis or obstruction, and amniotic fluid loss from chronic amniotic fluid leak both result in similar features.

HEENT/Airway: Hypertelorism, epicanthal folds, low-set ears, flattened, beaked nose, micrognathia.

Chest: Pulmonary hypoplasia. Respiratory failure is a common cause of immediate postnatal death.

Cardiovascular: A variety of congenital cardiac defects have been described.

Orthopedic: Spade-like hands.

GI/GU: May have renal agenesis.

Other: Maternal oligohydramnios.

Miscellaneous: Edith Potter was a prominent pediatric pathologist at the Chicago Lying-in Hospital. The condition now bearing her name has been described sporadically since the 1600s. Dr. Potter delineated the characteristics of this syndrome after performing a series of 5000 fetal and neonatal autopsies.

Anesthetic Considerations: Pulmonary hypoplasia may require urgent intubation and sophisticated mechanical ventilatory strategies immediately after delivery. Direct laryngoscopy may be difficult secondary to micrognathia. Renal dysfunction in infants requires precise titration of perioperative fluids and has implications for the choice of anesthetic drugs.

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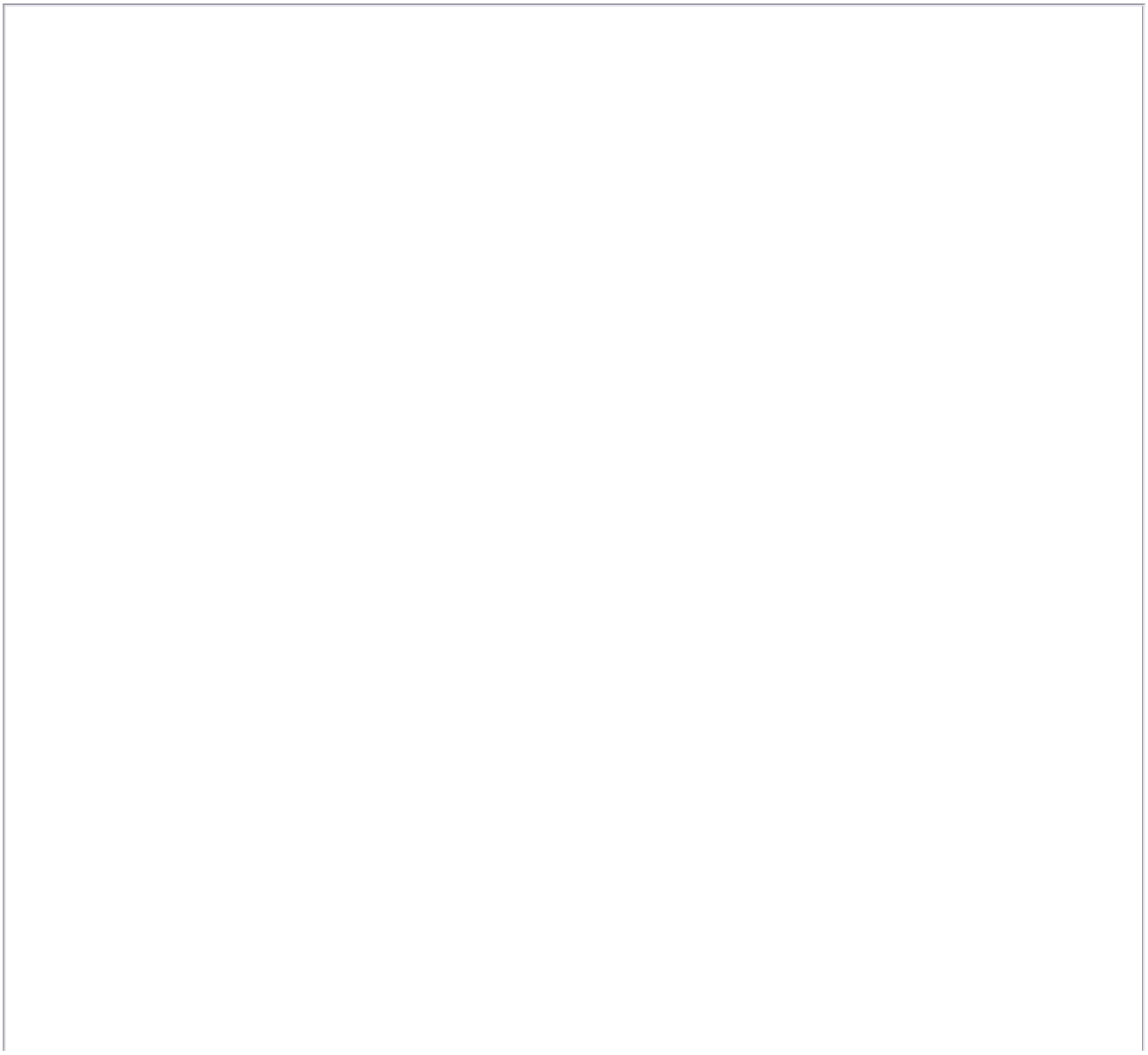
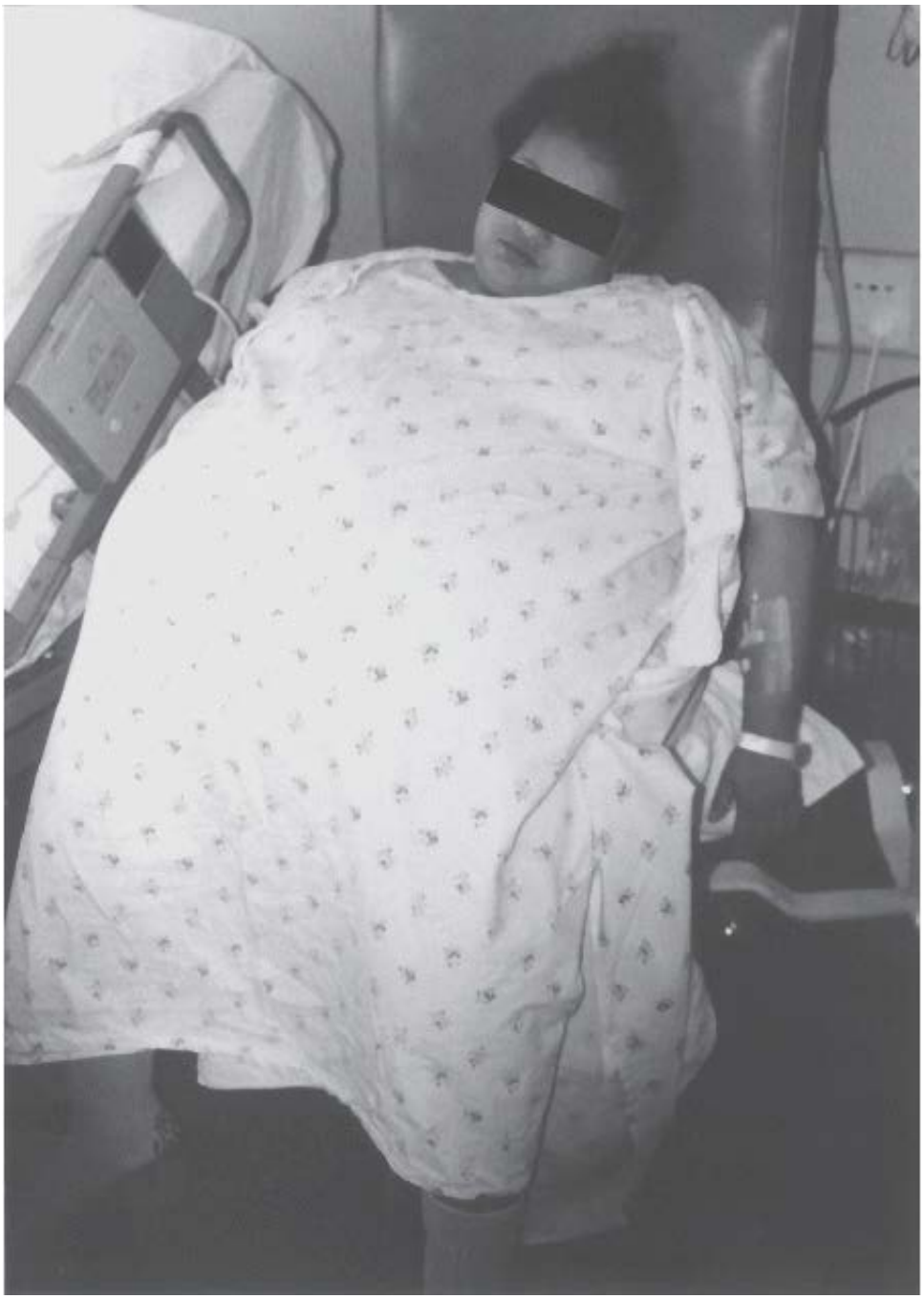
Prader-Willi syndrome

MIM #: 176270

This autosomal dominant disorder is classically characterized by hypotonia, hypomentia, and hypogonadism that is associated with obesity. There is phenotypic variability, and many patients do not display the classic body habitus. This continuous gene disorder is due to a partial deletion of the long arm of chromosome 15 between 15q11 and 15q13. Similar deletions are present in Angelman syndrome (see earlier), although the origin of the chromosomal deletion is maternal in Angelman syndrome and paternal in Prader-Willi syndrome. Contiguous genes involved in the deletion are the paternal copies of the imprinted *SNRPN* (small nuclear ribonucleotide polypeptide N) gene, the *necdin* gene, and possibly other genes. The main clinical features of the syndrome include decreased fetal activity, obesity, hypotonia, intellectual disabilities, short stature, hypogonadotropic hypogonadism, and small hands and feet. Neonatal hypotonia may cause feeding difficulties early on, but the characteristic hyperphagia begins by several years of age. Maladaptive behaviors, often revolving around access to food, develop in late childhood and adolescence.





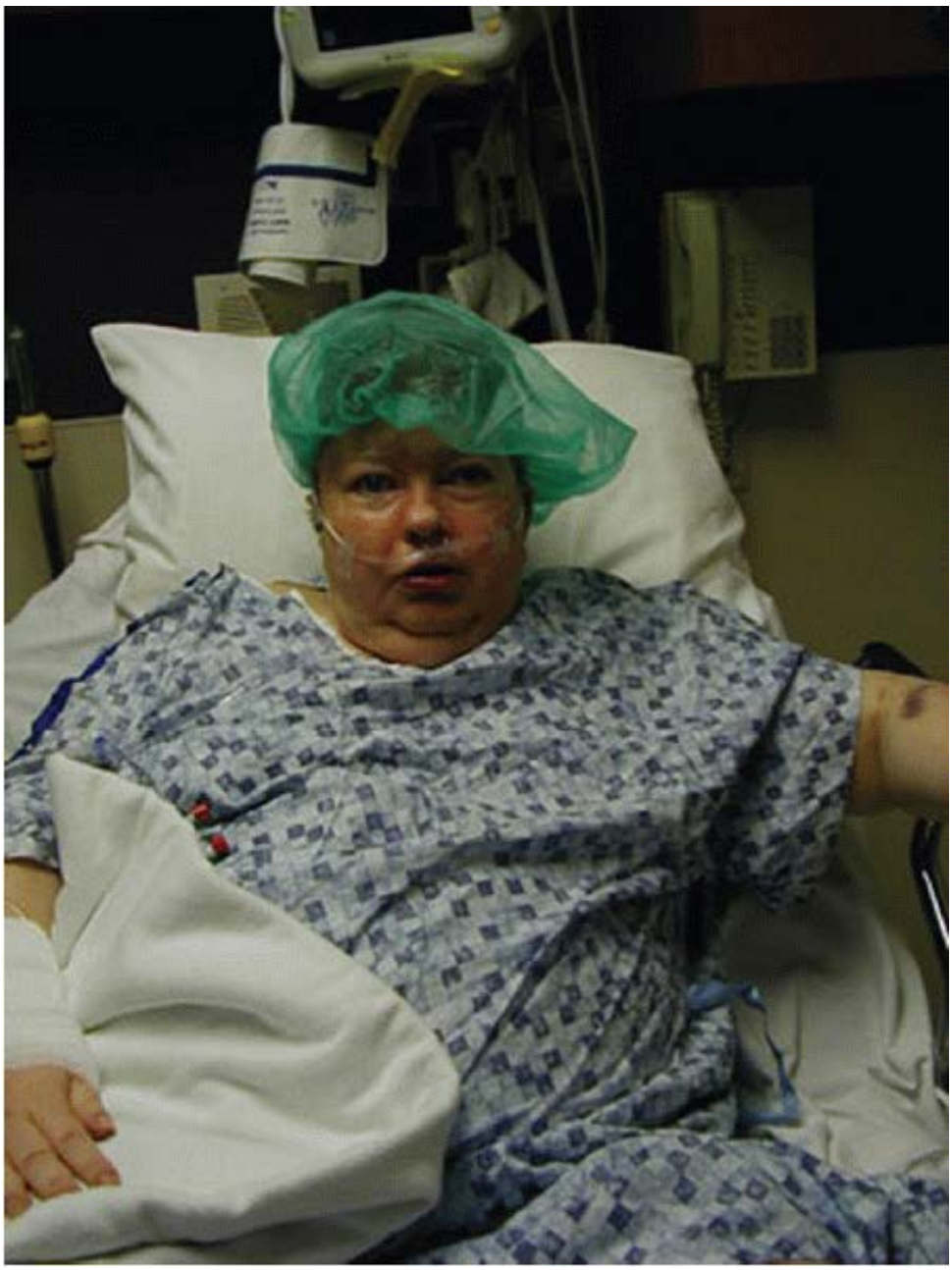
Prader-Willi syndrome. FIG. 1. This 125-kg 19-year-old young lady with Prader-Willi syndrome has massive central obesity. She has severe intellectual disability and motor delay. She does not talk, is not ambulatory, and has a history of seizures.

HEENT/Airway: Narrow bifrontal diameter. Strabismus, myopia. Dental enamel hypoplasia. Viscous saliva.

Chest: Neonatal asphyxia secondary to hypotonia and hypoventilation. Poor cough and restrictive lung disease from hypotonia may result in recurrent pulmonary infections. May be Pickwickian (chronic pulmonary hypoventilation secondary to obesity). Hypoventilation and sleep apnea may be related, at least in part, to an abnormality of

peripheral chemoreceptor pathways (10). May have sleep apnea.

Cardiovascular: May have pulmonary hypertension secondary to chronic hypoventilation. Arrhythmias may develop, primarily, premature ventricular contractions. May have hypertension.



Prader-Willi. FIG. 2. This 118-kg 47-year-old man was admitted for dental restorations. He has pulmonary arterial hypertension and right ventricular failure secondary to multiple pulmonary emboli. He is on home oxygen. Additional medical problems included systemic hypertension, depression, hyperthyroidism, gastroesophageal reflux, hyperlipidemia, anemia, and newly diagnosed type II diabetes. He is not very verbal and requires assistance walking and toileting. Despite his obesity, he was an easy intubation. He required readmission 2 days later for dehydration secondary to mouth discomfort. Hospitalization for undereating seemed somewhat ironic.

Neuromuscular: Hypotonia beginning at birth, which may require gavage feedings for several months. Improvement in cough, cry, and feeding over the 1st year. Intellectual disability with average IQ 50 to 60. There are food-related behavior problems. Labile temperament and temper tantrums are common. May have psychotic episodes. Tend to be relatively insensitive to pain. Tend to pick excessively at sores. Can have central apnea and temperature lability, due to hypothalamic (or parasympathetic) dysfunction.

Orthopedic: Short stature. Small hands and feet with tapered fingers. Hypermobile joints. Scoliosis and kyphosis.

GI/GU: Prolonged feeding problems as infants, which converts to uncontrollable hyperphagia in the 2nd year of life. Ischemic gastroenteritis has been reported. There is an increased incidence of rumination. Cryptorchidism and hypoplastic penis and scrotum in boys, hypoplastic labia in girls, and hypogonadotropic hypogonadism in both sexes. Precocious puberty has been reported.

Other: Decreased fetal activity, mild prenatal growth retardation. Morbid obesity with insatiable hunger and hypoglycemia beginning at approximately 1 year of age. Plethoric obesity and striae are common. Noninsulin-dependent diabetes mellitus in the adolescent/adult. Survival is probably normal if weight and diabetes can be controlled, but is shortened otherwise. May have increased risk of myeloid leukemia. Erythrocytosis may develop secondary to chronic hypoventilation. Rarely, some degree of central adrenal insufficiency. Hypopigmented, photosensitive skin with light hair and blue eyes. Growth hormone treatment has been used to increase height velocity and decrease body mass index (BMI).

Miscellaneous: Charles Dickens in *The Pickwick Papers* described “a fat and red-faced boy in a state of somnolency,” which may have been the first written description of Prader-Willi syndrome. *The Pickwick Papers* is also the origin of the term “Pickwickian,” a term used to describe someone who has chronic pulmonary hypoventilation secondary to obesity.

Anesthetic Considerations: Laryngoscopy and tracheal intubation may be difficult secondary to morbid obesity. Patients may steal food and may not be truly NPO as expected. This, plus obesity and the increased incidence of rumination, suggests that all of these patients should be considered at high risk for gastric aspiration (11). Secretions may be viscous. Use preoperative sedation and opioids with caution due to respiratory depression. Obesity may result in desaturation with induction of anesthesia because of increased airway closure and decreased functional residual capacity. Bronchospasm has been reported after induction (9). The presence of decreased pulmonary reserve and obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period (3). Postoperative pulmonary edema has been reported.

Venous access and identification of landmarks for regional anesthesia may be difficult secondary to morbid obesity. Perioperative blood glucose should be monitored, and younger patients may require glucose-containing intravenous fluids, whereas older patients with type II diabetes may require insulin to maintain normoglycemia. Patients may have cor pulmonale or exhibit intraoperative arrhythmias (primarily premature ventricular contractions). Temperature regulation may be impaired, and patients may exhibit perioperative hypothermia or hyperthermia. Central adrenal insufficiency with an abnormal stress response is possible but rare. Obese patients require lower-than-expected drug doses on a per-kilogram basis. Succinylcholine has been used without problems. Growth hormone treatment has been implicated in an increased risk of obstructive apnea, respiratory infection, and sudden death (4).

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Progeria

Synonym: Hutchinson-Gilford syndrome

MIM #: 176670

This rare autosomal dominant disorder is characterized by accelerated aging. There is progressive alopecia, decreased subcutaneous fat, and skeletal degeneration.

There is early and progressive coronary artery disease, with death usually occurring in the mid-teens secondary to ischemic heart disease. Although the inheritance pattern is not certain, there is evidence to support both autosomal dominant and autosomal recessive inheritance, and recently *de novo* mutations are being frequently invoked. The syndrome is caused by a mutation in the lamin A gene (*LMNA*). The specific mutation (from position 154,375,028 to 154,375,029 on the long arm of chromosome 1) resembles a splice donor, and 150 nucleotides in the *LMNA* gene are deleted. The abnormal protein ("progerin") remains permanently anchored to the inner nuclear membrane, binding other proteins and causing blebs to form, disrupting mitosis and altering gene expression. Interestingly, there is some evidence that fibroblasts from older individuals express the progerin form of lamin A, despite the fact that the gene is not mutated. This has led to speculation that progerin may play a role in the normal aging process.

HEENT/Airway: Thin calvarium, facial hypoplasia. May have microphthalmia, cataracts. May have low-frequency conductive hearing loss. Beak-like nose. Dental anomalies include missing, hypoplastic, and discolored teeth with dental caries. Oral motor abnormalities. May have decreased temporomandibular joint mobility. Micrognathia. High-pitched voice.

Chest: Thin ribs and small thoracic cage.

Cardiovascular: Progressive coronary artery disease in childhood. Progressive aortic and/or cerebral arterial atherosclerosis. Decreasing vascular function with aging. Early onset of hypertension. Death is usually secondary to myocardial infarction or congestive heart failure. Patients may benefit from percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. May develop premature calcific degeneration of aortic and mitral valves.

Neuromuscular: Intelligence is normal. Cerebrovascular disease may develop in childhood. Can have transient ischemic attacks. Intracranial hemorrhages have been reported after even minor trauma.

Orthopedic: Short stature. Arthritic, stiff joints with decreased range of motion. "Horse-riding" stance. Thin, fragile long bones. Early osteoporosis, pathologic fractures. Skeletal hypoplasia, dysplasia, and degeneration. Nail hypoplasia. Coxa valga.

Other: Thin skin, with progressive pigmentary changes. Alopecia. Decreased subcutaneous fat. Prominent scalp veins. No sexual maturation. May have diabetes. May have prolonged prothrombin time and elevated platelet count.

Miscellaneous: The first reference to this syndrome may have been in the *St. James Gazette* in 1754: "March 19, 1754 died in Glamorganshire of mere old age and a gradual decay of nature at 17 years and 2 months, Hopkins Hopkins, the little Welshman, lately shown in London. He never weighed more than 17 pounds." The first description of this syndrome in the medical literature was by Hutchinson in 1886. It was later called "progeria" by Gilford in 1904. The word *progeria* means "premature aging." Hutchinson wrote his own epitaph: "A Man of Hope and Forward-Looking Mind."

Anesthetic Considerations: Although patients appear old, they are emotionally and developmentally appropriate for their chronologic age and need to be related to as such. Lack of subcutaneous fat may make a good mask fit difficult. Limited mouth opening and fragile skin has resulted in lip and buccal tears from placement of an oral bite block (5). Micrognathia and decreased temporomandibular joint mobility can make direct laryngoscopy and

endotracheal intubation very difficult (6). Patients may require a smaller-than-expected endotracheal tube. Patients are likely to have abnormal dentition (4), and their teeth are susceptible to loss. Patients must be carefully positioned because of osteoporosis and the potential for pathologic fractures. The thin, fragile skin must be properly padded. Lack of subcutaneous fat may lead to perioperative hypothermia.

Patients are assumed to have coronary artery disease, with myocardium at risk for ischemia. Patients may be on chronic ß-blockers, which should be continued. Patients may also have significant cerebrovascular disease.

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Progressive diaphyseal dysplasia

See Camurati-Engelmann syndrome

Progressive hereditary nephritis

See Alport syndrome

Progressive myoclonus epilepsies syndrome

See Ramsay Hunt syndrome

Prolidase deficiency

MIM #: 170100

This autosomal recessive disease results in intellectual disabilities, chronic dermatitis, and recurrent infections. Prolidase (peptidase D) is one of the peptidases. It is involved in the metabolism of certain dietary oligopeptides (imidopeptides, as found in gelatin) in the intestinal epithelium and in the metabolism of collagen. It is found in a wide variety of organs, including the brain. There is wide variability in the clinical expression of this disorder, and there are also codominantly expressed alleles that can affect prolidase structure without affecting function.

HEENT/Airway: Severely affected patients may have prominent skull sutures, ptosis, hypertelorism, and proptosis. Low posterior hairline. Small beaked nose. Narrow upper lip. Chronic ear and sinus infections are common.

Neuromuscular: Variable intellectual disabilities. Abnormal gait and posture.

Orthopedic: Foot amputation has been required because of severe lower leg ulcerations.

GI/GU: Hepatosplenomegaly, abnormal spleen histology.

Other: The skin rash consists of diffuse telangiectasis, petechiae, purpura, ecchymosis, or ulceration, particularly of the lower leg. Increased incidence of infection. Topical proline has been suggested for leg ulcer treatment. Can have lupus-like disease.

Anesthetic Considerations: Patients must be carefully positioned and padded perioperatively due to fragile skin, particularly if they have lower leg ulcerations. Patients may be receiving steroids to treat the rash and may require perioperative stress doses of steroid.

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Proline oxidase (dehydrogenase) deficiency

See Hyperprolinemia type I

Prolonged QT syndrome

See Long QT syndrome

Propionic acidemia

Synonym: Ketotic hyperglycinemia

MIM #: 606054

This autosomal recessive disease is the result of a defect in the gene for the mitochondrial enzyme propionyl-CoA carboxylase. This enzyme occurs as a tetrameric protein whose two protein subunits are encoded by genes located on chromosome 13 and chromosome 3. Propionyl-CoA carboxylase is an important enzyme near the end of the catabolic pathway for several essential amino acids, including isoleucine and valine, as well as three-carbon fatty acids. The result is accumulation of propionyl-CoA. Propionyl-CoA is an inhibitor of the synthesis of *N*-acetylglutamate, which is required for the conversion of ammonia to urea. Some of the highest ammonia levels ever recorded have been in patients with this disease. Propionic acidemia also results in secondary carnitine deficiency. Propionyl-CoA is split into propionic acid and coenzyme A. The propionic acid is responsible for acidosis in this disease. The disease usually presents with life-threatening episodes of ketoacidosis, from inhibition of the citric acid cycle by propionic acid. Clinical exacerbations are associated with increased dietary protein or intercurrent infection. Symptoms are usually exacerbated when weaning from breast milk because breast milk is relatively low in protein. Propionyl-CoA carboxylase is also affected by abnormalities of biotinidase and holocarboxylase synthetase, both of which affect the availability of biotin, a cofactor that binds to the alpha (chromosome 13) subunit.

There are several phenotypic presentations. The most severe form presents in the neonatal period. An intermittent late-onset form presents in older children and adolescents with acute episodes associated with catabolic stress or increased protein intake. In between episodes, patients are asymptomatic. The chronic progressive form can present as a digestive form with recurrent vomiting, or a neurologic form with muscle weakness and developmental delay. Liver transplantation has been offered to ameliorate symptoms.

HEENT/Airway: Corneal ulcerations. Puffy cheeks, exaggerated “Cupid's bow” upper lip. May have optic nerve atrophy.

Chest: Respiratory insufficiency secondary to neuromuscular involvement.

Cardiovascular: May develop cardiomyopathy.

Neuromuscular: Intellectual disability, which can be minimized or completely avoided with dietary protein restriction. Hypotonia. If untreated, anorexia progresses to lethargy, obtundation, seizures, coma, and death. There are spongiform changes in the white matter similar to those seen with other aminoacidemias. Magnetic resonance imaging scans show occasional basal ganglia changes and can have basal ganglia ischemic stroke. Visual hallucinations.

GI/GU: Severe vomiting during episodes of acidosis. Hepatomegaly. Renal tubular acidosis with hyperuricemia. Interstitial nephritis.

Other: Hyperammonemia. Ketoacidosis during acute exacerbations. Anorexia, failure to thrive. Neutropenia. Anemia and thrombocytopenia in infancy. Hypogammaglobulinemia. Psoriaform rash, alopecia, skin desquamation.

Miscellaneous: Propionic acid is one of the things that gives Swiss cheese its taste (made by the bacterium *Propionibacterium*). Since the enzyme defect is found throughout the body, liver transplantation is not curative, but will ameliorate symptoms. Recurrent courses of antibiotics can be used to inhibit formation of propionic acid by gut flora.

Anesthetic Considerations: Glucose level, ammonia level, pH, and renal function should be obtained preoperatively. The hematocrit and platelet count should be ascertained preoperatively in infants. Anesthetic management is directed toward avoiding the events that precipitate metabolic acidosis in these patients. Protein-restricted diets should be continued perioperatively. One child became comatose when tube feedings were instituted for failure to thrive. If the patient is receiving bicarbonate and/or carnitine, these should be continued in the perioperative period. Hypoxia, hypotension, and dehydration must be avoided. Patients should receive adequate perioperative glucose (intravenously if necessary) to minimize protein catabolism. It is advisable to avoid lactic acid-containing fluids such as lactated Ringer's or Hartmann's solution. An orogastric tube or throat packs should be placed for surgery with the potential for oral or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load and trigger an acute decompensation.

Medications that decrease gut motility should be curtailed (6). Propofol may be contraindicated because its emulsion is high in polyunsaturated fats (7). Drugs derived from propionic acid, including ibuprofen, naproxen, ketoprofen, and oxaprozin, should be avoided (7). Ester hydrolyzed muscle relaxants (succinylcholine, atracurium, and cis-atracurium) can be metabolized to propionic acid, but the implications of a very short course are unclear. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

Patients may have increased aspiration risk due to hypotonia or abnormal gag reflex from acid metabolites. Peripheral venous access may be difficult. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Patients with cardiomyopathy require an appropriately tailored anesthetic. Postoperatively, patients are at risk for respiratory embarrassment secondary to fatigue, hypotonia, and/or upper airway obstruction.

Figure: See **Appendix D**

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Protein C deficiency

MIM #: 176860, 612304

Protein C deficiency is one of the causes of hereditary thrombophilia, a familial propensity to develop venous thromboembolism. Protein C deficiency is usually inherited in an autosomal dominant fashion, with marked phenotypic variability. Caused by a mutation in the gene *PROC*, it is found in 3% to 4% of people who develop venous thromboembolism. There is a

more severe autosomal recessive form of protein C deficiency, which is also caused by a mutation in the gene *PROC*. Protein C is a vitamin K-dependent plasma protein, which is activated by thrombin. Once activated, it functions as an important anticoagulant by inactivating factors VIIIa and Va, thereby permitting fibrinolysis. Two major subtypes of heterozygous protein C deficiency have been described. Type I deficiency (most common) is characterized by diminished synthesis of protein C, with plasma protein C levels approximately 50% of normal. Symptoms are severe when the level of protein C is less than approximately 25% of normal. In type II deficiency, plasma protein C levels are in the normal range, but the protein is dysfunctional. Protein C deficiency is present in approximately 10% of families with inherited thrombophilia and in approximately 5% of individuals with deep vein thromboses. Heterozygous protein C deficiency is associated with an almost sevenfold increase in the incidence of deep vein thrombosis over that in a normal person. Human protein C concentrate is available for the prevention and treatment of venous thrombosis.

Chest: Can have pulmonary embolism.

Cardiovascular: Increased risk of myocardial infarction. Recurrent thrombosis of the deep veins of the legs, the iliofemoral veins, and the mesenteric veins. Approximately 40% will develop pulmonary emboli. May develop superficial thrombophlebitis. May develop cerebral venous thrombosis. Thromboses may be spontaneous or associated with other risk factors (contraceptive pill use, pregnancy, surgery, or trauma). Onset of thrombotic events is usually in the third decade of life.

GI/GU: Can have renal vascular thromboses.

Other: Patients with protein C deficiency may develop skin necrosis when placed on warfarin therapy. Infants with protein C deficiency may rarely develop *purpura fulminans*, with plasma protein C levels less than 1% of normal and frank disseminated intravascular coagulation.

Miscellaneous: First described in 1981 when Griffin and colleagues were investigating the cause of recurrent thrombophlebitis and pulmonary emboli in a 22-year-old whose family history included a father with recurrent thrombophlebitis and pulmonary emboli who had a stroke at the age of 43 and a myocardial infarction at the age of 45, a paternal uncle with recurrent thrombophlebitis and pulmonary emboli, a paternal grandfather who died suddenly at the age of 45 after a period of immobility (presumptive pulmonary embolism), and a paternal great-

grandfather who died unexpectedly of a stroke at the age of 61.

Anesthetic Considerations: Routine tests of coagulation will be normal. Prophylactic perioperative anticoagulation is already recommended for all patients where warranted, and identification of a hypercoagulable state would not alter this recommendation. Neuraxial anesthesia should be avoided in patients who are anticoagulated. Hypovolemia and hypotension might be expected to worsen the endogenous defect. Protein C concentrate, or lacking that, fresh frozen plasma may be used in the acute treatment of life-threatening thrombosis.

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Protein S deficiency

MIM #: 612336, 614514

Protein S deficiency is one of the causes of hereditary thrombophilia, a familial propensity to develop venous thromboembolism. Protein S deficiency is usually inherited in an autosomal dominant fashion, with significant phenotypic variability. It is due to mutations in the gene *PROS1*. There is a more severe form of protein S deficiency, which is inherited in an autosomal recessive fashion and which is also due to mutations in the gene *PROS1*. Protein S is a vitamin K-dependent plasma protein. Protein S is a cofactor for protein C, and its presence accelerates the inactivation of factors VIIIa and Va by protein C. In plasma, approximately 60% of the total protein S exists in a complex with complement, and 40% is free. Only the free fraction is active in modulating the anticoagulant effects of protein C. Three subtypes of heterozygous protein S deficiency have been identified. Type I deficiency (classic) is characterized by a decrease in total

protein S, a decrease in free protein S, and a decrease in the functional activity of the free fraction. Type II deficiency is characterized by a decrease in the functional activity of free protein S with normal levels of total and free protein S. Type III deficiency is characterized by normal levels of total protein S, with a decrease in the amount and functionality of the free fraction. Protein S deficiency is present in approximately 10% of families with inherited thrombophilia and in approximately 5% of individuals with deep vein thrombosis. Protein S deficiency is associated with a risk of thrombosis similar to that in protein C deficiency, approximately a sevenfold increase in the incidence of deep vein thrombosis over that in normal persons. Because of its pronounced phenotypic variability, protein S deficiency is the most difficult of the hereditary thrombophilias to diagnose.

Cardiovascular: Deep vein thromboses, superficial thrombophlebitis, and pulmonary emboli. May also have thrombosis of the mesenteric, renal, axillary, or cerebral veins. Thromboses may be spontaneous or associated with other risk factors (contraceptive pill use, pregnancy, surgery, or trauma). Onset of thrombotic events is usually in the third decade of life. Can have arterial occlusive disease including premature coronary arterial disease.

Other: Patients with protein S deficiency may develop skin necrosis when placed on warfarin therapy. Purpura fulminans in neonates has been described in association with homozygous protein S deficiency. A case has been reported with protein S deficiency and Sneddon syndrome (see later). Low levels of protein S have been associated with intrauterine growth retardation and pregnancy loss in fetuses of affected women.

Miscellaneous: First described in 1984 by Comp and colleagues, 3 years after the elucidation of protein C deficiency. The “S” in protein S comes from Seattle, where it was discovered.

Anesthetic Considerations: Routine screening tests for coagulation will be normal. Prophylactic perioperative anticoagulation is already recommended for all patients where warranted, and identification of a hypercoagulable state would not alter this recommendation. Neuraxial anesthesia should be avoided in patients who are anticoagulated. Hypovolemia, hypotension, and hypothermia should be avoided as they may increase the risk of thrombosis. Antifibrinolytics would be expected to worsen the endogenous defect. Emergent treatment of life-threatening thrombosis would include fresh frozen plasma. Unlike protein C deficiency (see earlier), there is no purified preparation of the protein.

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Proteus syndrome

MIM #: 176920

This disorder is due to mosaicism for a somatic activating mutation (i.e., not present in germ cells) in the gene *AKT1*, an oncogene. *AKT1* mediates a variety of cell processes such as cell proliferation and apoptosis. Presumably, without mosaicism, the mutation would be fatal. The disease becomes apparent soon after birth, with hemihypertrophy or partial gigantism. The gene *PTEN*, a tumor suppressor gene, negatively regulates *AKT1*, and rarely this phenotype can be due to mutations in *PTEN*. Gross deformities develop by late childhood. The syndrome has manifestations in a variety of organs. The main characteristics are hemihypertrophy, subcutaneous tumors (hamartomas), and macrodactyly. Patients often require plastic surgery or amputations. The clinical manifestations are highly variable.

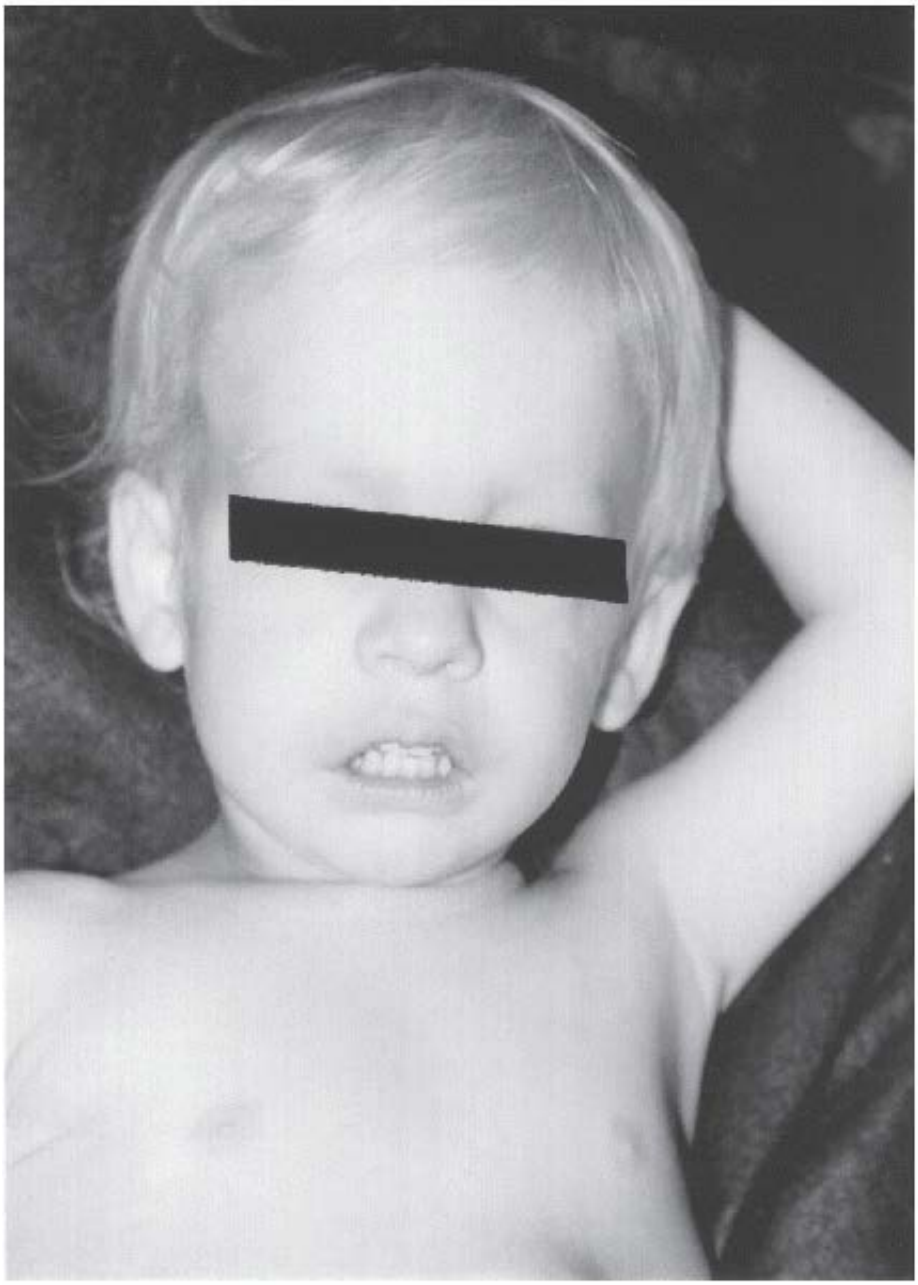
HEENT/Airway: Macrocephaly with cranial hyperostosis (calvarium, facial bones, or mandible). May have retinal and/or optic nerve abnormalities. Epibulbar dermoids. A thickened epiglottis has been reported. Fixed torticollis has been reported.

Chest: Cystic lung disease may become symptomatic. Can have restrictive lung disease from scoliosis. Occasional pectus excavatum. May develop mesothelioma. Can have pulmonary embolism.

Cardiovascular: Occasional hypertrophic cardiomyopathy and cardiac conduction defects. Pulmonary embolism has been reported with or without deep venous thrombosis.

Neuromuscular: Intelligence is usually normal, but some may have moderate intellectual disability.

Seizures. Vertebral anomalies and tumor infiltration have caused spinal stenosis with neurologic sequelae. Meningiomas.



Proteus syndrome. FIG. 1. This young boy has obvious body asymmetry. (Courtesy of Dr. K. Lin and the Craniofacial Anomalies Clinic, University of Virginia Health System.)

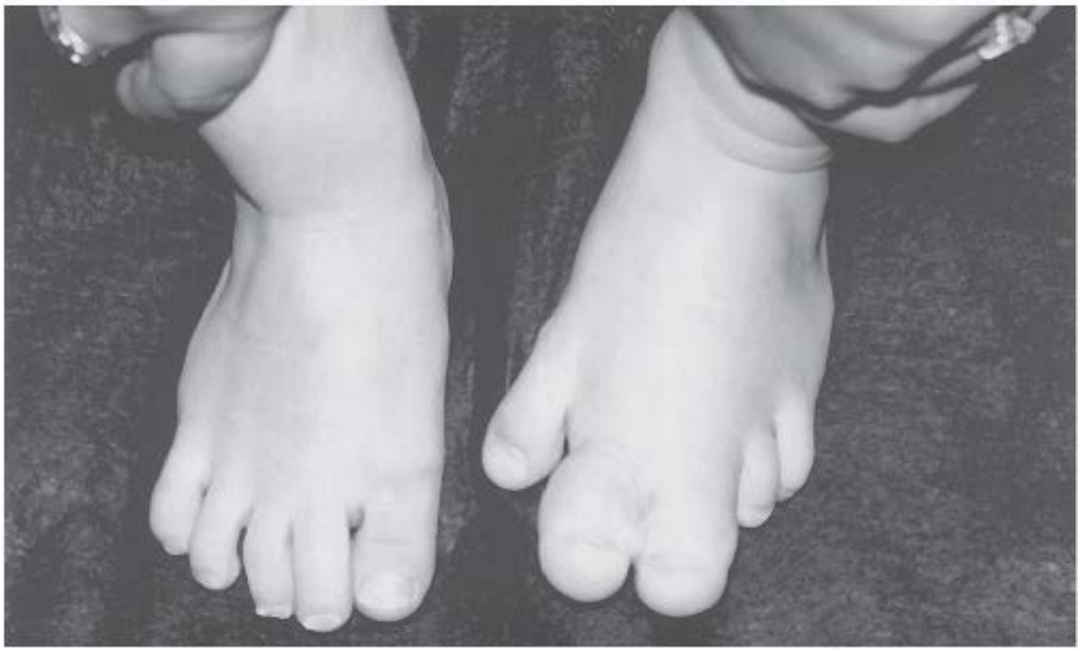
Orthopedic: Tall. Hemihypertrophy—somatic overgrowth can be generalized or focal. Macrodactyly (partial

gigantism of the hands and feet) and syndactyly. Soft tissue hypertrophy of the hands or feet. The neck may be elongated from vertebral enlargement. Hemivertebrae, dysplastic vertebrae, dystrophic discs, and spondylomegaly are common. Scoliosis and kyphosis. Surgical resection of tumors often leaves a keloid with healing.

GI/GU: Occasional renal abnormalities. Ovarian cystadenoma and testicular tumors.

Other: Subcutaneous hamartomatous tumors. Hyperpigmented areas that look like pigmented nevi. Thickened skin on the palms and soles. Lipomas and lymphangiomas. May have hypogammaglobulinemia. May have deep vein thromboses.

Miscellaneous: This syndrome was first described by Cohen and Hayden. The name “Proteus syndrome” was used by Wiedemann. It alludes to Proteus, a figure in Greek mythology who took on many forms to avoid capture. This syndrome also has variable (“protean”) presentations. Joseph Merrick, the “elephant man,” probably had Proteus syndrome and not neurofibromatosis, as has been suggested in the past. Mosaicism of oncogene mutations likely increases a person's risk for the development of malignancies.



Proteus syndrome. FIG. 2. Asymmetric macrodactyly of the toes of the boy in Photo 1. (Courtesy of Dr. K. Lin and the Craniofacial Anomalies Clinic, University of Virginia Health System.)

Anesthetic Considerations: The high incidence of cervical spine abnormalities makes laryngoscopy and endotracheal intubation likely difficult. Patients may also exhibit a thickened epiglottis. A 4-month-old baby has been anesthetized without difficulty (9), a 7-year-old boy has required the use of a McCoy levering laryngoscope because of an enlarged epiglottis (6), and a 14-year-old boy has been intubated using awake fiberoptic bronchoscopy because of fixed torticollis (10). The presence of cystic lung disease is a relative contraindication to the use of nitrous oxide and high peak airway pressures with positive-pressure ventilation. There is emerging evidence that these patients are at increased risk of death from pulmonary embolism (7). Patients with cardiac disease require an appropriately tailored anesthetic.

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Prune belly syndrome

Synonym: Eagle-Barrett syndrome

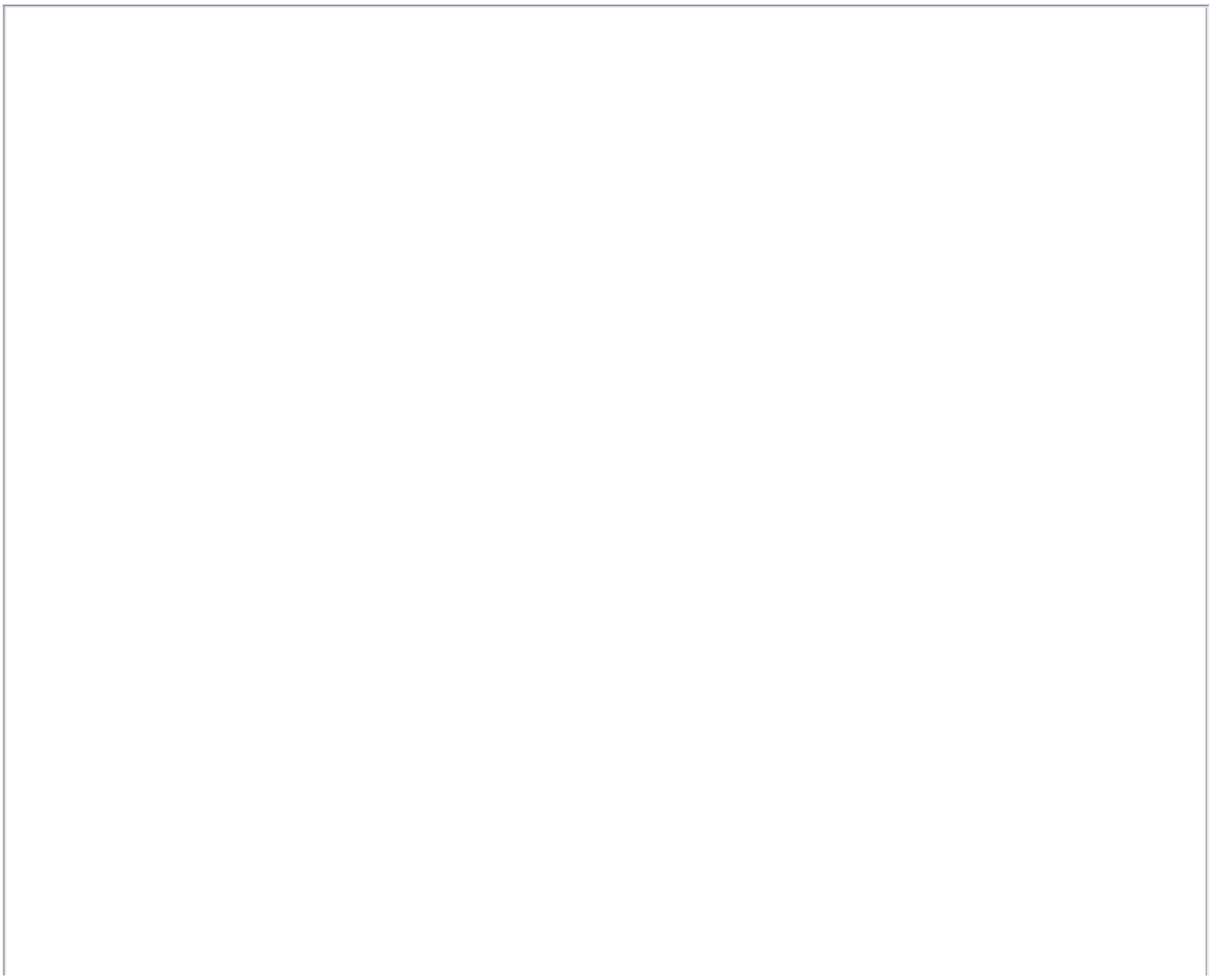
MIM #: 100100

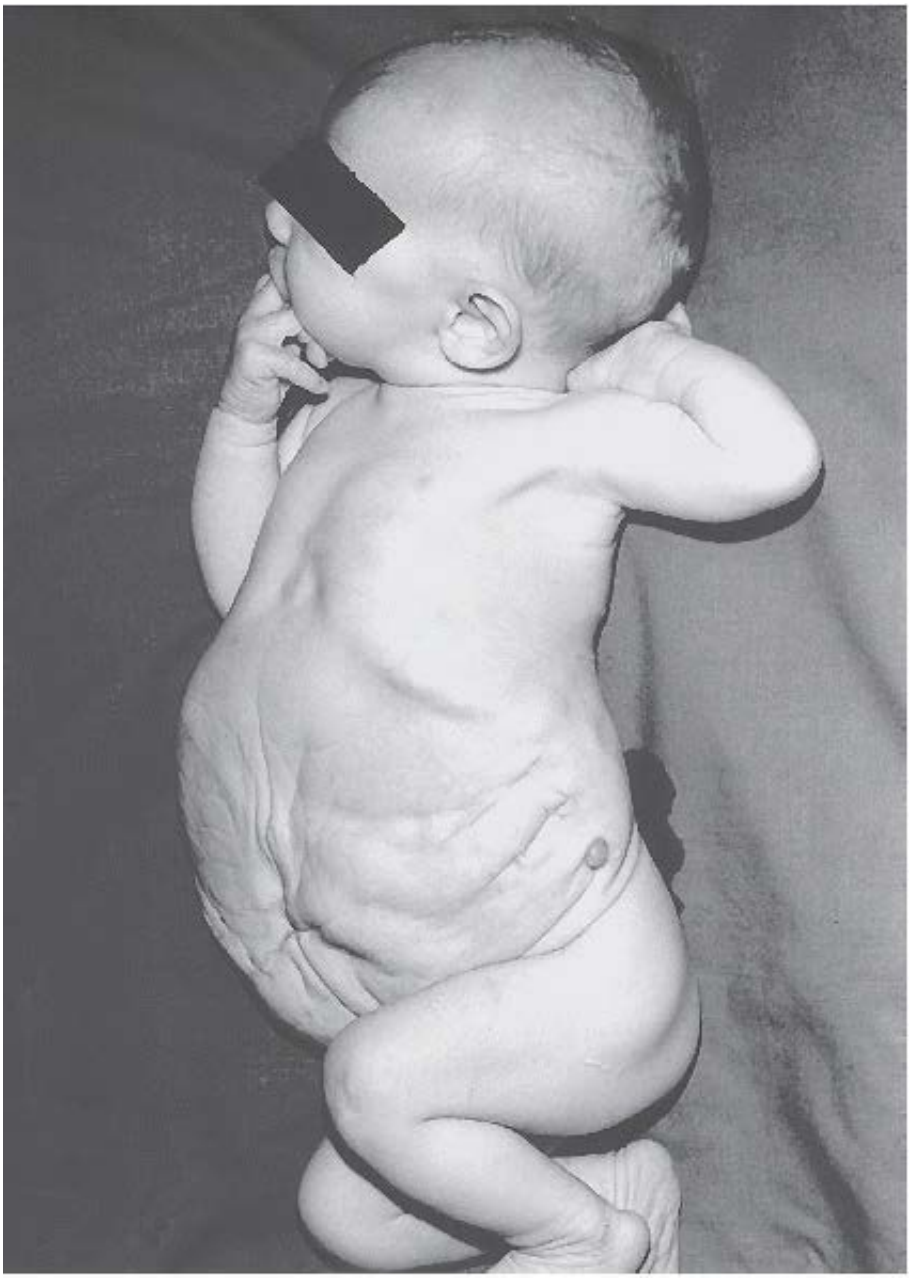
This disease is characterized by absent abdominal wall musculature with wrinkled overlying skin, urinary tract dilatation, and cryptorchidism. It occurs much more commonly in boys, with a male:female ratio of 20:1. This

autosomal recessive disorder is due to mutations in the gene *CHRM3*, which encodes a muscarinic cholinergic receptor. That would seem unlikely to explain the gender inequality. Familial cases have a somewhat higher incidence of females, but still less than 30%. There may be a primary defect in mesenchymal development that is responsible for both the muscle deficiency and the genitourinary abnormalities. Alternatively, this syndrome may be secondary to distal urinary tract obstruction that occurs *in utero*, leading to the characteristic abdominal and genitourinary findings. Less likely, there may be a vascular etiology for this syndrome, which has been proposed to account for the high incidence of associated lower extremity anomalies. However, the lower extremity anomalies are just as likely to be due to compression of the iliac vessels by the dilated urinary tract *in utero* as they are to any primary vascular insufficiency.

HEENT/Airway: Oligohydramnios can result in Potter's facies (hypertelorism, epicanthal folds, low-set ears, flattened, beaked nose, micrognathia) from *in utero* compression (see Potter syndrome, earlier). Impaired papillary constriction. Dry mouth. There may be dental abnormalities.

Chest: Pulmonary hypoplasia can occur as a consequence of distal urinary tract obstruction and oligohydramnios. Severely affected patients may die in the neonatal period from pulmonary hypoplasia. Deficient abdominal musculature weakens the ability to cough effectively and increases the risk of respiratory infections. Chronic bronchitis is common. The diaphragm is relatively flat, and the accessory muscles are relatively more important. Pneumothorax and pneumomediastinum occur in infants even without significant pulmonary hypoplasia. May have pectus excavatum.





Prune belly syndrome. Typical infant with relatively severe deficiency of abdominal wall musculature. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Cardiovascular: Associated cardiac defects occur in 10% and include patent ductus arteriosus, atrial septal defect, ventricular septal defect, and tetralogy of Fallot.

Orthopedic: Congenital dislocation of the hips and clubfoot deformity are common. May have polydactyly, syndactyly. May have scoliosis, torticollis. Compression of the iliac vessels by the dilated urinary tract *in utero* may lead to lower limb deficits.

GI/GU: Absent or deficient anterior abdominal wall musculature. Overlying skin lies in redundant folds, hence the name “prune belly.” Chronic constipation secondary to abdominal muscle deficiency. May have imperforate anus,

malrotation of the gut. Bilateral cryptorchidism. Severe bladder and ureteral dilatation, usually with no apparent obstruction. Hydronephrosis with small dysplastic kidneys is common. Can have posterior urethral valves. Recurrent urinary tract infections are a common complication. Renal failure may develop.

Miscellaneous: Although the name "prune belly syndrome" has been attributed to Osler, he did not use the term.

Anesthetic Considerations: Renal function should be evaluated preoperatively. Renal insufficiency has

implications for perioperative fluid management and the choice of anesthetic drugs. Although an infant has been reported whose micrognathia resulted in unsuccessful intubation attempts but easy and successful placement of a laryngeal mask airway (LMA) (3), this is not a routine characteristic of the disorder. The response to neuromuscular blockers is normal, although neuromuscular blockade is unnecessary for abdominal surgery because of the paucity of abdominal wall musculature. If respiratory dysfunction is suspected, intubation and controlled ventilation should be employed intraoperatively. Postoperative respiratory complications are common secondary to pulmonary hypoplasia (if present) and a weak cough. An abdominal binder may improve the efficacy of coughing. Medications that produce respiratory depression should be used sparingly. A thoracic epidural has been shown to improve postoperative respiratory function (5). Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Pseudoachondroplasia

Synonym: Pseudoachondroplastic spondyloepiphyseal dysplasia

MIM #: 177170

This autosomal dominant disorder is due to a mutation in the gene encoding cartilage oligomeric matrix protein

(*COMP*), which leads to the production of soft cartilage that deforms with stress. Bones exposed to stress (such as the ankles and knees) are affected, while others (such as the skull) are not. It is suggested that the disorder is an endoplasmic reticulum storage disease, caused by improper folding of the mutant *COMP* with increased cell death of growth plate chondrocytes. Mutations in the same gene are responsible for at least some cases of Fairbank-type multiple epiphyseal dysplasia (see multiple epiphyseal dysplasia, earlier). Children with pseudoachondroplasia appear normal at birth, but have progressive and disproportionate short stature by 2 years of age and eventually resemble patients with achondroplasia. Unlike achondroplasia, the head and face remain normal in pseudoachondroplasia.

HEENT/Airway: Normal head and face.

Chest: Spatulate ribs.

Neuromuscular: Normal intelligence. Compression of the cervical cord from chronic atlantoaxial dislocation or spinal stenosis has been reported.

Orthopedic: Acquired short-limb dwarfism. Odontoid hypoplasia. Short, hyperlax fingers (allowing "telescoping" of the fingers). Ulnar deviation of the wrists and limited extension of the elbows. Ligamentous laxity of the legs. Genu valgum or varum. All long bones are short with widened metaphyses and irregularities of developing epiphyses. Platyspondyly in childhood, normalizing somewhat in adulthood. Kyphosis, scoliosis, lumbar lordosis. Premature, progressive, and severe osteoarthritis—many patients will require hip replacement in their 30s.

Miscellaneous: This syndrome was first described by Maroteaux and Lamy, but their names are given to a different syndrome.

Anesthetic Considerations: Careful and stable positioning of the head, particularly during laryngoscopy, is necessary because of the possibility of odontoid hypoplasia and joint laxity. Patients must be carefully positioned and padded perioperatively secondary to limited extension of the elbows and generalized joint laxity.

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Pseudoachondroplastic spondyloepiphyseal dysplasia

See Pseudoachondroplasia

Pseudohermaphroditism, male

See 17-Ketosteroid reductase deficiency; 5α-Reductase deficiency; 17,20-Desmolase deficiency

Pseudohyperaldosteronism

See Liddle syndrome

Pseudo-Hurler polydystrophy

See Pseudo-Hurler syndrome

Pseudo-Hurler syndrome

Synonym: Mucolipidosis III; Mucolipidosis III alpha/beta; Pseudo-Hurler polydystrophy

MIM #: 252600

This autosomal recessive disorder is due to a deficiency in *N*-acetylglucosamine-1-phosphotransferase (*GNPTAB*). This disease has many of the features of Hurler syndrome, but develops more slowly and lacks mucopolysaccharidurıa. In this disease, newly synthesized enzyme is released into the extracellular stroma rather than being stored in the lysosomes. The defect is the same as that found in mucolipidosis II (I-cell disease; see earlier), and the reason for the more benign progression of pseudo-Hurler syndrome is unknown.

Before the biochemistry of the mucolipidoses was understood, it was recognized that these patients had features of both the mucopolysaccharidoses and the sphingolipidoses, hence the name “mucolipidosis.”

HEENT/Airway: Thickened skull with prominent occiput. Coarse facies with prominent forehead and broad nose. Corneal opacities on slit-lamp examination, mild retinopathy, hyperopic astigmatism. Mucolipid storage with enlarged tongue, particularly the base. May also have mucolipid storage in the epiglottis, tonsils, larynx, and trachea. May have temporomandibular joint destruction. May have prognathism. Short neck.

Cardiovascular: Thickened valves, aortic insufficiency. Symptomatic involvement is rare.

Neuromuscular: Intelligence is usually normal. May have mild intellectual disability.

Orthopedic: Short stature. Odontoid hypoplasia. Dysostosis of multiple bones, generally more severe in boys than in girls. Multiple stiff joints, including the spine. Flexion contracture of the fingers and toes causing “claw hand/claw foot.” Carpal tunnel syndrome. Progressive destruction of the hip. Avascular necrosis of the talus. Lumbar lordosis.

GI/GU: Umbilical hernia. Hepatosplenomegaly.

Other: Thickened skin. Patients may be taking pamidronate for bone pain.

Miscellaneous: Although first described by Maroteaux and Lamy, that eponym goes to a completely different disease.

Anesthetic Considerations: Anesthetic management of patients with pseudo-Hurler syndrome has not been reported, and the following refers to the related, but usually more severe, I-cell disease (see earlier). Direct laryngoscopy and tracheal intubation may be very difficult and may become more difficult as the patient ages. It may be difficult to maintain a patent airway with a mask, even with an oral airway. In one case, a laryngeal mask airway helped, and in another, it did not (1). Odontoid hypoplasia has been reported in pseudo-Hurler syndrome, and the possibility of an unstable neck should be considered. If the patient's tracheal wall is thickened, an endotracheal tube that is smaller than predicted may be required. Patients with chronic airway obstruction must be observed closely postoperatively. Patients should be carefully positioned and padded secondary to joint

stiffness.

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Pseudohypohyperparathyroidism

Included in Pseudohypoparathyroidism

Pseudohypoparathyroidism

Synonym: Albright hereditary osteodystrophy. (Includes pseudopseudohypoparathyroidism and pseudohypohyperparathyroidism)

MIM #: 103580, 603233

Pseudohypoparathyroidism describes a group of diseases characterized by target cell (renal tubular or osseous) insensitivity to parathyroid hormone. Hypocalcemia and hyperphosphatemia are prominent features. There are two major types of pseudohypoparathyroidism.

Type I is caused by the inability of parathyroid hormone to activate renal cell adenylyl cyclase, with subsequent deficient production of cyclic adenosine monophosphate (cAMP). Type Ia, the most common form of pseudohypoparathyroidism, is due to a defect in the alpha subunit of the gene encoding stimulatory G protein ($G_{s\alpha}$), with loss of the protein, and resistance of target tissues to the effects of parathyroid hormone. The affected gene is called *GNAS1*. It is inherited in an autosomal dominant fashion, and the

defect is due to inactivation of one allele—all patients are heterozygous. The situation is more complex as exons and promoter regions are methylated on one parental side, and transcripts are derived from only the nonmethylated allele. There are also a variety of splice variants. In several tissues (including the proximal renal tubule), only the maternally derived allele is expressed. Because this G protein is required for responsiveness to multiple hormones, there are usually other associated peptide hormone endocrinopathies, including hypothyroidism and gonadal dysfunction. The distinctive skeletal and developmental features of type Ia represent classic Albright hereditary osteodystrophy. Type Ib is probably due to abnormalities in signal transduction at the parathyroid hormone receptor limited to the kidney. $G_{s\alpha}$ is normal, and clinical manifestations are limited to those associated with parathyroid hormone activity. The physical appearance in type Ib is normal. Patients with type Ib do not have multiple endocrinopathies, but isolated hypothyroidism has been reported. Most cases of type Ib have occurred sporadically, but inheritance may be autosomal dominant. Type I disease is treated with vitamin D (1,25-

dihydroxyvitamin D_3 or dihydrotachysterol) and oral phosphate binders.

In some families with type Ia pseudohypoparathyroidism, some members exhibit the abnormal habitus but are not resistant to parathyroid hormone. They have normal serum calcium and phosphate levels. These individuals have **pseudopseudohypoparathyroidism** (*MIM #:* 612463). It may be that this is determined by whether the abnormal gene is maternally (pseudohypoparathyroidism) or paternally (pseudopseudohypoparathyroidism) derived.

Type II disease is due to the inability of cAMP to initiate parathormone-directed metabolic events. Patients have a normal physical appearance. Treatment is the same as for type I.

Pseudohypohyperparathyroidism (*MIM #:* 103580) describes a group of patients with parathyroid hormone resistance that is limited to the renal tubules. There is normal bone response to the elevated parathyroid hormone levels, and these patients have the osseous manifestations of hyperparathyroidism, namely, subperiosteal resorption and osteitis fibrosa cystica.

HEENT/Airway: Thickened skull, round face. Subcapsular cataracts. Enamel hypoplasia and failure or delayed tooth eruption. Short neck. May have laryngeal spasm from hypocalcemia.

Cardiovascular: The QT interval is prolonged in the presence of hypocalcemia.

Neuromuscular: May have mild intellectual disability. Hypocalcemia may lead to muscle hyperexcitability, with tetany, seizures, or muscle cramps. Perivascular calcifications in the region of the basal ganglia.

Orthopedic: Short stature. May have cervical vertebral anomalies. Short metacarpals, metatarsals, and phalanges (brachydactyly). The hallmark finding is short fourth (or fifth) metacarpals, although other fingers can be affected. Increased bone density. Spinal stenosis has been rarely reported in children.

Patients with type II disease may have subperiosteal bone resorption and osteitis fibrosa cystica.

GI/GU: Renal function is normal. May have hypogonadism.

Other: Hypocalcemia, hyperphosphatemia. Obese or stocky habitus. Cutaneous or subcutaneous calcifications. Serum calcium levels fluctuate, and may be in the normal range.

Miscellaneous: Albright, the Boston physician who is the founder of the subspecialty of endocrinology, postulated in his original report that the defect was one of end organ hormone resistance. This is the same Albright of McCune-Albright syndrome. He also described vitamin D-resistant rickets (once known as Albright-Butler-Bloomberg syndrome).

Anesthetic Considerations: Serum calcium level should be evaluated and corrected preoperatively. Hypocalcemia may lead to laryngeal spasm, a prolonged QT interval, and/or tetany. Hyperventilation should be avoided as it will reduce ionized calcium levels. Patients should be assessed preoperatively for the presence of other endocrinopathies. Direct laryngoscopy and tracheal intubation may be difficult secondary to obesity and a short neck.

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Pseudometatrophic dysplasia

See Kniest syndrome

Pseudopseudohypoparathyroidism

Included in Pseudohypoparathyroidism

Pseudothalidomide syndrome

Synonym: SC phocomelia syndrome; Roberts syndrome

MIM #: 269000, 268300

This autosomal recessive disorder is characterized by symmetric limb reduction deformities that resemble phocomelia, flexion contractures, craniofacial anomalies, and a variety of other minor abnormalities. Patients with this disorder appear to have abnormal centromere separation, caused by mutations in the *ESCO2* gene. Mutations in *ESCO2* cause SC phocomelia syndrome and Roberts syndrome, and it is likely that the two syndromes are the same entity, often referred to as the "pseudothalidomide syndrome." Roberts syndrome is the more severe of the two. There is wide clinical variability, even within families.

HEENT/Airway: Microcephaly. Wormian bones. Occasional frontal encephalocele or craniosynostosis. Capillary hemangiomas of the face, forehead, and ears. Hypertelorism. Bluish sclerae. Corneal clouding. Hypoplastic ear cartilage with absent lobules. Thin nares with hypoplastic nasal cartilage. May have cleft lip or palate. Micrognathia. Short neck, nuchal cystic hygroma.

Cardiovascular: Atrial septal defect, valvar aortic stenosis, and premature myocardial infarction have all been reported.

Neuromuscular: Mild to severe intellectual disabilities. Multiple small intracranial aneurysms have been reported, and a patient who developed moyamoya disease (see earlier) has also been reported.

Orthopedic: Short stature. Symmetrical limb reduction defects (phocomelia), more severe in the upper limbs. Long bones of extremities can be hypoplastic to absent. Flexion contractures of multiple joints. Radiohumeral synostosis. Malformed hands. Syndactyly.

GI/GU: Accessory spleen. Cryptorchidism, hypospadias. Occasional renal anomaly, including polycystic kidneys, horseshoe kidney.

Other: Prenatal growth failure. Children may have sparse, silvery blond hair. Occasional thrombocytopenia.

Miscellaneous: John Roberts was a plastic surgeon from Philadelphia. Clearly, the name "pseudothalidomide"

came later, because Roberts practiced at the turn of the last century, long before there were cases of phocomelia caused by maternal use of thalidomide. The “SC” comes from the first initials of the surnames of two families described by Herrmann in 1969. The earliest description of pseudothalidomide syndrome may have been by Deboze in 1672, who reported the autopsy of a deceased infant who had been put on public display in Lyon.

Anesthetic Considerations: Thrombocytopenia may occur, and consideration should be given to obtaining a preoperative platelet count. Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia and a short neck. Limb reduction deformities may severely limit sites for peripheral vascular access, and radial anomalies may affect ease of access to the radial artery. Phocomelia may make fixation of an appropriate-sized blood pressure cuff difficult, and falsely high pressures may be displayed by noninvasive monitors. An appropriately sized blood pressure cuff should cover two-thirds of the upper arm length. Patients must be carefully positioned and padded secondary to flexion contractures of the joints.

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Pseudovaginal perineoscrotal hypospadias

See 5α-Reductase deficiency

Pseudoxanthoma elasticum

MIM #: 177850, 264800

This usually autosomal recessive, but occasionally autosomal pseudodominant, disorder is marked by abnormal elastic fibers that degenerate and calcify over time. Most of the clinical manifestations are due to disease of medium-sized arteries. Multiple organ systems can be affected, most prominently the skin, the eyes, and the cardiovascular system. It is caused by mutations in the *ABCC6* gene, which encodes an ATP-dependent transmembrane transporter.

HEENT/Airway: Angioid streaks on the retina (secondary to degeneration of elastic tissue) are often diagnostic. Visual acuity is decreased, particularly when vascular changes result in vitreous or subretinal hemorrhage. The oral mucosa may be involved. Involvement of the larynx has been reported in a single patient (6).

Chest: Benign breast calcifications.

Cardiovascular: Endocardial thickening and calcification. Abnormal diastolic function. Calcified endocardial bands have been reported. Involvement of the conduction tissues may result in arrhythmias and sudden death. There can also be valve involvement, including mitral valve prolapse. Early calcification (1 year) of a heterograft mitral valve has been reported. Premature coronary arterial disease. Hypertension. There can be calcification of the peripheral arteries, and patients may have symptomatic peripheral vascular disease (claudication) or aneurysms. Carriers of the gene can also have accelerated atherosclerosis.

Neuromuscular: Cerebrovascular involvement includes aneurysms, premature occlusive disease, hemorrhage, or infarction. Calcified falx cerebri. Increased incidence of psychiatric problems.

GI/GU: High incidence of gastrointestinal hemorrhage, even after minor mucosal trauma. There are intestinal submucosal lesions similar to the xanthoma-like skin lesions. May have hematuria secondary to renal artery involvement. The vaginal mucosa may be involved. Uterine bleeding on occasion requires hysterectomy.

Other: Skin changes are often the earliest manifestation. Yellowish xanthoma-like skin patches ("pseudoxanthoma") are found primarily on the neck, axillary and inguinal folds, cubital area, and periumbilical area. They have a "Moroccan leather" quality, which has more prosaically been likened to plucked chicken skin. The disease may be accelerated during pregnancy. Placental involvement may result in intrauterine growth retardation.

Anesthetic Considerations: Laryngeal involvement precluding routine laryngoscopy and intubation has been reported in one patient (6). Vascular access, both venous and arterial, may be difficult because of vascular involvement and involvement of the overlying skin. The effect of invasive arterial catheters on the progression of local vascular disease is unknown. The high incidence of gastric bleeding is a relative contraindication to nasogastric tubes and transesophageal echocardiography. Regional anesthesia has been successfully used in parturients (4). The possibility of cerebrovascular disease and intracranial aneurysms should be considered. Involvement of the endocardium or the cardiac valves and the possibility of premature cardiovascular disease should also be considered. Patients with valvular disease should receive perioperative prophylactic antibiotics as indicated.

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PTEN MATCHS syndrome

See Riley-Smith syndrome

Pterygium syndrome

See Multiple pterygium syndrome

Purine nucleoside phosphorylase deficiency

MIM #: 613179

This disease is inherited in an autosomal recessive fashion. Purine nucleoside phosphorylase catalyzes the lysis of the purine nucleosides (deoxy)inosine and (deoxy)guanosine to their purine bases and the corresponding ribose-1-phosphate, with eventual metabolism to uric acid. Deficiency of this enzyme results in accumulation of deoxyinosine and deoxyguanosine, which are particularly toxic to T cells. Accumulation of deoxyguanosine triphosphate, which inhibits ribonucleotide reductase, blocks DNA synthesis and prevents the cellular proliferation required for an immune response. Purine nucleoside phosphorylase deficiency therefore leads to defective T-cell immunity. With time, there can also be B-cell dysfunction because of abnormal interaction with T cells. Patients are particularly susceptible

to viral infections, which can be fatal, and patients have succumbed to disseminated vaccinia or varicella infections, lymphosarcoma, or graft-versus-host disease from nonirradiated transfused blood. Intermittent transfusions with (irradiated) red blood cells supply adequate exogenous enzyme. Bone marrow (and hematopoietic stem cell) transplantation is curative but does not reverse the neurologic involvement, although there was some neurologic improvement in one stem cell transplantation recipient.

HEENT/Airway: Sinusitis and otitis media. Atrophic tonsils.

Chest: Recurrent upper respiratory tract infections. Small thymus.

Neuromuscular: Intellectual disabilities, developmental delay, and behavioral disorders. Spastic diplegia or tetraparesis, dysequilibrium syndrome, pyramidal tract signs, Babinski sign, and exaggerated reflexes.

Other: Failure to thrive. Repeated infections, particularly viral, which may be fatal. T-cell function more severely affected than B-cell function. Autoimmune disease (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and systemic lupus erythematosus). May have neutropenia. B-immunoblastic-type malignant lymphoma. Hypouricemia. Live virus vaccines should be avoided.

Miscellaneous: Adenosine deaminase is the next enzyme in this metabolic pathway, and its absence results in severe combined immune deficiency.

Anesthetic Considerations: Good aseptic technique is imperative. The patient's hematocrit and platelet count should be evaluated preoperatively. Blood products must be irradiated to avoid graft-versus-host disease. Patients with autoimmune disease may be taking steroids and may require perioperative stress doses of steroids. Spasticity might make perioperative positioning difficult.

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Pycnodysostosis

See Pyknodysostosis

Pyknodysostosis

MIM #: 265800

This autosomal recessive disease is due to a mutation of the cathepsin K gene. The cathepsins are in the papain family of cysteine proteases. These proteases are involved with multiple functions. Cathepsin K is highly expressed in osteoclasts. In this disorder, osteoclasts demineralize bone appropriately but are unable to adequately degrade the organic material. The primary clinical manifestations are osteosclerosis and short stature. Patients often require medical attention for fractures, which can be sustained even after relatively mild trauma. Although results are still preliminary, growth hormone treatment may be useful in improving adult height.

HEENT/Airway: Frontal and occipital prominence, wormian bones, wide sutures with delayed closure. Can have craniosynostosis. Persistence of anterior fontanelle, absent frontal sinus, and mastoid air cells. Midface hypoplasia. Prominent nose and narrow, grooved palate. Dental abnormalities including delayed eruption of deciduous and permanent teeth, hypodontia, irregular permanent teeth, dental caries. Hypoplastic mandible and mandibular rami, with obtuse angle of the mandible. May have mandibular fractures. Pharyngeal narrowing, associated with an increased risk of obstructive sleep apnea.

Chest: Hypoplastic or aplastic clavicles, with loss of lateral end. Clavicular fractures.

Neuromuscular: Intellectual disabilities have been reported in some.

Orthopedic: Short stature (adult height <5 feet). Osteosclerosis with bone fragility and fractures even after mild trauma, particularly in the lower extremities. Osteolysis of the distal phalanges, especially of the index finger. Wrinkled skin over the dorsum of distal fingers. Flattened, grooved nails. Spondylolysis of L4 and L5. Scoliosis.

Other: Rarely pancytopenia secondary to hyperostosis.

Miscellaneous: First described by Maroteaux and Lamy, but their names are given to a different syndrome. The artist Toulouse-Lautrec (whose parents were first cousins) is thought to have had pyknodysostosis (by Maroteaux and Lamy among others), but this assertion has also been contested (5,6). It was suggested that large open fontanelles were the reason he wore a hat much of the time. The spelling “pykno…” tends to

be used by American authors and “pycno…” by British authors (and by Maroteaux and Lamy originally).

Anesthetic Considerations: Recall that despite the child-size stature, the patient's intelligence is usually normal for his or her chronologic age. Dental abnormalities should be documented preoperatively. It is possible that laryngoscopy and intubation could be difficult due to midface and mandibular abnormalities, but this has not been reported. Spondylolysis of L4 to L5 may have an impact on the decision to perform a neuraxial anesthetic in this location. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Patients must be carefully positioned and padded secondary to bone fragility. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

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Pyle disease

See Pyle metaphyseal dysplasia

Pyle metaphyseal dysplasia

Synonym: Pyle disease; Metaphyseal dysplasia, Pyle type

MIM #: 265900

There are many types of metaphyseal chondrodysplasia—see also Jansen type, McKusick type (cartilage-hair hypoplasia syndrome), Schmid type, Shwachman syndrome, and Spahr type [not included in this text (*MIM #:* 250400)]. This autosomal recessive type of metaphyseal chondrodysplasia is distinguished by characteristic radiographic findings (Erlenmeyer flask deformity—grossly widened metaphyses of the long bones with marked cortical thinning and osteoporosis). Despite the striking radiographic findings, patients usually are asymptomatic. The most common clinical finding is genu valgum. Minimal involvement of the cranial bones distinguishes this syndrome from the craniometaphyseal dysplasias. The responsible gene and gene product are unknown.

HEENT/Airway: Mild thickening of the calvarium, which can encroach on cranial foramina with nerve compression. May have supraorbital hyperplasia. Poorly pneumatized paranasal sinuses. Dental caries and misplaced teeth. May have prognathism.

Chest: Thickened sternal head of ribs and medial head of clavicles.

Orthopedic: Patients are often tall. "Erlenmeyer flask-like" flaring of the long bones, most prominently of the distal femur and proximal tibia. Broad proximal humerus, distal radius, and ulna. Cortical thinning and osteoporosis in the long bones. Limited elbow extension. May have scoliosis or platyspondyly. Genu valgum is a prominent feature. Fractures.

Miscellaneous: Edwin Pyle was an orthopedic surgeon in Waterbury, Connecticut.

Anesthetic Considerations: When meeting the patient preoperatively, be sensitive to the possibility that they might have visual and/or hearing impairment from nerve compression. Carious teeth may be dislodged during laryngoscopy. Distal radial and ulnar abnormalities may affect ease of access to the radial artery. Patients must be carefully positioned and padded secondary to osteoporosis and the risk of fracture.

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Pyruvate dehydrogenase deficiency

MIM #: 312170

This usually X-linked disorder is a relatively common defect of mitochondrial energy metabolism. Deficiency of pyruvate dehydrogenase prevents entry of pyruvate into the citric acid cycle by preventing the conversion of pyruvate to acetyl-CoA in the mitochondria, with the subsequent accumulation of lactate and pyruvate. Pyruvate dehydrogenase is actually a complex of three catalytic enzymes: pyruvate decarboxylase (El), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3). X-linked mutations in the E1 enzyme component are the most common cause of this disorder. Also involved are two cofactors, thiamine pyrophosphate and lipoate. Regulation of

the enzyme system is further modified by stimulation from a specific phosphatase and inhibition from a specific kinase. The nervous system is predominantly affected as acetyl-CoA in the brain is derived exclusively from pyruvate. A small subset of patients will be thiamine responsive.

The clinical manifestation of this disorder ranges from benign intermittent ataxia without acidosis (chronic form) to severe acidosis with death in early infancy (early fatal form). Patients with the chronic form often have acute exacerbations that are precipitated by infection, prolonged fasting, or other stimuli of gluconeogenesis. Acute

exacerbations are characterized by lactic acidosis, hypotonia, ataxia, confusion, lethargy, and coma. The clinical phenotype may resemble Leigh disease (see earlier). Girls usually have the chronic form, whereas boys usually have the early fatal form. Affected girls are carriers of the X-linked trait, and this is one of the few X-linked conditions in which female heterozygotes manifest significant clinical symptoms.

HEENT/Airway: Dysmorphic facial features in some, similar to those seen with fetal alcohol syndrome, including microcephaly, short palpebral fissures, ptosis, microphthalmia, maxillary hypoplasia, posteriorly rotated, prominent ears, eustachian tube dysfunction, short nose, thin upper lip with smooth philtrum, cleft lip or palate, malocclusion, micrognathia, and short neck. E3 deficiency is associated with optic atrophy and laryngeal stridor.

Chest: May have episodes of hyperventilation secondary to acidosis.

Neuromuscular: El and E2 deficiencies are associated with progressive and severe neurologic dysfunction. E3 deficiency is associated with lethargy and irritability. Agenesis of the corpus callosum or cystic brain lesions in the early fatal type. Hypotonia, seizures, intellectual disabilities, spasticity, and central respiratory depression. Episodic ataxia. Stress has been reported to exacerbate neurologic symptoms.

Other: E2 and E3 deficiencies are associated with lactic acidosis. Acidosis may be precipitated by a high carbohydrate diet with E2 deficiency, but not with E3 deficiency.

Miscellaneous: Elevated fetal acid aldehyde has been suggested as the common link with fetal alcohol syndrome, explaining the similar facial features. Interestingly, this gene is autosomal in marsupials and is known to be located on a fragment of marsupial chromosome that was later translocated to the short arm of the X chromosome after the divergence of marsupials and primordial mammals. Carbohydrate-sensitive ataxia can be controlled by a ketogenic diet.

Anesthetic Considerations: Avoid hypothermia, decreases in cardiac output, and other physiologic conditions, which may lead to lactic acidosis (3,5). Lactate-containing intravenous fluids (such as Ringer's lactate) should be avoided because they increase the lactate load. Patients who are acidotic may need treatment with bicarbonate. Hypocarbia inhibits pyruvate decarboxylase and could worsen lactic acidosis. Except for those with carbohydrate-sensitive ataxia, patients should receive ample perioperative glucose to maintain serum glucose in the high-normal range. Although barbiturates and volatile anesthetics can inhibit mitochondrial respiration, induction of anesthesia with thiopental has been used without any complications in the phenotypically similar Leigh disease (see earlier). Patients are predisposed to central respiratory depression and should be closely monitored for respiratory depression perioperatively.

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Pyruvate kinase deficiency

MIM #: 266200

Pyruvate kinase (PK) deficiency is an autosomal recessive disease. There are four PK isozymes: L in liver, R in red blood cells, M_1 in muscle, and M_2 in white blood cells and platelets. M_1 and M_2 are derived from the same gene, by alternative RNA splicing. PK converts phosphoenolpyruvate to pyruvate in red blood cells, one of the last steps in the anaerobic glycolytic pathway. Mature red cells, lacking mitochondria, are dependent on anaerobic glycolysis. Thus, PK-deficient red blood cells are depleted of adenosine triphosphate and have an abbreviated life span. The clinical presentation varies from severe hemolytic anemia to chronic, compensated hemolytic anemia; from hydrops fetalis and fetal demise to diagnosis in adulthood. Pyruvate kinase deficiency is the most common cause of hereditary nonspherocytic hemolytic anemia. Pregnancy and intercurrent viral infections may exacerbate hemolysis. There are many genetic variants, and most patients are

in fact compound heterozygotes (two different mutations) rather than homozygotes (two copies of the same mutation).

HEENT/Airway: Severely affected children have frontal bossing secondary to excessive erythropoiesis in the cranial marrow cavity.

Cardiovascular: Rare phlebitis and arterial thrombosis, including carotid artery thrombosis.

Neuromuscular: Rare spinal cord compression from extramedullary hematopoietic tissue.

GI/GU: Splenomegaly. Chronic hemolysis may require a splenectomy, which usually results in improvement, but not cure. Increased incidence of bilirubinate gallstones and cholecystitis.

Other: Normocytic anemia, thrombocytosis, hyperbilirubinemia. Levels of glycolytic intermediaries such as 2,3-diphosphoglycerate are increased, which causes a shift in the oxygen-hemoglobin desaturation curve to the right, reducing the symptoms of anemia. Patients who have received multiple transfusions may have iron overload. Increased risk for fetal loss in affected mothers who are anemic.

Miscellaneous: Pyruvate kinase deficiency is the most common enzyme abnormality of the glycolytic pathway in humans. It is common in basenji dogs and also occurs naturally in beagles, West Highland terriers, and cats. Pyruvate kinase deficiency in mice (and humans) protects against malaria, at least in human erythrocytes *in vitro*. Hematopoietic stem cell transplantation is curative.

Anesthetic Considerations: The patient's hematocrit should be evaluated preoperatively. Patients are generally well adapted to the chronically low hemoglobin levels. Patients may have developed hemochromatosis. Patients may have had a splenectomy and be at increased risk for infections.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

R

Ramsay Hunt syndrome

Synonym: Progressive myoclonus epilepsies syndrome

Note: “Ramsay Hunt syndrome” is also used to describe postherpetic (varicella-zoster) otitis.

MIM #: 159700

This Ramsay Hunt syndrome represents a heterogeneous collection of disorders that are distinguished by cerebellar ataxia, seizure disorder, and myoclonus. “Ragged-red” fibers are seen on muscle biopsy. Ragged-red fibers represent mitochondria, and this entity is probably a pathophysiologic process of mitochondria. There are three Ramsay Hunt syndromes, related by the fact that they were described by the same person. Described here is Type I. Type II is a postherpetic otitis, and the rare Type III is an occupational neuropathy of the deep palmar branch of the ulnar nerve.

Neuromuscular: Cerebellar ataxia, myoclonus, intention tremor. Grand mal seizures. There are lesions of the dentate nucleus, as was postulated by Hunt, and degeneration of the globus pallidus.

Other: May have psychiatric disease, including psychosis.

Miscellaneous: Given the heterogeneity of this syndrome, some have argued that Ramsay Hunt syndrome, type I, does not represent a useful clinical rubric and should be discarded. James Ramsay Hunt was one person.

Anesthetic Considerations: Although there is a paucity of clinical evidence, succinylcholine should be used with caution in these myopathic patients because of the risk of an exaggerated hyperkalemic response. Myoclonus is common and is difficult to differentiate from true motor seizures.

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Rapp-Hodgkin ectodermal dysplasia

Synonym: Hypohidrotic ectodermal dysplasia, autosomal dominant type

MIM #: 129400

This autosomal dominant type of hypohidrotic ectodermal dysplasia is marked by hypohidrosis or anhidrosis (decreased or absent sweating), cleft lip or palate, and ectodermal dysplasia. It is due to mutations in the gene *TP63*. AEC syndrome (see earlier), ADULT syndrome (not discussed here, *MIM #:* 103285), limb-mammary syndrome (not discussed here, *MIM #:* 603543), SHFM4 (split-hand/foot malformation, not discussed here, *MIM #:* 605289), and some cases of EEC syndrome (see earlier) are allelic disorders. There are actually many syndromes of ectodermal dysplasia, all having different degrees of hypohidrosis, different degrees of ectodermal dysplasia, and different inheritance patterns, and there can be overlapping phenotypes. (See also AEC syndrome, Clouston syndrome, EEC syndrome, Pachyonychia congenita syndrome.)

HEENT/Airway: High forehead. Ptosis. Lacrimal duct anomalies. Absent lateral third of the eyebrow. May have hearing loss—usually secondary to chronic otitis media, which is more likely in patients with palatal incompetence. Can have atresia of external auditory canals; in one case, cicatricial stenosis developed in adulthood and was not amenable to correction. Flat nasal bridge, narrow nose, hypoplastic alae nasi. Maxillary hypoplasia. Small mouth. Hypoplastic teeth. Cleft lip or palate, cleft uvula, velopharyngeal incompetence.

Neuromuscular: Speech development may be delayed secondary to velopharyngeal incompetence or hearing loss.

Orthopedic: Short stature. Nail dysplasia. May have syndactyly, ectrodactyly.

GI/GU: Hypospadias. May have labial anomalies.

Other: Hypohidrosis or anhidrosis, secondary to hypoplastic sweat glands. Thin skin. Thin, wiry hair. Alopecia.

Miscellaneous: The p63 protein is degradated by the E3 ubiquitin ligase “Itch.”

Anesthetic Considerations: Patients may become hyperthermic perioperatively secondary to hypohidrosis or anhidrosis. Dental anomalies should be documented preoperatively. Patients must be carefully padded perioperatively to protect their thin skin.

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Refsum disease

Note: This is distinct from infantile Refsum disease

MIM #: 266500

This autosomal recessive disease is a disorder of lipid metabolism caused by a defect in the gene coding the enzyme phytanoyl-CoA hydroxylase. Affected patients are unable to metabolize phytanic acid, which comes from dietary sources. Phytanic acid then accumulates in the body. The hallmark findings are retinitis pigmentosa, chronic polyneuropathy, and cerebellar abnormalities. Most patients also have nonspecific electrocardiographic changes. Onset of symptoms is generally at the end of the first decade, and the general course is one of progressive deterioration, although exacerbations may accompany infections, surgery, or pregnancy. With stress, phytanic acid stores are rapidly mobilized from the liver. There may be some recovery after an acute exacerbation. The disease may be controlled, and neural function improved, by a diet lacking chlorophyll, phytol, and phytanic acid. Phytol, a component of chlorophyll, is converted to phytanic acid. Phytanic acid is toxic to mitochondrial complexes I to III and Na^+ to K^+ ATPase, suggesting the pathology may be related to an effect on energy metabolism.

Infantile Refsum disease (see earlier) is a genetically and biochemically distinct disorder. It is therefore probably inappropriately named.

HEENT/Airway: Retinitis pigmentosa, poor vision in low light (night blindness), diminished peripheral vision, lens opacities, miosis, nystagmus, ptosis. Nerve deafness. Anosmia.

Cardiovascular: Nonspecific electrocardiographic (EKG) changes, including atrioventricular conduction block and bundle branch block. Congestive cardiomyopathy.

Neuromuscular: Chronic polyneuropathy (motor and sensory). Cerebellar ataxia, diminished or absent deep tendon reflexes, intention tremor. Elevated cerebrospinal fluid protein without pleocytosis.

Orthopedic: Multiple epiphyseal dysplasia. Syndactyly, bilaterally short fourth metacarpals. Pes cavus, hammer toe.

Other: Ichthyosis, ranging from mild hyperkeratosis of the palms and soles to full truncal ichthyosis.

Miscellaneous: A leading Norwegian neurologist in his day, Refsum described this disorder as his medical thesis. The disorder is most common in those of

Scandinavian descent. Phytol is found in many dietary fats and dairy products. The phytol in chlorophyll, the major dietary source, is not well absorbed. Lipid apheresis can lower phytanic acid levels.

Anesthetic Considerations: Exacerbations of this disease can accompany surgery, infection, or pregnancy. A baseline EKG with rhythm strip should be evaluated preoperatively. Patients with cardiac disease require an appropriately tailored anesthetic. Because of the risk of hyperkalemia, succinylcholine should be avoided in patients with significant motor neuropathy.

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Respiratory chain disorders

See Complex I deficiency, Complex II deficiency, Complex III deficiency, Complex IV deficiency, or Complex V deficiency

Retinoic acid embryopathy

Synonym: Fetal retinoid syndrome

MIM #: 243440

This syndrome is due to the teratogenic effects of retinoic acid [isotretinoin, 1,3-*cis*-retinoic acid (Accutane®)]. Abnormalities occur primarily in the face, heart, and central nervous system. The DiGeorge syndrome (see earlier) may be seen in association with *in utero* exposure to retinoic acid. The findings here are similar to those found with excessive maternal vitamin A exposure.

HEENT/Airway: Microcephaly, facial asymmetry. Hypertelorism. Small ears or absent external ears with stenosis of the external auditory canal. Facial nerve paralysis ipsilateral to the ear abnormality. Mottled teeth. Cleft palate. Micrognathia.

Cardiovascular: A variety of congenital cardiac malformations, particularly conotruncal malformations and aortic arch abnormalities.

Neuromuscular: Intellectual disabilities. Hydrocephalus. Structural brain defects, particularly in the posterior fossa. Facial nerve paralysis ipsilateral to the ear anomalies.

Other: Abnormalities of the thymus and parathyroid. May have DiGeorge syndrome.

Miscellaneous: The risk to the fetus appears to occur only when maternal ingestion occurs after the 15th day of pregnancy. Maternal use before conception is not thought to be teratogenic. Exposure to topical tretinoin (Retin-A®) does not appear to be associated with fetal malformations (1).

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia. Patients with parathyroid dysfunction may have abnormal levels of serum calcium. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Rett syndrome

MIM #: 312750, 613454

This syndrome of progressive encephalopathy occurs almost exclusively in girls. It is X-linked dominant, usually lethal in male hemizygotes. Severity is thought to be related to the X-inactivation pattern. It is caused by mutations in the X-linked gene *MECP2*, encoding methyl-CpG-binding protein-2, resulting in arrested development of neuronal cells. Patients are normal at birth and develop normally until 6 to 18 months of age, when developmental regression begins. After a period of neurologic decline, there can be a prolonged phase of stability or improvement. Survival into adulthood is possible. Some patients maintain a degree of hand and speech use, and have been classified as having the preserved speech variant (PSV) of Rett syndrome. An early onset, and more severe, form of Rett syndrome can be caused by mutations in the gene *FOXG1*, which encodes a developmental transcription factor. This early-onset form is characterized by neonatal hypotonia and seizures.

HEENT/Airway: Acquired microcephaly (head circumference is normal at birth). Bruxism. There may be an increased incidence of upper airway obstruction.

Chest: Wakefulness is associated with periods of abnormal respiration, characterized by intermittent hyperventilation and occasional apnea. This normalizes with sleep. Kyphoscoliosis may result in restrictive lung disease.

Cardiovascular: Prolonged QT interval. Can have bradycardia. May have reduced heart rate variability. May be at increased risk for sudden cardiac death. Vasomotor change in the lower extremities.

Neuromuscular: Normal development until 6 to 18 months of age, then rapid regression to severe dementia and autism. Behavioral problems. Axial hypotonia and limb spasticity are common. Also have choreoathetosis, dystonia, ataxia, and myoclonic jerks. Stereotypic hand movements (hand wringing). Decreased sensitivity to pain. Seizures (both absence and tonic-clonic).

GI/GU: Gastroesophageal reflux. Constipation.

Orthopedic: Acquired short stature. Kyphoscoliosis, hip dislocation, osteopenia, pathologic fractures. Hands and feet are small, with short fourth or fifth metacarpals and metatarsals.

Other: Poor growth, cachexia. May have diabetes. Rett described increased ammonia concentrations, but this is not a consistent finding. Increased serum and cerebrospinal fluid lactate have also been reported.

Children classically exhibit stereotypic hand movements, described as “hand washing” or “hand wringing.” Music is said to have a calming effect and to stop stereotypical behaviors. May awaken at night with uncontrollable screaming. Depo-Provera is said to worsen behavioral problems.

Miscellaneous: Rett was a Viennese pediatrician who described this syndrome after observing two unrelated girls exhibiting similar hand movements while sitting next to each other in his waiting room.

Anesthetic Considerations: Medical procedures may induce behavioral problems. Moderate difficulty with laryngoscopy and intubation has been reported by several groups (2). Patients may be more sensitive to sedative

drugs, with faster onset of anesthesia and prolonged emergence (8,13). A decreased requirement for propofol for procedural sedation with increased incidence of prolonged apnea has been reported (4). Patients may have a prolonged QT interval and may be at risk for sudden cardiac death. Factors that can prolong the QT interval should be avoided. Patients with advanced disease are at increased risk for perioperative aspiration. Chronic use of anticonvulsant medications affects the metabolism of some anesthetic drugs. Muscle wasting obligates careful perioperative positioning. Positioning and vascular access may also be made more difficult by contractures. The thin body habitus may predispose patients to perioperative cooling. Kyphoscoliosis and abnormalities in the control of respiration predispose these patients to postoperative respiratory complications. An abnormal respiratory pattern has been reported on awakening from general anesthesia (1). Delayed recovery from anesthesia is common. When titrating analgesics, recall that these patients often exhibit decreased sensitivity to pain. There are elevated CSF endorphin levels, and the respiratory abnormalities resolve with naloxone. Consider postoperative ICU admission secondary to respiratory control abnormalities.

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Rhizomelic chondrodysplasia punctata

See Chondrodysplasia punctata—autosomal recessive type

Ribbing-type multiple epiphyseal dysplasia

Included in Multiple epiphyseal dysplasia

Richner-Hanhart syndrome

See Tyrosinemia II

Rieger syndrome

See also Axenfeld-Rieger syndrome

MIM #: 180500

This autosomal dominant syndrome is an association of the originally described Rieger anomaly of the anterior segment of the eye with later-described dental abnormalities. The development of glaucoma is common. The Rieger anomaly (findings limited to the peripheral anterior segment of the eye plus abnormalities of the iris) can also occur with several other dysmorphic syndromes. This disorder is most often due to a mutation in the homeobox transcription factor gene, *PITX2*, which maps to the long arm of chromosome 4.

The similarity of anterior chamber angle abnormalities in Axenfeld anomaly, Rieger anomaly, and Rieger syndrome has led to the conjecture that these three categories represent a spectrum of developmental disorders. Ophthalmologists use the term Axenfeld-Rieger syndrome to categorize most of these patients, based on clinical findings. Patients may have surgery shortly after birth or later in childhood, for glaucoma or other ocular problems.

HEENT/Airway: Maxillary hypoplasia. Microcornea with corneal opacity, dysplasia of the iris, anterior synechiae. Glaucoma is common. Blindness. Hypertelorism, telecanthus. Broad nasal bridge, thin upper lip, short philtrum, protruding lower lip. Underdeveloped maxilla. Microdontia and hypodontia, usually of upper incisors.

Cardiovascular: Congenital cardiac defects have been described in rare families.

Neuromuscular: A single kindred has been described that also had myotonic dystrophy.

GI/GU: Failure of involution of the periumbilical skin. Anal stenosis or imperforate anus. Hypospadias.

Other: May have growth hormone deficiency.

Miscellaneous: In the mouse embryo, *PITX2* gene mRNA localizes to the periocular mesenchyme, the maxillary and mandibular epithelium, and the umbilicus, all areas affected in the human syndrome. Herwigh Rieger was an Austrian ophthalmologist with an interest in genetic diseases of the eye.

Anesthetic Considerations: Keep in mind that patients may have impaired vision. Dental abnormalities should be documented preoperatively. Care should be taken to prevent dental damage during laryngoscopy. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. A case of difficult intubation and postextubation airway obstruction in a neonate has been reported (4).

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Rigid spine syndrome

MIM #: 602771

This autosomal recessive myopathy, also called rigid spine muscular dystrophy-1, is characterized by skeletal muscle myopathy and fibrous shortening of the spine extensor muscles, leading to limited flexion of the thoracolumbar and, in particular, the cervical spine. Movement of other joints may also be limited, particularly the elbow joint. The disorder is caused by a mutation in the *SEPN1* gene. *SEPN1* encodes a selenoprotein-containing glycoprotein. It is suggested that this protein plays a role in redox homeostasis and protection against oxidative stress. Mutations in this gene are also responsible for multiminicore myopathy and desmin-related myopathy with Mallory bodies (neither is discussed in this text).

HEENT/Airway: Facial weakness. Nasal high-pitched speech. High-arched palate. The neck is extremely hyperlordotic. The trachea is significantly narrowed.

Chest: Most have clinically significant respiratory muscle weakness. May also have restrictive lung disease secondary to restricted chest wall mobility and the development of kyphoscoliosis. Respiratory failure develops in

some patients.

Cardiovascular: May have a cardiomyopathy. May have right ventricular failure due to respiratory insufficiency.

Neuromuscular: Skeletal muscle myopathy. Creatine kinase levels are close to normal.

Orthopedic: Short stature. Markedly restricted cervical spine flexion. Restricted movement of

thoracolumbar spine. Kyphoscoliosis. Contractures of multiple joints, particularly the elbow joint.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be very difficult secondary to the extremely hyperlordotic cervical spine and restrictions in cervical spine movement. Note that the normal kyphotic bend of endotracheal tubes opposes the curve of the trachea in these patients. The trachea may be significantly narrowed. An endotracheal tube that is smaller than predicted may be appropriate. Tracheal rupture has been reported, possibly due to multiple attempts at laryngoscopy and tracheal intubation (7).

Succinylcholine should be avoided in patients with skeletal muscle myopathy because of the risk of exaggerated hyperkalemia. Patients must be carefully positioned and padded perioperatively secondary to multiple joint contractures. Patients may have a cardiomyopathy or right ventricular failure secondary to respiratory insufficiency. Most patients have clinically significant respiratory muscle weakness, and some have restrictive lung disease secondary to restricted chest wall mobility and kyphoscoliosis. Patients are at risk for postoperative respiratory complications and may experience postoperative respiratory failure.

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Riley-Day syndrome

See Familial dysautonomia

Riley-Smith syndrome

Synonym: Bannayan-Riley-Ruvalcaba syndrome; Bannayan-Zonana syndrome; Ruvalcaba-Myhre syndrome PTEN-MATCHS syndrome

MIM #: 153480

This autosomal dominant syndrome is characterized by macrocephaly, intestinal hamartomatous polyps, multiple benign neoplasms, abnormal pigmentation of the penis, and frequently a lipid storage myopathy. It results from a mutation of the gene *PTEN* (for "phosphatase and tensin homologue deleted on chromosome ten"), which is a tumor suppressor gene. It has been suggested that the defect is allelic with Cowden syndrome (see earlier), with which it has overlapping clinical features. Intestinal polyps are often diagnosed in childhood when patients present with intussusception or rectal bleeding. In patients exhibiting myopathy, a deficiency in muscle carnitine has been documented, and carnitine replacement therapy has been beneficial. Unlike Cowden syndrome, malignant transformation has not been found in Riley-Smith syndrome. Another synonym, PTEN-MATCHS syndrome, has been proposed, invoking **M**acrocephaly, **A**utosomal dominant, **T**hyroid disease, **C**ancer, **H**amartomata, and **S**kin abnormalities. Creative acronyms seem to be a specialty of dysmorphologists and multicenter cardiology clinical trials.

HEENT/Airway: Macrocephaly (without hydrocephalus), scaphocephaly. Hypertelorism, downslanting palpebral fissures, strabismus. High-arched palate. Occasional tongue polyps. Hypertrophy of Waldeyer's tonsillar ring causing airway obstruction has been reported.

Chest: May have pectus excavatum. May have supernumerary nipples.

Neuromuscular: Mild intellectual disability (although this has been recently questioned), gross motor delay, speech delay. May have pseudopapilledema. Most patients have a lipid storage myopathy, primarily involving the proximal muscles. Hypotonia. Intracranial hemangiomas or arteriovenous fistulae can bleed. Seizures, particularly in those with intracranial bleeds. Can have spinal epidural lipomatosis. May develop meningioma.

Orthopedic: Scoliosis. May exhibit joint hypermobility. Macrodactyly. Can have vascular malformations of the extremities.

GI/GU: Ileal and colonic hamartomatous polyps. Intussusception. Nonelevated pigmentary penile lesions. Enlarged penis and testes.

Other: Large for gestational age. Subcutaneous, cranial, or osseous neoplasms—usually lipomas, occasionally hemangiomas. Lipomas tend to regress with time. Diabetes mellitus and Hashimoto thyroiditis have been reported. Acanthosis nigricans.

Anesthetic Considerations: Patients should be euthyroid prior to elective surgery. A high-arched palate might make laryngoscopy and intubation more difficult. Patients with a significant myopathy probably should not receive succinylcholine secondary to the risk of exaggerated hyperkalemia. Chronic use of

anticonvulsant medications may affect the metabolism of some anesthetic drugs. Care should be taken with the perioperative positioning of patients with hyperextensible joints. It is possible for arteriovenous connections to cause high-output cardiac failure in infants. Possible spinal or epidural hemangiomas make neuraxial anesthesia

contraindicated unless their presence has been excluded.

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Roberts syndrome

See Pseudothalidomide syndrome

Robin sequence

See Pierre Robin sequence

Robinow syndrome

Synonym: Fetal face syndrome

MIM #: 180700, 268310

A type of mesomelic dysplasia, this usually autosomal dominant disorder has as its main features short stature, flat facies (“fetal face”), short forearms, and hypoplastic genitalia. This syndrome is etiologically heterogeneous. The autosomal dominant type is caused by mutations in the gene *WNT5A*. Its gene product is involved with cell signaling. An autosomal recessive form has been shown to be caused by mutations in the gene *ROR2*, a receptor tyrosine kinase. *ROR2* acts as a receptor for *WNT5A*. The autosomal recessive form tends to be more severe than the autosomal dominant form.

HEENT/Airway: Macrocephaly, frontal bossing, dolichocephaly, large anterior fontanelle. Flat facies, depressed nasal bridge. Hypertelorism, prominent eyes, upslanting palpebral fissures, epicanthal folds. Conductive hearing

loss has been reported. Posteriorly rotated ears. Small, upturned nose, long philtrum. Triangular-shaped mouth, malaligned teeth. High-arched palate. May have gingival hypertrophy. May have cleft lip or palate. May have bifid tongue. Ankyloglossia (adhesion of the tongue to the palate). Micrognathia.

Chest: Rib anomalies. May have pectus excavatum.

Cardiovascular: Congenital cardiac defects, particularly right ventricular outlet obstruction.

Neuromuscular: Occasional intellectual disability or developmental delay. May have seizures.

Orthopedic: Normal to mild short stature. Mesomelic or, less commonly, rhizomelic limb shortening. Short forearms. Small hands. Clinodactyly, brachydactyly, broad thumbs and toes. Nail dysplasia. May have congenital hip dislocation. Hemivertebrae, especially thoracic. Fused and hemivertebrae particularly in the recessive type. Scoliosis. Multiple rib and vertebral anomalies in the recessive form.

GI/GU: May have umbilical hernia. Hypoplastic genitalia—cryptorchidism, small penis, hypoplastic labia majora, small clitoris. May have vaginal atresia. Primary hypogonadism, although may have normal fertility. May have renal anomalies. May have inguinal hernias.

Other: May have growth hormone deficiency. Low testosterone levels in boys. Impaired hypothalamic-pituitary axis or hormonal response of ovaries in girls.

Anesthetic Considerations: Micrognathia may make laryngoscopy and tracheal intubation more difficult, although this has not been encountered in the small number of patients whose anesthetic course has been reported. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Impairment of pulmonary function by scoliosis has not yet been reported in this syndrome.

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ROHHAD syndrome

MIM #: None

This acronym stands for **R**apid-onset **O**besity, **H**ypoventilation, **H**ypothalamic dysfunction, and **A**utonomic **D**ysfunction. The hallmarks are hyperphagia followed several years later by central apnea and hypothalamic dysfunction resulting in panhypopituitarism. Neural crest tumors are found in approximately one-third of patients. The frequency of neuroectodermal tumors has suggested extension of the name to ROHHADNET.

HEENT/Airway: Mydriasis, decreased constriction to light.

Chest: Alveolar hypoventilation—obstructive and central apnea. Reduced ventilatory response to carbon dioxide. Hypoventilation can require noninvasive nighttime ventilation. Can be serious enough to cause significant desaturation. Cardiorespiratory deaths have occurred.

Cardiovascular: Bradycardia. Reduced heart rate variability. Orthostatic hypotension. Cor pulmonale.

Neuromuscular: Seizures. Autonomic dysfunction.

Orthopedic: Cold hands and feet.

GI/GU: Constipation. Dysmotility.

Other: Hyperphagia. Sudden, rapid increase in weight. Panhypopituitarism, which can include diabetes insipidus with hypernatremia, hypothyroidism, and adrenal insufficiency. Diaphoresis. Temperature dysregulation (hyper- and hypothermia). Neural crest tumors.

Anesthetic Considerations: The complex endocrine manifestations make consultation with an endocrinologist a good idea, particularly concerning continuation/modification of medications perioperatively, such as desmopressin. Avoid prolonged fasting, which involves withholding of water. Patients may have polydipsia and/or hyperphagia, so they should be carefully observed immediately preoperatively for surreptitious oral intake. Electrolyte levels must be assessed perioperatively and appropriate intravenous fluid chosen accordingly. Autonomic dysfunction could produce gastroparesis. This combined with obesity leads to an increased risk of perioperative aspiration. Temperature dysregulation is common—both hyper- and hypothermia may occur. Autonomic dysfunction could cause hypotension with (re)positioning or postoperative ambulation. Patients may not respond normally to acute volume loss or fluid shifts. Similarly, acute pneumoperitoneum may not be well tolerated. Chronic use of anticonvulsant medications may alter the metabolism of anesthetic drugs, requiring more frequent dosing. Both central apnea and panhypopituitarism are good indications for elective postoperative ICU admission. Patients may require postoperative mechanical ventilation. Patients may have an altered perception of pain.

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Rokitansky malformation sequence

See Rokitansky-Kuster-Hauser syndrome

Rokitansky-Kuster-Hauser syndrome

Synonym: Mayer-Rokitansky-Kuster syndrome; Mayer-Rokitansky-Kuster-Hauser syndrome; Rokitansky malformation sequence

MIM #: 277000

This autosomal dominant disorder involves hypoplasia or absence of the vagina and a rudimentary, usually bicornuate, uterus. The lower vagina, derived from the urogenital sinus, is normal, but ends blindly. The fallopian tubes and ovaries are normal. Endocrinologic function is normal. Secondary sexual characteristics are normal. There is primary amenorrhea. It is caused by a mutation in the gene *WNT4*. Most cases are sporadic, but there are some instances of familial occurrence. The Rokitansky-Kuster-Hauser syndrome may be a part of another malformation sequence, such as the MURCS association (see earlier). Successful pregnancy has been reported after vaginal reconstruction and uterus transplantation.

Cardiovascular: One report of associated pulmonary stenosis.

Orthopedic: One report of associated scoliosis.

GI/GU: Aplasia or dysgenesis of mullerian duct derivatives. Absence or severe hypoplasia of the upper

two-thirds of the vagina and uterus. Primary amenorrhea. Inguinal hernias can contain the uterus, fallopian tube, or ovary. Chronic renal tubulointerstitial disease has been reported.

Anesthetic Considerations: There are no specific anesthetic concerns other than exhibiting sensitivity toward young girls having gynecologic procedures.

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Romano-Ward syndrome

Included in Long QT syndrome

Romberg disease

Synonym: Parry-Romberg disease

MIM #: 141300

This sporadic syndrome of uncertain etiology is characterized by progressive atrophy of the soft tissue and bone on one side of the face, trigeminal neuralgia, changes of the hair and skin, and Jacksonian seizures that occur contralateral to the facial changes. It has been suggested that this syndrome may represent focal scleroderma. Immunosuppressive agents may be beneficial.

HEENT/Airway: Slowly progressive atrophy of the soft tissue on one side of the face. There may be atrophy of the underlying facial bones. The lower part of the face tends to be more severely affected. Heterochromia. Enophthalmos, ptosis. Small, misshapen ear. Hemiatrophy of the tongue. Delayed eruption of the teeth, malocclusion. Short body and ramus of the mandible.

Neuromuscular: Trigeminal neuralgia. Jacksonian seizures, which occur contralateral to the facial changes. Migraine-like headaches. Horner syndrome. Ataxia.

Other: Hyperpigmentation, vitiligo. Alopecia, hair color changes.

Romberg disease. Note the asymmetric facial hypoplasia in this 17-year-old girl admitted for plastic surgery.

Miscellaneous: Romberg was the world's first clinical neurologist, having been appointed lecturer in neurology at the University of Berlin in 1834. He is also the Romberg of Romberg's sign, an indicator of posterior column dysfunction.

Anesthetic Considerations: Although there is facial asymmetry, the ease of laryngoscopy and tracheal intubation should not be affected unless there is significant mandibular hypoplasia. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. There is a single case report of rhabdomyolysis and

hyperkalemic arrest following succinylcholine, despite prior uncomplicated use (1).

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Rothmund-Thomson syndrome

Synonym: Poikiloderma congenitale syndrome

MIM #: 268400

This autosomal recessive disorder is characterized by poikiloderma (atrophic plaques with telangiectasia), cataracts, and possibly other ectodermal dysplasias. There is wide variability in the clinical expression. The disorder is caused by mutations in the DNA helicase gene *RECQL4*, leading to defective repair of DNA. It is allelic with Baller-Gerold syndrome (see earlier).

HEENT/Airway: Microcephaly. Microphthalmia, microcornea. Juvenile cataracts, corneal dystrophy, glaucoma. Saddle nose. Dental abnormalities include microdontia, hypodontia, ectopic eruption, missing teeth, dental caries. Prognathism.

Neuromuscular: May have intellectual disabilities.

Orthopedic: Proportionate short stature. May have small hands and feet, hypoplastic to absent thumbs, syndactyly, forearm reduction defects. May have absent patella, clubfoot deformity. Osteoporosis. Atrophic nails. Development of osteosarcomas has been described in a number of patients. Can have kyphoscoliosis.

GI/GU: May have anteriorly placed anus, annular pancreas. Hypogonadism, cryptorchidism.

Other: There are many skin changes including irregular erythema typically beginning on the cheeks progressing to poikiloderma (telangiectasias, scarring, irregular pigmentation and depigmentation, atrophic dermatitis), most marked in sun-exposed areas. Sparse, prematurely gray hair. Hypohidrosis or anhidrosis. Hyperkeratotic lesions may be verrucous. Photosensitivity. Dysplastic nails. Anemia. Risk of basal cell and squamous cell skin cancers.

Miscellaneous: August von Rothmund was a 19th-century, Bulgarian-born German ophthalmologist. Matthew Thomson, a British dermatologist, reported a similar disorder 55 years later.

Anesthetic Considerations: When meeting patients preoperatively, recall that they may have loss of vision. If anemia is suspected, a preoperative hematocrit should be obtained. Dental abnormalities should be documented preoperatively. Patients may become hyperthermic perioperatively secondary to hypohidrosis or anhidrosis. Vascular access may be challenging secondary to skin changes and small hands and feet. Patients must be carefully positioned and padded secondary to atrophic changes in the skin. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Rotor syndrome

MIM #: 237450

This autosomal recessive disease leads to conjugated hyperbilirubinemia. Clinically, it is very similar to the Dubin-Johnson syndrome (see earlier). The disorder is due to mutations in the closely located genes SLCO1B1 and SLCO1B3, both organic ion transporters. The disease is benign, with an unaltered life expectancy. Other diseases of hepatic bilirubin metabolism include Crigler-Najjar and Gilbert syndromes (see earlier).

GI/GU: Intermittent hyperbilirubinemia/jaundice. Routine liver function tests are normal. The absence of abnormal hepatic pigmentation is one way to differentiate this disorder from Dubin-Johnson syndrome.

Miscellaneous: Rotor was an orchid breeder, and in addition to having a syndrome named after himself, he also has an orchid named after himself (Vanda merrillii var. rotorii).

Anesthetic Considerations: These patients are asymptomatic, and there are no specific anesthetic considerations. Although sulfonamides, some cephalosporins, and intravenous contrast agents can increase free bilirubin levels by

displacing bilirubin from albumin, no currently used anesthetic agents are known to displace bilirubin to a degree that would contraindicate their use. Hepatic synthetic function is normal in these patients. The stress of surgery or a perioperative infection may exacerbate the hyperbilirubinemia. These gene products mediate hepatic reuptake of bilirubin glucuronide. It has been suggested (but never demonstrated) that this might confer the risk of drug toxicities.

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Rubinstein-Taybi syndrome

MIM #: 180849, 613684

This autosomal dominant disorder is characterized by intellectual disabilities, broad thumbs and first toes, and craniofacial abnormalities. Almost all cases arise from *de novo* mutations. There is significant variation in the clinical presentation. Rubinstein-Taybi syndrome can be caused by a defect in the gene encoding the CREB-binding protein, a transcriptional coactivator that is involved in the cyclic adenosine monophosphate-mediated induction of intracellular protein synthesis. Production of this coactivator is stimulated by protein kinase A. A severe subset is due to a contiguous gene deletion affecting *CREBBP* and neighboring genes. A small percentage of patients (3%) will have so-called type 2 disease due to mutations in the gene *EP300*. The phenotypically overlapping Floating-Harbor syndrome (see earlier) is due to mutations in the gene *SRCAP*, a coactivator of *CREBBP*.

HEENT/Airway: Microcephaly. Frontal bossing. May have large anterior fontanelle with delayed closure of the fontanelle. Apparent hypertelorism. Thick, arched eyebrows. Nasolacrimal duct stenosis, downslanting palpebral fissures, ptosis, glaucoma, cataracts, strabismus, iris coloboma. Low-set or malformed external ears. Recurrent otitis. Hypoplastic maxilla, broad nasal bridge. Beaked nose, deviated nasal septum. May have choanal atresia. Short upper lip and pouting lower lip. Microstomia. High-arched palate. Dental crowding, enamel hypoplasia. Micrognathia. Abnormal grimacing smile with almost closing of the eyes. May have easily collapsible larynx. One report of congenital tracheal stenosis (3). Obstructive sleep apnea has been reported.

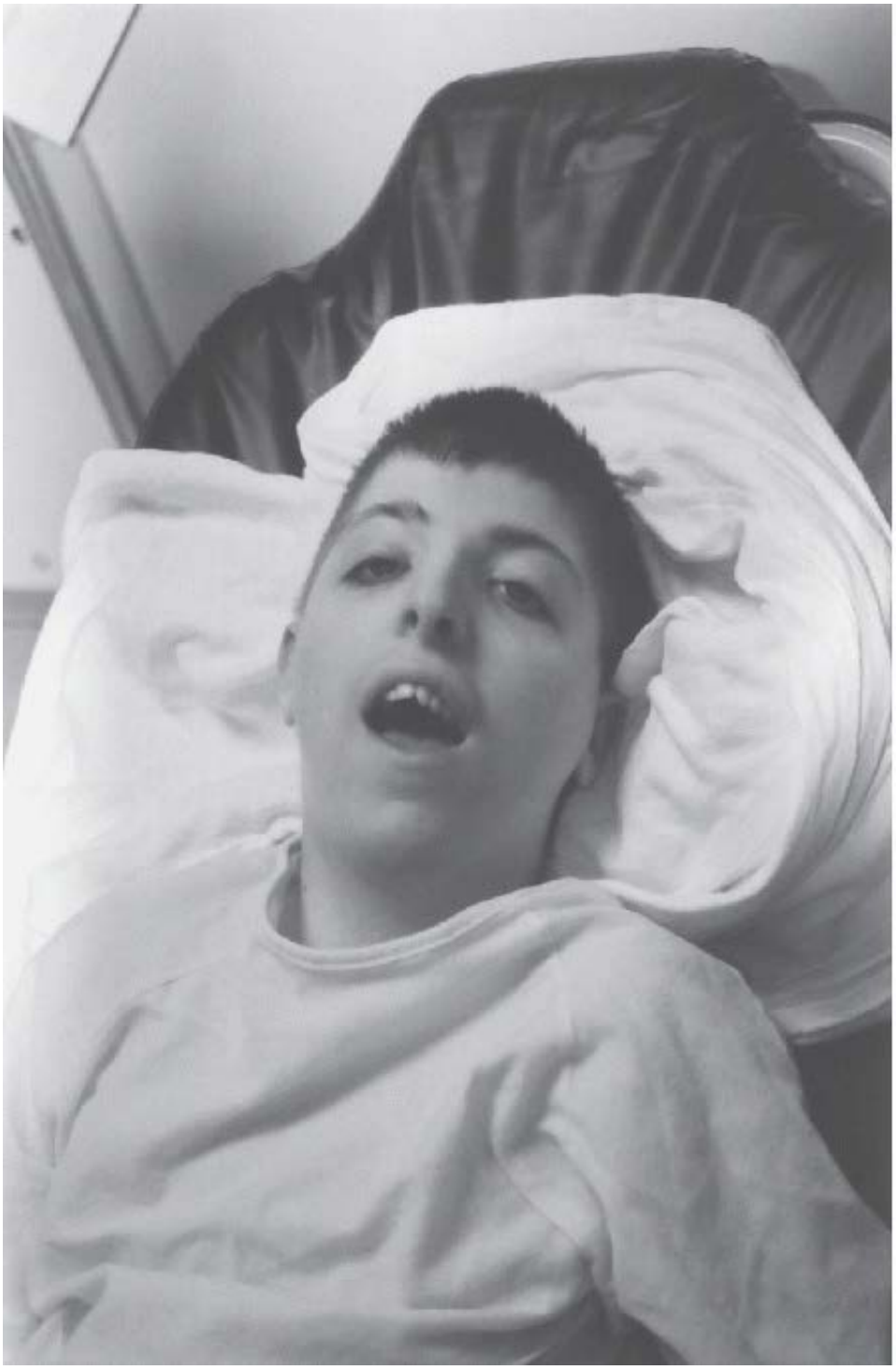
Rubinstein-Taybi syndrome. FIG. 1. Typical broad first toe and polydactyly of a 12-month-old child with Rubinstein-Taybi syndrome. His thumbs were equally broad.

Chest: Recurrent respiratory infections. May have sternal anomalies, pectus excavatum.

Cardiovascular: Approximately one-third have congenital cardiac defects, of a variety of acyanotic types. One patient has been reported with Wolff-Parkinson-White syndrome (see later).

Neuromuscular: Moderate to severe intellectual disability and motor retardation. Speech delay. Hypotonia. Stiff, unsteady gait. May have seizures, hyperreflexia. Large foramen magnum, agenesis of the corpus callosum. Mood lability. Behavioral problems that worsen with age.

Orthopedic: Short stature. Broad thumbs and first toes. Clinodactyly of the fifth finger. Flaring of the ilia, slipped capital femoral epiphyses, flat feet. May have patella dislocation. Joint hypermobility. Scoliosis, cervical kyphosis. Stiff gait. Spina bifida occulta. Retarded osseous maturation.



Rubinstein-Taybi syndrome. FIG. 2. This 16-year-old with Rubinstein-Taybi syndrome has obstructive sleep apnea and has had delayed emergence from several anesthetics, including desflurane.

GI/GU: Feeding difficulties, copious secretions. Constipation. Cryptorchidism, shawl scrotum, hypospadias. Occasional renal anomaly.

Other: Postnatal growth deficiency. Postpubertal obesity. Hirsutism. Premature thelarche. Asthma and other allergic manifestations are common. Capillary hemangiomas. Increased risk of leukemia and intracranial tumors.

Miscellaneous: Drs. Rubinstein and Taybi did not know each other while independently preparing to publish a report of this syndrome. A third physician known to both of them realized that the descriptive features in their case reports were the same. Rubinstein and Taybi then jointly published the first paper on this syndrome.

Anesthetic Considerations: Craniofacial abnormalities may make direct laryngoscopy and tracheal intubation difficult (8,9). Laryngoscopy with a variety of fiberoptic laryngoscopes has been successful. Hyperkyphosis may affect patient positioning, particularly at induction. Choanal atresia, if present, precludes the use of a nasal airway or placement of a nasogastric tube. A smaller-than-expected endotracheal tube might be required. Copious secretions and a high incidence of feeding difficulties in these patients suggest that they routinely be considered an aspiration risk (4,12). Use of a Pro-Seal laryngeal mask airway in an adult patient has been reported with passage of a gastric tube to decompress the stomach (8). Postoperatively, there is a risk of apnea, respiratory obstruction, and respiratory failure (7). The collapsible larynx may be problematic perioperatively, particularly in the postanesthesia care unit (14). The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

A single patient with Rubinstein-Taybi syndrome has been described in whom arrhythmias developed after succinylcholine and atropine/neostigmine. This is likely to have been an isolated case and has not been reported since (13). Succinylcholine has subsequently been used without incident in a patient with Rubinstein-Taybi syndrome (12). One patient was reported to have had delayed awakening after anesthesia with both isoflurane and propofol, given on separate occasions (11). Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Russell-Silver dwarf

See Russell-Silver syndrome

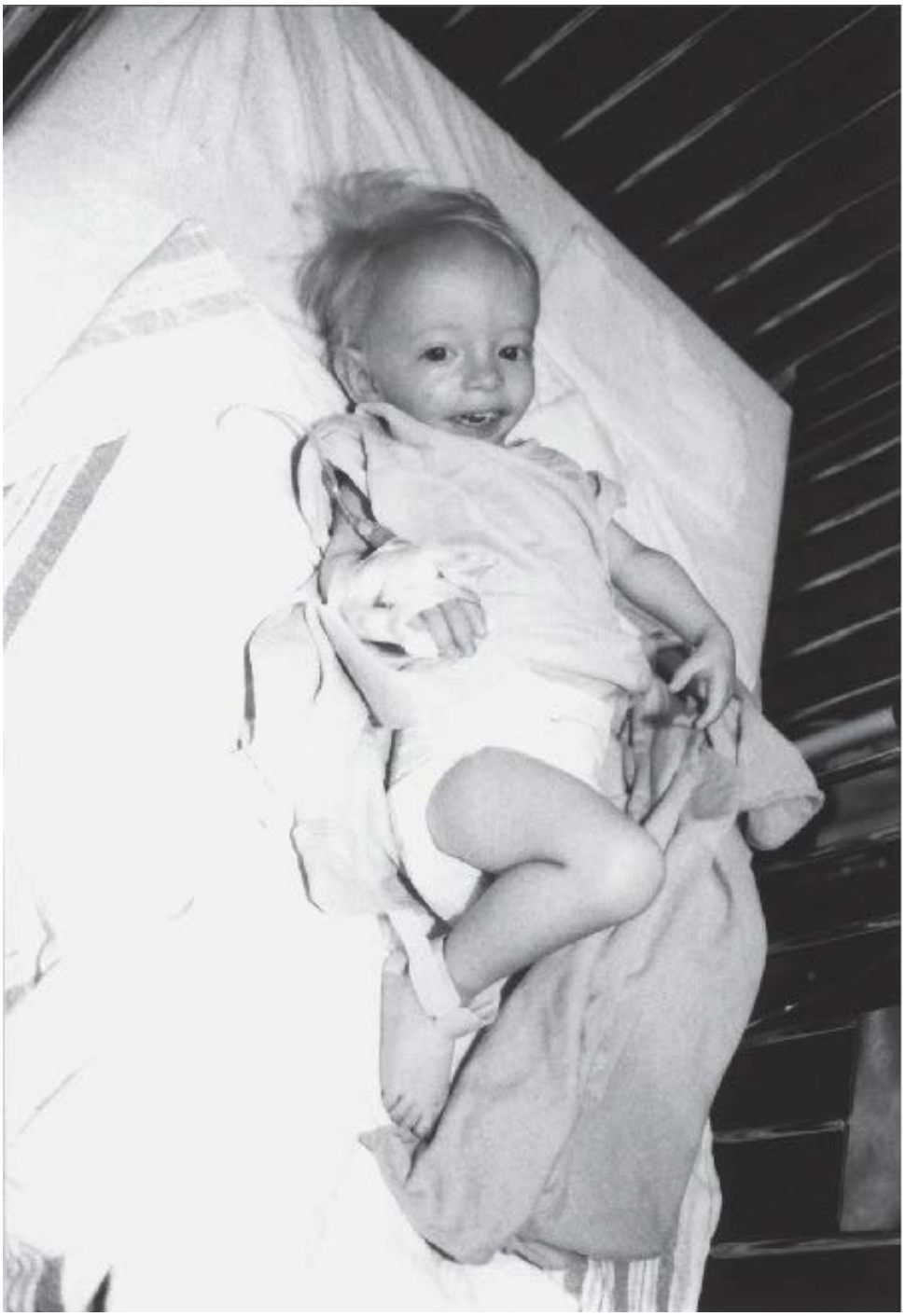
Russell-Silver syndrome

Synonym: Russell-Silver dwarf

MIM #: 180860

This syndrome is characterized by short stature of prenatal onset, triangular facies, skeletal asymmetry, and clinodactyly of the fifth finger. Most cases have been sporadic, and the inheritance pattern is uncertain. There is more than one genetic defect that can cause this syndrome (genetic heterogeneity). Over 50% are due to epigenetic DNA hypomethylation at the telomeric imprinting control region on chromosome 11p15 involving the genes *H19* and *IGF2*. About 10% are due to maternal disomy of chromosome 7. Russell-Silver patients can have some response to long-term exogenous growth hormone.

HEENT/Airway: Late closure of the anterior fontanelle. The head appears large in relation to the face, which is small and triangular, and the body, which is also small ("pseudohydrocephalus"). Head circumference is actually in the normal range. The sclerae may be bluish in early infancy. Refractive errors. Downturned corners of the mouth. Micrognathia.



Russell-Silver syndrome. FIG. 1. A 7-kg, 2-year-old boy with Russell-Silver syndrome. Note the wide forehead and narrow mandible. He had chronic problems with hypoglycemia and received 10% dextrose

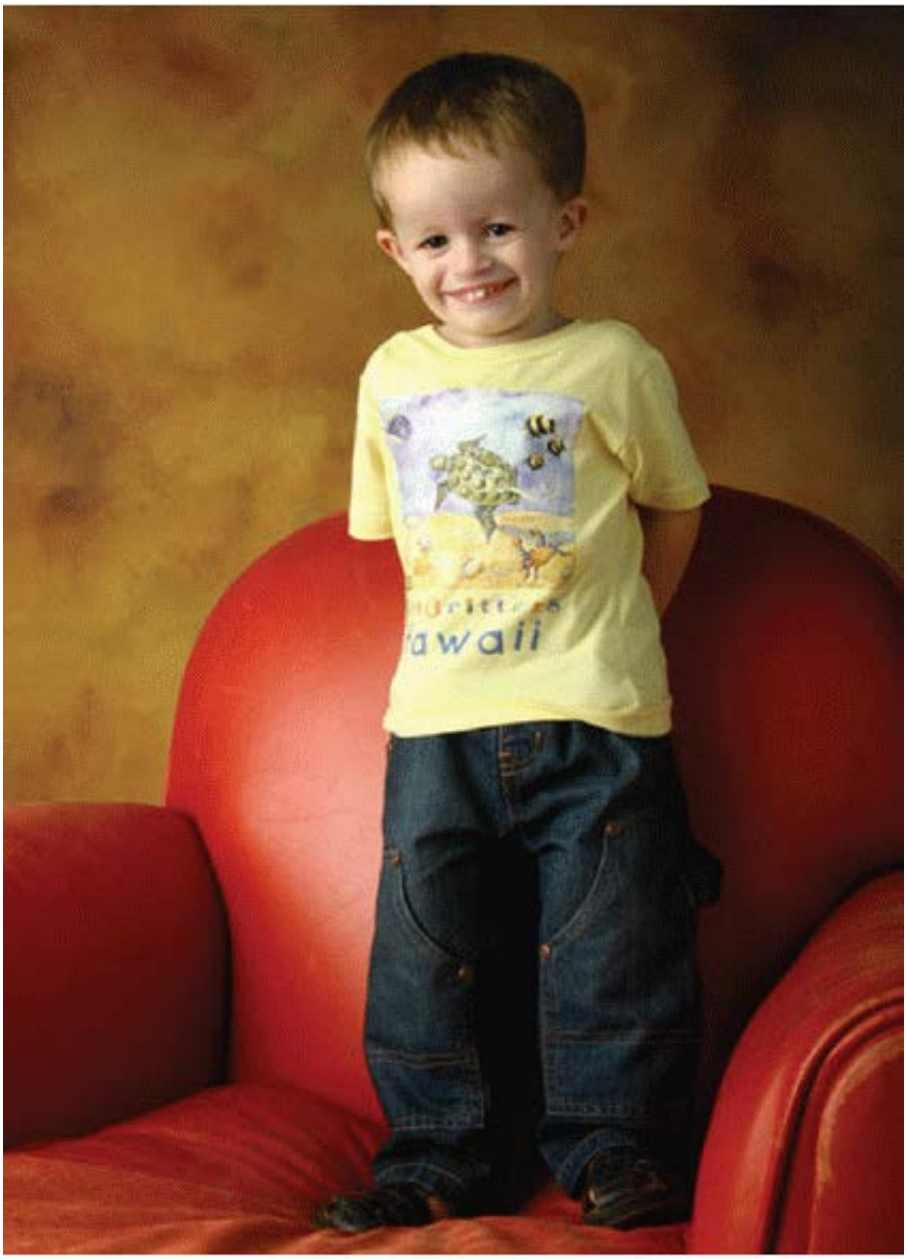
perioperatively. His trachea was difficult to intubate. At another hospital, after a prior surgery, he crawled out of bed and fell to the floor in the postanesthesia care unit. The staff had been misled by his small size and had assumed he was too young to crawl.

Neuromuscular: Intelligence is usually normal. Occasional developmental delay. Infants tend to be weak.

Orthopedic: Short stature; children improve in weight and height throughout childhood and adolescence. May have scoliosis. Skeletal asymmetry, particularly of the limbs. Hemihypertrophy. May have congenital hip dysplasia. Camptodactyly. Clinodactyly of the fifth finger. Can have vertebral anomalies, absent sacrum, or coccyx.

GI/GU: Gastroesophageal reflux, esophagitis. Cryptorchidism. Precocious sexual development. May have hypospadias, posterior urethral valves, renal anomalies. May have inguinal hernia.

Other: Small for gestational age, but with normal head circumference. Feeding problems. Occasional growth hormone deficiency. Café au lait spots. Excessive sweating during infancy. Elevated urinary gonadotropins. Risk of fasting hypoglycemia from approximately 10 months until 2 to 3 years of age. May be associated with a variety of cancers, including testicular seminoma, hepatocellular carcinoma, Wilms tumor, and craniopharyngioma. Can have precocious puberty.



Russell-Silver syndrome. FIG. 2. An older boy with Russell-Silver syndrome. Note that the head is disproportionately large in comparison to the face.

Miscellaneous: Henry Silver was a leading figure in American pediatrics. He was the Chair of Pediatrics at the University of Colorado and was one of the first to describe the battered child syndrome. He was also a leading early proponent of nurse practitioners.

Hypermethylation at this site (chromosome 11p15) is seen in 5% to 10% of those with Beckwith-Wiedemann syndrome (see earlier), an overgrowth syndrome.

Anesthetic Considerations: Recall that despite the child-size stature, patients have intelligence that is normal for their chronologic age. Direct laryngoscopy and tracheal intubation may be difficult secondary to facial deformities

and micrognathia. Obtaining a good mask seal may be difficult secondary to facial asymmetry. Because of their extreme small size, patients may require an endotracheal tube that is smaller than predicted by age. There is a high incidence of gastroesophageal reflux, and patients may be at risk for perioperative aspiration (3). These patients often exhibit

fasting hypoglycemia, particularly during the toddler years (2). Extended perioperative fasting must be avoided. Intravenous glucose-containing fluids should be used and serum glucose levels monitored perioperatively in all patients, not just those with a history of hypoglycemia (4). If drug doses are calculated on a per-kilogram basis, the increased surface area-to-weight ratio in these patients may result in underdosing. The absence of significant fat stores may allow for more rapid awakening after the use of volatile anesthetics. Poor insulation from inadequate subcutaneous fat, high surface-to-mass ratio, and a relatively large head all contribute to the development of perioperative hypothermia.

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Ruvalcaba syndrome

Note: This disorder is distinct from Ruvalcaba-Myhre syndrome/Bannayan-Riley-Ruvalcaba syndrome (see Riley-Smith syndrome, earlier).

MIM #: 180870

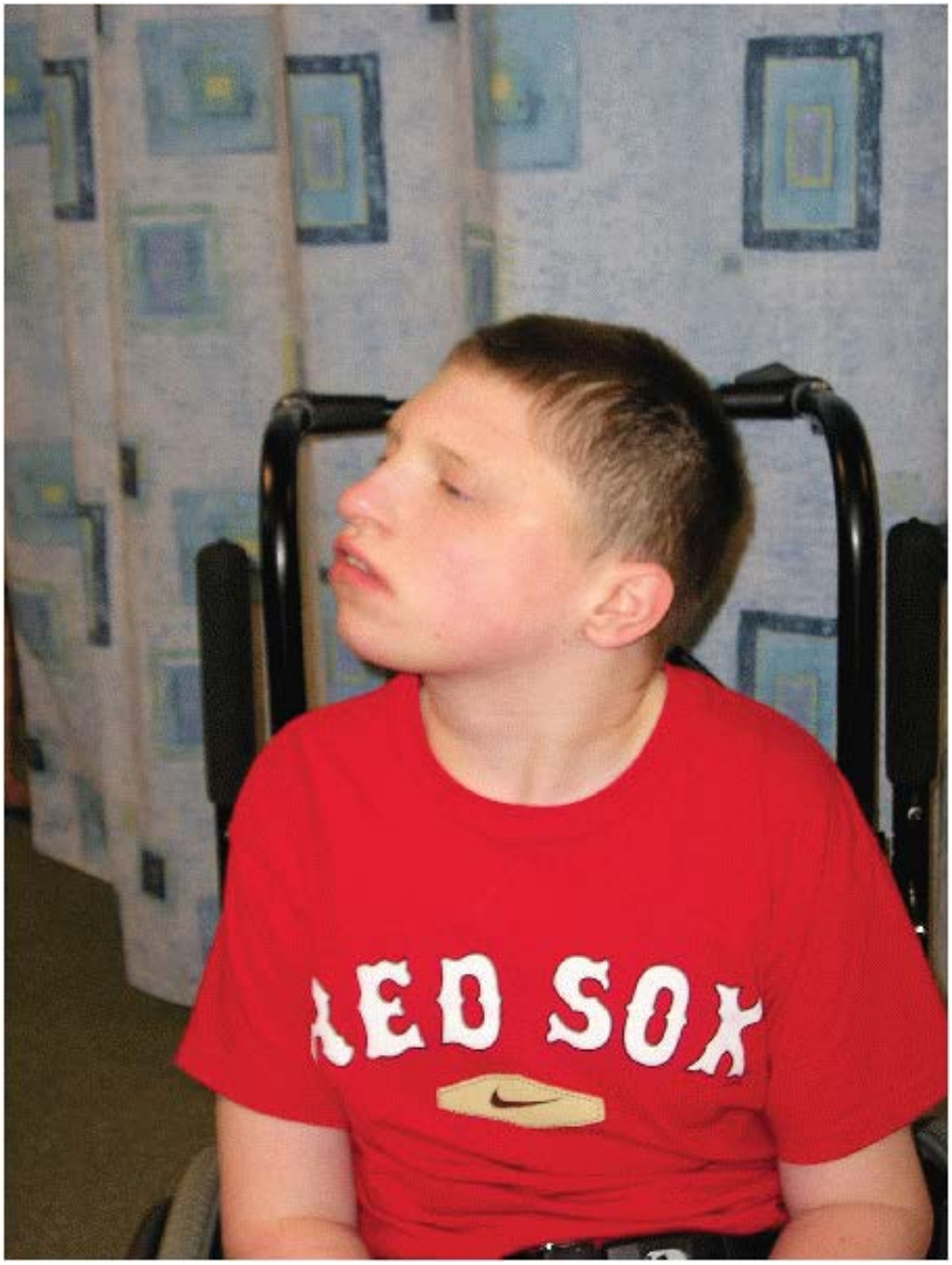
Ruvalcaba syndrome is an autosomal dominant disorder with neurologic and facial manifestations. The responsible gene and gene product are not known.

HEENT/Airway: Microcephaly. Oval face, high forehead. Downslanting palpebral fissures. Hooked nose. Hypoplastic maxilla. Small mouth. Crowded teeth. Thin lips. Pointed mandible.

Chest: Narrow thoracic cage. Pectus carinatum.

Neuromuscular: Intellectual disabilities. Congenital hydrocephalus. Dandy-Walker malformation.

Orthopedic: Short stature. Kyphoscoliosis. Short metatarsals and metacarpals, proximally displaced thumbs, clinodactyly. Small feet. Limited elbow extension. Osteochondritis of spine.



Ruvalcaba syndrome. A young teen with Ruvalcaba syndrome. Note the microcephaly, high forehead, hooked nose, hypoplastic maxillae, and relatively narrow thorax.

GI/GU: Hiatal hernia with gastroesophageal reflux has been reported. Inguinal hernia. Renal abnormalities. Cryptorchidism.

Other: Hypoplastic skin lesions. Delayed puberty.

Anesthetic Considerations: Laryngoscopy may be difficult in patients with a small mouth. Patients with a hiatal hernia or gastroesophageal reflux are at increased risk for perioperative aspiration, and consideration should be given to a rapid sequence anesthetic induction and intubation.

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Ruvalcaba-Myhre syndrome

See Riley-Smith syndrome

Ruvalcaba-Reichert-Smith syndrome

See Ruvalcaba syndrome

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

S

Sacral agenesis

See Caudal regression syndrome

Saethre-Chotzen syndrome

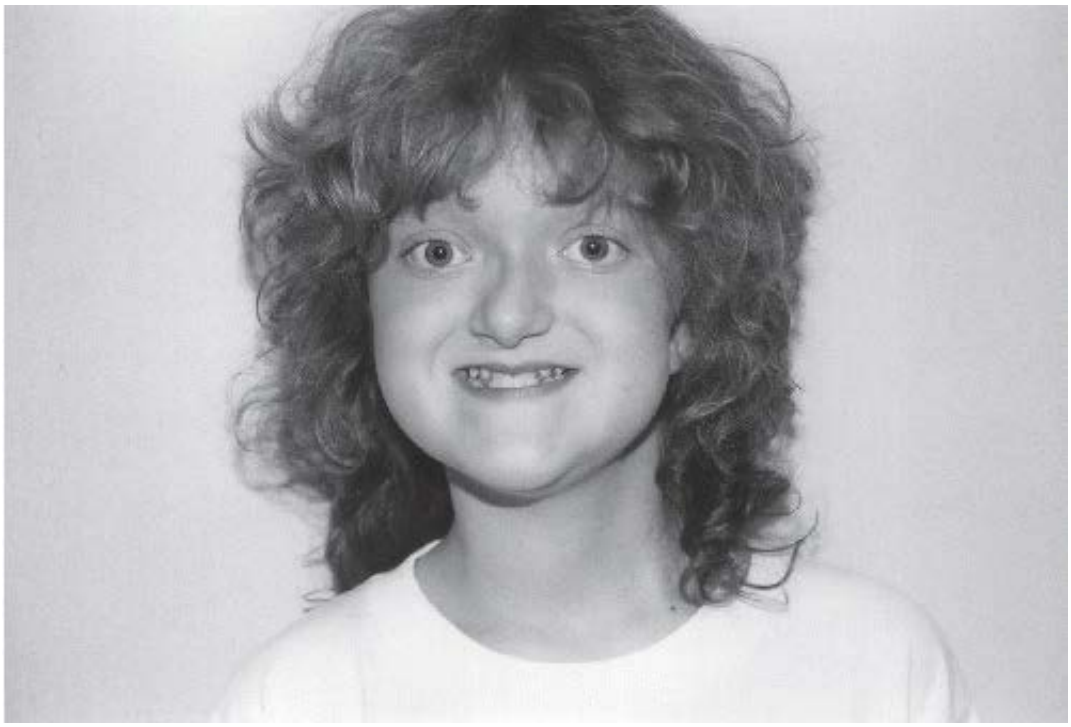
Synonym: Acrocephalosyndactyly type III

MIM #: 101400

This autosomal dominant disorder, one of the acrocephalosyndactyly syndromes, is characterized by brachycephaly, maxillary hypoplasia, and syndactyly. There is wide variability in clinical expression. The disorder is due to mutations in the *TWIST1* gene. The gene product of the *TWIST1* gene is a transcription factor. At least one individual with the Saethre-Chotzen phenotype had a mutation in the gene *FGFR2*.

HEENT/Airway: Craniosynostosis of one or more sutures, brachycephaly, plagiocephaly, acrocephaly. Maxillary hypoplasia. Late closure of fontanelles, ossification defects, and hyperostosis of the skull. Facial asymmetry, low frontal hairline. Shallow orbits with orbital asymmetry, ptosis, strabismus. Hypertelorism. A subtype has eyelid anomalies. Prominent crus across external ear. May have sensorineural hearing loss. Long, thin, pointed nose; deviated nasal septum. High-arched, may have cleft uvula or cleft palate. Facial appearance tends to improve with age through childhood.

Chest: Short clavicles.



Saethre-Chotzen syndrome. FIG. 1. This young girl with Saethre-Chotzen syndrome was scheduled for Laforte III midface advancement surgery.

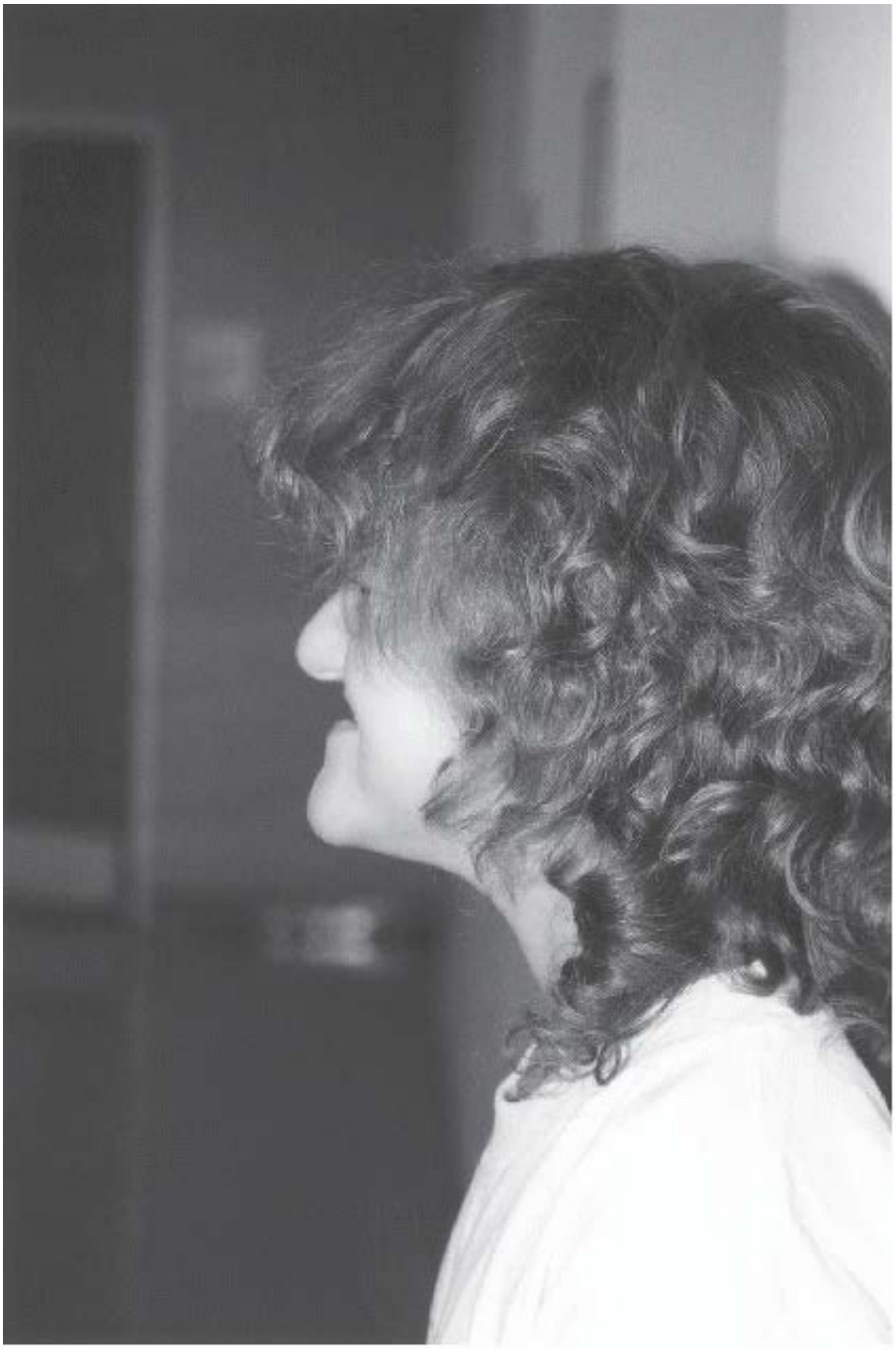
Neuromuscular: Intelligence is usually normal; may have some developmental delay. Rarely, craniosynostosis causes increased intracranial pressure, leading to intellectual deterioration. May have seizures.

Orthopedic: Occasional small stature. Cutaneous syndactyly. Small distal phalanges, clinodactyly of fifth finger, digitalization of thumbs, limited elbow extension. Radioulnar synostosis. Broad great toes with valgus deformity. Brachydactyly. Contractures of elbows and knees. May have cervical vertebral fusion, which may be progressive throughout childhood.

GI/GU: May have cryptorchidism. Occasional renal anomalies. Occasional anorectal malformation.

Other: It is suggested that there is an increased incidence of breast cancer.

Miscellaneous: Mice with mutations in the *TWIST* gene have skull and limb abnormalities similar to those of Saethre-Chotzen syndrome. Saethre was a Norwegian psychiatrist. He was active in the Norwegian resistance and was executed by the Nazis. The first patient he saw with this syndrome was referred to him for schizophrenia.



Saethre-Chotzen syndrome. FIG. 2. Lateral view of the girl in Figure 1.

Anesthetic Considerations: Unlike the other acrocephalosyndactyly syndromes, Saethre-Chotzen syndrome does not involve craniofacial features that are likely to lead to difficulty with direct laryngoscopy and tracheal intubation (1,6), although significant cervical vertebral fusion might make laryngoscopy and tracheal intubation more difficult. Patients may have elevated intracranial pressure, in which case precautions should be taken to avoid further elevations in pressure. Clavicular anomalies may make placement of a subclavian venous catheter or

an infraclavicular block more difficult. Patients must be carefully positioned and padded secondary to contractures.

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Saldino-Noonan-type short rib-polydactyly syndrome

See Short rib-polydactyly syndrome

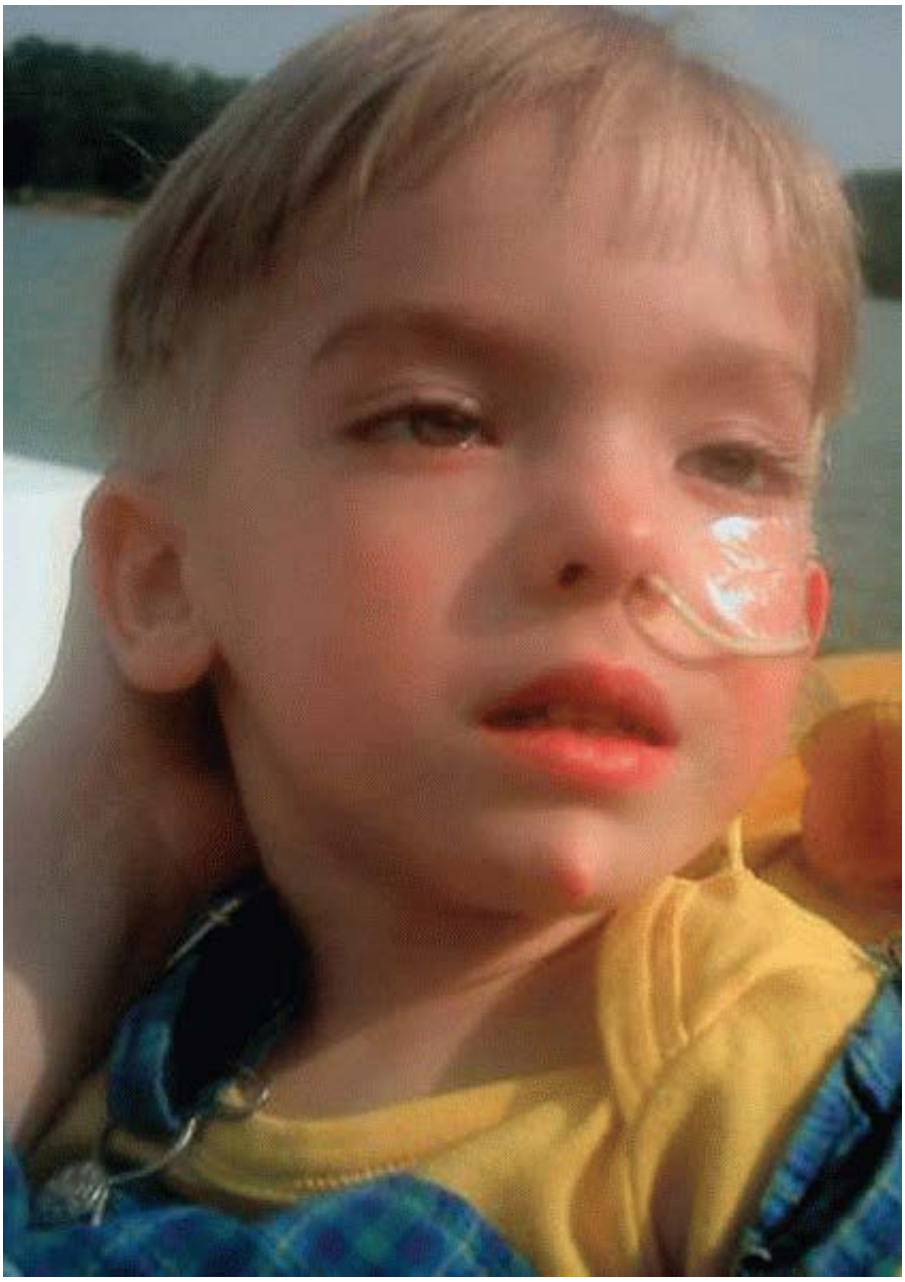
Sandhoff disease

Synonym: GM_2 gangliosidosis, type II

MIM #: 268800

This autosomal recessive disease with multiple alleles is due to abnormal accumulation of GM_2 ganglioside in neural tissue. Tay-Sachs disease (see later) is also due to accumulation of GM_2 ganglioside. Gangliosides are components of the outer cell membrane. They have a hydrophobic ceramide moiety anchoring them in the cell membrane and a hydrophilic oligosaccharide chain extending into the extracellular space. Although their function is unknown, they have been implicated as binding sites for a variety of viruses, bacterial toxins, growth factors, and interferons. Defects may occur in the alpha-subunit of hexosaminidase A (Tay-Sachs disease, deficient hexosaminidase A isoenzyme; see later) or the beta-subunit of hexosaminidase A (Sandhoff disease, deficient

hexosaminidase A and B), or there may be a defect in the GM_2 activator protein (both isoenzymes are present, but hexosaminidase A is nonfunctional). The clinical presentation of Sandhoff disease is generally similar to that of the biochemically related Tay-Sachs disease. The presence of hepatosplenomegaly in Sandhoff disease differentiates the two. Autonomic dysfunction is a prominent clinical manifestation. Death often occurs by age 3. There is some clinical heterogeneity, presumably due to allelic variations, and in some cases, onset of disease can be in adulthood. Preliminary encouraging results have been obtained with miglustat, an inhibitor of glucosylceramide synthase, which catalyzes the first step in the synthesis of glucose-based glycolipids.



Sandhoff disease. A young boy with Sandhoff disease. Note the need for head support.

HEENT/Airway: Macrocephaly. Coarse facies. Cherry-red spot in the macular area, blindness. Macroglossia. Dysarthria.

Cardiovascular: Orthostatic hypotension. Cardiomegaly.

Neuromuscular: Autonomic dysfunction. Progressive intellectual and motor deterioration. Cerebellar ataxia, pyramidal tract signs, hyperreflexia with exaggerated

startle reflex. Muscle weakness and muscle wasting with fasciculations. Peripheral neuropathy has been reported. Dementia with aging.

Orthopedic: High lumbar gibbus deformity.

GI/GU: Hepatosplenomegaly, recurrent abdominal pain, chronic diarrhea. Impotence, mild urinary incontinence.

Other: Impaired sweating. Heat intolerance.

Miscellaneous: Sandhoff disease has been reported in a pet rabbit and a toy poodle among other animals.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be more difficult secondary to macroglossia. Perioperative intravascular volume should be optimally maintained secondary to autonomic dysfunction and the possibility of orthostatic hypotension. Similarly, patients should ambulate carefully postoperatively because of the risk of postural hypotension. Widespread autonomic dysfunction may affect perioperative cardiovascular stability and temperature regulation. Succinylcholine is contraindicated in patients with significant muscle wasting because of the risk of hyperkalemia.

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Sandifer syndrome

MIM #: None

This disorder describes the paroxysmal dystonic posturing in children that is caused by gastroesophageal reflux. The posturing resolves completely after resolution of the reflux. It has been diagnosed in adults as well.

HEENT/Airway: Episodic extension and lateral deviation of the head.

GI/GU: Gastroesophageal reflux. Hiatal hernia should be strongly suspected. May have delayed gastric emptying.

Anesthetic Considerations: By definition, these patients have gastroesophageal reflux. They also often have delayed gastric emptying. A rapid sequence induction with tracheal intubation is indicated. These episodes can look superficially like seizures and must be differentiated from true seizures.

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Sanjad-Sakati syndrome

Synonym: Hypoparathyroidism-retardation-dysmorphism syndrome

MIM #: 241410

This autosomal recessive disorder is caused by mutations in the gene encoding tubulin-specific chaperone E (*TBCE*). Chaperones are a group of proteins that aid in proper protein folding. It is marked by congenital hypoparathyroidism with short stature and intellectual disabilities. It is mostly found in people of Arabian descent. The allelic Kenny-Caffey syndrome (see earlier) is also due to a mutation in this gene and is similarly found predominantly in Middle Eastern populations.

HEENT/Airway: Microcephaly. Deep-set eyes. Corneal opacities. Microphthalmos (or nanophthalmos). Large floppy ears. Depressed nasal bridge with beaked nose. Long philtrum with thin upper lip. Micrognathia. Pointed chin. Dental anomalies. May have redundant supraglottic mucosa.

Chest: Can have chronic pulmonary infections. Obstructive and central apnea have been reported.

Neuromuscular: Developmental delay. Seizures. May have intracranial calcifications.

Orthopedic: Severe intrauterine and postnatal growth failure. Proportional dwarfism. Neonatal pathologic

fractures have been reported. May have scoliosis.

GI/GU: Cryptorchidism.

Other: Essentially absent parathormone levels causing hypocalcemia and hypophosphatemia. Can have neonatal hypocalcemia. Low growth hormone and insulin-like growth factor. Prone to recurrent bacterial infections, but immune function is apparently normal.

Anesthetic Considerations: The serum calcium level should be evaluated preoperatively and corrected as necessary. Alkalosis will worsen ionized hypocalcemia. Dental anomalies need to be characterized preoperatively. Children may have difficulty cooperating and require premedication. Micrognathia might make laryngoscopy and intubation difficult. Endotracheal tube size is better predicted by patient size rather than age-related nomograms. Small size makes endobronchial placement more likely. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs. Obstructive or sleep apnea or recurrent pulmonary infections make postoperative observation in an ICU a consideration.

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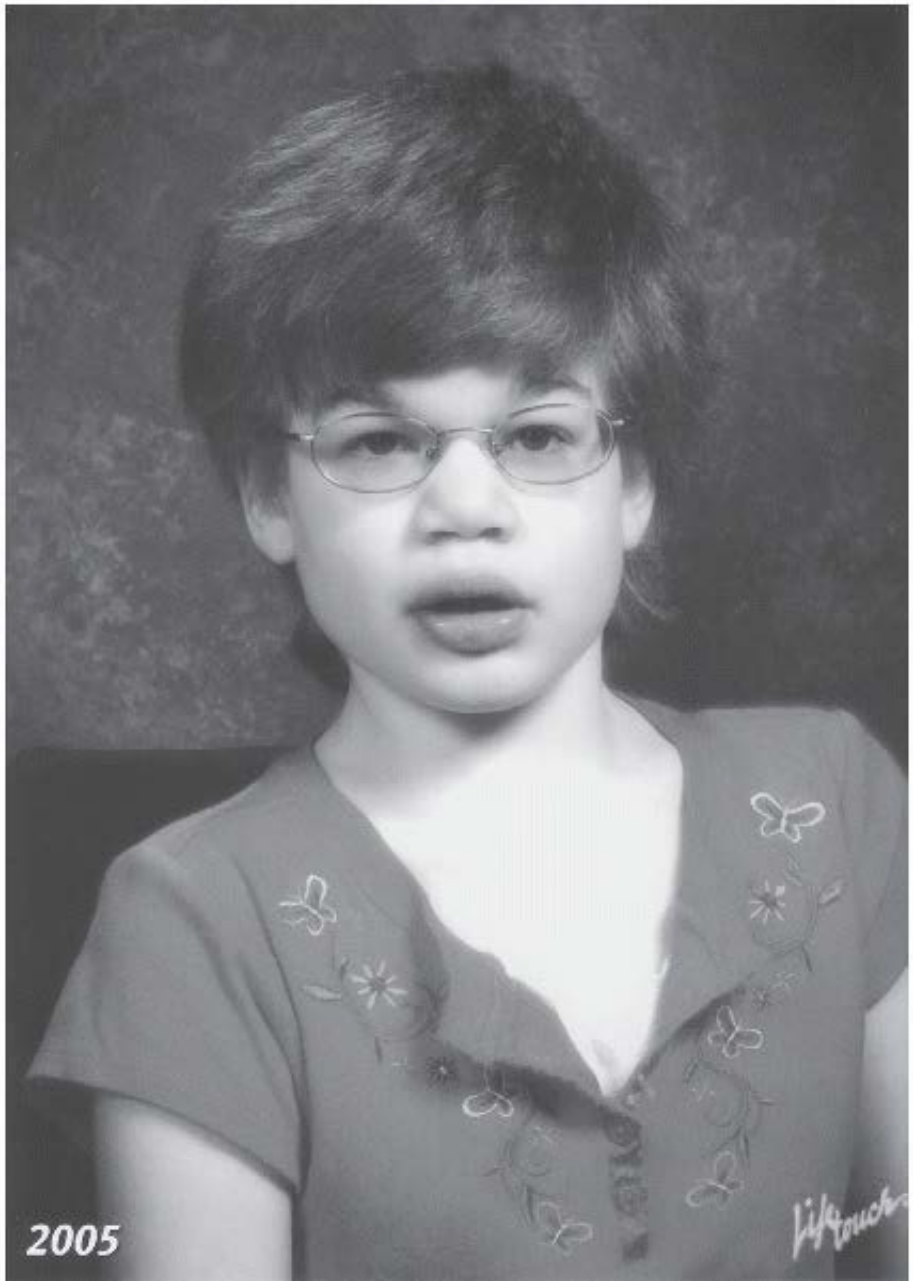
Sanfilippo syndrome

Synonym: Mucopolysaccharidosis III

MIM #: 252900, 252920, 252930, 252940

There are four biochemically distinct forms of Sanfilippo syndrome, all autosomal recessive, which are essentially indistinguishable clinically, although type A is said to be the most severe with a shorter life expectancy. Sanfilippo syndrome is a lysosomal storage disease associated with the accumulation of heparan sulfate. Type A involves a defect in *N*-sulfoglucosamine sulfohydrolase, type B involves a defect in alpha-*N*-acetylglucosaminidase, type C involves a defect in alpha-glucosaminide *N*-acetyltransferase, and type D involves a defect in *N*-acetylglucosamine-6-sulfatase. Compared with the other mucopolysaccharidoses, Sanfilippo syndrome has relatively severe central nervous system involvement and relatively mild systemic organ involvement. The mean age at onset of symptoms is 2½ years. Typically, patients experience progressive neurodegeneration over the first decade of life and death occurs in the second or third decade, although some patients experience a more benign clinical course.

HEENT/Airway: Thickened skull. Mild coarsening of facies. Corneas are clear. Synophrys. Hearing loss. Poor speech.



Sanfilippo syndrome. Fourth grade school photo of a 10-year-old girl with Sanfilippo syndrome.

Chest: Patients with mucopolysaccharidoses are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Cardiac involvement is rare, but mitral insufficiency requiring surgical valvuloplasty has been reported. Asymmetric septal hypertrophy has been reported.

Neuromuscular: Severe intellectual disabilities. Behavioral problems including hyperactivity. Patients may be aggressive and destructive. May have ventricular enlargement. May have seizures.

Orthopedic: Usually have normal stature, occasional short stature. Claw-hand deformity. Stiff joints. Ovoid

thoracolumbar vertebrae. May have osteoporosis. Osteonecrosis of the femoral head.

GI/GU: Mild hepatosplenomegaly in children, but not in adolescents or adults. Recurrent diarrhea in childhood. Umbilical and inguinal hernias.

Other: Sleep disturbances. Hypertrichosis. At risk for misdiagnosis as a primary behavioral disorder.

Anesthetic Considerations: Preoperative management can be challenging in these patients with severe

behavioral problems, particularly since they have normal strength. Difficult intubation may be encountered more frequently as patients age, although the incidence and severity of a difficult airway are much lower than with other mucopolysaccharidoses (8). The laryngeal mask airway has been used successfully in patients with mucopolysaccharidoses (7). Patients must be carefully positioned and padded perioperatively secondary to stiff joints. Treatment with anticonvulsant medications may affect the metabolism of some anesthetic drugs.

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SC phocomelia syndrome

See Pseudothalidomide syndrome

SCAD deficiency

See Short-chain acyl-CoA dehydrogenase deficiency

Scheie syndrome

Synonym: Mucopolysaccharidosis IS

MIM #: 607016

This autosomal recessive disorder is due to an absence of alpha-L-iduronidase, which is involved in the degradation of glycosaminoglycans (mucopolysaccharides). There is accumulation of dermatan sulfate. Different mutations in this same gene are responsible for Hurler syndrome, Scheie syndrome, and the intermediate Hurler-Scheie syndrome. These more correctly represent a spectrum of mucopolysaccharidosis I, with Scheie syndrome being the most benign. Lifespan is generally normal. Treatment with recombinant human alpha-L-iduronidase can significantly improve some clinical manifestations of the disease, and bone marrow transplantation has provided very good long-term results. However, bone marrow transplantation appears to have minimal effects on the progression of skeletal disease. The disease is mild enough that it may escape diagnosis until adulthood.

HEENT/Airway: Clouding of corneas, myopia, may develop glaucoma. Does not manifest the coarse facies of other mucopolysaccharidoses. Hearing loss. Broad mouth with full lips. Macroglossia. Prognathism. Short neck. Obstructive sleep apnea.

Chest: Patients with mucopolysaccharidoses are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Aortic valve involvement with stenosis or insufficiency. Mitral valve involvement. Severe airway obstruction may lead to pulmonary hypertension and cor pulmonale.

Neuromuscular: Intelligence is normal. Compression of the cervical spinal cord from thickened meninges (“pachymeningitis cervicalis”) can occur, but less frequently than in Hurler-Scheie syndrome. Intellectual deterioration and psychosis may develop.

Orthopedic: Normal stature. Joint limitation. Short, broad hands and feet. Claw hand, small carpal bones, carpal tunnel syndrome. Trigger thumb. Genu valgum. Stiff, painful feet. Pes cavus. Dysplasia of the femoral head. Lumbar-sacral spondylolisthesis can compress the spinal cord.

GI/GU: Umbilical and inguinal hernias, hepatomegaly.

Other: Hirsutism.

Miscellaneous: Harold Scheie was the chair of ophthalmology at the University of Pennsylvania. During WWII, Scheie treated Lord Louis Mountbatten who had injured his eye in a jeep accident. Scheie was able to save Mountbatten's eye, and they remained friends for the rest of their lives.

A deficiency of lysosomal alpha-L-iduronidase also occurs in Plott hound dogs.

Anesthetic Considerations: A case has been reported in the Japanese literature of a 35-year-old with Scheie syndrome with normal mouth opening in whom

limited mouth opening developed after induction of anesthesia with fentanyl, thiopental, and vecuronium. The tracheas of patients with Hurler syndrome, which is more severe, may be extremely difficult to intubate successfully (see Hurler syndrome, earlier). The laryngeal mask airway has been used successfully in patients with mucopolysaccharidoses (4). Patients must be carefully positioned and padded perioperatively because of limitations in joint mobility. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Patients with cardiac disease should receive an appropriately tailored anesthetic.

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bone marrow transplantation. *Paediatr Anaesth* 1992;2:317-324.

Scheuermann disease

MIM #: 181440

This autosomal dominant form of juvenile kyphosis is the most frequent cause of kyphosis in adolescents. The responsible gene and gene product are not known.

Chest: Severe kyphosis can cause restrictive lung disease.

Orthopedic: Kyphosis. Wedging of vertebral bodies and disk space narrowing seen radiographically. Rare spinal cord compression. Spinal epidural lipomatosis. Back pain.

Miscellaneous: The disorder can also occur in quadrupedal nonhuman primates.

Anesthetic Considerations: Patients will need to be carefully positioned secondary to kyphosis. Patients with severe kyphosis may have restrictive lung disease. They are at increased risk for perioperative respiratory complications. Good perioperative chest physiotherapy may be beneficial in these patients.

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Schilder disease

MIM #: 272100

This term is of historic interest only. It was used to refer to the entities that are now known as Krabbe disease, metachromatic leukodystrophy, and adrenoleukodystrophy. Now that these specific diagnoses can be made, it is no longer useful to use this term. For more information, see the discussions of each of these individual entities.

Miscellaneous: Born in Vienna, and later practicing at New York University, Paul Schilder was an early pioneer of psychoanalysis, although his ideas differed from some of Freud's concepts. The archetypal absent-minded professor, Schilder was killed in 1940 at the age of 54 years when he was hit by an automobile in New York City

while crossing the street against traffic with an armload of books.

Anesthetic Considerations: See the discussions of each of these individual entities.

Schindler disease

Synonym: Alpha-*N*-acetylgalactosaminidase deficiency; Alpha-galactosidase B deficiency (Includes Kanzaki disease)

MIM #: 609241, 609242

This autosomal recessive disease is due to a deficiency in the lysosomal enzyme alpha-*N*-acetylgalactosaminidase (alpha-NAGA) (also called alpha-galactosidase B), which leads to neuroaxonal dystrophy and severe neurologic impairment. This enzyme cleaves terminal alpha-galactosyl and alpha-*N*-acetylgalactosaminyl residues in glycoproteins and sphingolipids. The specific material that is stored has not been identified. Alpha-galactosidase A is the enzyme that is deficient in Fabry disease (see earlier).

There is a separate mutation of this gene that results in a significantly milder disease of adulthood, referred to as type II Schindler disease, or **Kanzaki disease** (*MIM #:* 609242). This disease of adult onset is marked by disseminated angiokeratomas of the skin, cytoplasmic vacuoles of the skin and kidney, dilated conjunctival vessels and tortuous retinal vessels, and gastric mucosal telangiectasis. In Kanzaki disease, there is no neuroaxonal dystrophy or neurodegeneration. The following discussion refers to Schindler disease, and not to the milder Kanzaki disease.

HEENT/Airway: Strabismus, nystagmus, optic atrophy, cortical blindness.

Cardiovascular: Cardiomyopathy has been reported in one patient.

Neuromuscular: Development is normal for the first 9 to 12 months and is then followed by profound neurodevelopmental regression. Hypotonia. Muscle atrophy. Myoclonic seizures, spasticity. By 4 to 5 years of age, children are essentially unresponsive to external stimuli. Decorticate posturing. The myenteric plexus is also affected by the storage of abnormal material, possibly leading to gastroparesis.

Miscellaneous: The parents of the propositi of this disease preferred not to have it named after their family or their village (in Germany), so it was named after the physician who labored to diagnose their children, Dr. Schindler.

Anesthetic Considerations: If there is diffuse enteric autonomic involvement with gastroparesis, a rapid sequence induction of anesthesia is indicated. Succinylcholine is contraindicated in patients with significant muscle atrophy because of the risk of hyperkalemia. Perioperative positioning may be difficult secondary to spasticity. Pulmonary complications are possible in profoundly affected patients by nervous system degeneration.

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Schinzel-Giedion syndrome

Note: This syndrome is distinct from both Schinzel syndrome (ulnar-mammary syndrome, not discussed in this text, *MIM #:* 181450) and Langer-Giedion syndrome (see earlier).

MIM #: 269150

This autosomal dominant disorder has as its primary manifestations severe postnatal growth deficiency and profound intellectual disabilities. Death often occurs before the age of 2 years, usually secondary to profound central nervous system dysfunction. It is due to mutations in the gene *SETBP1*.

HEENT/Airway: Sclerotic skull base, multiple wormian bones, long patent metopic suture, large fontanelles and sutures. Prominent forehead, midface hypoplasia. Occasional facial hemangiomas. Apparent proptosis due to shallow orbits, hypertelorism. Alacrima, corneal hypesthesia. Low-set ears. Short nose with anteverted nares. Choanal atresia or stenosis. Occasional macroglossia. Short neck with redundant skin.

Chest: Broad ribs, hypoplastic first ribs. Long clavicles, short sternum. Hypoplastic nipples.

Cardiovascular: Approximately one-third have congenital heart disease.

Neuromuscular: Profound intellectual disabilities. Seizures, spasticity, opisthotonos. Ventriculomegaly secondary to cerebral atrophy. Intraventricular bands, subependymal pseudocysts. Lissencephaly.

Orthopedic: Postnatal growth deficiency—short stature. Broad cortex and increased density of long bones. Shortened forearms and legs. Simian crease, hypoplasia of distal phalanges, hyperconvex nails, occasional postaxial polydactyly. Hypoplastic/aplastic pubic bones. Widening of distal femurs, tibial bowing, clubfoot deformity. Occasionally, the fifth toe overlaps the fourth.

GI/GU: Hypospadias, cryptorchidism, short penis, hypoplastic scrotum in boys; hypoplasia of labia majora or minora, hymenal atresia, short perineum in girls. Renal and ureteral anomalies. Hydronephrosis.

Other: Hypertrichosis. Embryonal tumors have been reported as well as hepatoblastoma and sacrococcygeal teratomas.

Anesthetic Considerations: Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Care must be taken when passing one of these tubes in patients with choanal stenosis. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Schizencephaly

MIM #: 269160

Schizencephaly is a unilateral or bilateral brain defect in which there is infolding of gray matter along a hemispheric cleft, typically parasylvian. It can be caused by mutations in the genes *EMX2*, *SIX3*, or *SHH* leading to defects in neuronal migration. Other causes have been ascribed to teratogens, prenatal infection, maternal trauma, young maternal age, and maternal alcohol use. It has also been described as a component of a variety of dysmorphic syndromes. Portions of the hemispheres can be absent and replaced with CSF. The clinical features depend on the severity of the defect. Patients with small clefts not involving the motor strip have a good prognosis. Careful surgical resection can produce good seizure control. Some cases of schizencephaly appear to be familial.

HEENT/Airway: Can have optic nerve hypoplasia.

Neuromuscular: Intellectual disabilities. Seizures that can be intractable. Hypotonia. Spasticity, hemiparesis. Can have psychological problems.

Anesthetic Considerations: Succinylcholine is relatively contraindicated in patients with hemiparesis because of the risk of hyperkalemia in patients with denervation of muscle. Chronic use of anticonvulsant medications may alter the metabolism of anesthetic drugs, requiring more frequent dosing.

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Schmid-type metaphyseal dysplasia

See Metaphyseal chondrodysplasia, Schmid type

Schönlein-Henoch purpura

See Henoch-Schönlein purpura

Schwartz-Jampel syndrome

Synonym: Chondrodystrophica myotonia (Includes Stuve-Wiedemann syndrome)

MIM #: 255800

This autosomal recessive disorder is one of the myotonic syndromes. The most common myotonic syndrome is myotonic dystrophy (see earlier). Schwartz-Jampel syndrome is characterized by myotonia, blepharophimosis, and joint limitation. Schwartz-Jampel syndrome type 1 is due to a mutation in the gene that encodes perlecan, the major proteoglycan component of basement membranes. It is thought that perlecan may interact with acetylcholine and/or voltage-gated ion channels with resultant hyperexcitability. Three subtypes of Schwartz-Jampel syndrome have been described: Type 1A is the classic type. It involves moderate bony dysplasia, and the diagnosis is usually made in childhood. Type 1B has more severe bone dysplasia and this results in diagnosis at birth, with myotonia following later. Type 2 is the most severe form and can present with reduced fetal movement and usually results in neonatal death from respiratory and feeding problems. Type 2 Schwartz-Jampel syndrome is genetically distinct. It is also known as neonatal Schwartz-Jampel syndrome or **Stuve-Wiedemann syndrome** (*MIM #*: 601559). Stuve-Wiedemann syndrome is caused by a mutation in the gene *LIFR* (leukemia inhibitory factor receptor), an interleukin-6 cytokine. There are clinical similarities to the Whistling face syndrome (see later) and the Marden-Walker syndrome (see earlier).

HEENT/Airway: Sad, fixed facies. Low hairline. Narrow palpebral fissures, blepharophimosis, myopia, cataracts. Long irregular eyelashes. Absent corneal and blink reflexes and corneal opacities in older children with Stuve-Wiedemann syndrome. Low-set ears. Overfolded helices. Very small mouth and micrognathia from tense puckering of the perioral muscles. Smooth tongue with absent fungiform papillae in older children with Stuve-Wiedemann syndrome. Small mandible. Crowding of teeth with malocclusion. Short neck with decreased range of motion. Small larynx with high-pitched or hoarse nasal voice. May have obstructive sleep apnea. Feeding and swallowing difficulties that can be severe in Stuve-Wiedemann syndrome.

Chest: Pectus carinatum. Severe kyphoscoliosis may cause restrictive lung disease. Severely affected neonates may have recurrent aspiration pneumonia and respiratory distress.

Cardiovascular: There have been several reports of pulmonary hypertension in Stuve-Wiedemann

syndrome, possibly related to premature closure of the ductus arteriosus.

Neuromuscular: Generalized myotonia, which refers to delayed relaxation of contracted muscle. Examples include the inability to release a handshake (“action myotonia”) or the sustained contraction with direct tapping or stimulation of a tendon reflex (“percussion myotonia”—best elicited by tapping the thenar eminence or finger extensors). In some mildly affected patients, myotonia may only be apparent on electromyography. There may be muscle hypertrophy or muscle atrophy. Some degree of intellectual disability in 20% to 25%. Occasional long-term survivors with Stuve-Wiedemann syndrome can have a clinical picture similar to dysautonomia.

Orthopedic: Short stature. Progressive joint contractures, with joint limitation. Single transverse palmar crease. Carpal tunnel syndrome. Bowing of the long bones, ankle valgus, pes planus. Osteoporosis. May have shortened long bones. Kyphoscoliosis, lumbar lordosis. Congenitally dislocated hip. Cleft vertebrae. Coxa vara or valga. Osteoporosis with pathologic fractures in older children with Stuve-Wiedemann syndrome. The skeletal abnormalities cause a particular gait, called by Schwartz and Jampel “marionette-like,” whereas others have

likened it to a “winding doll.”

GI/GU: Umbilical and inguinal hernias. Small testes.

Other: Episodes of hyperthermia, especially in Stuve-Wiedemann syndrome, which may be fatal. There have been rare cases of Stuve-Wiedemann syndrome associated with mitochondrial respiratory chain disorders.

Miscellaneous: This syndrome was actually first reported by Catel and by Pinto and de Sousa. The inability to express emotions by changing facial expression can be a significant problem for children and adolescents. The baseline facial appearance may be seen as suffering or crying.

Anesthetic Considerations: Laryngoscopy and tracheal intubation may be very difficult in these patients because of a very small mouth, limited mouth opening, micrognathia, jaw muscle rigidity, short neck with limited range of motion, and a small larynx (3,5,10,12). The laryngeal mask airway (LMA) has been used successfully (3).The passage of an endotracheal tube through a laryngeal mask airway has been reported in an awake 2.5-kg neonate after unsuccessful direct laryngoscopy and fiberoptic intubation (10).

Anesthetic or surgical manipulations may induce myotonic contractions, as can cold or shivering. The patient's body temperature should be maintained as close to normal as possible for this reason. Even pain from the intravenous injection of propofol may cause myotonic contractions. Neither regional anesthesia nor muscle relaxants prevent or reverse myotonic contractions. Drugs that have been used to attenuate the contractions are quinine, procainamide, phenytoin, volatile anesthetics, and steroids. When all else fails, infiltration of the muscle with a local anesthetic has been recommended.

These patients may have abnormal drug reactions. Succinylcholine is best avoided in patients with muscle disuse, secondary to the risk of an exaggerated hyperkalemic response. Resistance to rocuronium has been demonstrated (6). Anticholinesterase drugs used to reverse nondepolarizing muscle relaxants can precipitate myotonia, and the use of shorter-acting muscle relaxants that do not require reversal has been recommended.

Patients with lung disease secondary to recurrent aspiration or skeletal deformities are at increased risk for postoperative pulmonary complications. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. In addition, pulmonary hypertension should be excluded in children with Stuve-Wiedemann syndrome. Patients must be carefully positioned and padded because of joint contractures and joint limitation. Contractures may make intravenous access more challenging. Children with Stuve-Wiedemann syndrome can have reduced sensation to pain.

Temperature regulation is abnormal, and close attention should be paid to maintaining normothermia. Severe hyperthermia has been reported in association with both types 1 and 2. It is thought that these incidents represent abnormal thermoregulation rather than true malignant hyperthermia. Although some have subsequently opted to use non-triggering anesthetics (3,5), triggering agents have also been used without incident (2). The caution about malignant hyperthermia continues to appear in the literature of case reports and reviews.

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SCIDS

See Severe combined immunodeficiency syndrome

Schimmelpenning-Feuerstein-Mims syndrome

See Nevus sebaceous of Jadassohn

Sclerosteosis

MIM #: 269500

This autosomal recessive sclerosing bone dysplasia is characterized by osseous hyperostosis and syndactyly. Thick, dense bone can produce distortion of the face and compression of neural structures. It is caused by a mutation in the gene encoding sclerostin (*SOST*), which is important in modulating osteoblastic activity. The pathogenesis is thought to be related to hyperactivity of osteoblasts. The milder van Buchem disease (*MIM #:* 239100), not discussed here, is due to a deletion downstream of the *SOST* gene that removes a *SOST*-specific regulatory element.

HEENT/Airway: Facial distortion with relative midface hypoplasia. Proptosis, which may lead to blindness in adulthood. Strabismus. Deafness secondary to occlusion of foramina by cranial hyperostosis. Dental malocclusion. Prognathism. Prominent, sometimes asymmetric jaw.

Chest: Broad dense scapulae, ribs, and clavicles.

Neuromuscular: Facial and other cranial nerve palsies secondary to impingement of foramina by cranial hyperostosis. Intracranial pressure may be elevated from calvarial overgrowth and can be fatal. Impaction of the medulla has resulted in sudden death. Most patients require prophylactic craniectomy.

Orthopedic: Tall stature. Dense tubular long bones. Cutaneous syndactyly of second and third fingers, which may be asymmetric. Metaphyseal dysplasia. Radial deviation of terminal phalanges. Atrophic nails. Genu valgum.

Miscellaneous: Most reported cases have been in the Afrikaner population of Dutch descent in South Africa. Interestingly, this disorder has also been reported in a part of Brazil that had been occupied by the Dutch in the 17th century.

Anesthetic Considerations: Facial asymmetry and bony overgrowth may make mask ventilation and/or tracheal intubation difficult. The proptotic eyes must be carefully protected perioperatively. Hypercapnea should be avoided in the presence of increased intracranial pressure. Possible medullary compression suggests close postoperative observation for respiratory depression.

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Sebaceous nevus syndrome

See Nevus sebaceus of Jadassohn

Sebastian syndrome

Included in Fechtner syndrome

Seckel syndrome

MIM #: 210600

This autosomal recessive dysmorphic syndrome is characterized by extreme short stature, microcephaly, and a beak-like nose. Many patients survive well into adulthood. There is genetic heterogeneity, and a total of seven Seckel syndromes have thus far been delineated, each due to abnormalities in a different gene. Seckel syndrome type 1 is due to mutations in the gene encoding ataxia-telangiectasia and RAD3-related protein (ATR), a regulator of genomic integrity.

HEENT/Airway: Microcephaly. Premature synostosis, receding forehead. Large eyes, downsloping palpebral fissures. Retinal degeneration. Childhood glaucoma has been reported. May have optic lens dislocation. Low-set, malformed ears. Beak-like nose. May have cleft lip/palate. High-arched palate. Partial anodontia, enamel hypoplasia. Retrognathia. May have laryngeal stenosis.

Chest: Eleven pairs of ribs.

Cardiovascular: One report of AV canal defect. May have systemic hypertension.

Neuromuscular: May have intellectual disabilities, which can be severe. Brain is small, with simple folding pattern. Pleasant personality; may be easily distracted. May have Arnold-Chiari malformation. May have intracranial aneurysm. May have seizures.

Orthopedic: Extreme proportionate short stature. Simian crease, clinodactyly of the fifth finger, hypoplasia of the proximal radius with dislocation of the radial head. Gap between the first and second toes, clubfoot deformity, hypoplasia of proximal fibula, inability to fully extend knee, dislocation of the hip. May have pes planus, scoliosis.

GI/GU: Cryptorchidism. Occasional hypoplastic external genitalia. May have renal insufficiency.

Other: Prenatal onset of severe growth deficiency. Sparse hair. Friable veins. Occasional hypoplastic anemia or pancytopenia. May have increased risk of hematologic malignancies. Hypopigmented macules.

Miscellaneous: This syndrome was given the rather unfortunate derogatory name “bird-headed dwarfism” by Virchow. He also called it nanocephaly. Seckel wrote the defining paper in 1960.

Caroline Crachami, a Sicilian-born dwarf who gained notoriety as one of the most extreme cases of dwarfism ever recorded when she was exhibited in England in 1824, probably had Seckel syndrome.

Anesthetic Considerations: Patients have extreme short stature and should be addressed in a manner that is appropriate for their chronologic and intellectual age rather than their height age. Dental abnormalities should be documented preoperatively. Retrognathia may make direct laryngoscopy and tracheal intubation more difficult (1), although there is only one such case report. Endotracheal tube calculations based on age will overestimate the appropriate tube size. Similarly, smaller laryngeal masks than predicted for age should be used. Friable veins may make intravenous access challenging. Postoperative apneic spells were reported in one patient (2).

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Segawa syndrome

MIM #: 128230

This usually autosomal dominant disorder is one of a levodopa-responsive, progressive dystonia with diurnal variation. There is dystonic posturing and disordered movement, beginning in one limb in childhood, but involving all limbs by approximately 5 years after clinical onset. The symptoms are somewhat similar to Parkinson's disease. There is evidence of genetic heterogeneity, but it is usually caused by a mutation in the gene encoding guanosine triphosphate (GTP) cyclohydrolase I. This enzyme is the rate-limiting step in the conversion of GTP to tetrahydrobiopterin (BH4), a cofactor for tyrosine hydroxylase, in turn the rate-limiting step for the synthesis of dopamine. Tetrahydrobiopterin has a relatively short half-life, and it may be that synthesis is inadequate and levels fall during daytime activity, resulting in the clinical worsening at the end of the day. There is a marked response to L-dopa. Mutations in the gene encoding tyrosine hydroxylase can cause a rare autosomal recessive form of this disease. There can be significant phenotypic variability even within families. The disease is more severe in females than males. GTP cyclohydrolase I activity is normally higher in males.

HEENT/Airway: Expressionless face. Drooling. May have hearing loss. Torticollis.

Neuromuscular: Dystonic posturing, slowed movement, rigidity. Focal dystonia (e.g., writer's cramp). Truncal involvement is uncommon. Symptoms are improved after sleep and worsen toward evening. Symptoms are markedly improved by levodopa. Exaggerated deep tendon responses and apparent Babinski sign (pseudopyramidal signs).

Other: May have a variety of psychiatric manifestations—anxiety, depression, obsessive-compulsive, and eating disorders—probably secondary to defects in central dopamine, serotonin, and/or norepinephrine synthesis.

Anesthetic Considerations: Regional and general anesthesia have been used successfully. Torticollis may make airway management more challenging. Because this disease affects muscle, succinylcholine should probably be used with care, although both succinylcholine and a nondepolarizing neuromuscular blocker have been

used without problems (3). Phenothiazines, butyrophenones, metoclopramide, and other dopaminergic blockers may exacerbate movement disorders in general and should be specifically avoided in this disorder of dopamine synthesis. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects.

There are potential complications associated with higher-dose levodopa therapy in general, including tachycardia and increased cardiac irritability, increased glomerular filtration rate with lower intravascular volume and orthostatic hypotension, and decreased production of norepinephrine with substitution of dopamine, which is a less

potent pressor. Ketamine, which has several sympathomimetic effects, has been used successfully in patients taking levodopa. There were no untoward effects in a patient who was taking relatively low doses of levodopa and had both general and epidural anesthesia for cesarean sections (3). No complications were reported in a patient who underwent a series of electroconvulsive therapy (ECT) treatments.

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Seip syndrome

See Lipodystrophy

Seip-Lawrence syndrome

Included in Lipodystrophy

Senter syndrome

Synonym: Senter-KID syndrome; KID syndrome

MIM #: 148210, 242150

This congenital ectodermal disorder has been documented to occur in both autosomal dominant and autosomal recessive forms. The primary manifestations are an ichthyosiform rash with focal hyperkeratosis and sensorineural deafness. KID is an acronym for **K**eratitis, **I**chthyosis, and **D**eafness. A corneal dystrophy can also be disabling. Autosomal dominant cases are caused by a mutation in the connexin-26 gene (*GJB2*), a gap junction protein. Since most cases are sporadic, they likely represent fresh mutations. The recessive form involves hepatic disease, growth failure, and intellectual disability in addition to the features of the dominant form. The responsible gene and gene product are not known.

HEENT/Airway: Sparse eyebrows, eyelashes, and scalp hair. Progressive corneal opacification with progressive vascularization and photophobia. Eventual destruction of the cornea and development of keratoderma, a scarlike deposition over the cornea with vision loss. Congenital sensorineural deafness. Malformed teeth, lesions of the mouth, scrotal tongue.

Neuromuscular: Occasional intellectual disability.

Orthopedic: Tight heel cords, variable flexion contractures.

GI/GU: Cryptorchidism. Occasional Hirschsprung disease (see earlier). Cirrhosis in the autosomal recessive form.

Other: Ichthyosiform rash with hyperkeratosis of the palms, soles, elbows, and knees. Hypohidrosis (decreased sweating). Growth failure in the autosomal recessive form. Variable alopecia. Variable nail dystrophy. Squamous cell carcinoma of skin and tongue. Malignant pilar tumors (cancers of the hair follicle). Fungal and bacterial mucocutaneous infections, which can be chronic and which can lead to septicemia.

Anesthetic Considerations: When meeting the patient before surgery, recall that he or she may have significant vision and/or hearing loss. Patients with photophobia may be extremely sensitive to the bright lights in operating rooms. Hypohidrosis may lead to overheating. Proper perioperative positioning may be difficult secondary to contractures.

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Senter-KID syndrome

See Senter syndrome

Septooptic dysplasia

Synonym: de Morsier syndrome

MIM #: 182230

This syndrome is characterized by optic nerve hypoplasia with midline defects of the prosencephalon. Most patients have hypothalamic hypopituitarism with associated multiple hormone deficiencies. About two-thirds have hypopituitarism, two-thirds have an absent septum pellucidum, and one-third have the full spectrum of optic nerve hypoplasia, pituitary gland hypoplasia, and midline brain malformations. It can be caused by a mutation in the murine homeobox gene *HESX1*, although a vascular etiology has also been suggested. In some patients, there is evidence of a vascular pathogenetic etiology. Children are at risk for sudden death from an intercurrent viral infection, presumably secondary to adrenal insufficiency (5).

HEENT/Airway: Diminished visual acuity from optic nerve hypoplasia, occasionally including visual field defects. Congenital nystagmus.

Cardiovascular: One uncommon allelic variant also results in cardiomyopathy.

Neuromuscular: Agenesis of the corpus callosum. Absence or abnormality of the septum pellucidum and hypothalamic/pituitary dysfunction. Schizencephaly (see earlier). Neurologic signs and symptoms are variable. Some patients may have almost no neurologic findings and are of normal intelligence, whereas others have intellectual disabilities, learning disabilities, delayed motor development, spastic quadriparesis, corticospinal tract involvement, and hypotonia or clumsiness. Occasional athetosis, seizures, autism, cranial nerve palsy, attention deficit disorders. May have neonatal apnea.

Orthopedic: Small stature. May have digital anomalies.

Other: Hypothalamic hypopituitarism with low levels of growth hormone, prolactin, thyroid-stimulating hormone, adrenocorticotrophic hormone (ACTH), luteinizing hormone, follicle-stimulating hormone, and antidiuretic hormone although some may have just isolated deficits. Hypopituitarism can result in recurrent hypoglycemia.

Miscellaneous: First described by Reeves, named “septooptic dysplasia” by de Morsier, and fully delineated by Selna Kaplan and coworkers.

Anesthetic Considerations: Patients with hypothalamic hypopituitarism require chronic hormone and steroid replacement. Glucocorticoid and antidiuretic hormone deficiency are the most problematic perioperatively. Most patients require perioperative stress doses of steroids. Urine output may be an inadequate measure of intravascular volume in the face of both treated and inadequately treated diabetes insipidus. Temperature regulation could be affected by hypothalamic dysfunction.

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Severe combined immunodeficiency syndrome

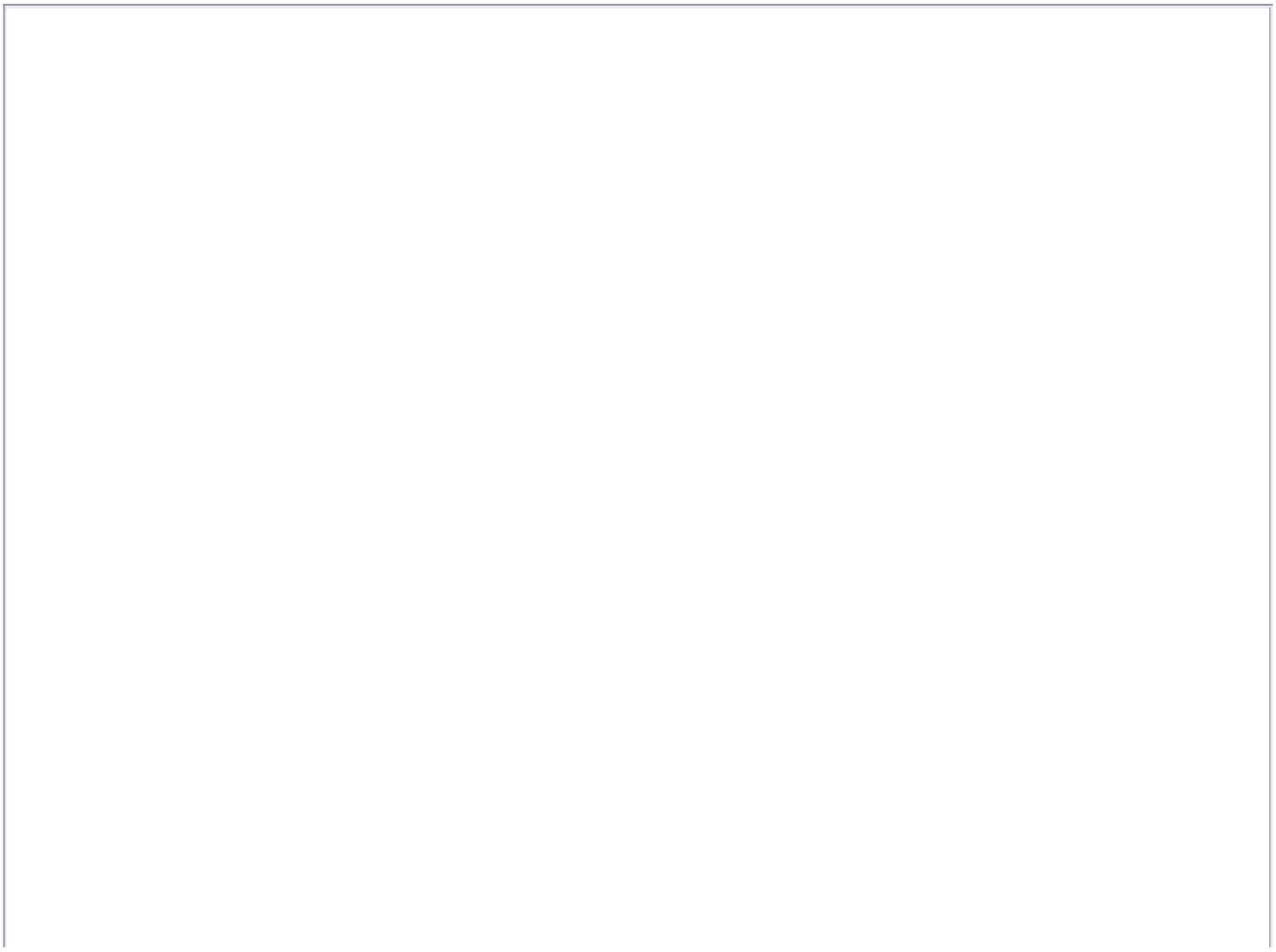
Synonym: SCIDS (Includes Bare lymphocyte syndrome and Swiss-type agammaglobulinemia)

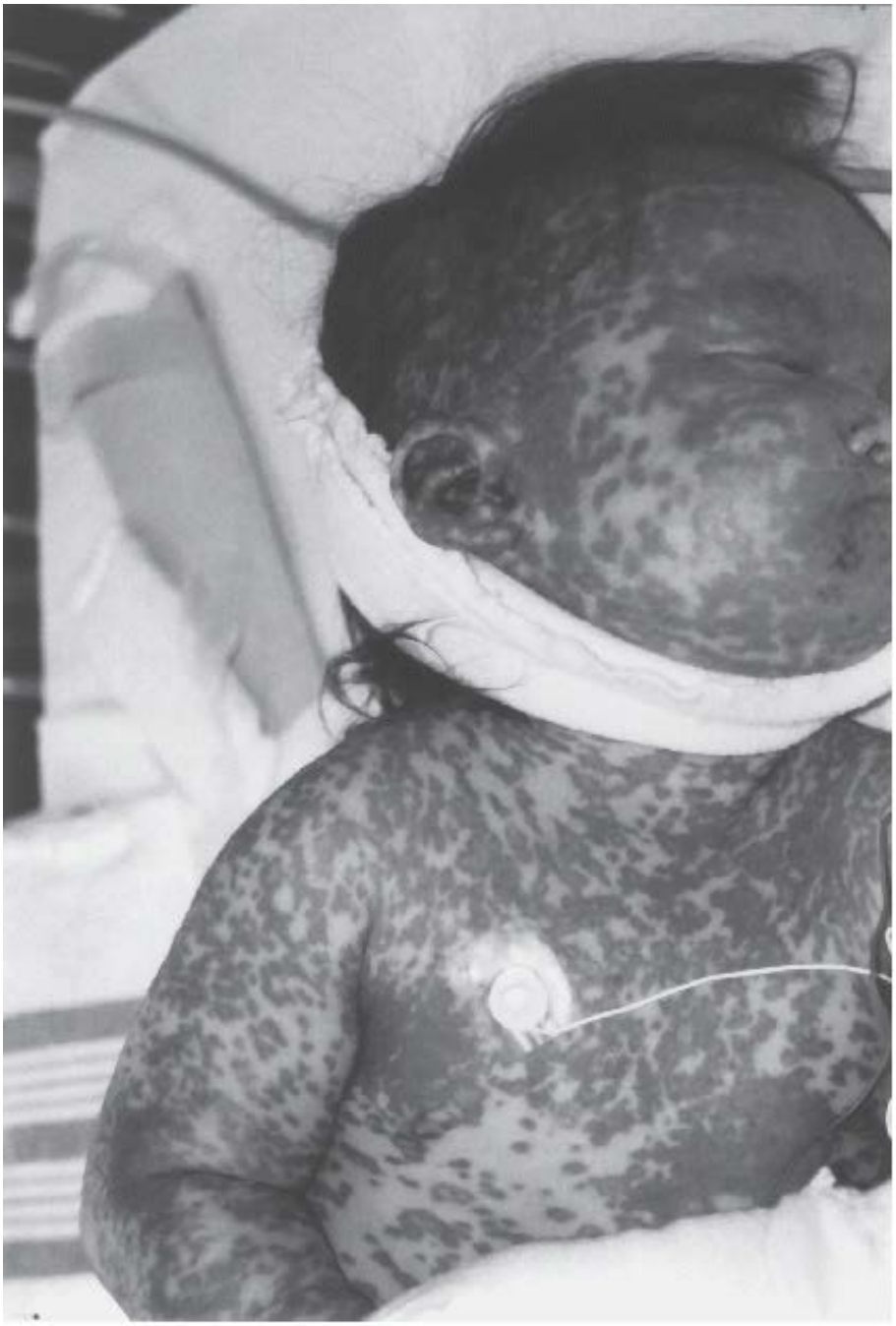
MIM #: 102700, 300400, 209920, and others

This rubric covers at least eleven distinct entities, both autosomal recessive and X-linked, which in general result in deficiency of both T- and B-cell function. All are marked by severe, life-threatening infections. One form also has agranulocytosis, and another has just a deficiency of T cells. About one-half of cases are X-linked and one-half are autosomal recessive. X-linked SCIDS has been diagnosed by linkage studies to a region of the X chromosome that codes for the gamma chain of interleukin-2R. Autosomal recessive SCIDS may also be associated with deficiency of the enzyme adenosine deaminase (see earlier Adenosine deaminase deficiency) or Janus-associated kinase (JAK3). SCIDS has been associated with cartilage-hair hypoplasia syndrome, a type of metaphyseal chondrodysplasia (see earlier), and acrodermatitis enteropathica secondary to dietary zinc deficiency. Treatment with zinc is curative in this group. Otherwise, the treatment of SCIDS most commonly involves bone marrow transplantation. *Ex vivo* gene therapy has been used successfully to restore the immune system in patients with X-linked SCIDS (2).

The **Bare lymphocyte syndrome** is an autosomal recessive disorder in which lymphocytes do not express the major histocompatibility antigens. It involves a defect in a gene regulating surface expression of these antigens, rather than a defect in the structural gene for them. T cells (but not B cells) recognize antigens only when they are presented by another cell in association with a class II major histocompatibility antigen.

These antigens are also required for a variety of cytotoxic and immunoregulatory functions.





Severe combined immunodeficiency syndrome. A 17-month-old boy with severe combined immunodeficiency syndrome and disseminated varicella (chickenpox). The rash had become confluent on his face, and at the time this photograph was taken, a second crop of vesicles had developed, some superimposed on earlier, healing lesions. He required transfer to the intensive care unit.

Swiss-type agammaglobulinemia is more of an historical term describing autosomal recessive SCIDS that is associated with thymic aplasia and the absence of both T and B cells.

HEENT/Airway: Persistent candidiasis of the mouth and face.

Chest: Recurrent pneumonia.

GI/GU: Persistent esophageal candidiasis. Diarrhea.

Other: Failure to thrive. Persistent candidal diaper rash. May have graft-versus-host disease if transfused. Children are anergic to skin tests. Variable deficiency in immunoglobulins.

Miscellaneous: When vaccination for smallpox was universal, disseminated vaccinia was a common cause of death for these infants. Live polio virus may cause paralytic polio. Other live vaccines, such as measles and bacille Calmette-Guerin (BCG), may cause serious disease.

Anesthetic Considerations: Transfused blood products must be irradiated to prevent graft-versus-host disease. Meticulous perioperative sterile technique is required. Electrolyte and fluid status should be evaluated preoperatively in the presence of diarrhea. Severe esophageal candidiasis may be a relative contraindication to the use of an esophageal stethoscope or nasogastric tube. Recurrent pulmonary infections may complicate intraoperative and/or postoperative ventilation.

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Severe X-linked neutropenia

Included in Wiskott-Aldrich syndrome

Shah-Waardenburg syndrome

Included in Waardenburg syndrome

Short-chain acyl-CoA dehydrogenase deficiency

Synonym: SCAD deficiency

MIM #: 201470

This autosomal recessive disease is due to a defect in the gene for short-chain acyl-CoA dehydrogenase (SCAD), which is a mitochondrial enzyme required for the metabolism of short-chain fatty acids. The disorder is marked by hypotonia, metabolic acidosis, and developmental delay. SCAD is much less common than is MCAD (medium-chain acyl-CoA dehydrogenase deficiency; see earlier). There are two distinct phenotypes of SCAD. One type presents in infants with acute acidosis and muscle weakness. The other type is a chronic myopathic disease of middle-aged adults. The infantile type is due to a generalized deficiency of SCAD, whereas the adult type is due to a deficiency of short-chain acyl-CoA (butyryl-CoA) that is limited to skeletal muscle mitochondria and a secondary deficiency

of muscle carnitine. The phenotype of SCAD is highly variable, ranging from asymptomatic to severe, based on the specific allelic variation.

Fatty acids are oxidized in mitochondria. After mobilization from adipose tissue, they are taken up by the liver and other tissues and converted to acyl-CoA esters in the cytoplasm. They enter mitochondria as carnitine esters and become reesterified as acyl-CoA esters. Beta-oxidation results in the liberation of electrons. As beta-oxidation proceeds, the acyl chain is gradually shortened, and this first step in the oxidation process is catalyzed by acyl-CoA dehydrogenases with differing, but overlapping, chain-length specificities. These are very long chain, long-chain, medium-chain, and short-chain acyl-CoA dehydrogenases.

Treatment is with a fat-restricted diet and supplemental carnitine, but is only partially effective. Episodes of nonketotic hypoglycemia, common in medium- and long-chain acyl-CoA dehydrogenase deficiencies, are less common here because most of the fatty acid chain can be metabolized in patients with SCAD deficiency by the other acyl-CoA dehydrogenases.

Cardiovascular: Rare cardiomyopathy.

Neuromuscular: Developmental delay, hypotonia, and progressive muscle weakness (neonatal type). Lipid accumulation in type I fibers. Lipid storage myopathy of type I fibers (adult type).

GI/GU: Hepatosplenomegaly with fatty changes, cholestasis, and focal hepatic necrosis.

Orthopedic: Can have scoliosis.

Other: Neonatal acidosis, poor feeding, failure to thrive, hyperammonemia. Occasional hypoglycemia. Secondary carnitine deficiency. May have cyclic vomiting.

Anesthetic Considerations: Although not as critical an issue as with the other disorders of beta-oxidation where hypoglycemia is more common (e.g., LCAD, MCAD, and VLCAD deficiencies), prolonged perioperative fasting should be avoided. Serum glucose levels should be monitored, and patients may need perioperative glucose supplementation. Lactated Ringer's solution is not contraindicated in this disorder. The use of propofol is at least of theoretical concern in patients with disorders of fatty acid metabolism (3). Patients with a significant myopathy probably should not receive succinylcholine secondary to the risk of hyperkalemia. Bupivacaine should be used with care, as inhibition of mitochondrial fatty acid transport in an already carnitine-deficient patient may lead to exaggerated cardiotoxicity. Another consideration with the use of local anesthetics in carnitine-deficient patients is that treatment of local anesthetic toxicity with intravenous lipid might further impair mitochondrial function by overwhelming the beta-oxidation pathway with a high lipid load. In light of this, the risks and benefits of regional anesthesia should be carefully weighed.

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Short rib-polydactyly syndrome

[Includes Type I (Saldino-Noonan type), type II (Majewski type)]

MIM #: 263520, 613091

This lethal autosomal recessive disorder is characterized by short ribs, thoracic dysplasia, and polydactyly. There are five types of short rib-polydactyly syndrome. All are lethal in early infancy. **Type I (Saldino-Noonan type)** and **type II (Majewski type)** are described here. Type I is due to mutations in the gene *DYNC2H1,* which is required for ciliary function—the DYN is for dynein. Type II is due to mutations in the gene *NEK1*. Type III (Verma-Naumoff syndrome, *MIM #:* 263510), type IV (Beemer-Langer syndrome, *MIM #:* 269860), and type V (*MIM #:* 614091) are not discussed here. It is suggested that there is a spectrum between type II disease and Mohr syndrome (see earlier). In addition, it has been suggested that Jeune syndrome (see earlier) and type III disease are variants of a single ciliopathy.

HEENT/Airway: *Type I:* Deficient ossification of calvarium. Occasional neonatal teeth.

Type II: Low-set, small, malformed ears. Short, flat nose. Midline cleft lip, cleft palate. Hypoplasia of the epiglottis and/or larynx. Occasional microglossia, lobulated tongue.

Chest: *Type I:* Short, horizontal ribs and narrow thorax.

Type II: Short, horizontal ribs. Very narrow thorax, pulmonary hypoplasia. High clavicles.

Cardiovascular: *Type I:* Cardiac defects include transposition of the great vessels, double-outlet left ventricle, double-outlet right ventricle, endocardial cushion defect, and hypoplastic right heart.

Type II: Occasional persistent left superior vena cava.

Neuromuscular: *Type II:* Occasional brain anomalies—pachygyria, hypoplasia of the cerebellar vermis, and absence of olfactory bulbs.

Orthopedic: *Type I:* Short stature, very short limbs. Postaxial polydactyly of hands or feet. Occasional preaxial polydactyly. Syndactyly, underossified phalanges. Metaphyseal irregularities of long bones, with spurs extended

longitudinally from medial and lateral segments. Small iliac bones with horizontal acetabular roof.

Type II: Short stature with disproportionately short limbs. Both preaxial and postaxial polydactyly of hands or feet. Syndactyly, brachydactyly, underossified phalanges. Short, rounded metacarpals and metatarsals. Premature ossification of proximal epiphyses of humeri and femora. Very short tibiae. Inadequate vertebral ossification.

GI/GU: *Type I:* Imperforate anus. Defects of cloacal development. Occasional sex reversal (female phenotype with a 46XY karyotype). Polycystic kidneys.

Type II: GI tract atresia. May have absent gallbladder. Ambiguous genitalia. Multiple glomerular cysts and focal dilatation of distal tubules of kidney.

Other: Fetal hydrops.

Miscellaneous: *NEK1* is an acronym, sort of, for never in mitosis gene A-related kinase. Apparently, the naming rights for type V are still available.

Anesthetic Considerations: Patients may have severe respiratory disease secondary to thoracic dysplasia or pulmonary hypoplasia. Airway management may be challenging, particularly in type II. Clavicular anomalies may make placement of a subclavian venous catheter or an infraclavicular block more difficult. Patients with renal insufficiency need careful titration of perioperative fluids. Renal insufficiency also affects the choice of perioperative drugs and drug dosages. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Shprintzen syndrome

See Velocardiofacial syndrome

Shprintzen-Goldberg syndrome

MIM #: 182212

This autosomal dominant syndrome combines most of the features of Marfan syndrome with craniosynostosis. It is

due to mutations in the gene *SKI*, a TGF-beta repressor. SK stands for Sloan-Kettering. The full name is V-SKI avian sarcoma viral oncogene homolog. Like Marfan syndrome, this is a generalized connective tissue dysplasia. Unlike Marfan syndrome, there is intellectual disability and skeletal muscle hypotonia.

HEENT/Airway: Craniosynostosis. Microcephaly, dolichocephaly. Prominent forehead. Exophthalmos. Telecanthus, hypertelorism. Downslanting palpebral fissures. Myopia. Low-set, posteriorly rotated ears. Maxillary and mandibular hypoplasia. Upturned nose. High-arched palate. Soft tissue hypertrophy of the palate (causing "pseudocleft" palate). Unlike patients with Marfan syndrome, these patients do not have ectopia lentis.

Chest: Obstructive apnea. Pectus carinatum and excavatum, thin twisted ribs. Thirteen pairs of ribs.

Cardiovascular: Aortic root dilatation, aortic dissection. Mitral valve prolapse. Rare tortuosity of carotid or vertebrobasilar arteries.

Neuromuscular: Hypotonia. Intellectual disabilities, developmental delay. Arnold-Chiari I malformation.

Orthopedic: Tall stature. Arachnodactyly and camptodactyly. Abnormalities of C1-C2 (fusion or subluxation). Scoliosis. Joint laxity. Bowing of the long bones, flared metaphyses. Pes planus. Hammer toe.

GI/GU: Multiple abdominal and inguinal hernias.

Other: Fragile skin. Lack of subcutaneous fat.

Anesthetic Considerations: Mandibular hypoplasia may make direct laryngoscopy and tracheal intubation difficult. Patients must be carefully positioned and padded because of skin fragility, lack of subcutaneous fat, and joint laxity. Hemodynamic stability is crucial in patients with aortic dilatation or dissection. Patients are usually tall and would presumably require additional local anesthetic for neuraxial blocks. Lack of fat might predispose to perioperative hypothermia. There has

been a high incidence of postoperative complications following scoliosis surgery.

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Shwachman syndrome

Synonym: Shwachman-Diamond syndrome, Shwachman-Bodian-Diamond syndrome

MIM #: 260400

Shwachman syndrome is a type of metaphyseal chondrodysplasia that is inherited in an autosomal recessive fashion. There are many types of metaphyseal chondrodysplasia—see also Jansen type, McKusick type (cartilage-hair hypoplasia syndrome), Pyle type, Schmid type, and Spahr type [not included in this text (*MIM #:* 250400)]. Shwachman syndrome is marked primarily by exocrine pancreatic insufficiency, intermittent neutropenia (most commonly) or pancytopenia, metaphyseal chondrodysplasia, and other hematologic and immunologic abnormalities. Genetically confirmed cases without pancreatic dysfunction have been described. Both deficiencies in myeloid precursors and diminished neutrophil chemotaxis have been described. The hematologic and immunologic abnormalities that can be seen with this syndrome are similar to those that can be seen in the McKusick type of metaphyseal chondrodysplasia (cartilage-hair hypoplasia syndrome; see earlier). The disease is due to a mutation in the *SBDS* (Shwachman-Bodian-Diamond syndrome) gene that may play a role in RNA metabolism. It has been suggested that primary atrophy of the pancreas presenting in middle age may represent one end of the spectrum of this disease.

HEENT/Airway: Otitis media. Subglottic stenosis has recently been reported in two children.

Chest: Short ribs with widely flared costochondral junctions. Can narrow thoracic cavity with reduced chest wall compliance. Recurrent pneumonia.

Cardiovascular: Cardiomegaly and myocardial necrosis and fibrosis are uncommon.

Neuromuscular: Mild intellectual disability, hypotonia, motor delay.

Orthopedic: Moderate short stature. Short extremities. Metaphyseal chondrodysplasia—irregular metaphyses, focal hypomineralization of epiphyses. Cubitus valgus, syndactyly, clinodactyly. Kyphoscoliosis. Osteomyelitis.

GI/GU: Malabsorption and diarrhea secondary to exocrine pancreas dysfunction. Inexplicably, steatorrhea is not a prominent feature. Pancreatic function may improve somewhat with aging. Hepatomegaly. Type I renal tubular acidosis. Nephrocalcinosis.

Other: The exocrine pancreas is replaced by fat. The islets of Langerhans cells remain functional. Intermittent pancytopenia—normocytic/normochromic anemia, thrombocytopenia, leukopenia, neutropenia. Immunologic abnormalities, with frequent bacterial infections. Hematologic malignancy can develop. Can have behavioral/social/psychological problems.

Miscellaneous: Scott Hamilton, the well-known figure skater and 1984 Olympic Gold Medal winner, has Shwachman syndrome.

This Diamond is Dr. Louis Diamond, also of Diamond-Blackfan syndrome. Dr. Shwachman cared for many children with cystic fibrosis. He noted a subgroup of children with exocrine pancreatic insufficiency who had neutropenia, and mentioned this to his colleague Dr. Diamond, a hematologist.

Anesthetic Considerations: Baseline hematocrit and platelet count should be obtained. Patients may have

immunologic abnormalities and are at increased risk for development of a perioperative infection. Good aseptic technique is imperative. Patients must be carefully positioned and padded perioperatively because of their orthopedic abnormalities. Severe thoracic cage involvement causing asphyxiating thoracic dysplasia as in Jeune syndrome (see earlier) has been described. Poor nutrition, fatty acid deficiency, and fat-soluble vitamin deficiency should not be a problem with appropriate pancreatic replacement therapy. Subglottic stenosis has been reported.

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Shwachman-Bodian-Diamond syndrome

See Shwachman syndrome

Shwachman-Diamond syndrome

See Shwachman syndrome

Sialidosis

Synonym: Mucolipidosis I

MIM #: 256550

This autosomal recessive disease is due to a deficiency in neuraminidase (sialidase) that cleaves the sialyl linkages of several oligosaccharides and glycopeptides with the resultant accumulation or excretion of sialic acid bound to a variety of oligosaccharides and/or glycoproteins. Sialidosis type I is the milder form with clinical onset in the second decade and type II the more severe, with an earlier and variable onset (congenital, infantile, or juvenile forms). Type I is marked by cherry-red macular spots and progressive myoclonus. Type II more resembles the phenotype of the mucopolysaccharidoses.

HEENT/Airway: Type I: Cherry-red macular spots. Decreased visual acuity with progressive visual loss. Impaired color vision. Night blindness. Nystagmus.

Type II: Hurler-like facies. Corneal opacities. May have cherry-red macular spots. Sensorineural hearing loss. Large tongue. Upper airway obstruction. Short immobile neck. Laryngomalacia. Obstructive sleep apnea.

Chest: Thoracic kyphosis. Pectus carinatum. Restrictive lung disease.

Cardiovascular: Type II: Cardiomegaly, cardiomyopathy.

Neuromuscular: Type I: Progressive myoclonus worsened by smoking or related to the menstrual cycle. Seizures. Gait disturbances. Muscle weakness. Slurred speech.

Type II: Intellectual disabilities. Ataxia. Myoclonus.

Orthopedic: Scoliosis. Dysostosis of multiple bone. Short stature in type II.

GI/GU: Type II: Hepatosplenomegaly. May have inguinal hernias.

Other: Type II: Fetal hydrops.

Anesthetic Considerations: Patients with type I disease are likely taking anticonvulsant medications. Chronic use of anticonvulsant medication alters the metabolism of some anesthetic drugs. Anesthetic considerations for patients with type II disease have not been described but would presumably mirror those of the phenotypically related mucopolysaccharidoses. Because of the abnormal facies, a regular pediatric mask may not fit adequately, and it has been suggested that in these cases, the mask be applied upside down, with the narrower nasal bridge over the mouth. If there is redundant airway soft tissue, a nasal airway may be useful. Thickening of the soft tissues, an enlarged tongue, and a short, immobile neck may make laryngoscopy extremely difficult. Laryngoscopy may become more difficult with age. Regional anesthesia has been used successfully (2). Positioning may be difficult if contractures are present. Postoperative respiratory complications are common, particularly in the presence of obstructive sleep apnea, and patients should be observed closely in the postanesthesia care unit for evidence of airway compromise. Patients with cardiomyopathy require an appropriately tailored anesthetic.

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Sickle cell disease

MIM #: 603903

This archetypal molecular disease occurs when valine is substituted for glutamate at the sixth N-terminal position in the beta-chain of hemoglobin, due to a substitution of thymine for adenine in the gene that encodes this protein. Sickle cell disease is inherited in an autosomal recessive fashion. It is most prevalent in people of African descent, although it is also seen

in people who are not clearly of African descent. The heterozygous state has been shown to confer some protection from malaria infection, which may account for the prevalence of this genetic defect in populations of African origin. Sickle cell disease in Arabic populations tends to be milder.

To maximize the oxygen-carrying capacity of the red blood cell and efficiently package hemoglobin into the red blood cell, hemoglobin must be extremely soluble. Desaturation of the sickle form of hemoglobin results in polymerization of hemoglobin, forming large aggregates called tactoids, which deform the red blood cells into the typical sickle shape. The extent of polymerization is related to the intracellular concentration of hemoglobin S to approximately the 15th power (!). Homozygous patients make only hemoglobin S (HgbS), and their red blood cells begin to sickle at oxygen saturations below 85% (p_aO_2 of 40 to 50 mm Hg), with near complete sickling at a saturation of 38%. The presence of fetal hemoglobin (HgbF) leads to a relative decrease in HgbS, a protective effect that may be seen until approximately 6 months of age. Sickling is exacerbated by cold, stasis, exertion, infection, dehydration, and hypoxemia. Heterozygous patients make both hemoglobin A (HgbA) and HgbS, and their red blood cells do not begin to sickle until the oxygen saturation is below 40% (p_aO_2 of 25 to 30 mm Hg), well below saturations in venous blood, so sickling with sickle cell trait (the heterozygous state) is rarely if ever problematic without concomitant stasis.

At oxygen saturations less than 80%, sickled hemoglobin has a decreased affinity for oxygen (a right-shifted oxygen-hemoglobin dissociation curve with a higher P_{50}). In addition, the Bohr effect is more pronounced in sickle hemoglobin, so that for a given drop in pH, there is a greater decrease in oxygen affinity. Both of these effects facilitate unloading of oxygen to tissues, presumably allowing better organ function at low hematocrits. On the other hand, the higher P_{50} favors the formation of deoxyhemoglobin, which increases the polymerization of hemoglobin, particularly as the pH drops.

The pathophysiologic consequences of sickle cell disease are secondary to two main factors: small vessel obstruction in a wide variety of organs by sickle cells (vasoocclusive events) and hemolytic anemia (the half-life of SS cells is approximately 12 days, compared with 120 days for normal red blood cells). Occlusive episodes can be extremely painful, and patients often have multiple hospital admissions for pain control. One etiologic factor in vasoconstriction is scavenging of nitric oxide by free hemoglobin. Vasoocclusive pain crises and acute chest syndrome are related to high steady state white cell concentrations and higher hemoglobin levels, while other complications, such as cholelithiasis, leg ulcers, priapism, and pulmonary arterial hypertension, are related to low hemoglobin levels and increased intravascular hemolysis.

In addition to vasoocclusion and anemia, there is some evidence that sickle cell disease reflects a state of chronic inflammation and that some of the sequelae of sickle cell disease are inflammatory secondary to repeated ischemia-reperfusion from vasoocclusion. There are higher-than-normal levels of activated fibrocytes that increase during vasoocclusive crises. It is suggested that activated fibrocytes play a role in sickle cell lung disease. In addition, activation of invariant NKT (iNKT) cells, a type of T cell that is implicated in sickle cell lung disease, can

be decreased with adenosine 2A agonists, which can modulate hypoxia-reoxygenation-induced exacerbation of pulmonary disease.

The clinical severity of this disease can also be affected by the presence of other abnormalities in the hemoglobin gene. SC disease occurs when the patient has the gene for both sickle cell hemoglobin (valine at the sixth position) and hemoglobin C (lysine at the sixth position). These patients have a chronic mild hemolytic anemia and a peripheral blood smear similar to that seen in hemoglobin C disease (multiple target cells). Because the degree of hemolysis is less, the hematocrit is usually higher than in patients with SS disease. There is significant clinical variability, but potential complications of SC disease include all of those seen with SS disease. Elevated levels of fetal hemoglobin, hemoglobin F, also appear to be somewhat protective. Sickle ß-thalassemia occurs when an individual inherits both the genes for sickle cell disease and ß-thalassemia (see later). The severity of symptoms depends on the specific type of thalassemia.

HEENT/Airway: Frontal bossing and prominent maxilla from increased marrow space. Eye changes are similar to those of diabetes, with neovascularization, microvascular retinopathy, vitreous hemorrhage, and retinal detachment. Eye changes are particularly common in SC disease. Functional asplenism is associated with hypertrophy of other lymphoid tissue, including the tonsils and adenoids. This can lead to chronic mouth breathing that can exacerbate the maxillary changes. Obstructive sleep apnea.

Chest: Pulmonary infarctions (acute chest syndrome) accompanied by chest pain, fever, tachypnea, elevated white cell count, wheezing, or cough. Pain crises in ribs, vertebrae, and sternum can lead to respiratory splinting. Pulmonary arterial hypertension. Risk of pulmonary infections and fat emboli from necrosed bone marrow. Bronchopulmonary anastomoses causing intrapulmonary right-to-left shunting. Inhaled nitric oxide has been used successfully in a limited series of patients with acute chest syndrome and resulted in decreased pulmonary hypertension and improved oxygenation (34).

Patients with sickle cell disease have an increased incidence of airway hyperreactivity (32).

Cardiovascular: Cardiomegaly that is usually secondary to the anemia, but may be due to congestive failure. Myocardial fibrosis from prior sickling. There can be pulmonary arterial hypertension secondary to pulmonary infarctions, increasing the risk of death. Endothelial dysfunction is intimately involved with complications such as deep vein thrombus formation.

Neuromuscular: May have findings ranging from transient ischemic attacks to true stroke. Young children are more prone to thrombotic strokes, whereas adults more commonly have hemorrhagic infarcts. A chronic transfusion program has been shown to lower central nervous system complications in children who have transcranial Doppler results indicating a higher risk for stroke. Nitric oxide has been used successfully in an instance of perioperative stroke (11).

Orthopedic: Skeletal deformities from marrow hyperplasia and pain crises, particularly dactylitis (hand-foot syndrome), especially in children under 5 years of age. Multiple bone infarcts with arthropathies as sequelae. Thoracic kyphosis, lumbar lordosis. Aseptic/avascular necrosis and leg ulcers. Aseptic necrosis of the hip is particularly common in SC disease. Growth failure, possibly related to zinc deficiency.

GI/GU: With time, there is complete infarction (auto-infarction) of the spleen with immune incompetence. However, before complete infarction, the spleen can suddenly enlarge and trap red blood cells, white blood cells, and platelets—a splenic sequestration—with an acute drop in hematocrit that can be life threatening. Gallstones are common, and cholecystectomy is the most frequent surgical procedure in these patients. Liver function is spared, but intrahepatic sickling can cause painful hepatic enlargement. Transaminases are often slightly elevated.

Painful priapism can develop. Renal impairment begins in childhood and is common by adulthood. Renal

involvement includes inability to concentrate urine (isosthenuria), polyuria, proteinuria, impaired potassium excretion, impaired acidification of urine, pyelonephritis, and glomerulonephritis. There can also be papillary necrosis and painless hematuria. Renal papillary necrosis is particularly common in SC disease.

Other: Hemolytic anemia. The peripheral blood smear always has sickle forms, and their presence is not diagnostic of a crisis. Patients may be taking hydroxyurea, which has been shown to elevate fetal hemoglobin levels and decrease morbidity.

A variety of infections can be associated with an acute hemolytic crisis. Lack of splenic function renders patients particularly susceptible to infection with encapsulated organisms, such as pneumococci, meningococci, and *Hemophilus*. All patients should have received pneumococcal, meningococcal, and *Hemophilus* vaccines when age appropriate. Younger children and infants should be receiving antibiotic splenic prophylaxis, with some older children, particularly those who have undergone surgical splenectomy, receiving prophylaxis into adulthood or lifelong. Patients also are at increased risk for *Staphylococcus aureus* and Salmonella osteomyelitis and splenic abscesses. Increased risk for hypercoagulable complications. Inflammation increases the expression of cell adhesion molecules on the endothelium, with increased adhesion of sickled cells and additional vascular occlusion.

Over 50% of pregnant women with SS disease have a crisis during the pregnancy, and many of those have a major complication. Preeclampsia with volume depletion and vasoconstriction favors sickling. Many signs of preeclampsia, such as abdominal pain, hypertension, renal dysfunction, and congestive heart failure, may be difficult to differentiate from complications of sickle cell disease. There is an increased incidence of preeclampsia (14% to 20% vs. 4%), placental abruption (4.5% vs. 0.3%), placenta previa (1.5% vs. 0.4%), and intrauterine growth retardation in pregnant patients with sickle cell disease. Up to a quarter of parturients have a sickling complication within 2 days of delivery (7). In general, however, pregnant patients with sickle cell disease have a good outcome. Pregnant patients with sickle cell trait should be similar to the general population, although a single intrapartum maternal death was reported, presumably due to aortocaval compression, with the sudden release of a large amount of hypoxemic, acidotic, sickled blood immediately after delivery (41).

Miscellaneous: The disease was first described by James Herrick in 1910. The second description, following shortly, was from the University of Virginia. The ascertainment of an abnormal hemoglobin protein by Linus Pauling and colleagues in 1949 made this the first “molecular disease.”

Anesthetic Considerations: Medical complications of sickle cell disease can be easily misdiagnosed as surgical problems (see Table 5).

There is currently significant inter-practitioner variability in the clinical management of these patients (3). Perioperative complications, such as pain crises and acute chest syndrome, are not uncommon. Perioperative care should be coordinated with a hematologist whenever possible. Routine preoperative investigations should include a hematocrit, plasma urea and creatinine, urine dipstick, and a chest radiograph. Factors known to enhance the likelihood of sickling must be avoided perioperatively: namely, cold, stasis, exertion, infection, dehydration (as from a protracted preoperative

fast), hypoxemia, and acidosis. Hypotension is more appropriately treated with fluids rather than with vasoconstrictors. Hypovolemia is poorly tolerated due to the renal concentrating defect. Increased plasma tonicity can encourage sickling, so furosemide or mannitol, as frequently used in neurosurgical operations, may increase risk. Avoidance of stasis should be a goal of positioning and padding. Also, efforts should be made to avoid compression of the inferior vena cava when the patient is prone. Pneumatic compression devices may help decrease lower extremity stasis. Due to a history of multiple red cell transfusions and the development of alloantibodies, it may be more difficult than usual to find optimally crossmatched blood. There is one report of delayed onset of atracurium muscle relaxation possibly related to larger volumes of distribution (4). The incidence

of postoperative complications is not necessarily diminished by regional (vs. general) anesthesia (37).

TABLE 5. Potential misdiagnoses in sickle cell disease

Pathology	Mistaken surgical diagnosis
Bone infarcts (often febrile)	Infective arthritis, osteomyelitis
Acute hemolysis	Surgical jaundice (biliary stones often present)
Sequestration with falling hemoglobin	Acute hemorrhage
Splenic infarct, pulmonary infarct, pneumonia	Acute abdomen

The safety of tourniquets for orthopedic procedures is unclear. There does not seem to be any increased risk in patients with sickle cell trait, and the risk may be small in patients with sickle cell disease (19,21,33), although it has been suggested that a higher level of (protective) fetal hemoglobin in those Hgb SS study patients accounts for the uneventful use of a tourniquet. However, there have been multiple reports of safe tourniquet use, particularly when accompanied by exsanguination of the limb prior to inflation of the tourniquet. Similarly, transient, uncomplicated clamping of major extremity vessels for femoropopliteal bypass has been reported (29), although that patient also had elevated levels of fetal hemoglobin.

The development of an intraoperative crisis can be masked by general anesthesia. If muscle relaxants have been used, a change in the respiratory status or the development of seizures may go unrecognized. Postoperative analgesics may mask the pain from pain crises. Postoperatively, the acute chest syndrome may mimic aspiration pneumonitis, and back pain or neurologic problems may be attributed to regional anesthesia. Transfusion-related acute lung injury (TRALI) can mimic acute chest syndrome, but resolves more rapidly (23). Acute chest syndrome occurs in up to 10% to 16% of patients after cholecystectomy or splenectomy and typically involves the ipsilateral lower lobe. The treatment of acute chest syndrome includes increased FiO_2, CPAP, mechanical ventilation if necessary, bronchodilators, antibiotics, incentive spirometry, adequate hydration, red blood cell transfusion if appropriate, and sometimes nitric oxide.

During sickle crises, hemoglobin saturation measured by pulse oximetry tends to overestimate the true oxygen saturation. This is explained by the increase in carboxyhemoglobin found in hemolytic anemias.

Transfusion practices have been summarized in a helpful review (8). Transfusion triggers remain unclear. A recent Cochrane Review was unable to arrive at a firm conclusion (2). The hemoglobin or hemoglobin S level required for elective or even urgent surgery was arbitrarily and dogmatically defined for many years (hemoglobin > 10 g/dL, hemoglobin S < 30%), but currently there is no true consensus. Minor surgery can usually be safely undertaken without preoperative transfusions. Aggressive perioperative transfusion regimens have been associated with a high incidence of transfusion-related complications. Patients may have red blood cell antibodies from multiple transfusions, making cross-matching difficult. Excessive simple transfusion may actually increase the risk of

sickling, because viscosity (and sludging) is increased, with still enough sickle hemoglobin around to sickle. Partial exchange transfusion can lower the concentration of sickle hemoglobin without increasing intravascular volume or inordinately increasing hematocrit. Plasma and platelets can be separated and reinfused intraoperatively (9). There are currently three principal approaches:

1. Recommendations from the Perioperative Transfusion in Sickle Cell Disease Study Group (38) have been widely accepted. These investigators examined a total of 604 surgeries performed on 551 sickle cell patients in a randomized, prospective, multicenter trial. Patients were randomly assigned either to an aggressive transfusion group, who were transfused preoperatively until they reached a hemoglobin S level of less than 30%, or to a conservative transfusion group, who were transfused preoperatively until their hemoglobin level was elevated to 10 g/dL, with no specific hemoglobin S level required. The frequency of serious complications was similar in both groups. However, there were twice as many transfusion-related complications in the aggressively transfused group than in the conservatively transfused group (14% vs. 7%). The Study Group concluded that there is no advantage to (and that there is risk associated with) an aggressive preoperative transfusion regimen versus a conservative transfusion regimen. In light of these findings, most clinicians no longer recommend an aggressive perioperative transfusion regimen. This study did not include a non-transfused control group.
2. A simple transfusion regimen of 15 mL/kg of packed red blood cells approximately 1 month prior

   to surgery has been commonly undertaken for years. This increases hemoglobin from approximately 6 to 8 g/dL to approximately 10 g/dL and decreases hemoglobin S from approximately 100% to approximately 65%. The shorter-lived SS cells die off, and the higher hematocrit inhibits new SS cell production. A second transfusion 2 weeks later maintains the hematocrit and decreases hemoglobin S to less than 40%. A final transfusion is given on the day before surgery, depending on the final laboratory results. Patients with the SC variant have higher baseline hematocrits and therefore may require a partial exchange transfusion rather than a simple transfusion. In one recent study of patients having low- to medium-risk surgery, outcomes were better with preoperative transfusion (to a hemoglobin of 10 g/dL if baseline < 9 g/dL, or partial exchange to a hemoglobin S of <60% in patients with higher baseline hemoglobin) (1).
3. Because the merits of preoperative transfusion have not been clearly demonstrated, and the real risks of transfusion-related complications have been delineated, many practitioners advocate no routine preoperative transfusion. It seems likely that routine transfusions are unnecessary for short procedures with limited heat or fluid loss (14).

Cardiopulmonary bypass is not problematic in patients with sickle cell trait, and there are routinely excellent results in patients with sickle cell disease. Good results have also been reported with SC disease. There are no consensus guidelines for intraoperative temperature, hematocrit, or hemoglobin S level (17,18,27,30,39). In young infants needing cardiopulmonary bypass, hemodilution associated with priming the pump has been adequate to reduce hemoglobin S levels to acceptable levels (6). Use of a warm first dose of cardioplegia to flush out any red cells from the coronary circulation has been suggested (6). The use of cell saver devices is not recommended by manufacturers but they have been used successfully without sequelae (40).

Patients with sickle cell disease may be tolerant to the effects of opioid medications because of long-term use secondary to chronic pain. Larger doses of opioids may be necessary to control postoperative pain, and adjunctive pain control measures such as regional analgesia and non-opioid pain medications should be considered. Achievement of adequate postoperative analgesia is critical to the success of incentive spirometry and early postoperative mobilization.

Epidural anesthesia has been reported to resolve priapism (10), but there are also case reports of priapism developing following the placement of an epidural. Epidurals have been shown to be useful for difficult-to-control

abdominal pain and vasoocclusive crises in the legs during pregnancy.

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Siemerling-Creutzfeldt disease

See Adrenoleukodystrophy

Simpson dysmorphia syndrome

See Simpson-Golabi-Behmel syndrome

Simpson-Golabi-Behmel syndrome

Synonym: Simpson dysmorphia syndrome

MIM #: 312870

This X-linked recessive overgrowth disorder was reported separately by Simpson et al., Golabi et al., and Behmel et al. The major clinical manifestations are hypertelorism; a broad, flat nose; and bony overgrowth abnormalities. Half of the affected patients have died of unknown causes by age 6 months. Female carriers sometimes have mild clinical manifestations. There is marked variability within and among families, and there is evidence of genetic heterogeneity. At least some cases have been ascribed to a defect in the *GPC3* gene, which encodes a proteoglycan, glypican 3, that plays a role in the control of growth of the embryonic mesodermal tissues. There is a suggestion that abnormalities in the adjacent gene, *GPC4*, could also cause the syndrome. Simpson-Golabi-Behmel syndrome type 2 (*MIM #:* 300209) has been associated with a mutation in the gene *CXORF5* (also known as *OFD1*).

HEENT/Airway: Macrocephaly, coarse facies. Downslanting palpebral fissures, hypertelorism, cataracts, retinal detachment, coloboma of optic disk. Cup-shaped ears, earlobe creases. Can have hearing loss. Flat nasal bridge, short upturned nose. Midline groove of lower lip, macrostomia. Macroglossia. Tethered tongue, perioral or palatal spotty pigmentation. High-arched palate, occasional submucous cleft lip and cleft palate. Midline grooved lower lip. Large jaw. Malocclusion. Short neck. May have laryngeal web.

Chest: Pectus excavatum, cervical ribs, 13 pairs of ribs. Congenital diaphragmatic hernia has been reported. Supernumerary nipples.

Cardiovascular: Conduction abnormalities, tachyarrhythmias. A variety of congenital cardiac defects (in approximately 30% of patients)—including ventricular septal defect, pulmonic stenosis, transposition of the great arteries, and patent ductus arteriosus. Rare coronary artery fistulae.

Neuromuscular: Intelligence is usually in the normal range. Clumsy.

Orthopedic: Tall stature. Broad, short hands and fingers, occasional postaxial polydactyly, syndactyly of second and third fingers and toes, nail hypoplasia, broad thumb, and great toe. Fusion of C2-C3 posteriorly. Six lumbar vertebrae and sacral and coccygeal abnormalities. Occasional scoliosis.

GI/GU: Umbilical and inguinal hernias. Occasional pyloric stenosis, malrotation of the gut, choledochal cysts, hepatomegaly, splenomegaly. Meckel diverticulum. Occasional hypospadias, cryptorchidism, large kidneys, cystic kidneys.

Other: Large for gestational age—may weigh as much as 5.8 kg at birth. Neonatal hypoglycemia. Thickened or dark skin. Risk of embryonal tumors. Increased risk of neonatal and early infantile death.

Miscellaneous: The first documented family described the look of its affected members as “bulldog”-like.

Glypican 3 seems to form a complex with insulin-like growth factor 2 (IGF2). Interestingly, Beckwith-Wiedemann syndrome, another overgrowth syndrome, seems to be due to excessive IGF2.

Anesthetic Considerations: Difficult intubation has not been reported, but is a potential concern in these patients with macroglossia, short neck, and cervical spine fusion that may limit neck mobility (5). A patient with a laryngeal web has been reported (3). Cardiac conduction abnormalities are common, and careful perioperative monitoring of cardiac rhythm is indicated. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Neonates are at risk for hypoglycemia. Caudal spine abnormalities might make caudal analgesia difficult.

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Sirenomelia

See Caudal regression syndrome

Sjögren-Larsson syndrome

MIM #: 270200

This autosomal recessive disorder is due to abnormal function of the enzyme fatty aldehyde dehydrogenase (FALDH), which catalyzes the oxidation of mediumand long-chain fatty acids. The disorder predominantly affects the skin and nervous system. Treatment with dietary long-chain fatty acid restriction and supplementation of medium-chain triglycerides has been generally disappointing.

HEENT/Airway: Pigmentary retinal degeneration, yellow-white dots on the retina. Corneal opacities. Photophobia.

Neuromuscular: Intellectual disabilities, delayed motor function, spastic quadriplegia, dysarthria, seizures. White matter demyelination.

Orthopedic: May have short stature. Thoracic kyphosis.

Other: Most are born somewhat prematurely (mean 35.6 weeks). Apparently the highly active lipid in the fetal urine is inflammatory and induces labor. Congenital ichthyosis, neonatal ecchymoses. The rash may originally be erythrodermic and gradually evolve into pruritic ichthyosis. Hyperkeratosis with normal sweating. Normal hair and nails. With time, the face is spared and skin changes are concentrated on the neck, lower abdomen, and in skin flexures. Thick palms and soles. Relative heat intolerance.

Miscellaneous: This Sjögren is different from the Sjögren of Sjögren syndrome (keratoconjunctivitis sicca). The disorder is common in northern Sweden where it is estimated that it was introduced about 600 years ago.

Anesthetic Considerations: Ichthyosis does not predominantly affect the dorsum of the hands and feet, leaving them available for vascular access. Patients with photophobia may be extremely sensitive to the bright lights in operating rooms. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs.

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Sly syndrome

Synonym: Mucopolysaccharidosis VII; Beta-glucuronidase deficiency

MIM #: 253220

This autosomal recessive mucopolysaccharidosis, due to a deficiency of the lysosomal enzyme beta-glucuronidase, may be clinically similar to Hurler syndrome, or may be milder (and without intellectual disability). The disease severity ranges from lethal hydrops fetalis to mild forms with survival into adulthood. There is accumulation of heparan sulfate, keratan sulfate, chondroitin-4-sulfate, and chondroitin-6-sulfate. A neonatal form of Sly syndrome has been reported, with hydrops fetalis, dysostoses, and other findings of a lysosomal storage disease. Enzyme replacement therapy is not currently available for this mucopolysaccharidosis.

HEENT/Airway: Coarse facies. Fine corneal opacities. Recurrent otitis media, conductive hearing loss. Short neck.

Chest: Pectus carinatum. Patients with a mucopolysaccharidosis are susceptible to pulmonary hemorrhage after bone marrow transplantation.

Cardiovascular: Mitral and aortic valve involvement with thickening and insufficiency. Aortic dissection. May have involvement of coronary arteries leading to coronary stenosis. Infiltration of the conduction system and complete heart block in a child with previously normal conduction was related to entry of a guidewire into the right ventricle (3).

Neuromuscular: Intelligence is usually normal, but may have mild intellectual disability.

Orthopedic: Odontoid hypoplasia and an unstable cervical spine have been reported in association with Sly syndrome (1). Short stature. Thoracolumbar gibbus deformity, progressive kyphoscoliosis. Multiple bone dysostoses, joint stiffness and contractures. Genu valgum.

GI/GU: Hepatosplenomegaly. Inguinal and umbilical hernias.

Other: Hirsutism.

Miscellaneous: The longest known survivor with Sly syndrome was 37 years old at the time of her death. The disorder has also been reported in Brazilian terriers and in a domestic shorthair cat from California, USA.

Anesthetic Considerations: The cervical spine should be evaluated preoperatively, or one should progress on the assumption of an unstable neck. Difficult laryngoscopy and tracheal intubation have not been reported with Sly syndrome, but have been reported in patients with other mucopolysaccharidoses. The laryngeal mask airway has been used successfully in other patients with mucopolysaccharidoses (1). Perioperative cardiac complications may occur as a result of valvular insufficiency, coronary artery stenosis, and/or infiltration of the conducting system (3). Hemodynamic stability is crucial in patients with aortic dilatation or dissection.

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Smith-Lemli-Opitz syndrome

MIM #: 270400

The etiology of this autosomal recessive syndrome has been ascribed to abnormal function of 7-dehydrocholesterol reductase, an enzyme involved in the biosynthesis of cholesterol. 7-Dehydrocholesterol is the second-to-last sterol in the Kandutsch-Russell cholesterol biosynthetic pathway. Patients have elevated 7-dehydrocholesterol levels and low cholesterol levels. The main features of the syndrome are intellectual disability, anteverted nostrils, ptosis, syndactyly of the second and third toes, and hypospadias and cryptorchidism in boys. Because of the block in cholesterol synthesis, dietary cholesterol might be an essential nutrient, but dietary cholesterol would not be expected to remedy the central nervous system manifestations because of the blood-brain barrier. Cholesterol is a component of some lipoproteins that have significant signaling functions. Some of the manifestations of this syndrome may be secondary to abnormal functioning of these proteins in the embryo. Some had suggested the existence of a type II disease, which includes the most severely affected patients, but it is likely that these patients merely represent the more severe end of a clinical spectrum. It is theorized that some manifestations of the disorder may be related to dysregulation of the sonic hedgehog pathway.

HEENT/Airway: Microcephaly; high, square forehead. Ptosis, epicanthal folds, strabismus, opsoclonus, demyelination of optic nerve, cataracts. Low-set ears. Short nose with anteverted nostrils. Small, narrow tongue,

broad alveolar ridges, cleft palate. Dysphagia. Micrognathia.

Chest: Pulmonary hypoplasia, single-lobed lungs. Recurrent aspiration, pneumonia. Pneumonia is a leading cause of death.

Cardiovascular: Congenital heart disease, particularly tetralogy of Fallot and ventricular septal defect.

Smith-Lemli-Opitz syndrome. FIG. 1. This 9-year-old with Smith-Lemli-Opitz syndrome is 46 XY, but was born with micropenis and is being raised as a female.

Neuromuscular: Moderate to severe intellectual disabilities, variable muscle tone (hypotonic in infancy becoming hypertonic), seizures, demyelination of brain and peripheral nerves, hypoplasia, and abnormal morphogenesis of various brain structures. Irritability with shrill screaming during infancy. Behavioral problems, including autism. May have holoprosencephaly.

Orthopedic: Prenatal growth retardation. Postaxial polydactyly, syndactyly of second and third toes, simian crease, flexed fingers, metatarsus adductus. Dislocated hips.

GI/GU: Feeding problems, vomiting, gastroesophageal reflux, pyloric stenosis, inguinal hernias, hepatic dysfunction, rectal atresia, Hirschsprung disease (see earlier). Hypospadias, cryptorchidism, ambiguity of external male genitalia with micropenis, bifid or hypoplastic scrotum, male pseudohermaphroditism, renal hypoplasia, ureteropelvic junction obstruction, renal duplication, hydronephrosis, renal cysts.

Other: Failure to thrive. Photosensitivity. Usually have blond hair. Many are born in breech presentation. Stillbirths and early neonatal deaths may occur. Even though cholesterol is a steroid precursor, there is generally no adrenal dysfunction although adrenal insufficiency has been reported in a very small number of children.

Smith-Lemli-Opitz syndrome. FIG. 2. A 6-year-old girl with Smith-Lemli-Opitz syndrome. She has many findings including a small mandible, crowded teeth, microcephaly, and bifid uvula. Her trachea had been intubated successfully, but it had been suggested to her parents that in the future, a fiberoptic intubation be done with a smaller-than-normal endotracheal tube.

Miscellaneous: Among Caucasian North Americans, the incidence of this syndrome places it only behind cystic fibrosis and phenylketonuria. It is probably the first multiple malformation syndrome for which a specific biochemical etiology was ascribed. David Smith was an American pediatrician and pioneering dysmorphologist. His book, *Recognizable Patterns of Human Malformation*, is a classic reference known to all pediatricians and geneticists.

Anesthetic Considerations: Behavioral problems, particularly aggressive behavior, may complicate induction and postoperative care (5). Sedative medications may be ineffectual (7). Consider preoperative evaluation of renal function in patients with a history of renal abnormalities that predispose to renal insufficiency. Direct laryngoscopy and tracheal intubation may be difficult secondary to micrognathia and dysmorphic facial features. Fiberoptic intubation has been used as the initial technique for airway management in a number of anesthetics (5). The laryngeal mask airway (LMA) has also been used successfully to establish an airway (3,4). Vomiting and gastroesophageal reflux are common, and patients are at increased risk for perioperative aspiration. Patients may have chronic lung disease secondary to recurrent aspiration and pneumonia. Patients with congenital heart disease should receive an appropriately tailored anesthetic. Sensitivity to gender issues in intersex patients is important, although these

patients may not have sufficient intellectual development to appreciate the issues.

Although there are two case reports of increased muscle rigidity after a volatile anesthetic (one with and one without succinylcholine) (9,10), this is apparently not a systematic response of patients with this syndrome and this syndrome is not associated with malignant hyperthermia (5,8).

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Smith-Magenis syndrome

Synonym: 17p-syndrome

MIM #: 182290

This autosomal dominant disorder is almost always due to a microdeletion on chromosome 17, but can rarely be due to an isolated mutation in the gene *RAI1*, which is within that region. Potocki-Lupski syndrome (*MIM #:* 610883, not discussed here) has an overlapping phenotype and is due to a duplication in this region. Classic features of Smith-Magenis syndrome include brachycephaly, midface hypoplasia, prognathism, hearing loss, hypotonia, intellectual disability, and sometimes a peripheral neuropathy. The peripheral neuropathy may be related to that of Charcot-Marie-Tooth disease (see earlier), as a form of that disorder maps to the same region.

HEENT/Airway: Midface hypoplasia, broad face, brachycephaly. Deep-set eyes. Multiple ocular abnormalities. Sensorineural or conductive hearing loss. Polyembolokoilamania (insertion of foreign bodies into the ears). Broad nasal bridge. May have cleft lip or cleft palate. Hoarse speech. Prognathism.

Cardiovascular: Congenital heart defects.

Neuromuscular: Hypotonia in infancy. Neuropathic weakness. Can have decreased sensitivity to pain. Speech delay. Moderate intellectual disability, but can be mild or borderline. Ventriculomegaly. Behavioral problems including attention deficit, head banging, and aggressive outbursts, but patients are also often eager to please. Self-destructive behavior with head banging, onychotillomania (pulling out fingernails and toenails), and the aforementioned polyembolokoilamania. Self-hugging. Compulsive licking of fingers and flipping book/magazine pages. Apparently able to recall a wide range of subject-specific trivia.

GI/GU: Structural renal anomalies.

Orthopedic: Scoliosis, brachydactyly. Pes planus. Can have excessive arm skin folds.

Other: Hypothyroidism. Sleep disturbances, possibly with absent REM sleep. Daytime somnolence due to an inverted or diurnal melatonin circadian rhythm. Immunoglobulin deficiency.

Anesthetic Considerations: Thyroid status and renal status should be assessed preoperatively. Premedication may be particularly helpful in these patients with behavioral problems. Excessive arm skin folds may make intravenous access challenging. Patients can have decreased sensitivity to pain and temperature. Succinylcholine may be contraindicated with neonatal hypotonia.

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Sneddon syndrome

MIM #: 182410

This noninflammatory arteriopathy of medium-sized arteries is marked by livedo reticularis (a persistent purplish discoloration of the skin caused by blood vessel pathology) and cerebrovascular disease. It is likely inherited in an autosomal dominant fashion.

Cardiovascular: Multiple occlusion of mediumsized arteries. May be associated with rheumatic or

other valvular disease. May have systemic arterial hypertension. May be predisposed to developing arterial and venous thromboses.

Neuromuscular: Multiple strokes and transient ischemic attacks. Recovery from strokes is often complete. May have intellectual disabilities. May have moyamoya like pattern (see earlier). Arteriopathy involves meninges, superficial cortical vessels, and the periventricular white matter. Headache and vertigo often precede other symptoms by years.

GI/GU: May have renal involvement.

Other: Livedo reticularis. Approximately half the patients have had lupus anticoagulant or antiphospholipid antibody.

Miscellaneous: "Livedo reticularis" is used in the European literature to reflect this cutaneous vascular phenomenon when it disappears with skin warming and "livedo racemosa" for the findings that persist after warming. American usage refers to "cutis marmorata" for the rash that disappears with warming and "livedo reticularis" for the permanent change. Sneddon, despite being British, used the term livedo reticularis when describing the permanent skin changes associated with "his" syndrome.

Anesthetic Considerations: Note that patients may be on anticoagulant medications and may likely be hypercoagulable without them. Patients should be evaluated preoperatively for cardiac disease and systemic hypertension. Preoperative renal function should be evaluated. Patients (including children) should be managed perioperatively as if they have cerebrovascular disease, and the use of invasive monitoring may be justified. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Measures should be taken perioperatively to prevent venous thrombosis. Intraoperative thromboelastography has proven useful (1). Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Sotos syndrome

Synonym: Cerebral gigantism

MIM #: 117550, 614753

This disorder is marked by the prenatal onset of excessive growth. Most cases have been sporadic, but it has occurred in identical twins, and other familial cases have also been reported. Sotos syndrome-1 is caused by mutations in the gene *NSD1*, which encodes a coregulator of androgen receptors. Sotos syndrome-2 is caused by mutations in the gene *NFIX*, which encodes nuclear factor I, a ubiquitously expressed protein that stimulates gene transcription. Abnormalities in this gene are also responsible for Marshall-Smith syndrome (see earlier).

HEENT/Airway: Excessive head growth in early infancy with macrocephaly, dolichocephaly, prominent forehead. Hypertelorism, strabismus, downslanting palpebral fissures. Can have conductive hearing loss. High-arched palate, macroglossia, exostoses of the alveolar ridge, premature eruption of teeth, hypodontia (first and second premolars). Prognathism.

Chest: Recurrent pulmonary infections in infancy.

Cardiovascular: A variety of congenital cardiac defects has been reported.

Neuromuscular: The incidence of mild or borderline intellectual disability is high, and children may be hyperactive or aggressive. Neonatal hypotonia. Mild hydrocephalus has been reported. May have seizures.

GU/GU: May have recurrent inguinal hernias.

Orthopedic: Bone age is advanced. Large hands and feet. Arm span greater than height. Joint hypermobility. Congenital flexion contractures of the feet. Growth is rapid for the first few years of life, but final height may be normal. Kyphoscoliosis.

Other: There may be glucose intolerance with increased somatomedin and growth hormone. Hyper- or hypothyroidism. Early menarche. May have reduced helper T cells. These patients seem to be at increased risk for the development of a variety of benign and malignant tumors. Can have transient hyperinsulinemic hypoglycemia in infancy.

Anesthetic Considerations: Behavioral expectations should be based on age and not size. The smooth induction of anesthesia may be challenging if the patient exhibits significant behavioral problems. Teeth should be assessed

no reports of difficulty with intubation. A prominent occiput can make head positioning somewhat difficult. Most children have needed an endotracheal tube sized appropriately for age, but one teenaged male has been reported who required a larger-than-normal tube. Patients must be carefully positioned perioperatively because of their joint hypermobility. Infants are at risk for hypoglycemia. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Spastic paraplegia-1

See MASA syndrome

Spherocytosis

See Hereditary spherocytosis

Spielmeyer-Vogt disease

Synonym: Neuronal ceroid lipofuscinosis; Vogt-Spielmeyer disease (Includes Batten disease)

MIM #: 204200

This autosomal recessive disorder is one of several lipofuscinoses, which are lysosomal disorders with profound central nervous system degeneration secondary to lipofusin accumulation in the brain. Spielmeyer-Vogt disease is due to a mutation in the *CLN3* gene. Other neuronal ceroid lipofuscinoses include Santavuori-Haltia (CLN1, not discussed in this text), Jansky-Bielschowsky disease (CLN2; see earlier), and Kuf diseases (CLN4, not discussed in this text). Spielmeyer-Vogt disease has also been called Batten disease, but **Batten disease** is now more commonly used to encompass all forms of neuronal ceroid lipofuscinosis. The CLN3 gene product is a lysosomal enzyme, and its absence in Spielmeyer-Vogt disease results in accelerated apoptosis of photoreceptors and neurons. Onset of symptoms is at about 4 to 10 years of age, and death is at 20 to 40 years of age. The age of onset varies among the neuronal ceroid lipofuscinoses.

HEENT/Airway: Rapid progressive visual loss with blindness by 6 to 14 years of age. Retinitis pigmentosa, macular degeneration, optic atrophy, abolished electroretinogram.

Neuromuscular: Psychomotor regression, intellectual disabilities, dementia, extrapyramidal signs, cerebellar signs, seizures, dysarthria, cerebral atrophy. Behavioral changes. Lipofuscin accumulation in neuronal perikaryon.

Other: Vacuolated lymphocytes. Autonomic dysregulation, including abnormal thermal regulation.

Anesthetic Considerations: When meeting patients, recall that they are likely to be blind. Patients may be bedridden with muscle atrophy, so the use of succinylcholine may be associated with exaggerated hyperkalemia, although it has been used without incident in one patient (6). Autonomic dysregulation is common and can lead to bradycardia during surgery (3). Perioperative hypothermia can result from abnormal thermal regulation (3,8). Seizures can be difficult to control and can occur perioperatively. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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Spinal muscular atrophy

[Includes spinal muscular atrophy type 0, spinal muscular atrophy type I (acute Werdnig-Hoffmann disease), spinal muscular atrophy type II (chronic

Werdnig-Hoffmann disease), and spinal muscular atrophy type IV. See Kugelberg-Welander disease for spinal muscular atrophy type III.]

MIM #: 253300, 253550, 271150

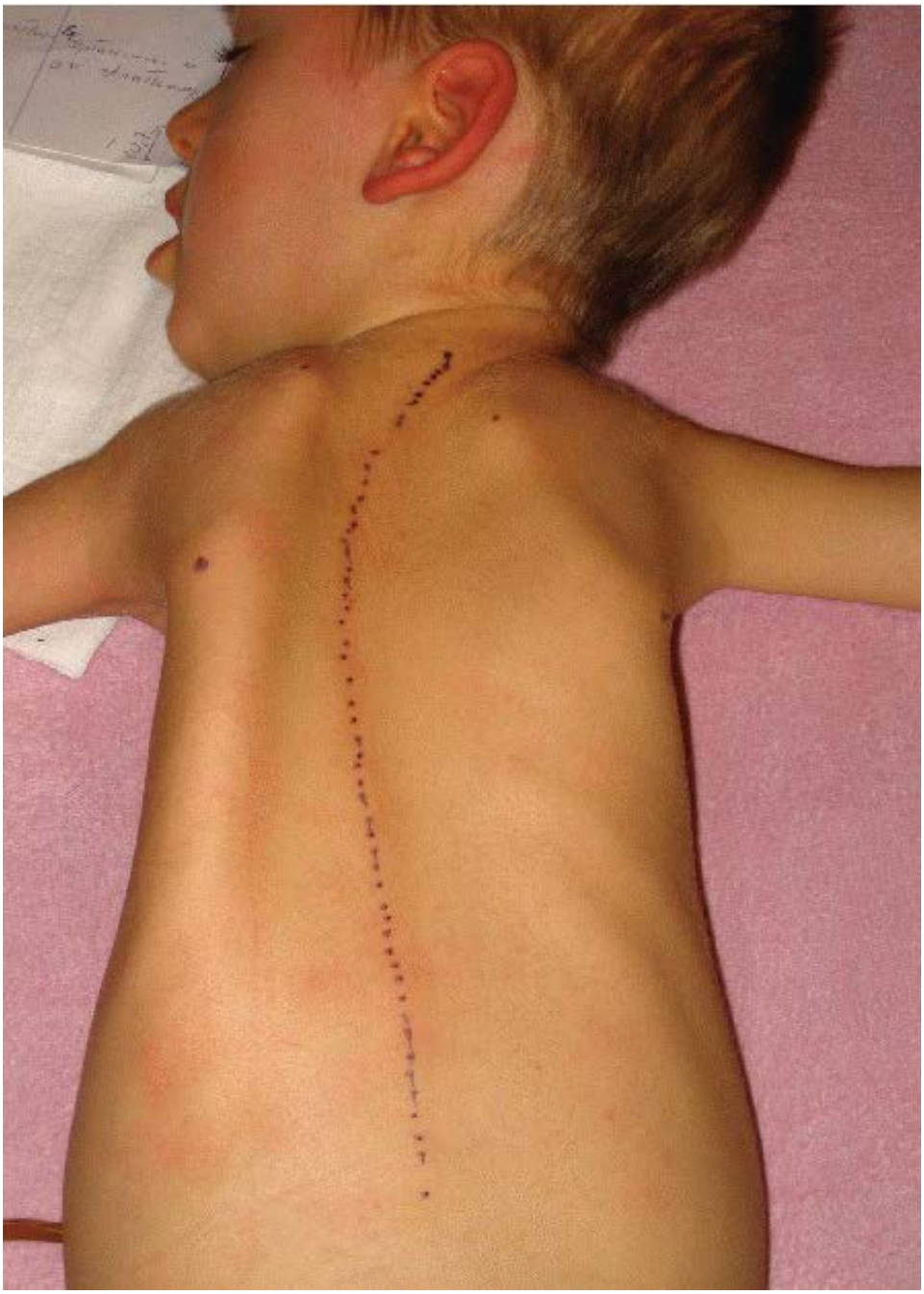
This autosomal recessive disease of anterior horn cells and cranial nerve nuclei involves a defect in the telomeric gene *SMN1* (survival of motor neuron 1). This same gene is affected in spinal muscular atrophy types I, II, III, and IV, and these disorders are allelic. The gene product is involved with RNA processing. Several clinical phenotypes have been described, and the clinical manifestations can vary within a given family. Disease severity can be modified by changes in expression and/or number of the centromeric copy of the gene, termed *SMN2*, with increased gene numbers associated with less severe disease. Approximately half of SMA I patients and 20% of SMA II patients have abnormalities in the gene *NAIP*, the gene encoding neuronal apoptosis inhibitory protein, which may play a role in disease modification. A **spinal muscular atrophy type 0** has also been described, with fetal onset and profound respiratory insufficiency at birth. There has also been described an uncommon X-linked adult-onset type V disease.

Spinal muscular atrophy type I (acute Werdnig-Hoffmann disease, acute infantile spinal muscle atrophy) presents in the first 6 months of life. One-third present in utero with decreased fetal movement. There is often associated bulbar dysfunction. Survival beyond 2 years of age is uncommon, as death usually occurs secondary to respiratory failure. Aggressive respiratory support measures can extend survival into adolescence.

Spinal muscular atrophy type II (chronic Werdnig-Hoffmann disease, intermediate spinal muscle atrophy) presents at approximately 6 months of age when, after previously normal development, motor milestones become delayed. The trunk and proximal limb muscles are predominantly involved. Children can usually sit unsupported, but only the strongest will be able to stand and will not be able to ambulate independently. There can be periods of stability in the progression of the disease, and some patients can have a stable course after an initial period of progressive weakness. At least 70% survive into adulthood. Muscle biopsies tend to show fewer atrophic muscle fibers than in type I, but there is significant overlap, and muscle biopsy results do not always correlate with prognosis.

Spinal muscular atrophy type III (juvenile spinal muscle atrophy) is known as Kugelberg-Welander disease (see earlier).

Spinal muscular atrophy type IV is the adult form. The mean age at onset of symptoms is 35 years. This disease is relatively benign with preservation of distal musculature.



Spinal muscular atrophy type I (acute Werdnig-Hoffmann disease). This young Polish boy has spinal muscular atrophy type I. The muscle wasting is evident and he is developing scoliosis.

HEENT/Airway: *Type I:* Difficulty with swallowing and handling secretions. Atrophy and visible fasciculations of the tongue. Extraocular and facial muscles are spared.

Type II: Difficulties with chewing and swallowing are rare. Tongue fasciculations and atrophy in approximately one-half of patients.

Type IV: Tongue fasciculations.

Chest: *Type I:* Respiratory distress. Intercostal weakness is more profound than is diaphragmatic weakness. Shallow respirations, paradoxical respiratory pattern with diaphragmatic breathing. Death is often from pulmonary infection with respiratory failure. Infants who present with decreased movement *in utero* have decreased lung volumes.

Type II: Respiratory embarrassment from severe scoliosis. Recurrent infections. The most severely affected might require noninvasive ventilation, and patients may require ventilatory support postoperatively or with acute illness.

Type IV: Respiratory failure can be fatal.

Cardiovascular: Congenital heart disease has been rarely reported in very severe cases.

Neuromuscular: *Type I:* Hypotonia, profound weakness, absent deep tendon reflexes. Normal intelligence and development (except for motor skills). No sensory loss. Bulbar dysfunction.

Type II: Fine tremor of the hands. Deep tendon reflexes diminished or absent. Normal intelligence. No sensory loss. Bulbar involvement only in the most severely affected.

Type IV: Symmetric muscle weakness and atrophy, proximal > distal, legs > arms. Hand tremors.

Orthopedic: *Type II:* Kyphoscoliosis. Late contractures. Can have pseudohypertrophy of the calves. Osteopenia.

GI/GU: *Type I:* Feeding problems due to muscle weakness. Gastroesophageal reflux.

Type II: Feeding problems due to muscle weakness, but some stronger patients can develop obesity due to inactivity. May have gastroesophageal reflux.

Other: *Type I:* Intrauterine growth retardation.

Type II: Pregnancy can be associated with worsening of symptoms and premature labor. Restrictive lung disease can also be exacerbated by the enlarging uterus.

Miscellaneous: The disorder was described independently by Werdnig and Hoffmann.

Anesthetic Considerations: Remember that these children have normal intelligence, and interactions with them should be age appropriate. With aging, there is an increasing incidence of limited mouth opening due to ankylosis of the mandibular joint. Patients with bulbar disease may be at increased risk for perioperative aspiration. Reflux is universal in type I disease and common in type II disease. The lack of energy stores in body fat increases the risk of hypoglycemia. Perioperative positioning may be difficult secondary to severe kyphoscoliosis. Succinylcholine is contraindicated because of the risk of exaggerated hyperkalemia. Nondepolarizing muscle relaxants should be titrated and given only as needed. Motor evoked potentials are preserved and can be used for monitoring during spine surgery. Both spinal and epidural anesthesias have been tolerated, although spinal deformities may make placement difficult. Parturients have a higher incidence of cesarean section due to weak abdominal wall muscles. Patients may require prolonged postoperative respiratory support and hospitalization even after minor procedures. Patients with types I and II disease will likely need postoperative management or observation in an intensive care unit.

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Spinal muscular atrophy type III

See Kugelberg-Welander disease

Spinocerebellar ataxia type 3

See Joseph disease

Spondylocarpotarsal synostosis syndrome

MIM #: 272460

This autosomal recessive syndrome primarily involves abnormalities of the hands, feet, and spine. It is caused by a mutation in the gene encoding filamin B.

HEENT/Airway: Broad, round face. Hypertelorism. May have retinal abnormalities, lens opacification, narrowed retinal vessels. Sensorineural hearing loss, preauricular skin tags. Short nasal septum and broad nasal bridge. Cleft palate. Enamel hypoplasia.

Chest: Restrictive lung disease from scoliosis. Short thorax.

Orthopedic: Short stature with predominantly short trunk. Odontoid hypoplasia, C2-C3 subluxation. Failure of normal segmentation of thoracic vertebrae resulting in fused, or "block," vertebrae. If asymmetric, this causes

progressive scoliosis or lordosis. The fused spine is difficult to identify in early childhood before it is adequately ossified. Synostosis of carpal and tarsal bones. Postaxial polydactyly. Decreased range of motion of elbows. Pes planus.

GI/GU: Inguinal hernias. May have renal cysts.

Anesthetic Considerations: Be sensitive to the fact that patients may have hearing loss. Patients with odontoid hypoplasia may well have an unstable cervical spine. Patients with restrictive lung disease secondary

to severe scoliosis are at increased risk for perioperative respiratory complications.

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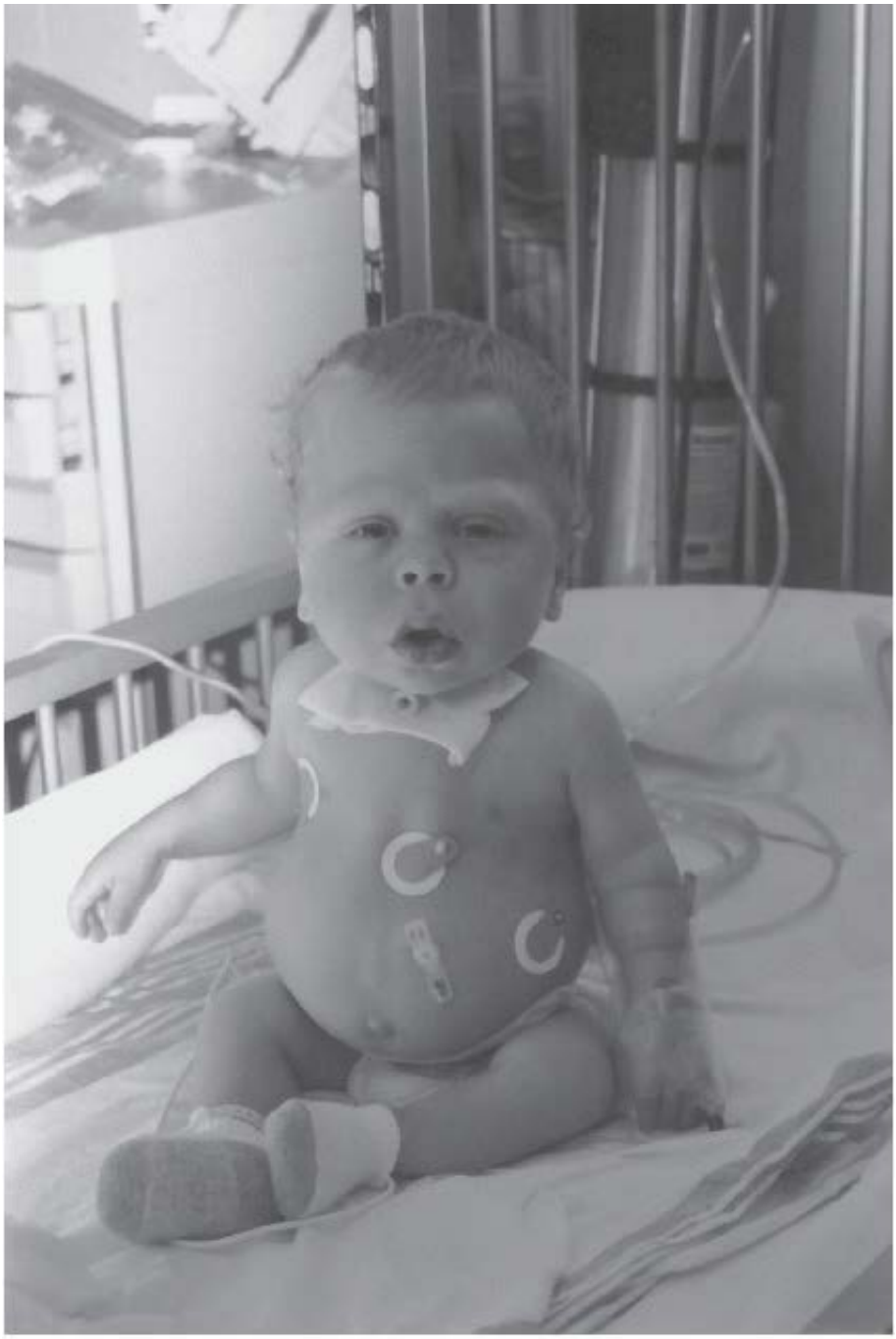
Spondylocostal dysostosis

See Jarcho-Levin syndrome

Spondyloepiphyseal dysplasia congenita

MIM #: 183900

This autosomal dominant dwarfing syndrome primarily involves the vertebral column and the epiphyses of long bones. Spondyloepiphyseal dysplasia congenita is due to a defect in the gene *COL2A1*, which encodes type II collagen. A variety of specific mutations have been described. Mutations in the *COL2A1* gene are also responsible for achondrogenesis, Kniest syndrome, and Stickler syndrome.



Spondyloepiphyseal dysplasia congenita. FIG. 1. This young boy with spondyloepiphyseal dysplasia congenita was previously misdiagnosed as having hypochondrogenesis. He has required a tracheostomy for laryngotracheobronchomalacia.

HEENT/Airway: Normocephalic. Flat facies, malar hypoplasia. Myopia and retinal detachment. Sensorineural hearing loss has been reported. Occasional cleft lip. Cleft palate. Short neck with limited flexion.

Chest: Restrictive lung disease from kyphoscoliosis. Pectus carinatum.

Neuromuscular: Hypotonia, weakness.

Orthopedic: Growth deficiency of prenatal onset. Disproportionate short stature with short trunk. Odontoid hypoplasia with atlantoaxial or other cervical instability. Thoracic kyphoscoliosis and lumbar lordosis. Narrowed intervertebral disk spaces. Diminished mobility of elbows, knees, and hips. May have diaphyseal pseudoarthrosis-like lesions. Coxa vara, dislocated hips. Lack of ossification of os pubis, proximal femur, and proximal tibia. Clubfoot deformity.

GI/GU: Hypoplasia of abdominal muscles, abdominal and inguinal hernias.

Other: The small pelvis will require cesarean section for delivery.

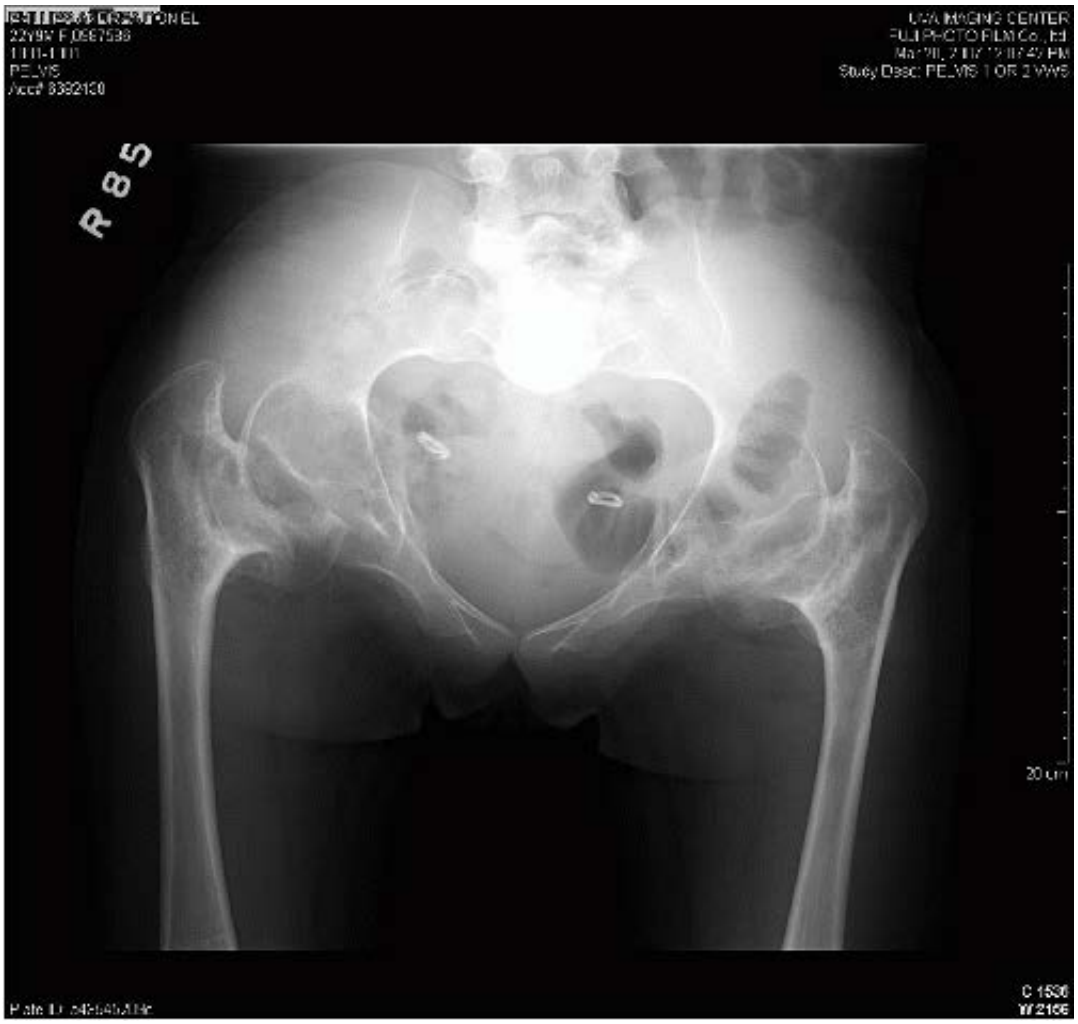
Spondyloepiphyseal dysplasia congenita. FIG. 2. The young boy in Figure 1 at 9½ years of age. His old tracheostomy and gastrostomy sites are apparent and he suffers from neck and joint pains.

Spondyloepiphyseal dysplasia congenita. FIG. 3. This 23-year-old young woman is approximately 4 feet (122 cm) tall and was admitted to the hospital for her second hip replacement. She has multiple problems including kyphosis, a small fourth cervical vertebra limiting neck extension, limited mouth opening, and a difficult airway, and she had had a retinal detachment.

Miscellaneous: While researching the lineage of an affected family he had identified at the Mayo Clinic, Stickler discovered that the first affected family member had been seen by Charles Mayo himself nearly 100 years earlier.

A full-length portrait of the French painter Achille Emperaire by Cézanne hangs in the Musée d'Orsay in Paris. The portrait suggests that Emperaire had spondyloepiphyseal dysplasia congenita.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be difficult secondary to a short neck and limited flexion (6). Patients may have cervical spine instability and there is a risk of cervical spine injury during laryngoscopy in these patients (4,7,8,10). Preoperative flexion/extension radiographs and fiberoptic intubation should be considered (7). Because of their small stature, patients may require a smaller-than-expected endotracheal tube. Patients with restrictive lung disease are at increased risk for perioperative respiratory complications. Limitations in joint mobility may make perioperative positioning difficult. Epidural anesthesia (with decreased volume of local anesthetic) has been used successfully for cesarean section (5,11).



Spondyloepiphyseal dysplasia congenita. FIG. 4. The pelvis of the woman in Figure 3.

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Spondyloepiphyseal dysplasia tarda

MIM #: 184100, 313400

This form of short-trunk dwarfism is inherited in an autosomal dominant or X-linked fashion. The gene and gene product responsible for the autosomal dominant form are not known, but the disorder is not due to a defect in the type II collagen gene, which is responsible for spondyloepiphyseal dysplasia congenita.

The X-linked form of spondyloepiphyseal dysplasia tarda has recently been ascribed to mutations in the gene *TRAPPC2*, which is involved in intracellular vesicle trafficking. Patients with spondyloepiphyseal dysplasia tarda are radiographically and clinically normal at birth, with degenerative changes becoming apparent in the second decade of life. Female carriers can have arthralgias in middle age.

HEENT/Airway: Normocephalic, flattened facies. Can have corneal opacities. Short neck.

Chest: Pectus carinatum.

Neuromuscular: Spastic paraplegia from thoracic disk herniations has been reported.

Orthopedic: Short-trunk dwarfism. Odontoid hypoplasia occurs, but less frequently than in other dwarfism syndromes. Cervical subluxation. Cervical spine problems may worsen with age. Flattened, dysplastic vertebral bodies. Kyphoscoliosis, lumbar lordosis. Mild scoliosis. Extremities are shortened in proportion to the trunk. Degenerative changes in the femoral head. Bony changes lead to secondary arthritis. Eventually develop painful, stiff hips, shoulders, and cervical and lumbar spine. Arthritis often becomes disabling by late adulthood. Coxa vara. Hip replacement often needed by age 40 years.

GI/GU: Nephrotic syndrome has been reported in one family.

Anesthetic Considerations: Patients with odontoid hypoplasia may have an unstable cervical spine. Preoperative flexion/extension radiographs and fiberoptic intubation should be considered. Difficulty with intubation has not been reported, but is a concern given the cervical spine disease. Spine and joint disease may make prolonged positioning on the operating table uncomfortable.

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Spondylometaphyseal dysplasia

Synonym: Kozlowski spondylometaphyseal dysplasia

MIM #: 184252

The main features of this autosomal dominant disorder are progressive short-trunk (short spine) dwarfism, irregular metaphyses, and pectus carinatum. At least seven subtypes of spondylometaphyseal dysplasia have been described, primarily based on radiographic differences. All of the spondylometaphyseal dysplasias affect both the spine ("spondylo") and the metaphyses of the long bones. The Kozlowski type is the most common and is due to mutations in the gene *TRPV4* (transient receptor potential cation channel, subfamily V, member 4), which mediates calcium influx in ciliated epithelial cells in response to a variety of stimuli. Mutations in this gene also cause metatropic dysplasia (see earlier). Mutations in the gene *PCYT1A* cause spondylometaphyseal dysplasia with cone-rod dystrophy (not discussed here, *MIM #:* 608940). The gene product of the *PCYT1A* gene is responsible for an important step in phosphatidylcholine synthesis. A syndrome of spondylometaphyseal dysplasia with combined immunodeficiency and autoimmune disease has been termed the Roifman-Costa syndrome (not discussed here, *MIM #:* 607944).

HEENT/Airway: Normal facies. Short neck. May have ophthalmologic abnormality diagnosed as retinitis pigmentosa or pigmentary retinal degeneration. May have cone-rod dystrophy.

Chest: Pectus carinatum. Short ribs with flared ends. Restrictive lung disease from kyphoscoliosis and diminished functional residual capacity from body habitus. Thoracic hypoplasia can result in mild to moderate neonatal respiratory problems and later susceptibility to respiratory infections.

Orthopedic: Short stature, primarily due to a short trunk (short spine). Short stature usually apparent between 1 and 4 years of age. Platyspondyly. Kyphoscoliosis. Odontoid hypoplasia with atlantoaxial instability. Irregular metaphyses, rachitic-like, particularly in the proximal femurs that are apparent by about 6 years of age. Limited joint mobility by approximately 18 months of age. Contracted pelvis and coxa vara. Anterior narrowing of the thoracolumbar vertebrae on lateral radiographs.

Other: May have immunodeficiency or autoimmune disease.

Anesthetic Considerations: Patients may have atlantoaxial instability secondary to odontoid hypoplasia. Because of growth deficiency, patients may require a smaller-than-expected endotracheal tube, which also is not inserted as deeply as in normal adults. Patients must be carefully positioned and padded secondary to limited joint mobility.

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dysplasia. *Anesthesiology* 1985;63:548-550.

Spondylothoracic dysplasia

See Jarcho-Levin syndrome

Stargardt disease

Synonym: Juvenile macular degeneration

MIM #: 248200

Stargardt disease is an autosomal recessive disorder associated with macular degeneration. It is the most common cause of macular degeneration in children. The disease involves the accumulation of lipofuscin in the retinal epithelium. Most cases are due to a mutation in the gene *ABCA4*, which encodes an ATP-binding cassette protein. This protein is a "flippase"—it catalyzes a 180-degree rotation of a specific phospholipid and simultaneously moves it from the inner to the outer phospholipid bilayer. This protein is expressed in (at least) blue rod photoreceptors. This class of proteins is involved in the energy-dependent transfer of a wide variety of substrates across membranes. There are several other causes of Stargardt disease. Stargardt disease-3 is due to mutations in the gene *ELOVL4*, required for the synthesis of very long chain fatty acids, and Stargardt disease-4 is due to abnormalities in the gene *PROM1*, which encodes a highly conserved glycoprotein. Stargardt disease-2 was designated in error. There has been preliminary success from treatment with stem cells, isotretinoin (Accutane) and dobesilate.

HEENT/Airway: Loss of central vision that is slowly progressive. Peripheral vision remains intact. Slow dark adaptation. There may be "pisciform" lesions seen throughout the fundus. The foveal reflex is absent or grayish, and there may eventually be depigmentation and chorioretinal atrophy of the macula. The degree of vision loss parallels the degree of macular involvement.

Miscellaneous: This disease is also known as "fundus flavimaculatus," which historically has been used to refer to disease with more pronounced peripheral involvement, whereas "Stargardt disease" has been used to refer to disease with more pronounced macular involvement. They are currently thought to represent different parts of the spectrum of the same disease process. Nonsense truncating mutations in *ABCA4* have resulted in Stargardt disease while missense mutations affecting uncharged amino acids have resulted in fundus flavimaculatus.

Anesthetic Considerations: When meeting the patient preoperatively, recall that he or she may have significant vision loss.

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Steinert disease

See Myotonic dystrophy

Steroid 5α-reductase 2 deficiency

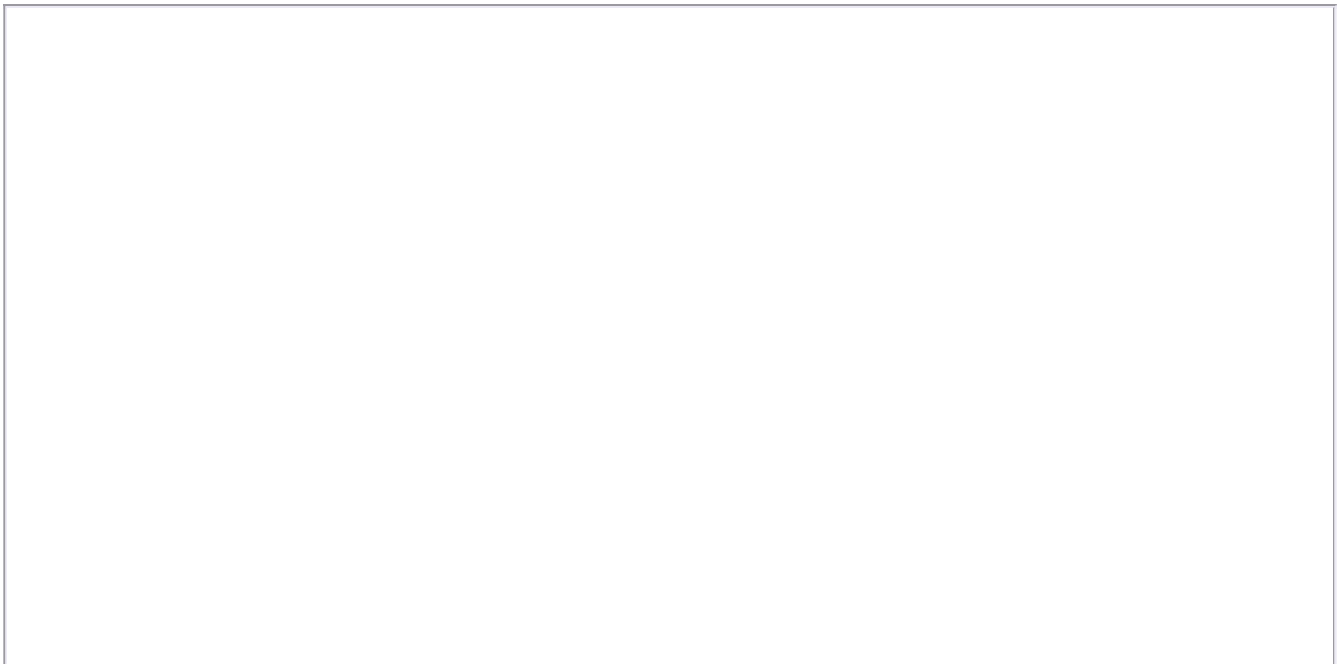
See 5α-reductase deficiency

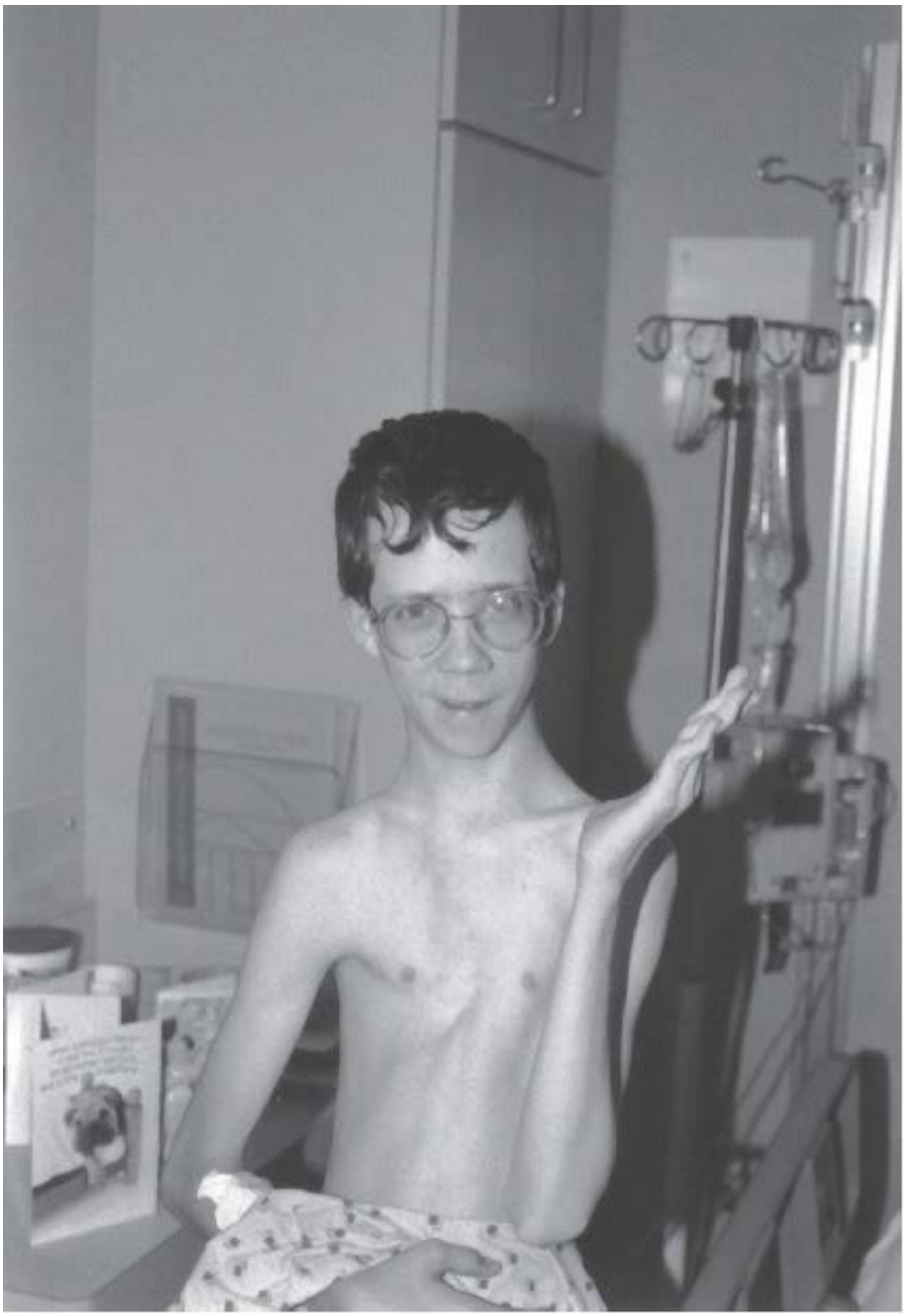
Stickler syndrome

MIM #: 108300

This autosomal dominant disorder exhibits extensive clinical variability. It was originally described as an arthroophthalmopathy. It is due to mutations in the gene *COL2A1*, which encodes type II collagen, a major component of cartilage, vitreous, and nucleus pulposus, all of which can be involved. These patients may also have associated Pierre Robin syndrome (see earlier). Mutations in the *COL2A1* gene are also responsible for achondrogenesis, Kniest syndrome, and spondyloepiphyseal dysplasia congenita (see earlier). One subtype of type I, also due to abnormalities in *COL2A1*, has solely or predominantly eye findings.

A second form of Stickler syndrome (type II) is due to a mutation in the gene *COL11AI*. A third form of Stickler syndrome (type III) is due to a mutation in the gene *COL11A2*. Type III Stickler syndrome does not include ocular abnormalities. Less common autosomal recessive forms are types IV (due to abnormalities in *COL9A1*) and V (due to abnormalities in *COL9A2*). Recently, disease due to a mutation in *COL9A3* has been described.





Stickler syndrome. FIG. 1. Hyperextensible joints in a 16-year-old boy with Stickler syndrome. He has had repair of pectus excavatum and has a small mandible, a high-arched palate, mitral valve prolapse, and noncardiac chest pain.

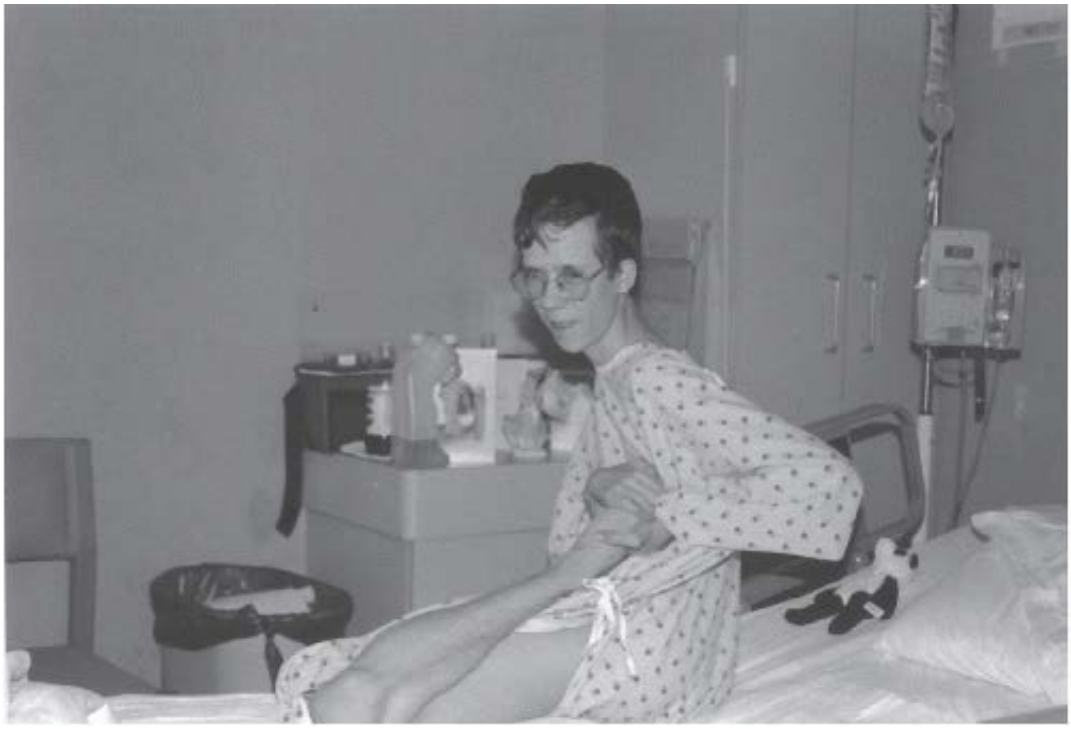
HEENT/Airway: Flat facies. Epicanthal folds, myopia, dislocated lens, glaucoma, chorioretinal degeneration, retinal detachment, vision loss, cataracts. Type I presents within the first decade of life. Type II has a characteristic atypical vitreous. Sensorineural hearing loss; can have conductive hearing loss. Anteverted nares, flat nasal bridge. Cleft palate; may have bifid uvula, tooth anomalies. Micrognathia (may be associated with Pierre Robin syndrome; see earlier).

Chest: Pectus excavatum.

Cardiovascular: Mitral valve prolapse is common.

Neuromuscular: Normal intelligence. Hypotonia.

Orthopedic: Marfanoid habitus. Hyperextensible joints, joint pains, arachnodactyly. Short stature, narrow long bones, abnormal leg epiphyses. Mild spondyloepiphyseal dysplasia. Scoliosis, kyphosis, lumbar lordosis. Platyspondyly. Herniation of thoracic disks, flat vertebrae. Pes planus, genu valgus, hip subluxation, Legg-Calvé-Perthes disease (see earlier), clubfoot deformity. Arthralgias in childhood, arthritis in adulthood. May require total hip replacement in adulthood.



Stickler syndrome. FIG. 2. Additional demonstration of hyperextensible joints.

Miscellaneous: This disorder has been suggested as a possible diagnosis for President Lincoln and his son Tad.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be very difficult in patients with a small mandible. Recall that patients may have vision loss. Some patients may have hearing loss. Patients must be carefully positioned perioperatively secondary to joint laxity and arthritis. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

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Stiff-baby syndrome

Synonym: Hyperekplexia (hyperexplexia); Kok disease

MIM #: 149400

This syndrome is due to a defect in the gene encoding the $alpha_1$-subunit of the (inhibitory) glycine receptor. It can be autosomal dominant or autosomal recessive. It is characterized by marked muscle rigidity immediately after birth and an abnormal startle response, presumably from lack of normal inhibition. A mutation in the gene encoding the beta-subunit of the glycine receptor has been implicated in the cause of type II

hyperekplexia. It has recently been suggested that defects in the presynaptic glycine transporter GlyT2 could result in a presynaptic cause of the disease.

HEENT/Airway: Staccato cry.

Respiratory: Episodes of stiffness can cause apnea or aspiration. Episodes of apnea have been fatal.

Cardiovascular: Episodes of stiffness can cause bradycardia or heart block.

Neuromuscular: Exaggerated startle, palmomental, and snout reflexes. The exaggerated startle response can be elicited by a loud noise or a glabellar tap. It is triggered by cold, stress, fatigue, or rainy weather. This exaggerated startle response is sometimes accompanied by a generalized hypertonic response causing the patient to fall down. There is flexion hypertonia while awake, which resolves with sleep. Muscle rigidity persists during infancy but gradually resolves during the first few years of life, though can reappear during adolescence. Myoclonic jerks while asleep. The electromyogram shows continuous muscle activity even when resting quietly. Nerve conduction is normal. In the major form, abnormal fetal movements can be detected and onset is shortly after birth. In the minor form, there is an exaggerated startle response but without additional findings such as generalized stiffness.

Orthopedic: Congenital hip dislocation.

GI/GU: Infants may have choking, vomiting, and dysphagia, which has been fatal. Inguinal and umbilical hernias.

Miscellaneous: The symptoms are similar to those of the “stiff man” syndrome of adults, which has multiple

etiologies. This syndrome probably represents the hereditary form of the stiff man syndrome.

It is possible, but unlikely, that the interestingly named “jumping Frenchmen of Maine” syndrome is related. Interest in this latter syndrome inspired Gilles de la Tourette to investigate what later became his eponymous disease.

Anesthetic Considerations: Premedication and parental presence would seem a good idea if otherwise appropriate. EMLA cream should be used for awake intravenous catheter placement. Sudden loud noises that could produce a hypertonic episode should be avoided. Benzodiazepines can prevent and control spasms. Propofol and other GABA-ergic and glycinergic agents would seem good choices. Propofol has been shown to compensate for an inadequate glycine receptor response in a mouse model of the disease. When respiration is impeded, Vigevano's maneuver, forced flexion of the head and legs toward the trunk, can be lifesaving. Patients must be closely observed in the postanesthesia care unit. Although tapping on the supraorbital nerve can reliably produce exaggerated startle response patterns, there have been no reports of this occurring secondary to the pressure of a facemask.

One studied infant was relatively resistant to succinylcholine and did not have an abnormal rise in serum potassium. Responses to pancuronium and neostigmine were normal (6). In another report, however, there was marked train of four electromyographic fade (57%) following sevoflurane induction, and resistance to succinylcholine neuromuscular blockade was not observed (5).

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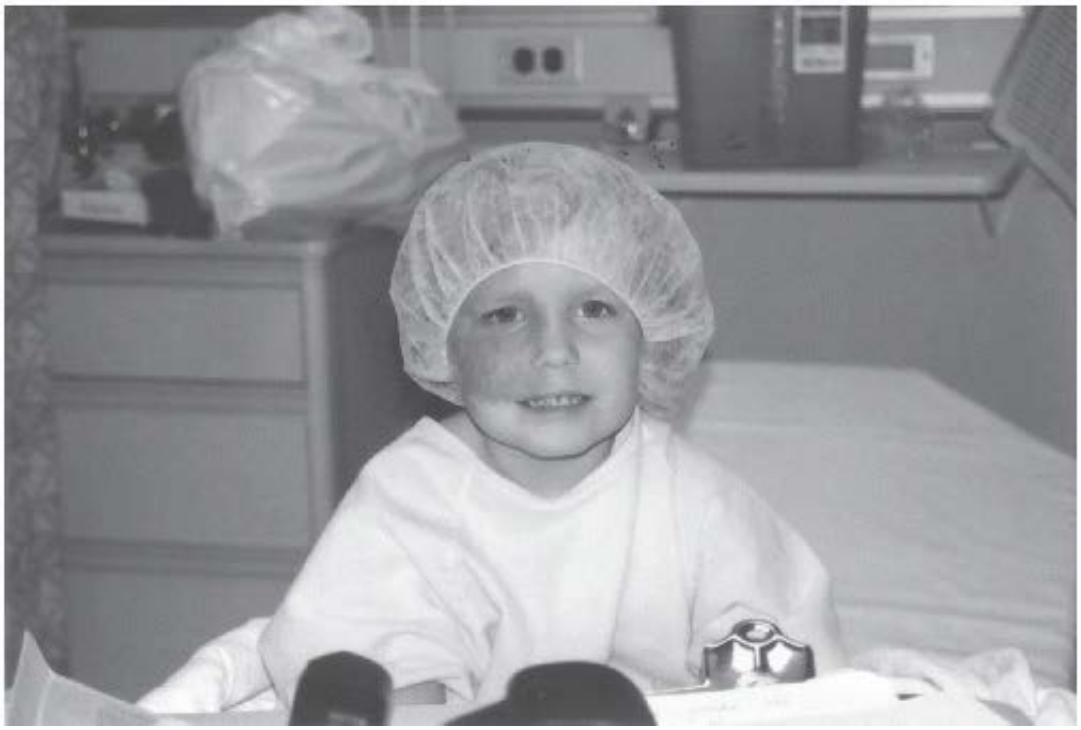
Sturge-Weber syndrome

MIM #: 185300

The classic findings of this syndrome are capillary or cavernous hemangiomas (port-wine stain, nevus flammeus) in the cutaneous distribution of the trigeminal nerve, angiomas of the meninges of the ipsilateral hemisphere with a seizure disorder and intellectual disabilities, and linear intracranial calcifications. Sturge-Weber syndrome appears to be due to somatic mutations in the gene *GNAQ*, which couples cell surface receptors to intracellular signaling pathways. Initiation activates the exchange of GTP for GDP. Somatic mosaic mutations in this gene can also cause nonsyndromic port-wine stains. The clinical course of Sturge-Weber syndrome is variable. Patients may have Sturge-Weber syndrome along with manifestations of Klippel-Trenaunay-Weber syndrome (see earlier).

HEENT/Airway: The hallmark finding is a facial port-wine stain, or angioma, in the distribution of the first or second division of the trigeminal nerve. Congenital glaucoma is common. Retinal vessel varicosities, choroid hemangiomas, retinal detachment, optic atrophy. Angiomas can involve the mucous membranes of the lip, tongue, nose, palate, larynx, and trachea. There

may be hypertrophy of the bones and soft tissues in the regions immediately adjacent to areas of facial angioma.



Sturge-Weber syndrome. FIG. 1. This 5-year-old is receiving laser treatment for the port-wine stain. She has well-controlled seizures.

Chest: Vascular abnormalities have been reported in the lung.

Cardiovascular: High-output heart failure is a rare consequence of shunting through intracranial angiomas. Vessels in the angiomas have an incidence of spontaneous bleeding and have abnormal autoregulation. Patients may be on antiplatelet drugs for recurrent thromboses.

A variety of congenital heart defects have been reported in patients with Sturge-Weber syndrome, but it is unclear

if this is part of the syndrome or a chance association.

Neuromuscular: Vascular changes can be found in the meninges, brain, and pituitary. Leptomeningeal angiomas are ipsilateral to the facial port-wine stain, most commonly in the occipital and posterior parietal lobes. Many patients have seizures, which can be intractable and lead to intellectual disabilities. Patients can also have hemiatrophy of the brain and hemiplegia. Progressive hemiparesis, focal seizures, and rarely cerebral hemorrhage. The classic radiologic findings are intracranial parallel “tram track” or “railroad track” calcifications, which are almost always present, but rarely before age 2 years. These are thought to be due to stasis resulting in ischemia and calcification. Arachnoid hemangiomas are very common. There can also be deep arteriovenous malformations.

GI/GU: Colonic ischemia and hematemesis from gastric bleeding have been reported.

Other: Angiomas can also be found on the trunk and extremities.

Sturge-Weber syndrome. FIG. 2. Three unrelated teenage girls with Sturge-Weber syndrome. (Courtesy of the Sturge-Weber Foundation and Rick Guidotti of Positive Exposure.)

Miscellaneous: Sturge first described the clinical features of the disease. Weber described the intracranial calcifications 50 years later. F. Parkes Weber was a British physician who had an interest in rare disorders and uncommon syndromes. Weber's father came from Germany to Britain (where he became physician to Queen Victoria), and Weber continued to pronounce his last name with the “W” pronounced as the Germanic “V.” He had an encyclopedic knowledge of rare disorders. It is said that when, at a meeting of the Royal Society of Medicine, he first announced that he had not heard of a certain syndrome, such cheers and applause broke out from the audience that the meeting had to be abandoned. He wrote a total of 1200 medical papers.

Sturge-Weber syndrome is one of the neuroectodermal disorders, or phakomatoses, along with neurofibromatosis, nevus sebaceus syndrome of Jadassohn, tuberous sclerosis, and von Hippel-Lindau syndrome. “Phakos” is Greek for a lentil or lens-shaped spot. It differs from the other phakomatoses by the absence of a cutaneous pigment abnormality, an absence of increased risk for the development of tumors, and lack of heritability. There are at least 17 synonyms for this disorder.

Anesthetic Considerations: Angiomas of the mouth and upper airway may make mask ventilation difficult and may interfere with laryngoscopy and intubation. Nasal intubation or the placement of a nasogastric tube should be avoided due to the risk of nasopharyngeal involvement. Rupture of an angioma can result in uncontrolled hemorrhage. Because these vessels have abnormal autoregulation, intraoperative blood pressure should be well controlled. Meticulous perioperative eye protection is indicated in these patients.

Atropine and scopolamine should be avoided in patients with glaucoma because of their mydriatic effects. Anticholinergic drugs used with anticholinesterases for reversal of neuromuscular blockade are acceptable. Succinylcholine also raises intraocular pressure transiently, but appears to be safe in patients with well-controlled intraocular pressure. Succinylcholine is relatively contraindicated in patients with hemiplegia secondary to the risk of exaggerated hyperkalemia. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs.

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Stuve-Wiedemann syndrome

See Schwartz-Jampel syndrome

Succinate-coenzyme Q reductase deficiency

See Complex II deficiency

Sugarman syndrome

Included in Oral-facial-digital syndrome, type I

Sulfite oxidase deficiency

Included in Molybdenum cofactor deficiency

Summitt syndrome

Included in Carpenter syndrome

Swiss-type agammaglobulinemia

Included in Severe combined immunodeficiency syndrome

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

T

Tangier disease

MIM #: 205400

This autosomal recessive disorder is characterized by a deficiency of high-density lipoproteins (HDL) and storage of cholesterol esters in multiple tissues. This disease is caused by a defect in apolipoprotein A-1. The structural gene for this protein is normal, and the defect is due to a mutation in the ATP-binding cassette-1 gene (*ABCA1* gene), which controls extrusion of the membrane lipid extracellularly. The lipid deposits are extralysosomal within foamy histiocytes. Familial HDL deficiency is due to abnormalities in the same gene, and so is allelic.

HEENT/Airway: Facial diplegia. Ptosis, ocular muscle palsies, diplopia. Corneal infiltration; one-fourth have corneal opacifications that do not impair vision. Decreased corneal sensation. Ectropion and incomplete lid closure can cause eye injury from exposure. Two-thirds have enlarged, orange tonsils secondary to cholesterol ester storage, which is a hallmark of the disorder.

Cardiovascular: Can have lipid deposits on mitral and tricuspid valves and in the pulmonary artery. There is a moderately increased incidence of premature coronary disease, which is further increased in the presence of other risk factors and in older patients.

Neuromuscular: There can be one of three neuropathic syndromes: an asymmetric relapsing type that can involve cranial nerves; a symmetric, slowly progressive type primarily involving the lower extremities; and a syringomyelia-like type that is slowly progressive and presents with dissociated sensory and motor loss in the face and arms before extending to the lower extremities. The peripheral neuropathy is due to accumulation of storage material in Schwann cells. There is no autonomic neuropathy. There can be muscle wasting. Loss of sensation to heat and pain can cause susceptibility to burns. Abnormalities in proprioception are uncommon.

Orthopedic: Hand muscle wasting.

GI/GU: Hepatomegaly (with normal function). Splenomegaly with hypersplenism. The rectal mucosa is routinely involved on biopsy. The ileum and colon, but not the jejunum, are also frequently involved, but only approximately 8% have intermittent diarrhea.

Asymptomatic focal depositions in the renal pelvis, ureter, and tunica albuginea of testes. Very uncommon cases of pancreatic deposition mimicking a tumor.

Other: Hemolytic anemia, thrombocytopenia, and platelet dysfunction have been reported. Circulating stomatocytes. Decreased circulating monocytes. Circulating chylomicronemia even in fasting patients. Deposition in histiocytes causes lymphoid tissue enlargement. Lymph nodes and thymus are also orange from cholesterol ester storage. Hypocholesterolemia and low levels of HDL. Hypertriglyceridemia. Focal depositions in the skin.

Miscellaneous: In this case, Tangier refers not to the city in Morocco but to Tangier Island in the Chesapeake Bay,

where the first cases were described.

Anesthetic Considerations: The hematocrit and platelet count should be evaluated preoperatively in patients with hypersplenism. In addition, there may be a thrombasthenia (abnormal platelet function with normal platelet number). Consider perioperative desmopressin for abnormal platelet count or function. Older patients should be evaluated preoperatively for coronary artery disease. Mask ventilation could potentially be difficult with tonsillar enlargement and loss of muscle tone with induction of anesthesia, which could be mediated with a nasopharyngeal airway. These patients are at risk for perioperative eye injury secondary to incomplete lid closure, and meticulous perioperative eye care is imperative. Preexisting neuropathic abnormalities might interfere with the evaluation of complications of regional anesthesia. Regional anesthesia is also relatively contraindicated in the presence of an abnormal platelet count or function. Succinylcholine may be contraindicated in patients with neuropathy and muscle atrophy secondary to the risk of exaggerated hyperkalemia. Sleep apnea is possible from excessive pharyngeal lymphatic tissue. Note that patients may have diminished sensation to heat and pain.

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TAR syndrome

See Thrombocytopenia-absent radii syndrome

Tarui disease

See Glycogen storage disease type VII

Taybi syndrome

See Otopalatodigital syndrome, type I

Tay-Sachs disease

Synonym: GM_2 gangliosidosis, type I (Includes Bernheimer-Seitelberger disease)

MIM #: 272800

Tay-Sachs disease is one of a group of disorders due to defective degradation and abnormal accumulation of GM_2 ganglioside. Defects can occur in the alpha-subunit of hexosaminidase A (Tay-Sachs disease, deficient hexosaminidase A isoenzyme) and the beta-subunit of hexosaminidase A (Sandhoff disease, deficient hexosaminidase A and B; see earlier), or there can be a defect in the GM_2 activator protein (both isoenzymes are

present, but hexosaminidase A is nonfunctional). All result in accumulation of GM_2 ganglioside in neuronal lysosomes. Depending on the degree of severity of the enzyme deficiency caused by any one specific mutation, the disease can present as an infantile disease (classic Tay-Sachs disease), juvenile GM_2 gangliosidosis (**Bernheimer-Seitelberger disease**), or as adult-onset GM_2 gangliosidosis. However, there is significant clinical variability, and such classification schemes are arbitrary. The juvenile form may represent a compound heterozygote state: one Tay-Sachs gene and another different allelic mutation. The clinical manifestations of Tay-Sachs disease are primarily neurologic. The disease is classically associated with visualization of a cherry-red spot on the retina. There is no hepatosplenomegaly, as is seen in Sandhoff disease. Death with the juvenile form is typically in the first 2 years of life.

Gangliosides have both a hydrophobic ceramide moiety and a hydrophilic oligosaccharide chain. They are components of the outer cell membrane, with the hydrophobic moiety anchoring it in the membrane and the hydrophilic chain extending into the extracellular space. Although their function is unknown, they have been implicated as binding sites for a variety of viruses, bacterial toxins, growth factors, and interferons.

HEENT/Airway: *Classic Tay-Sachs:* Macrocephaly. The classic cherry-red spot in the area of the macula is normal macula surrounded by areas turned white by storage material. Progression to blindness. Poorly coordinated swallowing leads to difficulty handling

oral secretions. Most require nasogastric or gastrostomy feeding.

Juvenile type: Cherry-red spot not as consistent a finding. Optic atrophy and retinitis pigmentosa. Loss of vision.

Adult type: Vision usually normal.

Chest: Increased risk of recurrent aspiration. Poor cough. Recurrent infections.

Neuromuscular: *Classic Tay-Sachs:* Early excessive startle response. Hypotonia, progressive weakness, psychomotor retardation, exaggerated startle response, eventual spasticity. Seizures. Both upper and lower motor neuron disease. Eventually an unresponsive, vegetative state.

Juvenile type: Similar, but later onset.

Adult type: Spinocerebellar, pyramidal tract, and lower motor neuron disease. Psychosis, particularly hebephrenic schizophrenia, episodic depression. Normal intelligence, which can be masked by severe dysarthria and other motor involvement. Early weakness or tremor. Anterior horn cell dropout and group atrophy.

GI/GU: There is no organomegaly.

Miscellaneous: Warren Tay was a British ophthalmologist (and surgeon, pediatrician, and dermatologist, described as a "walking dictionary") who first described the bilateral cherry-red spots. Bernard "Barney" Sachs was an American neurologist who, 6 years later, independently described the clinical features of the disease, under the name "familial amaurotic idiocy." Although classically linked to Ashkenazi Jewish populations (heterozygote incidence about 1:30), the incidence is actually higher in certain Louisiana Cajun and Pennsylvania Dutch populations. A naturally occurring animal Tay-Sachs disorder occurs in Jacob sheep.

Anesthetic Considerations: Difficult airways have not been reported in Tay-Sachs disease. Be aware that patients can have visual limitations. Patients are at increased risk for perioperative aspiration. Chronic use of anticonvulsant medications can affect the metabolism of some anesthetic drugs. Succinylcholine should be avoided in this disease with lower motor neuron involvement and muscle wasting because of the risk of exaggerated hyperkalemia.

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Telecanthus-hypospadias syndrome

See Hypertelorism-hypospadias syndrome

Tetrahydrobiopterin (BH4) deficiency

Included in Phenylketonuria

Thalassemia

(Includes Cooley's anemia, Hemoglobin H disease, and Hemoglobin S-thalassemia)

MIM #: 604131, 613985, 613978

The thalassemias are a group of hereditary anemias caused by defective synthesis of either the alpha-chain (alpha-thalassemias) or beta-chain (beta-thalassemias) of hemoglobin. Heterozygotes have mild anemia. Homozygotes have severe anemia. The thalassemias represent the most common single gene disorders in the world. Hematopoietic stem cell transplantation has proven successful in severely symptomatic individuals.

Over 40 thalassemia variants have been described. Unbalanced synthesis of alpha- and beta-chains leads to unstable hemoglobin and early erythrocyte death, mostly in the marrow. Individuals can inherit the genes both for thalassemia and for a structurally abnormal hemoglobin, or for two different types of thalassemia, making for a diverse clinical presentation. Diseases in which there is no synthesis of the affected chain are noted by a superscript “zero,” and those with diminished chain synthesis are noted by a superscript “+.” There can be compensatory extramedullary hematopoiesis. Foci of extramedullary hematopoiesis can be so large that they can mimic tumors.

Beta-thalassemias: The heterozygous disease is known as thalassemia minor. The homozygous disease is known as thalassemia major, or **Cooley's anemia.** In homozygous disease, unpaired alpha-hemoglobin precipitates as inclusion bodies in early red cell precursor cells. These cause the intramedullary destruction of red cells and the ineffective erythropoiesis of this disorder. Excessive globin chains are apparently adequately lysed by proteolytic mechanisms. Severe anemia becomes apparent with the postnatal switch from fetal gamma-chain production to beta-chain production. Transfusions will decrease the excessive production of alpha-hemoglobin; however, it carries with it the risks of chronic iron overload.

Alpha-thalassemias: Alpha-thalassemias are prevalent in Southeast Asia. There are normally four alpha-chain

genes and alpha-thalassemia results from the deletion of two or more genes. Absence of two genes is associated with an iron-unresponsive microcytic anemia. Absence of three genes results in **hemoglobin H disease**, a moderately severe anemia resembling thalassemia major (Cooley's anemia). In hemoglobin H disease, there is a

marked imbalance between alpha-chain synthesis (which is reduced) and beta-chain synthesis, resulting in the formation of hemoglobin H (four beta-chains). The unpaired beta-chains precipitate in erythroblasts during erythropoiesis and in circulating red cells causing ineffective hematopoiesis and hemolytic anemia. In addition, approximately 10% of the total hemoglobin is hemoglobin Barts (four gamma-chains). Hemoglobin H precipitates with red blood cell aging and causes increased splenic uptake. Hemoglobin Barts and hemoglobin H have an increased affinity for oxygen (the oxygen dissociation curve is shifted to the left of normal) and therefore contribute less to oxygen transport. Hemoglobin H disease primarily results in hemolysis, with only mild impairment of erythropoiesis. Absence of all four alpha-chain genes results in fetal hydrops; the dominant hemoglobin is hemoglobin Barts (four gamma-chains). The altered oxygen dissociation properties of this hemoglobin make oxygen unavailable to tissues, resulting in fetal demise. A severely symptomatic subtype of hemoglobin H disease, hemoglobin Constant Spring has been appearing with increasing incidence on the United States west coast.

A combination of the genes for sickle cell disease (see earlier) and thalassemia results in a disease more severe than either alone, known as **hemoglobin S-thalassemia.** In this disorder, there is moderately severe microcytic hemolytic anemia in addition to vasoocclusive crises. On occasion, no hemoglobin A is present (hemoglobin S-beta^0-thalassemia).

HEENT/Airway: Bone marrow hyperplasia secondary to extramedullary hematopoiesis results in characteristic changes, including frontal bossing, a prominent maxilla, and a relatively sunken nose. “Hair-on-end” appearance of the skull bones on radiographs.

Cardiovascular: There can be cardiac involvement from hemosiderosis secondary to chronic hemolysis or repeated transfusions. Cardiac failure, arrhythmias, or conduction disturbances can occur.

Neuromuscular: Hypercoagulability resulting in cerebral thrombosis can occur in some. Intracranial extramedullary hematopoiesis simulating a tumor is a rare complication.

Orthopedic: Progressive bony changes from extramedullary hematopoiesis in thalassemia major. Osteoporosis with pathologic fractures.

GI/GU: Unconjugated hyperbilirubinemia in thalassemia major. Massive splenomegaly and hypersplenism in untransfused or undertransfused thalassemia major. Gallstones. Hemosiderosis from iron loading with chronic transfusions (controllable with chelation therapy). Hypogonadism.

Other: *Thalassemia minor:* Mild hypochromic, microcytic anemia with hemoglobin levels 2 to 3 g/dL below normal for age. There are target cells, ovalocytes, and basophilic stippling. Hemoglobin A_2 levels are elevated.

Thalassemia major: Profound anemia requiring chronic blood transfusions. Large numbers of circulating nucleated red blood cells.

Alpha-thalassemias: Hemoglobin synthesis (often hemoglobin H—four beta-chains) proceeds at a normal pace in the marrow (normal hematopoiesis). There is, however, decreased red blood cell life span because of increased splenic uptake.

Increased risk of bacterial infections in all severe forms. Hypercoagulability in some.

Anesthetic Considerations: Perioperative care should be coordinated with a hematologist whenever possible. The hematocrit must be evaluated preoperatively. Nucleated red blood cells can artifactually elevate the white blood cell count by automated methods. A thorough preoperative cardiac evaluation is indicated in patients who can have cardiac involvement from hemosiderosis (secondary to chronic hemolysis or repeated transfusions). Elevated lactate dehydrogenase levels reflect the ineffective hematopoiesis. The changes in facial bones from marrow

hyperplasia have been reported to cause difficulties in visualizing the vocal cords. Splenomegaly may result in thrombocytopenia. Patients who have had a splenectomy can be at increased risk of infection with encapsulated organisms.

Infections and oxidant drugs can precipitate hemolysis in hemoglobin H disease. Anesthetic-related oxidant drugs include prilocaine, nitroprusside, sulfonamides, penicillin, vitamin K, and aspirin. Hemoglobin H precipitates with prolonged exposure to temperatures at or below 4°C, but there have been no reported problems with cold cardioplegia (6).

There is a single report of use of a cell saver in a patient with beta-thalassemia. Although apparently successful, excessive hemolysis was noted and additional wash volume was required (4). Red blood cells do not show increased fragility during cardiopulmonary bypass.

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Thanatophoric dwarfism

Synonym: Thanatotrophic dysplasia

MIM #: 187600, 187601

This severe autosomal dominant short-limb (micromelic) dwarfism is usually fatal in the neonatal period, but some survive into childhood. Thanatophoric dysplasia is characterized by severe short-limbed dwarfism, macrocephaly, and significant underdevelopment of the thorax. Both types I and II disease are caused by mutations in *FGFR3*, fibroblast growth factor 3. Those with short curved femurs and with mild or absent cloverleaf skull (kleeblattschaedel; see earlier) are designated type I. Type II disease is associated with relatively straight femurs and always has cloverleaf skull. A less severe mutation in *FGFR3* can result in the phenotype hypochondroplasia (see earlier). Achondroplasia (see earlier) is also an allelic disorder.

HEENT/Airway: Macrocephaly, frontal bossing.

Respiratory: Narrow thorax. Short ribs. Markedly reduced thoracic volumes are often lethal. Scapular anomalies.

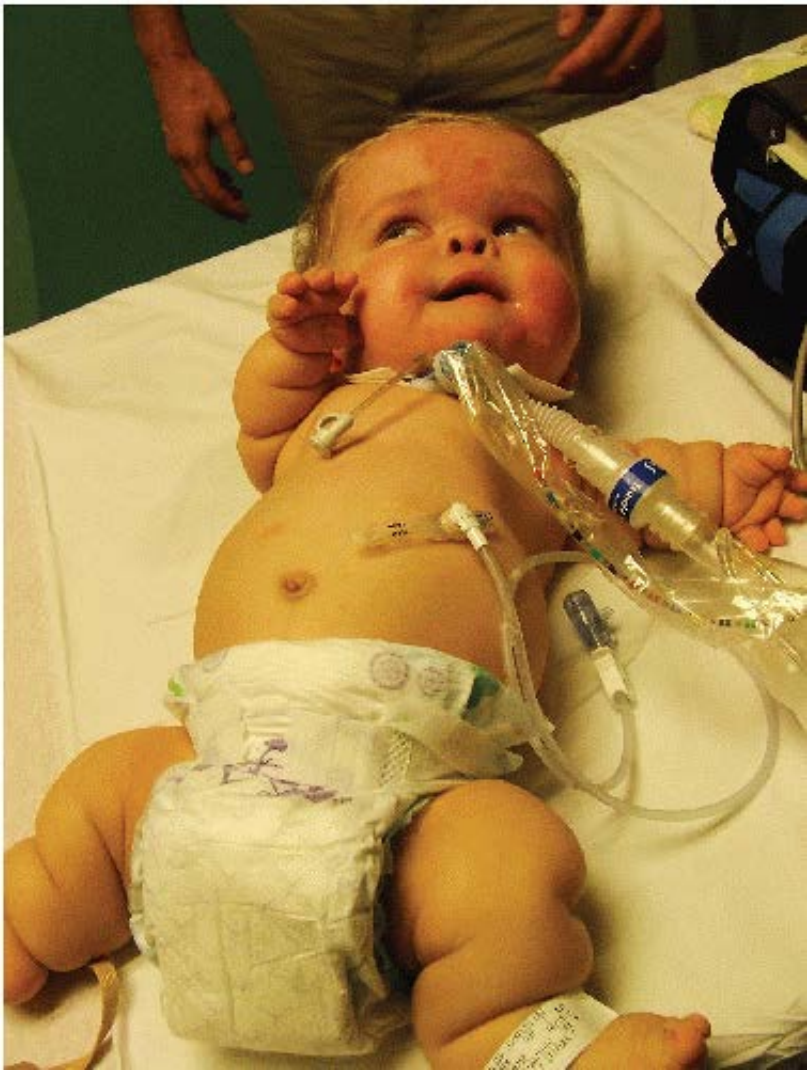
Neuromuscular: Brainstem compression from stenosis at the foramen magnum can be lethal. Megalencephaly. Temporal lobe dysplasia. Profound hypotonia and intellectual disabilities if patient survives.

Orthopedic: Very short ribs and bones of the extremities at birth. Short, bowed legs (type I). Thin femurs likened to “French telephone receivers” with irregular, flared metaphyses. Marked platyspondyly with widened intervertebral spaces. No caudal narrowing of the spinal canal. Small iliac bones.

Other: Acanthosis nigricans. Polyhydramnios.

Miscellaneous: Acanthosis nigricans also occurs in Crouzon syndrome, similarly caused by defects in *FGFR3*. The term thanatophoric is derived from a Greek word meaning “bearing death,” as infants with thanatophoric dysplasia are usually stillborn or die in the neonatal period.

Anesthetic Considerations: Patients require careful perioperative positioning and padding secondary to orthopedic abnormalities (1). Peripheral venous access may be difficult. Intraoperative neuromonitoring has proven beneficial in a case of foramen magnum stenosis (1).



Thanatophoric dwarfism. This 11 ½-month-old boy with type I disease has slight developmental delay and is being weaned from his tracheostomy.

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Thanatotrophic dysplasia

See Thanatophoric dwarfism

Thomsen disease

See Myotonia congenita

Thomsen-type myotonia congenita

See Myotonia congenita

Thoracic-pelvic-phalangeal dystrophy

See Jeune syndrome

Thoracoabdominal syndrome

See Pentalogy of Cantrell

Thrombocytopenia-absent radius syndrome

Synonym: TAR syndrome

MIM #: 274000

This autosomal recessive disorder is distinct from the somewhat similar Fanconi anemia (see earlier). Thrombocytopenia is worst in infancy and can be precipitated by viral illness. Adults usually have no problems except menorrhagia. Most cases are due to compound heterozygosity of the gene *RBM8A*.

HEENT/Airway: Brachycephaly. Port-wine stain of forehead. Strabismus, ptosis. Small, upturned nose. Epistaxis. Can have cleft palate. Can have micrognathia.

Cardiovascular: Congenital heart disease, most commonly tetralogy of Fallot, coarctation, or atrial septal defect.

Neuromuscular: Can have sequelae of intracranial hemorrhage. Can have hypoplastic arm or shoulder musculature.

Orthopedic: All have bilateral absence of radii. Hypoplasia or unilateral or bilateral absence of ulnae. Despite radial abnormality, thumb always present. Abnormal humerus or shoulder. Short stature. Dislocated hips, subluxation of knees, coxa valga, dislocated patella, femoral and tibial torsion, ankylosis of knee, small feet, abnormal toe placement, nonpitting edema of the dorsum of the foot in neonates. Small stature. Arthritis of the ankles and knees. Can have spina bifida.

GI/GU: Pancreatic cysts, Meckel's diverticulum, hepatosplenomegaly. Renal anomalies including malrotation of the kidney.

Other: Thrombocytopenia at birth with diminished or absent megakaryocytes, eosinophilia, anemia, hypogammaglobulinemia. Seborrheic dermatitis, excessive sweating. Cow's milk allergy is common and can precipitate thrombocytopenia, eosinophilia, or leukemoid reaction. Rare acute leukemia.

Anesthetic Considerations: The platelet count and hematocrit must be evaluated preoperatively. Patients may require perioperative platelet transfusions. Nasotracheal and nasogastric tubes are relatively contraindicated secondary to the risk of epistaxis. Limb anomalies may make vascular access more challenging and might require careful positioning. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Thurston syndrome

Included in Oral-facial-digital syndrome, type I

Tibial aplasia-ectrodactyly syndrome

MIM #: 119100

This is an autosomal dominant disorder with wide clinical variability. The responsible gene and gene product are unknown. Two types, types 1 and 2, map to different chromosomes. The disorder has as its principal manifestations ectrodactyly (“lobster claw” deformity of the hand) and absence of the long bones of the arms and legs.

HEENT/Airway: Cup-shaped ears.

Chest: Bifid xiphoid.

Orthopedic: Ectrodactyly of the hand (“lobster claw” or “split” hand), also of the feet. Proximally placed thumbs, absent middle finger, syndactyly. Absence of fingers, tarsals, metatarsals, and toes. Extra preaxial digit. Absence of the long bones of the extremities, most commonly tibial aplasia or hypoplasia, also fibular or femoral aplasia or hypoplasia, and aplasia of the radius, ulna, or humerus. Aplasia of the patella.

Miscellaneous: A patient with this syndrome was described by Ambroise Paré, the great surgeon, in 1575.

Anesthetic Considerations: Limb abnormalities can complicate vascular access, particularly in infants.

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Timothy syndrome

Included in Long QT syndrome

Toriello-Carey syndrome

MIM #: 217980

The inheritance pattern for this dysmorphic syndrome remains uncertain. It is likely autosomal recessive, and the responsible gene and gene product are not currently known. It may represent a syndrome of midline structures—primarily affecting the face, brain, and heart. Death in early infancy can occur.

HEENT/Airway: Macrocephaly. Telecanthus, short palpebral fissures. Abnormally shaped ears. Small nose with anteverted nostrils. Pierre Robin sequence, cleft palate, micrognathia. Laryngeal abnormalities. Redundant neck skin.

Chest: Congenital tracheal stenosis has been described.

Cardiovascular: Congenital cardiac disease.

Neuromuscular: Agenesis of the corpus callosum. Hypotonia. Developmental delay. May have seizures.

Orthopedic: Short hands.

GI/GU: Anteriorly placed anus has been reported, as has a case with gastrointestinal dysmotility. Two cases have

been reported with pancreatic insufficiency.

Other: Postnatal growth retardation.

Anesthetic Considerations: Laryngoscopy and intubation can be extremely difficult in these patients with (sometimes severe) micrognathia and laryngeal abnormalities. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Toulouse-Lautrec Disease

See Pyknodysostosis

Touraine-Solente-Golé syndrome

See Pachydermoperiostosis syndrome

Tourette syndrome

Synonym: Gilles de la Tourette syndrome

MIM #: 137580

This neurologic condition, occurring primarily in male patients, is characterized by motor and vocal tics with behavioral abnormalities. Onset is usually between 2 and 14 years of age, and about 10% of cases are familial. It is likely that the disease is mild in many people and does not come to medical attention. In 1885, de la Tourette noted that there were mildly affected family members of classically affected patients. The disorder can be due to mutations in several genes. It is thought that the underlying defect might be related to an abnormality of the dopaminergic system with disinhibition of the limbic system. This condition is most frequently treated with haloperidol and dopamine antagonists. There is a 4:1 male:female predominance.

Neuromuscular: The disease begins with involuntary tic-like movements. These can include blinking, facial grimaces, shoulder shrugging, and head jerking. There can be complex sequences of coordinated motions, including bizarre gait, jumping, kicking, body gyrations, and seductive or obscene gestures. The tics wax and wane, and there is an irresistible urge before the tics, followed by relief after it. They may be temporarily suppressed. With progression, there may be echolalia, grunting, coprolalia (verbalized obscenities), palilalia (repetition of a word or phrase more and more rapidly), and self-mutilation with aggressive or obsessive-

compulsive behavior. Boys usually have more motor and vocal symptoms, whereas girls tend to have more obsessive-compulsive behavioral manifestations. A significant number of patients also have sleep disorders, and tics can occur during sleep. Sleep disorders include restlessness, insomnia, enuresis, sleep-walking, nightmares, and bruxism.

Miscellaneous: Coprolalia, although the most noted symptom in the popular media, is relatively uncommon (approximately 8% of patients). It has been suggested that Samuel Johnson, the lexicographer, had Tourette syndrome. It has also been suggested that Mozart had Tourette syndrome, which would explain his predilection for cursing and his interest in nonsense words.

De la Tourette, a French neurologist, never saw the first patient he described (7). His interest in the area was raised by international interest in Beard's report of the Jumping Frenchmen of Maine. The first Tourette patient, the Marquise de Dampierre, was 26 years of age when she was reported by Itard in 1825 (“the case of the cursing marquise”). In 1885, de la Tourette selected her case as the paradigm of the syndrome. The syndrome

was immediately named in honor of Tourette by his boss and mentor, the preeminent French neurologist of his day, Charcot, who was categorizing neurologic syndromes. De la Tourette differentiated this disorder from Sydenham and other choreas. Charcot preferred the euphonious eponym “Gilles de la Tourette syndrome,” over using the last name only. Late in his career, de la Tourette was shot in the head in his consulting room by a distraught patient. Subsequently, his behavior became increasingly erratic, and he was confined to a mental hospital, where he died in 1904.

Anesthetic Considerations: The fear of losing control when confronted with a stressful situation (anesthesia and surgery) is of concern to many patients and their families. Time needs to be taken to discuss the anesthetic experience with patients, allow them to convey their specific concerns, and assure them that the anesthesia and operating teams are not uncomfortable with the patient's condition and are willing to tailor their approach to the patient's specific concerns. Midazolam has been reported to inhibit tics (4).

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Townes-Brocks syndrome

MIM #: 107480

This autosomal dominant dysmorphic syndrome is due to an abnormality of the *SALL1* gene, which encodes a transcription factor. There is significant clinical variability. Primary manifestations involve the external ear, the digits, and the anus.

HEENT/Airway: Microcephaly. Facial asymmetry. External ear anomalies including pointed upper pinna ("satyr ear") and occasional deafness. May have retrognathia. Obstructive apnea and severe dysphagia have been reported.

Cardiovascular: Cardiac defects.

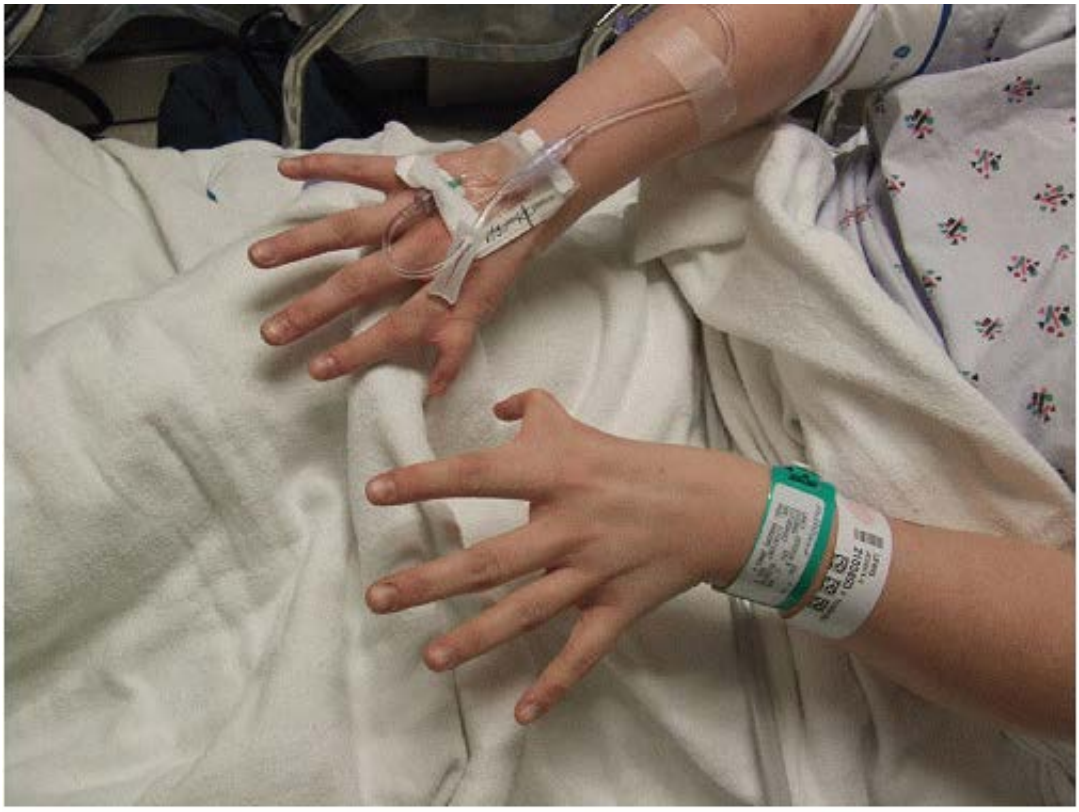
Townes-Brocks syndrome. FIG. 1. This 24-year-old young woman has had prior surgery for tetralogy of Fallot. She has an asymmetric face when smiling or talking and has bilateral microtia.

Neuromuscular: Rare intellectual disability.

Orthopedic: Hypoplastic, broad, bifid thumbs, or triphalangeal thumbs. Preaxial polydactyly. Fusion of hand bones. Absent or hypoplastic third toe. Clinodactyly of fifth finger. Syndactyly of fingers and toes.

GI/GU: Stenotic, imperforate, or malplaced anus. Rectovaginal or rectoperineal fistula. Bifid uterus. Dysphagia, duodenal atresia. Renal hypoplasia, urethral valves, vesicoureteral reflux, hypospadias, cryptorchidism. Can progress to chronic renal insufficiency.

Other: Rare congenital hypothyroidism. One case with growth hormone deficiency has been described.



Townes-Brocks syndrome. FIG. 2. Her bilaterally abnormal thumbs are apparent.

Miscellaneous: In at least one species, and probably more, the homologous gene is regulated by the gene *sonic hedgehog*.

Anesthetic Considerations: Baseline renal function should be assessed. Hand abnormalities may complicate vascular access. Patients with congenital heart disease should receive an appropriately tailored anesthetic. One

child has been reported who was difficult to intubate at birth and 6 months of age, improved somewhat by age 11 months, and was not difficult thereafter (2).

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Transcobalamin II deficiency

MIM #: 275350

Transcobalamin II is the major plasma transport protein for vitamin B_{12} Its absence results in early and severe megaloblastic anemia. This autosomal recessive disease is due to a defect in the gene *TCN2* (*TC2*). There are several alleles. Transcobalamin II and intrinsic factor are required for the transport of B_{12} from the gut to the bloodstream. Serum cobalamin levels are normal, and circulating B_{12} attaches instead to the R binder protein, whose function is not known. Patients are treated with supplemental cobalamin and sometimes also with folate.

Neuromuscular: Can be neurologically normal or can have delayed intellectual development, ataxia, and pyramidal tract signs if untreated.

GI/GU: Diarrhea, vomiting, atrophy of intestinal mucosa, ulcerative stomatitis, intestinal disaccharidase deficiency.

Other: Neonatal failure to thrive. Hematologic disease consists of megaloblastic anemia, neutropenia, thrombocytopenia, and bleeding diathesis. Agammaglobulinemia and inadequate antibody response to antigens. Normal cellular immunity. Severe infections.

Anesthetic Considerations: The hematocrit must be evaluated preoperatively. Meticulous aseptic technique is indicated in patients with immune deficiency. Nitrous oxide should be avoided because it irreversibly inactivates B_{12} by oxidizing its cobalt moiety and in addition inactivates the B_{12}-dependent enzyme methionine synthetase.

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Trapezoidocephaly-synostosis syndrome

See Antley-Bixler syndrome

Treacher Collins syndrome

Synonym: Mandibulofacial dysostosis; Franceschetti-Klein syndrome

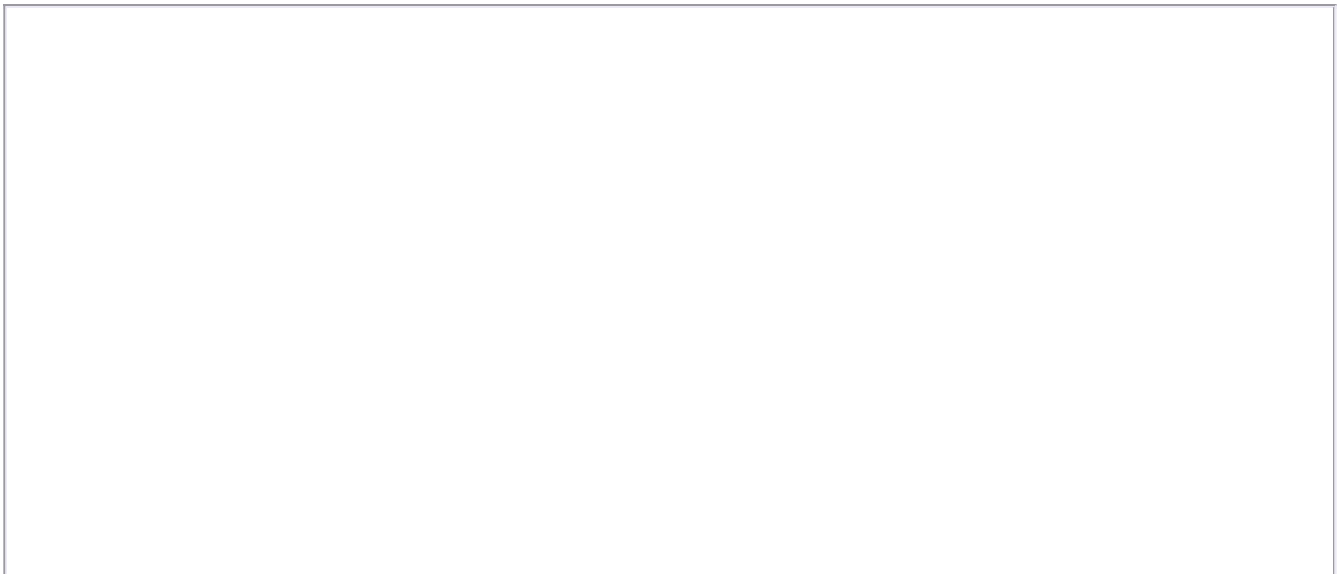
MIM #: 154500

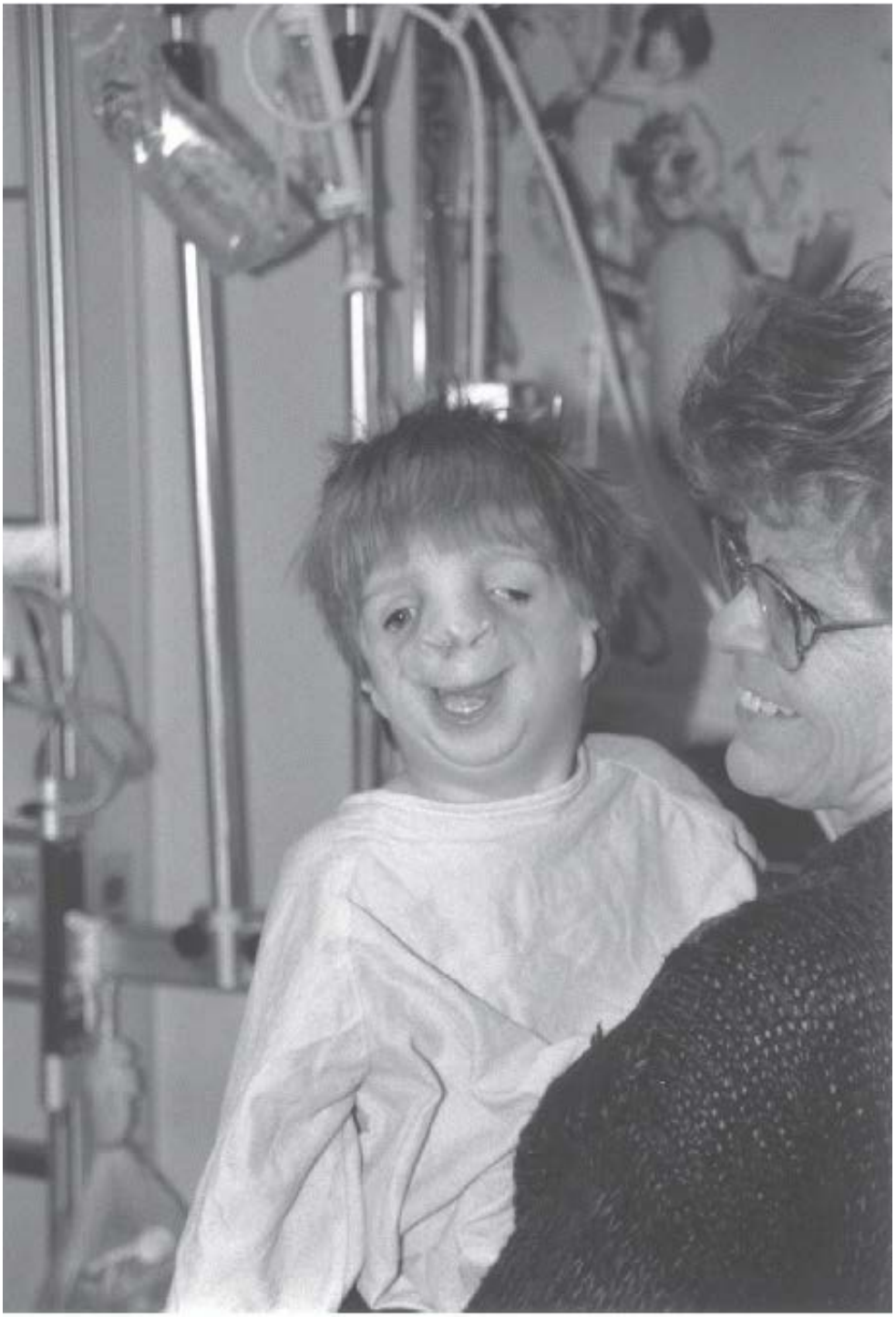
Treacher Collins syndrome is an autosomal dominant disorder, although most cases represent fresh mutations. There is significant clinical variability even within families. The involved gene has been sequenced and has been named both *TCOF1* and *treacle*. The encoded protein plays a critical role during ribosome biogenesis in cranial neural crest cells. There are two additional uncommon variants, Treacher Collins syndrome 2 and 3, due to mutations in the genes *POLR1D* and *POLR1C*, respectively.

The major manifestations include malar hypoplasia, downslanting palpebral fissures, colobomas of the lower eyelid, external ear abnormalities often involving hearing loss, and mandibular and pharyngeal hypoplasia. Patients commonly come to the operating room for plastic surgery.

HEENT/Airway: Hypoplasia of the malar bones with or without cleft zygoma. Scalp hair spreading onto the cheek. Downsloping palpebral fissures, coloboma of the lower lid, partial to complete absence of the lower eyelashes, visual loss, microphthalmia. Low-set ears, often with atresia of the external canal and conductive deafness, preauricular blind fistulae. Absent parotid gland. Small mouth. High-arched palate, cleft lip or palate. Malocclusion of the teeth. Mandibular hypoplasia. Flat coronoid and condyloid processes. Obstructive sleep apnea is common. Narrow airway due to pharyngeal hypoplasia, which can cause respiratory distress and necessitate a tracheostomy.

Cardiovascular: Can have congenital cardiac defect.





Treacher Collins syndrome. FIG. 1. This 3-year-old boy has had a cleft lip repaired but still has a cleft palate. He has bone conduction hearing and wears hearing aids on his mastoids. He has some speech. An experienced pediatric anesthesiologist had not been able to intubate his trachea previously. The current general anesthetic, for dental surgery, was done easily with a laryngeal mask airway.

Neuromuscular: Intelligence is usually normal.

GI/GU: Occasional cryptorchidism.

Miscellaneous: Edward Treacher Collins was one person, a British ophthalmologist. He used his mother's maiden name and his paternal family's name without a hyphen. Because Treacher Collins was one person, the syndrome is correctly Treacher Collins syndrome, not Treacher-Collins syndrome. On the other hand, the syndrome was, in fact, first described by Toynbee.

Anesthetic Considerations: Direct laryngoscopy and tracheal intubation may be extremely difficult or impossible secondary to severe mandibular hypoplasia, a small mouth, and a narrow airway. On occasion, laryngoscopy may obstruct an otherwise patent airway. Laryngoscopy often becomes more difficult with aging (2). Multiple papers have reported on the successful use of a variety of fiberoptic and video laryngoscopes, the lightwand, and other airway devices. Laryngeal mask airways have been used successfully (2,4,6,8) and have proven particularly useful (2). Spontaneous ventilation may be improved by placing the patient prone so that the tongue does not fall posteriorly into the pharynx. In one small series, mandibular distraction surgery did not improve the laryngeal view (1). The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period.

Treacher Collins syndrome. FIG. 2. Lateral view of the boy in Fig. 1, showing external ear deformity.

Although patients may appear extremely dysmorphic, intelligence is usually normal. When talking with the patient, remember that he or she may have some hearing loss. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Trichodentoosseous syndrome

MIM #: 190320

This autosomal dominant disorder is marked by kinky hair, enamel hypoplasia, and sclerotic bone. There appears to be abnormal synthesis of both keratin and enamel. The disorder is due to mutations in *DLX3*, the distal-less

homeobox 3 gene. It has been suggested that there are two types of trichodentoosseous syndrome. Type II additionally includes microcephaly, obliterated mastoids and frontal sinuses, and thickened calvarium, with normal enamel and long bone density.

HEENT/Airway: Dolichocephaly, partial craniosynostosis with dolichocephaly, thickened calvarium. Obliteration of calvarial diploic space. Poorly pneumatized mastoids. Narrow external ear canals. Small, widely spaced teeth. Teeth have enlarged pulp chamber size [taurodontism (*tauro* = bull)], increased dental caries. Poor enamel. Teeth often become abscessed and are lost by the third decade. Square jaw.

Orthopedic: Increased bone density of the skull, long bones, and spine. Brittle nails with peeling of nails.

Other: Hair is kinky at birth, but may straighten with age.

Anesthetic Considerations: Teeth are prone to premature loss. Dental abnormalities should be documented preoperatively, and extreme care should be exercised during laryngoscopy.

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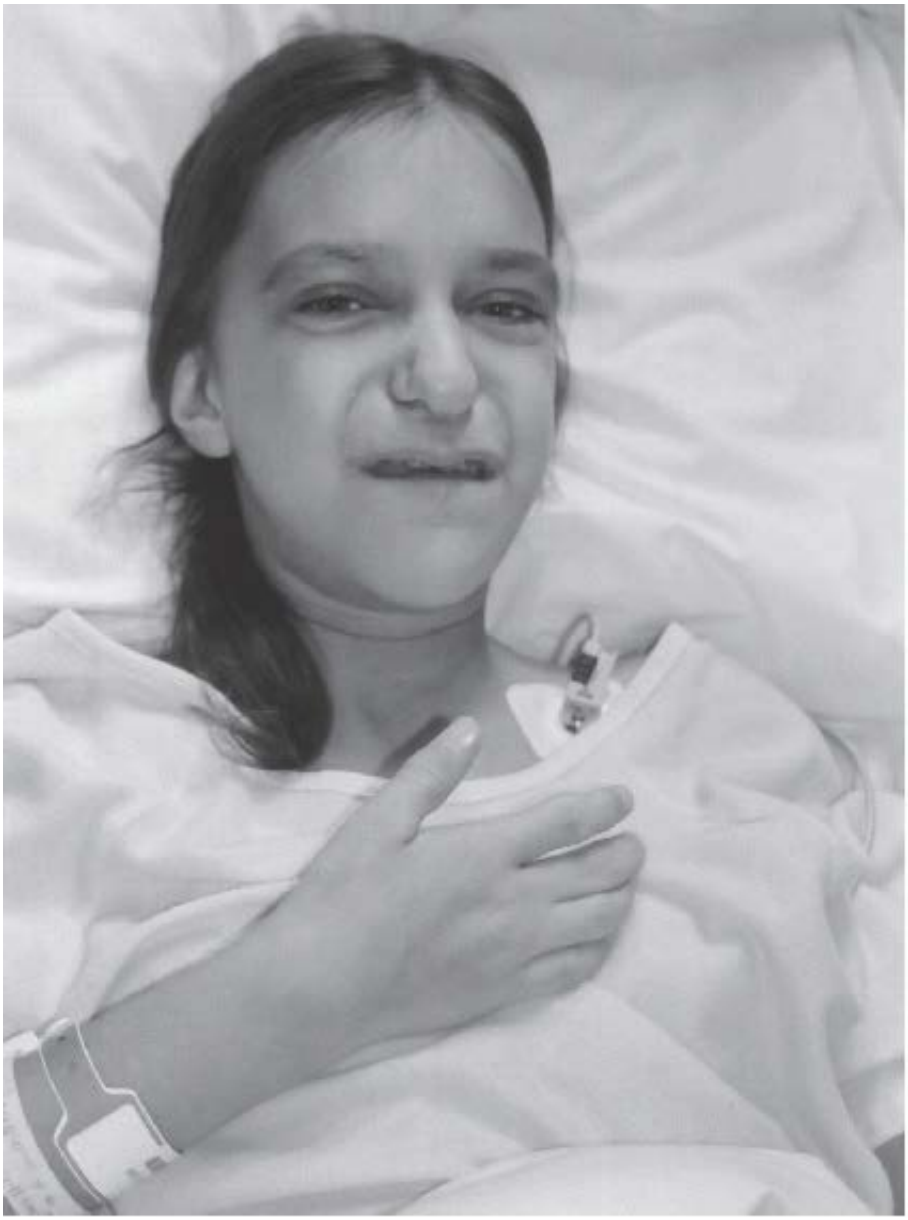
Trichorhinophalangeal syndrome, type I

(Includes Trichorhinophalangeal syndrome, type III)

MIM #: 190350

Features of this autosomal dominant syndrome include characteristic facies with a bulbous nose and cone-shaped epiphyses. It is due to mutations in the gene *TRPS1*, which encodes a putative transcription factor. Langer-Giedion syndrome (see earlier), also known as trichorhinophalangeal syndrome, type II, is due to a deletion of at least two genes in the same area, including *TRPS1*. **Trichorhinophalangeal syndrome, type III** (*MIM #:* 190351), also due to mutations in *TRPS1*, has as additional features brachydactyly and profound short stature.



Trichorhinophalangeal syndrome, type I. This 14-year-old girl with trichorhinophalangeal syndrome, type I has poor dentition, thin hair and a bulbous nose. Her chin groove is not well seen in this figure. She has multiple bone spurs.

HEENT/Airway: Can have craniosynostosis. Protruding ears. Bulbous nose. Long, prominent philtrum. High-arched palate. Thin upper lip. Abnormal dentition with caries. Delayed tooth eruption. Can have micrognathia. Horizontal groove on chin. Deep voice.

Chest: Can have recurrent upper respiratory tract infections. Can have pectus carinatum.

Neuromuscular: Rare intellectual disability, hypotonia in infancy.

Orthopedic: Mild growth deficiency. Cone-shaped epiphyses after age 2 years. Wide middle phalangeal joint with short metacarpals and metatarsals. Hypoplastic nails. Split distal radial epiphyses. Premature degenerative hip

disease. Winged scapulae. Scoliosis. Lordosis. Can have hyperextensible joints. Late-onset osteopenia, arthralgias, and osteoarthritis. Type III disease has brachydactyly with short metacarpals and very short stature.

Other: Thin, sparse, relatively hypopigmented hair. Eyebrows thin laterally. Thin nails.

Miscellaneous: *TRPS1* is overexpressed in breast cancer cells.

Anesthetic Considerations: Can have recurrent upper respiratory tract infections, which may lead to cancellation of elective cases. Direct laryngoscopy and endotracheal intubation may be difficult secondary to micrognathia. Abnormal dentition may be more easily injured during laryngoscopy. Patients who have hyperextensible joints must be carefully positioned perioperatively.

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Trichorhinophalangeal syndrome, type II

See Langer-Giedion syndrome

Trifunctional protein deficiency

See Mitochondrial trifunctional protein deficiency

Triose phosphate isomerase deficiency

MIM #: 190450

This disease, inherited in an autosomal dominant fashion, is due to a deficiency of triose phosphate isomerase. There are several alleles. Triose phosphate isomerase catalyzes the interconversion of dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, a step in the glycolytic pathway. This enzyme is present in all tissues, and deficiency of the enzyme results in multisystem disease, unlike other enzyme defects of this pathway, which result in purely or primarily red blood cell hemolysis.

Cardiovascular: Sudden cardiac death, presumably secondary to arrhythmia.

Neuromuscular: Intelligence is usually normal. Weakness, hypotonia, absent limb reflexes, spasticity, myopathy, and unintelligible speech. Lower motor neuron involvement, as well as pyramidal tract signs, tremor, dystonia, and dyskinesia from brainstem and basal ganglia involvement. Normal sensation.

Orthopedic: Fixed deformities of the hands and legs.

GI/GU: Splenomegaly. Cholelithiasis, cholecystitis.

Other: Moderately severe nonspherocytic hemolytic anemia. Neonatal hyperbilirubinemia. Increased susceptibility to infection. Hemolytic episodes precipitated by infections. Anemia in the chronic stage is generally mild. Sudden death without obvious cause.

Anesthetic Considerations: The hematocrit should be evaluated preoperatively. Metoclopramide can lead to extrapyramidal effects and probably should be avoided. Phenothiazines, butyrophenones, and other dopaminergic blockers may exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects. Succinylcholine may be contraindicated in this disease with pronounced lower motor neuron involvement because of the risk of an exaggerated hyperkalemic response. Patients are at risk for sudden death, presumably secondary to arrhythmia.

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Trismus-pseudocamptodactyly syndrome

See Dutch-Kentucky syndrome

Trisomy 3p

MIM #: None

This disorder involves trisomy of a portion of the short arm of chromosome 3. It can be acquired as part of a balanced parental translocation or can arise *de novo*. Most patients die within the first few years of life.

HEENT/Airway: Brachycephaly, asymmetric skull with frontal bossing. Flat occiput. Epicanthal folds, hypertelorism. Iris coloboma, microphthalmia, down-slanting palpebral fissures. Low-set ears. Small nose, depressed nasal bridge. Choanal atresia. Cleft lip or palate. Short neck.

Cardiovascular: Can have congenital heart defects.

Neuromuscular: Developmental delay. Holoprosencephaly. Hypotonia. Febrile seizures.

Orthopedic: Short hands and feet, camptodactyly, excessive fingerprint whirls. Hemivertebrae.

GI/GU: Can have esophageal or colonic/anal atresia. Hypoplastic genitalia.

Anesthetic Considerations: Despite the facial features and short neck, a difficult airway was not a problem in the single case reported. That child did, however, require an endotracheal tube two sizes smaller than predicted for age because of a narrow glottis (1). Choanal atresia precludes placement of a nasal airway, nasal intubation, or placement of a nasogastric tube. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Trisomy 4p

MIM #: None

This disorder involves trisomy of the short arm of chromosome 4. All affected people have severe intellectual disabilities. The specific findings depend on the specific chromosome section that is duplicated.

HEENT/Airway: Microcephaly, small, flat forehead, prominent supraorbital ridges, eyebrows meet in midline (synophrys). Microphthalmia, uveal colobomas. Enlarged ears, thickened helix and antihelix. Flat nasal bridge. Cleft lip or palate, macroglossia, pointed chin. Irregular teeth, small, poor dentition. Pointed mandible, short neck.

Chest: Absent or additional ribs. Respiratory problems as a complication of feeding problems. Broad chest with aging. Widely spaced nipples.

Cardiovascular: May have cardiac defects.

Neuromuscular: Moderate to most likely severe intellectual disabilities. Severe language delay. Behavioral problems. Hypertonic during infancy, then hypotonic. Seizures. Absence of corpus callosum.

Orthopedic: Prenatal-onset growth deficiency. Clinodactyly of fifth finger, camptodactyly, preaxial polydactyly, hypoplastic nails. Congenitally dislocated hips, clubfoot deformity, syndactyly of second and third toes. Prominent heel. Kyphoscoliosis, vertebral anomalies, joint contractures. Stiff, unsteady gait.

Trisomy 4p. A 6-month-old, 4.8-kg infant with trisomy 4p. The very puffy hands with redundant skin made venous access in the hands impossible.

GI/GU: Micropenis, cryptorchidism, hypospadias.

Other: Tend to be overweight. Puffy hands with redundant skin.

Anesthetic Considerations: Severe intellectual disabilities or behavioral problems make the smooth induction of anesthesia a challenge. Teeth should be assessed carefully preoperatively because of the likelihood of poor dentition. The large tongue and short neck might make direct laryngoscopy and tracheal intubation more difficult, particularly in infants. Puffy hands with redundant skin may make venous access difficult. Scoliosis and contractures may make optimal positioning more difficult. Chronic use of anticonvulsant medications may affect

the metabolism of some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Trisomy 8

MIM #: None

Patients with this syndrome are mosaic for trisomy 8/normal, as full trisomy 8 is lethal. There does not seem to be a correlation between the degree of impairment and the percentage of trisomic cells. The major manifestation is variable intellectual disability.

HEENT/Airway: Expressionless face. Strabismus, hypertelorism. Cataracts, corneal opacities. Heterochromia. Prominent, cupped ears with thickened helices, conductive hearing loss. Prominent nares. Everted lower lip, cleft lip, high-arched palate. Micrognathia. Short or webbed neck.

Chest: Widely spaced nipples. Pectus carinatum.

Cardiovascular: Can have cardiac defects.

Neuromuscular: Mild to severe intellectual disability, clumsiness, seizures.

Orthopedic: Variable height, from short to tall. Camptodactyly of fingers and toes, deep creases on palms and soles, simian crease, abnormal nails. Short metacarpals and metatarsals. Dysplastic hips, absent patellas. Vertebral anomalies, scoliosis. Contractures of major joints.

GI/GU: Jejunal duplication, gastric leiomyosarcoma. Renal and ureteral anomalies, cryptorchidism.

Other: Anemia, factor VII deficiency. Mediastinal germ cell tumors. Myelodysplastic syndrome, periodic fever, erythema nodosum. Behçet disease, particularly intestinal disease, has been associated with trisomy 8 and myelodysplastic syndrome.

Miscellaneous: Acquired trisomy 8 is associated with myeloid malignancies and myelodysplastic syndrome.

Anesthetic Considerations: Micrognathia and a short neck may make laryngoscopy and tracheal intubation difficult. Consider evaluating the baseline hematocrit and clotting status. Major joint contractures may make perioperative positioning more difficult. Chronic use of anticonvulsant medications may affect the metabolism of

some anesthetic drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Trisomy 9

MIM #: None

Trisomy 9 can occur as a mosaic or as a partial trisomy (trisomy 9p). The degree and severity of manifestations in mosaics are proportional to the number of cells with trisomy. Patients with the syndrome are typically neurologically devastated. Death often occurs in infancy or young childhood; however, survival into adulthood is occasionally possible.

HEENT/Airway: *Mosaic:* Sloping forehead, narrow bifrontal diameter. Cloverleaf skull (kleeblattschaedel; see earlier). Narrow, upslanting palpebral fissures; microphthalmia; coloboma; absent optic tracts. Corneal clouding. Low-set, posteriorly rotated, misshapen ears. Short, prominent nasal bridge and slit-like nostrils. Prominent upper lip, cleft palate. Micrognathia. Short, webbed neck.

9p: Microcephaly, delayed closure of fontanelles and sutures. Hypertelorism, downslanting palpebral fissures. Cup-shaped ears. Prominent nose. Downturned corner of the mouth, cleft lip or palate. Micrognathia. Webbed neck.

Chest: Narrow chest. Mosaic can have 13 ribs and thoracic vertebrae. One case has been reported with segmental distribution of complete tracheal rings. The authors inferred that this was due to tissue mosaicism.

Cardiovascular: Can have congenital cardiac defects.

Neuromuscular: Severe intellectual disabilities. Poor formation of gyri. Can have cysts of choroid plexus or arachnoid. Midline fusion defect of the cerebellum.

Orthopedic: Mosaic: Growth deficiency, primarily prenatal. Kyphoscoliosis, which can be congenital. Simian crease. Abnormal positioning or function of several joints. Hypoplastic sacrum and pelvis. Nonpitting edema of legs. Hypoplastic toes.

9p: Growth deficiency, primarily postnatal. Kyphoscoliosis, usually developing in adolescence. Short fingers and toes, small nails, clinodactyly of the fifth finger, simian crease. Congenital dislocation of the hip. Clubfoot deformity.

GI/GU: Bile duct proliferation, gastroesophageal reflex. Feeding difficulties. Hypoplastic external genitalia. Cryptorchidism, hypospadias, micropenis. Renal anomalies. Delayed puberty.

Other: Severe failure to thrive.

Anesthetic Considerations: Baseline renal function should be assessed preoperatively. Gastroesophageal reflux is common, and patients are at increased risk for perioperative aspiration. Micrognathia and short neck may make direct laryngoscopy and tracheal intubation difficult. Perioperative positioning may be complicated by abnormal joints and kyphoscoliosis. Patients with congenital heart disease should receive an appropriately tailored

anesthetic.

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Trisomy 13

Synonym: Patau syndrome

MIM #: None

This syndrome is caused by trisomy of all or a large part of chromosome 13. Those affected have multiple craniofacial, cardiac, neurologic, and renal anomalies. Life expectancy is limited. Ninety-five percent die within the first 6 months. Five to six percent survive to age one or older, and survival to over 5 years of age has been reported. Survival is somewhat better for girls and blacks. Clinical manifestations are variable in patients who are mosaics or who are trisomic for only part of the chromosome, and survival is generally longer in these patients.

HEENT/Airway: There is a characteristic occipital scalp defect. Microcephaly, wide sagittal suture and fontanelles. Capillary hemangioma of the forehead. Microphthalmia, anophthalmia, cyclopia, iris coloboma, hypertelorism, cataracts, retinal dysplasia and optic nerve hypoplasia, limited vision. Low-set ears, abnormal helices, deafness (probably defects in organ of Corti). Broad, flat nose. Cleft lip, cleft palate, cleft tongue. Micrognathia. Loose skin over posterior neck.

Chest: Pectus carinatum or short, barrel chest can develop in older children. Thin posterior ribs; may have missing ribs.

Cardiovascular: Over 80% have cardiac anomalies of a variety of types. The most common are ventricular septal defect, tetralogy of Fallot, and double-outlet right ventricle. Calcified pulmonary arterioles.

Trisomy 13. An infant with trisomy 13. The string from her mouth is attached to a retainer to aid in bottle feeding. She has required surgical repair of a cleft lip and palate and placement of a gastrostomy tube. She began to crawl at age 5 years.

Neuromuscular: Apneic episodes in infancy are common. Holoprosencephaly with agenesis of the corpus callosum, absent olfactory nerves, cerebellar hypoplasia. Meningocele, meningomyelocele, other neural tube defects. Severe intellectual disabilities, sometimes with seizures.

Orthopedic: Polydactyly, flexion deformities of the hands, retroflexible thumb, simian crease, camptodactyly, syndactyly. Can have radial aplasia. Prominent heel, rocker-bottom feet, clubfoot deformity. Thoracic kyphoscoliosis. Joint subluxation can develop in older children.

GI/GU: Inguinal and umbilical hernias common. Malrotation, omphalocele, large gallbladder, Meckel's diverticulum. Microscopic pancreatic dysplasia is a specific finding of trisomy 13. Somatic trisomy 13 has been reported in hepatoblastoma, and hepatoblastoma has been reported in two 15-month-old children. Most patients have renal anomalies, including unilateral renal agenesis, renal and urogenital duplication, hydronephrosis, and polycystic kidneys. Cryptorchidism, abnormal scrotum, hypospadias, bicornuate uterus, hypoplastic ovaries, abnormal insertion of fallopian tubes.

Other: Multiple capillary hemangiomas. High persistent levels of fetal hemoglobin.

Miscellaneous: Probably first described by Bartholin in 1657; Patau recognized the syndrome to be due to a trisomy.

Anesthetic Considerations: The short neck, small mouth, and micrognathia can make direct laryngoscopy and

tracheal intubation difficult, and a “cannot intubate” scenario has been reported. Patients are at risk for perioperative apnea and must be monitored closely for respiratory adequacy. Radial anomalies may make placement of a radial arterial catheter more difficult. Flexion deformities and joint subluxation can make perioperative positioning difficult. The lumbosacral area should be closely examined for cutaneous evidence of an underlying spinal dysraphism prior to caudal or epidural injections. Unexpected subarachnoid entry during attempted caudal anesthesia in a 4-year-old has been reported (2). Patients with renal insufficiency require careful titration of perioperative fluids and careful dosing of renally excreted medications. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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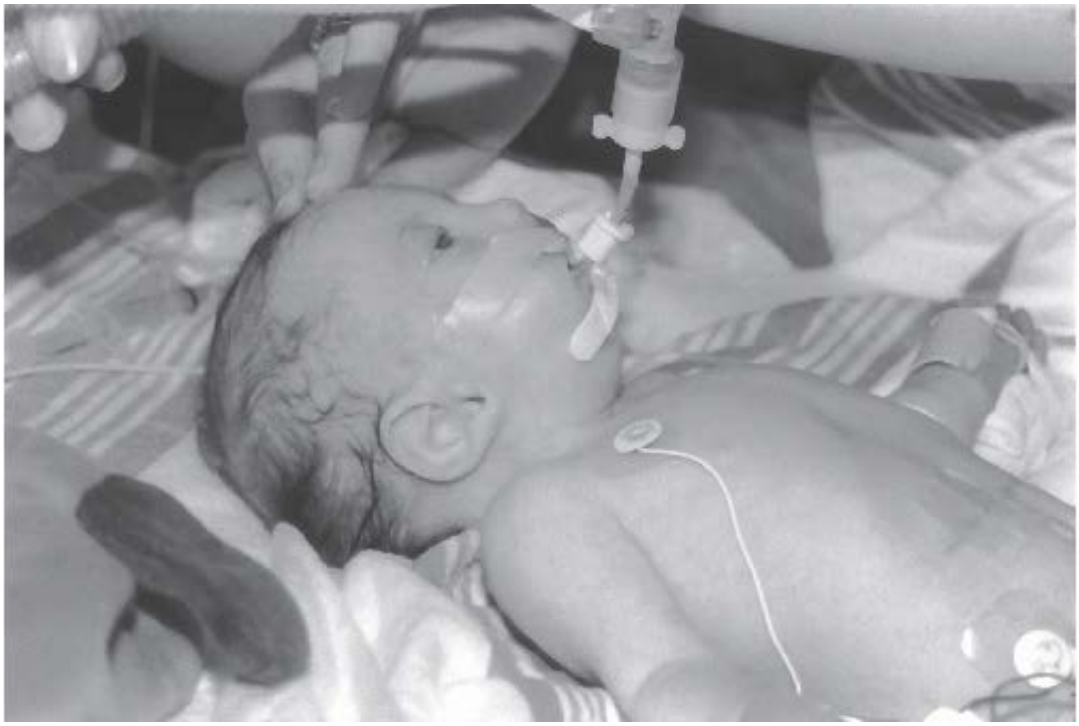
Trisomy 18

Synonym: Edwards syndrome

MIM #: None

This syndrome is caused by trisomy of all or a large part of chromosome 18. Patients characteristically have severe intellectual disability and a limited potential for survival, characteristic clenched hands noted at birth, and a short sternum. This is a relatively common genetic syndrome, with an incidence of 3 per 1000 live births. The risk increases with older maternal age. For unknown reasons (higher intrauterine death rate for boys?), girls outnumber boys by three to one. Most individuals with trisomy 18 die *in utero*. Of those born alive, most need resuscitation at birth and nonetheless die within the first two weeks. Of those born alive, 13% have required surgery in the

neonatal period. Ninety to 95% die within the first year of life. There are reports of survival into adolescence. Longer-term survivors usually have trisomy 18 mosaicism or have only partial trisomy. Trisomy 18 is the second most common autosomal trisomy after trisomy 21.



Trisomy 18. FIG. 1. This 4-month-old with trisomy 18 had surgery for volvulus at another hospital. Cardiac surgery for a ventricular septal defect was refused at that hospital due to the genetic defect. Micrognathia made tracheal intubation difficult, and a fiberoptic intubation was done via a laryngeal mask airway. She weighs 2.6 kg and also has a rectovaginal fistula.

HEENT/Airway: Prominent occiput, narrow cranium. May have microcephaly, large fontanelles. Short palpebral fissures. May have epicanthal folds, ptosis, corneal opacity. Low-set, malformed ears. May have sensorineural hearing loss. Small mouth. High-arched palate. Can have cleft lip or palate. Micrognathia. Upper airway obstruction is common.

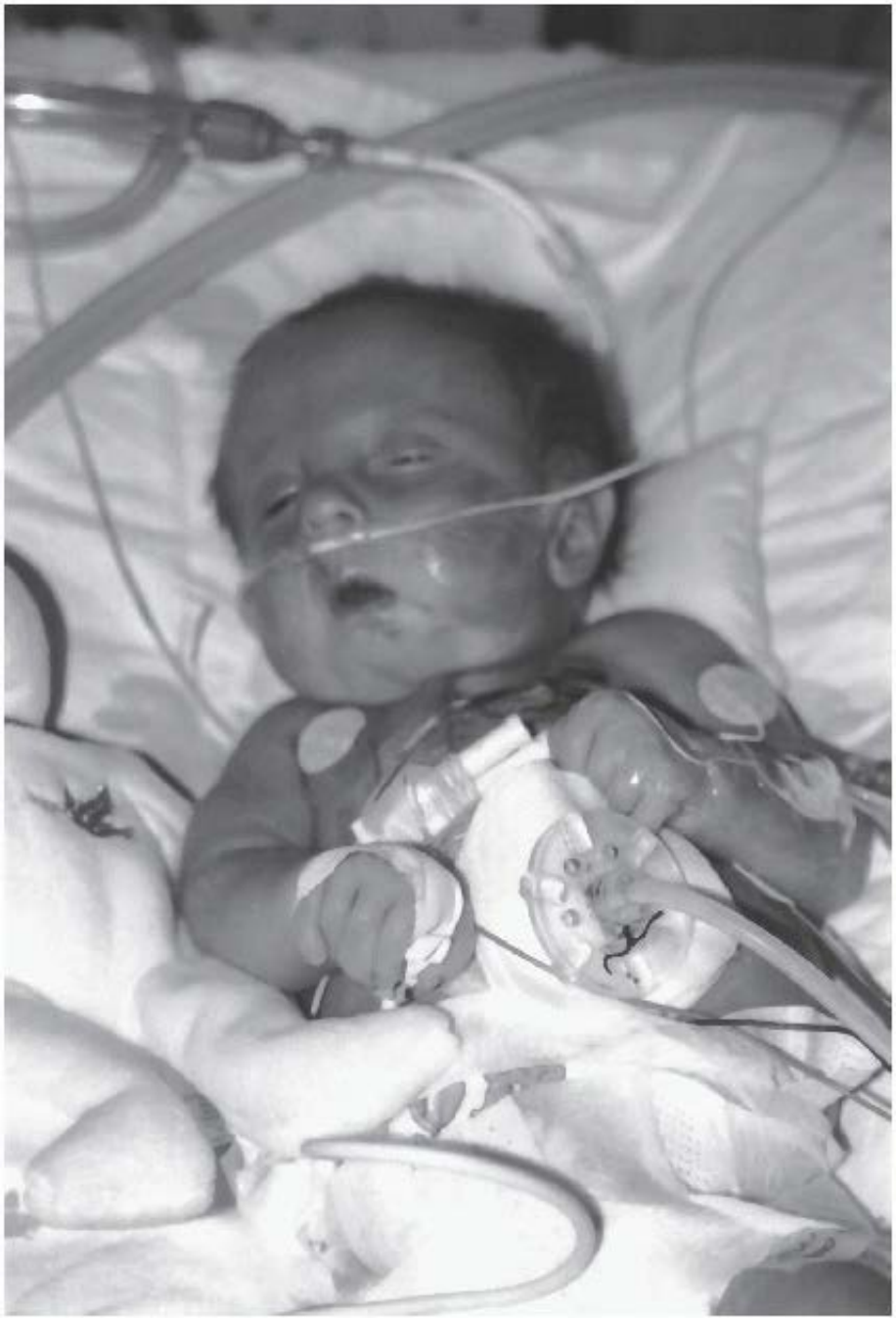
Chest: Short sternum. Can have broad thorax with widely spaced nipples. Occasional diaphragmatic muscle hypoplasia with possible eventration. Can have absence or malformation of the right lung.

Cardiovascular: The incidence of cardiac malformations is >95%. Multiple congenital cardiac lesions are possible, including ventricular septal defect, atrial septal defect, patent ductus arteriosus, bicuspid aortic valve, pulmonic valvular stenosis, and coarctation of the aorta. Can have aberrant subclavian artery. Conduction defects have also been reported.

Neuromuscular: Severe intellectual disability. Weak cry, hypotonia in the neonatal period. Recurrent apnea in the neonatal period. Hypertonia after the neonatal period. Can have holoprosencephaly.

Orthopedic: Characteristic clenched hands at birth, with index finger overlapping the third finger and fifth finger

hypoplastic, or absent thumb. Can have simian crease. Nail hypoplasia. Low-arched dermal ridge pattern on the fingertips. Small, narrow pelvis and limited hip abduction. Can have clubfoot deformity, rocker-bottom feet, syndactyly of the second and third toes. Short stature.



Trisomy 18. FIG. 2. This 1-month-old 2.3-kg infant is mosaic for trisomy 18. She has been operated on for malrotation of the gut.

GI/GU: Feeding problems are common. Inguinal and umbilical hernias are common. Cryptorchidism. Can have omphalocele, Meckel's diverticulum, malrotation, anal anomalies, ectopic pancreatic or splenic tissue. Can have renal anomalies, including ectopic kidney, horseshoe kidney, polycystic kidney, hydronephrosis, duplication of the collecting system.

Other: Failure to thrive. Redundant skin. Cutis marmorata. Decreased muscle mass, subcutaneous tissue, and fat.

Anesthetic Considerations: Neonates are at high risk for perioperative apnea. Direct laryngoscopy and tracheal intubation may be difficult in these patients who have small mouths and micrognathia. Placement of a subclavian intravenous catheter may be contraindicated because an aberrant subclavian artery may be present. Decreased subcutaneous tissue may make perioperative temperature regulation more difficult. Patients with renal insufficiency require careful titration of perioperative fluids and careful dosing of renally excreted drugs. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Trisomy 21

See Down syndrome

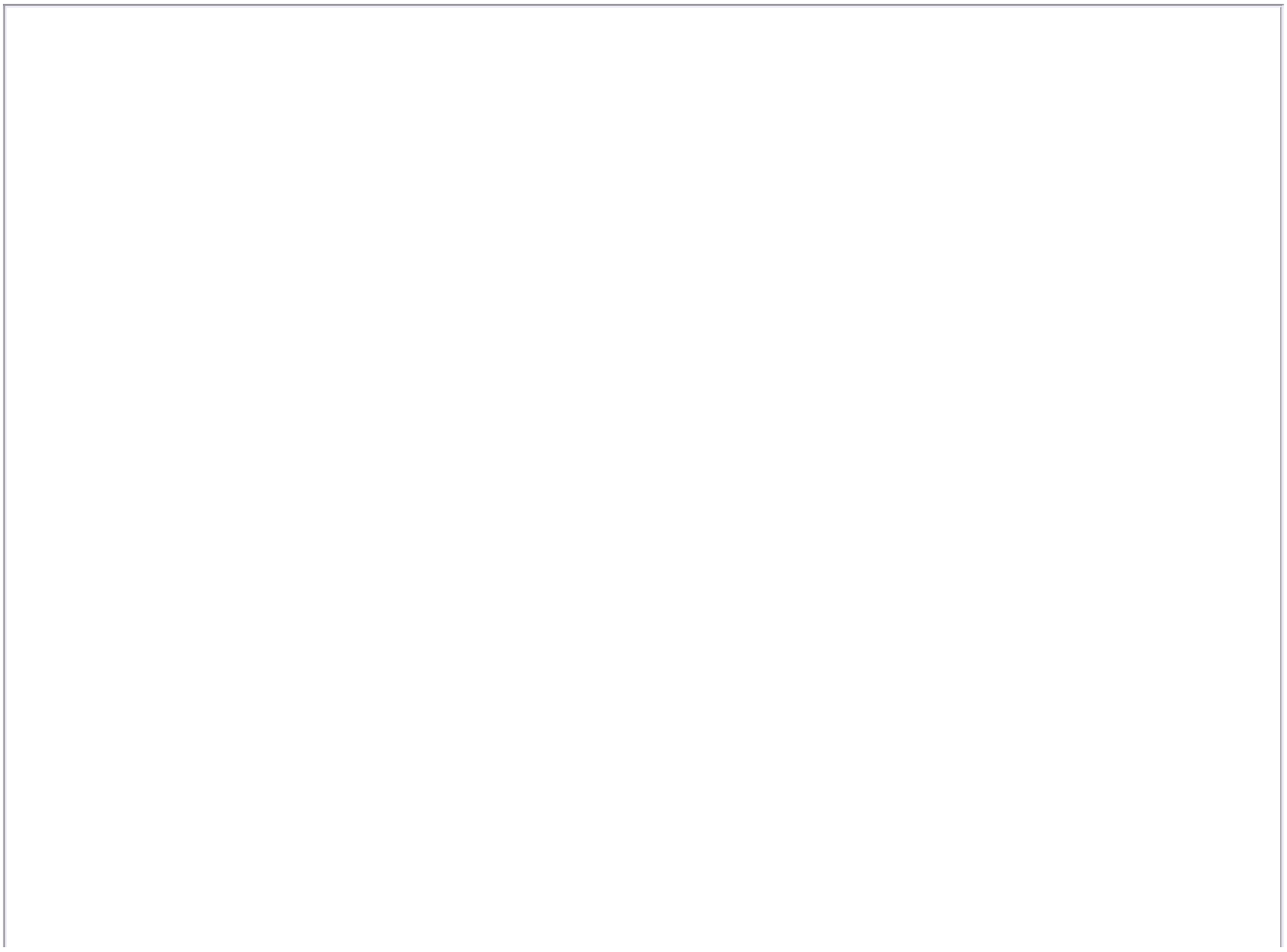
Tuberous sclerosis

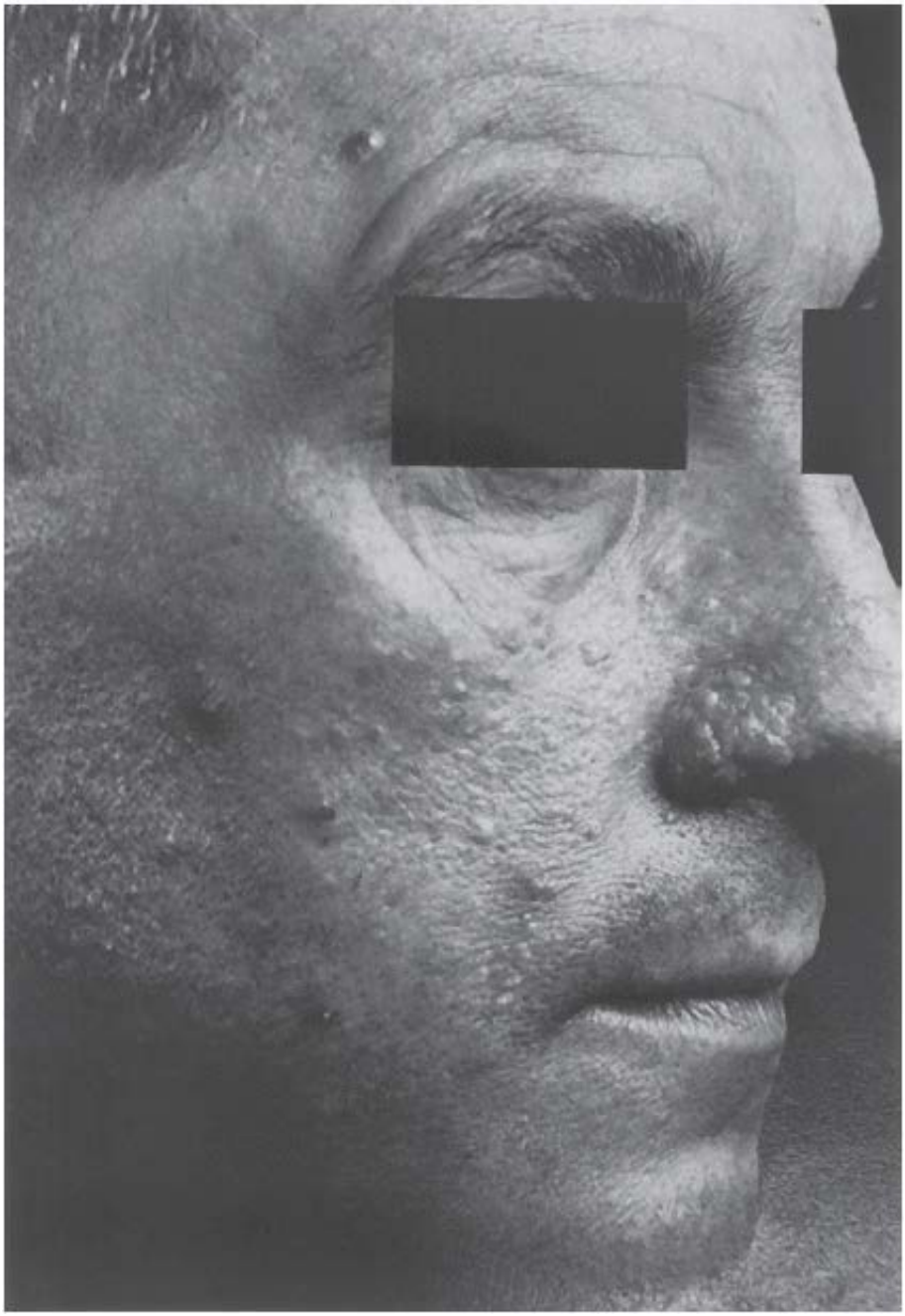
MIM #: 191100

This autosomal dominant disorder is characterized by the classic triad of intellectual disability, seizures, and adenoma sebaceum (fibroangiomas). Tuberous sclerosis is one of the most common autosomal dominant diseases. New mutations are relatively common. There is wide variability in the clinical manifestations, and there is progression of the clinical disease with aging. Abnormalities in two genes, *TSC1* and *TSC2*, which encode hamartin and tuberin, can cause the syndrome. In general, abnormalities in *TSC2* result in more severe disease. The *TSC1-TSC2* complex normally inhibits the activity of the gene *mTOR* ("mammalian target of rapamycin"). Lack of inhibition leads to the growth of a variety of tumors. Because of this, sirolimus (rapamycin) has been suggested as a potential therapy (2). The *TSC2* gene is located adjacent to the polycystic kidney disease 1 gene, which might account for the renal cysts that can develop in some patients with tuberous sclerosis.

HEENT/Airway: Adenoma sebaceum (more correctly, fibroangiomas), typically on the malar areas of

the face. Multiple retinal astrocytomas, choroid hamartomas, hypopigmented lesions of the iris. Pitting of tooth enamel. Oral tumors, fibromas, or papillomas.





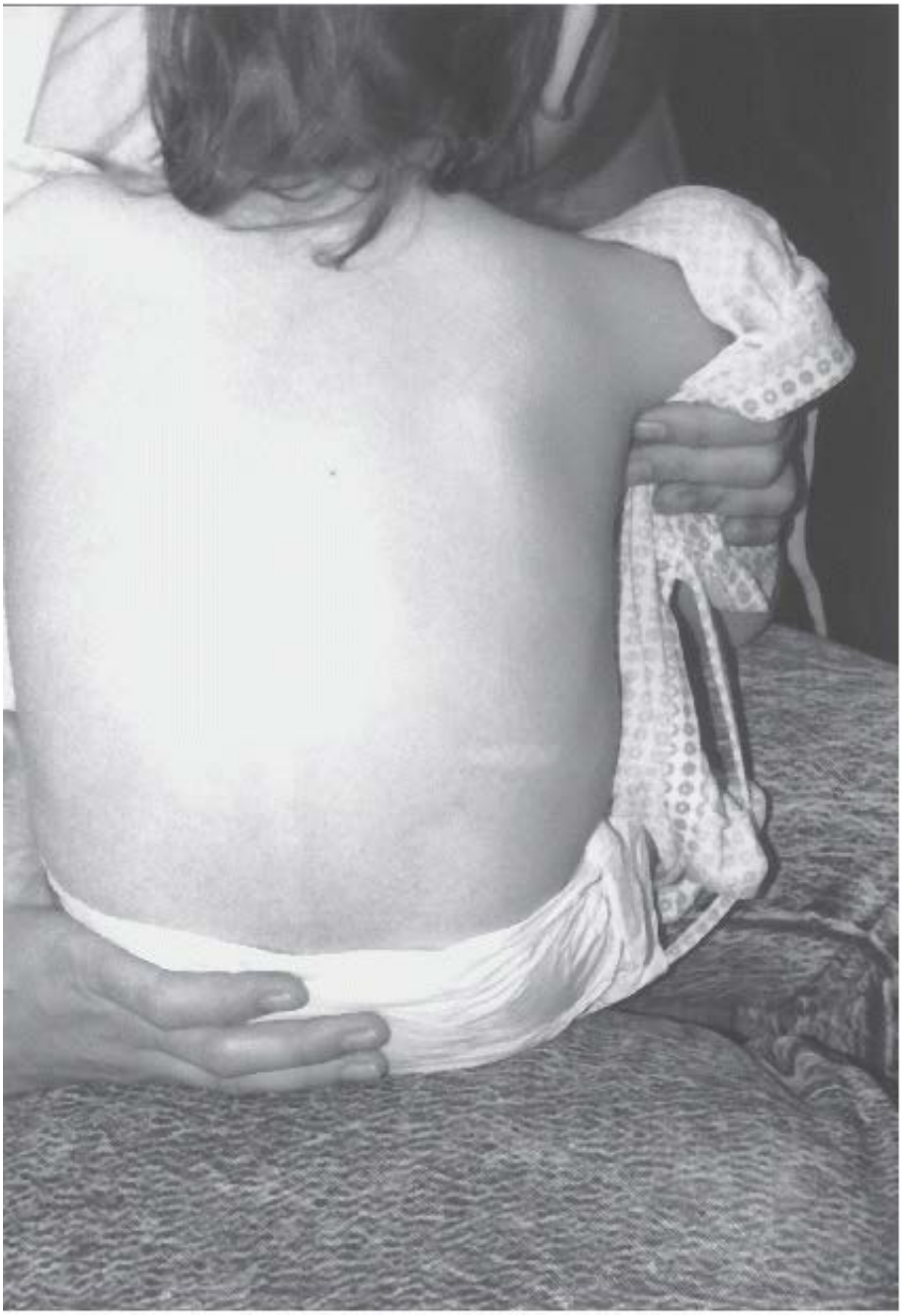
Tuberous sclerosis. FIG. 1. Typical adenoma sebaceum on the face. (Courtesy of Dr. Kenneth E. Greer, Department of Dermatology, University of Virginia Health System.)

Chest: Pulmonary involvement is rare and tends to occur in women in the third or fourth decade. The features are similar to pulmonary lymphangiomyomatosis with cystic changes and can cause pneumothoraces. Can have diffusion defects and airway obstruction. Pulmonary or pleural hamartomas can develop. Patients can have dyspnea, spontaneous pneumothorax, hemoptysis, and respiratory failure.

Cardiovascular: Cardiac rhabdomyomas are almost pathognomonic. They may be single or multiple and in any chamber; may result in obstruction to blood flow, arrhythmias, or heart block; and can rarely embolize. These

tumors are very common during fetal life and most involute or become relatively smaller with postnatal growth. Wolff-Parkinson-White syndrome (see later) has also been reported. Abdominal aortic aneurysms have been reported in infants and children. Can have aneurysms or narrowing of other major arteries.

Neuromuscular: Intellectual disability is common. Seizures occur in most patients. Infantile spasms, a particular type of seizure ("salaam seizures"), are particularly common. Lennox-Gastaut syndrome (see earlier). Autism and other behavioral problems are common. Intellectual disabilities, seizures, and behavioral problems are particularly associated with mutations in *TSC2*. Brain lesions include giant cell astrocytomas and subependymal periventricular nodules, which can calcify or cause hydrocephalus. Tubers (hence "tuberous sclerosis") are focal areas of loss of normal brain architecture, often surrounded by gliosis, and are apparent on MRI scanning. They can calcify or undergo cystic degeneration but do not undergo malignant transformation. Sacrococcygeal chordomas.



Tuberous sclerosis. FIG. 2. Typical lens-shaped, hypopigmented, mountain ash leaf spots in a young boy with a history of seizures, cardiac rhabdomyoma with supraventricular tachycardia, hypertension, and renal angiolipoma.

Orthopedic: Periungual fibromas around the fingertips are particular to this disease. Separation of periosteum from underlying bone can cause palpable cysts in the phalanges and long bones.

GI/GU: Tumors can involve the GI tract at many levels, including the mouth, esophagus, stomach, intestines, pancreas, or liver. Adrenal angiolipomas can develop. Renal angiomyolipomas, often multiple and bilateral. The combination of renal angiomyolipomas and cysts is characteristic of the disease and is usually asymptomatic, although renal failure or hematuria may

occur. Because renal angiomyolipomas have atypical vasculature, there is a risk of spontaneous life-threatening hemorrhage, particularly in lesions > 3cm. Renal carcinomas can develop. Spontaneous hemorrhage into angiolipomas or rupture can lead to retroperitoneal bleeding, which can worsen with intraoperative manipulation. Growth of renal tumors appears to be accelerated during pregnancy, increasing the risk of rupture or hemorrhage.

Other: The cutaneous manifestations also include shagreen patches (roughened skin likened to shark skin), typically over the lower trunk, and hypopigmented, elliptical, or lenticular-shaped (“mountain ash leaf”) macules that are particularly well seen under ultraviolet light (Wood's lamp). Can have café au lait spots. A wide variety of endocrinopathies have been described, including the otherwise uncommon papillary adenoma of the thyroid.

Miscellaneous: The “tuberous” in tuberous sclerosis likens the cerebral tumors to tubers, such as the potato. “Adenoma sebaceum” is not actually an adenoma, and the sebaceous glands are involved only secondarily. Tuberous sclerosis is one of the phakomatoses, or neurocutaneous diseases. Other phakomatoses include neurofibromatosis, nevus sebaceus syndrome of Jadassohn, Sturge-Weber syndrome, and von Hippel-Lindau syndrome. “Phakos” is Greek for a lentil or lens-shaped spot.

Anesthetic Considerations: Oropharyngeal or laryngeal tumors may hinder tracheal intubation. Patients deserve a baseline cardiac assessment to evaluate the potential complications of cardiac rhabdomyomas. Obstructive cardiomyopathy from rhabdomyomas can occur. Chronic use of anticonvulsant medications may alter the metabolism of some anesthetic drugs.

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Turcot syndrome

MIM #: 276300

This autosomal recessive disorder is characterized by malignant tumors of the central nervous system and adenomatous polyposis of the colon. Turcot syndrome can be due to a defect in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Heterozygous mutations in these genes result in hereditary nonpolyposis colorectal cancer. A similar phenotype arises in the autosomal dominant disorder familial adenomatous polyposis (see earlier; Gardner syndrome), due to mutations in the gene *APC* (adenomatosis polyposis coli). Presentation has been reported in a previously healthy 67-year-old.

Neuromuscular: Gliomas, astrocytomas, glioblastoma multiforme, cerebellar medulloblastomas.

GI/GU: Adenomatous gastrointestinal polyps, colon adenocarcinoma. Although most polyps are colonic, they can also occur in the stomach, duodenum, or small bowel. Patients with 20 to 100 gastrointestinal polyps > 3 cm in diameter have a very high risk of malignant transformation, which generally occurs in the second or third decade of life. Gastric carcinoma. Focal nodular hyperplasia of the liver.

Other: Café au lait spots, axillary freckling. Multiple lipomas. Multiple basal cell carcinomas. Leukemia. Papillary carcinoma of the thyroid. Radiosensitivity.

Anesthetic Considerations: There are no specific anesthetic considerations in the absence of critically placed central nervous system tumors. Marginally indicated radiologic studies should be avoided in these radiosensitive patients.

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intestinal polyposis (Turcot's syndrome): report of a case and critical analysis of the literature. *Neurosurgery* 1991;28:449-452.

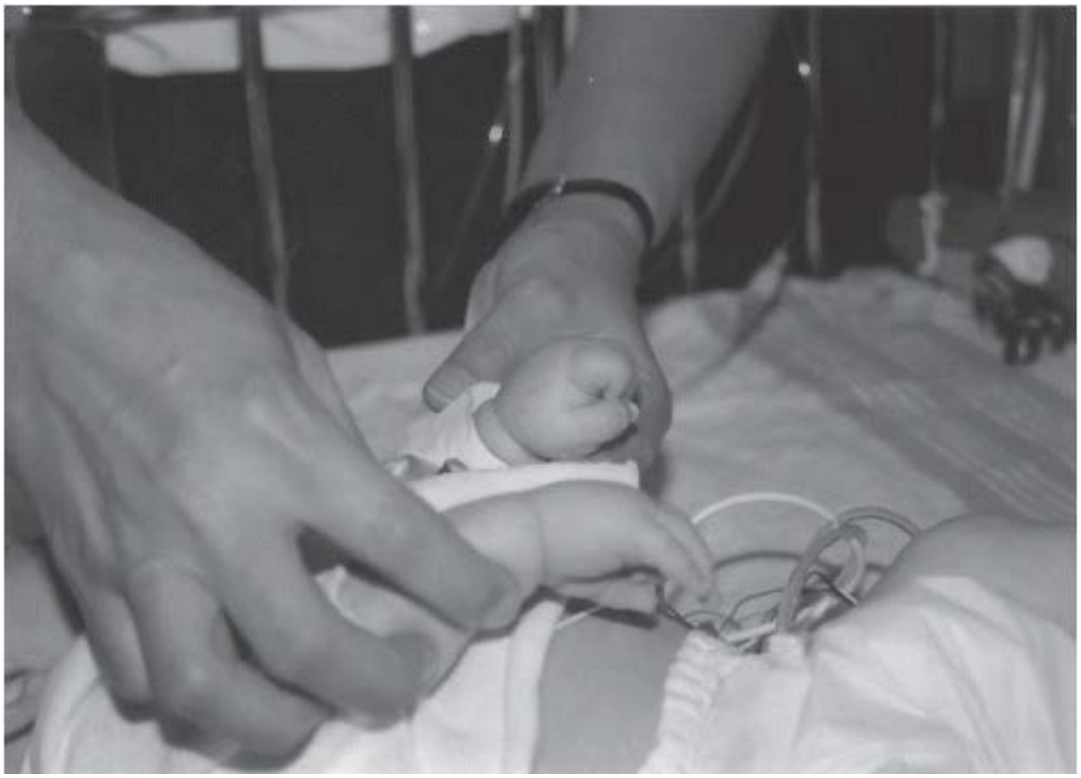
Turner syndrome

Synonym: XO syndrome

MIM #: None

This well-known syndrome in girls is due to a single X chromosome (45, XO). However, more than half of the patients with Turner syndrome are mosaics (45, XO/46, XX). Mosaics usually have fewer or milder

clinical manifestations. Short stature, webbed neck, and gonadal dysgenesis are the most universal features. Treatment with growth hormone can increase final adult height, and there is synergy with concurrent treatment with low-dose estrogen. The paternal X chromosome is the one most likely to be missing.

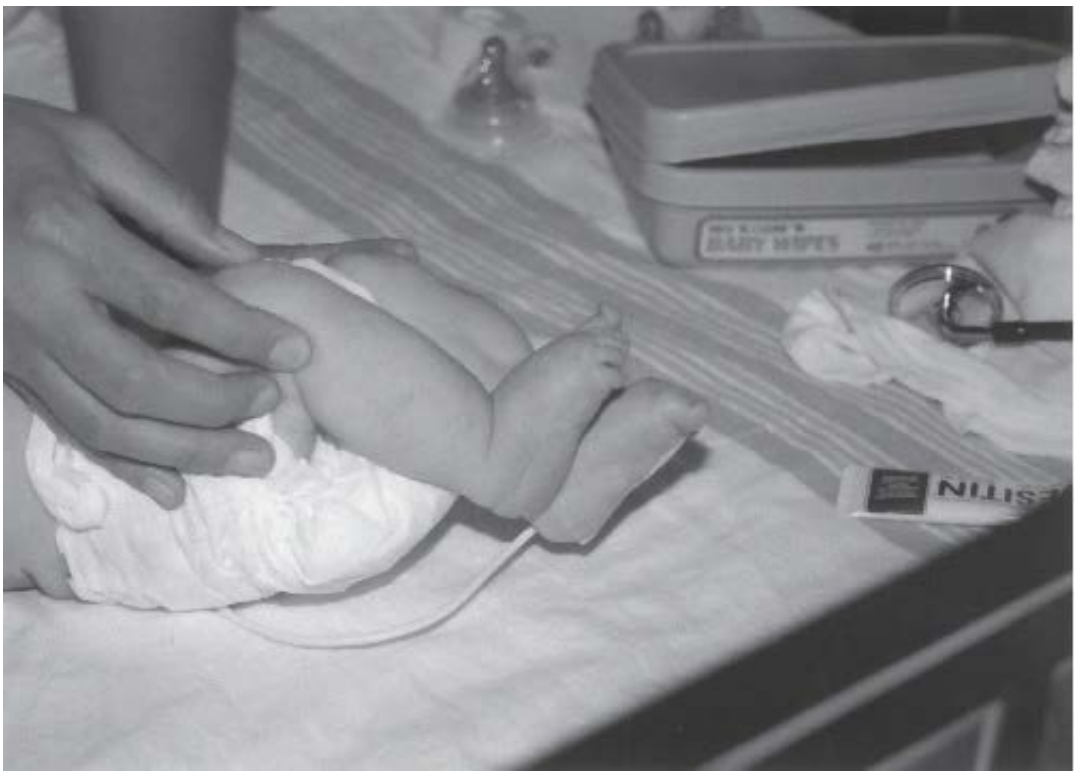


Turner syndrome. FIG. 1. Puffy hands in a 6-week-old infant with Turner syndrome (2.9-kg product of a full-term pregnancy) admitted to the hospital for a sepsis workup. It can be easily appreciated that the puffiness might make venous access challenging.

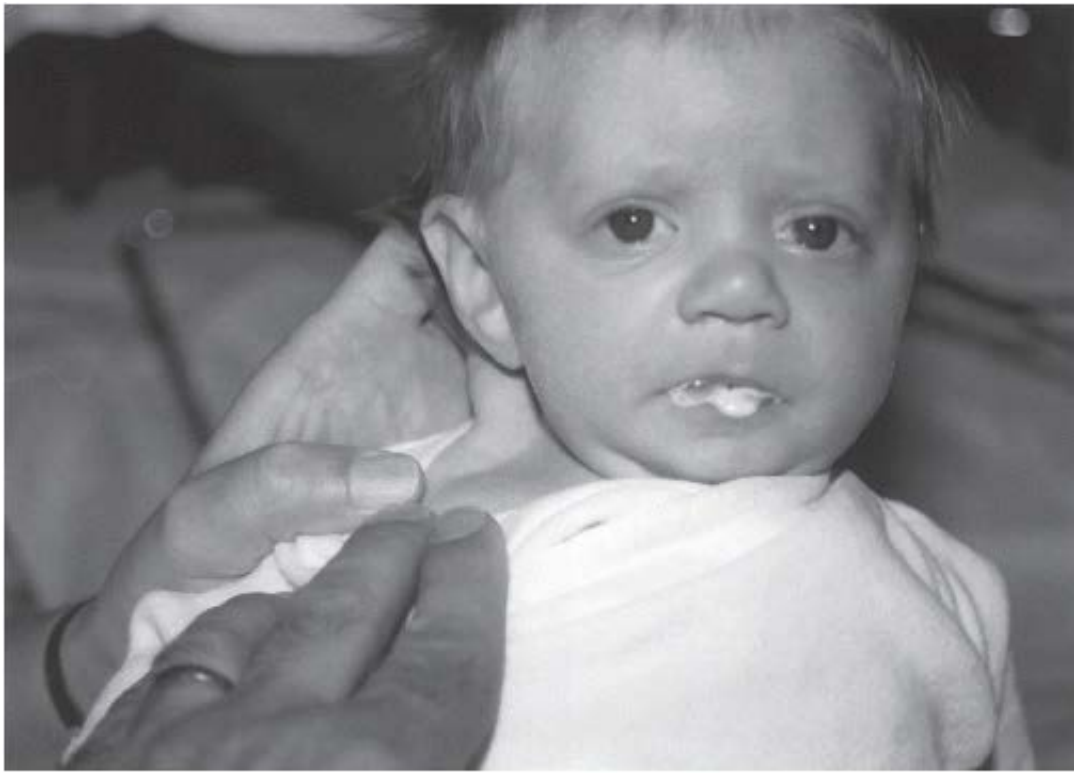
HEENT/Airway: Low posterior hairline. Strabismus, amblyopia, ptosis, inner canthal folds, cataracts. Red-green color blindness with the same frequency as normal males. Protruding external ear, recurrent otitis media,

progressive sensorineural hearing loss. High-arched palate. Palatal dysfunction can be worsened by adenoidectomy. Micrognathia. Short, webbed neck (a residuum of fetal lymphedema).

Chest: Broad, “shield-like” chest. Mild pectus excavatum.



Turner syndrome. FIG. 2. Puffy feet in the same infant.



Turner syndrome. FIG. 3. Photograph of the same infant showing the webbed neck.

Cardiovascular: Coarctation of the aorta and bicuspid aortic valve. Aortic dissection in adults even without coarctation, although almost always associated with coarctation, bicuspid aortic valve, or systemic arterial hypertension. Even though coarctation and bicuspid aortic valve are most commonly associated with the syndrome, the relative risk (vs. the general population) of partial anomalous pulmonary venous return is actually higher, although the absolute incidence is lower than that of the other two lesions. Hypertension.

Neuromuscular: Intelligence is normal or slightly diminished, but nonverbal learning disabilities (visual-spatial-organizational skills) are common. Motor delays.

Orthopedic: Short stature [mean adult height of 55 inches (140 cm)]. Increased carrying angle of the elbows (cubitus valgus), short fourth metacarpal or metatarsal, narrow or deeply set nails. Dislocated hips, tibial exostoses, prominent medial tibial and femoral condyles causing knee pain. Scoliosis, kyphosis. Puffy hands and feet (a residuum of fetal lymphedema). This can become more prominent with growth hormone or estrogen therapy. Dislocation of the patella. Madelung deformity of the radial head, seen in Leri-Weill dyschondrosteosis (see earlier), is uncommonly found.

GI/GU: Abnormal liver function tests in adults are common. Increased incidence of Crohn's disease and ulcerative colitis. Gonadal dysgenesis or agenesis with streak ovaries, absent thelarche and menarche. Most will require hormone therapy to initiate puberty. Can have dyspareunia from a small vagina or an atrophic vaginal lining. Fertility is rare and occurs mostly in women who are mosaics, but there is an increased incidence of spontaneous fetal loss

and aneuploidy in fetuses carried to term. Pregnancy rates with oocyte donation approximate that of the general

population. Older patients will be on long-term estrogen and progestin replacement therapy. Renal anomalies, including horseshoe kidney, but renal function is usually normal. A small number can develop obstructive uropathy from a duplicated collecting system.

Other: Small for gestational age. Tend to be overweight. Patients may be receiving chronic growth hormone treatment. Insulin resistance with type 2 diabetes. Hypothyroidism (Hashimoto thyroiditis, associated with antithyroid antibodies). Increased incidence of keloid formation and pigmented nevi. Mosaics are at increased risk for development of gonadoblastoma. May have an increased risk for development of neuroblastoma and related tumors. Hypercholesterolemia.

Miscellaneous: Although patients with Turner syndrome are said to have widely spaced nipples, careful measurement showed that they have only the appearance of widely spaced nipples.

Henry Turner was an endocrinologist who was the Professor of Medicine at the University of Oklahoma. The syndrome was actually described in the literature by Ullrich several years before Turner. In fact, Morgagni appears to have described a case in the 17th century.

Anesthetic Considerations: Patients should be spoken to in a manner appropriate for their chronologic age, not their height age. The short, webbed neck may make direct laryngoscopy and tracheal intubation more difficult. Patients have been reported with short tracheal lengths, making appropriate location of the tip of a normal length endotracheal tube difficult. Hypothyroidism, when present, could result in delayed gastric emptying, alterations in drug metabolism and impaired temperature regulation. Puffy hands and feet can make venous access challenging. Adult patients can be hypertensive and are at risk for aortic dissection. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Tyrosinemia I

Note that there are three types of tyrosinemia. The sections on types II and III follow.

Tyrosinemia I is an autosomal recessive disorder due to a deficiency of fumarylacetoacetate hydrolase. In the past, it has been called “tyrosinosis,” “hereditary tyrosinemia,” and “congenital tyrosinosis.” It is also known as hepatorenal tyrosinemia. This enzyme fumarylacetoacetate hydrolase is involved in a final stage of tyrosine catabolism, where it catalyzes the conversion of fumarylacetoacetic acid to fumaric acid and acetoacetic acid. Acute and chronic forms have been described even within the same family and are thought to be due to the amount of residual enzyme activity. A variety of specific mutations in the gene have been described. Death is often secondary to hepatic failure. Liver damage is prenatal in origin, occurring in the absence of tyrosinemia.

Diminished enzyme activity leads to the accumulation of metabolites of another, unaffected degradation pathway. Succinylacetate, a metabolite of tyrosine, is structurally similar to maleic acid, an inhibitor of renal tubular function, and may be responsible for the renal tubular dysfunction. Succinylacetone is structurally related to delta-aminolevulinic acid, which inhibits porphobilinogen synthase (delta-aminolevulinic acid dehydratase), leading to elevated levels of delta-aminolevulinic acid and symptoms of porphyria (see earlier). Succinylacetone also inhibits renal tubular transport of glucose and amino acids. Other compounds that are produced in excess are capable of inhibiting methionine synthase.

In addition to liver transplantation, treatment has included NTBC, an inhibitor of 4-hydroxyphenylpyruvate dioxygenase, which prevents the formation of maleylacetoacetate and fumarylacetoacetate. Early treatment has apparently removed the risk of hepatocellular carcinoma and neurologic decompensation.

HEENT/Airway: Epistaxis. Severe bruxism. Macroglossia has been reported.

Chest: Mechanical ventilation may be required for weakness during an acute exacerbation.

Cardiovascular: Can have hypertrophic cardiomyopathy, systemic arterial hypertension.

Neuromuscular: Polyneuropathy. There are episodes of vomiting, and peripheral neuropathy with severe pain, extensor hypertonia, muscle weakness, and self-mutilation. Hypertonia can be misidentified as seizures or opisthotonos. Episodes can include

autonomic findings and paralysis. Episodes often follow an infection. There usually is normal neurologic function between episodes. Can exhibit developmental delay, but development is usually normal, and level of consciousness is normal during neurologic crises.

Orthopedic: Hypophosphatemic rickets.

GI/GU: Episodes of abdominal pain, vomiting, diarrhea, and paralytic ileus. Hepatic failure beginning in infancy. Hepatomegaly, chronic liver disease (chronic active hepatitis with fatty infiltration), cirrhosis, ascites. Hepatocellular carcinoma is common and can develop in young childhood. Can have acute episodes of hepatic failure associated with infection or other catabolic stress. Painful abdominal crises similar to those seen with porphyria. In some hepatocytes in many patients, mutations revert to the normal sequence, and these cells form nodules with normal enzyme activity. These can be difficult to differentiate noninvasively from nodules of hepatocellular carcinoma. Hyperplastic pancreatic islets. Melena. Renal tubular acidosis. Hypophosphatemic rickets. Fanconi syndrome (see earlier), renal swelling, hematuria. Can develop renal failure.

Other: Failure to thrive. Tyrosinemia. An odor similar to boiled cabbage. Intermittent fever. Normocytic anemia, possible thrombocytosis, prolonged prothrombin time. Coagulopathy, which is in excess of other liver function abnormalities, can be symptomatic and is not correctable by vitamin K. Hypocholesterolemia. There can be hypoglycemia unresponsive to glucagon. Hypoproteinemia. Can have edema and ecchymoses of the skin.

Miscellaneous: NTBC was originally developed as an herbicide.

Anesthetic Considerations: There are no reports of the anesthetic management of a patient with tyrosinemia I. However, given the biochemical similarity with porphyria, it would seem prudent to use the same precautions (see Porphyria, earlier). Abdominal pain may be misdiagnosed as a surgical abdomen. Liver function should be evaluated preoperatively. Hepatic failure may lead to abnormal coagulation and may affect protein binding of some anesthetic drugs. Even without liver dysfunction, patients may have a bleeding dyscrasia. Clotting parameters should be evaluated prior to regional anesthesia. Coagulopathy will not be vitamin K responsive. Serum glucose levels should be monitored perioperatively, and patients should receive glucose supplementation as needed without protracted preoperative fasting. During acute episodes, adequate calories to prevent or minimize catabolism should be supplied. Patients may require mechanical ventilation during a neurologic crisis. Pain associated with neurologic crises may require opioid analgesics. Renal output may not closely reflect intravascular volume status. See Fanconi syndrome (earlier) for renal metabolic consequences. Patients may have hypertension or hypertrophic cardiomyopathy. Nitrous oxide can also inhibit methionine synthase and probably should be avoided in this disorder.

Figure: See **Appendix B**

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Tyrosinemia II

Synonym: Richner-Hanhart syndrome

MIM #: 276600

This oculocutaneous syndrome is due to an autosomal recessive deficiency of hepatic tyrosine aminotransferase, the rate-limiting first enzyme in tyrosine catabolism. Some families have been reported with skin lesions, but no eye lesions, and vice versa. In general, eye lesions predate the skin lesions. Ocular and cutaneous lesions respond to a protein-restricted or phenylalanine-restricted diet.

HEENT/Airway: Lacrimation, photophobia, redness, mild herpetiform corneal lesions, dendritic ulcers, and rarely corneal and conjunctival plaques. Neovascularization. Corneal scarring, nystagmus, glaucoma. Hyperkeratosis of the tongue.

Neuromuscular: Intellectual disabilities, self-mutilation. Fine motor abnormalities.

Other: Hyperkeratotic lesions of the palms and soles, which can be painful. Tyrosinemia. Growth retardation. Untreated maternal disease may be deleterious to the fetus, which can have abnormal neurologic development.

Miscellaneous: The association of this clinical syndrome with tyrosinemia was suggested 35 years after its description by Richner and later by Hanhart. A similar disease occurs in minks.

Anesthetic Considerations: Consideration should be given to patients with photophobia in brightly lit operating rooms. Dietary limitations (protein or phenylalanine restrictions) should be maintained perioperatively. An orogastric tube or throat packs should be placed for surgery with the potential for oral

or intestinal bleeding because blood aspirated into the gastrointestinal tract after oral or nasal surgery might present an excessive protein load. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma.

Figure: See **Appendix B**

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Tyrosinemia III

Synonym: 4-Hydroxyphenylpyruvic acid dioxygenase (oxidase) deficiency

MIM #: 276710

This autosomal recessive disorder of tyrosine metabolism is due to deficient activity of 4-hydroxyphenylpyruvic acid dioxygenase, which is also known as 4-hydroxyphenylpyruvate acid oxidase. The responsible gene has been sequenced and named the *HPD* gene. Three disorders have been linked to abnormalities in this gene: tyrosinemia III, **hawkinsinuria**, and transient tyrosinemia of the newborn. Hawkinsinuria results from a heterozygous mutation. Transient tyrosinemia is caused by an immature enzyme in concert with high dietary phenylalanine and tyrosine and relative ascorbate deficiency. The clinical findings of tyrosinemia III disease are limited to the nervous system.

HEENT/Airway: There are no eye findings.

Neuromuscular: Acute intermittent ataxia, lethargy. Psychomotor development may be abnormal; mild intellectual disability. Can have seizures.

GI/GU: Hepatic function is normal.

Other: Tyrosinemia.

Anesthetic Considerations: Any dietary restrictions should be continued perioperatively. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs.

Figure: See **Appendix B**

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832.

Tyrosinosis

MIM #: 276800

There is some confusion over the terms “tyrosinosis” and “tyrosinemia.” It has been suggested that “tyrosinosis” be reserved for an exceedingly rare condition that involves an autosomal recessive defect in liver tyrosine transaminase. It is likely that most patients carrying a diagnosis of “tyrosinosis” will in fact have tyrosinemia (see Tyrosinemia I, II, or III, earlier).

Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

U

Ubiquinone-cytochrome c oxidoreductase deficiency

See Complex III deficiency

Uhl anomaly

Synonym: Arrhythmogenic right ventricular dysplasia

MIM #: 107970

This peculiar autosomal dominant defect consists of the absence of muscle in the right ventricle with few, if any, myocardial cells and replacement with fibrous or fibrofatty tissue, forming a thin "parchment paper-like" right ventricle. The disorder is due to abnormalities in the gene *TGFB3*, which encodes a transforming growth factor. The term arrhythmogenic right ventricular dysplasia encompasses a larger number of lesions than Uhl anomaly, which represents a single type. Brugada syndrome (see earlier), for example, is another type. Naxos disease (heart plus wooly hair and palmoplantar keratoderma) and Carvajal syndrome (similar, but left ventricular disease predominates) are other types (neither is described here). There are currently 12 types of right ventricular dysplasia described, each caused by a mutation in a separate gene. Many of these encode desmosomal proteins.

The age at onset of symptoms is generally from 10 to 50 years. The most common presenting symptoms are chest pain, arrhythmias, and dyspnea. Sudden death, presumably secondary to arrhythmia, can occur.

Cardiovascular: The right ventricular anterior wall is preferentially affected, with replacement of normal muscle with fat and fibrous tissue. There can be recurrent, sustained ventricular tachycardia, with a

left bundle branch configuration. Associated cardiac defects are uncommon, although there can be associated tricuspid insufficiency. Right-to-left shunting through a patent foramen ovale can result in cyanosis. There is often impressive cardiomegaly on the chest radiograph. The electrocardiogram shows large P waves and a small QRS, particularly over the right precordial leads.

GI/GU: There can be hepatomegaly secondary to congestion, and severe involvement with ascites has been reported.

Miscellaneous: Appropriate attachment of the tricuspid valve annulus differentiates this entity from Ebstein anomaly on echocardiography.

Anesthetic Considerations: Perioperative death can occur (at induction, intraoperatively, and within 2 hours postoperatively), even with a history of uncomplicated surgeries and anesthetics. Since emotional stress can trigger arrhythmias, good preoperative sedation is indicated. If the patient is taking beta-blockers preoperatively, these should be continued during the perioperative period. Efforts should be made to minimize pulmonary vascular resistance. It is possible that passage of a pulmonary arterial catheter will induce ventricular arrhythmias more

easily than in normal hearts, and there is an increased risk of right ventricular perforation. With significant congestion, hepatic function can be abnormal, which could affect coagulation and drug metabolism. Surgical options include a so-called one and one-half ventricle repair (utilizing a Glenn anastomosis) with or without volume reduction of the right ventricle, or a full Fontan operation. Patients may have had placement of an implantable cardioverter-defibrillator (ICD), which should be interrogated and the defibrillator function disabled immediately prior to surgery. Although it has been suggested that halothane be avoided, there are no data suggesting inherent safety of any particular anesthetic drug.

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Urbach-Wiethe disease

See Lipoid proteinosis

Uridine diphosphate galactose epimerase deficiency

Synonym: Galactose epimerase deficiency

MIM #: 230350

This autosomal recessive disorder is due to deficient activity of uridine diphosphate (UDP) galactose epimerase, which catalyzes the conversion of UDP-galactose to UDP-glucose, in the interconversion pathway of galactose to glucose and in the synthesis of galactose when only glucose is available. This enzyme deficiency is occasionally included in the term “galactosemia” (see earlier).

There are two forms of this disorder. One form is benign and affects only red and white blood cell enzyme activity. Patients are asymptomatic. The other, more rare, form has findings that are similar to those of galactose-1-

phosphate uridyltransferase deficiency, the defect in classic galactosemia. The enzyme deficiency here is more generalized. However, recent work suggests that these disorders represent a spectrum rather than two distinct entities. The treatment of this defect differs somewhat from that of the other two disorders causing galactosemia. Galactose cannot be synthesized from glucose with deficiency of UDP-galactose epimerase, so some dietary galactose is required. Galactose is required for the synthesis of complex carbohydrates and galactolipids.

HEENT/Airway: Sensory deafness. May be at risk for cataracts.

Neuromuscular: Delayed intellectual and motor development. Hypotonia.

GI/GU: Jaundice, vomiting, hepatosplenomegaly.

Other: Failure to thrive. Generalized aminoaciduria. May have elevated blood galactose.

Miscellaneous: Abnormal urine levels of galactose are not identified by current urine test strips because they use glucose oxidase, which is specific for glucose. Older tablet techniques (we are showing our age) identified all reducing sugars, including galactose.

Anesthetic Considerations: Patients may be on a galactose-limited (not galactose-free) diet, which should

be continued perioperatively. Perioperative temperature maintenance may be difficult in these small, thin children.

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Urticaria-deafness-amyloidosis syndrome

Synonym: Muckle-Wells syndrome

MIM #: 191900

This autosomal dominant disorder has as its primary manifestations progressive cochlear deafness, urticaria, and renal amyloidosis. The disorder is due to mutations in the gene *NLRP3*, which encodes cryopyrin. This gene is predominantly expressed in peripheral leukocytes. It is considered an autoinflammatory disease—one in which the inflammatory episode is unprovoked. Treatment with anakinra, an interleukin-1 receptor antagonist, has met with success in improving hearing loss and other symptoms. This is currently one of the few treatable causes of congenital sensorineural hearing loss.

HEENT/Airway: Episodic conjunctivitis. Absent organ of Corti, cochlear nerve atrophy. Aphthous ulcers of mouth.

Orthopedic: Episodic arthralgias.

GI/GU: Amyloid infiltration of the kidney. Nephrotic syndrome. Renal failure.

Other: Urticaria. Periodic fever. Can have candidiasis of the mouth and perineum. Elevated erythrocyte sedimentation rate. Increased sensitivity to cold. Episodes of malaise, rigor, chills, aching pains, and urticarial rash.

Anesthetic Considerations: When meeting with the patient before surgery, recall that he or she may have hearing loss. Baseline renal function should be assessed preoperatively. There are no guidelines regarding the safety of histamine-releasing drugs in this disease that involves urticaria, and there is no information regarding the effects of perioperative hypothermia, as the urticarial lesions can be induced by cold air but not by ice cubes or cold water.

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V

VACTERL association

See VATER association

Valproate

See Fetal valproate syndrome

van Buchem disease

See Sclerosteosis

van der Woude syndrome

Synonym: Lip pit-cleft lip syndrome

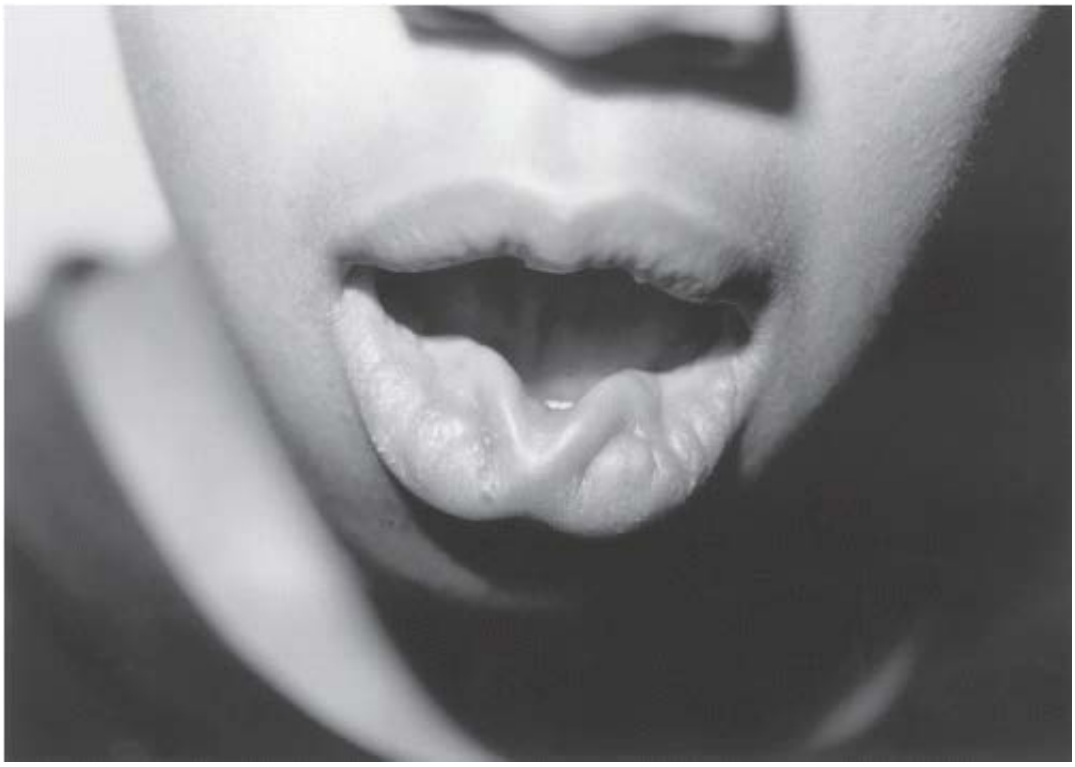
MIM #: 119300

This autosomal dominant disorder, usually due to a mutation in the gene encoding *IRF6*, interferon regulatory factor 6, is an association of cleft lip or palate with pits of the lower lip, which represent accessory salivary glands. There is some clinical heterogeneity, and some family members may have cleft lip, whereas others do not. Almost all have lip pits. The accessory salivary glands can produce an annoying watery discharge and so may be surgically removed. This disorder is allelic with popliteal pterygium syndrome (see earlier). Several families without *IRF6* mutations have been found to have mutations in *GRHL3* (grainyhead-like 3), a transcription factor first identified in *Drosophila*.

HEENT/Airway: Cleft lip, cleft palate, cleft uvula. Lower lip pits (accessory salivary glands). Hypotonic lower lip can produce lip asymmetry and protruding lower lip. Hypodontia with missing incisors, canines, or bicuspids. Syngnathia, an adhesion of the maxilla and the mandible, has been reported, as have other oral synechiae.

Miscellaneous: Single nucleotide polymorphisms in interferon regulatory factor 6 are thought to be a major

contributor to the development of cleft lip with or without cleft palate.



van der Woude syndrome. Typical lower lip in a boy with van der Woude syndrome. (Courtesy of Dr. K. Lin and the Craniofacial Anomalies Clinic, University of Virginia Health System.)

Anesthetic Considerations: Dental abnormalities should be documented preoperatively to avoid mistakenly assuming that teeth have been dislodged intraoperatively. Oral synechiae and syngnathism have resulted in markedly limited mouth opening, which required nasal intubation and caused postoperative obstructive apnea in a neonate (3). In one review, children with van der Woude syndrome had more postoperative complications, and more major postoperative complications, than did nonsyndromic children having cleft lip or palate surgery.

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Varadi-Papp syndrome

Included in Oral-facial-digital syndrome, type I

VATER association

(Includes VACTERL association)

MIM #: 192350, 314390

VATER stands for **V**ertebral anomalies, **A**nal atresia, **T**racheoesophageal fistula, **E**sophageal atresia, and **R**adial and renal dysplasia, any combination of which can be present in a particular patient. The association of these diverse anomalies is sporadic, and the etiology of the association is unknown, although there is an increased incidence in children of diabetic mothers. VATER association can also occur as part of a larger pattern of malformations, such as in trisomy 18. The VATER association has also been referred to as the **VACTERL association** (**V**ertebral anomalies, **A**nal atresia, **C**ardiac malformations, **T**racheoesophageal fistula, **E**sophageal atresia, **R**enal anomalies, **L**imb anomalies). In any event, the acronyms cover only the most common findings. There can be others.

A separate entity, VATER with hydrocephalus from aqueductal stenosis, has been described as having both autosomal and X-linked inheritance.

HEENT/Airway: Corneal anesthesia with secondary corneal injury has been reported. Can have choanal atresia. Can have micrognathia. Laryngeal stenosis, tracheal atresia.

Chest: Tracheoesophageal fistula. Respiratory distress from an ectopic bronchus has been reported. Esophageal atresia. Rib anomalies.

Cardiovascular: A variety of congenital cardiac defects can occur including VSD, tetralogy of Fallot, and transposition of the great vessels.

Orthopedic: Vertebral anomalies such as hemivertebrae, dysplastic vertebrae, vertebral fusion. Radial dysplasia. Can have dysplastic thumb. Preaxial polydactyly, syndactyly.

GI/GU: Esophageal atresia with tracheoesophageal fistula, duodenal atresia, imperforate anus with or without fistula. Defects of external genitalia including hypospadias. Renal anomalies.

Other: Single umbilical artery.

Anesthetic Considerations: Infants with tracheoesophageal fistula should have a cardiac examination to exclude congenital heart disease as part of the association. The anesthetic management of tracheoesophageal fistula is complicated, particularly with respect to positioning the endotracheal tube to ventilate both lungs adequately without distending the stomach through the fistula. Many techniques exist to accomplish this (4). Because patients can have choanal atresia, it is important to confirm nasopharyngeal patency prior to passing any type of nasal tube.

Baseline renal status should be assessed preoperatively. Limb anomalies may limit options for vascular access. Radial anomalies may make placement of a radial arterial catheter more difficult. Patients with

congenital heart disease should receive an appropriately tailored anesthetic. Successful epidural anesthesia has been reported in a parturient with known but unspecified vertebral anomalies.

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Velocardiofacial syndrome

Synonym: Shprintzen syndrome

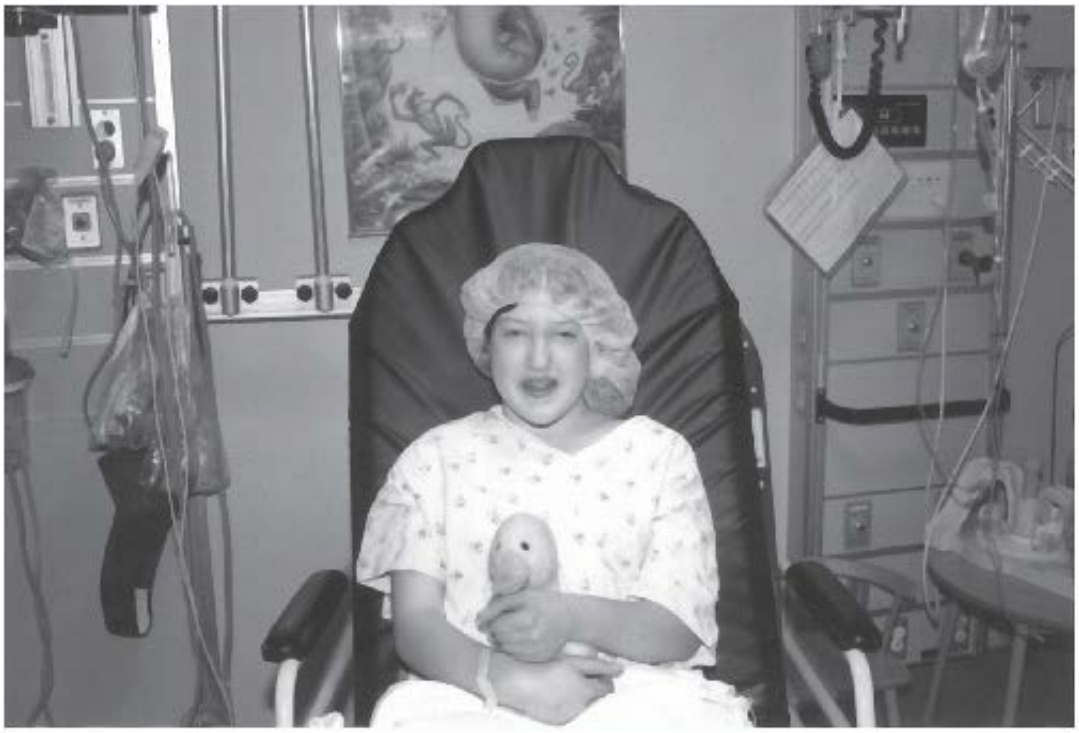
MIM #: 192430

This autosomal dominant syndrome is due to the same defect as the DiGeorge syndrome (see earlier), namely, a microdeletion of chromosome 22 (22q11), and the two syndromes have significant clinical overlap. Velocardiofacial syndrome has been ascribed to the *TBX1* gene, which resides in the center of the DiGeorge deletion region. T-box genes encode transcription factors involved in the regulation of developmental processes. The syndrome consists of cleft palate, typical facies, cardiac anomalies, and learning disabilities.

HEENT/Airway: Microcephaly. Myopathic facies. Narrow palpebral fissures, small optic discs, tortuous retinal vessels, cataracts. Minor external ear anomalies. Prominent nose with bulbous tip and deficient alae nasi. There is a high incidence of missing permanent teeth. Small, open mouth, pharyngeal hypotonia, cleft palate (can be submucous), velopharyngeal insufficiency with nasal speech. Decreased pharyngeal lymphoid tissue. Micrognathia, retrognathia. May have subglottic stenosis or laryngeal anomalies.

Cardiovascular: Congenital heart disease, in particular conotruncal defects such as tetralogy of Fallot. May have right aortic arch, vascular ring. Medial displacement of internal carotid arteries.

Neuromuscular: Learning disabilities, intellectual disabilities. Blunt or inappropriate affect. Psychiatric illness is common, particularly schizophrenia. Also said to be associated with rapid cycling bipolar disorder. Psychiatric problems can occasionally be the presenting finding in adolescents and adults.



Velocardiofacial syndrome. This 14-year-old girl with velocardiofacial syndrome has had a laryngeal web and cleft and a vascular ring. She has an asymmetric face and residual subglottic stenosis.

Orthopedic: Short stature. Thin hands and feet, hyperextensible hands and fingers. Scoliosis (although could be secondary to thoracic surgery).

GI/GU: Umbilical and inguinal hernias.

Other: Neonatal hypocalcemia, thymic aplasia with T-cell immunodeficiency, hypothyroidism.

Miscellaneous: *ARVCF*, the armadillo repeat gene, can be deleted in velocardiofacial gene, and these deletions are perhaps more likely to also result in schizophrenia.

Anesthetic Considerations: The serum calcium level should be evaluated in neonates preoperatively. Dentition should be carefully assessed preoperatively because some teeth may be missing. Micrognathia or retrognathia can make laryngoscopy and tracheal intubation very difficult. Blood for transfusion should be irradiated because patients often have T-cell defects, leaving them at risk for graft versus host disease. Hypothyroidism, when present, could result in delayed gastric emptying, alterations in drug metabolism, and impaired temperature regulation. Medial displacement of the internal carotid arteries increases the risk of major bleeding during pharyngeal surgery such as tonsillectomy. Patients with congenital heart disease should receive an appropriately tailored anesthetic. This region of chromosome 22 also includes the gene encoding catechol *O*-methyltransferase (*COMT*), responsible for degrading catecholamines. A patient has been reported with unexpected tachycardia from epinephrine containing local analgesic given during dental surgery, possibly from being hemizygous for *COMT*.

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Very long chain acyl-CoA dehydrogenase deficiency

MIM #: 201475

This inborn error of metabolism is an autosomal recessive disease caused by a defect in the gene for very long chain acyl-CoA dehydrogenase, one of several acyl-CoA dehydrogenases, which are mitochondrial enzymes required for the beta-oxidation of fatty acids. The major clinical manifestations are hypertrophic cardiomyopathy, pericardial effusion, steatosis, and hypoglycemia. Treatment by supplying most of the dietary fat as medium-chain triglycerides has improved survival (7). Children may also be advised to consume frequent meals of carbohydrate-rich foods that are low in long-chain fatty acids.

Fatty acids are oxidized in mitochondria. After mobilization from adipose tissue, they are taken up by the liver and other tissues and converted to acyl-CoA esters in the cytoplasm. They enter mitochondria as carnitine esters and become reesterified as acyl-CoA esters. Beta-oxidation results in the liberation of electrons. As beta-oxidation proceeds, the acyl chain is gradually shortened, and this first step in the oxidation process is catalyzed by acyl-CoA dehydrogenases with differing, but overlapping, chain-length specificities. These are very long chain, long chain, medium-chain, and short-chain acyl-CoA dehydrogenases.

The phenotype is somewhat variable, with three general subtypes: an early, severe form with cardiomyopathy and early death presenting in infancy, a less severe form presenting in childhood, and an adult-onset myopathic form, which lacks cardiomyopathy. Episodes of acute decompensation can be initiated by fasting, viral illnesses, exercise, cold, or emotional distress, including the prospect of surgery (4).

Cardiovascular: Essentially all patients except those with adult-onset disease have cardiomyopathy, including hypertrophic cardiomyopathy. Pericardial effusion. Cardiomyopathy is a common cause of death and can regress with appropriate treatment.

Neuromuscular: Weakness associated with fasting or infection. Exercise-induced rhabdomyolysis and myoglobinuria, preventable by dietary carbohydrates before exercise. Elevated serum creatine kinase during acute decompensations. Muscle pains and stiffness with exercise in older patients.

GI/GU: Emesis. Hepatomegaly, steatosis. Elevated liver enzymes during acute decompensation.

Other: Hypoketotic hypoglycemia. Lactic acidosis. Marked lipid accumulation in many tissues. Decreased plasma carnitine.

Miscellaneous: One family was investigated for infanticide after the sudden deaths of three infants following normal deliveries.

Anesthetic Considerations: Perioperative fasting must be avoided, and patients should receive perioperative glucose supplementation. Perioperative fasting was believed to be the cause of death in a child with previously unrecognized disease (5). Myopathic episodes can be triggered by fasting, emotional distress, cold, exercise, or infection. During periods of stress and metabolic decompensation, patients may need a very large amount of intravenous glucose (up to 10 to 15 mg/kg/min). Rhabdomyolysis can occur with normoglycemia, so creatine kinase levels should be followed. The degree and type of myocardial involvement should be delineated before surgery, and the anesthetic should be tailored accordingly.

Propofol emulsion contains predominantly long-chain fatty acids, mainly C18, and propofol may inhibit mitochondrial entry of long-chain fatty acids and inhibit the respiratory chain. Propofol is probably contraindicated in these patients. Interestingly, the propofol infusion syndrome in children sedated with propofol in the intensive care unit has many similarities with this syndrome. Ringer's lactate should be avoided in cases of metabolic decompensation with lactic acidosis. Volatile anesthetic agents are also associated with increases in free fatty acid concentration during the early phase of anesthesia.

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Vitamin D-resistant rickets

Synonym: X-linked hypophosphatemic rickets

MIM #: 307800

X-linked dominant vitamin D-resistant rickets is the most common form of hereditary rickets. It is due to excess levels of fibroblast growth factor-23 (FGF23), a novel phosphaturic hormone made primarily in bone. Excess FGF23 leads to an inability to reabsorb filtered phosphate by the proximal renal tubule brush border membrane. This results in phosphate wasting and severe hypophosphatemia. Excessive FGF23 also impairs regulation of 1,25-hydroxy-vitamin D 1-α-hydroxylase activity and increases activity of the degrading enzyme 24-hydroxylase, both of which lead to lower-than-appropriate levels of 1,25-dihydroxy vitamin D_3. In most patients, the defect is due to mutations in the phosphate-regulating endopeptidase gene (*PHEX*). In general, the disease is more severe in men than in women.

There are three other entities that also produce hypophosphatemic rickets due to excessive FGF23. An autosomal dominant form is due to structural abnormalities in the fibroblast growth factor gene, *FGF23*, making it resistant to proteolytic cleavage. Oncogenic osteomalacia is associated with small, primitive tumors, in which elevated levels of fibroblast growth factor or other phosphaturic substances are considered paraneoplastic. A recently described autosomal recessive form is due to mutations in the gene *DMP1*, leading to absence of posttranslational regulation of FGF23 and subsequent increased FGF23 blood levels. In oncogenic osteomalacia associated with a single tumor, removal of the tumor is curative.

Treatment for almost all forms of hypophosphatemic rickets is with oral phosphorus supplementation and 1,25-dihydroxy vitamin D_3 (calcitriol). Complications of this therapy can include hypercalcemia, hypercalciuria, nephrocalcinosis, and secondary or tertiary hyperparathyroidism. Anti-FGF23 antibodies have been proposed as a therapeutic approach and have proven effective in experimental rodent models. Short stature can be normalized with treatment beginning in the first year of life.

HEENT/Airway: Craniosynostosis, particularly sagittal, with frontal bossing. Craniotabes in infants (a pingpong ball-like effect elicited by pressure on the parietal bones). Sensorineural deafness has been reported. Abnormal dentin formation and spontaneous tooth pulp and gingival abscesses.

Chest: Rachitic rosary (prominent rib costochondral junctions).

Cardiovascular: Hypertension and left ventricular hypertrophy have been reported in treated adults. Cardiac calcifications have been reported in cases of tertiary hyperparathyroidism and hypercalcemia.

Neuromuscular: Spinal stenosis from ossification of the ligamentum flavum and thickening of the laminae with cord compression has been reported in both untreated and treated patients.

Orthopedic: Rickets in children, osteomalacia in adults. Short stature, bowed legs, waddling gait. Extraskeletal

ossification, particularly of tendons and ligaments. Painful degenerative joint disease similar to ankylosing spondylitis in adulthood. Metaphyseal widening, particularly of the lower extremities.

Other: Hypophosphatemia from renal phosphate wasting. Calcium levels are normal, unlike other types of rickets associated with defects in vitamin D metabolism, which produce hypocalcemia. Thus, tetany and other manifestations of hypocalcemia are not seen. 1,25-dihydroxy vitamin D3 levels are low despite hypophosphatemia.

Anesthetic Considerations: Serum calcium and phosphorus levels must be evaluated in patients on phosphate and vitamin D therapy. Although not reported, it is possible that abnormal teeth could make dental injury during laryngoscopy more likely. Older patients who may have osteomalacia must be carefully positioned and padded perioperatively. Neuraxial anesthesia may be technically difficult when there is calcification of the ligamentum flavum.

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Vogt-Spielmeyer disease

See Spielmeyer-Vogt disease

Vohwinkel syndrome

See Senter syndrome

von Gierke disease

Synonym: Glycogen storage disease type I; Glucose-6-phosphatase deficiency

MIM #: 232200, 232220

Type 1 glycogen storage disease is the most commonly recognized of the glycogenoses. This autosomal recessive disease is due to a lack of hepatic and renal glucose-6-phosphatase (type 1A). Glucose-6-phosphatase catalyzes the interconversion of glucose-6-phosphate and glucose in the Embden-Meyerhof pathway. This enzyme is crucial for allowing the production of glucose from glycogen stores (glycogenolysis) or from gluconeogenesis. The glucose-6-

phosphate that is formed in the absence of the glucose-6-phosphatase enzyme is instead eventually converted to lactate. Decreased phosphatase causes decreased hepatic adenosine triphosphate, which in turn affects purine synthesis and causes hyperuricemia. Lactate itself also competitively inhibits renal tubular secretion of urate. Hypophosphatemia can occur secondary to excessive cellular accumulation of phosphorus as glucose-6-phosphate.

Type 1B disease, also autosomal recessive, is due to deficiency of the carrier protein that transports glucose-6-phosphate across the microsomal membrane to the enzyme in hepatocytes and leukocytes. The enzyme itself is intact. Clinical findings are the same as for type 1A, with additional findings as indicated.

Patients with von Gierke disease are treated with frequent high-carbohydrate feedings during the day and nasogastric or gastrostomy carbohydrate feedings overnight to maintain adequate serum glucose levels. Hypoglycemia is often very well tolerated, suggesting that these patients can use alternative substrates to supply brain glucose.

HEENT/Airway: "Doll-like" facies. Lipemia retinalis. Gouty tophi. Nosebleeds. Oral lesions in type IB, including hyperplastic gingiva.

Cardiovascular: Hypertension in adults. Pulmonary hypertension has been reported.

Neuromuscular: Poorly controlled disease with recurrent hypoglycemia can result in neurologic injury.

Orthopedic: Short stature. Osteopenia. Hyperuricemic gout.

GI/GU: Hepatomegaly. Benign hepatic adenomatous nodules are common and can cause massive bleeding. They uncommonly undergo malignant degeneration. Hepatic adenomas have developed in adults who have been treated appropriately for many years. Hepatic cirrhosis has been reported in one boy with type 1B disease. Crohn's disease, chronic inflammatory bowel disease, and perianal abscesses in type 1B. Rarely, pancreatitis as a complication of hyperlipidemia. Renal enlargement, renal calcification, uric acid stones, and nephropathy. Adult patients can have proteinuria, hematuria, or decreased creatinine clearance with progressive renal insufficiency. Delayed puberty. Polycystic ovaries.

Other: Life-threatening hypoglycemia, associated with metabolic acidosis, occurs even after brief periods of fasting. Hypoglycemia is more likely to occur with an unstable diet or with intercurrent illness. Hypophosphatemia, hyperuricemia. Hypertriglyceridemia and hypercholesterolemia. Lipemic plasma. Xanthomas. Platelet dysfunction with a bleeding diathesis mirrors the clinical state. Platelet dysfunction is not due to an absence of glucose-6-phosphatase in the platelets and improves as biochemical derangements are corrected. Anemia (related to hepatic adenomas in type 1A and enterocolitis in type 1B). Poorly controlled patients have growth failure. Intermittent severe neutropenia and recurrent infections in type 1B. Symptoms can be exacerbated during pregnancy. Absent hyperglycemic response to epinephrine or glucagon.

Miscellaneous: Edgar von Gierke was a prominent German pathologist. Patients with von Gierke disease are resistant to the inebriating effects of ethanol, due to its accelerated metabolism. This was the first metabolic defect for which an enzymatic defect was identified.

Anesthetic Considerations: A preoperative fast without supplemental glucose must be avoided. Serum glucose should be monitored perioperatively, and perioperative intravenous fluids should contain glucose. Intravenous fluids containing lactate should be avoided in patients with chronic lactic acidosis. Infants can be obese as a result of frequent demand and nocturnal feedings, which might increase the aspiration risk and make vascular access challenging. In cases of hypoglycemia and no venous access, delivery of 10% glucose-containing fluid by subcutaneous clysis (an old technique) or intraosseous infusion has been suggested (4). Also, raw cornstarch orally (1.6 g/kg) can

maintain blood glucose levels for 4 to 6 hours (4). Renal function should be established preoperatively, particularly in adult or poorly controlled patients. Poorly controlled patients can have symptomatic platelet dysfunction. Platelet function has been reported to improve with both intensive glucose therapy for 24 to 48 hours and desmopressin (DDAVP). Propofol may increase urinary uric acid excretion (6), and this may be a consideration during longer cases using propofol anesthesia or sedation. In addition, there have been several cases reported where pancreatitis developed after the use of propofol (5). A case has been presented where it was postulated that decreases in the bispectral index score were related to decreasing blood glucose levels rather than to changes in anesthetic state (3). Recall that patients will have an absent hyperglycemic response to glucagon. Type 1B patients are at risk for postoperative infectious complications.

Figure: See **Appendix E**

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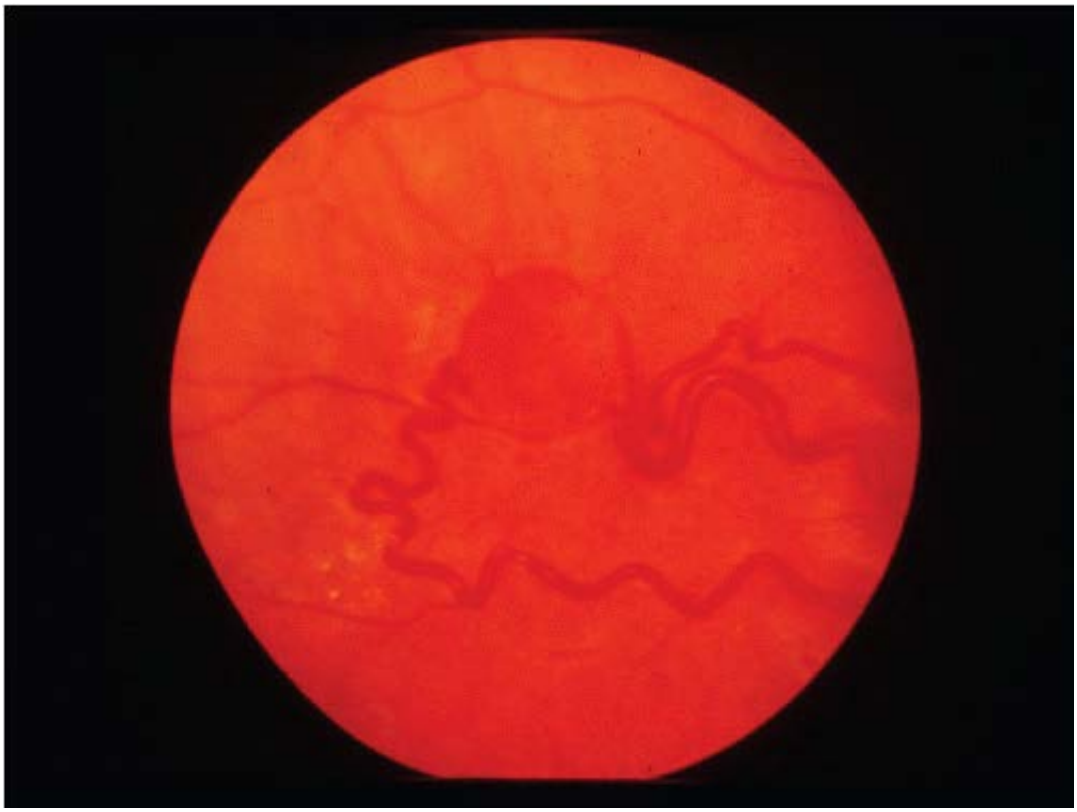
von Hippel-Lindau disease

MIM #: 193300

This autosomal dominant disease is characterized by multiple hemangioblastomas of the retina, central nervous system, and viscera. The hemangioblastomas lack a tight junction and so are prone to leak plasma. The von Hippel-Lindau gene, *VHL*, functions as a recessive tumor suppressor gene, and it is thought that inactivation of both alleles of *VHL* is critical for the development of tumors. One copy of the gene is inherited as a genetic mutation from a parent, and loss of activity of the second gene copy probably occurs as an acquired mutation or chromosomal rearrangement. The protein product of *VHL* posttranslationally modifies hypoxia-inducing factor (HIF) in an oxygen-dependent manner. Thus, with the loss of this gene product, there is excessive production of HIF and gene products targeted by HIF, such as a variety of growth factors and erythropoietin. Approximately half the people carrying the defective gene have only one symptomatic lesion and are unlikely to be diagnosed as having the syndrome.



von Hippel-Lindau syndrome. A retinal angioma with feeder vessels.

Two types of von Hippel-Lindau syndrome have been described. Families with type I disease do not have pheochromocytoma, while families with type II disease are at risk for developing pheochromocytoma. Type II mutations are missense mutations. Type II disease has been further divided into type 2A (with pheochromocytoma), type 2B (with pheochromocytoma and renal cell carcinoma), and type 2C (with isolated pheochromocytoma without hemangioblastoma or renal cell carcinoma).

HEENT/Airway: Retinal vascular hamartomas are distinctive for this disease and are typically its earliest manifestation in type I patients. Capillary hemangiomas, exudative retinopathy, retinal detachment. Tumors of the endolymphatic sac of the ear leading to hearing loss, tinnitus, vertigo, and seventh nerve dysfunction.

Chest: Pulmonary cysts, oat cell carcinoma. Can have pulmonary hemangiomas.

Cardiovascular: Cerebellar tumors can produce episodic hypertension similar to that seen with pheochromocytoma.

Neuromuscular: Cerebellar, medullary, and spinal cord hemangioblastomas. Spinal cord involvement has been reported in up to 100% of patients. Cord lesions are typically single, cervicothoracic, and asymptomatic but can be lumbosacral or involve the

cauda equina. Half of these patients have meningeal varicosities. Hemangioblastomas have also been found in nerve roots and in vertebrae. Intramedullary tumors are associated with syringomyelia in most. Spinal cord hemangiomas can bleed if patients develop hypertension. Cerebellar tumors typically present with signs of increased intracranial pressure, and only occasionally with subarachnoid hemorrhage.

GI/GU: Hepatic adenomas, hepatocellular carcinoma. Pancreatic cysts, islet cell tumors. Renal cysts, ovarian cysts. Hypernephromas and renal cell carcinomas are common. Can have adenomas of the adrenals and bilateral cystadenomas of the epididymis. Females can have mesosalpinx cystadenomas, the equivalent.

Other: Erythrocytosis. Although the hemangioblastomas are benign, they can cause damage based on their location. Pheochromocytomas develop in 7% to 19% overall and can be the presenting finding in type II patients. Symptoms can develop, or become exacerbated, with pregnancy.

Miscellaneous: von Hippel described the retinal lesions. Lindau recognized the association of retinal angiomas (von Hippel disease) and similar tumors of the cerebellum and elsewhere in the central nervous system. Actually, Treacher Collins was the first to recognize the angiomatous nature of the retinal lesions, several years before von Hippel reported his patients. The term “Lindau's disease” was coined by Harvey Cushing.

von Hippel-Lindau syndrome is one of the neuroectodermal disorders, or phakomatoses—along with neurofibromatosis, nevus sebaceus syndrome of Jadassohn, Sturge-Weber syndrome, and tuberous sclerosis. “Phakos” is Greek for a lentil or lens-shaped spot.

Anesthetic Considerations: Spinal cord involvement is usually in the cervicothoracic region, well above the level at which a lumbar catheter would be placed. In fact, epidural and spinal anesthesia has been used successfully for cesarean section (4,8,11) and neurosurgery (to limit the cerebrovasodilatory effects of general anesthetics) (9). However, the incidence of spinal cord involvement would indicate caution in the use of epidural or spinal anesthesia. Preoperative magnetic resonance imaging can delineate the location and extent of spinal hemangiomas. Patients with cerebellar involvement can have increased intracranial pressure, in which case precautions must be taken to avoid further increases in pressure. In addition, these tumors can bleed. Cerebellar tumors can produce episodic hypertension similar to that seen with pheochromocytoma. Since pheochromocytomas are not uncommon and can be undiagnosed, unexpected and otherwise unexplained intraoperative hypertension should at least raise the suspicion of pheochromocytoma.

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von Recklinghausen disease

See Neurofibromatosis

von Voss-Cherstvoy syndrome

See DK-phocomelia syndrome

von Willebrand disease

MIM #: 193400, 277480, 613554

von Willebrand disease is the most common inherited bleeding disorder in humans. The most common symptom is mucocutaneous bleeding. von Willebrand factor (vWF) serves as the first link between platelets and injured blood vessels by binding to platelet receptors GpIb and GpIIb-3a and to ligands within the exposed vessel wall. It is also

the carrier in plasma for factor VIII, localizing it to the initial platelet plug. The disease is due to quantitative or qualitative abnormalities. Type 1 disease, the most common variant (approximately 70% of cases), has low amounts of normal vWF. Almost all the remaining patients have type 2 disease, with qualitative abnormalities with abnormal structure and/or function of vWF. This can be due to

mutations that affect the assembly or secretion of large multimers or which increase peripheral proteolysis. Symptoms are generally mild, and the clinical phenotype differs among the type 2 subtypes. Type 2A results in selective loss of the largest vWF multimers and defective platelet-dependent vWF functions. Type 2B results from a gain-of-function mutation in the platelet binding domain, resulting in excessive platelet binding and circulating thrombocytopenia. Type 2M results in decreased binding at the GpI receptor but without multimer defects. Type 2N is associated with mutations in the factor VIII binding domain of vWF, resulting in a mild hemophilia A-like disorder. Type 3, the least common (1% to 5%) and the most severe, is associated with very low or undetectable levels of vWF and also moderate decreases in factor VIII.

Type 1 disease is autosomal dominant. Type 2 disease is autosomal dominant, although rare cases of recessive disease have been reported. Type 3 disease has been inconsistently reported as autosomal recessive. There is significant clinical variability within type 1, even within families, and laboratory and clinical findings can be discrepant even within an individual. Patients with mild or moderate type 1 disease may experience amelioration of symptoms in the second or third decade of life. von Willebrand disease may also be acquired in association with malignancy, autoimmune disease, and some drugs and in some patients with cardiac valvular disease. Acquired disease is clinically similar to type 2A disease.

HEENT/Airway: Epistaxis, gingival bleeding.

Orthopedic: Hemarthroses are rare and usually only occur with major joint trauma, most commonly in type 3 disease. Muscle hematomas in type 3 disease.

GI/GU: Can have gastrointestinal bleeding. Menorrhagia.

Other: Easy bruising. Prolonged bleeding time. Thrombocytopenia in type 2B during times of increased vWF synthesis, such as pregnancy, as a neonate, or postoperatively, but the thrombocytopenia is rarely low enough to result in excessive bleeding.

Miscellaneous: The first described patient, a young Finnish girl, died from hemorrhage in adolescence when she began menstruating. Individuals with blood type O have baseline vWF levels about 25% less than others but are asymptomatic.

Anesthetic Considerations: Excessive bleeding with trauma and dental extractions. Patients can have delayed bleeding after tonsillectomy. Types 1 and 2A can be treated with desmopressin (DDAVP), which induces vWF and factor VIII secretion from endothelial cells and which increases plasma vWF levels by a factor of 2 to 3. Severe cases of type I or type 2A or 2M are treated with DDAVP plus vWF-containing concentrates such as Humate-P® (also known as Haemate-P® and Hemate P®) Alphanate® or others. Some with types 2A or 2M will be unresponsive to DDAVP. Types 2B, 2N, and 3 are treated with vWF-containing concentrates. Approximately 80% of type 1 patients will respond to DDAVP, and response to one dose predicts responses to future doses. Type 2N and type 3 patients generally do not respond to DDAVP. DDAVP could potentially worsen type 2B disease as the high molecular weight vWF released from storage has a high affinity for GpIb binding sites and can worsen thrombocytopenia. DDAVP is administered 1 hour preoperatively and then every 12 hours for 2 to 4 doses, after which the clinical response is lost. DDAVP therapy is associated with a risk of dilutional hyponatremia, particularly at the extremes of age. It may be relatively contraindicated in patients with coronary artery disease due to a possible increased risk of coronary artery thrombosis. Cryoprecipitate is an alternative for patients who do not respond to DDAVP and when inactivated factor concentrates are not available. Antifibrinolytics are useful particularly for mucosal bleeding.

It is suggested that in patients requiring treatment with concentrates, goals for activity are approximately 50% to 80% in major trauma, surgery, or central nervous system hemorrhage, greater than 50% for childbirth, greater than 30% to 50% for dental extractions or minor surgery, and 20% to 80% for mucous membrane bleeding or menorrhagia. Since the half-life of factor VIII is longer than that for vWF, treatment can potentially result in excessive factor VIII levels and increase the risk of venous thromboembolism. Thromboelastography has been suggested as a method of following therapy in real time (2). Autologous red cells, plasma, and platelets can be collected prior to elective surgery with expected significant blood loss. Multidisciplinary planning with hematologists and surgeons should precede elective surgery.

vWF levels generally rise during pregnancy. However, because of this, type 2B disease may worsen during pregnancy (6). Because of the general improvement during gestation, neuraxial analgesia has been reported in a very few parturients (1), but because of the variability in clinical type and degree of symptoms in all, it should be undertaken after discussions with the patient's hematologist to weigh the risks and advantages. The risk of neonatal disease is not an indication for cesarean section.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

W

Waardenburg syndrome

(Includes Klein-Waardenburg syndrome and Shah-Waardenburg syndrome)

MIM #: 193500

This autosomal dominant disorder is a well-known clinical syndrome that classically consists of congenital deafness and a white forelock as a sign of partial albinism. It is one of several auditory-pigmentary syndromes. Four types have been described: Type 1, due to mutations in the *PAX3* gene, has lateral displacement of the inner canthi of the eyes. *PAX* genes encode transcription factors. Numerous distinct mutations in this gene have been described. The gene product is thought to be involved in early neuronal development. Type 2 is genetically heterogeneous and does not have this lateral displacement. Some cases of type 2 are due to mutations in the gene *MITF*, which encodes a transcription factor important for melanocyte differentiation. Type 3, known as **Klein-Waardenburg syndrome** (*MIM #:* 148820), is uncommon and has the manifestations of type I plus dysplasia of the upper limbs and muscles. This type represents an allelic mutation of the *PAX3* gene. Type 4 is due to mutations in one of several genes and is associated with Hirschsprung disease (see earlier). Type 4 is sometimes referred to as **Shah-Waardenburg syndrome** (*MIM #:* 277580). There is some clinical heterogeneity, and some patients with Waardenburg syndrome are not deaf.

HEENT/Airway: White forelock, which can be present at birth and then become pigmented, or which can persist. Lateral displacement of the inner canthi (“dystopia canthorum”), not present in type 2. Short palpebral fissures, medial flaring of bushy eyebrows, synophrys, hypopigmented fundus, hypochromic pale blue iris, heterochromic irises. Congenital cochlear deafness, unilateral or usually bilateral, with aplasia of the posterior semicircular canal. Wide nasal bridge with hypoplastic alae nasi. Smooth philtrum. Cleft lip and palate have been reported. Broad prognathic mandible.

Chest: Supernumerary ribs.

Type 3: Aplasia of the first two ribs.

Neuromuscular: Spina bifida.

Type 3: Spastic paraplegia, intellectual disabilities.

Orthopedic: Scoliosis. Supernumerary vertebrae.

Type 3: Flexion contractures, sacral abnormalities, fusion of carpal bones, syndactyly.

GI/GU: Hirschsprung disease in type 4—this can be very long segment and even total colonic aganglionosis. Esophageal or anal atresia. Absent vagina and adnexa.

Other: Premature graying, hypopigmented skin lesions.

Miscellaneous: Described independently by Petrus Waardenburg and David Klein. Waardenburg was a Dutch ophthalmologist who made contributions in the field of genetic ophthalmology. He was the first to suggest that Down syndrome was due to a chromosomal abnormality (1932). His last medical paper was published when he was 84 years old.

The association of pigmentary abnormalities and deafness is known in many animal species, and its occurrence in cats was commented upon by Darwin. Neural tube defects are also found in the “splotch” mouse, which carries a mutation in the homologous gene.

Anesthetic Considerations: When meeting patients before surgery, recall that they may have significant hearing loss.

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WAGR syndrome

See Aniridia-Wilms tumor association

Walker-Warburg syndrome

Included in Muscle-eye-brain disease

Warfarin

See Fetal warfarin syndrome

Watson syndrome

MIM #: 193520

This autosomal dominant syndrome was originally described by Watson as involving pulmonic stenosis, dull intelligence, café au lait spots, and short stature. The clinical syndrome has been expanded since Watson's original description. The disorder is due to a mutation in the neurofibromatosis gene (*NF1*). Clinically, the syndrome overlaps with neurofibromatosis (see earlier), although there are significant differences.

HEENT/Airway: Relative macrocephaly. Lisch nodules of the iris are common. Short neck.

Chest: Pectus excavatum.

Cardiovascular: Valvar pulmonary stenosis, which may be severe. Ectasia of the coronary arteries.

Neuromuscular: Low normal intelligence. Watson syndrome is not thought of as having the neurologic manifestations of neurofibromatosis, although one family with central nervous system involvement on magnetic resonance imaging scan has been reported.

Orthopedic: Short stature. Limited knee and ankle movement. Scoliosis.

GI/GU: Retroperitoneal or visceral neurofibromas.

Other: Café au lait spots, axillary freckling, small numbers of neurofibromas.

Anesthetic Considerations: Patients must be carefully positioned and padded secondary to limited lower extremity movement. Isolated pulmonic stenosis is usually well tolerated. Patients with severe pulmonary stenosis should receive an appropriately tailored anesthetic.

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Weaver syndrome

Synonym: Weaver-Smith syndrome

MIM #: 277590

The hallmarks of this usually sporadic, but occasionally autosomal dominant, syndrome are accelerated growth, abnormal facies, and camptodactyly. It is due to mutations in the gene *EZH2* (homologue 2 of Drosophila enhancer of zeste), which encodes a histone methyltransferase that serves to initiate epigenetic silencing of genes involved in cell fate decisions. *EZH2* is a protooncogene.

HEENT/Airway: Macrocephaly, flat occiput. Hypertelorism, epicanthal folds, strabismus, down-slanting palpebral fissures. Large ears. Depressed nasal bridge, long philtrum. Underdeveloped teeth. Large, thick tongue. Relative micrognathia (retrognathia). Prominent chin and chin crease. Short, broad neck with excessive fat (“bull neck”). Low-pitched, hoarse voice with dysarthric speech.

Neuromuscular: Developmental delay, usually mild. Tantrums and behavioral problems. Hypertonia, seizures. Abnormal cerebral vessels.

Orthopedic: Accelerated growth and maturation, beginning prenatally. Advanced bone age. Weight is

increased more than height. Large hands, camptodactyly, broad thumbs, prominent finger pads, hyperextensible

fingers, deeply set nails. Carpal bone age more advanced than phalanges. Limited extension of the elbows and knees. Coxa valga. Foot deformities. Kyphosis. Scoliosis. Unstable upper cervical spine has been reported.

Weaver syndrome. This girl has the typical facies of Weaver syndrome with a “bull neck” and prominent ears.

GI/GU: Inguinal or umbilical hernias. Cryptorchidism.

Other: Loose skin, thin hair. Neoplasia has been reported in some.

Miscellaneous: Also found in Brown Swiss cattle.

Anesthetic Considerations: The bull neck and small mandible (relative to the large head) make visualization of the larynx very difficult. Based on two cases, it has been suggested that the difficulty in laryngoscopy might improve with age (1). Behavioral problems can make the smooth induction of anesthesia a challenge. Excessive fat on the limbs can make intravenous access difficult. Patients require careful perioperative positioning. Chronic use of anticonvulsant medications may affect the metabolism of some anesthetic drugs. An unstable cervical spine is not generally considered to be a part of this syndrome, but has been reported.

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Weaver-Smith syndrome

See Weaver syndrome

Weber-Christian disease

MIM #: None

This chronic disease involves relapsing fever and panniculitis. The etiology of this disease is unknown, and there can be a variety of systemic manifestations. There is a female predominance. It has been suggested that this is an autoimmune disease, and a number of patients have gone on to acquire other autoimmune disorders. Steroid and other immunosuppressive treatments have been used with variable success.

HEENT/Airway: Orbital involvement with panniculitis of the retrobulbar fat with proptosis.

Chest: Pleural panniculitis. Mediastinitis has been reported.

Cardiovascular: Myocardial involvement with heart failure. There can be vascular fragility.

Neuromuscular: Myalgias. Xanthogranulomas arising from the dura mater can occur.

Orthopedic: Arthritis and arthralgias.

GI/GU: Ileal and colonic perforations have been reported secondary to focal disease. Acalculous cholecystitis. Pancreatic or adrenal involvement. Splenic vein occlusion with the development of varices from intraabdominal disease has been reported. Ureteral obstruction from retroperitoneal fibrosis. Membranous glomerulonephritis associated with circulating immune complexes.

Other: Erythematous lesions of the arms and legs from involvement of subcutaneous fat are usually the earliest manifestation, followed by subcutaneous atrophy. Mammary calcifications on mammography. Fever and edema are common. Anemia, leukopenia, and hypocomplementemia. Circulating immune complexes.

Miscellaneous: See Sturge-Weber syndrome for a discussion of Weber. Henry Christian, a native of Virginia, was the first physician in chief at the Peter Bent Brigham Hospital in Boston.

Anesthetic Considerations: The manifestations of this disease are protean, and perioperative care must be tailored (as always) to the individual. The hematocrit should be evaluated preoperatively. Trauma to fat by heat, cold, or pressure should be avoided. Myocardial depressant agents should be used with care if there is evidence of myocardial involvement. Patients taking immunosuppressive drugs can have electrolyte abnormalities. Patients who have been taking steroids require perioperative stress doses. A history of relapsing fever can complicate the interpretation of postoperative fever.

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Weill-Marchesani syndrome

MIM #: 277600, 608328, 614819

This disorder can be autosomal recessive or autosomal dominant. The hallmark features are ectopia lentis, short stature, and brachydactyly. The recessive form is usually due to abnormalities in the gene *ADAMTS10* (encoding a zinc-dependent protease). A second

recessive form is due to mutations in the gene *LTBP2*, which encodes a transforming growth factor-beta binding protein. The dominant form is due to mutations in the gene *FBN1*, which encodes fibrillin. Abnormalities in this gene are also responsible for Marfan syndrome (see earlier) and geleophysic dysplasia-2 (see earlier), with which it shares skeletal and joint features.

HEENT/Airway: Brachycephaly. Lens dislocation (common), small round lens (very common), myopia, glaucoma (common and can be congenital), cataract, blindness. Depressed nasal bridge. Mild maxillary hypoplasia with narrow palate. Malformed, malaligned teeth.

Cardiovascular: Can have subvalvar aortic stenosis or other cardiac defects. Prolongation of the QT interval has been reported.

Neuromuscular: Usually normal intelligence; may have mild intellectual disability.

Orthopedic: Proportionate short stature. Brachydactyly, broad phalanges. Carpal tunnel syndrome. Stiff joints (particularly hands). Scoliosis. Spina bifida occulta. Narrow spinal canal.

Other: Thick skin.

Anesthetic Considerations: When meeting the patient before surgery, recall that he or she may have vision loss and intelligence will be appropriate for chronologic age, not height age. Consider obtaining a preoperative ECG to evaluate the QT interval. Endotracheal intubation can be difficult due to limited mouth opening. A laryngeal mask airway (LMA) has been used successfully. Endotracheal tube depth should be appropriate for patient height. Patients must be carefully positioned and padded perioperatively secondary to joint stiffness. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. Metabolism of ester anesthetics might be inhibited by anticholinesterases taken for glaucoma. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Werdnig-Hoffmann disease

See Spinal muscular atrophy

Werner syndrome

MIM #: 277700

This autosomal recessive disorder is one of apparent premature aging. The disorder is due to abnormalities in the gene *RECQL2*, which encodes a helicase. Helicases regulate DNA synthesis, and its gene product catalyzes DNA unwinding. Some patients with “atypical Werner” syndrome have their disorder due to abnormalities in the gene *LMNA*, which encodes a nuclear lamin. Lamins are proteins that determine the size and shape of the nucleus. Cells from Werner patients are capable of only about one-third of the doublings when cultured *in vitro* compared to normal cells. Children are normal until a failure of the pubertal growth spurt, and other signs and symptoms then follow. The mean age at death is 47 years, with cancer (mostly osteosarcoma and meningioma) the most common cause.

HEENT/Airway: Prematurely aged face. Cataracts. Retinal degeneration. Beaked nose. Premature loss of teeth. Vocal cord atrophy with high-pitched, hoarse voice.

Cardiovascular: Premature atherosclerosis with calcification, hypertension.

Neuromuscular: Muscle hypoplasia. Organic brain syndrome with calcification of the media (Monckeberg arteriosclerosis).

Orthopedic: Short stature [mean height in Caucasian populations of 5 feet 1 inch (157 cm) in males and 4 feet 9 inch (146 cm) in females]. Normal as children, but do not have an adolescent growth spurt. Thin, spindly extremities, small hands and feet. Atrophy of distal extremities. Osteoporosis.

GI/GU: Hypogonadism. Adrenal atrophy.

Other: Loss of subcutaneous fat. Patches of stiffened scleroderma-like skin on the face and lower legs, ulcerations of the skin, thin dermis. Hyperkeratotic palms and soles. Sparse hair. Premature graying and balding. Type II diabetes. Metastatic calcifications. Hypercholesterolemia and hypertriglyceridemia. Increased incidence of a wide variety of malignancies. Mild hyperthyroidism. Increased sensitivity to DNA-damaging drugs, such as chemotherapeutic drugs.

Miscellaneous: Werner reported this disorder as his doctoral thesis in 1904. He was a German general practitioner. Most reported cases have been Japanese.

Anesthetic Considerations: Teeth should be inventoried preoperatively because of premature loss. Loss of subcutaneous fat may make perioperative temperature maintenance difficult. There is a risk of perioperative cardiac ischemia. It is not clear whether drug metabolism mirrors that of elderly patients, although this would be a reasonable assumption. Insulin resistance is treatable with drugs that sensitize insulin action. Cataract surgery has been complicated by wound dehiscence.

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Whelan syndrome

Included in Oral-facial-digital syndrome, type I

Whistling face syndrome

Synonym: Distal arthrogryposis, type 2A; Freeman-Sheldon syndrome; Craniocarpotarsal dysplasia

MIM #: 193700

This usually autosomal dominant disorder is thought to be a slowly progressive myopathy. It is considered to be a distal arthrogryposis, of which ten types have been delineated (this is type 2A). The disorder is due to mutations in the gene *MYH3*, which encodes embryonic skeletal muscle myosin heavy chain 3. Increased muscle tone leads to many of the features of this syndrome, including masklike "whistling" facies, ulnar deviation of the hands, and clubfoot deformity. There are rare reports of an autosomal recessive form of whistling face syndrome.

HEENT/Airway: Full forehead and prominent supraorbital ridges. Can have microcephaly. Abnormal radiologic appearance of the floor of the anterior cranial fossa of the skull. Increased tone and fibrosis of the facial muscles causes an immobile, masklike facial expression. Can have epicanthal folds, ptosis, telecanthus, blepharophimosis. Deeply sunken eyes with hypertelorism. Strabismus. Hearing loss. Broad nasal bridge. Small nose. Hypoplastic alae nasi with notching. Long philtrum. Fibrotic bands around the mouth result in microstomia, pursed lips, and the "whistling face" appearance. High-arched palate. Small tongue and limited palatal movement, which results in nasal speech. Small mandible. Mound of subcutaneous tissue demarcated by "H"-shaped dimple on the chin. Muscle contractures cause cephalad positioning of the larynx. Pharyngeal muscle myopathy can lead to chronic airway obstruction, and children requiring tracheostomy have been rarely reported. Can have short neck.

Chest: Intercostal myopathy and abnormal development of the bony thorax (pectus excavatum). Dysphagia and recurrent vomiting can lead to aspiration pneumonia. Kyphosis, often presenting later in life, can cause restrictive lung disease. Sleep disordered breathing.

Cardiovascular: Cor pulmonale can develop secondary to chronic airway obstruction.

Neuromuscular: Intelligence is usually normal, but intellectual disability occurs in approximately one-third. Generalized myopathy. Increased muscle tone. Can have spina bifida occulta. Can have seizures.

Orthopedic: Kyphoscoliosis develops with time at congenitally malformed vertebrae. Multiple joint contractures can develop. Camptodactyly. Ulnar deviation of the hands. Flexion contractures of the fingers. Adduction of the thumbs. Clubfoot deformity and toe contractures. Can have hip dislocation.

GI/GU: Can have dysphagia and recurrent vomiting. Inguinal hernias. Cryptorchidism.

Miscellaneous: Ernest Freeman was a British orthopedic surgeon. Joseph Sheldon was a British physician who later became the president of the International Association of Gerontologists. The patient in the original case report by Freeman and Sheldon in 1938 had postoperative pneumonia and empyema.

Anesthetic Considerations: The fixed microstomia is not relieved by muscle relaxants. The combination of microstomia, micrognathia, neck shortening, and cephalad positioning of the larynx may make direct laryngoscopy and visualization of the vocal cords extremely difficult or impossible. A laryngeal mask airway (LMA) has been used successfully as a primary airway (8) and to guide fiberoptic intubation (10). The small mouth may not accept an LMA (7), and the LMA can be folded to fit in the small mouth (5).

Chronic airway obstruction can be present in patients with pharyngeal muscle myopathy. Chronic lung disease may have developed in patients with a history of recurrent aspiration pneumonia. Acute aspiration is a risk in those patients with dysphagia and vomiting. There is an increased incidence of postoperative respiratory

complications, in part due to intercostal muscle myopathy and abnormal development of the bony thorax.

Deformities of the hands and feet can make peripheral vascular access more difficult. Patients require careful perioperative positioning because of kyphoscoliosis and extremity contractures. Spina bifida occulta can occur and should be considered prior to utilizing a caudal or epidural block. Although there are no data, succinylcholine

should be used with caution in this myopathy because of the risk of exaggerated hyperkalemia; however, we are aware of its use without hyperkalemic complications in a relatively large number of patients (Berry FA, University of Virginia, personal communication).

Whistling face syndrome has been associated with muscle rigidity after the administration of anesthetic agents (particularly halothane), but has not been associated with malignant hyperthermia (12,13,14).

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Wiedemann-Rautenstrauch syndrome

See Neonatal progeroid syndrome

Wildervanck syndrome

Synonym: Cervicooculoacoustic syndrome

MIM #: 314600

This sporadic syndrome consists primarily of Klippel-Feil sequence (fused cervical vertebrae), abducens palsy with a retracted globe (Duane syndrome), and congenital deafness. The etiology of this syndrome is unknown. Because most patients have been female, the possibility of X-linked dominant inheritance with lethality in boys has been raised, although it is more likely that inheritance is multifactorial. Patients can have severe torticollis, which exacerbates the craniofacial abnormalities.

HEENT/Airway: Asymmetric facies with a low hairline. Can have maxillary, malar, or mandibular hypoplasia. Abducens palsy with retraction of the eye and narrowing of the palpebral fissure of the affected eye on adduction. Pseudopapilledema. Epibulbar dermoids. Deafness due to bony abnormalities of the inner ear. Preauricular pits and skin tags. Can have cleft palate. Very short neck, Klippel-Feil sequence (fused cervical vertebrae). Torticollis.

Chest: Sprengel deformity (winged scapulae). Can have cervical ribs.

Cardiovascular: Can have cardiac defects.

Neuromuscular: Intelligence is usually normal. Can have occipital meningocele or other craniospinal abnormalities and brainstem abnormalities including low cranial nerve abnormalities. There is a case reported of vertebral artery dissection after strenuous physical activity.

Orthopedic: Can have growth deficiency.

GI/GU: Rare cholelithiasis or absent kidney.

Anesthetic Considerations: Consider having an interpreter present perioperatively to ease communication with those patients who are deaf. Diminished neck mobility secondary to the Klippel-Feil sequence or torticollis can make laryngoscopy and intubation extremely difficult, and fiberoptic techniques have been recommended. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Williams syndrome

Synonym: Williams-Beuren syndrome; Elastin arteriopathy

MIM #: 194050

This autosomal dominant disorder classically involves “elfin” facies, supravalvar aortic stenosis, and neonatal hypercalcemia. It is a continuous gene disorder caused by deletions on the long arm of chromosome 7, and the phenotype is due, at least in part, to a deletion of the elastin gene. However, as a continuous gene disorder, involvement of several other nearby genes in developing the clinical phenotype would account for the clinical heterogeneity.

HEENT/Airway: “Elfin” facies that coarsen with aging. Puffy eyes. Lacy, stellate iris pattern. Strabismus, esotropia. Hyperacusis. Mild-to-moderate high-tone hearing loss can develop in adolescents and adults. Depressed nasal bridge, anteverted nares. Long philtrum. Wide smile. Small teeth. Enamel hypoplasia. Harsh or brassy voice. A patient with bilateral vocal cord paralysis has been described.

Cardiovascular: An arteriopathy of medium and larger arteries due to thickening of the media from smooth muscle overgrowth. Aortic stenosis, typically supravalvar but also valvar or rarely subvalvar. Can have bicuspid aortic valve, mitral valve prolapse, mitral insufficiency, left coronary artery stenosis, myocardial ischemia. Can have myxomatous degeneration of the aortic and mitral valves. Superior displacement of the coronary artery ostia. Distorted aortic valve leaflets can obstruct either main coronary artery ostium. In the case of supravalvar aortic stenosis, the coronary arteries arise from the proximal, hypertensive aorta and can develop dysplastic, thickened walls with luminal narrowing. Multiple areas of peripheral pulmonary artery stenosis, which can resolve spontaneously. Abdominal aortic coarctation and narrowing of celiac, mesenteric, and renal arteries have been reported. Carotid ultrasounds show increased wall thickness in all cases. Hypertension, which can begin in childhood. More than 10% of patients will have a prolonged QTc. There is an overall 3% incidence of sudden death with a 30-year follow-up. Cardiovascular disease is more common and more severe in males.

Neuromuscular: Mild intellectual disability. Specifically, there appears to be poor visual motor integration. Attention deficit disorder. Language development is normal, and some components of language, such as social uses of language, can be relatively advanced, so intellectual disability is easily overlooked. Patients often have musical ability. Infantile hypotonia. Hypertonicity later. Cerebral artery stenoses with ischemic events. Can have type I Chiari malformation.

Williams syndrome. A young girl with Williams syndrome posing with her beauty pageant trophies. Her friendly personality is evident. (Courtesy of Dr. Sharon Hostler, University of Virginia Health System.)

Orthopedic: Short stature. The pubertal growth spurt occurs earlier in both girls and boys. Hypoplastic nails. Hallux valgus. Progressive joint limitation.

GI/GU: Chronic constipation, diverticulosis, inguinal hernias. Nephrocalcinosis, urinary anomalies, or stenoses with

recurrent urinary tract infections. A variety of renal structural anomalies. Renal artery stenosis.

Other: Neonatal hypercalcemia, although hypercalcemia can persist until adulthood. Although a classical finding, it is less commonly found than is diabetes. There is a high incidence of glucose intolerance. The incidence is high in general and yet higher with obesity. Can have hypothyroidism, which is usually subclinical. Early menarche. Premature graying of the hair.

Miscellaneous: As children, these patients are described as socially gregarious, friendly, and empathetic and as having a “cocktail party” personality. However, adults have a high incidence of anxiety, obsessions, and irritability. Although commonly asserted to be musically talented, and even to have perfect pitch, this claim has not been substantiated.

Born in New Zealand, Williams also spent time working in London. Presumably on his way to accept a job at the Mayo Clinic in the United States, Williams disappeared and was not heard from again. An unclaimed suitcase of his was discovered in a luggage office in London.

Anesthetic Considerations: Sudden death has been reported, outside of the hospital as well as during cardiac catheterization and during anesthesia (3,6,7). The risk of sudden death is thought to be related to the severity of the vascular stenoses or ischemic coronary disease, even in young children. The degree of supravalvar aortic stenosis does not correlate with the degree of coronary disease or risk. Patients with biventricular outflow obstruction or evidence of ischemic disease are thought to be at particular risk. Impairment in cardiac supply-demand can be related to ventricular hypertrophy (demand) or hypotension, tachycardia, or coronary artery disease (main coronary artery orifice obstruction from thickened aorta, adhesion of aortic valve leaflet obstructing orifice, coronary vessel abnormalities from chronic hypertension or primary arteriopathy) (supply). Prolonged QTc has been described in over 10% of children with Williams syndrome (1). Baseline electrocardiogram and echocardiogram should be obtained.

Ketamine is not optimal for patients with coronary artery involvement (6), and similarly epinephrine is relatively contraindicated in treating cardiac arrest if there is an appropriate rhythm present. Patients with outflow obstruction can have hypertrophied, underfilled ventricles. The anesthetic approach should generally mirror that taken for an adult with real or suspected coronary artery disease. Positioning may become more difficult with aging due to limitations in joint movement. Patients, particularly neonates, should be evaluated preoperatively for hypercalcemia.

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Williams-Beuren syndrome

See Williams syndrome

Williams-Campbell syndrome

MIM #: 211450

This rare, probably familial, disorder of bronchomalacia is characterized by deficiency of cartilage in the distal, subsegmental bronchi causing airway obstruction and cystic bronchiectasis. Respiratory symptoms can vary from severe, with death from respiratory failure, to mild, with survival into old age. Partial lung resection has not proven helpful.

Respiratory: Small airway collapse leading to air trapping and respiratory distress. Cystic bronchiectasis. Chronic cough, wheezing. Recurrent pulmonary infections.

Anesthetic Considerations: It has been suggested that spontaneous ventilation without muscle relaxation (which could decrease chest wall rigidity and worsen airway collapse) is the ideal perioperative ventilatory mode. Mechanical ventilation may exacerbate air trapping. If mechanical ventilation is necessary, consider utilizing a prolonged expiratory time and positive end-expiratory pressure (PEEP). Neuraxial analgesia may be a useful adjunct. These patients are at risk for postoperative respiratory complications, and close monitoring should continue into the postoperative period. Patients require good chest physiotherapy postoperatively and are at risk for postoperative respiratory infections. In one fatal case, it was suggested that the loss of airway pressure following tonsillectomy contributed to acute worsening of the airway disease (2).

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Wilson disease

Synonym: Hepatolenticular degeneration

MIM #: 277900

This autosomal recessive disorder of copper metabolism results in the intracellular accumulation of copper initially in the eye and the liver and eventually in many other tissues throughout the body, when copper overloaded hepatic cells die and release copper into the circulation. Children tend to present with hepatic disease, clinically similar to chronic active hepatitis. Older patients present with predominantly neurologic disease.

The responsible gene *ATP7B* encodes a cation-transporting ATPase. The gene product is thought to be similar to that causing Menkes kinky-hair syndrome (see earlier) in that both have the characteristics of a copper-transporting adenosine triphosphatase. The Wilson disease gene product is involved with the export of copper out of cells, whereas the Menkes kinky-hair syndrome gene product is involved with the transport of copper into cells.

Patients may be treated with a chelating agent. Treatment with penicillamine is associated with inhibition of pyridoxine-dependent enzymes requiring pyridoxine supplementation, zinc deficiency requiring zinc supplementation, fever, urticaria, systemic lupus erythematosus, hemolytic anemia, Goodpasture syndrome, and a syndrome resembling myasthenia gravis. Another chelating drug that has been used is trientine (triethylenetetramine dihydrochloride). Zinc supplementation has also been used therapeutically. Liver transplantation is curative.

HEENT/Airway: Kayser-Fleischer rings are pathognomonic—may require slit-lamp examination to identify. These are copper deposits in the Descemet membrane of the cornea. Kayser-Fleischer rings mirror neurologic involvement. Patients with hepatic disease only do not have them. “Sunflower” cataracts from copper deposition in the lens.

Cardiovascular: Cardiomyopathy is rare.

Neuromuscular: Copper accumulation in the brain, particularly the basal ganglia. Neurologic problems prominent in adolescents and adults. Degeneration of the basal ganglia, extrapyramidal signs. Dysarthria, dystonia, choreoathetosis, tremors, ataxia, peripheral neuropathy, seizures, parkinsonism. Intellectual impairment and pseudobulbar palsy occur late. Can have behavioral and psychiatric problems. The disease is fatal if untreated.

Orthopedic: Osteoarthropathy, chondrocalcinosis. Fingernails can exhibit “azure lunulae” (discoloration from copper).

GI/GU: Hepatic failure, which can be the presenting finding. Onset is gradual, but there can be acute episodes of hepatorenal failure with hemolysis (often fatal). Cirrhosis. Rarely hepatocellular carcinoma. Portal hypertension. Esophageal varices. Patients can have difficulty swallowing late in the disease. Calcified, pigmented gallstones. Pancreatic disease. Can have hypercalciuria, nephrocalcinosis with renal stones, renal tubular acidosis, Fanconi syndrome (see earlier).

Other: Acute hemolytic episodes. Anemia, neutropenia, thrombocytopenia. Hypoparathyroidism. Coagulopathy

with hepatic failure.

Miscellaneous: Samuel Wilson was a neurologist at the National Hospital, Queen Square, London. Seen by some as arrogant and insensitive, he once instructed a patient to “see to it that I get your brain when you die.” Wilson's paper describing the disease introduced the term “extrapyramidal.”

Anesthetic Considerations: This disease can affect numerous organ systems, and anesthesia care needs to be tailored (as always) to the individual patient. A preoperative baseline hematocrit and platelet count should be obtained, particularly in patients taking penicillamine. Hepatic failure may lead to abnormal coagulation and may affect protein binding of some anesthetic drugs. Hepatic biopsy specimens must be specially handled to avoid copper contamination. Anticonvulsant medications need to be continued (or a parenteral form substituted) and can affect the metabolism of some anesthetic drugs. Metoclopramide can cause extrapyramidal effects and probably should be avoided. Phenothiazines, butyrophenones, and other dopaminergic blockers can exacerbate movement disorders. Ondansetron should be safe as an antiemetic because it does not have antidopaminergic effects.

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Wiskott-Aldrich syndrome

(Includes X-linked thrombocytopenia; Severe X-linked neutropenia)

MIM #: 301000

The primary manifestations of this X-linked recessive immune deficiency disease are eczema, thrombocytopenia with small platelets, B-cell lymphomas, and

recurrent infection. Petechiae, bloody stools, and bruising can appear in the first days of life, and protracted bleeding after circumcision leads eventually to the diagnosis. The gene product of the responsible gene, called WASP for Wiskott-Aldrich syndrome protein, is involved in the organization of the actin cytoskeleton. WASP is only found in hematologic cells. Mutations in the *WASP* gene lead to various physiologic effects involving all of the hematopoietic cell lines, with platelets being the most severely affected. T cells from these patients have

deficient surface microvillus projections. In addition, deficits in the cell membrane glycoprotein sialophorin have been described. Many different mutations in the gene have been described. Wiskott-Aldrich syndrome has been reported in girls, due to nonrandom inactivation of X chromosomes. Splenectomy results in normalization of platelet size and often number. Bone marrow or umbilical cord blood transplantation is curative. Successful gene therapy has also been reported, either through the introduction of the gene via a *WASP*-expressing retroviral vector or by introducing a modified HIV virus into autologous hematopoietic stem cells.

A milder disease, **X-linked thrombocytopenia** (*MIM #:* 313900) that is associated with thrombocytopenia and milder eczema and immunodeficiency, is due to abnormalities in the *WASP* gene that result in diminished but not absent WASP protein. Another allelic disorder is **severe X-linked neutropenia** (*MIM #:* 300299), which involves neutropenia only.

HEENT/Airway: Recurrent oral infections can result in early tooth loss. Recurrent otitis media, sinusitis. Epistaxis.

Chest: Recurrent pulmonary infections.

Cardiovascular: An autoimmune vasculitis can affect the coronary arteries.

Neuromuscular: Intracranial hemorrhage. An autoimmune vasculitis can affect the cerebral arteries.

GI/GU: Bloody diarrhea. Patients may require a splenectomy to control thrombocytopenia. Renal insufficiency.

Other: Eczema. Thrombocytopenia, small platelet size (which normalizes after splenectomy), bleeding diathesis. Significantly increased incidence of autoimmune disorders. There are many varieties of autoimmune disease, including Coombs-positive hemolytic anemia, a juvenile rheumatoid arthritis-like disease, vasculitis that can affect coronary and cerebral vessels, and a superimposed idiopathic thrombocytopenic purpura-like thrombocytopenia that may become apparent only after splenectomy. Increased incidence of malignancies, particularly lymphoreticular. The most common malignancies are non-Hodgkin lymphoma and brain cancer. There is often a widespread peripheral lymphadenopathy. These nodes remain tumor free (unless widespread disseminated cancer develops).

Immune deficiency. The immune defects are selective, rather than global. There is variable immunoglobulin deficiency. The most common pattern is normal IgG, elevated IgA, and decreased IgM. Increased metabolism of immunoglobulins and albumin. Antibody responses are normal to some antigens and absent to others. There is absent antibody formation to all of the polysaccharide antigens, with low or absent isohemagglutinins and an inability to make antibody to capsular polysaccharides of *Haemophilus* or pneumococci. Selective T-cell abnormalities are present, and there is cutaneous anergy. Abnormal function of monocytes. Neutrophils have abnormal chemotactic, but normal bacteriocidal function. Patients are at particular risk from overwhelming chickenpox. Other infectious agents include *Streptococcus pneumoniae, Haemophilus influenzae, Candida albicans*, cytomegalovirus, herpes simplex, and *Pneumocystis carinii*. Disseminated vaccinia was a cause of death after receiving smallpox vaccination.

Miscellaneous: Wiskott, a German, described the disease 17 years before Aldrich, an American. Wiskott called it Werlhof's disease, the eponymous designation of thrombocytopenic purpura.

Anesthetic Considerations: Meticulous aseptic technique is imperative. The platelet count should be evaluated preoperatively, and platelet transfusion may be indicated. Neuraxial analgesia may be contraindicated with low platelet count. The hematocrit should be evaluated preoperatively. All transfused blood products must be irradiated to prevent graft-versus-host disease. Baseline renal function should be evaluated preoperatively. Patients who are taking steroids should receive perioperative stress doses of steroids.

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Wolf-Hirschhorn syndrome

See 4p-syndrome

Wolff-Parkinson-White syndrome

MIM #: 194200

Wolff-Parkinson-White syndrome (WPW) is an electrophysiologic syndrome due to the presence of Kent fibers, which are conduction fibers that run along the lateral margins of the atrioventricular valves, bypassing the atrioventricular node to enter the ventricular myocardium directly. Bypass of the atrioventricular node leads to a short PR interval (the normal atrioventricular node delay is bypassed) and the initial slow upstroke of the QRS, secondary to initial cell-to-cell transmission of the electrical impulse, until the normally conducted impulse finally gets through the atrioventricular node and depolarizes the ventricles rapidly through the His-Purkinje system. The presence of Kent fibers creates a potential reentry circuit increasing the risk for the development of paroxysmal supraventricular tachycardia. It is thought that these bypass tracts represent persistence of a normal fetal structure. WPW is most common in the neonatal period, and many cases spontaneously regress by approximately 6 months of age, when chronic treatment often can be stopped. Familial cases have been described, and a gene that encodes the gamma-2 regulatory subunit of AMP-activated protein kinase has been identified as the responsible gene. Ablation of the bypass tract in the catheterization laboratory is curative. Young infants can be asymptomatic until they present with profoundly symptomatic heart failure secondary to tachycardia. When a supraventricular tachycardia is present, the rate tends to be inversely proportional to the age, about 200 to 220 per minute in neonates to about 150 per minute in adults.

There are two types of WPW, diagnosed electrocardiographically. Type A represents a left-sided bypass tract and type B a right-sided bypass tract. WPW is somewhat similar to Lown-Ganong-Levine syndrome (see earlier).

Cardiovascular: Wolff-Parkinson-White syndrome can be associated with a variety of congenital cardiac defects, such as Ebstein anomaly of the tricuspid valve.

Type A: The electrocardiogram shows a short PR interval (<120 ms) and a delta wave at the onset of the QRS. There is a delta wave and a prominent R wave in leads V1 and V2.

Type B: Negative delta wave and a prominent S wave in leads V1 and V2.

Miscellaneous: One of us had the opportunity to speak with the patient who was case number two in the original case report of Wolff-Parkinson-White syndrome. He had been at that time a swimmer on the Yale swim team and confided that he had been unsure if he could trust young Dr. White (Paul Dudley White), a Harvard doctor.

Interestingly, Kent actually described Mahaim fibers (similar specialized conducting fibers, but nodoventricular) and Mahaim described Kent fibers. John Parkinson of Wolff-Parkinson-White syndrome is distinct from James Parkinson of Parkinson's disease.

Anesthetic Considerations: Episodes of reentrant tachycardia can be induced by sympathetic stimulation, so good preoperative sedation would seem reasonable. Perioperative increases in vagal tone, such as from drugs or gagging, may inhibit normal antegrade conduction through the atrioventricular node and unmask conduction down the bypass tract, with preexcitation (short PR interval and delta wave) becoming suddenly visible. Similarly, 1.0 mg of neostigmine (without an anticholinergic) has converted hemodynamically stable atrial fibrillation with a narrow QRS complex into hemodynamically unstable atrial fibrillation with a more rapid ventricular response and a wide QRS, presumably on the basis of increased vagal tone, enhancing accessory pathway conduction (2). Atropine produces normal atrioventricular conduction and can cause the delta wave to disappear. Atropine premedication would be relatively contraindicated as it could precipitate a pathologic tachycardia. Atrial fibrillation can develop during the increase in sympathetic tone during emergence from general anesthesia. Episodes of tachycardia have also occurred for the first time in a patient with concealed Wolff-Parkinson-White syndrome during spinal anesthesia (9) and have been induced by passing a central venous guidewire.

Isoflurane has been used without apparent problems during electrophysiologic mapping or radiofrequency catheter ablation (6,7), and it appears that sevoflurane can also be used for these procedures (4). Propofol and fentanyl have been used uneventfully for general anesthesia (3,7). Remifentanil, although it can cause bradycardia, has no effect on atrial-His conduction. Patients with congenital heart disease will require an appropriately tailored anesthetic.

Drugs and maneuvers that can be used perioperatively to convert paroxysmal supraventricular tachycardia are the same as for paroxysmal supraventricular tachycardia not associated with WPW: namely, adenosine, verapamil, beta-blockade, amiodarone, or overdrive pacing [transesophageal pacing has been used successfully (10)]. Drugs used to terminate tachycardia (adenosine or beta-blockers) can exacerbate reactive airway disease (5). $Beta_2$-agonists such as albuterol should not induce arrhythmias (8).

Verapamil and digoxin (without quinidine) are contraindicated for the treatment of atrial flutter or fibrillation in patients with WPW because they can accelerate the rate of conduction through the bypass tract and induce ventricular fibrillation. Procainamide may be useful for atrial fibrillation in this setting. Concurrent verapamil and propranolol

(and possibly other combinations of calcium channel blockers and beta-blockers) can cause significant bradycardia. Chronic therapy with amiodarone can cause hypothyroidism or pulmonary fibrosis. Calcium channel blockers, although they can be effective, are contraindicated in infants up to at least 6 and possibly 12 months of age, as immature myocardium is overly sensitive to extracellular ionized calcium levels in maintaining contractility. Blocking transsarcolemmal entry of calcium can be devastating in these infants.

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Wolfram syndrome

See DIDMOAD syndrome

Wolman disease

(Includes Cholesterol ester storage disease)

MIM #: 278000

This autosomal recessive disorder is due to deficient activity of lysosomal acid lipase (cholesterol ester hydrolase), which is encoded by the gene *LIPA*. The major function of this enzyme is the hydrolysis of cholesterol esters in various lipoproteins. Wolman disease results in widespread deposition of cholesterol esters and triglycerides in

lysosomes, with secondary fibrosis. There is massive infiltration and organomegaly of the liver, spleen, and other organs by macrophages loaded with cholesterol esters and triglycerides. Wolman disease has profound manifestations in infancy and is usually fatal in the first year of life. Both hematopoietic stem cell and umbilical cord blood transplantation have had some success.

Different alleles result in both Wolman disease and the milder disease, **cholesterol ester storage disease** (cholesteryl ester storage disease, *MIM #:* 278000). Cholesterol ester storage disease is associated with hepatomegaly and may not present until adulthood. It is sometimes associated with cirrhosis, portal hypertension, intestinal involvement, and hypercholesterolemia and hypertriglyceridemia, which can respond to treatment with statin drugs.

Cardiovascular: Pulmonary hypertension has been reported. Lipid deposition in vessels without gross atherosclerosis, perhaps due to early deaths.

Neuromuscular: Normal at birth, with deterioration within a few weeks.

GI/GU: Diarrhea, vomiting, steatorrhea, abdominal distention. Hepatic deposition of cholesterol esters and triglycerides, abnormal liver function tests, portal fibrosis. Hepatosplenomegaly, which can be massive. Esophageal varices. Involvement of small bowel mucosa, particularly the proximal small bowel. Adrenal gland deposition with enlargement and finely stippled calcification.

Other: Malabsorption, malnutrition. Failure to thrive. Anemia. Persistent low-grade fever. Foam cells in the bone marrow, vacuolated lymphocytes.

Miscellaneous: The first reported case was, in retrospect, that of Alexander, who reported what he called a case of Niemann-Pick disease with adrenal calcification.

Anesthetic Considerations: The hematocrit should be evaluated preoperatively. Hepatic insufficiency can affect the binding of some anesthetic drugs. The presence of esophageal varices is a relative contraindication to placement of a nasogastric tube.

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Authors: **Baum, Victor C.; O'Flaherty, Jennifer E.**
Title: ***Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood, 3rd Edition***

X

Xanthine dehydrogenase deficiency

Included in Molybdenum cofactor deficiency

Xanthinuria

Synonym: Hereditary xanthinuria

MIM #: 278300, 603592

This autosomal recessive disorder of renal stone formation is due to deficient activity of xanthine dehydrogenase (xanthine oxidoreductase). This enzyme catalyzes the conversion of xanthine and hypoxanthine to uric acid, the last step in purine catabolism. A significant number of patients are asymptomatic and are discovered fortuitously by low serum uric acid. Combined deficiency of xanthine oxidase and sulfite oxidase, due to a molybdenum cofactor deficiency (see earlier), is not uncommon. There are two biochemically distinct forms of xanthinuria. In xanthinuria type I, only xanthine dehydrogenase activity is deficient. In xanthinuria type II, there is deficiency of both xanthine dehydrogenase and aldehyde oxidase, purportedly due to an abnormality in molybdenum cofactor sulfurase. The only clinical difference is that type I patients can metabolize allopurinol, while type II patients cannot.

Neuromuscular: Myopathy with crystalline deposits of xanthine and hypoxanthine causing muscle pain and cramps has been reported. These may have been caused by exercise, which increases nucleotide turnover.

GI/GU: Hyperxanthinuria. Xanthine renal stones (brown, radiolucent), hematuria, hydronephrosis, renal colic, recurrent urinary tract infections, renal failure. Stones can occur during infancy. Infants can have intermittent hematuria and occasional orange-brown staining of diapers.

Other: Decreased serum uric acid. Failure to thrive. Patients may be on a low purine diet.

Miscellaneous: Hypoxanthine and xanthine accumulate during ischemia, and oxidants are produced upon reperfusion. Tissue injury from reperfusion injury can be ameliorated by inactivation of xanthine dehydrogenase (the enzyme also functions as an oxidase).

Anesthetic Considerations: Renal failure (if present) affects perioperative fluid management and the metabolism of some anesthetic drugs. Perioperative fluid administration must be adequate to maintain a diuresis and prevent further concentration of xanthine in the urine. Although xanthine is somewhat more soluble at an alkaline pH, alkalinization of the urine is not very effective. Methylxanthines such as theophylline and caffeine are not metabolized by xanthine oxidase and are not contraindicated.

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X-associated tremor/ataxia syndrome

Included in Fragile X syndrome

Xeroderma pigmentosum

MIM #: 194400, 278700, 278720, 278730, 278740, 278750, 278760, 278780, 278810

This disorder, of which there are many subtypes, is an autosomal recessive defect in the repair of ultra-violet-induced damage to DNA. The defect can be identified prenatally in cultured fibroblasts obtained by amniocentesis. De Sanctis-Cacchione syndrome (see earlier) is a severe subtype of xeroderma pigmentosum. Most of the clinical findings are related to excessive sensitivity to sunlight, including eye changes, atrophic and pigmentary skin changes, and actinic skin tumors. The severity of eye and skin lesions is related to the degree of sun exposure. Some subtypes involve neurologic abnormalities. It is thought that neurologic injury is secondary to neuron loss from DNA damage due to oxidative metabolism. Death is often secondary to cancer.

Patients with xeroderma pigmentosum have been classified into 10 complementation groups (A through I, plus a variant), each corresponding to a different gene. It may be that groups D and H are the same. These divisions are based on the ability of cells from one group to correct the defect when hybridized with cells from the other groups. Clinical findings vary somewhat among the groups. Groups A, C, and D are the most common. Neurologic problems are usually found in groups A and D patients, and they have the lowest level of DNA repair. Group C patients have the highest level of DNA repair, and have a longer life expectancy. Readers are directed to other sources, such as *Mendelian Inheritance in Man*, for a discussion of the

various genes, gene products, and biochemical pathophysiologies involved in the various types. This disorder is now grouped as one of the nucleotide excision repair (NER) disorders.

HEENT/Airway: Can have microcephaly. Photophobia, conjunctival injection, and corneal clouding or vascularization from exposure. Conjunctival, corneal, and lid tumors. Ectropion. Occasional sensorineural hearing deficit. Atrophic skin around the mouth sometimes limits mouth opening. Squamous cell carcinoma of the tip of the tongue, gingiva, or palate.

Neuromuscular: Progressive central nervous system deterioration with cerebral atrophy, choreoathetosis, ataxia, and spasticity. Brain tumors may develop.

Other: Skin abnormalities typically begin during early childhood. Excessive sensitivity to sunlight with severe sunburn, freckling, atrophy with irregular pigmentation, telangiectasis, angiomas, keratoses, basal cell and squamous cell carcinomas in sun-exposed areas. Skin cancers are of several types, but basal cell and squamous cell carcinomas are most frequent. Less common are keratoacanthoma, adenocarcinoma, melanoma, neuroma, sarcoma, or angiosarcoma. The median age for the development of the first skin cancer is 8 years. Nonskin cancers

such as brain or lung cancer or leukemia can develop. Can have frequent infections.

Miscellaneous: Xeroderma pigmentosum was first described by Moritz Kaposi (born Moritz Kohn). DNA repair mechanisms are abnormal in four other inherited diseases: ataxia-telangiectasia, Fanconi anemia, Bloom syndrome, and Cockayne syndrome.

Anesthetic Considerations: Perioperative radiographic studies are indicated only when absolutely necessary because these patients are sensitive to irradiation. Consideration should be given to patients with photophobia in brightly lit operating rooms. Limited mouth opening has not been reported to hinder laryngoscopy and tracheal intubation. It has been hypothesized that because volatile anesthetics can interfere with DNA repair they be avoided, and there has been a single case report of neurologic deterioration immediately following general anesthesia (1).

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2. DiGiovanna JJ, Kraemer KH. Shining a light on xeroderma pigmentosum. *J Invest Dermatol* 2012;132:785-796.

3. Lehmann AR, McGibbon D, Stefanini M. Xeroderma pigmentosum. *Orphanet J Rare Dis* 2011;6:70.

4. Brunner T, Jöhr M. Anesthetic management of a child with xeroderma pigmentosum. *Paediatr Anaesth* 2004;14:697-698.

X-linked alpha-thalassemia/Mental retardation syndrome

See ATR-X syndrome

X-linked hydrocephalus syndrome

See MASA syndrome

X-linked hypophosphatemic rickets

See Vitamin D-resistant rickets

X-linked thrombocytopenia

Included in Wiskott-Aldrich syndrome

XO syndrome

See Turner syndrome

XXXXX syndrome

See Penta X syndrome

XXY syndrome

See Klinefelter syndrome

XXXY syndrome

Included in Klinefelter syndrome

XXXXY

Included in Klinefelter syndrome

XXYY syndrome

Included in Klinefelter syndrome

XYY syndrome

MIM #: None

This disorder is due to an extra Y chromosome. These boys are 47, XYY. Most people with XYY are asymptomatic and are not diagnosed.

HEENT/Airway: Macrocephaly in some. Prominent glabella (the part of the forehead just above the nose). Hypertelorism. Long ears. Shallow palate, large teeth.

Chest: Mild pectus excavatum.

Cardiovascular: First-degree atrioventricular block.

Neuromuscular: Hypotonia. Decreased frontotemporal gray and white matter. Intelligence within the normal range, but usually less than siblings. Speech delay and learning disabilities. Behavioral problems with easy distractibility, hyperactivity, and temper tantrums. Aggressiveness is usually controllable by patients as they age, and behavioral problems are usually not significant for these boys as they get older. Relatively weak, with poor fine motor control and sometimes fine tremor. Psychiatric problems (schizophrenia) have been reported.

Orthopedic: Relatively long and thin body habitus with long fingers. Size is usually normal until a growth spurt at approximately 5 to 6 years of age. Radioulnar synostosis. Clinodactyly.

GI/GU: May have cryptorchidism, small penis, hypospadias. Testicular enlargement. Several case reports suggest an association with renal agenesis or dysplasia and Potter syndrome (see earlier) with XYY syndrome. Infertility from oligospermia or azoospermia has been reported.

Other: Severe acne during adolescence.

Anesthetic Considerations: Preoperative management may be challenging in patients with behavioral problems, particularly if they are hyperactive or aggressive. Baseline renal function should be evaluated as indicated.

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Y

Yunis-Varon syndrome

MIM #: 216340

Yunis-Varon syndrome is an autosomal recessive disorder primarily involving growth failure and orthopedic abnormalities. Survival is poor beyond the neonatal period. It is due to mutations in the gene *FIG4*. *FIG4* is a phosphatase that regulates phosphatidylinositol 3,5-bisphosphate in the membranes of intracellular transport vesicles. There are enlarged cytoplasmic vacuoles in neurons, muscle, and cartilage.

HEENT/Airway: Microcephaly. Dolichocephaly. Thin scalp hair, eyebrows, and eyelashes. Wide sutures and fontanelles. Short, upslanting palpebral fissures and cataracts. Protruding eyes. Chorioretinopathy has been reported in one family. Low-set ears. Dysplastic ears. Anteverted nares, short philtrum, thin lips. Premature loss of deciduous teeth. Micrognathia. Loose neck skin.

Chest: Hypoplastic or aplastic clavicles. Absent nipples. Recurrent pneumonia.

Cardiovascular: Tetralogy of Fallot or ventriculoseptal defect have been described in two patients. Cardiomyopathy or cardiomegaly is uncommon. Primary pulmonary hypertension has been reported.

Neuromuscular: Severe developmental delay. Agenesis of the corpus callosum, abnormal cerebellar vermis, arhinencephaly, pachygyria. Vacuolated neurons.

Orthopedic: Hypoplasia or agenesis of the thumbs and great toes; short, tapered fingers with nail hypoplasia; hypoplasia or agenesis of the middle and distal phalanges of the fingers and toes; syndactyly; simian crease. Abnormal or absent scapulae, absent sternal ossification. Dislocated hips.

GI/GU: A patient has been reported with atrophy of the left lobe of the liver with a hepatic vascular anomaly. Abnormal external genitalia with undescended testes, micropenis, or hypospadias.

Other: Prenatal growth deficiency with postnatal failure to thrive.

Anesthetic Considerations: Experiences with anesthesia have not been reported with this syndrome. A careful assessment should be made of the deciduous teeth preoperatively, which can be prematurely loose. Micrognathia may complicate direct laryngoscopy and tracheal intubation. A single child with upper airway obstruction with obstructive sleep apnea has been reported. The presence of obstructive sleep apnea may increase the risk of perioperative respiratory complications, and close monitoring should continue into the postoperative period. Abnormalities of the clavicles make placement of a subclavian venous catheter or an infraclavicular block more difficult. Patients with cardiac disease require an appropriately tailored anesthetic.

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1. Basel-Vanagaite L, Kornreich L, Schiller O, et al. Yunis-Varon syndrome: further delineation of the phenotype. *Am J Med Genet A* 2008;146:532-537.

2. Hennekam RCM, Vermeulen-Meiners C. Further delineation of the Yunis-Varon syndrome. *J Med Genet* 1989;26:55-58.

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Z

Zellweger syndrome

Synonym: Cerebrohepatorenal syndrome

MIM #: 214100

This autosomal recessive disorder, marked by craniofacial abnormalities, hepatomegaly, and abnormal brain development, is associated with generalized peroxisomal dysfunction and an absence of peroxisomes. It has been suggested that the same gene [peroxin-1 (*PEX1*)], the functioning of which is required for transportation of proteins into peroxisomes, is involved in infantile Refsum disease (see earlier), neonatal adrenoleukodystrophy (see earlier), and Zellweger syndrome. These three disorders may represent a continuum of peroxisome biogenesis disorders, with Zellweger syndrome being the most severe, neonatal adrenoleukodystrophy being the intermediate, and infantile Refsum disease being the least severe. In addition, the Zellweger phenotype can be caused by defects in a variety of other genes encoding peroxisomal proteins, including *PEX2, PEX3, PEX5, PEX6, PEX12*, and others. Early in life, symptoms may resemble a malabsorption syndrome. Life expectancy is approximately 6 months.

HEENT/Airway: High forehead. Large fontanelles with open metopic suture. Long, flat face, shallow, flat supraorbital ridges. Epicanthal folds, hypertelorism, puffy lids, corneal opacities, cataracts, glaucoma, Brushfield spots of the iris, gliosis of the optic nerve, retinitis pigmentosa. Abnormal external ears. Sensorineural deafness. High-arched palate, cleft palate. Micrognathia. Extra neck skinfolds.

Chest: Respiratory insufficiency secondary to hypotonia. Apnea. Aspiration pneumonia from gastroesophageal reflux.

Cardiovascular: Patent ductus arteriosus, septal defects, aortic abnormalities.

Neuromuscular: Hypotonia from birth. Retarded psychomotor development. Poor suck. Microgyria, failure of myelination and white matter development. Seizures. The electroretinogram, brainstem auditory evoked response, and somatosensory evoked response are grossly abnormal or not elicitable at all.

Orthopedic: Simian crease, camptodactyly. Contractures, particularly of the knees and fingers. Cubitus valgus, metatarsus adductus, talipes equinovarus. Punctate epiphyseal calcifications of a variety of flat bones.

GI/GU: Gastroesophageal reflux. Hepatomegaly, jaundice, cirrhosis, albuminuria. Cryptorchidism. Renal cortical cysts. Impaired adrenal cortical function or adrenal atrophy.

Other: Marked failure to thrive. Elevated levels of iron, copper, and very-long-chain fatty acids in the blood.

Miscellaneous: Zellweger syndrome is a good example of a disease that was originally thought to be a dysmorphic "multiple congenital anomaly" but was later found to have a clear physiologic and genetic basis. Rhizomelic chondrodysplasia punctata, which also results in punctate calcifications, is also a peroxisomal disorder.

Hans Zellweger, originally Swiss, spent 1937 to 1939 with Albert Schweitzer in Lambarene, Gabon.

Anesthetic Considerations: Keep in mind that patients may have impaired vision and/or hearing. Avoid protracted fasting. Micrognathia may make laryngoscopy and intubation difficult. Patients should be carefully positioned perioperatively secondary to contractures. Muscle relaxants should be used sparingly and only as needed in these hypotonic children. There may be altered binding of some anesthetic drugs, as well as a coagulopathy, in patients with hepatic disease. Chronic use of anticonvulsant medications alters the metabolism of some anesthetic drugs. Propofol should be used with caution in patients with peroxisomal disorders as they may be at higher risk for developing propofol infusion syndrome. Atropine and other anticholinergic medications are probably best avoided in patients with glaucoma. Adrenal response to stress may be inadequate, and patients may require perioperative stress doses of steroids. Patients with congenital heart disease should receive an appropriately tailored anesthetic.

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Authors: Baum, Victor C.; O'Flaherty, Jennifer E.
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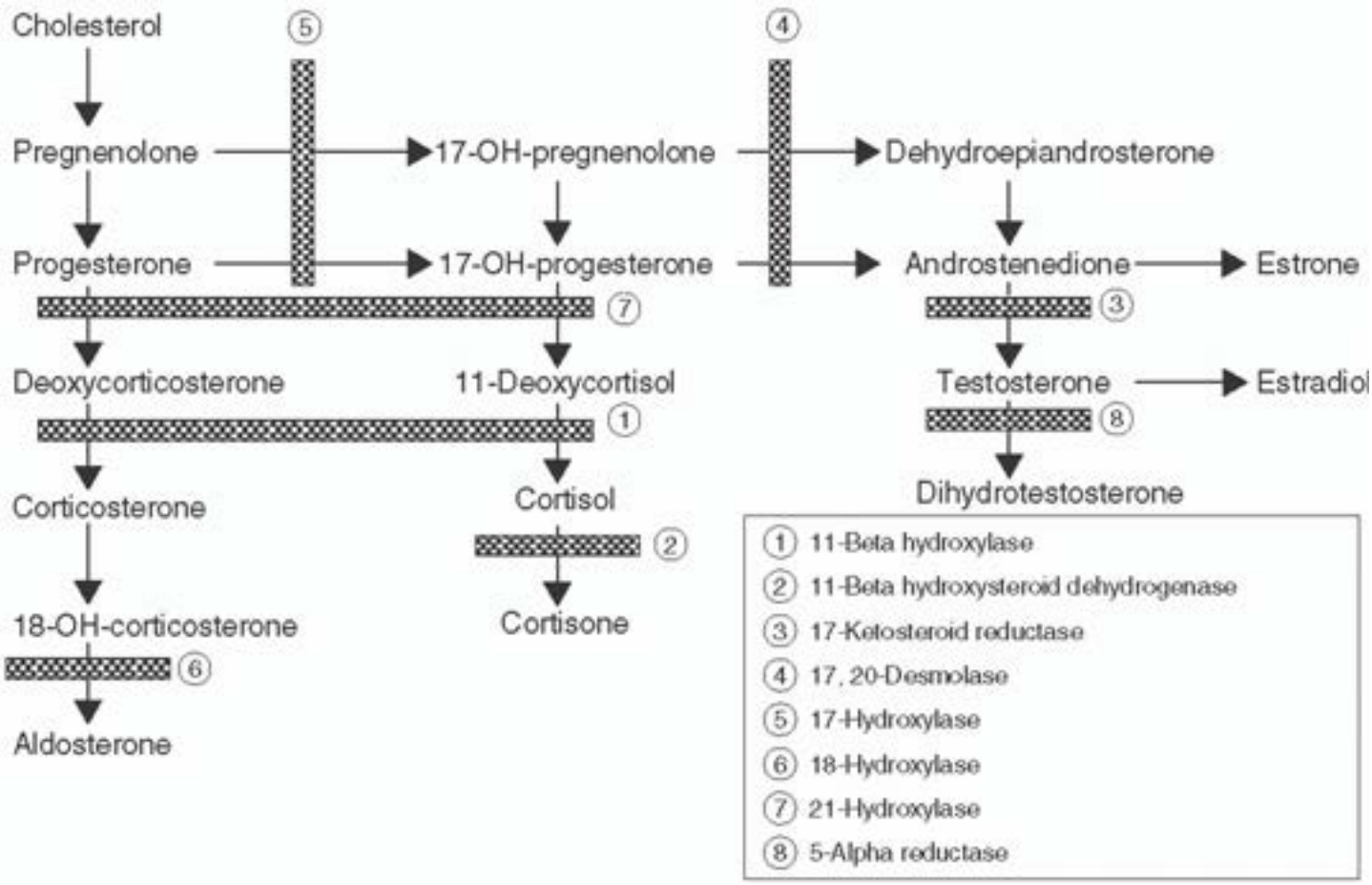
Appendix A:

Steroid Biosynthesis



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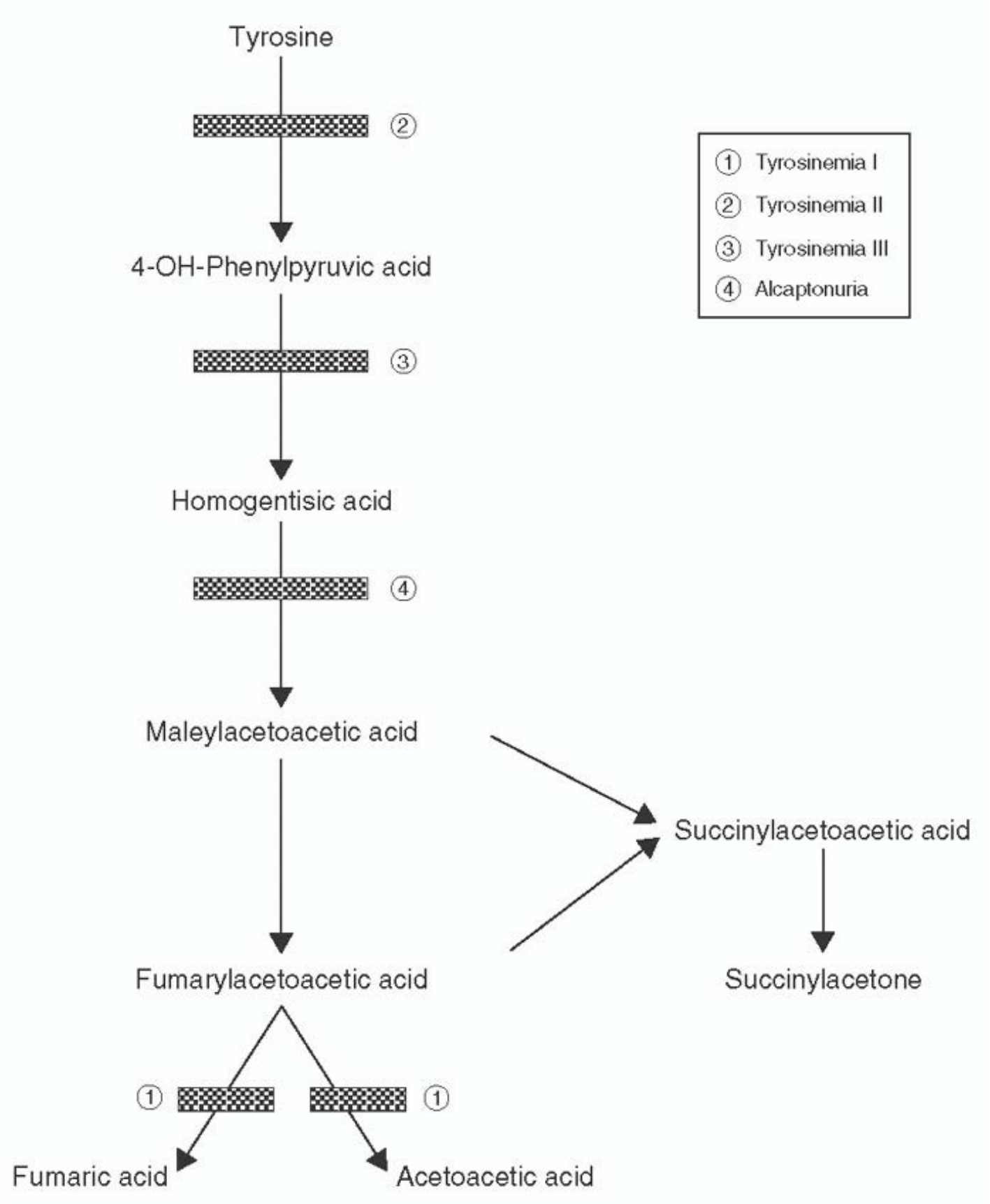
Appendix B:

Tyrosine Metabolism


Tyrosine
②
4-OH-Phenylpyruvic acid
③
Homogentisic acid
④
Maleylacetoacetic acid
Succinylacetoacetic acid
Succinylacetone
Fumarylacetoacetic acid
① ①
Fumaric acid
Acetoacetic acid
① Tyrosinemia I
② Tyrosinemia II
③ Tyrosinemia III
④ Alcaptonuria

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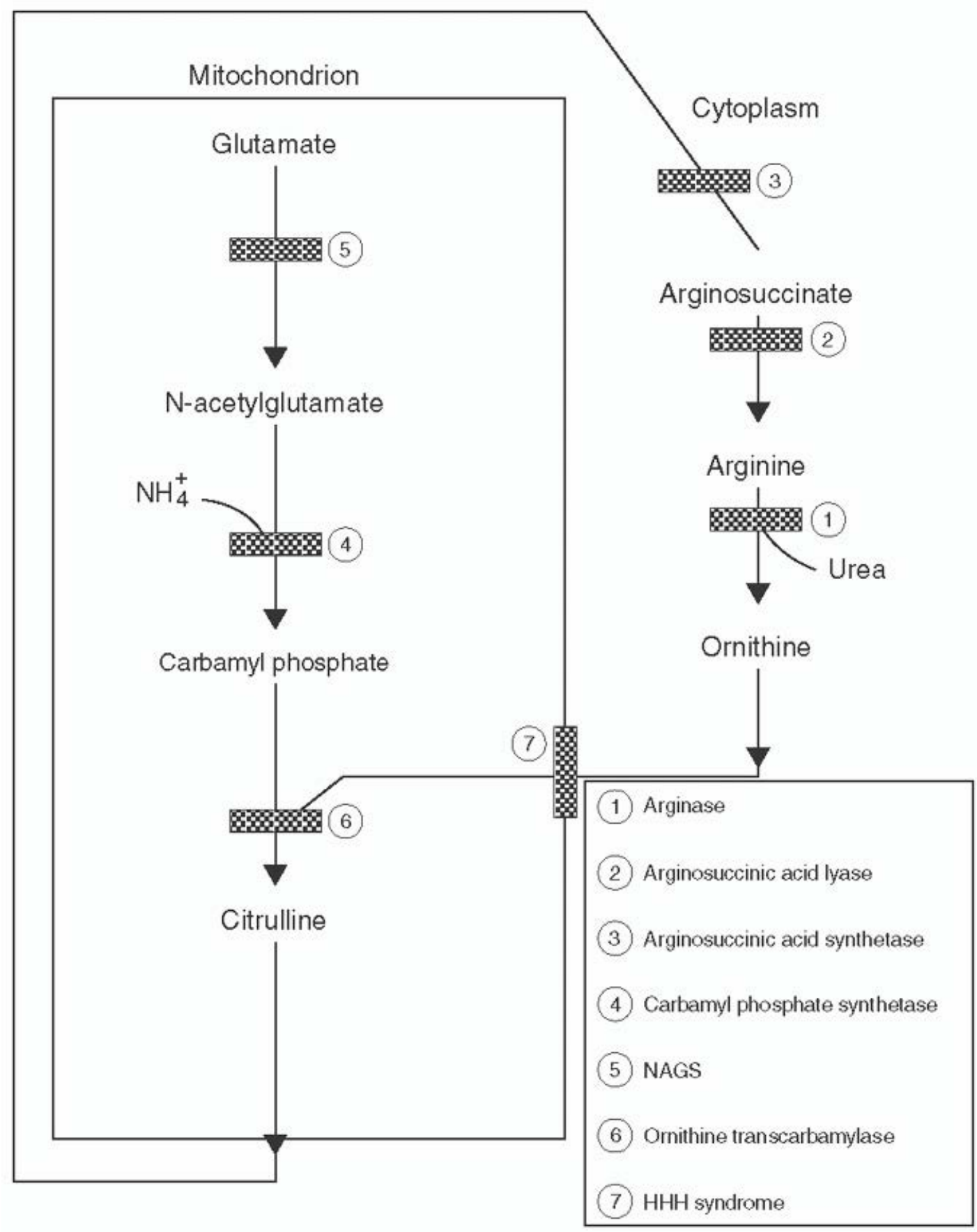
Appendix C:

Simplified Urea Cycle


Mitochondrion
Cytoplasm
Glutamate
5
3
Arginosuccinate
2
N-acetylglutamate
Arginine
NH_4^+
4
1
Urea
Carbamyl phosphate
Ornithine
7
6
Citrulline
1 Arginase
2 Arginosuccinic acid lyase
3 Arginosuccinic acid synthetase
4 Carbamyl phosphate synthetase
5 NAGS
6 Ornithine transcarbamylase
7 HHH syndrome

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Appendix D:

Metabolism of Branched-Chain Amino Acids