The Endocrine System

PART XXIV

Section 1

Disorders of the Hypothalamus and Pituitary Gland

Chapter 594

Hormones of the Hypothalamus and Pituitary

Eric I. Felner and Briana C. Patterson

The pituitary and hypothalamus are the major regulators of an elaborate hormonal system. The pituitary gland receives signals from the hypothalamus and responds by sending pituitary hormones to target glands. The target glands produce hormones that provide negative feedback at the level of the hypothalamus and pituitary (Figs. 594.1 and 594.2). This feedback mechanism enables the pituitary to regulate the amount of hormone released into the bloodstream by the target glands. The pituitary's central role in this hormonal system and its ability to interpret and respond to a variety of signals have led to its designation as the *master gland*. Table 594.1 lists the hypothalamic and pituitary hormones and their functions.

ANATOMY

The pituitary gland is located at the base of the skull in a saddle-shaped cavity of the sphenoid bone called the **sella turcica**. The bony structure protects and surrounds the pituitary bilaterally and inferiorly. The dura, a dense layer of connective tissue, forms the roof of the sella turcica. An external layer of the dura continues into the sella turcica to form its lining. As a result, the pituitary is extradural and is not normally in contact with cerebrospinal fluid. The pituitary gland is connected to the hypothalamus by the pituitary stalk. The pituitary gland is composed of an anterior (adenohypophysis) and a posterior (neurohypophysis) lobe. The anterior lobe constitutes approximately 80% of the gland.

EMBRYOLOGY

The anterior pituitary gland originates from Rathke's pouch as an invagination of the oral ectoderm. It then detaches from the oral epithelium and becomes an individual structure of rapidly proliferating cells. By 6 weeks of gestation, the connection between **Rathke's pouch** and oropharynx is completely obliterated. The pouch establishes a direct connection with the downward extension of the hypothalamus, which gives rise to the pituitary stalk. Persistent remnants of the craniopharyngeal duct, the original connection between Rathke's pouch and the oral cavity, can develop into adamantinous **craniopharyngiomas** (see Chapter 546).

VASCULAR SUPPLY

The arterial blood supply of the pituitary gland originates from the internal carotid via the inferior, middle, and superior **hypophyseal arteries**. This network of vessels forms a unique portal circulation connecting the hypothalamus and pituitary. The branches of the superior hypophyseal arteries penetrate the stalk and form a network of vessels that traverse the pituitary stalk and terminate in a network of capillaries within the anterior lobe. It is through this portal venous system that hypothalamic hormones are delivered to the anterior pituitary gland. Anterior pituitary hormones, in turn, are secreted into a secondary plexus of portal veins that drain into the dural venous sinuses.

ANTERIOR PITUITARY CELL TYPES

A series of sequentially expressed transcriptional activation factors directs the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. The consequences of pathogenic variants in several of these genes are evident in human forms of multiple pituitary hormone deficiency. Five cell types in the anterior pituitary produce six peptide hormones. **Somatotropes** produce growth

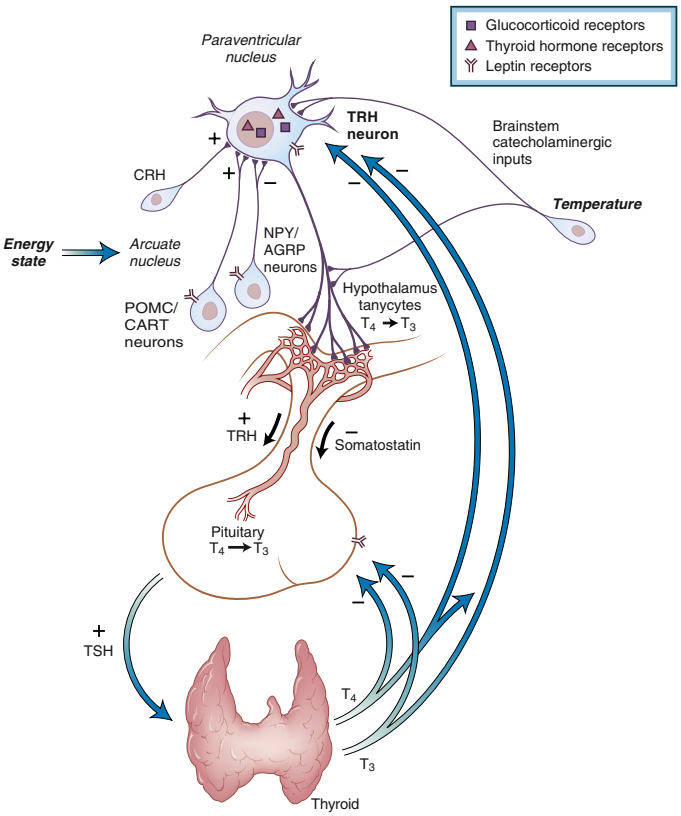

Fig. 594.1 Regulation of the hypothalamic-pituitary-thyroid axis. AGRP, Agouti-related peptide; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyrotropin. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.9.)*

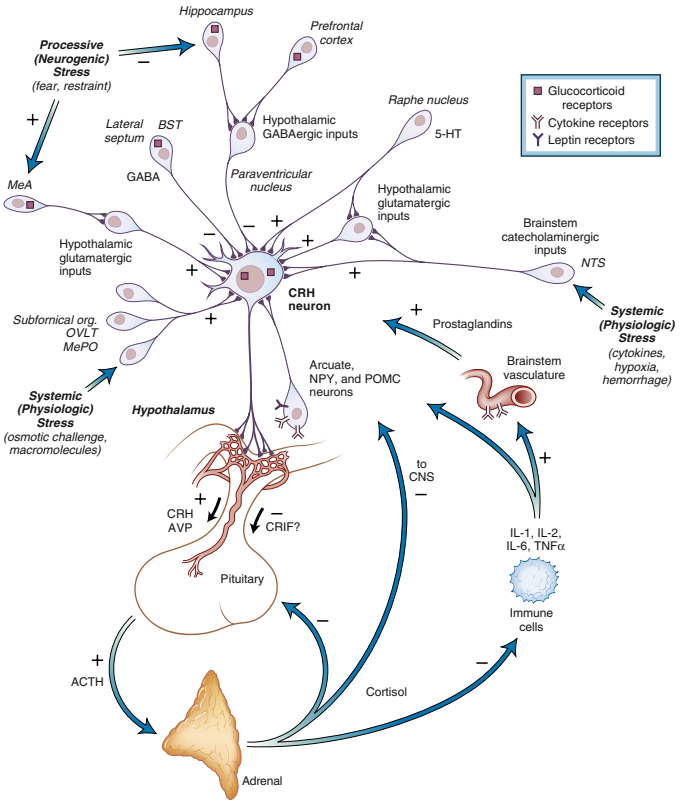

Fig. 594.2 Regulation of the hypothalamic-pituitary-adrenal axis. ACTH, Adrenocorticotropic hormone; AVP, arginine vasopressin; BST, bed nucleus of the stria terminalis; CNS, central nervous system; CRH, corticotropin-releasing hormone; CRIF, corticotropin release–inhibiting factor; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; IL-1, interleukin 1; MeA, medial amygdala; MePO, medial preoptic nucleus; NPY, neuropeptide Y; NTS, nucleus of the tractus solitarius; OVLT, organum vasculosum of the lamina terminalis; POMC, proopiomelanocortin; TNF-α, tumor necrosis factor-α. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.18.)*

hormone (GH), **lactotropes** produce prolactin (PRL), **thyrotropes** make thyroid-stimulating hormone (TSH), **corticotropes** express proopiomelanocortin (POMC), the precursor of adrenocorticotropic hormone (ACTH), and **gonadotropes** express luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Growth Hormone

Human GH is a 191–amino acid, single-chain polypeptide that is synthesized, stored, and secreted by somatotropes in the pituitary. Its gene *(GH1)* is the first in a cluster of five closely related genes on the long arm of chromosome 17 (q22-24). The other four genes *(CS1, CS2, GH2,* and *CSP)* have >90% sequence identity with the *GH1* gene.

GH is secreted in a pulsatile fashion under the regulation of hypothalamic hormones. The alternating secretion of GH-releasing hormone (GHRH), which stimulates GH release, and somatostatin, which inhibits GH release, accounts for the rhythmic secretion of GH. Peaks of GH occur when peaks of GHRH coincide with troughs of somatostatin. **Ghrelin**, a peptide produced in the arcuate nucleus of the hypothalamus and in much greater quantities by the stomach, also stimulates GH secretion. In addition to these three hypothalamic hormones, physiologic factors play a role in stimulating and inhibiting GH. Sleep, exercise, physical stress, trauma, acute illness, puberty, fasting, and hypoglycemia stimulate the release of GH, whereas hyperglycemia, hypothyroidism, and glucocorticoids inhibit GH release (Fig. 594.3).

GH binds to receptor molecules on the surface of target cells. The GH receptor is a 620–amino acid, single-chain molecule with an extracellular domain, a single membrane-spanning domain, and a cytoplasmic domain. Proteolytically cleaved fragments of the extracellular domain circulate in plasma and act as a GH-binding protein. Similar to other members of the cytokine receptor family, the cytoplasmic domain of the GH receptor lacks intrinsic kinase activity; instead, GH binding induces receptor dimerization and activation of a receptor-associated Janus kinase (Jak2). Phosphorylation of the kinase and other protein substrates initiates a series of events that leads to alterations in nuclear gene transcription. The signal transducer and activator of transcription 5b (STAT5b) plays a critical role in linking receptor activation to changes in gene transcription.

The biologic effects of GH include increases in linear growth, bone thickness, soft tissue growth, protein synthesis, fatty acid release from adipose tissue, insulin resistance, and blood glucose. The mitogenic actions of GH are mediated through increases in the synthesis of **insulin-like growth factor** 1 (IGF-1), formerly named *somatomedin C*, a 70–amino acid single-chain peptide coded for by a gene on the long arm of chromosome 12 with considerable homology to insulin. Circulating IGF-1 is synthesized primarily in the liver and formed locally in mesodermal and ectodermal cells, particularly in the growth plates of children, where its effect is exerted by paracrine or autocrine mechanisms. Circulating levels of IGF-1 are bound to several different binding proteins and are related to blood levels of GH and nutritional status. The major binding protein is a 150-kDa complex (IGF-BP3) that is low in GH-deficient children. Human recombinant IGF-1 has been developed as a therapeutic in conditions characterized by primary IGF-1 deficiency, end-organ resistance to GH (e.g., **Laron syndrome**), and the development of antibodies for those individuals administered GH. **Insulin-like growth factor** 2 (IGF-2) is a 67–amino acid single-chain protein that is coded for by a gene on the short arm of chromosome 11 that is also homologous to insulin and IGF-1. Less is known about its physiologic role, but it appears to be an important mitogen in bone cells, where it occurs in a concentration many times higher than that of IGF-1.

Prolactin

PRL is a 199–amino acid peptide made in pituitary lactotropes. The regulation of PRL is unique because PRL is constitutively secreted by the pituitary unless it is actively inhibited by dopamine, a peptide produced by neurons in the hypothalamus. Disruption of the hypothalamus or pituitary stalk can result in elevated PRL levels. Dopamine antagonists, states of primary hypothyroidism, administration of thyrotropin-releasing hormone (TRH), hypothalamic injury secondary to radiation therapy, and pituitary tumors result in increased serum levels of PRL. Dopamine agonists and processes causing destruction of the anterior pituitary gland can reduce levels of PRL.

The primary physiologic role for PRL is the initiation and maintenance of lactation. PRL prepares the breasts for lactation and stimulates milk production postpartum. During pregnancy, PRL stimulates the development of the milk secretory apparatus, but lactation does not occur because of the high levels of estrogen and progesterone. After delivery, the estrogen and progesterone levels drop, and physiologic stimuli such as suckling and nipple stimulation signal PRL release and initiate lactation.

Thyroid-Stimulating Hormone

TSH consists of two glycoprotein chains (α, β) linked by hydrogen bonding: the α-subunit, which is composed of 89 amino acids and is identical to other glycoproteins (FSH, LH, and human chorionic gonadotropin), and the β-subunit, composed of 112 amino acids, that is specific for TSH.

TSH is stored in secretory granules and released into circulation primarily in response to TRH, which is produced by the hypothalamus. TRH is released from the hypothalamus into the hypothalamic-pituitary portal system and ultimately stimulates TSH release from

Table 594.1 Hormones of the Hypothalamus and Pituitary Gland

HORMONES	LOCATION	S/I	FUNCTION
ACTH	Anterior pituitary	S	Production and secretion of GCs, MCs, and androgens from adrenal gland
ADH	Posterior pituitary	S	Reabsorption of water into the bloodstream via renal collecting ducts
CRH	Hypothalamus	S	Secretion of ACTH
Dopamine	Hypothalamus	I	Secretion of PRL
FSH (females)	Anterior pituitary	S	Secretion of estrogen from ovary
FSH (males)	Anterior pituitary	S	Production of sperm from testis
GH	Anterior pituitary	S	Secretion of IGF-1
GHRH	Hypothalamus	S	Secretion of GH
Ghrelin	Hypothalamus	S	Secretion of GH
GnRH	Hypothalamus	S	Secretion of FSH and LH
LH (females)	Anterior pituitary	S	Ovulation and development of the corpus luteum
LH (males)	Anterior pituitary	S	Production and secretion of testosterone
Oxytocin	Posterior pituitary	S	Contractions of uterus at birth and release of milk from breast
PRL	Anterior pituitary	S	Promotion of milk synthesis
Somatostatin	Hypothalamus	I	Secretion of GH and TSH
TRH	Hypothalamus	S	Secretion of TSH and PRL
TSH	Anterior pituitary	S	Secretion of T_4 and T_3

ACTH, Adrenocorticotropic hormone; ADH, antidiuretic hormone; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GCs, glucocorticoids; GH, growth hormone; GHRH, growth hormone–releasing hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-derived growth factor 1; LH, luteinizing hormone; MCs, mineralocorticoids; PRL, prolactin; S/I, stimulate/inhibit; T_3, triiodothyronine; T_4, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone (thyrotropin).

pituitary thyrotropes. TSH stimulates release of thyroxine (T_4) and triiodothyronine (T_3) from the thyroid gland through the formation of cyclic adenosine monophosphate and the G protein second messenger system. In addition to the negative feedback inhibition by T_3, the release of TRH and TSH is inhibited by dopamine, somatostatin, and glucocorticoids.

Deficiency of TSH results in inactivity and atrophy of the thyroid gland, whereas excess TSH results in hypertrophy and hyperplasia of the thyroid gland.

Adrenocorticotropic Hormone

ACTH is a 39–amino acid single-chain peptide that is derived by proteolytic cleavage from POMC, which is a 240–amino acid precursor glycoprotein product of the pituitary gland. POMC also contains the sequences for the lipotropins, melanocyte-stimulating hormones (α, β, γ), and β-endorphin.

Secretion of ACTH is regulated by corticotropin-releasing hormone (CRH), a 41–amino acid peptide found predominantly in the median eminence but also in other areas in and outside of the brain. ACTH is secreted in a diurnal pattern. It acts on the adrenal cortex to stimulate cortisol synthesis and secretion. ACTH and cortisol levels are highest in the morning at the time of waking, are low in the late afternoon and evening, and reach their nadir within the first 2 hours after beginning sleep. Similar to TRH and TSH, CRH and ACTH function through the formation of cyclic adenosine monophosphate and the G protein second messenger system. Although CRH is the primary regulator of ACTH secretion, other hormones play a role. Arginine vasopressin, oxytocin, angiotensin II, and cholecystokinin stimulate release of CRH and ACTH, whereas atrial natriuretic peptide and opioids inhibit release of CRH and ACTH. Similar to the feedback inhibition T_3 has on TRH and TSH, cortisol also inhibits CRH and ACTH. Physiologic conditions, such as stress, fasting, and hypoglycemia, also stimulate release of CRH and ACTH.

Luteinizing Hormone and Follicle-Stimulating Hormone

Gonadotropic hormones include two glycoproteins: LH and FSH. They contain the same α subunit as TSH and human chorionic gonadotropin but distinct β subunits. Receptors for FSH on the ovarian granulosa cells and on testicular Sertoli cells mediate FSH stimulation of follicular development in the ovary and of gametogenesis in the testis. On binding to specific receptors on ovarian theca cells and testicular Leydig cells, LH promotes luteinization of the ovary and Leydig cell function of the testis (Fig. 594.4). The receptors for LH and FSH belong to a class of receptors with seven membrane-spanning protein domains. Receptor occupancy activates adenylyl cyclase through the mediation of G proteins.

LH-releasing hormone, a decapeptide, has been isolated, synthesized, and widely used in clinical studies. Because it leads to the release of LH and FSH from the same gonadotropic cells, it appears that it is the only gonadotropin-releasing hormone (GnRH).

Secretion of LH is inhibited by androgens and estrogens, and secretion of FSH is suppressed by gonadal production of inhibin, a 31-kDa glycoprotein produced by ovarian granulosa cells (females) and testicular Sertoli cells (males). Inhibin consists of α and β subunits joined by disulfide bonds. The β-β dimer activin also exists, and its actions generally oppose that of inhibin by stimulating FSH secretion. In addition to its endocrine effect, activin has paracrine effects in the testis. It facilitates LH-induced testosterone production, indicating a direct effect of Sertoli cells on Leydig cells.

POSTERIOR PITUITARY CELL TYPES

The posterior lobe of the pituitary is part of a functional unit, the neurohypophysis, that consists of the neurons of the supraoptic and paraventricular nuclei of the hypothalamus; neuronal axons, which form the pituitary stalk; and neuronal terminals in the median eminence or in the posterior lobe. Vasopressin (antidiuretic hormone

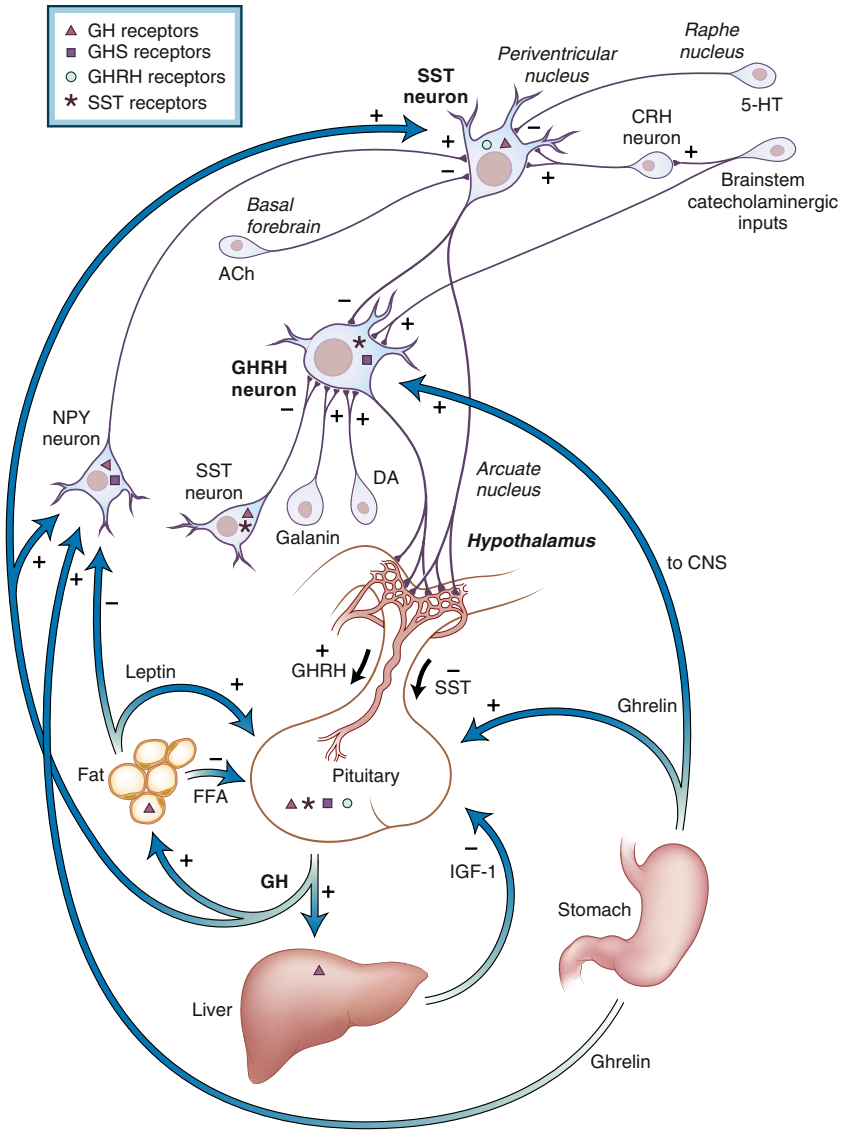

Fig. 594.3 Regulation of the hypothalamic-pituitary-growth hormone (GH) axis. GH secretion by the pituitary is stimulated by GH-releasing hormone (GHRH) and is inhibited by somatostatin (SST). Negative feedback control of GH secretion is exerted at the pituitary level by insulin-like growth factor 1 (IGF-1) and by free fatty acids (FFAs). GH itself exerts a short-loop negative feedback through activation of SST neurons in the hypothalamic periventricular nucleus. These SST neurons directly synapse on arcuate GHRH neurons and project axon collaterals to the median eminence. Neuropeptide Y (NPY) neurons in the arcuate nucleus also indirectly modulate GH secretion by integrating peripheral GH, leptin, and ghrelin signals and projecting to periventricular SST neurons. Ghrelin is secreted from the stomach and is a natural ligand for the GH secretagogue (GHS) receptor that stimulates GH secretion at both the hypothalamic and pituitary levels. On the basis of indirect pharmacologic data, it appears that release of GHRH is stimulated by galanin, γ-aminobutyric acid (GABA), and α_2-adrenergic and dopaminergic inputs and inhibited by SST. Secretion of SST is inhibited by muscarinic acetylcholine (ACh) and 5-HT-1D receptor ligands and increased by β_2-adrenergic stimuli and corticotropin-releasing hormone (CRH). CNS, Central nervous system; DA, dopamine; 5-HT, serotonin (5-hydroxytryptamine). *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.22.)*

[ADH]) and oxytocin are the two hormones produced by neurosecretion in the hypothalamic nuclei and released from the posterior pituitary. They are octapeptides and differ by only two amino acids.

Vasopressin

Vasopressin (ADH) regulates water conservation at the level of the kidney by increasing the permeability of the renal collecting duct to water. It stimulates translocation of water channels through its interaction with vasopressin 2 (V2) receptors in the collecting duct, which act through G proteins to increase adenylyl cyclase activity and increase permeability to water. These V2 receptors also mediate von Willebrand factor and tissue plasminogen activator. At higher concentrations, ADH activates vasopressin 1 (V1) receptors in smooth muscle cells and hepatocytes and exerts pressor and glycogenolytic effects through mobilization of intracellular calcium stores. Separate vasopressin 3

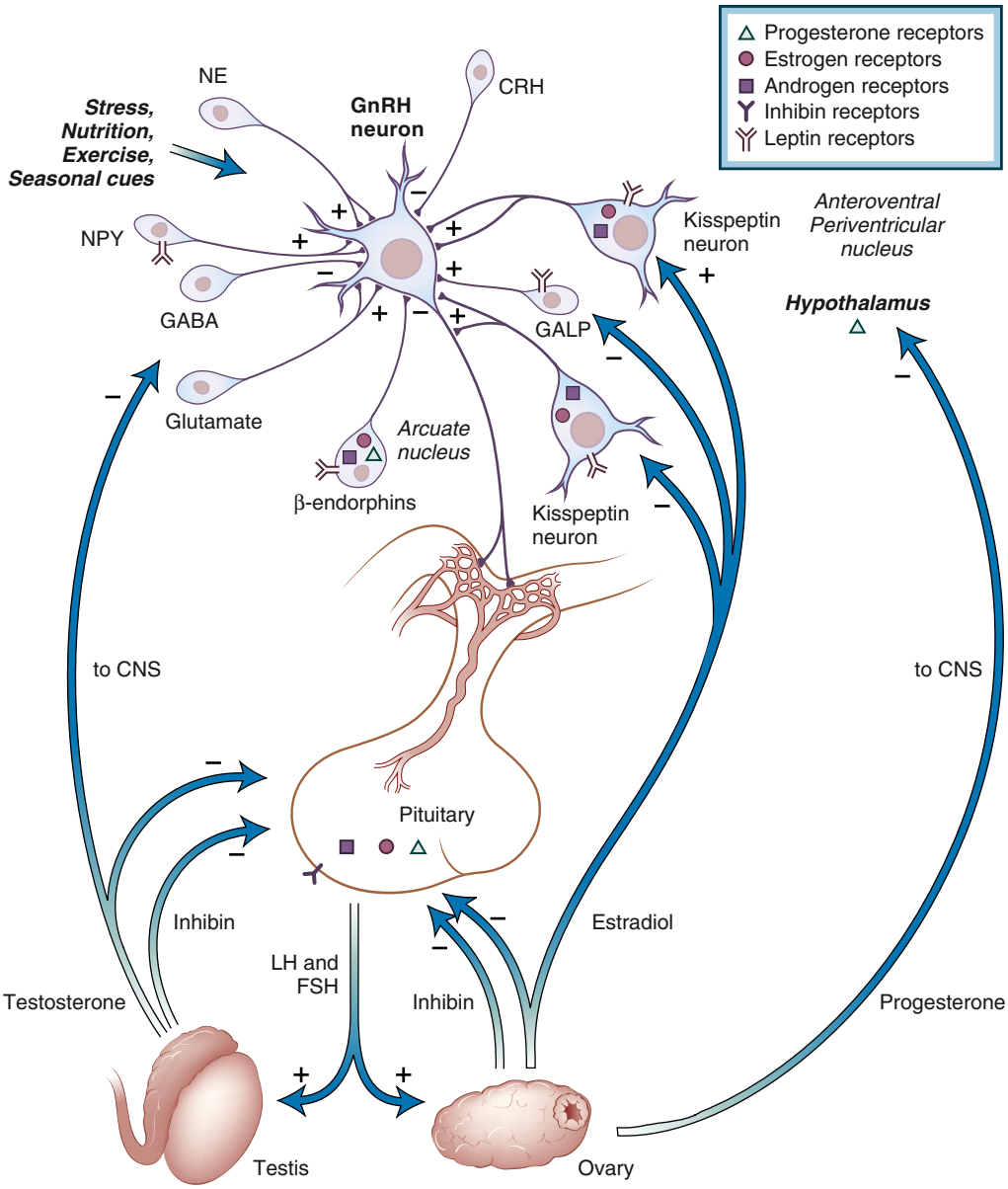

Fig. 594.4 Regulation of the hypothalamic-pituitary-gonadal axis. Schematic diagram of the hypothalamic-pituitary-gonadal axis showing neural systems that regulate gonadotropin-releasing hormone (GnRH) secretion and feedback of gonadal steroid hormones at the level of the hypothalamus and pituitary. CNS, Central nervous system; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GABA, γ-aminobutyric acid; GALP, galanin-like peptide; LH, luteinizing hormone; NE, norepinephrine; NPY, neuropeptide Y. *(From Low MJ. Neuroendocrinology. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 7.30.)*

(V3) receptors mediate stimulation of ACTH secretion. These effects involve phosphatidylinositol hydrolysis rather than cyclic adenosine monophosphate production.

Vasopressin and its accompanying protein neurophysin II are encoded by the same gene. A single preprohormone is cleaved, and both are transported to neurosecretory vesicles in equimolar amounts in the posterior pituitary.

Vasopressin has a short half-life and responds quickly to changes in hydration. The stimuli for its release are increased plasma osmolality, perceived by osmoreceptors in the hypothalamus, and decreased blood volume, perceived by baroreceptors in the carotid sinus of the aortic arch.

Oxytocin

Oxytocin stimulates uterine contractions at the time of labor and delivery in response to distention of the reproductive tract and stimulates smooth muscle contraction in the breast during suckling, which results in milk letdown. Studies suggest that oxytocin also plays a role in orgasm, social recognition, pair bonding, anxiety, trust, love, and maternal behavior. Most recently, through the interaction with its G protein–coupled receptor in pancreatic and adipose tissue, oxytocin appears to play a significant role in appetite regulation and obesity by inducing anorexia.

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Chapter 595

Hypopituitarism

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Hypopituitarism denotes underproduction of one or more pituitary hormones. Affected children have postnatal growth impairment and other endocrine deficiencies that are specifically corrected by hormone replacement. The incidence of *congenital* hypopituitarism is thought to be between 1 in 4,000 and 1 in 10,000 live births. An epidemiologic association between hypopituitarism and breech delivery has been reported, but the causal relationship is not understood. With expanding knowledge of the genes that direct pituitary development or hormone production, an increasing proportion of cases can be attributed to specific genetic alterations. Monogenic causes can only be identified in about 10% of persons with congenital hypopituitarism. The likelihood of finding a genetic alteration is increased by consanguinity and occurrence in siblings or across generations; however, in *most* cases of *isolated* **growth hormone deficiency (GHD)** and *sporadic* **multiple pituitary hormone deficiency (MPHD)**, no specific single-gene cause can be identified. It is likely that polygenic and/or environmental factors regularly play a role in the development of congenital hypopituitarism. The genes, hormonal phenotypes, associated abnormalities, and modes of transmission of several single-gene disorders causing congenital MPHD are shown in Table 595.1. Causes of *acquired* hypopituitarism, which usually has a later onset, has different causes (Table 595.2). Single-gene alterations causing disruption of the GH axis primarily are shown in Table 595.3.

MULTIPLE PITUITARY HORMONE DEFICIENCY

Genetic Forms (see Table 595.1)

Sequentially expressed transcriptional activation factors direct the differentiation and proliferation of anterior pituitary cell types. These proteins are members of a large family of DNA-binding proteins resembling homeobox genes. Alterations in different genes may produce different manifestations of MPHD. The *PROP1* and *POU1F1* genes are expressed later in pituitary development only in cells of the anterior pituitary and result in hypopituitarism without anomalies in other organ systems. The *HESX1, LHX3, LHX4, OTX2, SOX3,* and *PITX2* genes are expressed at earlier stages and are not restricted to the pituitary. Pathogenic alterations in these genes tend to produce phenotypes that extend beyond hypopituitarism to include abnormalities in other organs, and the degree of hypopituitarism is typically variable.

PROP1

PROP1 is found in the nuclei of somatotropes, lactotropes, and thyrotropes. Its roles include turning on *POU1F1* expression and downregulating *HESX1* expression. Although no genetic alteration can be identified in most patients with MPHD, pathogenic variants of *PROP1* are the most common explanation for recessive MPHD and are 10 times as common as the combined total of alterations in other pituitary transcription factor genes. Deletions of one or two base pairs in exon 2 are most common, followed by missense, nonsense, and splice-site pathogenic mutations. Anterior pituitary hormone deficiencies may not be evident in the neonatal period. The median age at diagnosis of GHD is around 6 years. Recognition of thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH) deficiencies is delayed relative to recognition of GHD. Anterior pituitary size is small in most patients, but in others there is progressive enlargement of the pituitary.

POU1F1 (PIT1)

POU1F1 (formerly *PIT1*) is a nuclear protein that binds to the GH and prolactin promoters. It is necessary for the emergence and mature function of somatotropes, lactotropes, and thyrotropes. Dominant and recessive pathogenic variants in *POU1F1* are responsible for complete deficiencies of growth hormone (GH) and prolactin and variable TSH deficiency. Affected patients exhibit nearly normal fetal growth but experience severe growth failure in the first year of life. With normal production of LH and FSH, puberty develops spontaneously, although at a later-than-normal age. These patients are not at risk for development of ACTH deficiency. Anterior pituitary size is normal to small.

HESX1

The *HESX1* gene is expressed in precursors of all five cell types of the anterior pituitary early in embryologic development. Pathogenic genetic variations in *HESX1* result in heterogeneous phenotypes with differences in development of the optic nerve and pituitary. The anterior pituitary may be hypoplastic or aplastic, and the posterior pituitary may be orthotopic or ectopic. Patients may have isolated GHD or MPHDs, with or without the **optic nerve hypoplasia syndrome**, historically called *septo-optic dysplasia* (incomplete development of the septum pellucidum with optic nerve hypoplasia and pituitary insufficiency). However, the majority of patients with optic nerve hypoplasia syndrome do not have *HESX1* gene alterations.

LHX3 and *LHX4*

The phenotype produced by recessive loss-of-function alterations of the *LHX3* gene resembles that produced by *PROP1* genetic variants. There are deficiencies of GH, prolactin, TSH, LH, and FSH but not ACTH. Some affected persons show enlargement of the anterior pituitary. The first patients to be described had the unusual findings of a short neck and a rigid cervical spine. Dominantly inherited pathogenic variations in the structurally similar *LHX4* gene consistently produce GH deficiency, with the variable presence of TSH and ACTH deficiencies. Additional findings can include a very small V-shaped pituitary fossa, **Chiari I malformation**, and an ectopic posterior pituitary.

Other Congenital Forms

Pituitary hypoplasia can occur as an isolated phenomenon or in association with more extensive developmental differences such as anencephaly or holoprosencephaly. Midline facial anomalies (cleft lip, palate; see Chapter 356) or the finding of a solitary maxillary central incisor may indicate a higher likelihood of GH or other anterior or posterior hormone deficiency (Fig. 595.1). At least 12 genes have been implicated in the complex genetic etiology of **holoprosencephaly**.

Hall-Pallister syndrome is caused by dominant loss-of-function alterations in the *GLI3* gene. Absence of the pituitary gland is accompanied by hypothalamic hamartoma, polydactyly, nail dysplasia, bifid epiglottis, imperforate anus, and anomalies of the heart, lungs, and kidneys. The combination of **anophthalmia** and **hypopituitarism** has been associated with pathogenic variants in the *SIX6, SOX2,* and *OTX2* genes.

Optic nerve hypoplasia syndrome may be detected as a result of clinical observation of nystagmus and visual impairment in infancy. Neuroimaging demonstrates optic nerve and brain abnormalities and is associated with anterior and/or posterior pituitary hormone deficiencies in up to 75% of cases (Fig. 595.2). Although these patients often show the triad of a small anterior pituitary gland, an attenuated pituitary stalk, and an ectopic posterior pituitary bright spot, the primary etiology of the hypopituitarism in this condition is thought to be hypothalamic dysfunction. GH deficiency is the commonly observed hormone deficiency, and other anterior pituitary hormone deficiencies are less common. Diabetes insipidus is reported in only about 5% of cases. The etiology is likely multifactorial and may involve interaction between genetic and environmental factors. In most cases, no single-gene alteration can be identified.

Severe, early-onset MPHD, including deficiency of ACTH, is often associated with the triad of anterior pituitary hypoplasia, absence or attenuation of the pituitary stalk, and an ectopic posterior pituitary bright spot seen on MRI. Most cases are sporadic, and there is a male predominance. Some are caused by pathogenic variants of the *SOX3* gene, located on the X chromosome.

Table 595.1 Etiologic Classification of Congenital and Genetic Forms of Multiple Pituitary Hormone Deficiency

GENE OR LOCATION	PHENOTYPE	INHERITANCE
GENETIC FORMS		
POU1F1 (PIT1)	GH, PRL deficiencies, variable TSH deficiency	AR, AD
PROP1	GH, TSH, PRL, LH, FSH deficiencies, variable ACTH deficiency, variable AP	AR
LHX3	GH, TSH, PRL, LH, FSH deficiencies, variable AP, ± short neck, limited neck rotation, sensorineural deafness	AR
LHX4	GH, TSH, ACTH deficiencies, small AP, EPP, variable Arnold-Chiari, cerebellar abnormalities	AD
TPIT	ACTH deficiency, severe neonatal form	AR
HESX1	GH deficiency, variable for others, small AP, EPP, optic nerve hypoplasia; septo-optic dysplasia	AR, AD
SOX2	LH, FSH deficiencies, variable GH deficiency, anophthalmia, microphthalmia, esophageal atresia, sensorineural hearing loss	AD
SOX3	Variable deficiencies, ± MR, EPP, small AP and stalk, developmental delay	XL
PITX2	Axenfeld-Rieger syndrome: hypogonadotropic hypogonadism, pituitary hypoplasia, anterior chamber abnormalities of the eye, dental hypoplasia	AD
GLI2	Hypopituitarism, holoprosencephaly, midline defects, polydactyly	AD
GLI3	Hall-Pallister syndrome, hypopituitarism	AD
SHH (Sonic Hedgehog)	GH deficiency with single central incisor	AD
OTX2	GH or combined deficiencies, anophthalmia or microphthalmia, coloboma, developmental delay	AD
TBX19	ACTH deficiency, neonatal hypoglycemia or cholestatic jaundice	AR
PC1	Hypogonadotropic hypogonadism, ACTH deficiency	AR
GIF, SHHT, SIX3	Pituitary stalk interruption syndrome: thin or absent pituitary stalk, hypoplasia of adenohypophysis, ectopic neurohypophysis, neonatal hypoglycemia, cholestasis, micropenis	Holoprosencephaly related gene group
FGF8	Hypopituitarism, holoprosencephaly	AD
FGFR1	Hypopituitarism, pituitary hypoplasia, agenesis of the corpus callosum, ocular defects	AD
PROKR2	GH, TSH and ACTH deficiencies, micropenis and neonatal hypoglycemia	AD, AR
UNKNOWN OR POLYGENETIC ETIOLOGY		
Congenital absence of pituitary gland		
Optic nerve hypoplasia syndrome/septo-optic dysplasia	Optic nerve hypoplasia, nystagmus, absent septum pellucidum, pituitary hypoplasia	

ACTH, Adrenocorticotropic hormone; AP, anterior pituitary; AD, autosomal dominant; EPP, ectopic posterior pituitary; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; MR, mental retardation; PRL, prolactin; AR, autosomal recessive; TSH, thyroid-stimulating hormone; XL, X-linked.

Acquired Forms

Any lesion that damages the hypothalamus, pituitary stalk, or anterior pituitary can cause pituitary hormone deficiency (see Table 595.2). Because such lesions are not selective, multiple hormonal deficiencies are usually observed. Diabetes insipidus is more frequent in *acquired* than in congenital hypopituitarism. The most common structural lesion of the pituitary causing childhood-onset acquired MPHD is craniopharyngioma (see Chapter 546). Central nervous system germinoma, optic pathway or hypothalamic glioma, histiocytosis, tuberculosis, sarcoidosis, toxoplasmosis, meningitis, pituitary abscess, and aneurysms can also cause hypothalamic-hypophyseal damage and dysfunction. Additionally, children treated with radiation therapy for central nervous system or nasopharyngeal tumors are at increased risk for GHD and other pituitary hormone deficiencies to the extent that the radiation field includes the hypothalamus and/or pituitary, even if the tumor itself is anatomically remote from the pituitary and hypothalamus. The magnitude of the risk and the timing of the emergence of pituitary hormone deficiencies depend on the dose of radiation to the hypothalamic-pituitary axis and the duration of elapsed time after radiotherapy is complete. High doses of radiation (>50 Gy) are likely to produce GH deficiency sooner than 1 year after irradiation, whereas other anterior pituitary hormone deficiencies may not appear until later. GH production appears to be particularly vulnerable to the effects of irradiation, even at lower doses, whereas deficiencies of ACTH, gonadotropins, and thyrotropin-releasing hormone (TRH)/TSH occur with declining frequency and typically occur at higher doses of radiation. Irradiation alone does not typically result in diabetes insipidus. Traumatic brain injury, including abusive head trauma, motor vehicle accidents, and chronic repetitive head injury, is an increasingly recognized cause of pituitary dysfunction related to damage to the pituitary, its stalk, or the hypothalamus.

ISOLATED GROWTH HORMONE DEFICIENCY AND INSENSITIVITY

Genetic Forms of Growth Hormone Deficiency

Isolated GHD is caused by abnormalities of the GH-releasing hormone receptor, GH genes, and certain genes located on the X chromosome (see Table 595.3).

Growth Hormone–Releasing Hormone Receptor

Recessive loss-of-function alterations in the receptor for GH-releasing hormone interfere with proliferation of somatotropes during pituitary development and disrupt the most important signals for release of GH. The anterior pituitary is small, in keeping with the observation that

Table 595.2 Causes of Acquired Pituitary Insufficiency

TRAUMATIC
Surgical resection
Radiation damage
Traumatic brain injury
INFILTRATIVE/INFLAMMATORY
Primary hypophysitis
Lymphocytic
Granulomatous
Xanthomatous
Secondary hypophysitis
Sarcoidosis
Langerhans cell histiocytosis
Granulomatosis with polyangiitis
Takayasu disease
Hemochromatosis
INFECTIONS
Tuberculosis
Pneumocystis jirovecii infection
Fungal (histoplasmosis, aspergillosis)
Parasites (toxoplasmosis)
Viral (cytomegalovirus)
VASCULAR
Pregnancy related
Aneurysm
Apoplexy
Diabetes
Hypotension
Arteritis
Sickle cell disease
NEOPLASTIC
Pituitary adenoma
Parasellar mass
Rathke cyst
Dermoid cyst
Meningioma
Germinoma
Suprasellar/optic pathway glioma
Craniopharyngioma
Hypothalamic hamartoma
Pituitary metastatic deposits
Hematologic malignancy
Leukemia
Lymphoma
FUNCTIONAL
Nutritional
Caloric restriction
Malnutrition
Excessive exercise
Nonspecific illness
Acute critical illness
Chronic renal failure
Chronic liver failure
Hormonal
Hyperprolactinemia
Hypothyroidism
Drugs
Anabolic steroids
Glucocorticoid excess
GnRH agonists
Estrogen
Dopamine
Somatostatin analog
Immune check-point inhibitors

Modified from Kaiser U, Ho KKY. Pituitary physiology and diagnostic evaluation. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 8.5, p. 193.

somatotropes normally account for >50% of pituitary volume. There is some compromise of fetal growth followed by severe compromise of postnatal growth.

GH1

The *GH1* gene is one of a cluster of five genes on chromosome 17q22-24. This cluster arose through successive duplications of an ancestral GH gene. Unequal crossing over at meiosis has produced a variety of gene deletions. Small deletions (<10 kb) remove only the *GH1* gene, whereas large deletions (45 kb) remove one or more of the adjacent genes (*CSL, CS1, GH2,* and *CS2*). The growth phenotype is identical with deletion of *GH1* alone or *GH1* together with one or more of the adjacent genes. Loss of the *CS1, GH2,* and *CS2* genes without loss of *GH1* causes deficiency of chorionic somatomammotropin and placental GH in the maternal circulation, but it does not result in fetal or postnatal growth retardation. Most children with *GH1* gene deletions respond very well to recombinant GH treatment, but some develop *antibodies* to GH and cease growing despite treatment.

Recessively transmitted pathogenic variants in the *GH1* gene produce a similar phenotype. Missense, nonsense, and frameshift alterations have been described. Autosomal dominant isolated GHD is also caused by variants in *GH1*. These alterations usually involve splice-site errors in intron 3 and result in a variant protein that lacks the amino acids normally encoded by exon 3. Accumulation of this protein interferes with the processing, storage, and secretion of the normal GH protein and may result in additional deficiencies of TSH and/or ACTH. There are several reports of alterations in *GH1* that lead to variant proteins with reduced biologic activity.

X-Linked Isolated Growth Hormone Deficiency

Two loci on the X chromosome have been associated with hypopituitarism. The first lies at Xq21.3-q22 in the region of the *BTK* gene. Pathogenic variants in this region produce hypogammaglobulinemia and isolated GHD. The second locus maps farther out on the long arm, at Xq24-q27.1, a region containing the *SOX2* transcription factor gene. Abnormalities in this locus have been linked to isolated GHD with intellectual disability and to MPHD with the triad of pituitary hypoplasia, missing pituitary stalk, and ectopic posterior pituitary gland.

Acquired Forms

The GH axis is more susceptible to disruption by acquired conditions than are other hypothalamic-pituitary axes. Recognized causes of acquired GHD include the use of radiotherapy for malignancy, meningitis, histiocytosis, and trauma.

Children who receive radiotherapy for central nervous system tumors, leukemia, or total body irradiation before hematopoietic stem cell transplant are at risk for developing GHD. Spinal irradiation results in disproportionately poor growth of the axial skeleton relative to the appendicular skeleton; this problem is not remediable with GH treatment. Growth typically slows during radiation therapy or chemotherapy, may improve for 1-2 years after cancer treatment, and then declines with the development of GHD. The dose and frequency of radiotherapy are important determinants of hypopituitarism. GHD is almost universal 5 years after therapy with a total dose ≥35 Gy. More subtle defects are seen with doses around 20 Gy. Deficiency of GH is the most common defect, but deficiencies of TSH and ACTH can also occur. The evaluation of GHD is more complicated when radiation-associated precocious puberty is also present. The clinician is likely to encounter children in the 8- to 10-year age range who are growing at rates that are normal for chronological age but subnormal for stage of pubertal development.

GROWTH HORMONE INSENSITIVITY

Abnormalities of the Growth Hormone Receptor

GH insensitivity is caused by disruption of pathways distal to the production of GH (Table 595.4). **Laron syndrome** involves pathogenic genetic variations in the GH receptor. Children with this condition clinically resemble those with severe isolated GHD. Birth length tends to be about 1 standard deviation (SD) below the mean, and severe short stature with lengths >4 SD below the mean is present by 1 year of age. Resting and stimulated GH levels tend to be high, and insulin-like growth factor (IGF) 1 levels are low. The GH receptor has an extracellular GH-binding domain, a transmembrane domain, and an

Table 595.3 Established Genetic Defects of the GH-IGF Axis Resulting in Isolated GH Deficiency, GH Insensitivity, or IGF-1 Deficiency

GENE	INHERITANCE	PHENOTYPE
ISOLATED GROWTH HORMONE DEFICIENCY		
GHRHR	AR	Type IB form of isolated **GHD**; low levels of GH production, but less severe than type 1A isolated **GHD**; may also be caused by pathogenic variants in GH1
GHS-R	AD	**GHD** and ISS
GH1	AR	Type IA form of isolated **GHD**, in utero growth retardation; absent GH production caused by gene deletion, antibodies to GH develop over time during treatment
GH1	AR	Type IB form of isolated **GHD**; low levels of GH production, but less severe than type 1A isolated **GHD**; may also be caused by pathogenic variants in GHRHR
GH1	AD	Type II form of isolated **GHD**; dominant negative pathogenic variants in GH1, which decrease GH secretion
BTK	XL	Type III form of isolated **GHD**; hypogammaglobulinemia
GH1	AD	Bioinactive GH molecule; rare, dominant negative pathogenic variant in GH1 that interferes with GHR signaling
GROWTH HORMONE INSENSITIVITY		
GHR	AR, AD	IGF-I deficiency; high GH level; normal, decreased or increased GHBP (depending on which domain of the receptor is affected); unresponsive to GH treatment
IGF-1 DEFICIENCY		
IGF1	AR	IGF-1 deficiency; IUGR and postnatal growth failure, sensorineural deafness, insulin resistance, microcephaly
STAT5b	AR	IGF-1 deficiency, variable immune defect, hyperprolactinemia, chronic pulmonary infections, eczema
ALS	AR	IGF-1 deficiency; variable postnatal growth failure, delayed puberty

AD, Autosomal dominant; ALS, acid-labile subunit; AR, autosomal recessive; GH, growth hormone; GHBP, GH-binding protein; GHD, growth hormone deficiency; GHRHR, GH-releasing hormone receptor; IGF, insulin-like growth factor; ISS, idiopathic short stature; IUGR, intrauterine growth retardation; XL, X-linked.
Modified from Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Table 10.3, p. 333.

Fig. 595.1 Solitary median maxillary central incisor at age 16 mo. *(From Giannopoulou EZ, Rohrer T, Hoffmann P, et al. Solitary median maxillary central incisor. J Pediatr. 2015;167:770, Fig. 2.)*

Fig. 595.2 Septo-optic dysplasia with agenesis of the septum pellucidum. Sagittal T1 weighted MR image shows that fornices are inferiorly positioned *(long arrow)*. The optic apparatus is hypoplastic *(short arrow)*; there is no identifiable neurohypophysis. *(From Rollins N. Congenital brain malformations. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 31.13.)*

intracellular signaling domain. Pathogenic alterations in the extracellular domain interfere with binding of GH. Serum GH-binding protein activity, representing the circulating form of the membrane receptor for GH, is generally low. Variants in the transmembrane domain can interfere with anchoring of the receptor to the plasma membrane. In these cases, circulating GH-binding protein activity is normal or high. Alterations in the intracellular domain interfere with JAK/STAT signaling.

Post-Receptor Forms of Growth Hormone Insensitivity

Some children with severe growth failure, high GH and low IGF-1 levels, and normal GH-binding protein levels have abnormalities distal to the GH binding and activation of the GH receptor. Several have been found to have pathogenic variations in the gene-encoding signal transducer and activator of transcription 5b (STAT5b). Disruption of this key intermediate connecting receptor activation to gene transcription produces growth failure similar to that seen in Laron syndrome. These patients also suffer from *immunodeficiency* and chronic pulmonary

Table 595.4 Proposed Classification of Growth Hormone Insensitivity

PRIMARY GH INSENSITIVITY (HEREDITARY DEFECTS)
GH receptor defect (may be positive or negative for GH-binding protein)
• Extracellular alteration (e.g., Laron syndrome)
• Cytoplasmic alteration
• Intracellular alteration
GH signal transduction defects (distal to cytoplasmic domain of GH receptor)
• Stat5b pathogenic variants
Insulin-like growth factor-1 defects
• IGF-1 gene deletion
• IGF-1 transport defect (pathogenic variant in ALS)
• IGF-1 receptor defect
Bioinactive GH molecule (responds to exogenous GH)
SECONDARY GH INSENSITIVITY (ACQUIRED DEFECTS)
Circulating antibodies to GH that inhibit GH action
Antibodies to the GH receptor
GH insensitivity caused by malnutrition, liver disease, catabolic states, diabetes mellitus
Other conditions that cause GH insensitivity

ALS, Acid-labile subunit; GH, growth hormone; IGF, insulin-like growth factor.
From Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Box 10.4.

infections, consistent with important roles for STAT5b in interleukin cytokine signaling.

IGF-1 Gene Abnormalities

Pathogenic alterations of the *IGF-1* gene produce severe prenatal and postnatal growth impairment. Microcephaly, intellectual disability, and deafness are present in patients with exon deletion and a missense variant. These patients can be expected to respond to recombinant IGF-1 treatment.

Insulin-Like Growth Factor–Binding Protein Abnormalities

Pathogenic variants in the gene encoding the acid-labile subunit of the circulating 165-kDa IGF-1, IGF-BP3, acid-labile subunit complex has been associated with short stature. Total IGF-1 levels were very low. The index case, with homozygosity for an acid-labile subunit alteration, did not show an increase in IGF-1 levels or an increase in growth rate during GH treatment.

IGF-1 Receptor Gene Abnormalities

Pathogenic variants in the gene encoding the IGF-1 receptor also compromise prenatal and postnatal growth. The phenotype does not appear to be as severe as that seen with the absence of IGF-1. Adult heights are closer to the normal range, and affected patients do not have intellectual disability or deafness.

CLINICAL MANIFESTATIONS

Congenital Hypopituitarism

The child with congenital hypopituitarism is usually of normal size and weight at birth, although those with MPHD and those with pathogenic genetic variants in the *GH1* or *GHR* gene have birth lengths that average 1 SD below the mean. Children with severe deficits in GH production or action typically fall more than 4 SD below the mean for length by 1 year of age. Those with less severe deficiencies grow at rates below the 25th percentile for age and gradually diverge from normal height percentiles. Delayed closure of the epiphyses permits growth beyond the normal age when growth should be complete. Features of GH insensitivity, including Laron syndrome, are somewhat distinct from GHD and MPHD and are noted in Table 595.5.

Infants with congenital dysfunction of the pituitary or hypothalamus may present with neonatal emergencies such as apnea, cyanosis, or severe hypoglycemia with or without seizures. Prolonged neonatal cholestatic jaundice is common. It involves elevation of conjugated and unconjugated bilirubin and may be associated with giant cell neonatal hepatitis. Nystagmus can suggest optic nerve hypoplasia syndrome (see Chapter 671). Micropenis with or without testicular maldescent in males provides an additional diagnostic clue. Deficiency of GH may be accompanied by hypoadrenalism (see Chapter 615.2) and hypothyroidism (see Chapter 603), along with gonadotropin deficiency (see Chapters 623.2 and 626.2).

Table 595.5 Clinical Features of Growth Hormone Insensitivity, Including Classic Laron Syndrome

GROWTH AND DEVELOPMENT
Near-normal birthweight
Slightly decreased birthweight
Severe postnatal growth failure
Delayed bone age (may be advanced relative to height age)
Micropenis in childhood; normal for body size in adults
Puberty may be delayed 3-7 yr
Normal sexual function and fertility
OTHER PHYSICAL CHARACTERISTICS
Sparse hair (before age 7 yr)
Frontal bossing
Normal head circumference
Small facies (resulting in craniofacial disproportion)
Hypoplastic nasal bridge
Shallow orbits
Delayed dentition
Blue sclerae
High-pitched voice
Hip dysplasia
Limited extension in elbows
LATE FINDINGS/OTHER COMPLICATIONS
Hypoglycemia in infants and children (fasting symptoms in some adults)
Delayed walking and motor milestones
Avascular necrosis of femoral head
Thin, prematurely aged skin
Osteopenia

From Sperling MA. *Pediatric Endocrinology,* 4th ed. Philadelphia: Elsevier; 2014: Box 10.5.

Toddlers and school-age children tend to present with proportionate short stature. On physical examination, the head may be round and the face short and broad. The frontal bone may be prominent, and the bridge of the nose is often depressed and saddle shaped. The nose may be small, but the nasolabial folds are well developed. The mandible and the chin may be underdeveloped, and the teeth, which erupt late, are often crowded. The neck is short, and the larynx is small. The voice is high-pitched and remains high after puberty. The extremities are well proportioned, with small hands and feet. Weight for height is often normal, but there may be an imbalance of lean mass and adipose tissue. The genitals are usually small for age in males, and sexual maturation may be delayed or absent as the child ages.

In teens with undiagnosed congenital hypopituitarism, short stature is expected. Additionally, facial, axillary, and pubic hair may be decreased, and the scalp hair is fine. Intelligence is usually normal for age, unless there are other structural brain abnormalities, and the children may seem precocious compared with younger children of a similar size.

Acquired Hypopituitarism

The child is normal initially, and manifestations similar to those seen in idiopathic pituitary growth failure gradually appear and progress. When complete or almost complete destruction of the pituitary gland occurs, signs of pituitary insufficiency are present. Atrophy of the adrenal cortex, thyroid, and gonads results in loss of weight, asthenia, sensitivity to cold, mental torpor, and absence of sweating. Sexual maturation fails to take place or regresses if already present. There may be atrophy of the gonads and genital tract with amenorrhea and loss of pubic and axillary hair. There is a tendency to hypoglycemia. Growth slows dramatically. Diabetes insipidus (see Chapter 596) may be present but can by obscured by the development of yet untreated central adrenal insufficiency.

If the lesion is an **expanding tumor**, symptoms such as headache, vomiting, visual disturbances, pathologic sleep patterns, decreased school performance, seizures, polyuria, and growth failure can occur. Documented slowing of growth can antedate neurologic signs and symptoms, especially with craniopharyngioma, yet neurologic and ophthalmologic complaints are more often the presenting problems. In other cases, evidence of pituitary insufficiency may first appear after surgical intervention. In children with craniopharyngioma, visual field defects, optic atrophy, papilledema, obesity, and cranial nerve palsy are common. Skeletal age may be delayed in acquired MPHD but may be relatively normal if the pituitary dysfunction is of very recent onset.

LABORATORY FINDINGS

MPHD and/or GHD should be suspected in infants with hypoglycemia, micropenis, congenital nystagmus, and prolonged conjugated hyperbilirubinemia and in older children with severe postnatal growth failure (Table 595.6). Criteria for short stature include height below the first percentile for age and sex or height >2 SD below sex-adjusted mid-parent height. Acquired GHD can occur at any age, and when it is of acute onset, height may be within the normal range. In both congenital and acquired GH deficiency, height velocity will be low relative to sex- and bone age–matched peers. A strong clinical suspicion is important in establishing the diagnosis because laboratory measures of GH sufficiency lack specificity. Random GH levels are not helpful in the evaluation of toddlers and older children because of the pulsatile secretion of GH, *whereas measurement of GH may be useful in the first 2 weeks of life when levels are tonically increased.* Observation of low serum levels of IGF-1 and the GH-dependent IGF-BP3 can be helpful, but IGF-1 and IGF-BP3 levels should be matched to normal values for skeletal age and sexual maturity rating, rather than chronological age. Values in the upper part of the normal range for age effectively exclude GHD. IGF-1 values in the lower part of the normal range may occur in normally growing children, children with impaired nutrition, or those with hypopituitarism. The expected range for IGF-1 in normal and GH-deficient children overlaps somewhat during infancy and early childhood. IGF-1 levels in isolation should not be used to diagnose GH deficiency.

Table 595.6 Evaluation of Suspected Growth Hormone Deficiency

History	• Birthweight and length • Obstetric complications • Breech presentation • Neonatal hypoglycemia • Prolonged neonatal jaundice/cholestasis • Review of systems for systemic illness • Diet history
Physical exam	• Linear growth failure (may be the only clinical feature present) Proportionate short stature Low height velocity • Weight for length appropriate or increased • Micropenis with or without testicular maldescent in males • Small midface • Cleft palate • High-pitched voice • Delayed dental eruption • Optic nerve hypoplasia
Imaging	• Radiologic evaluation of bone age • Central nervous system imaging to evaluate the hypothalamus/pituitary and to exclude other conditions
Laboratory evaluation	• Measurements of IGF-1 and IGF-binding protein levels • Assess thyroid function • Exclude chronic medical illness CBC, metabolic profile, inflammatory markers, celiac testing, urinalysis • Determination of peak GH levels after stimulation test
Treatment considerations	• Replacement with rhGH • Dosage adjustment IGF-1 Height velocity Pubertal status Body weight • Predictors of improved response to treatment Early initiation of treatment Higher rhGH dose • Monitor during treatment Height velocity IGF-1 levels Glucose metabolism Skeletal age Thyroid function, adrenal function

GH, Growth hormone; IGF, insulin-like growth factor; rhGH, recombinant human growth hormone.

After infancy, a definitive diagnosis of GHD traditionally requires demonstration of absent or low levels of GH in response to stimulation, but provocative testing may be omitted if the patient has the expected auxologic findings, a documented hypothalamic or pituitary defect, and at least one other pituitary hormone deficiency. A variety of provocative tests have been devised that rapidly increase the level of GH in normal children. These include administration of insulin, arginine, clonidine, levodopa, or glucagon. Macimorelin is an oral ghrelin agonist approved in the United States for growth hormone stimulation testing in adults, but not in children. *Because thyroid hormone is a prerequisite for normal GH synthesis, it must always be assessed and replaced, if needed, before provocative GH testing.* In chronic GHD, the demonstration of subnormal linear growth, a delayed skeletal age, and low peak levels of GH (<10 ng/mL) in each of two provocative tests are compatible with the diagnosis. In acute GHD, a high clinical suspicion of GHD and low peak levels of GH (<10 ng/mL) in each of two provocative tests are compatible with the diagnosis. This rather arbitrary cutoff point is higher than the criteria used for diagnosis of adult GHD. There is no consensus regarding adoption of criteria that account for age, sex, and GH assay characteristics. Some studies indicate that many GH-sufficient prepubertal children fail to achieve GH values >10 ng/mL with two pharmacologic tests; pretest, short-term sex steroid priming has been proposed to increase the diagnostic specificity of this testing.

In addition to establishing the diagnosis of GHD, it is necessary to examine other pituitary functions. Levels of TSH, free thyroxine or total thyroxine with T_3 resin uptake, ACTH, cortisol, gonadotropins, and gonadal steroids might provide evidence of other pituitary hormonal deficiencies. Antidiuretic hormone deficiency may be established by appropriate studies (see Chapter 596). Infants with clear clinical and biochemical evidence of multiple pituitary hormone deficiencies and supportive anatomic variants demonstrated on MRI of the brain may not require provocative GH testing.

RADIOLOGIC FINDINGS

Neurologic imaging should be obtained when the cause of hypopituitarism is not known. CT is appropriate for recognizing suprasellar calcification associated with craniopharyngiomas and bony changes accompanying histiocytosis. However, MRI is usually used as the initial test to anatomically characterize the pituitary and hypothalamus, as MRI provides a much more detailed view of the relevant anatomy. Many cases of severe early-onset MPHD show the triad of a small anterior pituitary gland, a missing or attenuated pituitary stalk, and an ectopic posterior pituitary bright spot at the base of the hypothalamus (Fig. 595.3). Subnormal anterior pituitary height, implying a small anterior pituitary, is common in genetic and idiopathic causes of isolated GHD. Craniopharyngiomas are rare tumors in childhood, but common causes of acquired hypopituitarism, whereas pituitary adenomas rarely cause hypopituitarism in children. Both hypoplastic and

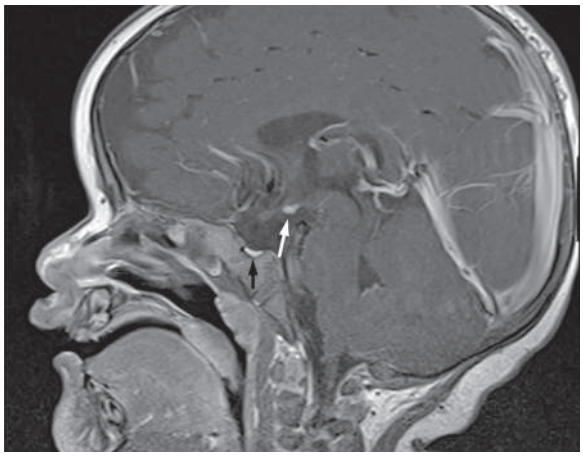

Fig. 595.3 Sagittal T1 weighted MRI shows an ectopic posterior pituitary *(white arrow)* and a small anterior pituitary *(black arrow). (From Giannopoulou EZ, Rohrer T, Hoffmann P, et al. Solitary median maxillary central incisor. J Pediatr. 2015;167:770, App Fig. 1.)*

markedly enlarged anterior pituitary glands are seen in patients with *PROP1* or *LHX3* gene alterations. Structural lesions causing isolated, acquired GHD are not common, but are important from a therapeutic perspective, such that MRI is usually recommended at the time of the diagnosis of GHD.

Skeletal maturation may be assessed with a plain film of the hand (bone age) and is delayed in patients with isolated GHD and may be even more delayed when there is combined GH and TSH deficiency. Importantly, in very recent or acute onset of hypopituitarism, initial assessment of skeletal age may not demonstrate the delay classically reported in congenital or long-standing hypopituitarism. Further, comorbid *central precocious puberty* may accelerate skeletal development when both precocious puberty and GHD are present, as may be seen in some patients with GHD after cranial irradiation. Dual-photon x-ray absorptiometry shows deficient bone mineralization, deficiencies in lean body mass, and a corresponding increase in adiposity, but it is not routinely recommended in the initial evaluation of pediatric GHD.

DIFFERENTIAL DIAGNOSIS

The causes of growth disorders are numerous. The differential diagnosis can be summarized broadly as follows: hormonal disorders, chronic illness, undernutrition, genetic conditions, nonsyndromic family trait, and constitutional delay of growth and development. Hormonal disorders include primary hypothyroidism and Cushing disease. Systemic conditions, such as inflammatory bowel disease, celiac disease, occult renal disease, and anemia, must be considered. Patients with systemic conditions often have a greater deficit of weight than length. Severe psychosocial deprivation may result in growth failure that mimics GH deficiency. Numerous **syndromic genetic** conditions include short stature as a manifestation, among other findings, whereas some specific genetic alterations may present with isolated short stature. These include Turner syndrome (see Chapter 99.4), pathogenic variants and deletions in *SHOX, ACAN, PTPN11,* and *IHH,* the skeletal dysplasias (see Chapter 735), and identifiable syndromes including Donohue *(INSR),* Kabuki *(KMT2D, KDM6A),* Noonan (RASopathy), Smith-Lemli Opitz *(DHCR7),* and Cornelia de Lange *(NIPBL, SMC1A, HDAC8, RAD21, SMC3).* Prenatal-onset short stature associated with being small for gestational age that persists during childhood may also be syndromic. Whole exome sequencing is helpful in identifying the specific syndrome.

Some otherwise normal children are short (i.e., >2.25 SD below the mean for age) and grow 5 cm/year or less but have normal levels of GH in response to provocative tests and normal spontaneous episodic secretion; this is often termed **idiopathic short stature**. Most of these children show increased rates of growth when treated with GH in doses comparable with those used to treat children with hypopituitarism. Plasma levels of IGF-1 in these patients may be normal or low. Several groups of treated children have achieved final or near-final adult heights. Different studies have found changes in adult height that range from −2.5 to +7.5 cm compared with pretreatment predictions. There are no methods that can reliably predict which of these children will become taller in adulthood as a result of GH treatment and which will have compromised adult height despite treatment.

Diagnostic strategies for distinguishing between permanent GH deficiency and other causes of impaired growth are imperfect. Children with a combination of genetic short stature and constitutional delay of growth have short stature, below-average growth rates, and delayed bone ages. Many of these children exhibit minimal GH secretory responses to provocative stimuli and may be treated with GH therapy. When children in whom idiopathic or acquired isolated GHD is diagnosed are treated with recombinant human GH and retested as adults, the majority have peak GH levels within the normal range.

Constitutional Growth Delay

Constitutional growth delay is one of the variants of normal growth commonly encountered by the pediatrician. Length and weight measurements of affected children are normal at birth, and growth is normal for the first 4-12 months of life. Height is sustained at a lower percentile during childhood. The pubertal growth spurt is delayed, so their growth rates persist at a lower prepubertal rate after their classmates have begun to accelerate. Detailed questioning often reveals other family members (often one or both parents) with histories of short stature in childhood, delayed puberty, and eventual normal stature. IGF-1 levels tend to be low for chronological age but within the normal range for bone age and sexual maturation rating. GH responses to provocative testing tend to be lower than in children with a more typical timing of puberty. The prognosis for these children to achieve normal adult height is guarded. Predictions based on height and bone age tend to overestimate eventual height to a greater extent in males than in females. Males with >2 years of pubertal delay can benefit from a short course of testosterone therapy to hasten puberty after 14 years of age. The cause of this variant of normal growth is thought to be persistence of the relative hypogonadotropic state of childhood.

TREATMENT

Although well-established treatments are available to replace the classical anterior pituitary hormone deficiencies, treatment must take into account patient age, pubertal maturation, and patient goals. Lifelong attention to correct administration of hormone replacement and monitoring for comorbidities are needed to optimize patient outcomes.

Recombinant human GH (rhGH) has been available by prescription since the 1980s. Multiple brands are marketed in the United States, which are therapeutically equivalent, with the major differences consisting of proprietary devices for subcutaneous injection and availability of solubilized liquid forms versus powders needing reconstitution before injection. Long-acting forms are under development and will need to demonstrate comparable efficacy, safety, and tolerability to the daily injections currently available.

The U.S. Food and Drug Administration (FDA) has approved eight pediatric indications for rhGH treatment to promote linear growth. They are GHD, Turner syndrome, chronic renal

failure before transplantation, idiopathic short stature, small-for-gestational-age short stature, Prader-Willi syndrome, *SHOX* gene abnormality, and Noonan syndrome. In the United States, FDA approval for a given indication does not ensure that a patient's insurance carrier will approve payment for the drug. Treatment should be started as soon as possible to narrow the gap in height between patients and their classmates during childhood and to have the greatest effect on mature height. For some infants with MPHD, initiation of rhGH treatment may be urgent to reduce the frequency and severity of episodes of hypoglycemia. The recommended initial dose of rhGH for treatment of GHD is 0.16-0.24 mg/kg/wk (22-35 μg/kg/day). Higher doses have been used during puberty and for non-GHD indications. Most currently available forms of rhGH are administered subcutaneously once daily, but a weekly preparation has been recently FDA approved for use in the United States.

Maximal response to rhGH occurs in the first year of treatment. Growth velocity during this first year is typically above the 95th percentile for age. With each successive year of treatment, the growth rate tends to decrease until it approximates a typical height velocity for skeletal age. If the growth rate drops below the 25th percentile, adherence should be evaluated before the dose is increased. IGF-1 may be measured as an objective assessment of adherence. GH therapy should be continued until near-final height is achieved. Criteria for stopping GH treatment include a decision by the adolescent that they are tall enough, a growth rate less than 1 inch per year, and a bone age greater than 14 years in females and greater than 16 years in males. Adolescents who have completed treatment for promotion of adult stature should be reevaluated for GHD based on adult criteria after treatment is complete. Some adolescents or young adults, particularly those with profound GHD and/or MPHD, may benefit from continuation of rhGH treatment as adults. The dose of rhGH is much lower in adults relative to growing teens. Children with hypopituitarism require coordinated transition to adult care and lifelong attention to their endocrine deficiencies.

Concurrent treatment with rhGH and a gonadotropin-releasing hormone agonist has been used in the hope that interruption of puberty will delay epiphyseal fusion and prolong growth. This strategy may increase adult height. Risks include increasing the discrepancy in physical maturity between GH-deficient children and their age peers, decreasing the upper to lower segment ratio, and impairing bone mineralization. There have also been attempts to forestall epiphyseal fusion in males by giving aromatase inhibitors, which inhibit the enzyme responsible for converting androgens to estrogens. These agents are not approved for this purpose in the United States, but some clinical trials have demonstrated an increase in predicted adult height with this approach.

Some patients develop either primary or central hypothyroidism while under treatment with GH. Similarly, there is a risk of developing adrenal insufficiency as an associated component of **hypopituitarism**. If unrecognized, this can be fatal. Periodic evaluation of thyroid and adrenal function is indicated for all patients diagnosed with GHD.

rhGH treatment may enhance the growth of non-GHD children as well. Intensive investigation is in progress to determine the full spectrum of short children who may benefit from treatment with GH. The FDA approval for use of GH in idiopathic short stature specifies a height below the 1.2 percentile (−2.25 SD) for age and sex, a predicted height below the 5th percentile, and open epiphyses. Studies of the effect of GH treatment on adult height suggest a median gain of 2-3 inches, depending on dose and duration of treatment.

In children with MPHD, replacement should also be directed at other hormonal deficiencies. In TSH-deficient patients, thyroid hormone replacement (levothyroxine) is given in full replacement doses. In ACTH-deficient patients, hydrocortisone should be prescribed in physiologic doses, about 8-12 mg/m^2/day. In patients deficient in both TSH and ACTH, initiation of adrenal replacement before thyroid hormone replacement is mandatory to reduce the risk of adrenal crisis. Individualized dose adjustment of hydrocortisone is needed to minimize the risk of side effects associated with excess glucocorticoid administration and prevent symptoms of adrenal insufficiency. *Increased doses of hydrocortisone are required to support vital functions and prevent adrenal crisis during illness or during and after surgical procedures (so-called "stress dosing.")*

In patients with a deficiency of gonadotropins, gonadal steroids are given at the appropriate time. Consideration of chronological age, height age, bone age, and psychosocial development may all play a role in determining the timing of initiation of low-dose sex steroid replacement in young adolescents. For infants with micropenis, one or two 3-month courses of monthly intramuscular injections of 25 mg of testosterone cypionate or testosterone enanthate can bring the penis to near-normal size without an inordinate effect on osseous maturation.

Recombinant IGF-1 (mecasermin) is approved for use in the United States for primary IGF-1 deficiency. It is given subcutaneously twice a day. Side effects are similar to rhGH, except that mecasermin can cause hypoglycemia. The risk of hypoglycemia is reduced by giving the injections concurrently with a meal or snack. In some situations, its use may be more efficacious than use of GH. These conditions include abnormalities of the GH receptor and *STAT5b* genes that alter GH signaling downstream. It may have utility for severe GHD in the rare patients who have developed clinically significant antibodies to administered rhGH. However, mecasermin is not an indicated treatment for most patients with GHD.

COMPLICATIONS AND ADVERSE EFFECTS OF GROWTH HORMONE TREATMENT

GH treatment influences glucose homeostasis. Fasting and postprandial insulin levels are characteristically low before treatment, and they normalize during GH replacement. GH treatment is associated with an increase in the risk for type 2 diabetes and no significant increase in the risk for type 1 diabetes.

Concerns have been raised about the safety of GH treatment in children who become deficient after treatment of brain tumors, leukemia, and other neoplasms. Long-term studies show no increase in risk of recurrence of craniopharyngioma, other brain tumors, or leukemia. Some studies indicate an increased risk of second neoplasms in cancer survivors treated with GH. However, other studies have found no increased risk for secondary brain tumors after adjustment for radiation therapy. Looking more broadly at young adults treated in childhood with GH for a variety of indications, the Safety and Appropriateness of Growth hormone treatments in Europe consortium (SAGhE) has reported an increase in cause-specific mortality due to circulatory and hematologic conditions, but no increase in all-cause mortality for youth treated with GH.

Other reported side effects include pseudotumor cerebri, slipped capital femoral epiphysis, gynecomastia, coarsening of features, and worsening of scoliosis. The risk of late development of Creutzfeldt-Jakob disease was limited to recipients of contaminated lots of extracted pituitary GH. No comparable risks have been seen with rhGH, which is the only pharmacologic form of hGH currently in clinical use.

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Chapter 596

Diabetes Insipidus

Carmen L. Soto-Rivera, David T. Breault, and Joseph A. Majzoub

Diabetes insipidus (DI) manifests clinically with polyuria and polydipsia and can result from either vasopressin deficiency (central DI, also known as arginine vasopressin [AVP] deficiency) or vasopressin insensitivity at the level of the kidney (nephrogenic DI [NDI], also known as AVP resistance). Both central DI and NDI can arise from inherited defects of congenital or neonatal onset or can be secondary to a variety of causes (Table 596.1).

PHYSIOLOGY OF WATER BALANCE

The control of extracellular tonicity (osmolality) and volume within a narrow range is critical for normal cellular structure and function (see Chapter 73.2). Extracellular fluid tonicity is regulated almost exclusively by water intake and excretion, whereas extracellular volume is regulated by sodium intake and excretion. The control of plasma tonicity and intravascular volume involves a complex integration of endocrine, neural, behavioral, and paracrine systems (Fig. 596.1). Vasopressin, secreted from the posterior pituitary, is the principal regulator of tonicity, with its release largely stimulated by increases in plasma osmolality over 283 mOsm/kg H_2O. Volume homeostasis is largely regulated by the renin-angiotensin-aldosterone system, with contributions from both vasopressin and the natriuretic peptide family.

Vasopressin, a 9–amino acid peptide, has both antidiuretic and vascular pressor activity and is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus. It is transported to the posterior pituitary via axonal projections, where it is stored awaiting release into the systemic circulation. The half-life of vasopressin in the circulation is 5-10 minutes, as it is rapidly degraded by a cysteine aminoterminal peptidase. The carboxyterminus of the vasopressin precursor, **copeptin**, is more stable than vasopressin, and blood concentrations of the two peptides are highly correlated when evaluating response to osmotic stimuli.

In addition to responding to osmotic stimuli, vasopressin is secreted in response to significant decreases in intravascular volume and pressure (minimum of 8% decrement) via afferent baroreceptor pathways arising from the aortic arch (carotid sinus) and volume receptor pathways in the cardiac atria and pulmonary veins. Osmotic and hemodynamic stimuli interact synergistically. Nausea is also a potent stimulus for vasopressin secretion.

The sensation of thirst and the release of vasopressin are regulated by cortical and hypothalamic neurons. The thirst threshold is approximately 10 mOsm/kg H_2O higher (i.e., 293 mOsm/kg H_2O) than the osmotic threshold for vasopressin release. Consequently, under conditions of hyperosmolality, vasopressin is released before thirst is initiated, allowing ingested water to be retained. Subsequently, anticipation of water ingestion by cortical and vasopressin-secreting neurons leads to a decrease in vasopressin release immediately before water ingestion, presumably to prevent subsequent hyponatremia. Chemoreceptors present in the oropharynx also downregulate vasopressin release after water ingestion. In addition, thirst drive decreases even before the ingested fluid lowers blood osmolality, presumably to prevent overdrinking leading to hyponatremia.

Vasopressin exerts its principal effect on the kidney via V2 (AVPR2) receptors located primarily in the collecting tubule, the thick ascending limb of the loop of Henle, and the periglomerular tubules. The human V2 receptor gene *(AVPR2)* is located on the long arm of the X chromosome (Xq28) at the locus associated with **congenital, X-linked, vasopressin-resistant DI**. Activation of the V2 receptor results in increases in intracellular cyclic adenosine monophosphate, which leads to the insertion of the aquaporin-2 water channel into the apical (luminal) membrane. This allows water movement along its osmotic gradient into the hypertonic inner medullary interstitium from the tubule lumen and excretion of concentrated urine. In contrast to aquaporin-2, aquaporin-3 and aquaporin-4 are expressed on the basolateral membrane of the collecting duct cells, and aquaporin-1 is expressed in the proximal tubule. These channels may also contribute to urinary concentrating ability.

Atrial natriuretic peptide, initially isolated from cardiac atrial muscle but also expressed in the brain, has several important effects on salt and water balance, including stimulation of natriuresis, inhibition of sodium resorption, inhibition of vasopressin secretion, and inhibition of vasopressin and aldosterone action in the renal tubules. Atrial natriuretic peptide is expressed in endothelial cells and vascular smooth muscle, where it appears to regulate relaxation of arterial smooth muscle. **Brain natriuretic peptide (BNP)**, synthesized and secreted by cardiac ventricular tissue, similarly induces natriuresis, whereas the physiologic role of C-type natriuretic peptide (CNP) has yet to be defined.

Table 596.1 Causes of Hypotonic Polyuria

CENTRAL (NEUROGENIC) DIABETES INSIPIDUS (DI)
Congenital (congenital malformations, autosomal dominant, arginine vasopressin [AVP] neurophysin pathogenic variants)
Drug or toxin induced (ethanol, diphenylhydantoin, snake venom)
Granulomatous (histiocytosis, sarcoidosis)
Neoplastic (craniopharyngioma, germinoma, lymphoma, leukemia, meningioma, pituitary tumor, metastases)
Infectious (meningitis, tuberculosis, encephalitis)
Inflammatory, autoimmune (lymphocytic infundibuloneurohypophysitis, immune check point inhibitors)
Trauma (neurosurgery, deceleration injury)
Vascular (cerebral hemorrhage or infarction, brain death)
Idiopathic
OSMORECEPTOR DYSFUNCTION
Granulomatous (histiocytosis, sarcoidosis)
Neoplastic (craniopharyngioma, pinealoma, meningioma, metastases)
Vascular (anterior communicating artery aneurysm or ligation, intrahypothalamic hemorrhage)
Other (hydrocephalus, ventricular or suprasellar cyst, trauma, degenerative diseases)
Idiopathic
INCREASED AVP METABOLISM
Pregnancy
NEPHROGENIC DIABETES INSIPIDUS
Congenital (X-linked recessive, AVP V2 receptor pathogenic variants, autosomal recessive or dominant, aquaporin-2 water channel pathogenic variants)
Drug induced (lithium, demeclocycline, cisplatin, methoxyflurane)
Hypercalcemia
Hypokalemia
Infiltrating lesions (sarcoidosis, amyloidosis)
Vascular (sickle cell anemia)
Mechanical (polycystic kidney disease, bilateral ureteral obstruction)
Solute diuresis (glucose, mannitol, sodium, radiocontrast dyes)
Idiopathic
PRIMARY POLYDIPSIA
Psychogenic (schizophrenia, obsessive-compulsive behaviors)
Dipsogenic (downward resetting of thirst threshold, idiopathic or similar lesions, as with central DI)

From Verbalis JG. Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al., eds. *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 16.2.

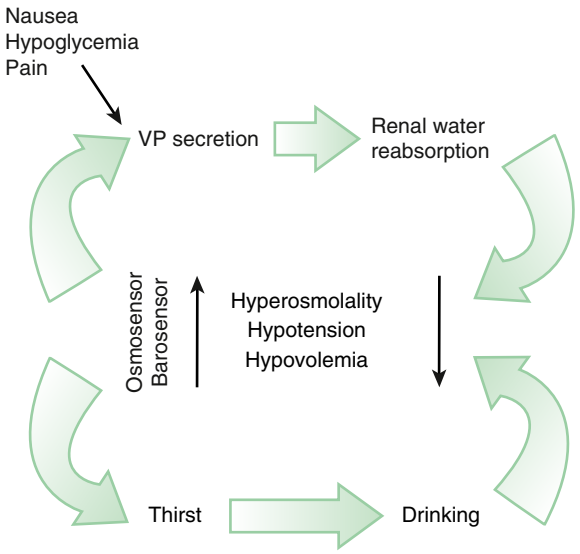

Fig. 596.1 Regulation of vasopressin secretion and serum osmolality. Hyperosmolality, hypovolemia, and hypotension are sensed by osmosensors, volume sensors, and barosensors, respectively. These stimulate both vasopressin secretion and thirst. Vasopressin, acting on the kidney, causes increased reabsorption of water (antidiuresis). Thirst causes increased water ingestion. The results of these dual negative feedback loops cause a reduction in hyperosmolality or in hypotension or hypovolemia. Additional stimuli for vasopressin secretion include nausea, hypoglycemia, and pain. *(From Srivasta A, Majzoub JA. Disorders of the posterior pituitary. In: Sperling MA, ed. Pediatric Endocrinology, 5th ed. Philadelphia: Elsevier; 2020: Fig. 12.6.)*

APPROACH TO THE PATIENT WITH POLYURIA, POLYDIPSIA, AND HYPERNATREMIA

The cause of pathologic polyuria or polydipsia (exceeding 2 L/m^2/24 hr) may be difficult to establish in children. Infants can present with irritability, failure to thrive, and intermittent fever. Patients with suspected DI should have a careful history taken, which should quantify the child's daily fluid intake and output and establish the voiding pattern, nocturia, and primary or secondary enuresis. A complete physical examination should establish the patient's hydration status, and the physician should search for evidence of visual and central nervous system dysfunction, as well as for other pituitary hormone deficiencies.

If pathologic polyuria or polydipsia is present, the following should be obtained: serum for osmolality, sodium, potassium, blood urea nitrogen, creatinine, glucose, hemoglobin A_{1c}, and calcium and urine for osmolality, specific gravity, and glucose determination. The diagnosis of DI is established if the serum osmolality is >300 mOsm/kg H_2O and the urine osmolality is <300 mOsm/kg. A baseline copeptin level above 20 pmol/L in this setting can confirm *nephrogenic* DI.

DI is unlikely if the serum osmolality is <270 mOsm/kg H_2O or the urine osmolality is >600 mOsm/kg. If the patient's serum osmolality is <300 mOsm/kg H_2O (but >270 mOsm/kg H_2O) and pathologic polyuria and polydipsia are present, a water deprivation test is indicated to establish the diagnosis of DI and to differentiate central from nephrogenic causes by assessing response to aqueous vasopressin at the end of the test.

Now that copeptin measurement is clinically available, test protocols aim to measure copeptin instead of AVP during water deprivation. Hypertonic saline infusion (3% saline) can also be given as an osmotic stimulus for copeptin secretion (instead of water deprivation tests), with a potentially higher diagnostic accuracy than water deprivation alone. In the inpatient postneurosurgical setting, central DI is likely if hyperosmolality (serum osmolality >300 mOsm/kg) is associated with urine osmolality less than serum osmolality. It is important to distinguish between polyuria resulting from postsurgical central DI and polyuria resulting from the normal diuresis of fluids received intraoperatively. Both cases may be associated with a large volume (>200 mL/m^2/hr) of dilute urine, although in patients with DI, the serum osmolality is high in comparison with patients undergoing postoperative diuresis.

CAUSES OF HYPERNATREMIA

Hypernatremia is discussed in Chapter 73.3.

Central Diabetes Insipidus

Central DI can result from multiple etiologies, including pathogenic variants in the vasopressin *(AVP)* gene; trauma (accidental or surgical) to vasopressin neurons; congenital malformations of the hypothalamus or pituitary; neoplasms; infiltrative, autoimmune, and infectious diseases affecting vasopressin neurons or fiber tracts; and increased metabolism of vasopressin. In approximately 10% of children with central DI, the etiology is idiopathic. Other pituitary hormone deficiencies may be present (see Chapter 595). *Over time, up to 35% of those with idiopathic central DI will develop other hormone deficiencies or have an underlying etiology identified.*

Autosomal dominant central DI usually occurs within the first 5 years of life and results from pathogenic variants in *AVP*. A number of these genetic variants can cause gene-processing defects in a subset of vasopressin-expressing neurons, which have been postulated to result in endoplasmic reticulum stress and cell death. **Wolfram syndrome**, which includes DI, diabetes mellitus, optic atrophy, and deafness, also results in vasopressin deficiency. Autosomal recessive pathogenic variants in the *WFS1* (most common) or *WFS2* (CISD2) genes, which give rise to endoplasmic reticulum proteins, are associated with this condition. Congenital brain abnormalities (see Chapter 631) such as **optic nerve hypoplasia syndrome** with agenesis of the corpus callosum, **Niikawa-Kuroki syndrome**, holoprosencephaly, and familial pituitary hypoplasia with absent stalk may be associated with central DI and defects in thirst perception (adipsia). Empty sella syndrome, possibly resulting from unrecognized pituitary infarction, can be associated with DI in children.

Trauma to the base of the brain and neurosurgical intervention in the region of the hypothalamus or pituitary are common causes of central DI. The **triphasic response** after surgery refers to an initial phase of transient DI, lasting 12-48 hours, followed by a second phase of syndrome of inappropriate antidiuresis (SIAD), lasting up to 10 days, which may be followed by permanent (or partial) DI. The initial phase may be the result of local edema interfering with normal vasopressin secretion; the second phase results from unregulated vasopressin release from dying neurons, whereas in the third phase, permanent DI results if more than 90% of the neurons have been destroyed.

Given the anatomic distribution of vasopressin neurons over a large area within the hypothalamus, **tumors** causing DI must either be very large and infiltrative or be strategically located near the base of the hypothalamus, where vasopressin axons converge before their entry into the posterior pituitary. Germinomas and pinealomas typically arise in this region and are among the most common primary brain tumors associated with DI. Germinomas can be very small and undetectable by MRI for several years after the onset of polyuria. Quantitative measurement of α-fetoprotein and β-human chorionic gonadotropin, often secreted by germinomas, should be performed in children with idiopathic or unexplained DI in addition to serial MRI scans. Craniopharyngiomas and optic gliomas can also cause central DI when they are very large, although this is more often a postoperative complication of the treatment for these tumors (see Chapter 546). Hematologic malignancies, such as acute myelocytic leukemia, can cause DI via infiltration of the pituitary stalk and sella.

Langerhans cell histiocytosis (see Chapter 556.2) and lymphocytic hypophysitis are common types of infiltrative disorders causing central DI, with **hypophysitis** as the cause in 50% of cases of "idiopathic" central DI. Infections involving the base of the brain (see Chapter 643), including meningitis (meningococcal, cryptococcal, listerial, toxoplasmal), congenital cytomegalovirus infection, and nonspecific

inflammatory diseases of the brain, may give rise to central DI that is often transient. Drugs associated with the inhibition of vasopressin release include ethanol, phenytoin, opiate antagonists, halothane, and α-adrenergic agents.

Nephrogenic Diabetes Insipidus

NDI can result from genetic or acquired causes. Genetic causes are less common but more severe than acquired forms of NDI. The polyuria and polydipsia associated with genetic NDI usually occur within the first several weeks of life but may become apparent only after weaning or with longer periods of nighttime sleep. Many infants initially present with fever, vomiting, and dehydration. Failure to thrive may be secondary to the ingestion of large amounts of water, resulting in caloric malnutrition. Long-standing ingestion and excretion of large volumes of water can lead to nonobstructive hydronephrosis, hydroureter, and megabladder.

Congenital X-linked NDI results from inactivating pathogenic variants of the vasopressin V2 receptor, *AVPR2*. **Congenital autosomal recessive NDI** results from defects in the aquaporin-2 gene, *AQP2*. An **autosomal dominant form of NDI** is associated with processing variants of the *AQP2* gene.

Acquired NDI can result from hypercalcemia or hypokalemia and is associated with lithium, demeclocycline, foscarnet, clozapine, amphotericin, methicillin, and rifampin. Impaired renal concentrating ability can also be seen with ureteral obstruction, chronic renal failure, polycystic kidney disease, medullary cystic disease, Sjögren syndrome, and sickle cell disease. Decreased protein or sodium intake or excessive water intake, as in primary polydipsia, can lead to diminished tonicity of the renal medullary interstitium, which impairs water reabsorption and thus the ability to concentrate the urine, leading to NDI.

TREATMENT OF CENTRAL DIABETES INSIPIDUS

Fluid Therapy

With an intact thirst mechanism and free access to oral fluids, a person with complete DI can maintain plasma osmolality and sodium in the high-normal range, although at great inconvenience. Neonates and young infants are often best treated solely with fluid therapy, given their requirement for large volumes (~3 L/m^2/24 hr) of nutritive fluid. The use of vasopressin analogs in patients with obligate high fluid intake is difficult given the risk of life-threatening hyponatremia. Although not FDA approved, the use of DDAVP (desmopressin) administered to infants with central DI, both as the diluted parenteral form given subcutaneously and as the diluted intranasal form given via the buccal mucosa, has been successful without causing severe hyponatremia. Patients with both central DI and NDI should ingest a diet without excessive solute (e.g., sodium chloride) to help decrease urine output when vasopressin action wanes.

Vasopressin Analogs

Treatment of central DI in older children is best accomplished with the use of DDAVP. DDAVP is available in an intranasal preparation (onset 5-10 minutes) and more commonly as tablets (onset 15-30 minutes). The intranasal preparation of DDAVP (10 μg/0.1 mL) can be administered by rhinal tube (allowing dose titration) or by nasal spray (10 μg/puff). Use of DDAVP oral tablets requires at least a 10-fold increase in the dosage compared with the intranasal preparation. Oral dosages of 25-300 micrograms every 8-12 hours are safe and effective in children. The appropriate dosage and route of administration are determined empirically based on the desired length of antidiuresis and patient preference. The use of oral DDAVP for the treatment of enuresis in older children should be regarded as a temporizing measure, given that it does not affect the underlying condition, and should be used with great caution given the risk of hyponatremia if water intake exceeds the capacity for renal clearance. To prevent water intoxication, patients should have at least 1 hour of urinary breakthrough between doses each day and be advised to drink only in response to thirst sensation, if present. The use of DDAVP nasal spray for childhood enuresis is no longer approved because of its risk of causing hyponatremia.

Aqueous Vasopressin

Central DI of acute onset after neurosurgery is best managed with continuous administration of synthetic aqueous vasopressin (Pitressin). Under most circumstances, total fluid intake must be limited to 1 L/m^2/24 hr during antidiuresis. A typical dosage for intravenous vasopressin therapy is 1.5 mU/kg/hr, which results in a blood vasopressin concentration of approximately 10 pg/mL. On occasion, after hypothalamic (but not transsphenoidal) surgery, higher initial concentrations of vasopressin may be required to treat acute DI, which has been attributed to the release of a vasopressin inhibitory substance. *Vasopressin concentrations >1,000 pg/mL should be avoided because they can cause cutaneous necrosis, rhabdomyolysis, cardiac rhythm disturbances, and hypertension.* Post-neurosurgical patients treated with vasopressin infusion should be switched from intravenous to oral fluids as soon as possible to allow thirst sensation, if intact, to help regulate osmolality.

Individuals with central DI caused by intracranial tumors that require chemotherapy often need hyperhydration with large amounts of intravenous fluids to prevent nephrotoxicity during treatment. Using a low-dose vasopressin continuous infusion to minimally concentrate urine above baseline can allow infusion of fluids over 1 L/m^2/day, while preventing the discomfort of full diuresis if done under careful monitoring of volume status and sodium levels.

TREATMENT OF NEPHROGENIC DIABETES INSIPIDUS

The treatment of acquired NDI focuses on eliminating, if possible, the underlying disorder, such as offending drugs, hypercalcemia, hypokalemia, or ureteral obstruction. Congenital NDI is often difficult to treat. The main goals are to ensure the intake of adequate calories for growth and to avoid severe dehydration. Foods with the highest ratio of caloric content to osmotic load (Na <1 mmol/kg/24 hr) should be ingested to maximize growth and to minimize the urine volume required to excrete the solute load. However, even with the early institution of therapy, growth failure and developmental disabilities are common.

Pharmacologic approaches to the treatment of NDI include the use of thiazide diuretics and are intended to decrease the overall urine output. Thiazides appear to induce a state of mild volume depletion by enhancing sodium excretion at the expense of water and by causing a decrease in the glomerular filtration rate, which results in proximal tubular sodium and water reabsorption. Indomethacin and amiloride may be used in combination with thiazides to further reduce polyuria. High-dose DDAVP therapy, in combination with indomethacin, has been used in some subjects with NDI. This treatment could prove useful in patients with genetic defects in the V2 receptor associated with a reduced binding affinity for vasopressin.

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Chapter 597

Other Abnormalities of Arginine Vasopressin Metabolism and Action

Carmen L. Soto-Rivera, David T. Breault, and Joseph A. Majzoub

Hyponatremia (serum sodium <130 mEq/L) in children is usually associated with severe systemic disorders and is most often a result of intravascular volume depletion, excessive salt loss, or hypotonic fluid overload, especially in infants (see Chapter 73).

The initial approach to the patient with hyponatremia begins with determination of the volume status. A careful review of the patient's history, physical examination (including changes in weight), and vital signs helps to determine whether the patient is hypovolemic or hypervolemic. Supportive evidence includes laboratory data such as serum electrolytes, blood urea nitrogen, creatinine, uric acid, urine sodium, specific gravity, and osmolality (Tables 597.1 and 597.2; see Chapter 73).

CAUSES OF HYPONATREMIA

Systemic Dehydration

The initial manifestation of systemic dehydration is often hypernatremia and hyperosmolality, which subsequently lead to the activation of vasopressin secretion and a decrease in water excretion. As dehydration progresses, hypovolemia and/or hypotension become a major stimulus for vasopressin release, further decreasing free water clearance. Excessive free water intake (orally or intravenous infusion of hypotonic fluids) with ongoing salt loss can produce hyponatremia. Urinary sodium excretion is low (usually <20 mEq/L), owing to a low glomerular filtration rate and concomitant activation of the renin-angiotensin-aldosterone system unless primary renal disease or diuretic therapy is present.

Table 597.1 Differential Diagnosis of Hyponatremia

DISORDER	INTRAVASCULAR VOLUME STATUS	URINE SODIUM
Systemic dehydration	Low	Low
Decreased effective plasma volume	Low	Low
Primary salt loss (nonrenal)	Low	Low
Primary salt loss (renal)	Low	High
Adrenal insufficiency	Low	High
SIAD	High	High
Cerebral salt wasting	Low	Very high
Decreased free water clearance	Normal or high	Normal or high
Primary polydipsia	Normal or high	Normal
Runner's hyponatremia	Low	Low
NSIAD	High	High
Pseudohyponatremia	Normal	Normal
Factitious hyponatremia	Normal	Normal

NSIAD, Nephrogenic syndrome of inappropriate antidiuresis; SIAD, syndrome of inappropriate antidiuresis.

Runner's Hyponatremia

Excess hypotonic fluid ingestion during long-distance running (e.g., marathon running) can result in severe hyponatremia from hypovolemia-induced activation of arginine vasopressin secretion coupled with excessive water ingestion and is correlated with weight gain, long racing time, and extremes of body mass index.

Decreased Effective Plasma Volume

Hyponatremia can result from decreased effective plasma volume, as found in congestive heart failure, cirrhosis, nephrotic syndrome, positive pressure mechanical ventilation, severe burns, bronchopulmonary dysplasia in neonates, cystic fibrosis with obstruction, and severe asthma. The resulting decrease in cardiac output leads to reduced water and salt excretion, as with systemic dehydration, and an increase in vasopressin secretion. In patients with impaired cardiac output and elevated atrial volume (congestive heart failure, lung disease), atrial natriuretic peptide concentrations are elevated further, leading to hyponatremia by promoting natriuresis. However, owing to the marked elevation of aldosterone in these patients, their urine sodium remains low (<20 mEq/L) despite this. Unlike dehydrated patients, these patients also have excess *total body* sodium from activation of the renin-angiotensin-aldosterone system and can demonstrate peripheral edema as well.

Syndrome of Inappropriate Antidiuresis

The syndrome of inappropriate antidiuresis (SIAD) is characterized by hyponatremia, an inappropriately concentrated urine (often >800 mOsm/kg H_2O), normal or slightly elevated plasma volume, normal-to-high urine sodium, and low serum uric acid. SIAD is uncommon in children, and most cases result from excessive administration of vasopressin in the treatment of central diabetes insipidus (vasopressin deficiency). It can also occur with increased intracranial pressure, encephalitis, brain tumors, head trauma, psychiatric disease, prolonged nausea, pneumonia, tuberculous and bacterial meningitis, AIDS, and in the postictal phase after generalized seizures (Table 597.3). SIAD is the cause of the hyponatremic second phase of the triphasic response seen after hypothalamic-pituitary surgery. It is found in up to 35% of patients 1 week after surgery and can result from retrograde neuronal degeneration with cell death and vasopressin release. Common drugs that have been shown to increase vasopressin secretion or mimic vasopressin action, resulting in hyponatremia, include oxcarbazepine, carbamazepine, chlorpropamide, vinblastine, vincristine, and tricyclic antidepressants.

Nephrogenic Syndrome of Inappropriate Antidiuresis

Gain-of-function pathogenic variants in the V2 vasopressin receptor gene, *AVPR2,* on chromosome Xq28 have been described in male

Table 597.2 Clinical Parameters to Distinguish Among Syndrome of Inappropriate Antidiuresis (SIAD), Cerebral Salt Wasting, and Central Diabetes Insipidus (DI)

CLINICAL PARAMETER	SIAD	CEREBRAL SALT WASTING	CENTRAL DI
Serum sodium	Low	Low	High
Urine output	Normal or low	High	High
Urine sodium	High	Very high	Low
Intravascular volume status	Normal or high	Low	Low
Blood pressure	Normal	Decreased/ orthostatic hypotension	Decreased/ orthostatic hypotension
Vasopressin level	High	Low	Low
BUN	Low	High	High

Table 597.3 Disorders Associated with Syndrome of Inappropriate Antidiuresis

CANCER	PULMONARY DISORDERS	CENTRAL NERVOUS SYSTEM DISORDERS	OTHER DISORDERS
Thymoma	Viral pneumonia	Encephalitis (viral or bacterial)	AIDS
Lymphoma	Bacterial pneumonia	Meningitis (viral, bacterial, tuberculous, fungal)	Prolonged exercise
Ewing sarcoma	Pulmonary abscess	Head trauma	Idiopathic (in older individuals)
Oropharyngeal tumor	Tuberculosis	Brain abscess	Nephrogenic
	Aspergillosis	Guillain-Barré syndrome	Acute intermittent porphyria
	Positive pressure ventilation	Subarachnoid hemorrhage or subdural hematoma	
	Asthma	Cerebellar and cerebral atrophy	
	Pneumothorax	Cavernous sinus thrombosis	
	Cystic fibrosis	Neonatal hypoxia	
		Shy-Drager syndrome	
		Rocky Mountain spotted fever	
		Delirium tremens	
		Cerebrovascular accident (cerebral thrombosis or hemorrhage)	
		Acute psychosis	
		Peripheral neuropathy	
		Multiple sclerosis	

Modified from Verbalis JG. Disorders of water balance. In Skorecki K, Chertow GM, Marsden PA, et al., eds, *Brenner & Rector's The Kidney,* 10th ed. Philadelphia: Elsevier; 2016: Table 16.6.

neonates with an SIAD-like clinical picture with undetectable vasopressin levels. Females are most often asymptomatic carriers. It is most commonly treated by fluid restriction, but oral urea has also been used to promote osmotic diuresis and increase water clearance. Germline activating pathogenic variants in *GNAS* have also been found in infants presenting with hyponatremia. Activating variants in the aquaporin-2 gene *(AQP2)* also give rise to the same syndrome.

Cerebral Salt Wasting

Cerebral salt wasting appears to be the result of hypersecretion of natriuretic peptides and is seen primarily with central nervous system disorders, including brain tumors, head trauma, hydrocephalus, neurosurgery, cerebrovascular accidents, and brain death. Hyponatremia is accompanied by elevated urinary sodium excretion (often >150 mEq/L), excessive urine output, hypovolemia, normal or high uric acid, and elevated atrial natriuretic peptide concentrations (>20 pmol/L). Thus it is distinguished from SIAD, in which normal or decreased urine output, normal or elevated blood volume, only modestly elevated urine sodium concentration, and an elevated vasopressin level occur. The distinction between cerebral salt wasting and SIAD is important because the treatment of the two disorders differs markedly. The existence of cerebral salt wasting has been controversial; however, current data support this entity as different from SIAD.

Primary Polydipsia (Increased Water Ingestion)

In patients with normal renal function, the kidney can excrete dilute urine with an osmolality as low as 50 mOsm/kg H_2O. To excrete a daily solute load of 500 mOsm/m^2 under these circumstances, the kidney must produce 10 L/m^2 of urine per day. Therefore to avoid hyponatremia, the maximum amount of water a person with normal renal function can consume daily is 10 L/m^2, or less if solute intake is lower. However, neonates cannot dilute their urine to this degree, putting them at risk for water intoxication if water intake exceeds 4 L/m^2/day (approximately 60 mL/hr in a newborn). Infants may develop transient hyponatremic seizures after being fed pure water without electrolytes rather than breast milk or formula.

Primary Salt Loss

Hyponatremia can result from the primary loss of sodium chloride, as seen in specific disorders of the kidney (congenital polycystic kidney disease, acute interstitial nephritis, chronic renal failure), gastrointestinal tract (gastroenteritis), and sweat glands (cystic fibrosis). The hyponatremia is not solely caused by salt loss, as it is often associated with hypovolemia, leading to an increase in vasopressin. Mineralocorticoid deficiency (hypoaldosteronism), pseudohypoaldosteronism (genetic or sometimes seen in children with urinary tract obstruction or infection), and diuretics can also result in loss of sodium chloride (Table 597.4). Low aldosterone states, such as primary adrenal insufficiency (Addison disease), are associated with salt wasting, hypovolemia, hyponatremia, hyperkalemia, and failure to thrive.

Decreased Free Water Clearance

Hyponatremia as a consequence of decreased renal free water clearance, even in the absence of an increase in vasopressin secretion, can result from adrenal insufficiency or thyroid deficiency or can be related to a direct effect of drugs on the kidney. Glucocorticoids are required for normal free water clearance in a vasopressin-independent manner. In patients with unexplained hyponatremia, adrenal and thyroid insufficiency should be considered. Patients with coexisting adrenal failure and diabetes insipidus might have no symptoms of the latter until glucocorticoid therapy unmasks the need for vasopressin replacement. Certain drugs can inhibit renal water excretion through direct effects on the nephron, thus causing hyponatremia; these drugs include high-dose cyclophosphamide, vinblastine, cisplatinum, carbamazepine, and oxcarbazepine.

Pseudohyponatremia and Other Causes of Hyponatremia

Pseudohyponatremia can result from hypertriglyceridemia (see Chapter 73.3). Elevated lipid levels result in a relative decrease in serum water content. As electrolytes are dissolved in the aqueous phase of the serum, they appear low when expressed as a fraction of the total serum volume. However, as a fraction of serum water, electrolyte content is normal. Modern laboratory methods that measure sodium concentration directly, independent of sample volume, do not cause this anomaly. Factitious hyponatremia can result from obtaining a blood sample downstream to the site of intravenous hypotonic fluid infusion.

Hyponatremia is also associated with hyperglycemia, which causes the influx of water into the intravascular space. Serum sodium decreases by ~1.6 mEq/L for every 100 mg/dL increment in blood glucose >100 mg/dL. Glucose is not ordinarily an osmotically active agent and does not stimulate vasopressin release, probably because it can equilibrate freely across plasma membranes. However, in the presence of insulin deficiency and hyperglycemia, glucose acts as an osmotic agent, presumably because its normal intracellular access to osmosensor sites is prevented. Under these circumstances, an osmotic gradient exists, stimulating vasopressin release.

TREATMENT

Patients with systemic dehydration and hypovolemia should be rehydrated with salt-containing fluids such as normal saline or lactated Ringer's solution. Because of activation of the renin-angiotensin-aldosterone system, the administered sodium is avidly conserved, and water diuresis quickly

Table 597.4 Pathogenic Gene Variants Associated with Hypoaldosteronism/ Pseudohypoaldosteronism (Type IV Renal Tubular Acidosis)

GENE CHROMOSOME OMIM	PATHOPHYSIOLOGY	PATHOGENIC VARIANT–CLINICAL MANIFESTATIONS–OMIM–INHERITANCE
PRIMARY HYPOALDOSTERONISM		
CYP21A2—cytochrome P450, subfamily XXIA, polypeptide 2 6p21.3 613815	P450c21—steroid 21-hydroxylase that converts 17 α-hydroxyprogesterone to 11-deoxycortisol and progesterone to 11-deoxycorticosterone in the adrenal zona fasciculata	Loss-of-function pathogenic variants decrease synthesis of cortisol and aldosterone, the latter resulting in the salt-losing form of classic congenital adrenal hyperplasia, AR–201910
CYP11B2—cytochrome P450, subfamily XIB, polypeptide 2 8q21 124080	P450c11B2—aldosterone synthase/corticosterone methyloxidase types I and II expressed only in the zona glomerulosa; hydroxylates deoxycorticosterone at carbon-11 and corticosterone at carbon-18 and oxidizes 18-hydroxycorticosterone to aldosterone	Loss-of-function pathogenic variants associated with severe salt loss and volume depletion but not with abnormalities of genital formation or glucocorticoid synthesis AR (CMOI 203400; CMOII 610600)
PSEUDOHYPOALDOSTERONISM TYPE I (PHA1)		
NR3C2—nuclear receptor subfamily 3, group C, member 2 (MR-mineralocorticoid receptor), 4q31.1 600983	Ligand-activated nuclear transcription factor that transmits aldosterone-mediated control of gene expression by binding to the mineralocorticoid response element in the promoter region of the target gene	Loss-of-function pathogenic variants in the MR lead to mineralocorticoid resistance and salt wasting, PHA1A, AD–177735
SCNN1A—sodium channel, non–voltage-gated, α-subunit 12p13.31 600228	Inactivating pathogenic variant of α-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B, AR–264350
SCNN1B—sodium channel, non–voltage-gated, β-subunit 16p12.2 600760	Inactivating mutation of β-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B, AR–264350
SCNN1G—sodium channel, non–voltage-gated, γ-subunit 16p12.2 600761	Inactivating mutation of γ-subunit of the epithelial sodium channel	Loss-of-function pathogenic variants in the epithelial sodium channel lead to mineralocorticoid resistance and salt wasting, PHA1B AR–264350
PSEUDOHYPOALDOSTERONISM TYPE II (PHA2) (GORDON SYNDROME)		
WNK4—protein kinase, lysine-deficient 4 17q21.31 601844	Multifunctional serine-threonine protein kinase whose substrate is SLC12A3, the thiazide-sensitive sodium/chloride co-transporter (NCCT)—OMIM 600968—that also regulates lysosomal degradation of NCCT and endocytosis of the KCNJ1 potassium channel	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2B, AD–614491
WNK1—protein kinase, lysine-deficient 1 12p13.33 605232	Serine-threonine protein kinase that inactivates WNK4 by phosphorylating its kinase domain	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2C, AD–614492
KLH3—Kelch-like 3 5q31.2 605775	Adaptor protein within the ubiquitination sequence that links WNK1 and WNK4 to CUL3	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2D, AD/AR–614495
CUL3—Cullin 3 2q36.2 603136	Scaffold protein that links to RING-box E3 ligase facilitating WNK4 ubiquitination and proteasomal destruction of WNK4	Gain-of-function pathogenic variants lead to hyperkalemia and hypertension, PHA2E, AD–614496

AD, Autosomal dominant; AR, autosomal recessive; CMO, corticosterone methyloxidase; OMIM, Online Mendelian Inheritance in Man.
From Root AW. Disorders of aldosterone synthesis, secretion, and cellular function. *Curr Opin Pediatr.* 2014;26:480–486, Table 1.

ensues as volume is restored and vasopressin concentrations decrease. Under these conditions, caution must be taken to prevent a too-rapid correction of hyponatremia (with a goal increase of <0.5 mEq/L/hr), which can result in central pontine myelinolysis characterized by discrete regions of axonal demyelination and the potential for irreversible brain damage.

Hyponatremia from a decrease in effective plasma volume caused by cardiac, hepatic, renal, or pulmonary dysfunction is more difficult to reverse. The most effective therapy is treatment of the underlying systemic disorder. Patients weaned from positive pressure ventilation undergo a prompt water diuresis and resolution of hyponatremia as cardiac output is restored and vasopressin concentrations decrease. Vaptans are a class of small-molecule arginine vasopressin V2 receptor antagonists (aquaretics) useful for the treatment of hypervolemic hyponatremia associated with severe congestive heart failure and chronic liver failure. Although these agents successfully increase plasma sodium, they also lead to increased thirst and plasma vasopressin levels, which can limit their effectiveness, can increase serum sodium more rapidly than is safe, and may cause hepatoxicity.

Patients with hyponatremia from primary salt loss require supplementation with sodium chloride and fluids. Initially, intravenous replacement with isotonic fluids containing sodium chloride (150 mEq/L) may be necessary. Hypertonic fluids (450 mEq/L sodium choride) should be reserved for treatment of acute neurologic deterioration caused by severe hyponatremia. Oral salt supplementation may be required subsequently. This treatment contrasts with that of SIAD, in which water restriction without sodium supplementation is the mainstay.

Emergency Treatment of Hyponatremia

The development of acute hyponatremia (onset <12 hr) or a serum sodium concentration <120 mEq/L may be associated with lethargy,

psychosis, coma, or generalized seizures, especially in younger children. Acute hyponatremia can cause cell swelling and lead to neuronal dysfunction or to cerebral herniation. *The emergency treatment of cerebral dysfunction resulting from acute hyponatremia includes water restriction and can require rapid correction with hypertonic 3% sodium chloride*. If hypertonic saline treatment is undertaken, the serum sodium should be raised only high enough to cause an improvement in mental status and, in no case, faster than 0.5 mEq/L/hr or 12 mEq/L/24 hr.

Treatment of Syndrome of Inappropriate Antidiuresis

Chronic SIAD is best treated by oral fluid restriction. With full antidiuresis (urine osmolality of 1,000 mOsm/kg H_2O), a normal daily obligate renal solute load of 500 mOsm/m^2 would be excreted in 500 mL/m^2 water. This, plus a daily nonrenal water loss of 500 mL/m^2, would require that oral fluid intake be limited to 1,000 mL/m^2/24 hr to avoid hyponatremia. In young children, this degree of fluid restriction might not provide adequate calories for growth. In this situation, a vaptan such as tolvaptan, although not FDA approved in children and may cause initial correction of hyponatremia too rapidly, may allow sufficient fluid intake for normal growth without concomitant hyponatremia. Urea has also been safely used to induce an osmotic diuresis in infants and children.

Treatment of Cerebral Salt Wasting

Treatment of patients with cerebral salt wasting consists of restoring intravascular volume with sodium chloride and water, as for the treatment of other causes of systemic dehydration. The underlying cause of the disorder, which is usually the result of acute brain injury, should also be treated if possible. Treatment involves the ongoing replacement of urine and sodium losses volume for volume.

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Chapter 598

Hyperpituitarism

Omar Ali

Hyperpituitarism is defined as the excessive secretion or production of one or more of the hormones produced by the pituitary gland. The anterior pituitary normally produces prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and the gonadotropin hormones (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]); overproduction of any of these hormones is possible, though all are relatively rare. The posterior pituitary stores and releases antidiuretic hormone (ADH) and oxytocin, both produced by neurons in the hypothalamus. Although extremely rare cases of hypothalamic neurocytomas producing excess ADH have been reported (mostly in adults), these are vanishingly rare and will not be considered any further. *Hyperpituitarism refers to the overproduction of one or more of the anterior pituitary hormones.*

SECONDARY HYPERPITUITARISM

Several of the anterior pituitary hormones (all except GH and prolactin) act on other endocrine glands and regulate their secretion. They are regulated by negative feedback loops from their target glands, and their secretion increases if the end organ is not producing enough hormone. This can lead in extreme cases to severe hypertrophy of the relevant anterior pituitary cells and is a normal physiologic response to target hormone deficiencies resulting in decreased hormonal feedback, such as in hypogonadism, hypoadrenalism, or hypothyroidism. In these cases of *secondary hyperpituitarism,* chronic pituitary hypersecretion occurs in response to target hormone deficiencies that leads to pituitary hyperplasia; in extreme cases this can even enlarge and erode the sella and, on rare occasions, increase intracranial pressure. Such enlargements should not be confused with *primary* pituitary tumors; they disappear, and elevated pituitary hormone levels readily suppress to normal when the underlying hormone deficiency is treated by replacement of end-organ hormones.

Primary hypersecretion of pituitary hormones is uncommon in childhood. The most commonly diagnosed adenoma during childhood is prolactinoma, followed by corticotropinoma, and then somatotropinoma, which secrete prolactin, corticotropin, and GH, respectively. There are a handful of case reports of **thyrotropinoma** in children and adolescents. There are no pediatric reports of gonadotropinoma, but hypothalamic hamartomas that secrete excess gonadotropin-releasing hormone are one cause of precocious puberty. In very rare cases, pituitary hyperplasia can also occur in response to stimulation by ectopic production of releasing hormones such as that seen occasionally in patients with Cushing syndrome secondary to corticotropin-releasing hormone excess or in children with acromegaly secondary to growth hormone–releasing hormone (GHRH) produced by a variety of systemic tumors.

The monoclonal nature of most pituitary adenomas implies that most originate from a clonal event in a single cell. In some cases, the pituitary tumors result from stimulation with hypothalamic-releasing hormones and in other instances, as in **McCune-Albright syndrome** (MAS), the tumor is caused by activating pathogenic variants of the *GNAS1* gene that codes for the α subunit of $G_s\alpha$, a guanine nucleotide-binding protein. The clinical presentation typically depends on the pituitary hormone that is hypersecreted. In addition, disruptions of growth regulation and/or sexual maturation are common as a result of either hormone hypersecretion or local compression by the tumor. MAS also features polyostotic fibrous dysplasia of bone and café-au-lait spots in a distinct distribution.

EXCESS GROWTH HORMONE SECRETION AND PITUITARY GIGANTISM

In young persons with open epiphyses, overproduction of GH results in **gigantism**; in persons with closed epiphyses, the result is **acromegaly**. Often some acromegalic features are seen with gigantism, even in children and adolescents. After closure of the epiphyses, the acromegalic features become more prominent.

Gigantism is rare, with only several hundred reported cases worldwide to date. It must be emphasized that the vast majority of patients with tall stature will not have gigantism. The normal distribution of height predicts that 2.3% of the population will be taller than 2 standard deviations (SD) (97.7%) above the mean, and many cases of tall stature will therefore be normal-variant familial tall stature; if their growth is in line with their midparental height and no other concerning features are present, then no further investigation is needed. In cases where the tall stature is unexpected or extreme, other etiologies of rapid linear growth such as precocious puberty and hyperthyroidism should be carefully excluded. Coexisting findings (e.g., dysmorphic facial features, neurocognitive problems, hemihypertrophy) may suggest syndromic or chromosomal causes of tall stature, such as Sotos, Weaver, Klinefelter, or XYY syndrome.

The cardinal clinical feature of gigantism is longitudinal growth acceleration secondary to GH excess. The usual manifestations consist of coarse facial features and enlarging hands and feet. In young children, rapid growth of the head can precede linear growth. Some patients have behavioral and visual problems. In most recorded cases, the abnormal growth became evident at puberty, but the condition has been established as early as the newborn period. Giants have rarely been reported to grow to a height of over 8 feet. In some cases, the patient may present with local effects of the pituitary tumor (headache, visual field defects, and other pituitary hormone deficiencies) as the main complaint, and there is at least one report of a patient presenting with diabetic ketoacidosis induced by GH excess. The presentation of gigantism is usually dramatic, unlike the insidious onset of acromegaly in adults.

Pituitary adenomas secreting GH are more common in males, but females may present at an earlier age. Tumors with *AIP* pathogenic

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Pituitary adenomas secreting GH are more common in males, but females may present at an earlier age. Tumors with *AIP* pathogenic

variants **(familial isolated pituitary adenoma)** are more common in males, are larger and invasive, and secrete GH or prolactin. **X-LAG syndrome (X-linked acrogigantism)** is a recognized cause of familial pituitary adenomas, and in these patients the rapid growth begins in infancy and is more frequent in females. Patients with MAS will usually exhibit other features, including polyostotic fibrous dysplasia, café-au-lait spots, and precocious puberty.

Pituitary tumors secrete extremely high levels of GH; approximately 50% of pituitary adenomas also exhibit hyperprolactinemia because they secrete both GH and prolactin. Adenomas can compromise other anterior pituitary function through growth or cystic degeneration. Secretion of gonadotropins, thyrotropin, or corticotropin may be impaired. Delayed sexual maturation or hypogonadism can occur. When GH hypersecretion is accompanied by gonadotropin deficiency, accelerated linear growth can persist for decades. In some cases, the tumor spreads outside the sella, invading the sphenoid bone, optic nerves, and brain. GH-secreting tumors in pediatric patients are more likely to be locally invasive or aggressive than are those in adults.

Acromegalic features consist chiefly of enlargement of the distal parts of the body, but manifestations of abnormal growth involve all portions. The circumference of the skull increases, the nose becomes broad, and the tongue is often enlarged, with coarsening of the facial features. The mandible grows excessively, and the teeth become separated. Visual field defects and neurologic abnormalities are common; signs of increased intracranial pressure appear later. The fingers and toes grow chiefly in thickness. There may be dorsal kyphosis. Fatigue and lassitude are early symptoms. GH levels are elevated and occasionally exceed 100 ng/mL. There is usually no suppression of GH levels by the hyperglycemia of a glucose tolerance test, and insulin-like growth factor 1 (IGF1) and insulin-like growth factor binding protein 3 (IGFBP-3) levels are consistently elevated in acromegaly and pituitary gigantism.

Diagnosis

GH hypersecretion should be screened for by testing IGF1 and IGFBP-3 levels. An elevated IGF1 level in a patient with appropriate clinical suspicion usually indicates GH excess. Potential confusion can arise in the evaluation of normal adolescents because significantly higher IGF1 levels occur during puberty than in adulthood; the IGF1 level must be age and gender matched. Serum IGFBP-3 levels are also sensitive markers of GH elevations and will be elevated in almost all cases. If IGF1 and/or IGFBP-3 levels are elevated, then the next step is to test for GH excess by doing an oral glucose-suppression test. The gold standard for the diagnosis of GH excess in adults is the failure to suppress serum GH levels to <1 ng/dL at any time during a 2-hour oral glucose tolerance test with 1.75 g/kg oral glucose challenge (maximum: 75 g). GH levels may not be suppressed to this level in normal adolescents, and a cutoff of 5 ng/mL may be more appropriate in this age-group. If laboratory findings suggest GH excess, the presence of a pituitary adenoma should be confirmed by MRI of the brain. In rare cases, a pituitary mass is not identified. This might be from an occult pituitary microadenoma or ectopic production of GHRH or GH. CT is acceptable when MRI is unavailable.

Genetic causes: Genetic pathogenic variants are recognized as being present in ~50% of cases, though many are sporadic. In a large series, detailed genetic testing revealed pathogenic variants in *AIP* in 29% of cases, X-LAG due to microdeletions at Xq26.3 in 10% of the cases, and MAS in 5% of the cases. No genetic abnormality was identified in 54% of the cases. Although GH-secreting adenomas eventually develop in up to 60% of patients with multiple endocrine neoplasia 1 (MEN1), most of these occur in adults and therefore cause acromegaly rather than gigantism. Increased GH secretion and GH-secreting adenomas may also be seen in neurofibromatosis; tuberous sclerosis; MEN4; Carney complex; and the paraganglioma, pheochromocytoma, and pituitary adenoma association known as *3PA*.

A genetics consultation and appropriate genetic testing is therefore indicated in all cases of pituitary gigantism.

Treatment

The goals of therapy are to remove or shrink the pituitary mass, to restore GH and secretory patterns to normal, to restore IGF1 and IGFBP-3 levels to normal, to retain the normal pituitary secretion of other hormones, and to prevent recurrence of disease.

For well-circumscribed pituitary adenomas, trans-sphenoidal surgery is the treatment of choice and may be curative. The tumor should be removed completely. The likelihood of surgical cure depends greatly on the surgeon's expertise and on the size and extension of the mass. Intraoperative GH measurements can improve the results of tumor resection. Trans-sphenoidal surgery to resect the tumors is as safe in children as in adults. At times, a transcranial approach might be necessary. The primary goal of treatment is to normalize GH and IGF1 levels. GH levels (<1 ng/mL within 2 hours after a glucose load) and serum IGF1 levels (age-adjusted normal range) are the best tests to define a biochemical cure.

If GH secretion and IGF1 levels are not normalized by surgery, the options include pituitary irradiation and medical therapy. Further growth of the tumor is prevented by irradiation in >99% of patients. The main disadvantage is the delayed efficacy in decreasing GH levels. GH is reduced by approximately 50% from the initial concentration by 2 years, by 75% by 5 years, and approaches 90% by 15 years. Multiple pituitary hormone deficiency is a predictable result of pituitary radiation, occurring in 40–50% of patients 10 years after irradiation.

Surgery fails to cure a significant number of patients, and radiotherapy may not work fast enough, so medical therapy has an important role in treating patients with GH excess. Treatment is effective and well tolerated with GH antagonists, long-acting somatostatin analogs, and in some cases, by dopamine agonists.

Pegvisomant is a GH-receptor antagonist that competes with endogenous GH for binding to the GH receptor. It effectively suppresses GH and IGF1 levels in patients with acromegaly caused by pituitary tumors and ectopic GHRH hypersecretion. Normalization of IGF1 levels occurs in up to 90% of patients treated daily with this drug for 3 months or longer. The adult dosage is 10-40 mg via subcutaneous injection once daily, although twice-weekly protocols have also been reported as highly successful. IGF1 levels and hepatic enzymes must be monitored. Combined therapy with somatostatin analogs and weekly pegvisomant injections also is effective. Pediatric experience is limited, but case reports indicate that it can successfully suppress IGF1 levels when used in doses of 10-30 mg/day.

The **somatostatin analogs** are frequently effective in the treatment of patients with GH excess. Octreotide suppresses GH to <2.5 ng/mL in 65% of patients with acromegaly and normalizes IGF1 levels in 70%. The effects of octreotide are well sustained over time. Tumor shrinkage also occurs with octreotide but is generally modest. Consistent GH suppression can be obtained with a continuous subcutaneous (SC) pump infusion of octreotide or with long-acting formulations, including long-acting octreotide and lanreotide. Octreotide injection in the pediatric population has been used at doses of 1-40 μg/kg/24 hr. In adults the long-acting form is used in a dose of 10-40 mg every month, but no pediatric dose range has been established.

For patients with both GH and prolactin oversecretion, **dopamine agonists, such as bromocriptine and cabergoline**, which bind to pituitary dopamine type 2 receptors and may also suppress GH secretion, can also be considered. Prolactin levels are often adequately suppressed, but GH levels and IGF1 levels are rarely normalized with this treatment modality alone. Tumor shrinkage occurs in a minority of patients. The effectiveness of these agents may be additive to that of octreotide. Cabergoline therapy at doses of 0.25-4.0 mg/wk (given 1-2 times per week) has been used in adults with acromegaly, and because of its less frequent dosing and lower incidence of side effects as compared to bromocriptine, this is now considered the dopamine agonist of choice in both adults and children. Side effects can include nausea, vomiting, abdominal pain, arrhythmias, nasal stuffiness, orthostatic hypotension, sleep disturbances, and fatigue.

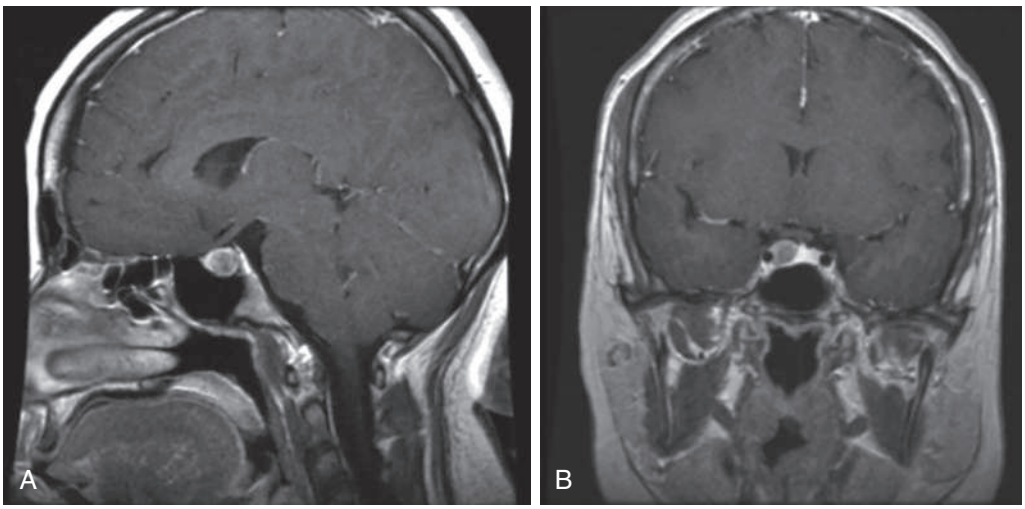

Fig. 598.1 Sagittal (A) and coronal (B) post-gadolinium T1-weighted MRI scans of a female with a microprolactinoma on the right side of the sella, who presented with amenorrhea and galactorrhea. Her serum prolactin was 89 ng/mL. *(From Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. J Clin Neurosci. 2015;22:1562–1567, Fig. 1, p. 1563.)*

TREATMENT OF NORMAL-VARIANT TALL STATURE

Patients who have **familial tall stature** and no other underlying pathology usually require no treatment other than reassurance. The use of the bone age to predict adult height might provide some comfort for them, as will general supportive discussions on the social acceptability of this condition. Although treatment is possible for females and males with excessive growth, its use should be restricted to patients with predicted adult height >3-4 SD above the mean (79 inches or 200 cm in males, 73 inches or 185 cm in females) *and* evidence of significant psychosocial impairment.

Sex steroids have been used in the treatment of tall stature and are designed to accelerate puberty and to promote epiphyseal fusion; these are therefore of little benefit when given in late puberty. The lack of extensive experience with this form of therapy and the risks of estrogen or androgen treatment for tall stature should be carefully weighed and discussed with the family, and treatment should be discouraged except in the most extreme cases. Detailed discussion with the child at the child's level is also advisable, as up to 40% of those who underwent such treatments are dissatisfied as adults and feel they were not sufficiently consulted about this course of action. Therapy is initiated ideally before puberty or in early puberty (no later than bone age of 14). In the extremely rare instances where treatment is desired, testosterone enanthate is used at a dose of 250-500 mg intramuscularly every 2 weeks for 6 months in males. In females, oral estrogens in various doses have been used to reduce the predicted height, but average height reduction may be only 1.1-2.4 cm. Therapy must begin before the bone age has reached 12 years. In the rare case where treatment is advised, oral ethinyl estradiol has been used at a dose of 0.15-0.5 mg/day until cessation of growth occurs**.** Short-term side effects have included benign breast disease, cholelithiasis, hypertension, menstrual irregularities, weight gain, nausea, limb pain, galactorrhea, and thrombosis. Reduced fertility later in life may be a potential long-term complication. An alternative to sex-steroid therapy is the use of epiphysiodesis (destruction of the growth plates) around the knee to limit linear growth, but this intervention also remains controversial, and its long-term safety profile and psychologic risks and benefits remain unknown.

HYPERSECRETION OF OTHER PITUITARY HORMONES

Prolactinoma

Prolactin-secreting pituitary adenomas are the most common pituitary tumors in adolescents. With the use of MRI, more of these tumors, particularly microadenomas (<1 cm in diameter), are being detected (Fig. 598.1). The most common presenting manifestations are headache, primary or secondary amenorrhea, and galactorrhea. The disorder affects more than twice as many females as males; most patients have undergone normal puberty before becoming symptomatic. Only a few have delayed puberty. In some kindreds with **type I multiple endocrine neoplasia syndrome**, prolactinomas are the presenting feature during adolescence. Familial cases and sporadic cases with de novo pathogenic variants of the *AIP* gene and X-LAG are being recognized more often as genetic testing becomes more common.

Prolactin levels may be elevated mildly (40-50 ng/mL) or markedly (10,000-15,000 ng/mL), and there is a correlation between tumor size and prolactin levels. Most prolactinomas in children are large (macroadenomas), cause the sella to enlarge, and, in some cases, cause visual field defects. Approximately 30% of patients with macroadenomas develop other pituitary hormone deficiencies, particularly GH deficiency. Alternatively, prolactin-secreting adenomas might also stain for and secrete excess GH and/or TSH.

Prolactinomas should not be confused with the hyperprolactinemia and pituitary hyperplasia that can occur in patients with **primary hypothyroidism**, which is readily treated with thyroid hormone (see Chapter 603). Moderate elevations (<200 ng/mL) of prolactin are also associated with a variety of medications (antipsychotics, metoclopramide, phenothiazines, verapamil, opioids), with pituitary stalk dysfunction such as can occur with craniopharyngioma, with chronic renal failure, with chronic stress (rarely >40 ng/mL), and with nipple stimulation; hyperprolactinemia may also remain idiopathic in some cases (Table 598.1).

Drug-induced hyperprolactinemia is especially common, and in most cases the level is less than 100 ng/mL, though risperidone can cause elevations up to 300 ng/mL. No further investigation is needed if elevations in these ranges are seen in patients on antipsychotic medications who do not have any other suspicious features.

In extremely rare cases, prolactin may be produced by tumors outside the pituitary; in these cases there will be hyperprolactinemia with no sign of a pituitary tumor on imaging and no response to cabergoline treatment.

In some cases, extreme hyperprolactinemia is associated with a *hook effect* that leads to factitiously low values on blood tests. In cases where clinical features are compatible with hyperprolactinemia, serial dilution of the laboratory specimen should be done to rule out this kind of measurement error. On the other hand, patients may have factitiously elevated prolactin levels on immunoassay as a result of the presence of prolactin polymers and dimers **(macroprolactinemia)** that are not physiologically active. In cases where an elevated prolactin is detected in an asymptomatic patient, unnecessary diagnostic workup and treatment can be avoided by performing polyethylene glycol precipitation to exclude the presence of macroprolactinemia, which is clinically benign.

Table 598.1 Causes of Hyperprolactinemia

PHYSIOLOGIC
Pregnancy and lactation/nipple stimulation
Stress
Exercise
Sexual intercourse
PHARMACOLOGIC
Antipsychotics
Typical
Phenothiazines
Haloperidol
Atypical
Risperidone
Clozapine
Olanzapine
Antidepressants
Tricyclics
Monoamine oxidase inhibitors
Selective serotonin reuptake inhibitors
Antihypertensives
Verapamil
Reserpine
α-Methyldopa
Antiemetics
Metoclopramide
Domperidone
H2 blockers
Cimetidine
Ranitidine
Opiates
Morphine
Methadone
Others
Estrogens
Cocaine
Heroin
Alcohol
Anesthetics
Marijuana
PATHOLOGIC
Prolactinoma
Nonfunctioning pituitary adenoma causing stalk effect
Craniopharyngioma
Meningioma
Germinoma
Empty sella syndrome
Lymphocytic hypophysitis
Hypothalamic-pituitary disease
Infiltrative diseases
Sarcoidosis
Histiocytosis X
Tuberculosis
Metastasis
OTHER DISEASE STATES
ROHHAD
Primary hypothyroidism
Chronic renal failure
Cirrhosis, severe hepatic insufficiency
Ectopic secretion of prolactin
Chest-wall lesions (trauma, surgery, herpes zoster virus)

ROHHAD, rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation.

From Wong A, Eloy JA, Couldwell WT, Liu JK. Update on prolactinomas. Part 1: clinical manifestations and diagnostic challenges. *J Clin Neurosci.* 2015;22:1562–1567, Table 2.

It should be noted that there are occasional cases of galactorrhea where the prolactin level is completely normal (even after serial dilution to rule out the hook effect); the galactorrhea is usually mild in such cases and is not associated with any other clinical finding. No further treatment or investigation is indicated in these cases, and minimal galactorrhea can be left untreated. If the amount of milk discharge is bothersome, then low-dose cabergoline (0.25 mg once or twice weekly) may be effective even if elevated prolactin levels are not present.

In most patients where the hyperprolactinemia is secondary to an adenoma, it can be effectively treated with dopamine agonists. Treatment leads to lowering of prolactin levels and tumor shrinkage in the vast majority of patients and even large adenomas can usually be treated without surgical intervention. Because of its greater efficacy and lower incidence of side effects, cabergoline is considered the drug of choice for treatment of hyperprolactinemia. The usual protocol is to begin with 0.25 mg twice weekly and then increase as needed to 1 mg twice weekly. Even higher doses may be needed in some patients but should be carefully monitored; high doses of cabergoline used for long periods in older patients with parkinsonism are associated with cardiac valvular abnormalities, though this has not been reported with the doses used in pediatric hyperprolactinemia; monitoring of cardiac valves with echocardiography may be advisable if high doses are used for a prolonged period.

When dopamine agonist treatment has been unsuccessful in lowering the serum prolactin concentration or the size of the adenoma, and when symptoms or signs attributable to hyperprolactinemia or adenoma size persist during treatment, trans-sphenoidal surgery may be considered. Very rare cases of malignant prolactinomas may require chemotherapy with temozolomide, but a cure is difficult in such cases.

Corticotropinoma

Corticotropinoma is very rare in children, but unlike other types of pituitary adenomas, its incidence is higher in younger children and decreases with age. **Cushing disease** refers specifically to an ACTH-producing pituitary adenoma that stimulates excess cortisol production and secretion (see Chapter 619). It is more common than primary adrenal causes of Cushing syndrome, except in younger children (younger than 5 years of age), in whom adrenal carcinomas and adrenal activating variants of MAS are rare but dominant causes of the syndrome. Adenomas causing Cushing disease are almost always microadenomas with a diameter of <5 mm and are significantly smaller than all other types of adenomas at presentation. The most sensitive indicator of excess glucocorticoid secretion in children is growth failure, which generally precedes other manifestations. Patients develop weight gain that may be centripetal rather than generalized. Pubertal arrest, hypertension, large purplish striae, fatigue, and depression are also common. In prepubertal children, males are more frequently affected than females.

Midnight salivary cortisol measurements can be used as a screening test for cortisol excess, but confirmation requires at least one additional test (either 24-hour urinary free cortisol or an overnight dexamethasone suppression test). Location of the microadenoma is usually determined by MRI, and bilateral inferior petrosal sinus sampling may be needed in difficult cases. Trans-sphenoidal surgery is the treatment of choice for Cushing disease in children. Initial remission rates of 70–98% of patients and long-term success rates of 50–98% are reported. Residual transient hypoadrenalism is often observed after surgery, lasting as long as 30 months. Pituitary radiotherapy is used if cortisol levels remain elevated and/or ACTH levels continue to be detectable. Successful treatment may not correct the height deficit, and GH deficiency may be present after treatment and should be treated as required.

Thyrotropinomas are extremely rare, with only a few cases reported in the pediatric age-group. They present with symptoms of hyperthyroidism as well as local symptoms such as headaches and visual field defects. Laboratory testing reveals elevated thyroid hormone levels with inappropriately unsuppressed TSH levels. Treatment consists of trans-sphenoidal surgery in most cases, though radiation may be needed if surgery is unsuccessful.

598.1 Overgrowth Syndromes

Jennifer M. Kalish

OVERGROWTH IN THE FETUS AND NEONATE

Maternal diabetes is the most common cause of infants being large for gestational age. Even in the absence of clinical symptoms or a family history, the birth of a large-for-gestational-age infant should lead to evaluation for maternal (or gestational) diabetes.

Overgrowth syndromes: A group of disorders associated with excessive somatic growth and growth of specific organs has been described and is collectively referred to as *overgrowth syndromes.* These disorders are caused in many cases by excess production and availability of IGF2 encoded by the gene *IGF2.* The best described of these syndromes is **Beckwith-Wiedemann syndrome** (BWS), which is an overgrowth malformation syndrome that occurs with an incidence of 1:10,340 births, equal in males and females. It is caused by genetic or epigenetic abnormalities in the 11p15 chromosomal region, with most cases being the result of epigenetic abnormalities (loss or gain of DNA methylation) of two imprinting control regions, IC1 and IC2. Other causes include pathogenic variants, duplications, deletions, and loss of heterozygosity in this region. The imprinted genes involved in BWS and associated childhood tumors include, in addition to *IGF2,* the noncoding RNA *H19,* which is involved in *IGF2* suppression, cyclin-dependent kinase inhibitor 1C *(CDKN1C),* potassium channel voltage-gated KQT-like subfamily member 1 *(KCNQ1),* and *KCNQ1*-overlapping transcript 1 (*KCNQ1OT1*, or long QT intronic transcript 1, *LIT1*). Approximately 10% of cases are familial, whereas the rest appear to be sporadic. Cardinal clinical features of BWS include macroglossia, omphalocele, lateralized overgrowth (hemihypertrophy), bilateral Wilms tumor, hyperinsulinism, and pathologic findings (adrenal cytomegaly, pancreatic adenomatosis, and mesenchymal dysplasia). Suggestive features include macrosomia, mid-glabellar capillary malformation (nevus flammeus), earlobe creases and pits, umbilical hernia or diastasis recti, hepatomegaly, nephromegaly, transient hypoglycemia, and embryonal tumors (hepatoblastoma and unilateral Wilms tumor) (Fig. 598.2). The hyperinsulinemia is a result of pancreatic β-cell hyperplasia. These children are predisposed to embryonal tumors, including Wilms tumor, hepatoblastoma, neuroblastoma, and adrenocortical carcinoma. Management focuses on the omphalocele, airway issues (a result of macroglossia), neonatal hyperinsulinism/hypoglycemia, leg length differences, and tumor screening. Because of the cancer risk, screening is recommended until the seventh birthday. Screening includes complete abdominal ultrasound and measurement of α-fetoprotein every 3 months through the fourth birthday and renal ultrasounds every 3 months until the seventh birthday. Thereafter, renal ultrasound is recommended in cases of renal malformation such as medullary sponge kidney and nephrocalcinosis.

Pathogenic variants in *GPC3* and *GPC4,* glypican genes (which code for an IGF2–neutralizing membrane receptor), cause **Simpson-Golabi-Behmel** syndrome (Fig. 598.3). Other syndromic causes of fetal overgrowth include **Costello syndrome**, **Weaver syndrome**, **Sotos syndrome** (Fig. 598.4), and **Perlman syndrome** (Tables 598.2 and 598.3 and Fig. 598.5).

Overgrowth in Childhood or Adolescence

Normal-variant, familial, or constitutional tall stature is by far the most common cause of tall stature. Almost invariably, a family history of tall stature can be obtained, and no organic pathology is present. The child is often taller than the child's peers throughout childhood and has typical health. There are no abnormalities in the physical examination, and laboratory studies, if obtained, are negative.

Exogenous obesity is associated with rapid linear growth and relatively early onset of puberty (more so in girls). Bone age is accelerated, leading to relative tall stature in childhood but adult height is typically normal.

Klinefelter syndrome (XXY syndrome) is a relatively common (1 in 500-1,000 live male births) chromosomal abnormality associated with tall stature, learning disabilities (including requirement for speech therapy), gynecomastia, and decreased upper body:lower body segment ratio. Affected boys can have hypotonia, clinodactyly, and hypertelorism. The testes are invariably small, although androgen production by Leydig cells is often in the low-normal range. Spermatogenesis and Sertoli cell function are defective and lead to infertility. Other genital abnormalities include relatively small phallus and an increased incidence of hypospadias and cryptorchidism.

Fig. 598.2 Beckwith-Wiedemann syndrome in newborn infants. *(Courtesy Dr. Michael Cohen, Dalhousie University, Halifax, Nova Scotia. From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier; 2022, Fig. 1, p. 221.)*

Fig. 598.3 Simpson-Golabi-Behmel syndrome. Affected 16-yr-old male. Note the ocular hypertelorism, broad flat nose, 2-3 syndactyly, and nail hypoplasia. *(From Jones KL, Jones MC, Del Campo M. Smith's Recognizable Patterns of Human Malformation, 8th ed. Philadelphia: Elsevier, 2022. Fig. 1, p. 225.)*

Fig. 598.4 Cerebral gigantism (Sotos syndrome) in an 8-yr-old male. The height age was 12 yr, and the bone age was 12 yr. IQ was 60. The electroencephalogram had abnormal findings. Note the prominence of the forehead and jaw and the large hands and feet. Sexual development was consistent with chronologic age. Hormone study results were normal. The adult height was 208 cm (6 ft 10 in); his sexual development was normal. He wears size 18 shoes.

Table 598.2 Differential Diagnosis of Tall Stature and Overgrowth Syndromes

FETAL OVERGROWTH
Maternal diabetes mellitus
Sotos syndrome *(NSD1)*
Weaver syndrome *(EZH2)*
Beckwith-Wiedemann syndrome (11p15 alterations)
Marshall-Smith syndrome *(NFIX)*
POSTNATAL OVERGROWTH LEADING TO CHILDHOOD OR ADULT TALL STATURE
Nonendocrine Causes
Familial (constitutional) tall stature
Exogenous obesity
Sotos syndrome *(NSD1)*
Weaver syndrome *(EZH2)*
Perlman syndrome *(DIS3L2)*
Simpson-Golabi-Behmel syndrome *(GPC3, GPC4)*
Marfan syndrome *(FBN1)*
Homocystinuria
Beckwith-Wiedemann syndrome (11p15 alterations)
Klinefelter syndrome (XXY)
Other syndromes with extra X or Y chromosomes
Overgrowth syndromes with intellectual disability *(DNMT3A, CHD8, HIST1H1E, EED)*
Endocrine Causes
Excess GH secretion caused by adenomas (pituitary gigantism)
X-linked acrogigantism (Xq26.3 duplication)
McCune-Albright syndrome or MEN associated with excess GH secretion
Aromatase deficiency and estrogen receptor defects
Precocious puberty (initial acceleration, ultimate short stature)
Hyperthyroidism (acceleration, but not adult tall stature)

GH, Growth hormone; MEN, multiple endocrine neoplasia.

XYY syndrome is associated with tall stature, severe acne in adolescence, increased incidence of learning disabilities, and behavioral problems, particularly impulsivity. Intelligence is usually in the normal range but may be 10-15 IQ points lower than their siblings. Other rare chromosomal abnormalities in which an excess number of X or Y chromosomes are present (e.g., XXX, XXXY, XYYY) are also associated with increased height.

Marfan syndrome is an autosomal dominant connective tissue disorder consisting of tall stature, arachnodactyly, thin extremities, increased arm span, and decreased upper body:lower body segment ratio (see Chapter 743). Additional abnormalities include ocular abnormalities (e.g., lens subluxation), hypotonia, kyphoscoliosis, cardiac valvular deformities, and aortic root dilation.

Homocystinuria is an autosomal recessive inborn error of amino acid metabolism caused by a deficiency of the enzyme cystathionine synthetase. It is characterized by intellectual disability when untreated, and many of its clinical features resemble Marfan syndrome, particularly ocular manifestations (see Chapter 105).

SOTOS SYNDROME

Children with Sotos syndrome (see Fig. 598.4) are typically above the 90th percentile for both length and weight at birth and may also have an increased head size. In other cases, macrocephaly becomes more apparent postnatally. Most cases of Sotos syndrome are caused by pathogenic variants in *NSD1*, but in the Japanese population most cases are attributable to microdeletions of the 5q35 region that includes this gene. Inheritance is autosomal dominant, but 95% of cases are a result of de novo (new) mutations. Incidence is estimated to be approximately 1 in 14,000 live births. The *NSD1* gene is thought to play a role in epigenetic regulation, but the exact mechanisms by which mutations lead to the features of Sotos syndrome are not yet understood.

Although it is characterized by rapid growth, there is no evidence that Sotos syndrome is caused by endocrine dysregulation. Growth is markedly rapid; by 1 year of age, affected infants are often taller than the 97th percentile in height. Accelerated growth continues for the first 4-5 years and then returns to a normal rate. Puberty usually occurs at the expected time but may occur slightly early. Adult height is usually in the upper-normal range.

Clinically the syndrome is characterized by a large (macrocephaly) dolichocephalic head, prominent forehead and jaw, hypertelorism, downslant of the palpebral fissures, high-arched palate, and large hands and feet with thickened subcutaneous tissue. Clumsiness and awkward gait are also noted, and affected children may have difficulty in sports, in learning to ride a bicycle, and in other tasks requiring coordination. Some degree of developmental disability affects most patients; in some affected children, perceptual deficiencies may predominate. Many different types of nonfebrile seizures have been reported, and up to 25% of patients with Sotos syndrome have seizures at some point in their life. Hyperinsulinism can also occur. Affected patients may be at somewhat increased risk for neoplasms, including neuroblastoma, hepatoblastoma, and leukemia, with a lifetime risk of between 2% and 4%. Osseous maturation is usually compatible with the patient's height, although

Table 598.3 Overgrowth Syndromes

SYNDROME	CLINICAL FEATURES	GENETIC ETIOLOGY	TUMOR SURVEILLANCE
Beckwith-Wiedemann syndrome (BWS)	Hypoglycemia, macroglossia, ear pits, omphalocele or umbilical hernia, lateralized overgrowth, organomegaly, high risk of embryonal tumors until age 7	Various genetic and epigenetic abnormalities in 11p15, most commonly in the IC2 region	Tumor surveillance until at least age 7 yr
Perlman syndrome	Macrosomia, unusual facies, nephroblastosis, severe hypotonia, very high risk of Wilms tumor	*DIS3L2* (DIS3 Like 3′-5′ exoribonuclease 2) (autosomal recessive)	Routine tumor surveillance recommended
Simpson-Golabi-Behmel syndrome	Coarse facial features, macroglossia, central groove lower lip, supernumerary nipples, cardiac and skeletal defects	*GPC3* (glypican 3) (X-linked recessive)	Tumor surveillance justified (per BWS protocol)
Sotos syndrome	Excessive growth in first 4 yr, dolichocephaly, macrocrania, typical facies, long limbs, seizures, hypotonia	*NSD1* deletion or variant (autosomal dominant) Rare familial cases *NFIX* (Nuclear Factor I X) may cause related Malan syndrome	Routine tumor screening not recommended
Tatton-Brown syndrome	Round face, heavy/horizontal eyebrows, narrow palpebral fissures, intellectual disability, and increased height	*DNMT3A* (DNA Methyltransferase 3 Alpha)	Routine tumor screening not recommended
Weaver syndrome	Broad forehead, hypertelorism, small chin, long philtrum, camptodactyly, redundant nuchal skin, heart and brain defects	*EZH2* (Enhancer of zeste homolog 2) gene in some cases	Routine tumor screening not recommended
PTEN-hamartoma syndromes (including Bannayan-Ruvalcaba-Riley)	Macrocephaly, hypotonia, pigmented skin, penile macules, lipomas, seizures	*PTEN* (phosphatase and TENsin homolog)(sporadic or autosomal dominant)	Tumor surveillance recommended
PIK3CA-related overgrowth spectrum	Brain overgrowth (megalencephaly), microgyria, cutaneous vascular malformations, syndactyly, seizures, developmental delay	Pathogenic variants in various PIK3 related genes, including *PIl3R2, AKT3, CCND2, PIK3CA,* etc.	Tumor surveillance is debated
Marfan syndrome	Facial gestalt, lens dislocation, arachnodactyly, scoliosis, pectus carinatum or excavatum, aortic root dilation	*FBN1* (Fibrillin 1) (autosomal dominant)	None
Loeys-Dietz syndrome	Marfan-like habitus, aortic root dilation, aortic dissection, vasculopathy (more aggressive than Marfan syndrome)	TGF-β pathway genes including *TGFBR1, TGFBR2, SMAD3,* and *TGFB2* (autosomal dominant)	None
Homocystinuria	Marfan-like habitus, developmental delay, lens dislocation	*CBS* gene (Cystathionine β-synthase) (autosomal recessive)	None
Lujan syndrome	Marfan-like habitus, intellectual disability, no eye or cardiovascular anomalies	*MED12* (Mediator Complex Subunit 12) gene (X-linked recessive)	None

advanced bone age has been reported. Scoliosis develops in up to 30% of cases, usually starting in school-age children. GH, IGF1, and other endocrine studies are usually normal; there is no distinctive laboratory or radiologic marker for the syndrome. Abnormal electroencephalograms are common; imaging studies often reveal an enlarged ventricular system, but intracranial pressure is normal. Genetic testing for *NSD1* pathogenic variants (or fluorescence in situ hybridization for 5q35 microdeletions in Japanese patients) is available and should be routinely used. Management is symptomatic and includes paying special attention to developmental and behavioral problems (which tend to improve with age), scoliosis, and seizure disorder. No specific treatment is needed for the overgrowth itself. There is no consensus on the need for cancer surveillance at this time.

Tatton-Brown Syndrome

Tatton-Brown syndrome is characterized by distinctive facial appearance (round face, heavy/horizontal eyebrows, and narrow palpebral fissures), intellectual disability, and increased height. It is caused by pathogenic variants in *DNMT3A*, a methyltransferase. Pathogenic variants in *DNMT3A* are also seen in hematologic malignances, which like *NSD1* and *EZH2*, show dual-gene functionality in overgrowth syndromes and myeloid neoplasms.

Hyperthyroidism in adolescents is associated with rapid growth but normal final adult height. It is almost always caused by Graves disease and is much more common in girls (see Chapter 606).

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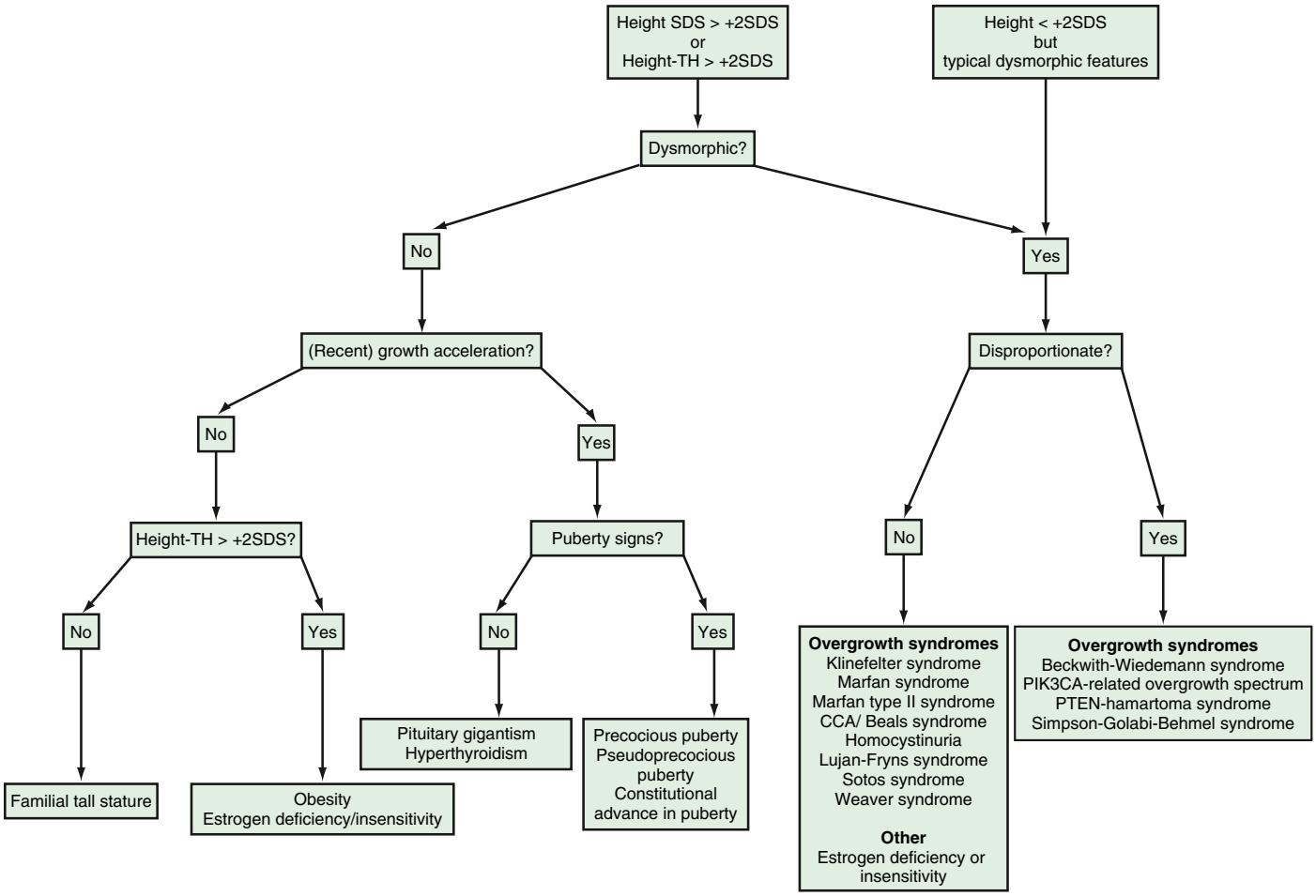

Fig. 598.5 Diagnostic algorithm for the differential diagnosis of tall stature and overgrowth syndromes. CCA, congenital contractural arachnodactyly; Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; *SDS*, standard deviation score. *(Adapted from Neylon OM, Werther GA, Sabin MA. Overgrowth syndromes. Curr Opin Pediatr. 2012;24:505–511, Fig. 1.)*

Chapter 599

Physiology of Puberty

Luigi R. Garibaldi and Wassim Chemaitilly

Between early childhood and approximately 8-9 years of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in females, testosterone in males). One to 3 years before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among the hypothalamus, pituitary, and gonads in the peripubertal period. By mid-puberty, LH pulses become evident even during the daytime and occur at about 90- to 120-minute intervals. A second critical event occurs in middle or late adolescence in females in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The *GnRH pulse generator* is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, neurokinin-B (stimulatory); γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). Pathogenic variants of *KISS1R* (previously known as *GPR54,* a G protein–coupled receptor gene whose ligand is kisspeptin) are a rare cause of autosomal recessive hypogonadotropic hypogonadism (loss-of-function pathogenic variants) or precocious puberty (gain-of-function pathogenic variants). The imprinted paternally expressed gene makorin RING finger protein 3 *(MKRN3)* has been described as a *brake* for the onset of puberty. Loss-of-function pathogenic variants of this gene are responsible for paternally transmitted familial precocious puberty in both sexes.

The interpretation of the hormonal changes of puberty is complex. Challenges with interpreting LH and follicle-stimulating hormone (FSH) measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion, which mandate serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland because serum LH concentrations tend to increase earlier in the course of the pubertal process in males than in females. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 years of age, before any increase in LH or sex hormones

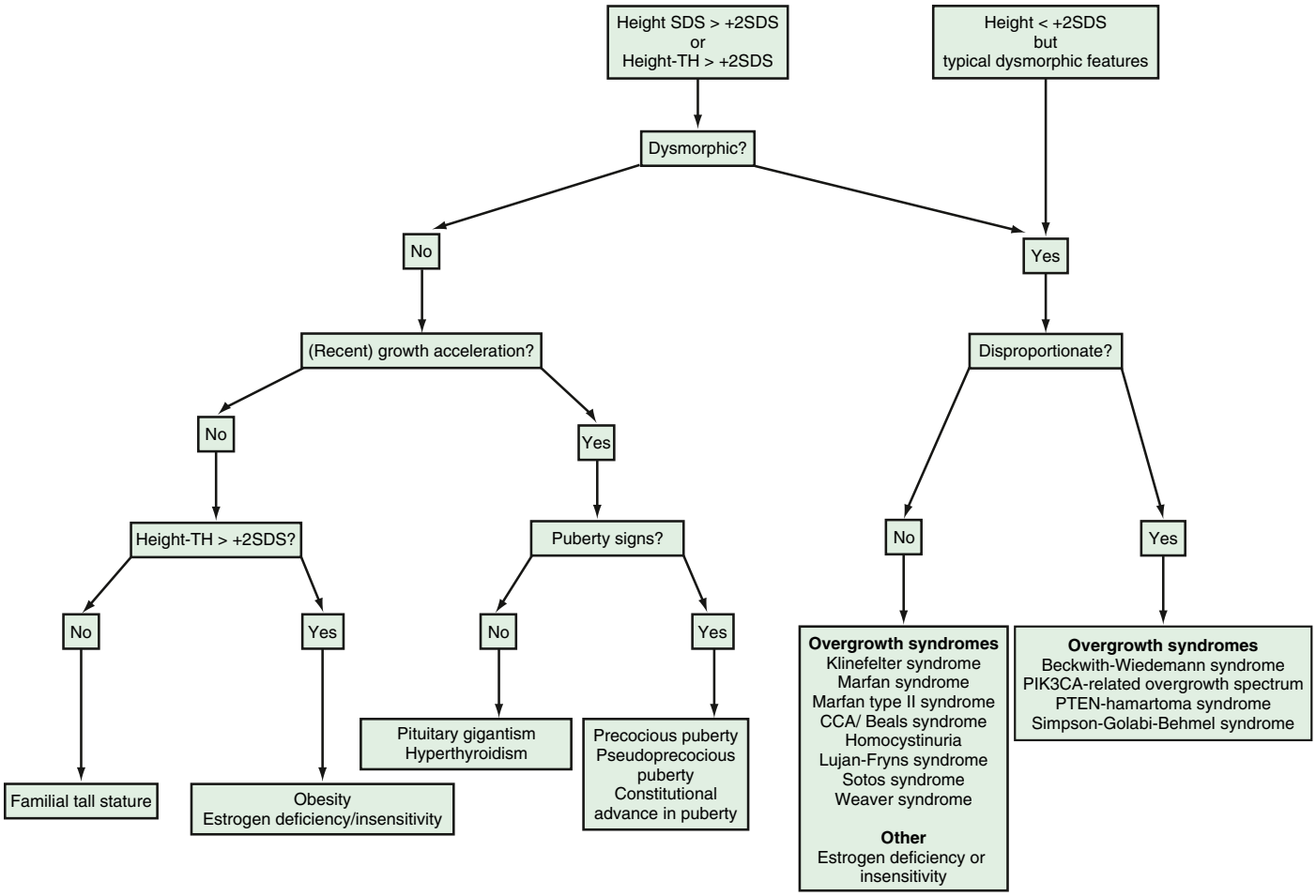

Fig. 598.5 Diagnostic algorithm for the differential diagnosis of tall stature and overgrowth syndromes. CCA, congenital contractural arachnodactyly; Height-TH, current height percentile >2 SDS from target height percentile, the latter based on midparental height calculation; *SDS*, standard deviation score. *(Adapted from Neylon OM, Werther GA, Sabin MA. Overgrowth syndromes. Curr Opin Pediatr. 2012;24:505–511, Fig. 1.)*

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Between early childhood and approximately 8-9 years of age (prepubertal stage), the hypothalamic-pituitary-gonadal axis is dormant, as reflected by undetectable serum concentrations of luteinizing hormone (LH) and sex hormones (estradiol in females, testosterone in males). One to 3 years before the onset of clinically evident puberty, low serum levels of LH during sleep become demonstrable. This sleep-entrained LH secretion occurs in a pulsatile fashion and reflects endogenous episodic discharge of hypothalamic gonadotropin-releasing hormone (GnRH). Nocturnal pulses of LH continue to increase in amplitude and, to a lesser extent, in frequency as clinical puberty approaches. This pulsatile secretion of gonadotropins is responsible for enlargement and maturation of the gonads and the secretion of sex hormones. The appearance of the secondary sex characteristics in early puberty is the visible culmination of the sustained, active interaction occurring among the hypothalamus, pituitary, and gonads in the peripubertal period. By mid-puberty, LH pulses become evident even during the daytime and occur at about 90- to 120-minute intervals. A second critical event occurs in middle or late adolescence in females in whom cyclicity and ovulation occur. A positive feedback mechanism develops whereby increasing levels of estrogen in midcycle cause a distinct increase of LH.

The increasing secretion of hypothalamic GnRH in a pulsatile fashion thus underlies the onset of pubertal development. The *GnRH pulse generator* is regulated by multiple neuropeptides, including glutamic acid, kisspeptin, neurokinin-B (stimulatory); γ-aminobutyric acid, preproenkephalin, and dynorphin (inhibitory). Pathogenic variants of *KISS1R* (previously known as *GPR54,* a G protein–coupled receptor gene whose ligand is kisspeptin) are a rare cause of autosomal recessive hypogonadotropic hypogonadism (loss-of-function pathogenic variants) or precocious puberty (gain-of-function pathogenic variants). The imprinted paternally expressed gene makorin RING finger protein 3 *(MKRN3)* has been described as a *brake* for the onset of puberty. Loss-of-function pathogenic variants of this gene are responsible for paternally transmitted familial precocious puberty in both sexes.

The interpretation of the hormonal changes of puberty is complex. Challenges with interpreting LH and follicle-stimulating hormone (FSH) measurements include the presence of multiple gonadotropin isoforms, immunoassay-related variability, and problems inherent to their pulsatile secretion, which mandate serial sampling in plasma. In addition, important sex differences exist in the maturation of the hypothalamus and pituitary gland because serum LH concentrations tend to increase earlier in the course of the pubertal process in males than in females. Adrenocortical androgens also have a role in sexual maturation. Serum levels of dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) begin to increase at approximately 6-8 years of age, before any increase in LH or sex hormones

and before the earliest physical changes of puberty are apparent; this process has been called *adrenarche*. DHEAS is the most abundant adrenal C-19 steroid in the blood, and its serum concentration remains fairly stable over 24 hours. A single measurement of this hormone is commonly used as a marker of adrenal androgen secretion. Although adrenarche typically precedes the onset of gonadal activity (gonadarche) by a few years, the two processes do not seem to be causally related, as evidenced by adrenarche and gonadarche being dissociated in conditions such as central precocious puberty and adrenocortical failure.

The effects of gonadal steroids (testosterone in males, estradiol in females) on bone growth and osseous maturation are critical. Both aromatase deficiency and estrogen receptor defects result in delayed epiphyseal fusion and tall stature in affected males. These observations suggest that estrogens, rather than androgens, are responsible for the process of bone maturation that ultimately leads to epiphyseal fusion and cessation of growth. Estrogens also mediate the increased production of growth hormone, which along with a direct effect of sex steroids on bone growth, is responsible for the pubertal growth spurt.

The age of onset of puberty varies and is more closely correlated with osseous maturation than with chronologic age (see Chapter 150). In females, the **breast bud** (thelarche) is usually the first sign of puberty (10-11 years), followed by the appearance of **pubic hair** (pubarche) 6-12 months later. The interval to the onset of **menstrual activity** (menarche) is usually 2-2.5 years but may be as long as 6 years. In the United States, at least one sign of puberty is present in approximately 95% of females by 12 years of age and in 99% of females by 13 years of age. Peak height velocity occurs early (at breast stage II-III, typically between 11 and 12 years of age) in females and always precedes menarche. The mean age of menarche is about 12.75 years. However, there are wide variations in the sequence of changes involving growth spurt, breast bud, pubic hair, and maturation of the internal and external genitalia.

In males, **growth of the testes** (≥4 mL in volume or 2.5 cm in longest diameter) and thinning of the scrotum are the first signs of puberty (11-12 years). These are followed by pigmentation of the scrotum and growth of the penis and by **pubarche**. Appearance of **axillary hair** usually occurs in mid-puberty. In males, unlike in females, acceleration of growth begins after puberty is well underway and is maximal at genital stage IV-V (typically between 13 and 14 years of age). In males, the growth spurt occurs approximately 2 years later than in females, and growth may continue beyond 18 years of age.

Genetic and environmental factors affect the timing for the onset of puberty. Population-based studies in the United States and Europe have suggested secular trends for earlier onset of puberty over the past few decades in females and, to a lesser degree, in males. African American, and to a lesser extent Hispanic, females *appear* to be more advanced in the development of secondary sex characteristics for age than White females. However, the timing of menarche has advanced only marginally (2.5-4 months) in White females and slightly more so (up to 6 months) in African American females. The Copenhagen Puberty Study showed that the earlier onset of breast development observed in females examined in 2006–2008 than those seen in 1991–1993 (means 10.9 years vs 9.9 years) *was not* associated with different levels of gonadotropins or estradiol when females of similar chronologic ages were compared between the two groups. Hence earlier breast development may not simply reflect earlier activation or maturation of the hypothalamic-pituitary-gonadal axis but could also stem from other factors such as increased adiposity or increased exposure to certain environmental agents. Positive correlations between the degree of adiposity and earlier pubertal development in females have been reported. Conversely, female athletes in whom leanness and strenuous physical activity have coexisted from early childhood frequently exhibit a marked delay in puberty or menarche, and they frequently have oligomenorrhea or amenorrhea as adults (see Chapter 732). Pubertal delay is also prevalent in males who are physically very active. Thus energy balance is closely related to the activity of the GnRH pulse generator and the mechanisms initiating and sustaining puberty, possibly via hormonal signals such as leptin; other adipokines; or by way of the central melanocortin-4 receptor (MC4R), which controls appetite, food intake, and energy expenditure.

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Chapter 600

Disorders of Pubertal Development

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INTRODUCTION

Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 years in females and 9 years in males. The variation in the age of the onset of puberty in normal children, particularly of different ethnicities, makes this definition somewhat arbitrary. It remains in use by most clinicians.

Depending on the primary source of the hormonal production, precocious puberty may be classified as **central** (also known as **gonadotropin dependent**, or **true**) or **peripheral** (also known as **gonadotropin independent**) (Table 600.1). **Central** precocious puberty (CPP) is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. In **peripheral** precocious puberty, some of the secondary sex characteristics appear, but there is no activation of the normal hypothalamic-pituitary-gonadal interplay. In this latter group, the sex characteristics may be isosexual or heterosexual (see Chapters 622-628).

Peripheral precocious puberty can also induce maturation of the hypothalamic-pituitary-gonadal axis and trigger the onset of central puberty at a later time. This mixed type of precocious puberty occurs in congenital adrenal hyperplasia, particularly after adrenal androgens are suppressed by treatment; McCune-Albright syndrome; and familial male-limited precocious puberty, when the bone age reaches the pubertal range (10.5-12.5 years).

600.1 Central Precocious Puberty

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CPP is defined by the onset of pubertal development due to the early activation of the hypothalamic-pituitary-gonadal axis before the ages of 8 and 9 years in females and males, respectively. It occurs 5- to 10-fold more frequently in females than in males and is usually sporadic. Although at least 90% of females have an idiopathic form, a structural central nervous system (CNS) abnormality may occur in 25–75% of males with CPP. **Genetic forms of CPP**, such as the paternally transmitted types due to pathogenic variants of *MKRN3* gene or, more rarely *DLK1,* may account for 5–10% of all cases of CPP. A high prevalence of CPP has been reported in females adopted from developing countries, particularly if adopted several months or years after birth, possibly related to undefined nutritional or environmental factors.

CLINICAL MANIFESTATIONS

In females, CPP should be suspected when breast development is noted before the age of 8 years. In males who have not been exposed to gonadotoxic agents, CPP usually manifests first via increased testicular size (volume ≥4 mL) and scrotal thinning before the age of 9 years. Sexual development in affected individuals generally follows the sequence observed in normal puberty. In females, early menstrual cycles may be more irregular than they are with normal puberty. The initial cycles are usually anovulatory, but pregnancy has been reported as early as 5.5 years of age (Fig. 600.1). In males, testicular biopsies have shown stimulation of all elements of the testes, and spermatogenesis has been observed as early as 5-6 years of age. In affected females and males, height, weight, and height velocity are accelerated. The increased rate of bone maturation results in early closure of the epiphyses and compromised adult height, particularly

Table 600.1 Classification of Sexual Precocity

TRUE PRECOCIOUS PUBERTY OR COMPLETE ISOSEXUAL PRECOCITY
(GNRH-Dependent Sexual Precocity or Premature Activation of the Hypothalamic GNRH Pulse Generator)

Idiopathic true precocious puberty
CNS tumors
Optic glioma associated with neurofibromatosis type 1
Hypothalamic astrocytoma
Other CNS disorders
Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum
Encephalitis
Static encephalopathy
Brain abscess
Sarcoid or tubercular granuloma
Head trauma
Hydrocephalus
Arachnoid cyst
Myelomeningocele
Vascular lesion
Cranial irradiation
True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids
True precocious puberty caused by pathogenic variants in the following genes:
KISS1R/GPR54
KISS1
MKRN3
DLK1

INCOMPLETE ISOSEXUAL PRECOCITY (HYPOTHALAMIC GNRH-INDEPENDENT)

Males
Gonadotropin-secreting tumors
hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma)
hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma)
Increased androgen secretion by adrenal or testis
Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies)
Virilizing adrenal neoplasm
Leydig cell adenoma
Familial male-limited precocious puberty (FMPP, "testotoxicosis") (autosomal dominant gonadotropin-independent precocious Leydig cell and germ cell maturation)
Cortisol resistance syndrome

Females
Ovarian cyst
Estrogen-secreting ovarian or adrenal neoplasm
Peutz-Jeghers syndrome with sex cord tumor with annular tubules (SCTAT)

Both Sexes
McCune-Albright syndrome
Hypothyroidism
Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics)

VARIATIONS OF PUBERTAL DEVELOPMENT
Premature thelarche
Premature isolated menarche
Premature adrenarche
Adolescent gynecomastia in males
Macroorchidism

HETEROSEXUAL PRECOCITY

Feminization in Males
Adrenal neoplasm
Chorioepithelioma
Testicular neoplasm (Peutz-Jeghers syndrome)
Increased extraglandular conversion of circulating adrenal androgens to estrogen
Iatrogenic (exposure to estrogens)

Virilization in Females
Congenital adrenal hyperplasia
CYP21 deficiency
CYP11B1 deficiency
3β-HSD deficiency
Virilizing adrenal neoplasm (with or without Cushing syndrome)
Virilizing ovarian neoplasm (e.g., arrhenoblastoma)
Iatrogenic (exposure to androgens)
Cortisol resistance syndrome
Aromatase deficiency

CNS, Central nervous system; CYP11B1, 11-hydroxylase; CYP21, 21-hydroxylase; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; 3β-HSD, 3β-hydroxysteroid dehydrogenase 4,5-isomerase; KISS1R/GPR54, kisspeptin receptor/G protein–coupled receptor 54.
Modified from Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 25.25, p. 1163.

if puberty begins at a very early age. Historically, approximately 30% of females and an even larger percentage of males achieved a height below the fifth percentile as adults *without* treatment. Mental development is usually compatible with chronological age. Emotional behavior and mood swings are common, but serious psychologic problems are rare.

Although the clinical course is variable, three main patterns of pubertal progression can be identified. Most females (particularly those younger than 6 years of age at the onset) and a large majority of males have rapidly progressive puberty, characterized by rapid physical and osseous maturation, leading to a loss of height potential. An increasing percentage of females (older than 6 years of age at the onset with an idiopathic form) and, rarely, males have a slowly progressive variant, characterized by parallel advancement of osseous maturation and linear growth, with preserved height potential. Very rarely, central puberty may regress spontaneously (*unsustained* CPP). This variability in the natural course of sexual precocity underscores the need for longitudinal observation at the onset of sexual development before treatment is considered.

LABORATORY FINDINGS

Sex hormone concentrations are usually appropriate for the stage of puberty in both sexes (Table 600.2). Despite the availability of sensitive and specific assays for sex hormones, random serum estradiol concentrations are low or undetectable in the early phase of sexual precocity in females, as they are in normal puberty. In males, serum testosterone levels are usually detectable or elevated by the time the parents seek medical attention, provided that an early morning blood sample is obtained. With the use of highly sensitive assays, serum LH concentrations are undetectable in prepubertal children in random blood samples but become detectable in 50–75% of females and a higher percentage of males with CPP. Unfortunately, a number of hospitals use only moderately sensitive immunoenzymatic assays for LH and often insensitive assays for estradiol and testosterone, which decreases the diagnostic yield of these measurements. Measurement of LH in serial blood samples obtained during sleep has very

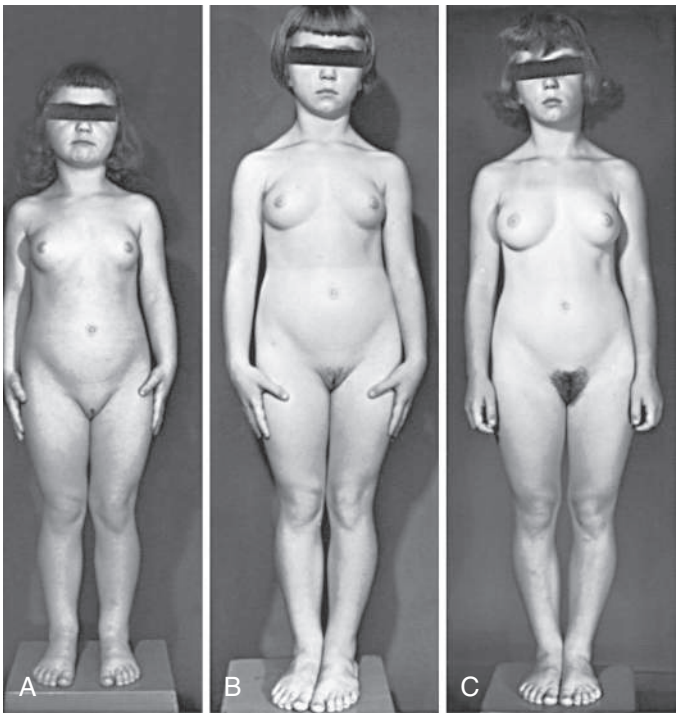

Fig. 600.1 Natural course of untreated idiopathic central precocious puberty. Patient (**A**) at 3 11/12, (**B**) at 5 9/12, and (**C**) at 8½ yr of age. Breast development and vaginal bleeding began at 2½ yr of age. Bone age was 7½ yr at 3 11/12 and 14 yr at 8 yr of age. Intelligence and dental age were normal for chronological age. Growth was completed at 10 yr; ultimate height was 142 cm (56 in). No effective therapy was available at the time this patient sought medical attention.

good diagnostic power and typically reveals a well-defined pulsatile secretion of LH in early puberty; it is, however, difficult to implement in a clinical setting. Dynamic tests using gonadotropin-releasing hormone (GnRH, intravenously; unavailable in the United States) or a GnRH agonist (leuprolide, subcutaneously) are helpful diagnostic tools, particularly for males, in whom a pubertal LH response (LH peak >5 IU/L) with predominance of LH over follicle-stimulating hormone (FSH) tends to occur early in the course of precocious puberty. In females with sexual precocity, however, the nocturnal LH secretion and the LH response to GnRH or GnRH agonist may be quite low at breast stages II to early III (LH peak, <5 IU/L), and the LH to FSH ratio may remain low until mid-advanced puberty. In such females with low LH response, the central nature of sexual precocity can be proven by detecting pubertal levels of estradiol (>50 pg/mL) 20-24 hours after stimulation with leuprolide.

Osseous maturation is variably advanced, often more than 2-3 standard deviations (SD). Pelvic ultrasonography in females reveals progressive enlargement of the ovaries, enlargement of the fundus, and then of the whole uterus to pubertal size. An MRI scan usually demonstrates physiologic enlargement of the pituitary gland, as seen in normal puberty; it may also reveal CNS pathology.

DIFFERENTIAL DIAGNOSIS

Organic CNS causes of central sexual precocity are more likely in males and in females who have rapid breast development, estradiol greater than 30 pg/mL, or are younger than 6 years of age. All children in these categories, and children with neurologic symptoms or signs, should undergo MRI scans of the brain and pituitary gland. Criteria for brain imaging in females older than 6 years are controversial, although some authorities recommend MRI scans for *all children* with CPP.

Gonadotropin-independent causes of isosexual precocious puberty must be considered in the differential diagnosis (see Tables 600.1 and 600.2). For females, these include tumors of the ovaries, autonomously functioning ovarian cysts, feminizing adrenal

Table 600.2 Differential Diagnosis of Sexual Precocity

DISORDER	PLASMA GONADOTROPINS	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANEOUS
GONADOTROPIN DEPENDENT					
True (central) precocious puberty	Prominent LH pulses (premature reactivation of GnRH pulse generator), initially during sleep	Pubertal LH response	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement	MRI of brain to rule out CNS tumor or other abnormality
GONADOTROPIN INDEPENDENT					
Males					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; MRI of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	High testosterone	Irregular, asymmetric enlargement of a testis	Testicular US
Familial, male-limited precocious puberty (FMPP, testotoxicosis)	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and length >2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Activating pathogenic variant of the LHCG receptor; autosomal dominant transmission
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, variable severity/age of onset; may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency

Continued

Table 600.2 Differential Diagnosis of Sexual Precocity—cont'd

DISORDER	PLASMA GONADOTROPINS	LH RESPONSE TO GNRH	SERUM SEX STEROID CONCENTRATION	GONADAL SIZE	MISCELLANEOUS
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS, DHEA, and/or androstenedione values	Testes prepubertal	CT or MRI of abdomen
Females					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Tumor often palpable on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, MRI, or US	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol, variable DHEAS increase	Ovaries prepubertal	Unilateral adrenal mass on CT or MRI
Nonclassical congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or in corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive
In Both Sexes					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal; estradiol may be quite high in girls	Ovarian enlargement (asymmetrical) on US; slight (usually symmetrical) testicular enlargement	Skeletal survey/bone scan for polyostotic fibrous dysplasia and skin examination for café-au-lait macules
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal; flat FSH, LH response	Estradiol often pubertal	Testicular enlargement; ovaries macrocystic	TSH very high, prolactin mildly elevated; T_4 low
INCOMPLETE PRECOCITY/VARIATIONS OF PUBERTY					
Premature thelarche	Prepubertal	Prepubertal LH	Prepubertal or early pubertal estradiol response	Ovaries prepubertal	Onset usually before 3yr of age
Premature adrenarche (males)	Prepubertal	Prepubertal LH response	Prepubertal testosterone; DHEAS value appropriate for pubic hair stage	Testes prepubertal	Onset usually after 6yr of age; more frequent in CNS-injured children
Premature adrenarche (females)	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS value appropriate for pubic hair stage	Ovaries prepubertal	Onset usually after 6yr of age; more frequent in brain-injured children

CNS, Central nervous system; CT, computed tomography; CYP, P450 cytochrome isoenzyme; DHEAS, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; 17-OHP, 17-hydroxyprogesterone; T_4, thyroxine; TSH, thyrotropin; US, ultrasonography.

Modified from Styne DM, Grumbach MM. Physiology and disorders of puberty. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.41, pp. 1196–1197.

tumors, McCune-Albright syndrome, and exogenous sources of estrogens. In males, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, human chorionic gonadotropin (hCG)–producing tumors, exposure to exogenous androgens, and familial male precocious puberty should be considered.

TREATMENT

Virtually all males and the large subgroup of females with *rapidly progressive precocious puberty,* including CPP beginning *before age 6 years,* are candidates for treatment. Females with slowly progressive idiopathic CPP do not seem to benefit in terms of height prognosis from GnRH agonist therapy. Former small-for-gestational-age infants may be at greater risk of short stature as adults and may require more aggressive treatment of precocious puberty, possibly in conjunction with human growth hormone (hGH) therapy. Certain patients require treatment predominantly for psychologic or social reasons, including children with special needs.

The observation that the pituitary gonadotropic cells require pulsatile, rather than continuous, stimulation by GnRH to maintain the ongoing release of gonadotropins provides the rationale for using GnRH agonists for treatment of CPP. By virtue of being more potent and having a longer duration of action than native GnRH, these GnRH agonists (after a brief period of stimulation) desensitize the gonadotropic cells of the pituitary to the stimulatory effect of endogenous GnRH and effectively halt the progression of central sexual precocity.

Long-acting formulations of GnRH agonists, which maintain fairly constant serum concentration of the drug for weeks or months, constitute the preparations of choice for treatment of CPP. In the United States, the available preparations include (1) **leuprolide acetate** (Lupron Depot Ped), in a dose of 0.2-0.3 mg/kg (7.5-15 mg) intramuscularly (IM) every 28 days; (2) longer-acting preparations of depot-leuprolide, including Lupron-Depot Ped 90-day, 11.25 or 30 mg IM every 3 months, or Fensolvi 45 mg subcutaneously every 24 weeks; (3) **histrelin** (Supprelin LA), a subcutaneous 50-mg implant with effects lasting at least 12 months; and (4) **triptorelin** (Triptodur), 22.5 mg IM every 24 weeks. Other preparations

are approved for treatment of precocious puberty in other countries. Recurrent sterile fluid collections at the sites of injections are an uncommon local side effect and occur in less than 1–3% of patients treated with IM depot-leuprolide. Breakage or malfunction of the histrelin implant is rare. Other available treatment options for children who cannot tolerate the products listed previously include subcutaneous injections of aqueous leuprolide, given once or twice daily (total dose 60 mcg/kg/24 hr), or intranasal administration of the GnRH agonist **nafarelin** (Synarel), 800 mcg bid. The potential for irregular compliance with daily administration, as well as the variable absorption of the intranasal route for nafarelin, may limit the efficacy and long-term benefit of the latter preparations. GnRH antagonists, including novel oral compounds, have not been investigated sufficiently in children and are not FDA approved.

Treatment results in decrease of the growth rate, generally to age-appropriate values, and an even greater decrease of the rate of osseous maturation. Some children, particularly those with greatly advanced (pubertal) bone age, may show marked deceleration of their growth rate and an arrest in the rate of osseous maturation. Treatment results in enhancement of the predicted height, more so in younger patients at diagnosis, male patients, and those children with more rapidly progressive CPP. In females, breast size may regress in those with Tanner stage II-III development but tends to remain unchanged in females with late stage III-V development or may even increase slightly because of progressive adipose tissue deposition. The amount of glandular tissue decreases. Pubic hair usually remains stable in females or may progress slowly during treatment, reflecting the gradual increase in adrenal androgens. Menses, if present, cease. Pelvic sonography demonstrates a decrease of the ovarian and uterine size. In males, there is a decrease of testicular size, variable regression of pubic hair, and decrease in the frequency of erections. Except for a reversible decrease in bone density (of uncertain clinical significance) and a reversible increase in body mass index (BMI) percentiles in some females, no serious adverse effects of GnRH analogs have been reported in children during or after treatment for sexual precocity. If treatment is effective, the serum sex hormone concentrations decrease to prepubertal levels (testosterone <10-20 ng/dL in males; estradiol <5-10 pg/mL in females). The serum LH and FSH concentrations, as measured by sensitive immunometric assays, decrease to less than 1 IU/L in most patients, although rarely does the LH return to truly prepubertal levels (<0.1 IU/L). Moreover, the incremental FSH and LH responses to GnRH stimulation decrease to less than 2-3 IU/L. Serum LH, FSH, and sex hormone levels are suppressed more completely and evenly by the histrelin implant than by GnRH agonist injections. Therapy is typically discontinued at a pubertal chronological age, after which puberty resumes promptly. In females, menarche generally appears at an average of 18 months (range 6-24 months) after cessation of IM therapy and somewhat earlier after removal of the histrelin implant. The addition of hGH to GnRH agonists has been used on an investigational basis in children with precocious puberty, markedly advanced bone age, and prediction of short stature. The available, albeit limited, data indicate that combined therapy may increase the adult height.

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600.2 Precocious Puberty Resulting from Organic Brain Lesions

Wassim Chemaitilly and Luigi R. Garibaldi

Hypothalamic hamartoma is the most common brain lesion causing CPP (Fig. 600.2). This congenital malformation consists of ectopically located neural tissue, within which glial cells can produce transforming growth factor-α (TGF-α), which has the potential to activate the GnRH pulse generator. On MRI, it appears as a small pedunculated mass attached to the tuber cinereum or the floor of the third ventricle or, less often, as a sessile mass (Fig. 600.3) that remains static in size over years.

A wide variety of other CNS lesions or insults, usually involving the hypothalamus by scarring, invasion, or pressure, have been associated with CPP (see Table 600.1). These include postencephalitic scars, tuberculous meningitis, tuberous sclerosis, severe head trauma, and hydrocephalus, either isolated or associated with myelomeningocele. Gonadotropin-dependent precocious puberty occurs in 26–29% of children with tumors developing within or near the hypothalamus or optic pathways. Low-grade gliomas, the most common types of such neoplasms, are highly prevalent (15–20%) in children with neurofibromatosis type 1 (NF-1) and constitute the main etiologic factor for the central sexual precocity encountered in a small subset (approximately 3%) of children with NF-1.

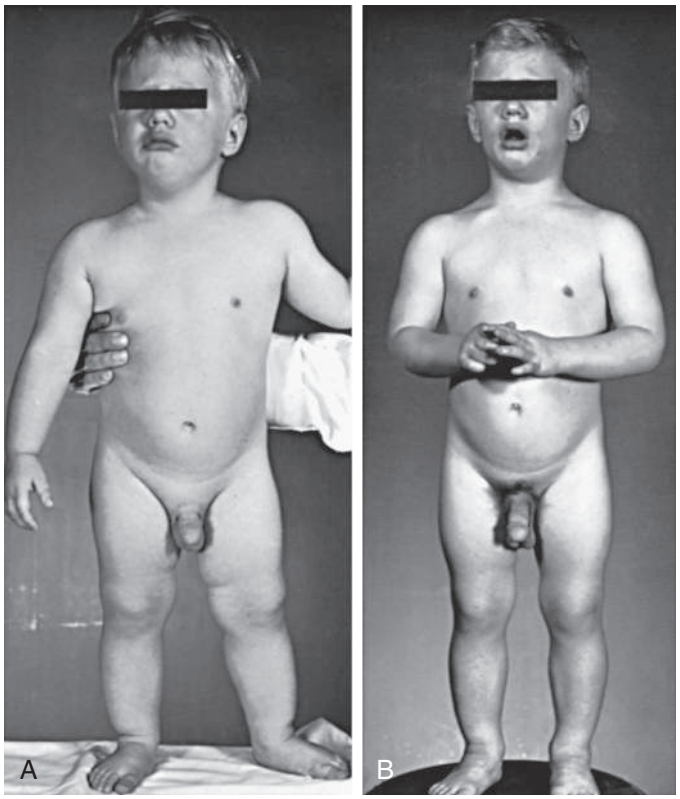

Fig. 600.2 Natural course of untreated precocious puberty with central nervous system lesion. Photographs at 1½ (A) and 2½ (B) yr of age. Accelerated growth, muscular development, osseous maturation, and testicular development were consistent with the degree of secondary sexual maturation. In early infancy, the patient began having frequent spells of rapid, purposeless motion; later in life, he had episodes of uncontrollable laughing with ocular movements. At 7 yr, he exhibited emotional lability, aggressive behavior, and destructive tendencies. Although a hypothalamic hamartoma had been suspected, it was not established until CT scanning became available when the patient was 23 yr of age. Epiphyses fused at 9 yr of age; final height was 142 cm (56 in). At 24 yr of age, he developed an embryonal cell carcinoma of the retroperitoneum.

About 50% of the tumors in the pineal region are germ cell tumors or astrocytomas; the remainder consists of a wide variety of histologically distinct tumor types. Pineal or hypothalamic germ cell tumors can cause CPP in males by secreting hCG, which stimulates the luteinizing hormone (LH) receptors in the Leydig cells of the testes (see Chapter 600.5).

CLINICAL MANIFESTATIONS

Hypothalamic hamartomas remain static in size or grow slowly and can be associated with gelastic or psychomotor seizures, but most often produce no signs other than precocious puberty. This is often rapidly progressive sexual precocity in very young children. For other lesions causing neurologic symptoms, the neuroendocrine manifestations may be present for 1-2 years before the tumor can be detected radiologically. Hypothalamic signs or symptoms such as diabetes insipidus, adipsia, hyperthermia, unnatural crying or laughing, obesity, and cachexia should suggest the possibility of an intracranial lesion. Visual signs (proptosis, decreased visual acuity, visual field defects) may be the first manifestation of an optic glioma.

The sexual precocity is always *isosexual,* and the endocrine patterns are generally those found in children without demonstrable organic

Fig. 600.3 MRI of a central nervous system lesion in a child with central precocious puberty. A 6-yr-old female was referred for stage IV breast development and growth acceleration. Serum luteinizing hormone and estradiol concentrations were in the adult range. The midsagittal T1-weighted image shows an isointense hypothalamic mass *(arrowheads)*, typical of a hamartoma. *(From Sharafuddin M, Luisiri A, Garibaldi LR, et al. MR imaging diagnosis of central precocious puberty: importance of changes in the shape and size of the pituitary gland. Am J Roentgenol. 1994;162:1167–1173.)*

lesions. In conditions other than hypothalamic hamartoma, growth hormone (GH) deficiency can occur and may be masked by the growth-promoting effect of the increased sex hormone levels. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements because these are affected by treatment-induced germ cell and Sertoli depletion. Pubic hair development, scrotal thinning, and penile size may be better indicators, and providers should not hesitate to measure serum LH and testosterone levels when in doubt.

TREATMENT

GnRH agonists (depot forms or implant) are the treatment of choice of tumor-induced CPP. Neurosurgical treatment has been shown to have limited efficacy and to be associated with high complication rates in a subset of patients with hypothalamic hamartoma and associated intractable gelastic or psychomotor seizures. Stereotactic radiation therapy (gamma knife surgery) and, more recently, MRI-guided laser therapy, have been proposed as possible alternatives in these instances. For other neurologic lesions, therapy depends on the nature and location of the pathologic process. Combined GH therapy should be considered for patients with associated GH deficiency. The final height outcome will also depend on other factors such as the burden of disease from the primary tumor, side effects of cancer treatments, and associated chronic health conditions

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600.3 Precocious Puberty After Irradiation of the Brain

Wassim Chemaitilly and Luigi R. Garibaldi

Children treated with cranial radiotherapy at a wide range of doses (18-50 Gy) are at an increased risk for gonadotropin-dependent precocious puberty. The prevalence of this condition in children treated with radiotherapy for tumors located outside of the hypothalamic pituitary or optic pathways region has been reported at 6.6%. Hydrocephalus, young age at exposure to radiation (<5 years), being female, and increased BMI are additional risk factors. This condition is often *associated with GH deficiency* and at times with other conditions (spinal irradiation, hypothyroidism) adversely affecting the adult height prognosis. Unless careful attention is paid to early signs of pubertal development in these children, the combination of GH deficiency and the growth-promoting effect of sex steroids often results in a normal growth rate at the expense of a rapidly advancing bone age and impaired adult height potential. The pubertal staging of males treated with gonadotoxic modalities such as high-dose alkylating agents or testicular radiotherapy should not rely on testicular volume measurements (see Chapter 600.2).

TREATMENT

GnRH analogs are effective in arresting pubertal progression, but concomitant GH (and/or thyroid hormone) deficiency should be diagnosed and treated promptly to improve the adult height prognosis.

Paradoxically, hypopituitarism with gonadotropin deficiency may subsequently develop as a late effect of high-dose CNS irradiation in patients with or without a history of precocious puberty, and it may require substitution therapy with sex steroids.

600.4 Syndrome of Precocious Puberty and Hypothyroidism

Wassim Chemaitilly and Luigi R. Garibaldi

The onset of puberty is usually delayed in children with mild forms of hypothyroidism. However, up to 50% of children with profound, untreated hypothyroidism of long duration may paradoxically develop precocious puberty (a condition known as **VanWyk-Grumbach syndrome**). **Hashimoto thyroiditis** is frequently the cause of such forms of hypothyroidism. Patients have the usual manifestations of hypothyroidism (see Chapter 603); the symptoms may be difficult to recognize in children with special needs. Children with precocious puberty caused by hypothyroidism have, contrary to other children with sexual precocity, decreased growth velocity and delayed bone age. Females may present with breast development and menstrual bleeding; the latter may occur even in females with minimal breast enlargement. Pelvic sonography may reveal large, multicystic ovaries. Males have testicular enlargement associated with modest or no penile enlargement. No pubic hair development occurs in either females or males. Enlargement of the sella, which is typical of long-standing primary hypothyroidism, may be demonstrated by skull film or MRI. Plasma levels of thyroid-stimulating hormone (TSH) are markedly elevated, often greater than 500 μU/mL, and those of prolactin and estradiol are mildly elevated. Although serum FSH is low and LH is undetectable, when measured by specific assays, the massively elevated concentrations of TSH appear to interact with the FSH receptor (specificity spillover), thus inducing FSH-like effects in the absence of LH effects on the gonads. The FSH-like effect suffices to induce estradiol secretion by the ovaries, whereas in males, testicular enlargement occurs without substantial testosterone secretion. Treatment of the hypothyroidism results in rapid return to normal of the biochemical and clinical manifestations. Possible progression to central puberty with rapid bone age advancement may occur in the months after the initiation of thyroid hormone replacement, a complication that would justify delaying puberty with GnRH analogs. Macroorchidism (testicular volume >30 mL) may persist in adult males despite adequate levothyroxine therapy. Children with a high risk of primary hypothyroidism, especially those with special needs such as patients with trisomy 21, should be screened at least annually via measurement of serum free T_4 and TSH levels.

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600.5 Chorionic Gonadotropin-Secreting Tumors: Paraneoplastic Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

hCG-secreting tumors are a rare cause of precocious puberty in males. Secretion of hCG activates luteinizing hormone/choriogonadotropin (LHCG) receptors in the Leydig cells causing testosterone production and virilization with minimal testicular enlargement. Testicular histology reveals interstitial cell hyperplasia with no spermatogenesis. Plasma levels of testosterone are elevated, whereas those of FSH and LH, as measured by specific assays, are low. Females with **hCG-secreting tumors** do not present with precocious puberty because the ovarian production of estradiol cannot occur in the absence of FSH stimulation.

HEPATIC TUMORS

All reported cases of hepatoblastoma causing isosexual precocious puberty have been in males, with the average age of onset of 2 years (range 4 months to 8 years). An enlarged liver or mass in the right upper quadrant should suggest the diagnosis. Plasma levels of hCG and α-fetoprotein (AFP) are usually markedly elevated and serve as useful markers for following the effects of therapy. As with other carcinomas of the liver, the prognosis for survival beyond 1-2 years from the time of diagnosis is poor.

INTRACRANIAL TUMORS

Nongerminomatous or mixed germ cell tumors, choriocarcinomas, teratomas, teratocarcinomas, and others account for <5% of intracranial tumors; are usually located in the neurohypophyseal area or the pineal area; and may cause precocious puberty in males if they secrete hCG—the mass effect can infrequently cause precocious puberty in females. Marked elevations of hCG and AFP often occur in the cerebrospinal fluid, although elevations in the blood may be modest. Treatment includes radiation, chemotherapy, and debulking surgery.

TUMORS IN OTHER LOCATIONS

Very rare locations include mediastinum, gonads, or even adrenal glands. Mediastinal germ cell tumors have been reported to cause precocious puberty in males with Klinefelter syndrome.

PERIPHERAL PRECOCIOUS PUBERTY

The adrenal causes of peripheral precocious puberty are discussed in Chapter 616, and the gonadal causes are discussed in Chapters 624 and 627.

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600.6 McCune-Albright Syndrome

Luigi R. Garibaldi and Wassim Chemaitilly

McCune-Albright syndrome, or precocious puberty with *polyostotic fibrous dysplasia* and abnormal pigmentation, is a syndrome of endocrine dysfunction associated with patchy cutaneous pigmentation and fibrous dysplasia of the skeletal system. It is a rare condition with a prevalence between 1/100,000 and 1/1,000,000, characterized by autonomous hyperfunction of one or more glands (which may include pituitary, thyroid, and adrenal glands). An activating missense pathogenic variant in the *GNAS1* gene encoding the α-subunit of G_S, the G protein that stimulates cyclic adenosine monophosphate (cAMP) formation, results in activation of receptors (adrenocorticotropic hormone [ACTH], TSH, FSH, and LH receptors) that operate via a cAMP-dependent mechanism, as well as cell proliferation. Because the pathogenic variant is postzygotic rather than genomic, it is present variably in different tissues (somatic mosaicism) and hence results in variable clinical expression and limited diagnostic sensitivity of genetic testing from leukocyte DNA or unaffected tissues. The diagnostic sensitivity may improve with new techniques, however. Precocious puberty has been described predominantly in females (Fig. 600.4) and is characterized by recurrent ovarian cysts, bouts of estrogen secretion, and vaginal bleeding in the context of modest breast development. The age at onset in females is usually 3-6 years but has been reported as early as 4-6 months of age. Serum levels of LH and FSH are suppressed, with no response to GnRH stimulation. Estradiol levels fluctuate from low to markedly elevated (>300 pg/mL), are often cyclic, and may correlate with the size of the cysts. Precocious puberty is less commonly reported in males with McCune-Albright syndrome. Testicular enlargement is often symmetric and is followed by the appearance of phallic enlargement and pubic hair development, as in normal puberty. Testicular histology has shown foci or nodules (often sonographically detectable) of Leydig cell hyperplasia. In females and males, when the bone age reaches the usual pubertal age range, gonadotropin secretion begins and CPP ensues and overrides the antecedent (gonadotropin-independent) puberty. In females, menses become more regular, but often not completely so, and fertility has been documented.

Pubertal progression is variable in these patients. Functioning ovarian cysts often disappear spontaneously; aspiration or surgical excision of cysts is rarely indicated. For those females with persistent or recurrent estradiol secretion, **aromatase inhibitors** (which inhibit the final step of estrogen biosynthesis) such as **letrozole** (1.25-2.5 mg/day PO) have proven safe and effective in limiting the estrogen effects on pubertal and osseous maturation. The same compounds have also been used in males in combination with **antiandrogens**. These medications are not approved by the FDA for this indication. Associated therapy with **long-acting analogs of GnRH** is indicated only for young children whose puberty has shifted from a gonadotropin-independent to a predominantly gonadotropin-dependent mechanism. Ovarian torsion is a severe complication of large ovarian cysts.

EXTRAGONADAL MANIFESTATIONS

The hyperthyroidism that occurs in this condition is usually clinically mild or subclinical, unlike that observed in **Graves disease**. Mildly elevated triiodothyronine levels, suppressed TSH levels, and nodular abnormalities on ultrasound have been reported. Thyroidectomy is rarely necessary.

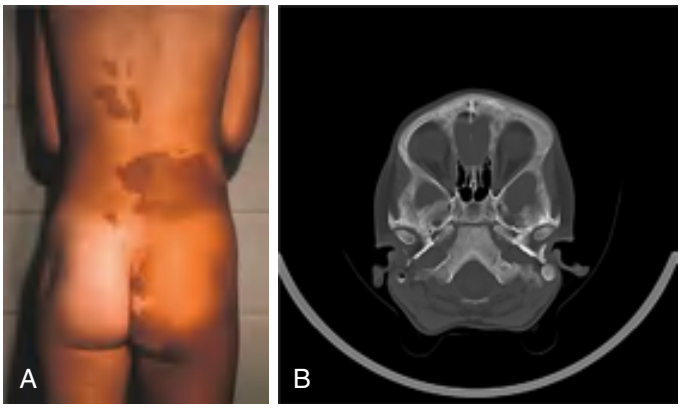

Fig. 600.4 Precocious puberty with McCune-Albright syndrome (MAS). **A,** A girl presented at 5 yr of age with early stage III breast development and vaginal bleeding. Note the extensive café-au-lait skin patches, some of which did not cross the midline. **B,** A girl presented with recurring episodes of mild breast enlargement and vaginal bleeding associated with ovarian cysts, starting at age 7 mo. She had no skin lesions and a negative skeletal survey and bone scan at age 4 yr. The diagnosis of MAS was established at 5 yr of age, when prominence of her left forehead and supraorbital ridge prompted a CT scan, which revealed unilateral thickening of the skull bones (**B**). Skull lesions are often hyperostotic, whereas long bone lesions usually have a lytic, "ground-glass" appearance.

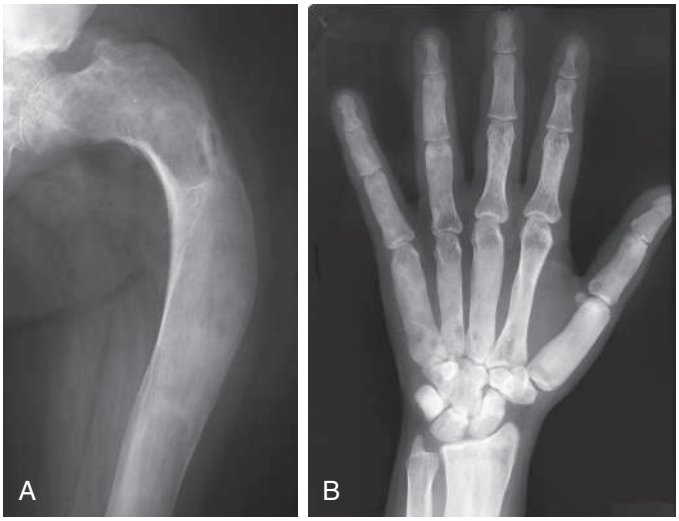

Fig. 600.5 Polyostotic fibrous dysplasia in a 22-yr-old female. **A,** The femur is expanded and bowed with a "shepherd's crook" deformity. The femoral trabeculae are replaced by a "ground-glass" matrix. **B,** Diffuse sclerosis is seen in the hand and wrist with mild expansion and indistinct transition from the cortex to medullary space. *(From Thapa MM, Kaste SC, Meyer JS. Soft tissue bone tumors. In: Coley BD, ed. Caffey's Pediatric Diagnostic Imaging, 13th ed. Philadelphia: Elsevier; 2019: Fig. 138.31.)*

Cushing syndrome caused by bilateral nodular adrenocortical hyperplasia has occurred only in neonates or young infants. ACTH levels are low, and cortisol is elevated and not suppressible by dexamethasone. The condition may resolve spontaneously; if not, treatment is bilateral adrenalectomy.

Increased secretion of GH occurs uncommonly and is manifested clinically by **gigantism** or **acromegaly**. The growth rate is increased (even in the absence of precocious puberty); serum levels of GH are elevated, increase during sleep, and are poorly suppressed by oral glucose. Serum levels of prolactin are increased in most patients. Less than 50% of the patients have a demonstrable pituitary tumor. Treatment includes octreotide or lanreotide—long-acting somatostatin analogs—to lower the elevated GH levels or pegvisomant to antagonize the effect of GH at the receptor level.

Fibrous dysplasia of (usually) multiple bones (polyostotic) represents a major cause of morbidity in this syndrome (Fig. 600.5). The base of the skull and the proximal femurs are most commonly involved, but any bone can be affected. Even in the absence of deformities, a CT scan of the cranium is recommended by several investigators. The prognosis is favorable for longevity, but deformities, repeated fractures, pain, and occasional cranial nerve compression may result from the bony lesions. Bone pain often responds to IV pamidronate or other bisphosphonates. Extensive bony lesions may be associated with phosphaturia because of oversecretion of FGF23, leading to rickets or osteomalacia. Extraglandular manifestations of this syndrome are rare, but cardiovascular and hepatic involvement (severe neonatal cholestasis) may be life threatening.

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600.7 Familial Male-Limited Gonadotropin-Independent Precocious Puberty

Wassim Chemaitilly and Luigi R. Garibaldi

This rare, autosomal dominant form of peripheral precocious puberty is transmitted from affected males and unaffected female carriers of the pathogenic variant to their male offspring. Signs of puberty appear by 2-3 years of age. The testes are only slightly enlarged. Testicular biopsies show Leydig cell maturation and, sometimes, marked hyperplasia. Maturation of seminiferous tubules may be present. Testosterone levels are variably elevated, often markedly so, even above the adult male range; however, baseline levels of LH are prepubertal, pulsatile secretion of LH is absent, and LH does not respond to stimulation with GnRH or a GnRH agonist. The cause for activation of Leydig cells independently of gonadotropin stimulation is a missense pathogenic variant of *LHCGR,* which encodes the LHCG receptor leading to constitutive activation of cAMP production. Osseous maturation may be markedly advanced; when it reaches the pubertal age range, hypothalamic maturation shifts the mechanism of pubertal development to a gonadotropin-dependent one. This sequence of events is similar to that occurring in children with McCune-Albright syndrome (see Chapter 600.6) or in those with congenital adrenal hyperplasia (see Chapter 616).

Gonadotropin-independent precocious puberty has been diagnosed in a few unrelated males with **type IA pseudohypoparathyroidism** with a specific pathogenic variant of *GNAS* that encodes the $G_s\alpha$ protein. This pathogenic variant is inactivating at normal body temperature and causes pseudohypoparathyroidism, but in the cooler temperature of the testes, it is constitutionally activating, resulting in adenyl cyclase stimulation and production of testosterone. Although this pathogenic variant differs from the constitutive LH receptor pathogenic variant, which usually causes familial male gonadotropin-independent precocious puberty, the end result is the same.

TREATMENT

Young males have been treated with ketoconazole (10-15 mg/kg/day in 8-hour divided doses), an antifungal drug that inhibits C-17,20-lyase and testosterone synthesis. Complications of ketoconazole include liver toxicity and tachyphylaxis. A combination of antiandrogens (such as spironolactone 50-100 mg bid, flutamide 125-250 mg daily or bid, or bicalutamide 25-50 mg daily) and **aromatase inhibitors** (letrozole 2.5 mg/day or anastrozole 1 mg/day) has been used—the latter compounds to suppress estrogens derived from androgens, which potently stimulate bone maturation. These medications are unable to revert the serum testosterone to normal (prepubertal) concentrations or completely offset the unfavorable effects of the elevated sex hormones. They slow down, but do not halt, the progression of puberty and may not improve the height prognosis. Males whose GnRH pulse generator has matured require combined therapy with GnRH agonists.

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600.8 Incomplete (Partial) Precocious Development

Wassim Chemaitilly and Luigi R. Garibaldi

Isolated development of the breasts in females and growth of sexual hair in both sexes without other signs of puberty are the two most common forms of incomplete precocity and are not unusual in a pediatric practice.

PREMATURE THELARCHE

This term applies to a sporadic, transient condition of isolated breast development that most often appears in the first 2 years of life. In some females, breast development is present at birth and persists. It may be unilateral or asymmetric and often fluctuates in degree. Growth and osseous maturation are normal or slightly advanced. The genitalia show no evidence of estrogenic stimulation. Breast development may regress after 2 years, often persists for 3-5 years, and is rarely progressive. Menarche generally occurs at a normal age, and reproduction is also normal. Basal serum levels of FSH and the FSH response to GnRH stimulation may be greater than that seen in normal controls. Plasma levels of LH and estradiol are typically undetectable. Pelvic ultrasound reveals normal-sized ovaries, but a few small (<9 mm) cysts are not uncommon.

In some females, breast development may be associated with definite evidence of systemic estrogen effects, such as growth acceleration or bone age advancement. Pelvic sonography may reveal enlarged ovaries and/or uterus. This condition, referred to as **exaggerated or atypical thelarche**, differs from CPP because it spontaneously regresses. Leuprolide or GnRH stimulation elicits a robust FSH response, a low LH response, and (after leuprolide only) a moderate estradiol increment at 24 hours (average 60-90 pg/mL). The pathogenesis of typical and exaggerated forms of thelarche is unclear. Delayed inactivation of the hypothalamic-pituitary-ovarian axis, which is active during the prenatal and early postnatal period, increased peripheral sensitivity to estrogens, and other possibilities are unproven hypotheses. In addition to a detailed history, a bone age should be obtained if there are any unusual features. Random serum concentrations of FSH, LH, and estradiol are generally low and not diagnostic. Pelvic ultrasound examination or leuprolide stimulation testing is occasionally indicated. Continued observation is important because the condition cannot be readily distinguished from true precocious puberty. Regression and recurrence suggest functioning **follicular cysts**. Occurrence of thelarche in children older than 3 years of age most often is caused by a condition other than **benign premature thelarche**.

PREMATURE PUBARCHE (ADRENARCHE)

This term has traditionally applied to the appearance of sexual hair before the age of 8 years in females or 9 years in males without other evidence of maturation. It is much more frequent in females than in males. The higher prevalence of this condition in African American and, to a smaller extent, Latino females in comparison to White females may suggest that the cutoff age for the definition of *premature* should be adjusted for different ethnic groups on epidemiologic data. Hair appears on the mons and labia majora in females and perineal and scrotal area in males; axillary hair generally appears later. Adult-type axillary odor is common. Affected children are often slightly advanced in height and osseous maturation. **Premature adrenarche** is an early maturational event of adrenal androgen production. It coincides with precocious maturation of the zona reticularis, traditionally believed to be associated with a decrease in 3β-hydroxysteroid dehydrogenase activity and an increase in C-17,20-lyase activity. These enzymatic changes result in increased basal and ACTH-stimulated serum concentrations of the Δ^5-steroids (17-hydroxypregnenolone and dehydroepiandrosterone [DHEA]) and, to a lesser extent, of the Δ^4-steroids (particularly androstenedione) compared with age-matched control subjects. One class of androgens, the 11-oxygenated steroids, have been reported to play an important role in adrenal physiology and pathology, including adrenarche. **Idiopathic premature adrenarche** is a slowly progressive condition that requires no therapy. However, a subset of patients presents with **atypical premature adrenarche** characterized by one or more features of systemic androgen effects, such as marked growth acceleration, clitoral (females) or phallic (males) enlargement, cystic acne, and advanced bone age (2 SD greater than the mean for age). In this subgroup, an ACTH stimulation test with measurement of serum 17-hydroxyprogesterone concentration is indicated to rule out **nonclassical congenital adrenal hyperplasia** due to 21-hydroxylase deficiency. The prevalence of nonclassical 21-hydroxylase deficiency is approximately 3–6% of unselected children with precocious pubarche; other enzyme defects (i.e., 3β-hydroxysteroid dehydrogenase or 11β-hydroxylase deficiencies) are extremely rare. Although idiopathic premature adrenarche has been considered a benign condition, longitudinal observations suggest that approximately 50% of females with premature adrenarche are at high risk for hyperandrogenism and **polycystic ovary syndrome**, alone or more often in combination with other components of so-called metabolic syndrome (insulin resistance possibly progressing to type 2 diabetes mellitus, dyslipidemia, hypertension, increased visceral fat) as adults. Whether the unfavorable progression to pubertal hyperandrogenism can be prevented by insulin-sensitizing agents (metformin 850-2000 mg/day) or lifestyle interventions (diet, exercise) remains to be proven in large studies. An increased risk of premature adrenarche and **metabolic syndrome** has been documented in children born small for their gestational age. This appears to be associated with insulin resistance and decreased β-cell reserve, perhaps as a consequence of fetal undernutrition.

PREMATURE MENARCHE

This is a rare entity, much less frequent than premature thelarche or premature adrenarche, and is a diagnosis of exclusion. In females with isolated vaginal bleeding in the absence of other secondary sexual characteristics, more common causes, such as vulvovaginitis, a foreign body (typically associated with malodorous discharge), or sexual abuse, and uncommon causes, such as urethral prolapse and sarcoma botryoides, must be carefully excluded. Most females with idiopathic premature menarche have only one to three episodes of bleeding; puberty occurs at the usual time, and menstrual cycles are normal. Plasma levels of gonadotropins are low, but estradiol levels may be occasionally elevated, probably owing to episodic ovarian estrogen secretion associated with ovarian follicular cysts that can be sometimes detected on ultrasound.

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600.9 Medicational Precocity

Luigi R. Garibaldi and Wassim Chemaitilly

Various medicaments can induce the appearance of secondary sexual characteristics (i.e., peripheral precocious puberty). Examples include the accidental ingestion of estrogens (including contraceptive pills) and the administration of anabolic steroids. Exogenous estrogens may produce a darkening of the areola that is not usually seen in central sexual precocity. The most common cause of medicational precocity is currently related to the widespread use of **testosterone gels or creams**, which are applied to the skin for treatment of male hypogonadism. Systemic absorption from the skin area of a male relative where the gel/cream was applied may result in elevated serum testosterone levels (50-100 mg/dL or higher), with ensuing virilization of exposed children and women. Intense application of diaper rash creams or ointments has recently been reported to cause mild pubarche, with an unclear mechanism.

Less commonly, estrogens in cosmetics, hair creams, and breast augmentation creams cause breast development in females and gynecomastia in males via percutaneous absorption. Lavender and tea tree oils have been associated with prepubertal gynecomastia in several reports. Genistein, a compound from soy, has estrogenic activity in mice, but data in humans are conflicting. The physical changes disappear after cessation of exposure to the hormones. A careful history focused on exploring the possibility of accidental exposure to, or ingestion of, sex hormones is important.

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600.10 Delayed or Absent Puberty

Peter M. Wolfgram

For hypofunction of testis, see Chapter 623. For hypofunction of ovaries, see Chapter 626.

Delayed puberty is the failure of development of any pubertal feature by 13 years of age in females or by 14 years of age in males. A lower cutoff may be appropriate in a child with a strong familial pattern of early puberty.

DIFFERENTIAL DIAGNOSIS

Delay or absence of puberty is caused by:

- Constitutional delay: A variant of normal.
- Hypogonadotropic hypogonadism: Low gonadotropin levels as a result of a defect of the hypothalamus and/or pituitary gland (Tables 600.3, 600.4, and 600.5).
- Hypergonadotropic hypogonadism: High gonadotropin levels as a result of a lack of negative feedback because of a gonadal problem (see Tables 600.3, 600.4, and 600.5). Females may have evidence of adrenarche with absence of normal breast development.

Table 600.3 Classification of Delayed Puberty and Sexual Infantilism

IDIOPATHIC (CONSTITUTIONAL) DELAY IN GROWTH AND PUBERTY (DELAYED ACTIVATION OF HYPOTHALAMIC GNRH PULSE GENERATOR)

HYPOGONADOTROPIC HYPOGONADISM: SEXUAL INFANTILISM RELATED TO GONADOTROPIN DEFICIENCY

CNS Disorders

Tumors
- Craniopharyngiomas
- Germinomas
- Other germ cell tumors
- Hypothalamic and optic gliomas
- Astrocytomas
- Pituitary tumors (including MEN-1, prolactinoma)

Other Causes
- Langerhans histiocytosis
- Postinfectious lesions of the CNS
- Vascular abnormalities of the CNS
- Radiation therapy
- Congenital malformations especially associated with craniofacial anomalies
- Head trauma
- Lymphocytic hypophysitis

Isolated Gonadotropin Deficiency

Kallmann syndrome (with hyposmia or anosmia; without anosmia)
GnRH receptor pathogenic variant
Congenital adrenal hypoplasia (*DAX1* pathogenic variant)
Isolated LH deficiency
Isolated FSH deficiency
Prohormone convertase 1 deficiency (PCI)

Idiopathic and Genetic Forms of Multiple Pituitary Hormone Deficiencies Including PROP1 Pathogenic Variant

Miscellaneous Disorders

See Table 600.4 for syndromic etiologies
Functional gonadotropin deficiency
- Chronic systemic disease and malnutrition
- Sickle cell disease
- Cystic fibrosis
- Acquired immunodeficiency syndrome (AIDS)
- Chronic gastroenteric disease
- Chronic renal disease
- Malnutrition

Miscellaneous Disorders (continued)
- Anorexia nervosa
- Bulimia
- Psychogenic amenorrhea
- Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)
- Hypothyroidism
- Diabetes mellitus
- Cushing disease
- Hyperprolactinemia
- Marijuana use
- Gaucher disease

HYPERGONADOTROPIC HYPOGONADISM

Males

The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter syndrome)
Other forms of primary testicular failure
- Chemotherapy
- Radiation therapy
- Testicular steroid biosynthetic defects
- Sertoli-only syndrome
- LH receptor mutation
- Anorchia and cryptorchidism
- Trauma/surgery

Females

The syndrome of gonadal dysgenesis (Turner syndrome) and its variants
XX and XY gonadal dysgenesis
- Familial and sporadic XX gonadal dysgenesis and its variants
- Familial and sporadic XY gonadal dysgenesis and its variants

Aromatase deficiency
Other forms of primary ovarian failure
- Premature menopause
- Radiation therapy
- Chemotherapy
- Autoimmune oophoritis
- Galactosemia
- Glycoprotein syndrome type 1
- Resistant ovary
- FSH receptor pathogenic variant
- LH/hCG resistance
- Polycystic ovarian disease
- Trauma/surgery
- Noonan or pseudo-Turner syndrome
- Ovarian steroid biosynthetic defects

CNS, Central nervous system; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin.
From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.15, p. 1129.

Table 600.4 Syndromes Associated with Pubertal Delay

	PHENOTYPE	GENETIC DEFECT
Prader-Willi syndrome	Cognitive impairment, morbid obesity, hypotonia	Deletions within paternally imprinted 15q 11.2-12 region
Bardet-Biedl syndrome	Cognitive impairment, obesity, retinitis pigmentosa, postaxial polydactyly	*BBS 1-11* (multiple loci) 20p12, 16q21, 15q22.3-23, 14q32.1
Biemond syndrome	Iris coloboma, polydactyly, short stature	
CHARGE anomaly	Coloboma, heart malformations, choanal atresia, growth retardation, genital anomalies and ear anomalies, HH, olfactory bulb aplasia, hypoplasia	*CHD7*
Adrenohypoplasia congenita	Primary adrenal deficiency	*NR0B1*
Septo-optic dysplasia	Small, dysplastic pale optic discs, pendular nystagmus, midline hypothalamic defect with diabetes insipidus, GH, ACTH, TSH, and LH/FSH deficiency, absent septum pellucidum	*HESX1*
Solitary median maxillary incisor syndrome	Prominent midpalatal ridge	*SHH 7q3*
Börjeson-Forssman-Lehmann syndrome	Cognitive impairment, gynecomastia, moderate short stature, truncal obesity	*PHF6*
Gordon Holmes syndrome	Cerebellar ataxia, dementia, chorioretinopathy, anterior hypopituitarism	*RNF216/OTUD4* *PNPLA6*

Modified from Howard SR, Dunkel L. Delayed puberty – phenotype diversity, molecular genetic mechanisms, and recent discoveries. *Endocrine Rev.* 2019;40:1285–1317, Table 3, p. 1301.

Table 600.5 Molecular Basis for Developmental Disorders Associated with Hypogonadotropic Hypogonadism

GENE	PHENOTYPE	COMPLEX PHENOTYPE
ISOLATED HYPOGONADOTROPIC HYPOGONADISM		
Kallmann Syndrome or Normosmic IHH (With the Same Pathogenic Gene Variant)		
KAL1 (Xp22.3)	X-linked Kallmann syndrome	Anosmia/hyposmia, renal agenesis, dyskinesia
FGFR1 (KAL2) (8p11.2)	Autosomal dominant Kallmann syndrome (± recessive)	Anosmia/hyposmia, cleft lip/palate
FGF8 (ligand for FGFR1) (10q25)		
NELF (9p34.3)	Autosomal dominant (?) Kallmann syndrome	
PROK2 (3p21.1)	Autosomal recessive Kallmann syndrome	
*PROKR2** (20p12.3)		
CHD7 (8p12.1)	Autosomal dominant (some)	CHARGE syndrome includes hyposmia
Normosmic Isolated Hypogonadotropic Hypogonadism		
GNRH1 (8p21-11.2)	Autosomal recessive	
*GNRHR** (4q13.2-3)	Autosomal recessive (± dominant)	
*GPR54** (19p13.3)	Autosomal recessive	
SNRPN		Prader-Willi syndrome
Lack of function of paternal 15q11-q13 region or maternal uniparental disomy		Obesity
LEP (7q31.3)	Autosomal recessive	Obesity
LEPR (1p31)	Autosomal recessive	Obesity
NR0B1 (DAX1) (X21.3-21.2)	X-linked recessive	Adrenal hypoplasia
TAC3 (12q13-12)	Autosomal recessive	
TACR3 (4q25)	Autosomal recessive	
Multiple Pituitary Hormone Deficiencies		
PROP1 (POU1F1)	Autosomal recessive GH, PRL, TSH, and LH/FSH (less commonly, later-onset ACTH deficiency)	
HESX1 (RPX)	Autosomal recessive; and heterozygous mutations Multiple pituitary deficiencies including diabetes insipidus, but LH/FSH uncommon	Septo-optic dysplasia
LHX3	Autosomal recessive GH, PRL, TSH, FSH/LH	Rigid cervical spine
PHF6	X-linked; GH, TSH, ACTH, LH/FSH	Börjeson-Lehmann syndrome: mental retardation; facies

*A G-protein–coupled receptor.
ACTH, Adrenocorticotropic hormone; CHD7, chromatin-remodeling factor; DAX1, dosage-sensitive sex reversal-adrenal hyperplasia congenita critical region on the X chromosome, gene 1; FGF, fibroblast growth factor; FSH, follicle-stimulating hormone; GH, growth hormone; GNRH, gonadotropin-releasing hormone; GPR54, kisspeptin G protein–coupled receptor 54; HESX1, homeobox gene expressed in ES cells; IHH, idiopathic hypogonadotropic hypogonadism; LEP, leptin; LH, luteinizing hormone; LHX3, lim homeobox gene 3; NELF, nasal embryonic luteinizing hormone–releasing factor; NR0B1, nuclear receptor family 0, group B, member 1; PHF6, plant homeodomain–like finger gene; PRL, prolactin; PROK2, prokineticin 2; PROP1, prophet of Pit-1; R, receptor; SNRPN, small nuclear ribonucleoprotein polypeptide SmN; TAC3, neurokinin 3; TSH, thyroid-stimulating hormone.
From Styne DM, Grumbach MM. Physiology and disorders of puberty. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*, 13th ed. Philadelphia: Elsevier; 2016: Table 25.19, p. 1138.

Constitutional Delay of Growth and Puberty

This is the most common cause of delayed puberty and a normal variant of pubertal timing. It is predominately diagnosed in males, likely as a result of ascertainment bias from referral patterns. The cause is unknown, but approximately 50% of affected patients have a first-degree relative with delayed puberty and/or late growth. This tendency can occur in a child of the same gender as the affected parent or in a child of the opposite gender. An affected child typically presents in early adolescence, when peers are beginning to develop and having growth spurts but the patient is not. The patient's height is usually at or below the third percentile. In a classic patient, the affected child had a normal length at birth, followed by a slowdown in height velocity between 6 months and 2 years of age that resulted in a decreased height percentile, and then normal or near-normal height velocity thereafter along this decreased height percentile. The physical examination findings are unremarkable, except at the typical age of puberty the child will have delayed pubertal development and growth. The cardinal diagnostic finding is a bone age that is moderately delayed (or younger appearing) than the typical bone age for the patient's actual chronological age. There may also be a history of delayed dentition. Without intervention, final adult heights usually reach or approximate the genetic target height range. However, rarely, children with constitutional delay may have a blunted pubertal growth spurt in relation to their peers and therefore may not reach their target height range.

Hypogonadotropic Hypogonadism

A variety of CNS anomalies or injuries may disrupt production of gonadotropins. The GnRH pulse generator may be disrupted by an interfering substance, such as excess prolactin, chronic illness, malnutrition, or excessive physical activity. The hypothalamic arcuate nucleus may be damaged by trauma, radiation, infection, infiltration, increased intracranial pressure, or surgery. The most common mass lesions are craniopharyngiomas, gliomas, and cysts. Of note, congenital conditions or malformations may have allowed enough GnRH, LH, and FSH for infantile development but may not be enough later to begin and sustain puberty.

Kallmann Syndrome

This is the combination of a deficiency of gonadotropins with an impaired or absent sense of smell. Other features may include color blindness, atrial septal defects, and renal structural anomalies (unilateral renal agenesis). The X-linked form is caused by a pathogenic variant of *KAL*; there are autosomal recessive and autosomal dominant forms.

LH and FSH deficiencies may be isolated or accompanied by multiple pituitary hormone deficiencies. The deficiency may be a result of pituitary damage from trauma, radiation, infection, sickle cell disease, compression by infiltrate or tumor, or autoimmune processes. In differentiating primary pituitary deficiency from that secondary to hypothalamic deficiency, the clinician should remember that all pituitary hormones, except prolactin, are stimulated by hypothalamic-releasing hormones; however, prolactin is inhibited by hypothalamic prolactin inhibitory factor (dopamine). Therefore if all pituitary hormones, including prolactin, are deficient, the problem is in the pituitary gland. If prolactin levels are present or even elevated but the other pituitary hormones are deficient, the problem is above the pituitary gland, in the stalk or hypothalamus. In the case of isolated LH and FSH deficiencies, the primary abnormality may lie within the pituitary-hypothalamic neurons producing GnRH or farther upstream of the GnRH-secreting neurons. In particular, defects in molecules required for proper migration of GnRH neurons (including the *KAL* gene) or lack of necessary signaling to GnRH-producing neurons (defects in kisspeptin or neurokinin B and their receptors) can result in LH and FSH deficiency through inappropriate GnRH secretion.

Hypergonadotropic Hypogonadism: Males

If the testes are small, they may have been damaged by torsion, sickle cell disease, infection, autoimmune disease, chemotherapy, or radiation and may not be able to respond to LH and FSH stimulation. If the male is of pubertal age (bone age is greater than 10 years) and the hypothalamus has matured, the serum LH and FSH will be high because of lack of testicular response. Also, if there is a problem with testicular LH receptors, the LH can be high but the testosterone will not appropriately increase.

Klinefelter Syndrome

This occurs in 1:500 males and is often associated with a 47,XXY karyotype; common features include reduced intelligence, adolescent gynecomastia (often severe), and small, firm testes. The testes rarely exceed 5 mL in volume (approximately 25% of the average adult volume). Patients are often tall and thin with an eunuchoid habitus and may have delayed puberty with high FSH and LH. Virilization may be incomplete, the phallus is often smaller than average, and infertility approaches 100%.

Hypergonadotropic Hypogonadism: Females

In this condition, the ovary may be unable to synthesize estrogen (an inherited metabolic defect), the ovary may not be formed normally (dysgenesis), or the ovary may have been damaged by any of the factors listed for testicular damage and by galactosemia.

The ovary may be intact but may not be stimulated by gonadotropins—for example, FSH is present but there is an FSH receptor problem, so estradiol is not made appropriately.

Turner Syndrome

The two most common features of Turner syndrome are short stature (involving the limbs to a greater degree than the trunk) and ovarian insufficiency with high FSH. Lymphedema and a webbed neck are diagnostic features present in a neonate. Additional features include shield chest, increased carrying angle (cubitus valgus), short fourth metacarpal, hypoplastic nails, renal anomalies, and left-sided heart defects (coarctation of the aorta, bicuspid aortic valve). Approximately 50% of affected females have no stigmata except short stature and thus are typically identified later. About 20% may have spontaneous puberty with functioning ovaries for at least a short period, which is in large part dependent on the child's karyotype; the infertility rate is greater than 99%.

Females with Delayed or Absent Adrenarche

If a female has advanced breast development but no androgen signs, she may have a disorder of androgen activity as occurs in **androgen insensitivity syndrome** (testicular feminization). In females, the androgens come predominantly from the adrenal glands (adrenarche). If the bone age is less than 8 years, adrenarche may simply be delayed (delayed adrenarche). However, if the bone age is older, there may be an inherited problem in androgen synthesis from an enzyme deficiency, or the adrenal may be damaged secondary to autoimmune, infectious, or hypoxic injury. In these latter conditions of adrenal damage, other signs of adrenal insufficiency would be evident.

DIAGNOSTIC APPROACH TO DELAYED PUBERTY

A normal growth rate with delayed, but not absent, puberty and a family history of late puberty suggest the diagnosis of constitutional delay of growth and puberty, which is the most commonly encountered cause. A bone age that correlates with the patient's current pubertal status but is delayed for their chronological age confirms the clinical impression; no other testing is necessary.

Initial evaluation should include:

- Medical history: trauma, illness, medications (e.g., stimulants, chemotherapy), radiation, infection, malnutrition, autoimmune problems, sickle cell disease status, stresses, growth records, galactosemia
- Review of symptoms: vision problems, headache, vomiting, inability to detect odors (hyposmia or anosmia), age at onset of androgen signs, age at onset of estrogen signs, small genitalia at birth, signs of primary adrenal insufficiency such as hyperpigmentation, need for deodorant, need to wash hair more frequently
- Family history: timing of maternal and paternal growth and pubertal development; siblings and cousins with delayed development
- Physical examination: signs of chronic disease, temperature, blood pressure, height, weight, head circumference, dental age, hyperpigmentation, pubic and axillary hair, adult body odor, evidence of skin and hair oils, visual fields, optic discs, ability to detect odors, breast development, vaginal cornification/discharge, penis size, scrotal development, testicular volume, pubic hair stages, neurologic status, affect or mood, intellectual ability, dysmorphic features

Initial laboratory evaluation screens for chronic disease (complete blood cell count, chemistry profile, sedimentation rate), hypothyroidism (free thyroxine and TSH), and hyperprolactinemia (prolactin level) should be obtained. If growth is slow, the clinician should measure insulin-like growth factor-1 level (marker of basal GH activity) and consider GH testing. The clinician should measure testosterone levels in males and estradiol levels in females.

Measurements of random FSH and LH and results of a GnRH stimulation test may differentiate between hypogonadotropic hypogonadism and primary gonadal failure (Figs. 600.6 and 600.7). Elevated gonadotropin levels support a diagnosis of primary gonadal failure. A random LH or an LH after GnRH is not typically helpful in distinguishing between constitutional delay and hypogonadotropic hypogonadism because with both diagnoses the LH will be low. However, the child with constitutional delay eventually develops an appropriate pubertal development and LH values. If there are elevated gonadotropins, chromosomal karyotyping can be performed (Klinefelter syndrome in males and Turner syndrome in females).

If Kallmann syndrome is being considered, an MRI scan may show abnormalities in the olfactory region. If a 46,XX female has unexplained ovarian failure, antiovarian antibodies and müllerian-inhibiting substance can assess ovarian follicle reserve and potential fertility. In males, an hCG stimulation test to evaluate ability to produce testosterone and a serum level of müllerian-inhibiting substance (secreted by

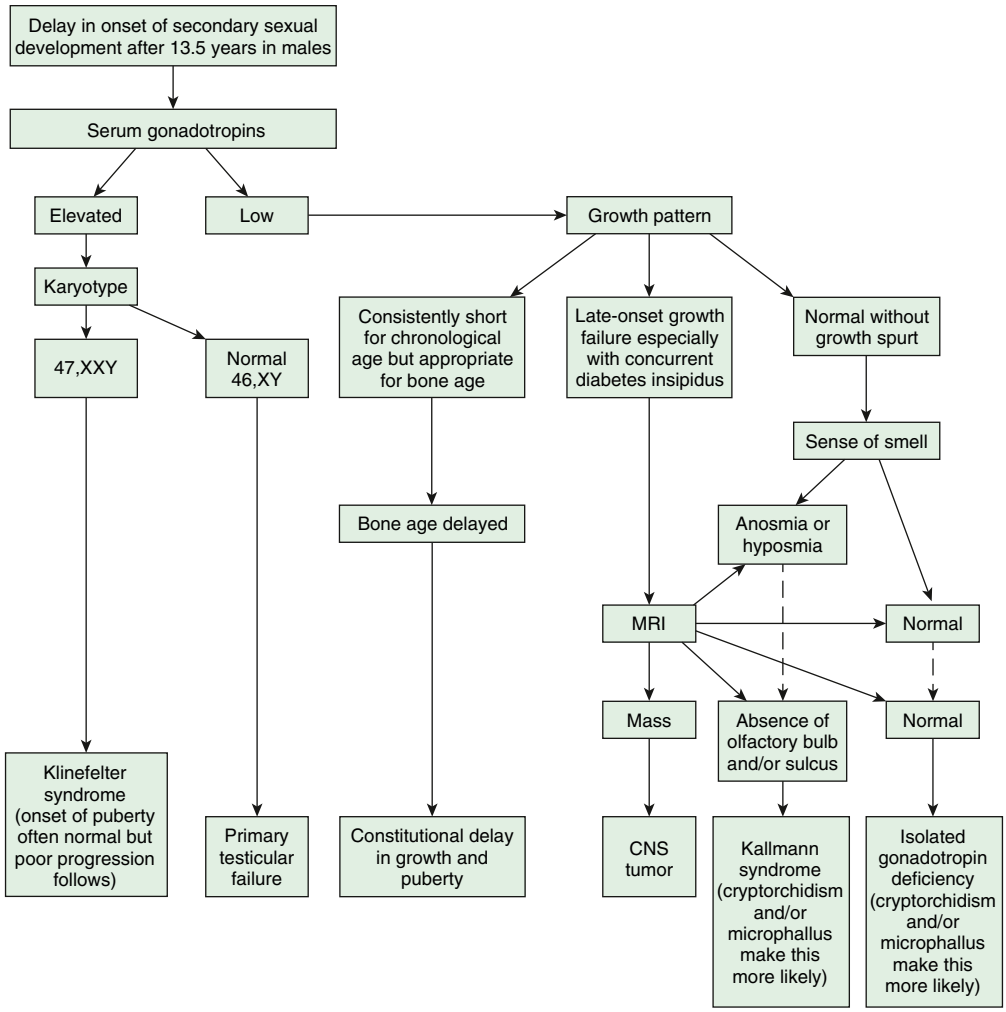

Fig. 600.6 Diagnostic algorithm for the evaluation of delayed puberty in males. CNS, Central nervous system; MRI, magnetic resonance imaging. *(From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 25.48.)*

Sertoli cells) are useful for determining whether functional testicular tissue is present.

TREATMENT OF DELAYED PUBERTY

If delayed puberty is a normal physiologic variant (constitutional delay of growth and puberty), sex steroid replacement is not medically necessary. Watchful waiting is usually the appropriate course of action. However, adolescent males with constitutional delay of growth and puberty who are short, underdeveloped, and psychologically compromised may benefit from a short course of testosterone therapy. This is usually given as long-acting intramuscular testosterone, at a dosage of 50-100 mg every 4 weeks for a course ranging between 6 and 12 months. Treatment is generally begun at about 14 years of age and, if possible, when the testes have enlarged to about 6-8 mL in volume. These doses stimulate height and weight gain, allow adequate virilization (increased pubic and axillary hair growth and penile enlargement), and do not typically suppress pituitary FSH and LH secretion, thereby allowing simultaneous endogenous pubertal progression (testicular enlargement). This narrows the physical gap between the patient and peers without causing undue advancement of bone age. Acne is the principal side effect, and the adult height is not altered. It is the hope that at the conclusion of treatment, the male will continue to grow and develop rapidly, with the testosterone treatment perceived as a jump starter of endogenous puberty. Additionally, a short course of a low-dose anabolic steroid, such as oxandrolone, can also be used in prepubertal and pubertal males, and low-dose estradiol has been used in prepubertal and pubertal females with constitutional delay.

Treatment of hypogonadism aims to mimic normal physiology with stepwise replacement of testosterone in males and estrogen and progesterone in females. For males with hypogonadism, low-dose parenteral testosterone is initiated at 50 mg every 4 weeks, with increases in 50-mg increments made over a 2- to 3-year period. Most adult males receive 200 mg every 2-4 weeks, which is based on the daily adult male testosterone production rate of 6 mg. Adult men can receive testosterone by patch, which is often associated with local irritation, or by gel, but, typically in growing adolescents, intramuscular testosterone is prescribed to allow more reliable control of testosterone activity.

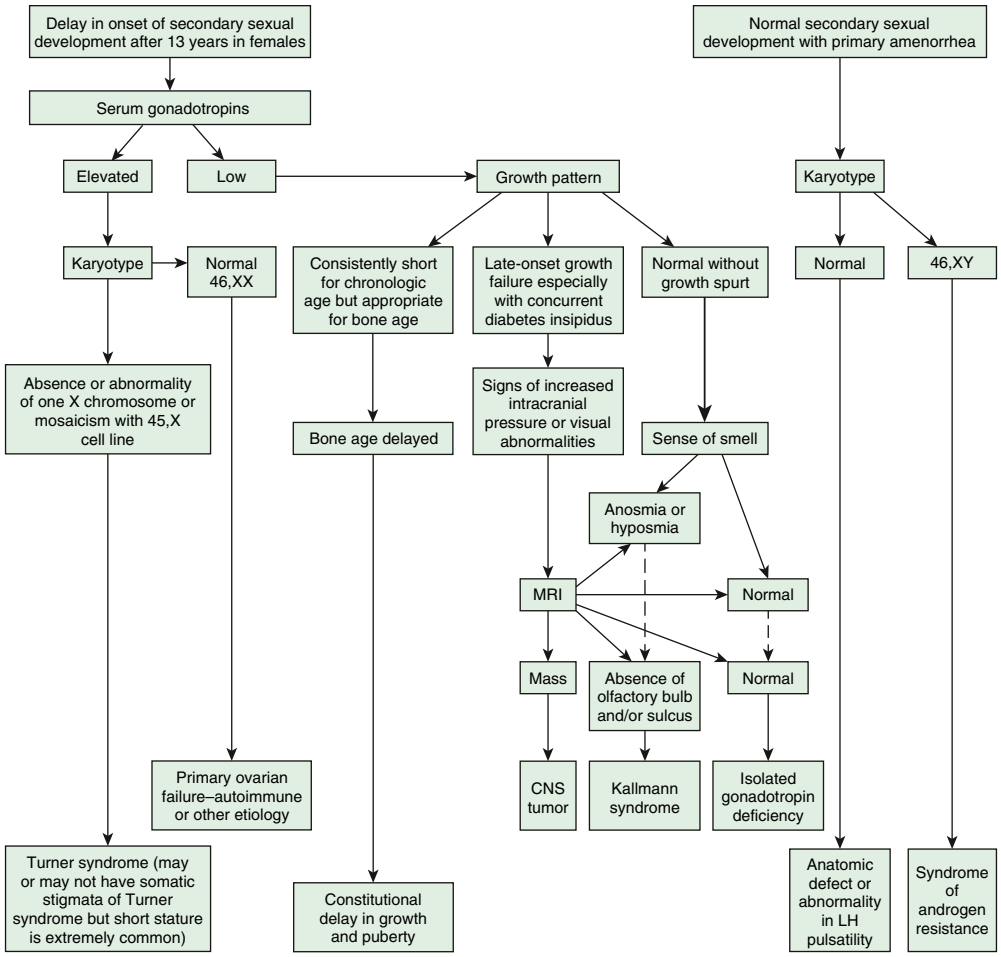

Fig. 600.7 Diagnostic algorithm for the evaluation of delayed puberty in females. CNS, Central nervous system; MRI, magnetic resonance imaging. *(From Styne DM, Grumbach MM. Physiology and disorders of puberty. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. Williams Textbook of Endocrinology, 13th ed. Philadelphia: Elsevier; 2016: Fig. 25.49, p. 1157.)*

For females with hypogonadism, daily estrogen therapy typically is provided through a transdermal 17β-estradiol patch 25 mcg/24 hr patch, which is more physiologic than oral preparations of the estrogens (conjugated estrogens [Premarin] or ethinyl estradiol) because transdermal therapy avoids initial first-pass hepatic metabolism. The transdermal or oral dose of estrogen (Premarin starts at 0.3 mg daily) is increased over the course of about 2 years. Two years of estrogen therapy without progesterone does not place the uterus at undue risk for hyperplasia and malignancy, but after 2 years (or sooner if spotting occurs prior), progesterone should be added. Options to consider when adding progesterone include continuing the 17β-estradiol patches or estrogen-only–containing pills (conjugated estrogens or ethinyl estradiol) in conjunction with oral medroxyprogesterone acetate (Provera), a progesterone eluting intrauterine device (IUD), or switching the patient to conventional oral contraceptives. If the patient is not put on a conventional oral contraceptive or a progesterone-eluting IUD, the estrogen (pill or patch) is prescribed on days 1-23 of the calendar month with the addition of medroxyprogesterone acetate on days 10-23. With this approach, withdrawal bleeding generally occurs between day 23 and the end of the month, although there can be some variability in the timing between patients.

Patients of either sex with hypogonadotropic hypogonadism are potentially fertile, but sex-steroid therapy alone is ordinarily not sufficient to initiate gametogenesis, although there are rare cases in males in which testosterone replacement alone has stimulated spermatogenesis. The general approach to fertility induction in either sex involves the addition of either cyclical gonadotropin therapy or pump-driven GnRH therapy at the age of desired conception. *When hypogonadotropic hypogonadism is present as one component of hypopituitarism, it is critical to adequately replace all deficient hormones* (see Chapter 595). In contrast, patients with primary hypogonadism have intrinsic gonadal damage and are normally infertile.

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Section 2

Disorders of the Thyroid Gland

Chapter 601

Thyroid Development and Physiology

Ari J. Wassner and Jessica R. Smith

FETAL DEVELOPMENT

The fetal thyroid arises from an outpouching of the foregut at the base of the tongue (foramen cecum) and migrates to its normal location below the cricoid cartilage by 8-10 weeks of gestation. The thyroid's bilobed shape is apparent by 7 weeks of gestation, and thyroid follicular cells capable of forming colloid are present by 10 weeks. Thyroglobulin synthesis begins at 4 weeks, iodine trapping occurs by 8-10 weeks, and synthesis and secretion of thyroxine (T_4) and, to a lesser extent, triiodothyronine (T_3) occur from 12 weeks of gestation. Several transcription factors, including NKX2.1, FOXE1, and PAX8, are important in thyroid gland morphogenesis and differentiation and possibly also in its caudal migration. Thyrotropin (TSH) secretion is evident by 10-12 weeks of gestation. Maturation of the hypothalamic-pituitary-thyroid axis occurs during the second half of gestation, but normal hormonal feedback relationships are not mature until 1-3 months of postnatal life. Other transcription factors, including PROP1 and POU1F1, are important for the differentiation and growth of pituitary thyrotrophs, along with somatotrophs and lactotrophs.

THYROID PHYSIOLOGY

The primary function of the thyroid gland is to synthesize T_4 and T_3, of which iodine is a critical component. The only known physiologic role of iodine is in the synthesis of these hormones, and iodine deficiency results in hypothyroidism. The daily recommended dietary allowance of iodine is 110-130 μg for infants, 90-120 μg for children, and 150 μg for adolescents and adults (see Chapter 605.3).

Ingested iodine reaches the thyroid gland as its ionized form, iodide [I^-]. Thyroid tissue has a unique avidity for iodide and can take up and concentrate it in the follicular lumen to synthesize thyroid hormone. Transport of iodide from the circulation into the thyroid follicular cell is facilitated by the transmembrane sodium–iodide symporter (NIS). Once taken up, iodide diffuses across the cell and is transported across the apical membrane into the colloid by pendrin (and likely another unidentified transporter).

To form thyroid hormone, trapped inorganic iodide is organified onto tyrosine residues of thyroglobulin in the follicular lumen, a reaction catalyzed by thyroperoxidase (TPO). This reaction requires the H_2O_2 produced by the enzyme DUOX2, which is expressed in conjunction with dual oxidase maturation factor 2 (DUOXA2). Thyroglobulin is a large homodimeric glycoprotein that contains 138 tyrosine residues. Iodination of specific tyrosine residues forms monoiodotyrosines (MITs) and diiodotyrosines (DITs), which are further coupled by TPO to produce T_4 or T_3. Once formed, T_4 and T_3 remain stored as part of thyroglobulin in the thyroid colloid until they are secreted through a process of follicular cell endocytosis of colloid followed by endolysosomal degradation of thyroglobulin to release T_4 and T_3.

The thyroid secretes T_4 and T_3 in a ratio of about 12 to 1. Although T_3 circulates at about one-fiftieth the concentration of T_4, T_3 is the physiologically active thyroid hormone because it binds the thyroid hormone receptor with 10- to 15-fold greater affinity than T_4. Only 20% of circulating T_3 is secreted directly by the thyroid, and the remainder is produced by conversion from T_4 in extrathyroidal tissues by iodotyrosine deiodinases (types 1 and 2).

Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism. Entry of T_4 and T_3 into cells is facilitated by specific thyroid hormone transporters, of which the most important is monocarboxylate transporter 8 (MCT8). Once inside the cell, T_4 is converted to T_3 by type 1 or 2 deiodinase. Intracellular T_3 enters the nucleus and binds to thyroid hormone receptors. Thyroid hormone receptors are members of the steroid hormone receptor superfamily, and three thyroid hormone receptor isoforms (α_1, β_1, and β_2) are expressed in different tissues. Binding of T_3 to a thyroid hormone receptor causes recruitment of co-activator molecules, transcription of messenger RNA, and protein synthesis. Deiodination, transmembrane transport, and thyroid hormone receptor expression provide multiple levels of tissue-specific modulation of thyroid hormone action in the face of a given level of circulating T_4.

Approximately 70% of circulating T_4 and 50% of T_3 are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only 0.03% of serum T_4 and 0.3% of T_3 are unbound (free T_4 and free T_3, respectively). Because the concentration or binding of TBG is altered in many clinical circumstances, its status must be considered when interpreting total T_4 or T_3 levels.

THYROID REGULATION

The thyroid is regulated by TSH, a glycoprotein hormone secreted by the anterior pituitary thyrotrophs. Binding of TSH to its receptor in the thyroid gland activates adenylate cyclase and stimulates all steps of thyroid hormone biosynthesis (see Fig. 594.1). TSH is a heterodimer composed of α and β subunits. The α subunit is common to luteinizing hormone, follicle-stimulating hormone, and chorionic gonadotropin, and the specificity of each hormone is conferred by its unique β subunit. TSH synthesis and release are stimulated by TRH, a tripeptide synthesized in the hypothalamus and secreted into the pituitary. In states of decreased thyroid hormone, TSH and TRH are increased, and increased thyroid hormone inhibits TSH and TRH production. TSH levels can be measured in serum, whereas circulating levels of TRH are not clinically measurable.

Further control of the level of circulating thyroid hormones occurs in the periphery. In many nonthyroidal illnesses, circulating T_3 levels fall because of decreased extrathyroidal production of T_3 by type 1 deiodinase and increased inactivation of T_4 (to reverse T_3) and T_3 (to T_2) by type 3 deiodinase. These changes may be induced by factors such as fasting, chronic malnutrition, acute illness, and certain drugs. Although levels of T_3 may be significantly decreased, levels of free T_4 and TSH may remain normal. The decreased levels of T_3 may be a physiologic adaptation, resulting in decreased rates of oxygen consumption, substrate use, and other catabolic processes.

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601.1 Thyroid Hormone Studies

Ari J. Wassner and Jessica R. Smith

SERUM THYROID HORMONES

Methods are available to measure many thyroid hormones in serum, including T_4, free T_4, T_3, and free T_3. The metabolically inert reverse T_3 (rT_3) is present in serum, but measuring rT_3 is rarely useful clinically. Direct assays for free T_4 are widely available and are reliable in healthy patients, but these assays may be less reliable during acute illness or with severe abnormalities of thyroid hormone binding. Therefore in such situations it may be preferable to measure total T_4 as an index of TBG binding or to measure free T_4 by the gold standard technique of equilibrium dialysis. The clinical utility of many free T_3 assays is limited by their poor standardization. Because normal thyroid function changes over time, age-specific reference ranges should be used when interpreting thyroid hormone testing in children, particularly in neonates and infants.

Measuring serum levels of TSH and free T_4 can diagnose most clinical thyroid disorders. Serum TSH is the most sensitive test for primary thyroid dysfunction, and it is elevated in primary hypothyroidism and suppressed in primary thyrotoxicosis. In central (secondary) hypothyroidism, serum TSH is low or inappropriately in the normal range despite low serum T_4 and free T_4 levels. Biotin supplements may cause a false elevation of T_4 and T_3 and a false decrease of TSH.

Thyroglobulin is a glycoprotein secreted through the apical surface of the thyroid follicular cell into the colloid. Thyroglobulin is measurable in the serum, and levels of thyroglobulin increase with TSH stimulation and in proportion to functional thyroid mass. Athyreotic infants have markedly reduced levels of thyroglobulin. In contrast, thyroglobulin levels may be increased in neonates and in patients with Graves disease and other forms of autoimmune thyroid disease, differentiated thyroid carcinoma, or endemic goiter.

FETAL AND NEWBORN THYROID

Fetal serum T_4 and free T_4 increase from midgestation to approximately 9.5 μg/dL and 1.4 ng/dL, respectively, at term. Fetal levels of T_3 are low before 20 weeks and then gradually increase to approximately 60 ng/dL at term. Reverse T_3 levels, however, are high in the fetus (300 ng/dL at 30 weeks) and decrease to 200 ng/dL at term. Serum levels of TSH gradually increase to 6 mIU/L at term. Approximately one third of fetal T_4 at term is derived from the transplacental passage of maternal T_4. Maternal T_4 plays a key role in fetal development, especially that of the brain, beginning before fetal synthesis of thyroid hormone begins. Therefore a fetus with congenital hypothyroidism may be partially protected by maternal T_4 if the mother is euthyroid but may be at risk for neurodevelopmental injury if the mother is hypothyroid.

Immediately after birth there is an acute release of TSH, with peak serum concentrations reaching 70-100 mIU/L 30 minutes after delivery in full-term infants. TSH declines rapidly over the ensuing 24 hours and more gradually over the next 5 days to <10 mIU/L. After the first 1-3 months of life, normal levels of TSH are <5 mIU/L. The postnatal surge in TSH stimulates an increase in levels of T_4 to approximately 16 μg/dL and of T_3 to approximately 300 ng/dL in about 4 hours. T_4 levels gradually decrease during the first 2 weeks of life to 10-12 μg/dL. T_3 levels decline during the first week of life to below 200 ng/dL. Reverse T_3 levels remain high for 2 weeks (200 ng/dL) and decrease by 4 weeks to around 50 ng/dL. In preterm infants, changes in thyroid function after birth are qualitatively similar to but quantitatively smaller than in full-term infants. Serum T_4 and T_3 levels are decreased in proportion to gestational age and birthweight.

SERUM THYROXINE-BINDING GLOBULIN

The thyroid hormones are transported in plasma bound primarily to TBG, a glycoprotein synthesized in the liver. TBG binds approximately 70% of T_4 and 50% of T_3. Estimating TBG binding is occasionally necessary because changes caused by various clinical conditions can affect measured levels of total (but not free) T_4 and T_3. TBG levels increase in pregnancy; in the newborn period; with hepatitis; and with the administration of estrogens (oral contraceptives), selective estrogen receptor modulators, heroin or methadone, mitotane, and 5-fluorouracil. TBG levels decrease with androgens, anabolic steroids, glucocorticoids, nicotinic acid, and L-asparaginase. These effects are the result of altered hepatic synthesis of TBG. Severe TBG deficiency may be caused by genetic variants, decreased production with hepatocellular disease, or massive protein loss in the gut (protein-losing enteropathies) or the urine (congenital nephrotic syndrome) (see Chapter 602). Some medications, including furosemide, salicylates, nonsteroidal antiinflammatory drugs, heparin, and free fatty acids, can elevate levels of free T_4 by inhibiting binding to TBG.

THYROID ULTRASONOGRAPHY

The primary clinical uses of thyroid ultrasound are to assess thyroid morphology and to evaluate the characteristics of thyroid nodules. In infants with congenital hypothyroidism, evaluation of the size and location of the thyroid may clarify the diagnosis of thyroid dysgenesis; however, the sensitivity of ultrasound is user-dependent, and it will not reliably detect ectopic thyroid glands. Ultrasound is more accurate than physical examination for estimating thyroid gland size and assessing thyroid nodules. Certain characteristics of thyroid nodules, such as irregular margins, microcalcifications, hypoechogenicity, and taller-than-wide shape, increase the likelihood that a thyroid nodule is malignant and guide decisions about the need for fine-needle aspiration. In children with autoimmune thyroiditis or Graves disease, ultrasound may reveal heterogeneous echotexture or changes in vascularity. However, ultrasound generally is not clinically useful in these conditions unless a thyroid nodule is suspected. Ultrasound may also be useful to evaluate thyroglossal duct cysts.

RADIONUCLIDE STUDIES

The availability of highly sensitive tests of thyroid function has decreased the necessity for radioiodine uptake studies except in specific clinical situations. The ability of the thyroid to take up and organify iodine can be evaluated by measuring the uptake of radioactive isotope ^{123}I (half-life: 13 hours). Technetium (^{99m}Tc) is also a useful radioisotope for children because it is trapped but not organified by the thyroid and has a half-life of only 6 hours. Thyroid scintigraphy can demonstrate the anatomic distribution of tracer uptake by thyroid tissue and may be indicated to assess for possible thyroid dysgenesis or ectopic thyroid tissue or to evaluate possible autonomous (hot) thyroid nodules. ^{131}I may be used to treat hyperthyroidism or thyroid cancer, but its use generally should be avoided for thyroid uptake and scintigraphy because of its cytotoxic effect.

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Chapter 602

Disorders of Thyroxine-Binding Globulin

Ari J. Wassner and Jessica R. Smith

Approximately 70% of circulating thyroxine (T_4) and 50% of triiodothyronine (T_3) are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only the unbound (free) fractions of these hormones, comprising 0.03% of serum T_4 and 0.3% of T_3, can exert biologic activity. Because regulation of the hypothalamic-pituitary-thyroid axis is mediated by the concentrations of free thyroid hormones, abnormalities of thyroid hormone binding tend to alter concentrations of total, but not free, thyroid hormones. *Therefore abnormalities in levels of TBG are not associated with clinical disease and do not require treatment.* They are usually discovered as an incidental finding of abnormally low or high levels of T_4 and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

Congenital TBG deficiency is an X-linked recessive trait that occurs in 1 in 1,700 male newborns. It is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected males have low levels of total T_4 (usually <4 μg/dL) and elevated T_3 resin uptake, but levels of free T_4 and thyrotropin (TSH) are normal. The diagnosis is confirmed by the measurement of absent or low serum levels of TBG, although rare cases may have normal concentrations of TBG with reduced affinity for T_4. No treatment is required, but testing may be indicated in potentially affected family members to avoid the incorrect diagnosis of hypothyroidism in the future. More than 40 different pathogenic variants have been reported in the TBG gene. **Acquired** causes of TBG deficiency are listed in Table 602.1.

TBG excess is a benign X-linked dominant variant that occurs in approximately 1 in 25,000 individuals. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, T_3 is variably elevated, TSH and free T_4 are normal, and T_3 resin uptake is decreased. Elevated serum levels of TBG confirm the diagnosis. Affected neonates have been found to have levels of T_4 as high as 95 μg/dL, which decrease to 20-30 μg/dL after 2-3 weeks. Affected patients are euthyroid, but family studies may be indicated to alert other affected family members. Acquired causes of TBG excess are listed in Table 602.1.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant variant caused by an abnormal albumin with a markedly increased affinity for T_4. This leads to increased serum concentrations of T_4 (and in some cases T_3) that can be mistaken for thyrotoxicosis. However, levels of free T_4, free T_3, and TSH are normal, and affected patients are euthyroid.

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Table 602.1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Nephrotic syndrome	Heroin, methadone
Protein-losing enteropathy	Mitotane
Nicotinic acid	5-Fluorouracil
L-Asparaginase	Perphenazine

Chapter 603

Hypothyroidism

Ari J. Wassner and Jessica R. Smith

Hypothyroidism is a state of insufficient thyroid hormone action at the tissue level. Hypothyroidism most often results from deficient production of thyroid hormone caused either by a defect in the thyroid gland itself (primary hypothyroidism) or by reduced thyrotropin (TSH) stimulation (central or secondary hypothyroidism; Table 603.1). Hypothyroidism may be present from birth (congenital) or may be acquired, although some acquired cases are due to congenital defects in which the onset of hypothyroidism is delayed.

CONGENITAL HYPOTHYROIDISM

Most cases of congenital hypothyroidism are caused by abnormal formation of the thyroid gland **(thyroid dysgenesis)**, and ~30% of cases are due to inborn errors of thyroid hormone synthesis **(dyshormonogenesis)** or other causes. Most infants with congenital hypothyroidism are detected by newborn screening programs in the first week after birth, before significant clinical signs or symptoms develop. In regions without newborn screening, severely affected infants usually manifest features within the first week of life, but in infants with milder hypothyroidism, the clinical manifestations may not be evident for weeks or months.

Epidemiology

The incidence of congenital hypothyroidism was initially reported to be 1 in 4,000 infants based on the earliest established neonatal screening programs. The incidence of diagnosis has increased to about 1 in 2,000, primarily because more stringent screening algorithms have resulted in the detection of milder cases of hypothyroidism, mostly in patients with a eutopic thyroid gland.

Etiology

See Table 603.1.

Primary Hypothyroidism

Thyroid Dysgenesis. Thyroid dysgenesis is the most common cause of permanent congenital hypothyroidism, accounting for 80–85% of cases. In approximately one third of cases of dysgenesis, no thyroid tissue is present **(agenesis)**. In the other two thirds of infants, rudiments of thyroid tissue are present, either in the normal position **(hypoplasia)** or in an **ectopic** location along the embryologic path of descent of the thyroid from the base of the tongue (lingual thyroid) to the normal position. Thyroid dysgenesis occurs twice as common in females as in males.

The cause of thyroid dysgenesis is largely unknown. The condition is usually sporadic, but familial cases have been reported rarely. Thyroid developmental anomalies, such as thyroglossal duct cysts and thyroid hemiagenesis, are present in 8–10% of first-degree relatives of infants with thyroid dysgenesis. However, most thyroid dysgenesis is unlikely to be genetic given the high degree of discordance among monozygotic twins.

A small minority (2–5%) of thyroid dysgenesis is caused by genetic defects in one of several transcription factors essential for thyroid morphogenesis and differentiation, including NKX2.1 (formerly TTF1), FOXE1 (formerly TTF2), and PAX8. NKX2.1 is expressed in the thyroid, lung, and central nervous system, and recessive pathogenic variants in *NKX2-1* cause thyroid dysgenesis, respiratory distress, and neurologic problems (chorea and ataxia) **(brain-lung-thyroid syndrome)**. Recessive pathogenic variants in *FOXE1* cause thyroid dysgenesis, spiky or curly hair, cleft palate, and sometimes choanal atresia and bifid epiglottis **(Bamforth-Lazarus syndrome)**. PAX8 is expressed in the thyroid and kidney, and dominant *PAX8* variants are associated with thyroid dysgenesis and kidney and ureteral malformations.

Chapter 602

Disorders of Thyroxine-Binding Globulin

Ari J. Wassner and Jessica R. Smith

Approximately 70% of circulating thyroxine (T_4) and 50% of triiodothyronine (T_3) are bound to thyroxine-binding globulin (TBG), and most of the remainder is bound to albumin and prealbumin (also called *transthyretin*). Only the unbound (free) fractions of these hormones, comprising 0.03% of serum T_4 and 0.3% of T_3, can exert biologic activity. Because regulation of the hypothalamic-pituitary-thyroid axis is mediated by the concentrations of free thyroid hormones, abnormalities of thyroid hormone binding tend to alter concentrations of total, but not free, thyroid hormones. *Therefore abnormalities in levels of TBG are not associated with clinical disease and do not require treatment.* They are usually discovered as an incidental finding of abnormally low or high levels of T_4 and may be a source of confusion in the diagnosis of hypothyroidism or hyperthyroidism.

Congenital TBG deficiency is an X-linked recessive trait that occurs in 1 in 1,700 male newborns. It is most often discovered through screening programs for neonatal hypothyroidism that measure levels of T_4 as the primary screening test. Affected males have low levels of total T_4 (usually <4 μg/dL) and elevated T_3 resin uptake, but levels of free T_4 and thyrotropin (TSH) are normal. The diagnosis is confirmed by the measurement of absent or low serum levels of TBG, although rare cases may have normal concentrations of TBG with reduced affinity for T_4. No treatment is required, but testing may be indicated in potentially affected family members to avoid the incorrect diagnosis of hypothyroidism in the future. More than 40 different pathogenic variants have been reported in the TBG gene. **Acquired** causes of TBG deficiency are listed in Table 602.1.

TBG excess is a benign X-linked dominant variant that occurs in approximately 1 in 25,000 individuals. It has been recognized primarily in adults, but newborn screening programs may uncover the condition in the neonate. The level of T_4 is elevated, T_3 is variably elevated, TSH and free T_4 are normal, and T_3 resin uptake is decreased. Elevated serum levels of TBG confirm the diagnosis. Affected neonates have been found to have levels of T_4 as high as 95 μg/dL, which decrease to 20-30 μg/dL after 2-3 weeks. Affected patients are euthyroid, but family studies may be indicated to alert other affected family members. Acquired causes of TBG excess are listed in Table 602.1.

Familial dysalbuminemic hyperthyroxinemia is an autosomal dominant variant caused by an abnormal albumin with a markedly increased affinity for T_4. This leads to increased serum concentrations of T_4 (and in some cases T_3) that can be mistaken for thyrotoxicosis. However, levels of free T_4, free T_3, and TSH are normal, and affected patients are euthyroid.

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Table 602.1 Causes of Acquired Thyroxine-Binding Globulin (TBG) Deficiency and Excess

DECREASED TBG	INCREASED TBG
Androgens	Estrogens
Anabolic steroids	Selective estrogen receptor modulators
Glucocorticoids	Pregnancy
Hepatocellular disease	Hepatitis
Severe illness	Porphyria
Nephrotic syndrome	Heroin, methadone
Protein-losing enteropathy	Mitotane
Nicotinic acid	5-Fluorouracil
L-Asparaginase	Perphenazine

Chapter 603

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Table 603.1 Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM

Defect of thyroid development (dysgenesis)
- Agenesis
- Hypoplasia
- Ectopia

Defects in thyrotropin (TSH) responsiveness
- TSH receptor–blocking antibodies
- Pathogenic variants in TSH receptor *(TSHR)*
- Defects in Gsα *(GNAS)*—pseudohypoparathyroidism

Defect in thyroid hormone synthesis (dyshormonogenesis)
- Defective iodide uptake into follicular cell: sodium–iodide symporter *(NIS)*
- Defective iodide transport from follicular cell into colloid: Pendred syndrome *(SLC26A4)*
- Iodide organification defects: thyroperoxidase *(TPO)*, dual oxidase 2 (*DUOX2*), dual oxidase maturation factor 2 *(DUOXA2)*
- Thyroglobulin synthesis defect: thyroglobulin (TG)
- Deiodination defect: iodotyrosine deiodinase (IYD)
- Thyroid hormone transport defect: monocarboxylate transporter 8 *(SLC16A2)*—X-linked

Iodine deficiency (endemic goiter)

Iodine excess

Maternal medications
- Iodides, amiodarone
- Methimazole, propylthiouracil
- Radioactive iodine (^{131}I)

CENTRAL (SECONDARY) HYPOTHYROIDISM

Isolated TSH deficiency
- Pathogenic variant in TSH β-subunit (TSHβ)—depending on variant measured TSH level may be low, normal, or elevated
- Pathogenic variant in TRH receptor *(TRHR)*
- Pathogenic variant in *IGSF1*—X-linked central hypothyroidism and macroorchidism (prolactin deficiency and variable GH deficiency)
- Pathogenic variant in other genes: *TBL1X, IRS4*

Multiple pituitary hormone deficiencies
- Pathogenic variant in *POU1F1*—deficiency of TSH, GH, and prolactin
- Pathogenic variant in *PROP1*—deficiency of TSH, GH, LH, FSH, prolactin, and variably ACTH
- Pathogenic variant in *HESX1*—variable deficiencies of TSH, GH, LH, FSH, prolactin, and ACTH
- Pathogenic variants in other genes: *OTX2, LHX3, LHX4, SOX3, FGF8, FGFR1, GLI2, LEPR*

ACTH, Adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone.

Inactivating variants in the TSH receptor *(TSHR)* have been described in patients with congenital hypothyroidism, including thyroid dysgenesis or hypoplasia. *TSHR* variants may be homozygous or heterozygous with or without a concurrent change in another congenital hypothyroidism gene (such as *DUOX2* or *TG*). Infants with a severe TSHR defect have elevated TSH levels and are detected by newborn screening, whereas patients with a mild defect may remain euthyroid without treatment.

Congenital hypothyroidism can occur in infants with **pseudohypoparathyroidism** type 1a. These patients have somatic inactivating variants of the G-protein stimulatory α-subunit $G_s\alpha$ (GNAS), leading to impaired signaling of the TSH receptor (see Chapter 612).

Defects in Thyroid Hormone Synthesis (Dyshormonogenesis). A variety of defects in thyroid hormone biosynthesis account for 15% of cases of permanent congenital hypothyroidism detected by neonatal screening programs (1 in 30,000-50,000 live births). Because increased TSH stimulation has a trophic effect on thyroid follicular cells, a **goiter** is often present. When the synthetic defect is incomplete, the onset of hypothyroidism may be delayed for months or years.

Defective Iodide Transport. Rare defects in iodide uptake are caused by pathogenic variants in the sodium-iodide symporter (NIS) responsible for concentrating iodide in the thyroid gland. In contrast to other defects of thyroid hormone synthesis, uptake of radioiodine and pertechnetate is low, as in cases of thyroid dysgenesis. However, impaired iodide transport may be suggested by the absence of normal salivary gland iodine uptake on scintigraphy. A reduced saliva:serum ratio of ^{123}I supports the diagnosis, which can be confirmed by genetic testing of *NIS*. This condition may respond to large doses of potassium iodide, but treatment with levothyroxine is more reliable and preferable.

Pendred syndrome is a clinical syndrome consisting of sensorineural deafness and goiter. This syndrome is caused by a pathogenic variant in the chloride-iodide transport protein pendrin *(SLC26A4)* expressed in the thyroid gland and the cochlea. Pendrin allows the transport of iodide across the apical membrane of the thyroid follicular cell into the colloid, where it undergoes organification and incorporation into the tyrosine residues on thyroglobulin. Patients with a variant in *SLC26A4* have impaired iodide organification and a positive perchlorate discharge test. Pathogenic variants in pendrin are a relatively common genetic cause of sensorineural deafness, but some patients diagnosed based on their hearing disorder have no goiter or thyroid dysfunction. This finding has fueled speculation that pendrin is not the sole apical iodine transporter in the thyroid, but no other specific transporter has been confirmed to date.

Defects of Iodine Organification. Defects of iodine organification are the most common type of thyroid hormone synthetic defect. After the thyroid takes up iodide, it is rapidly oxidized and incorporated into tyrosine residues on thyroglobulin. These reactions are catalyzed by the key enzyme thyroperoxidase (TPO) and require H_2O_2 generated locally by the dual oxidase 2 system (DUOX2 and DUOXA2). Defects can occur in any of these components of organification, and there is considerable clinical and biochemical heterogeneity. In the Dutch neonatal screening program, a complete organification defect was present in 1 in 60,000 live births, but the prevalence in other areas is unknown. A characteristic finding of organification defects is a marked discharge of thyroid radioactivity when perchlorate or thiocyanate is administered 2 hours after a test dose of radioiodine (perchlorate discharge of 40–90% of radioiodine compared with <10% in normal individuals). Numerous pathogenic variants in *TPO* have been reported in children with congenital hypothyroidism.

Pathogenic variants in *DUOX2* can cause permanent or transient congenital hypothyroidism. Previously, it was thought that monoallelic *DUOX2* variants cause transient disease and biallelic variants cause permanent disease, but the reverse has been observed in some cases, and this relationship remains variable and unclear. *DUOX2* variants have been reported in 15–40% of patients with apparent dyshormonogenesis, with pathogenic variant rates as high as 50–60% in studies from China and South Korea. Dual oxidase maturation factor 2 (DUOXA2) is required to express DUOX2 enzymatic activity, and recessive variants in *DUOXA2* are a rare cause of congenital hypothyroidism.

Defects of Thyroglobulin Synthesis. Defects of thyroglobulin synthesis are characterized by congenital hypothyroidism with goiter and absent or low levels of circulating thyroglobulin. More than 40 different pathogenic variants in the thyroglobulin gene *(TG)* have been described.

Defects in Deiodination. Monoiodotyrosine and diiodotyrosine normally are released from thyroglobulin along with thyroxine (T_4) and triiodothyronine (T_3). The *IYD* gene (formerly *DEHAL1*) encodes the thyroidal enzyme iodotyrosine deiodinase, which deiodinates these intermediates so that the liberated iodide is recycled into thyroid hormone synthesis. In patients with rare variants in *IYD,* urinary excretion of monoiodotyrosine and diiodotyrosine rapidly causes severe iodine deficiency, leading to hypothyroidism and goiter that may present soon after birth or may be delayed.

Defects in Thyroid Hormone Transport. Passage of thyroid hormone into cells is facilitated by specific plasma membrane transporters. Pathogenic variants in the transporter MCT8 *(SLC16A2),* located on the X chromosome, impair the movement of T_4 and T_3 into cells. This leads to severe neurologic manifestations, including profound developmental delay, reduced muscle mass, dysarthria,

athetoid movements, and hypotonia that evolves to spastic paraplegia **(Allan-Herndon-Dudley syndrome)**. This syndrome is also characterized by low serum T_4 levels, normal or mildly elevated serum TSH levels, and elevated serum T_3 levels. Treatment with thyroid hormone analogs that do not require MCT8 for transmembrane transport can improve hypermetabolism in this disorder but has little effect on the neurologic phenotype.

Thyrotropin Receptor–Blocking Antibodies. Maternal TSHR–blocking antibodies (TRBAbs) cause about 2% of cases of congenital hypothyroidism detected by neonatal screening programs (1 in 50,000-100,000 infants). Transplacentally acquired maternal TRBAbs inhibit the binding of TSH to its receptor in the neonate. This condition should be suspected whenever there is a history of maternal autoimmune thyroid disease, including autoimmune thyroiditis or Graves disease, maternal hypothyroidism, or transient congenital hypothyroidism in previous siblings. However, TRBAbs can occur in the absence of any maternal history. When suspected, levels of TRBAb (measured as thyrotropin-binding inhibitory immunoglobulin [TBII]) should be measured in the mother during pregnancy or after birth in the neonate. Affected infants and their mothers also can have TSHR-stimulating antibodies and TPO antibodies. Ultrasonography typically demonstrates a normally positioned but small thyroid gland; however, thyroid tissue often will not be detected by scintigraphy because the blockade of TSHR function suppresses thyroidal iodine uptake. Serum thyroglobulin levels are low for the same reason. Treatment with levothyroxine is required initially, but remission of hypothyroidism occurs in approximately 3-6 months once the TRBAbs are cleared from the infant's circulation. Correct diagnosis of this cause of congenital hypothyroidism prevents unnecessarily protracted treatment and alerts the clinician to possible recurrences in future pregnancies. The prognosis is generally favorable, but developmental delay may occur in patients whose mothers had unsuspected (and untreated) hypothyroidism caused by TRBAbs during pregnancy.

Radioiodine Administration. Neonatal hypothyroidism can occur when radioiodine is administered to a mother during (a usually unrecognized) pregnancy as treatment for Graves disease or thyroid cancer. The fetal thyroid is capable of trapping iodide by 70-75 days of gestation. Therefore a pregnancy test must be performed in any individual capable of pregnancy before ^{131}I is given, regardless of menstrual history or reported history of contraception. Administration of radioactive iodine to lactating individuals is also contraindicated because it is excreted in breast milk.

Iodine Exposure. Congenital hypothyroidism can result from fetal exposure to excessive iodine. Perinatal exposure can occur from iodine-based antiseptic used to prepare the skin for cesarean section or to paint the cervix before delivery. In the neonate, especially in those of low birthweight (LBW), topical iodine-containing antiseptics used in nurseries or perioperatively can cause transient hypothyroidism, which newborn screening tests may detect. In older children, excess iodine may be present in proprietary preparations used to treat asthma or in amiodarone, an antiarrhythmic drug with high iodine content. In most of these instances, a goiter is present (see Chapter 605). Hypothyroidism has also been reported in breastfed infants born to mothers who consume large amounts of iodine daily (up to 12 mg) in nutritional supplements or large quantities of iodine-rich seaweed. Iodine-induced hypothyroidism is transient once the exposure is discontinued and therefore is important to distinguish from other forms of congenital hypothyroidism.

Iodine Deficiency (Endemic Goiter). See Chapter 605.3.

Iodine deficiency or endemic goiter is the most common cause of congenital hypothyroidism worldwide. The recommended iodine intake in adults is 150 μg daily, increasing to 220 μg daily during pregnancy to allow for fetal iodine requirements. Despite efforts at universal salt iodization, in many countries economic, political, and practical obstacles continue to prevent the realization of this goal. Although the U.S. population is generally iodine sufficient, approximately 15% of women of reproductive age are iodine deficient. Borderline iodine deficiency is more likely to cause problems in preterm infants, who depend on a maternal source of iodine for normal thyroid hormone production and often receive insufficient dietary iodine from standard preterm infant formulas or parenteral nutrition that is low in iodine.

Central (Secondary) Hypothyroidism

Thyrotropin (TSH) Deficiency. Central hypothyroidism caused by TSH deficiency can occur in any condition associated with developmental defects of the pituitary or hypothalamus (see Chapter 595). Central hypothyroidism occurs in 1 in 16,000-30,000 infants. However, neonatal screening does not detect many cases, mainly because many screening programs are designed to detect only primary hypothyroidism by measuring neonatal TSH. The majority (75%) of infants with central hypothyroidism have additional pituitary hormone deficiencies and may present with hypoglycemia, persistent jaundice, micropenis or cryptorchidism (in males), and midline defects such as midline cleft lip or palate or midface hypoplasia.

Congenital TSH deficiency may be caused by pathogenic variants in genes encoding transcription factors essential to pituitary development or thyrotroph cell differentiation. *POU1F1* variants cause deficiency of TSH, growth hormone, and prolactin. Patients with *PROP1* variants also have deficiency of TSH, growth hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and variable deficiency of adrenocorticotropic hormone. *HESX1* pathogenic variants are associated with TSH, growth hormone, prolactin, and adrenocorticotropic hormone deficiencies and are found in some patients with optic nerve hypoplasia (septo-optic dysplasia syndrome; see Chapter 631). Variants in multiple other genes involved in pituitary development can cause central hypothyroidism (Table 603.1).

Isolated congenital deficiency of TSH is rare. The most common genetic cause is a pathogenic variant in *IGSF1,* which results in an X-linked syndrome of congenital central hypothyroidism and macroorchidism. The mechanism remains unclear, but IGSF1 deficiency may impair TRH receptor signaling in pituitary thyrotrophs. Prolactin deficiency is usually present, and some patients also have growth hormone deficiency. Central hypothyroidism occurs in about 10% of female carriers of IGSF1 deficiency. Patients with pathogenic variants in the gene encoding the TSH β-subunit *(TSHB)* have central hypothyroidism with very low TSH levels, although in some cases, TSH levels are normal or even elevated. In other cases, levels of the TSH α-subunit are elevated. Variants in *TRHR,* which encodes the TRH receptor, are a rare cause of congenital central hypothyroidism. In this condition, both TSH and prolactin fail to respond to TRH stimulation.

Thyroid Function in Preterm and Low Birthweight Infants

Postnatal thyroid function in preterm and LBW infants is qualitatively similar but quantitatively reduced compared with term infants. The cord blood T_4 concentration is decreased in proportion to gestational age and birthweight. The postnatal TSH surge is reduced, and very premature or very LBW infants experience a decrease in serum T_4 in the first week of life, in contrast to term infants in whom T_4 increases during this time. Serum T_4 gradually increases to the range observed in term infants by about 6 weeks of life. However, serum free T_4 concentrations are less affected than total T_4, and free T_4 levels may be normal when measured by the gold standard technique of equilibrium dialysis. Preterm and LBW infants also have a higher incidence of delayed TSH elevation and apparent transient primary hypothyroidism. Mechanisms underlying these changes in thyroid function in preterm and LBW infants may include immaturity of the hypothalamic-pituitary-thyroid axis, loss of the maternal contribution of thyroid hormone normally present in the third trimester, severe illness and complications of prematurity, and exposure to medications that can affect thyroid function (e.g., dopamine and glucocorticoids).

Clinical Manifestations

Before neonatal screening programs, congenital hypothyroidism was rarely recognized in the newborn because most affected infants are asymptomatic at birth, even if there is complete agenesis of the thyroid gland. This is because of transplacental passage of maternal T_4, which provides fetal levels that are approximately one-third normal at

birth. Because symptoms are usually not present at birth, the clinician depends on neonatal screening tests to diagnose congenital hypothyroidism. However, some infants escape newborn screening, and laboratory errors occur, so pediatricians must be alert for symptoms and signs of hypothyroidism if they develop. Birth weight and length are normal, but head size may be slightly increased because of myxedema of the brain. The anterior and posterior fontanels are open widely, and the presence of this sign at birth may be a clue to early recognition of congenital hypothyroidism (only 3% of normal newborns have a posterior fontanel wider than 0.5 cm). Prolonged jaundice (indirect hyperbilirubinemia) may be present because of delayed maturation of hepatic glucuronide conjugation. Affected infants cry little, sleep much, have poor appetites, and are generally sluggish. Feeding difficulties, especially sluggishness, lack of interest, somnolence, and choking spells during nursing, may be present during the first month of life. Respiratory difficulties, partly caused by macroglossia, include apneic episodes, noisy respirations, and nasal obstruction. There may be constipation that does not respond to treatment. The abdomen is large, and an umbilical hernia is often present. The temperature may be subnormal (often <35°C/95°F), and the skin may be cold and mottled, particularly on the extremities. Edema of the genitals and extremities may be present. The pulse is slow, and heart murmurs, cardiomegaly, and asymptomatic pericardial effusion are common. Macrocytic anemia is often present. Because symptoms appear gradually and may be nonspecific, the clinical diagnosis of neonatal hypothyroidism is often delayed.

Approximately 10% of infants with congenital hypothyroidism have associated congenital anomalies. Cardiac anomalies are most common, but anomalies of the nervous system and eye have also been reported. Infants with congenital hypothyroidism may have associated hearing loss. Pathogenic variants in specific genes involved in thyroid gland development result in congenital hypothyroidism with other syndromic features (Table 603.2).

If congenital hypothyroidism goes undetected and untreated, the clinical manifestations progress. Delay of physical and mental development becomes more severe over time, and by 3-6 months of age, the clinical picture is fully developed (Fig. 603.1). When deficiency of thyroid hormone is only partial, the symptoms may be milder and their onset delayed. Although breast milk contains significant amounts of thyroid hormones, particularly T_3, this is inadequate to protect the breastfed infant from the effects of congenital hypothyroidism.

In the patient with untreated congenital hypothyroidism, growth is stunted, extremities are short, and head size is normal or increased. The anterior fontanel is large, and the posterior fontanel may remain open. The eyes appear far apart, and the bridge of the broad nose is depressed. The palpebral fissures are narrow, and the eyelids are swollen. The mouth is kept open, and the thick, broad tongue protrudes. Dentition is delayed. The neck is short and thick, and there may be fat deposits above the clavicles and between the neck and shoulders. The hands are broad, and the fingers are short. The skin is dry and scaly, and there is little perspiration. Myxedema occurs mainly in the skin of the eyelids, the back of the hands, and the external genitalia. The skin shows general pallor with a sallow complexion. Carotenemia can cause a yellow discoloration of the skin, but the sclerae remain white. The scalp is thickened, and the hair is coarse, brittle, and scanty. The hairline reaches far down on the forehead, which usually appears wrinkled, especially when the infant cries.

Development is usually delayed. Hypothyroid infants appear lethargic and are late in acquiring gross and fine motor skills. The voice is hoarse, and they do not learn to talk. The degree of physical and intellectual delay increases with age. Sexual maturation may be delayed or even absent. The muscles are usually hypotonic, but in rare instances, generalized muscular pseudohypertrophy occurs **(Kocher-Debré-Sémélaigne syndrome)**. Affected older children can have an athletic appearance because of pseudohypertrophy, particularly in the calf muscles. Its pathogenesis is unknown; nonspecific histochemical and ultrastructural changes seen on muscle biopsy return to normal with treatment.

Some infants with mild congenital hypothyroidism have normal thyroid function at birth and are not identified by newborn screening programs. In particular, some children with ectopic thyroid tissue produce adequate amounts of thyroid hormone for some time (even years) until the abnormal thyroid tissue fails. Affected children come to clinical attention because of a growing mass at the base of the tongue or in the midline of the neck, often at the level of the hyoid. Occasionally, thyroid ectopy is associated with **thyroglossal duct cysts**. Surgical removal of ectopic thyroid tissue from a euthyroid patient usually results in hypothyroidism because most such patients have no other thyroid tissue.

Laboratory Findings

In countries where newborn screening is performed, this is the most important method for identifying infants with congenital hypothyroidism. Blood obtained by heelprick between 1 and 5 days of life is placed on a filter paper card and sent to a central screening laboratory. Most

Table 603.2 Genes and Thyroid Development

GENE	THYROID PHENOTYPE	OTHER FEATURES
FOXE1	Athyreosis	Cleft palate, choanal atresia, kinky hair, bifid epiglottis
NKX2-1	Athyreosis to normal gland	Respiratory distress syndrome, developmental delays/hypotonia, ataxia/choreoathetosis
PAX8	Athyreosis to normal gland	Cysts within thyroid remnants, kidney and urinary tract malformations
GLIS3	Athyreosis to normal gland	Congenital glaucoma; deafness; liver/kidney and pancreatic abnormalities
TSHR	Athyreosis to normal gland	None
NKX2-5	Athyreosis, ectopy	Cardiac defects

From Kim G, Nandi-Munshi D, Diblasi CC. Disorders of the thyroid gland. In: Gleason CA, Juul SE, eds. *Avery's Diseases of the Newborn*, 10th ed. Philadelphia: Elsevier; 2018, Table 98.3, p. 1396.

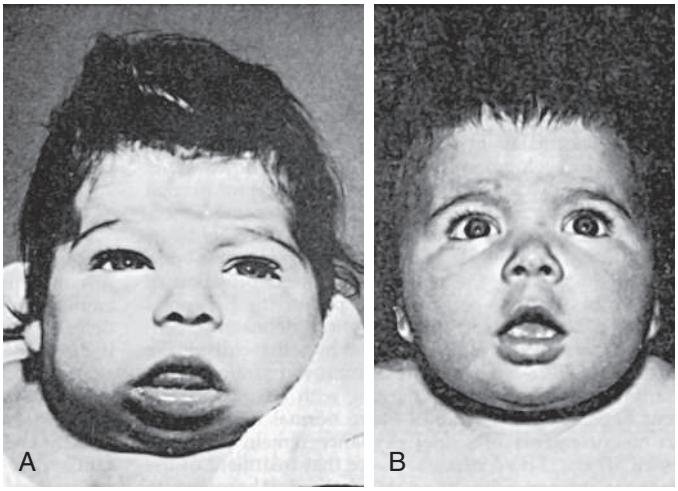

Fig. 603.1 Congenital hypothyroidism in an infant 6 mo of age. The infant ate poorly in the neonatal period and was constipated. She had persistent nasal discharge and a large tongue, was very lethargic, and had no social smile and no head control. **A,** Notice the puffy face, dull expression, and hirsute forehead. Tests revealed a negligible uptake of radioiodine. Osseous development was that of a newborn. **B,** Four months after treatment, note decreased face puffiness, decreased hirsutism of the forehead, and the alert appearance.

screening programs measure the level of TSH, which detects infants with primary hypothyroidism, including some with milder disease in whom TSH is elevated but T_4 is normal. However, this approach may not detect rarer disorders such as central hypothyroidism or primary congenital hypothyroidism with delayed TSH elevation. Some screening programs begin by measuring levels of T_4, followed by reflex measurement of TSH when the T_4 is low. This approach identifies infants with primary hypothyroidism, some with central hypothyroidism or delayed TSH elevation, and infants with thyroxine-binding globulin deficiency (a benign variant). All newborn screening results should be interpreted based on age-specific reference ranges, particularly in the first week of life (Table 603.3). Regardless of the approach used for screening, some infants escape detection because of technical or human errors, and clinicians must remain vigilant for clinical manifestations of hypothyroidism.

Several groups of patients deserve vigilance for congenital hypothyroidism. Infants with trisomy 21 or cardiac defects have an increased risk of congenital hypothyroidism. Monozygotic twins are usually *discordant* for congenital hypothyroidism. However, if twins are monochorionic, fetal hypothyroidism in the affected twin may be compensated by the normal twin through their shared fetal circulation. In such cases, the affected twin may go undetected on newborn screening in the first days of life and present later with untreated hypothyroidism. Preterm and LBW neonates have an increased incidence of congenital hypothyroidism and are more likely to have delayed TSH elevation that may be missed on initial screening. Therefore in all of these groups of infants, many newborn screening programs perform a routine second test 2-4 weeks after birth.

Patients with congenital hypothyroidism have low serum levels of T_4 and free T_4. Serum levels of T_3 are often normal and are not helpful for diagnosis. If primary hypothyroidism is present, levels of TSH are elevated, often to >100 mU/L in severe cases. Serum levels of thyroglobulin are usually low in infants with thyroid agenesis, defects of the TSH receptor (including *TSHR* pathogenic variants and TRBAb), or defects in the synthesis or secretion of thyroglobulin itself. In contrast, thyroglobulin levels are usually elevated in patients with thyroid ectopy and other defects of thyroid hormone synthesis, but there is a wide overlap of ranges.

Delay of osseous development can be shown radiographically at birth in approximately 60% of congenitally hypothyroid infants and indicates some deficiency of thyroid hormone during intrauterine life. The distal femoral and proximal tibial epiphyses, normally present at birth, are often absent (Fig. 603.2A). In untreated patients, the discrepancy between chronologic age and osseous development increases over time. The epiphyses often have multiple foci of ossification (epiphyseal dysgenesis; see Fig. 603.2B). Deformity (beaking) of the 12th thoracic or 1st or 2nd lumbar vertebra is common. X-rays of the skull show large fontanels and wide sutures, and intersutural (wormian) bones are common. The sella turcica may be enlarged and round, and in rare instances, there may be bony erosion and thinning. Formation and eruption of teeth can be delayed. Cardiac enlargement or pericardial effusion may be present.

Scintigraphy can help define the underlying cause in infants with congenital hypothyroidism, but treatment should not be delayed to obtain such imaging. ^{123}I–sodium iodide is superior to ^{99m}Tc–sodium pertechnetate for this purpose. Scintigraphy will demonstrate an ectopic thyroid gland, but the absence of uptake in disorders of the TSH receptor (including TRBAb) or NIS may be mistaken for thyroid agenesis. Ultrasound of the thyroid can document the presence or absence of an anatomically normal gland, but it can miss some ectopic glands that are detectable by scintigraphy. Demonstration of ectopic thyroid tissue or the absence of thyroid tissue in its normal location is diagnostic of thyroid dysgenesis and establishes the need for lifelong treatment. A normally located thyroid gland with normal or increased uptake indicates a defect in thyroid hormone synthesis. Although extensive evaluation can be performed to elucidate the precise nature of the synthetic defect, this rarely affects clinical management and is unnecessary in most cases. Similarly, genetic testing may reveal potentially relevant variants in 60% or more of patients with defects of thyroid hormone synthesis. However, such testing may be costly, is not always conclusive, and usually does not alter management.

Treatment

Levothyroxine (L-T_4) given orally is the treatment for congenital hypothyroidism. Although T_3 is the biologically active form of thyroid hormone, 80% of circulating T_3 is derived from deiodination of circulating T_4, and therefore treatment with L-T_4 alone restores normal serum levels of T_4 and T_3. The recommended initial dose of L-T_4 is 10-15 μg/kg/day (37.5-50 μg/day for most term infants), and within this range the starting dose can be adjusted based on the severity of hypothyroidism. Newborns with more severe hypothyroidism, as judged by a serum T_4 <5 μg/dL and/or imaging studies confirming aplasia, should be started at the higher end of the dosage range. Rapid normalization of thyroid function (ideally within 2 weeks) is essential in achieving optimal neurodevelopmental outcomes. Lower doses of L-T_4 (8-10 mcg/kg/day) may be considered for infants with mild hypothyroidism (mildly elevated TSH and normal free T_4).

L-T_4 should be prescribed in tablet form. A liquid L-T_4 preparation has been approved, but optimal dosing may differ slightly from the tablet form. Tablets should be crushed and mixed with a small volume (1-2 mL) of liquid. L-T_4 tablets should not be mixed with soy protein formulas, concentrated iron, or calcium because these can inhibit L-T_4 absorption. Although it is often recommended to administer L-T_4 on an empty stomach and avoid food for 30-60 minutes, this is not practical in an infant. As long as the method of administration is consistent, dosing can be adjusted based on serum thyroid test results to achieve the desired treatment goals. One trial has suggested that brand-name L-T_4 may be superior to generic formulations in children with severe congenital hypothyroidism.

The goals of treatment are to maintain serum TSH in the reference range for age and the serum free T_4 or total T_4 in the upper half of the reference range for age (see Table 603.3). Levels of serum T_4 or free T_4 and TSH should be monitored at recommended intervals (every 1-2 months in the first 6 months of life, and then every 2-4 months between 6 months and 3 years of age). Care should be taken to avoid undertreatment, which has been related to adverse neurodevelopmental outcomes, including decreased intelligence quotient (IQ).

About 35% of infants with congenital hypothyroidism and a normally located thyroid gland have transient disease and do not require lifelong therapy. In patients who might have transient disease, a trial of L-T_4 may be undertaken after 3 years of age for 4 weeks to assess whether the TSH rises significantly, indicating the presence of permanent hypothyroidism. Such a trial is unnecessary in infants with proven thyroid dysgenesis or in those who have previously manifested elevated levels of TSH after 6-12 months of therapy because of poor medication adherence or an inadequate dose of T_4.

Prognosis

Thyroid hormone is critical for normal neurodevelopment, particularly in the early postnatal months. Prompt diagnosis and initiation of adequate treatment of congenital hypothyroidism in the first 2 weeks of life are essential to prevent irreversible brain damage and normal growth and development. In most infants detected by newborn screening, verbal development, psychomotor development, and global IQ scores are similar to unaffected siblings. However, the most severely affected newborns—those with the lowest T_4 levels and most delayed skeletal maturation—may have reduced IQ and other neuropsychologic sequelae such as incoordination, hypotonia or hypertonia, or problems with attention or speech despite early diagnosis and adequate treatment. Psychometric testing can show problems with vocabulary and reading comprehension, arithmetic, and memory. Approximately 10% of children with congenital hypothyroidism have a neurosensory hearing deficit. Outcome studies in adults diagnosed and treated as neonates reveal delayed social development, lower self-esteem, and a lower health-related quality of life. The latter appears to be related to those individuals with lower neurocognitive outcomes and associated congenital malformations.

Delay in diagnosis or treatment, failure to rapidly correct the initial hypothyroidism, inadequate treatment, or poor adherence to treatment

Table 603.3 Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 µg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 µg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 µg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 µg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
First wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infant			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 µg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 µg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 µg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 µg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 µg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 µg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 µg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT_3U), SERUM			
Newborn	26–36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26–35%	×0.01	0.26-0.35 fractional uptake

Continued

Table 603.3 Thyroid Function Tests—cont'd

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA. Reference ranges for laboratory tests and procedures. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 17th ed. Philadelphia: WB Saunders; 2004:2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, et al. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metab*. 2012;97:3170–3178; Free T_3 from Elmlinger MW, Kuhnel W, Lambrecht H-G, et al. Reference intervals from birth to adulthood for serum thyroxine (T_4), triiodothyronine (T_3), free T_3, free T_4, thyroxine binding globulin (TBG), and thyrotropin (TSH). *Clin Chem Lab Med*. 2001;39:973–979.

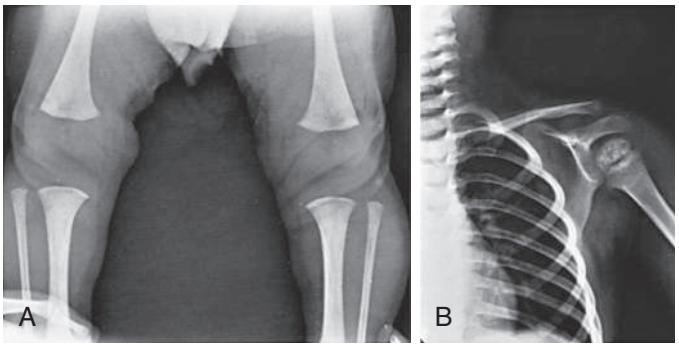

Fig. 603.2 Congenital hypothyroidism. **A,** Absence of distal femoral epiphyses in a 3-mo-old infant who was born at term. This is evidence for onset of the hypothyroid state during fetal life. **B,** Epiphyseal dysgenesis in the head of the humerus in a 9-yr-old girl who had been inadequately treated with thyroid hormone.

in the first 2-3 years of life may result in variable degrees of neurodevelopmental impairment. Without treatment, severely affected infants have profound intellectual disability and growth stunting. When hypothyroidism develops after 2 years of age, the outlook for neurodevelopment is much better even if diagnosis and treatment are delayed, which illustrates the critical dependence of brain development on thyroid hormone in the first year of life.

ACQUIRED HYPOTHYROIDISM

Epidemiology

Hypothyroidism occurs in approximately 0.3% (1 in 333) of school-age children. *Subclinical hypothyroidism* (defined as an elevated TSH with normal T_4 or free T_4) is more common, occurring in approximately 2% of adolescents. Autoimmune thyroiditis is the most common cause of acquired hypothyroidism: 6% of children age 12-19 years have evidence of autoimmune thyroiditis, and females are twice as likely to be affected as males. Although this condition typically arises in adolescence, it may present as early as the first year of life.

Etiology

The most common cause of acquired hypothyroidism (Table 603.4) is **autoimmune thyroiditis** (also called *Hashimoto* or *chronic lymphocytic thyroiditis*; see Chapter 604). Children with trisomy 21, Turner syndrome, Klinefelter syndrome, celiac disease, or type 1 diabetes mellitus are at higher risk for associated autoimmune thyroid disease (see Chapter 604), as are those with **autoimmune polyglandular syndromes** (**APSs**; see Chapter 608). APS type 1 (APS-1) is a rare autosomal recessive disorder caused by pathogenic variants in *AIRE*. It is classically characterized by the triad of mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency. Autoimmune thyroiditis is a less common feature (~10%), as are type 1 diabetes mellitus, primary hypogonadism, pernicious anemia, vitiligo, alopecia, nephritis, hepatitis, and gastrointestinal dysfunction. APS type 2 (APS-2) is far more common than APS-1, and its pathogenesis remains an obscure combination of genetic and environmental factors. APS-2 may consist of any combination of autoimmune thyroiditis (~70%), type 1 diabetes mellitus, celiac disease, or less common manifestations such as primary adrenal insufficiency, primary hypogonadism, pernicious anemia, and vitiligo. Patients with any of these other autoimmune conditions are at increased risk of developing hypothyroidism. For example, about 20% of children with **type 1 diabetes mellitus** develop thyroid autoantibodies and about 5% become hypothyroid.

In children with **trisomy 21**, thyroid autoantibodies develop in approximately 30%, and subclinical or overt hypothyroidism occurs in approximately 15–20%. In females with **Turner syndrome**, thyroid autoantibodies

Table 603.4 Etiologic Classification of Acquired Hypothyroidism

- Autoimmune
  - Autoimmune thyroiditis (Hashimoto thyroiditis)
  - Autoimmune polyglandular syndromes types 1 and 2 (APS-1, APS-2)
  - IPEX
  - Celiac disease
- Drug-induced
  - Excess iodide: amiodarone, nutritional supplements, expectorants
  - Anticonvulsants: oxcarbazepine, phenytoin, phenobarbital, valproate
  - Antithyroid drugs: methimazole, propylthiouracil
  - Miscellaneous: lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, aminoglutethimide, dopamine, amiodarone, tetracycline, ipilimumab, nivolumab
- Iatrogenic
  - Irradiation (e.g., cancer therapy, bone marrow transplant)
  - Radioactive iodine (^{131}I)
  - Thyroidectomy
- Systemic infiltrative disease
  - Cystinosis
  - Langerhans cell histiocytosis
- Consumptive: inactivation of thyroid hormone by large liver hemangiomas (type 3 deiodinase)
- Decreased sensitivity to thyroid hormone (*MCT8, SEC16A2, THRA, THRB* pathogenic variants)
- Hypothalamic-pituitary disease (often with multiple pituitary hormone deficiencies)
  - Central nervous system tumors (e.g., craniopharyngioma)
  - Meningoencephalitis
  - Cranial irradiation
  - Head trauma
  - Langerhans cell histiocytosis

IPEX, Immunodysregulation polyendocrinopathy X-linked.

develop in approximately 40%, and subclinical or overt hypothyroidism occurs in approximately 15–30%, rising with increasing age. Additional autoimmune conditions with an increased risk of hypothyroidism include immune dysregulation–polyendocrinopathy–enteropathy–X-linked syndrome (IPEX) and IPEX-like disorders, immunoglobulin G_4–related diseases, Sjögren syndrome, and multiple sclerosis. **Williams syndrome** is associated with subclinical hypothyroidism, but this does not appear to be autoimmune, and thyroid autoantibodies are absent.

Medications can cause acquired hypothyroidism. Some medications containing iodine (e.g., expectorants or nutritional supplements) may cause hypothyroidism through the Wolff-Chaikoff effect (see Chapter 605). Amiodarone, a drug used for cardiac arrhythmias and consisting of 37% iodine by weight, causes hypothyroidism in approximately 20–30% of treated children. Children treated with amiodarone should have serial monitoring of thyroid function.

Anticonvulsants, including phenytoin, phenobarbital, and valproate, may cause thyroid dysfunction, usually in the form of subclinical hypothyroidism. In some cases, this is because of their effect of stimulating hepatic cytochrome P450 metabolism and excretion of T_4. The anticonvulsant oxcarbazepine can cause central (secondary) hypothyroidism. Hypothyroidism can be caused by overtreatment with antithyroid drugs (methimazole or propylthiouracil) for Graves disease. Additional drugs that can produce hypothyroidism include lithium, rifampin, tyrosine kinase inhibitors, interferon-α, stavudine, thalidomide, and aminoglutethimide.

Children who receive **therapeutic irradiation**, such as for Hodgkin disease or other head and neck malignancies or before bone marrow transplantation, are at risk for thyroid damage and hypothyroidism. Approximately 30% of such children acquire elevated TSH levels within a year after therapy, and another 15–20% progress to hypothyroidism within 5-7 years. **Radioactive iodine** ablative treatment or **thyroidectomy** for Graves disease or thyroid cancer results in iatrogenic hypothyroidism. Thyroid tissue in a thyroglossal duct cyst may constitute the only source of thyroid hormone, and in this case, excision of the cyst results in hypothyroidism. Ultrasonographic examination or a radionuclide scan before surgery is indicated in these patients.

Children with **nephropathic cystinosis,** a disorder characterized by intralysosomal storage of cystine in body tissues, acquire impaired thyroid function. Hypothyroidism is usually subclinical but may be overt, and periodic assessment of TSH levels is indicated. By 13 years of age, two thirds of these patients require L-T_4 replacement.

Histiocytic infiltration of the thyroid in children with **Langerhans cell histiocytosis** (see Chapter 556.1) can result in hypothyroidism. Children with chronic **hepatitis C infection** are at risk for subclinical hypothyroidism that does not appear to be autoimmune.

Consumptive hypothyroidism can occur in children with large hemangiomas of the liver. These tumors may express massive amounts of the enzyme type 3 deiodinase, which inactivates T_4 and T_3, respectively, to the inert metabolites reverse T_3 and diiodothyronine (T_2). Hypothyroidism occurs when increased thyroidal secretion of thyroid hormones is insufficient to compensate for their rapid inactivation.

Some patients with mild forms of congenital hypothyroidism (thyroid dysgenesis or genetic defects in thyroid hormone synthesis) do not develop clinical manifestations until childhood. Although these conditions are often detected by newborn screening, very mild defects can escape detection and present later with apparently acquired hypothyroidism.

Any **hypothalamic** or **pituitary** disease can cause acquired central hypothyroidism (see Chapter 595). TSH deficiency may result from a hypothalamic-pituitary tumor (craniopharyngioma is most common in children) or from treatment for a tumor. Central hypothyroidism may develop in up to 10% of children receiving craniospinal irradiation. Other causes include head trauma or infiltrative diseases affecting the pituitary gland, such as Langerhans cell histiocytosis.

Clinical Manifestations

Slowing of growth is usually the first clinical manifestation of acquired hypothyroidism, but this sign often goes unrecognized (Figs. 603.3 and 603.4). Goiter is a common presenting feature of primary hypothyroidism. In autoimmune thyroiditis, the thyroid is typically nontender

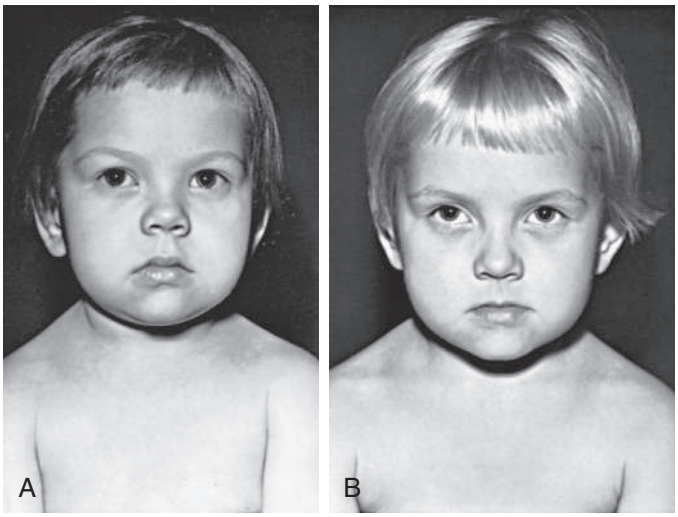

Fig. 603.3 **A,** Acquired hypothyroidism in a 6-yr-old female. She was treated with a wide variety of hematinics for refractory anemia for 3 years. She had almost complete cessation of growth, constipation, and sluggishness for 3 years. The height age was 3 years; the bone age was 4 years. She had a sallow complexion and immature facies with a poorly developed nasal bridge. Serum cholesterol, 501 mg/dL; radioiodine uptake, 7% at 24 hr; protein-bound iodine *(PBI),* 2.8 mg/dL. **B,** After therapy for 18 months, note the nasal development, increased luster and decreased pigmentation of hair, and maturation of the face. The height age was 5.5 years; the bone age was 7 years. There was a decided improvement in her general condition. Menarche occurred at 14 years. The ultimate height was 155 cm (61 in). She graduated from high school. The disorder was well controlled with daily L-thyroxine.

Fig. 603.4 **A,** This 12-yr-old male with hypothyroidism has short stature (108 cm, <3rd percentile), generalized myxedema, sleepy expression, protuberant abdomen, and coarse hair. Body proportions are immature for his age (1.25:1). **B,** Same boy 4 months after treatment. His height increased by 4 cm, and there is a marked change in body habitus owing to loss of myxedema, improved muscle tone, and bright facial expression. *(From LaFranchi SH. Hypothyroidism. Pediatr Clin North Am. 1979;26:33–51.)*

and firm, with a rubbery consistency and pebbly (bosselated) surface. Weight gain is mainly caused by fluid retention (myxedema), not true adiposity. Myxedematous changes of the skin, constipation, cold intolerance, decreased energy, and an increased need for sleep develop insidiously. School performance usually does not suffer, even in severely hypothyroid children. Additional features may include bradycardia, muscle weakness or cramps, nerve entrapment, and ataxia. Skeletal maturation is delayed, and the degree of delay reflects the duration of the hypothyroidism. Adolescents typically have delayed puberty. Older adolescent females may have menometrorrhagia, and some may develop galactorrhea because of increased TRH, which stimulates prolactin secretion. In fact, long-standing primary hypothyroidism can result in enlargement of the pituitary gland, sometimes leading to headaches and vision problems. This is believed to result from thyrotroph hyperplasia but may be mistaken for a pituitary tumor, particularly a prolactinoma if prolactin is elevated (see Chapter 595). Rarely, young children with profound hypothyroidism may develop secondary sex characteristics (pseudoprecocious puberty), including breast development or vaginal bleeding in females and testicular enlargement in males. It is hypothesized that this phenomenon results from abnormally high concentrations of TSH binding and stimulating the follicle-stimulating hormone receptor.

Laboratory abnormalities in hypothyroidism may include hyponatremia, macrocytic anemia, hypercholesterolemia, and elevated creatine phosphokinase. Table 603.5 lists complications of severe hypothyroidism, all of which normalize with adequate replacement of T_4.

Diagnostic Studies

Children with suspected hypothyroidism should undergo measurement of serum TSH and free T_4. Because the normal range for thyroid tests varies by age and is different in children than in adults, it is important to interpret results using age-specific reference ranges (see Table 603.3). Detection of autoantibodies to thyroglobulin or TPO is diagnostic of autoimmune thyroiditis. Measurement of urine iodine can confirm excess iodine exposure, if suspected. In cases of goiter resulting from autoimmune thyroiditis, ultrasonography typically shows diffuse enlargement and heterogeneous echotexture, but ultrasonography generally is not indicated unless the physical exam raises suspicion for a thyroid nodule. A bone age x-ray at diagnosis may suggest the duration and severity of hypothyroidism based on the degree of bone age delay.

Treatment and Prognosis

L-T_4 is the treatment for children with hypothyroidism. The dose on a weight basis gradually decreases with age. For children ages 1-3 years, the average daily L-T_4 dose is 4-6 μg/kg; for ages 3-10 years, 3-5 μg/kg; and for ages 10-16 years, 2-4 μg/kg. Treatment should be monitored by measuring serum TSH every 4-6 months and 4-6 weeks after any change in dosage, and TSH should be maintained in the age-specific reference range. In young children (under age 3 years), serum free T_4 should also be measured and ideally maintained in the upper half of the age-specific reference range. In older children with primary hypothyroidism, serum free T_4 need not be measured routinely but may be helpful in certain situations, such as to assess for poor medication adherence. In children with central hypothyroidism, in which TSH levels by definition do not reflect systemic thyroid status, serum free T_4 alone should be monitored and maintained in the upper half of the age-specific reference range.

During the first year of treatment, deterioration of schoolwork, poor sleeping habits, restlessness, short attention span, and behavioral problems may develop. However, these issues are transient and more easily managed if families are forewarned about them. Some practitioners feel that these symptoms may be partially ameliorated by starting at a lower dose of L-T_4 and advancing slowly. The development of persistent headaches or vision changes should prompt an evaluation for pseudotumor cerebri, a rare complication after initiation of L-T_4 treatment in older children (age 8-13 years).

In older children, after catch-up growth is complete, the growth rate provides a good index of the adequacy of therapy. In children with long-standing hypothyroidism, catch-up growth may be incomplete, and final adult height may be irremediably compromised (see Fig. 603.4).

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Table 603.5 Clinical Presentation and Implications of Hypothyroidism

	PRESENTATION	SIGNS AND IMPLICATIONS
General metabolism	Weight gain, cold intolerance, fatigue	Increase in body mass index, low metabolic rate, myxedema,* hypothermia*
Cardiovascular	Fatigue on exertion, shortness of breath	Dyslipidemia, bradycardia, hypertension, endothelial dysfunction or increased intima–media thickness,* diastolic dysfunction,* pericardial effusion,* hyperhomocysteinemia,* electrocardiogram changes*
Neurosensory	Hoarseness of voice, decreased taste, vision, or hearing	Neuropathy, cochlear dysfunction, decreased olfactory and gustatory sensitivity
Neurologic and psychiatric	Impaired memory, paresthesia, mood impairment	Impaired cognitive function, delayed relaxation of tendon reflexes, depression,* dementia,* ataxia,* carpal tunnel syndrome, and other nerve entrapment syndromes,* myxedema coma*
Gastrointestinal	Constipation	Reduced esophageal motility, nonalcoholic fatty liver disease,* ascites (very rare)
Endocrinologic	Infertility and subfertility, menstrual disturbance, galactorrhea	Goiter, glucose metabolism dysregulation, infertility, sexual dysfunction, increased prolactin, pituitary hyperplasia*
Musculoskeletal	Muscle weakness, muscle cramps, arthralgia	Creatine phosphokinase elevation, Hoffman syndrome,* osteoporotic fracture* (most probably caused by overtreatment)
Hemostasis and hematologic	Bleeding, fatigue	Mild anemia, acquired von Willebrand disease,* decreased protein C and S,* increased red cell distribution width,* increased mean platelet volume*
Skin and hair	Dry skin, hair loss	Coarse skin, loss of lateral eyebrows,* yellow palms of the hand,* alopecia areata*
Electrolytes and kidney function	Deterioration of kidney function	Decreased estimated glomerular filtration rate, hyponatremia*

*Uncommon presentation.
From Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. *Lancet.* 2017;390:1550–1560, Table 1.

Chapter 604

Thyroiditis

Jessica R. Smith and Ari J. Wassner

Thyroiditis refers to inflammation of the thyroid gland. Thyroiditis can be acute or chronic and can be categorized by etiology, pathology, and/or clinical features. Painful thyroiditis is typically due to infection or trauma, whereas painless thyroiditis is often autoimmune-mediated or due to drug exposure.

Depending on the etiology and phase of illness, patients with thyroiditis may be euthyroid, hypothyroid, or thyrotoxic. The classic pattern of thyroid function changes in transient forms of thyroiditis is thyrotoxicosis followed by hypothyroidism and then restoration of euthyroidism. In some cases, hypothyroidism can persist after transient thyroiditis. The thyrotoxicosis caused by thyroiditis is not due to increased thyroid hormone synthesis (in contrast to Graves disease), but rather release of preformed thyroid hormone from the damaged gland, which can last up to 60 days.

Treatment for patients with thyroiditis is directed at alleviating symptoms of pain and symptoms of thyrotoxicosis such as tachycardia, palpations, and tremors. Nonsteroidal antiinflammatory drugs (NSAIDs) usually alleviate thyroid pain effectively, but a short course of steroids (prednisone) can be considered if pain is severe. Because the thyrotoxicosis is caused by the release of preformed thyroid hormone, antithyroid drugs (which block thyroid hormone synthesis) are ineffective. Instead, treatment with β blockers (atenolol or propranolol) may be used to control cardiovascular symptoms until thyrotoxicosis resolves. Thyroid function tests should be monitored every 6-8 weeks until they normalize. If hypothyroidism is prolonged or symptomatic, replacement with levothyroxine may be initiated.

THYROIDITIS WITH PAIN

Acute infectious (suppurative) thyroiditis is uncommon in children and typically is preceded by a respiratory infection or pharyngitis. The most common pathogenic organisms are α-hemolytic streptococci and *Staphylococcus aureus,* followed by gram-negative organisms and anaerobic bacteria. Other pathogens, including mycobacteria, fungi, and pneumocystis, cause more indolent infection and occur in immunocompromised patients. Abscess formation can occur, and the left thyroid lobe is more commonly affected than the right. Recurrent episodes or detection of mixed bacterial flora suggest that the infection arises from a **piriform sinus fistula** or, less commonly, from a **thyroglossal duct** remnant. Acute infectious thyroiditis is characterized by acute onset of neck pain, thyroid tenderness, swelling, erythema, dysphagia, and decreased range of motion of the neck. Fever, chills, sore throat, and leukocytosis are common. Thyroid function is usually normal, but thyrotoxicosis can occur. A suspected abscess can be assessed by thyroid ultrasound, and fine needle aspiration can help identify the responsible microorganism. Treatment of a thyroid abscess includes incision and drainage and administration of parenteral antibiotics. After the infection subsides, a CT scan with contrast may be obtained to identify a fistulous tract that may require surgical resection.

Subacute thyroiditis (de Quervain disease, subacute granulomatous thyroiditis) is believed to have a viral or postviral etiology and is usually transient. It typically presents with low-grade fever, minimal thyroid tenderness, and laboratory evidence of thyrotoxicosis (suppressed TSH and elevated T_4 and T_3). Mild symptoms of thyrotoxicosis may be present, but radioiodine uptake is depressed in the thyrotoxic phase. The erythrocyte sedimentation rate (ESR) is increased. The course is variable but usually follows the classic pattern of thyrotoxicosis, hypothyroidism, and finally resolution to euthyroidism, usually occurring over several months. There is a strong association with HLA-B35.

Radiation thyroiditis can occur after treatment with radioactive iodine or external beam radiation. Thyroid pain and tenderness develop after 2-5 days because of radiation-induced destruction of the thyroid follicular cells and subsequent release of preformed thyroid hormone. The neck pain is responsive to antiinflammatory therapies.

Palpation- or trauma-induced thyroiditis can result from direct trauma to the thyroid gland, typically from surgery, accidental trauma, biopsy, or rarely, vigorous palpation.

THYROIDITIS WITHOUT PAIN

Autoimmune Thyroiditis (Hashimoto Thyroiditis, Chronic Lymphocytic Thyroiditis)

Autoimmune thyroiditis is the most common cause of thyroid disease in children and adolescents and accounts for many of the formerly designated *adolescent* or *simple* goiters. It is also the most common cause of acquired hypothyroidism, with or without goiter. Between 1 and 2% of school-age children and 6–8% of adolescents have positive thyroid autoantibodies as evidence of autoimmune thyroid disease.

Etiology

This typical organ-specific autoimmune disease results from a combination of inherited susceptibility in genes involved in immunoregulation and from environmental triggers, both poorly characterized. Early in the disease, there may be thyroid hyperplasia only. This is followed by infiltration of lymphocytes and plasma cells into thyroid follicles and formation of lymphoid follicles with germinal centers. Chronic inflammation eventually leads to follicular fibrosis and atrophy. Certain human leukocyte antigen (HLA) haplotypes (HLA-DR4, HLA-DR5) are associated with an increased risk of goiter and thyroiditis, and others (HLA-DR3) are associated with the atrophic variant of thyroiditis.

A variety of different autoantibodies to thyroid antigens are also present. Circulating antibodies to thyroperoxidase (TPO-Abs) or thyroglobulin (Tg-Abs) are detectable in most children with autoimmune thyroiditis and many patients with Graves disease. TPO-Abs are involved in activation of the complement cascade and antibody-dependent, cell-mediated cytotoxicity. Tg-Abs do not appear to play a role in the autoimmune destruction of the gland. TSH receptor-blocking antibodies (TRBAbs) may cause thyroid atrophy and have been demonstrated in 18% of patients with severe hypothyroidism (TSH >20 mU/L) caused by autoimmune thyroiditis.

Clinical Manifestations

Autoimmune thyroiditis is 4-6 times more common in females than in males. It can occur during the first 3 years of life but becomes more common after 6 years of age and reaches its peak incidence during adolescence. The most common clinical manifestations are goiter and growth deceleration. Goiter is primarily caused by thyroid inflammation and fibrosis, and it can appear insidiously and may be variable in size. In most patients, the thyroid is diffusely enlarged, firm, and nontender. In some patients the gland may be asymmetric. Most affected children are euthyroid and asymptomatic. Children who develop hypothyroidism may be symptomatic, but others may have no symptoms despite laboratory evidence of overt hypothyroidism. In some cases, autoimmune thyroiditis can cause transient thyroiditis as a result of autoimmune thyroid destruction (so-called *Hashitoxicosis*). Such children may present with manifestations of thyrotoxicosis, such as tremulousness, irritability, increased sweating, and hyperactivity. Ophthalmopathy can occur in autoimmune thyroiditis even in the absence of Graves disease, although this is rare in childhood.

The clinical course of autoimmune thyroiditis is variable. Goiter may persist or regress spontaneously. Most children who are euthyroid at presentation remain euthyroid, but a subset of patients develop hypothyroidism within months or years. In children who have subclinical hypothyroidism at diagnosis (elevated TSH, normal free thyroxine [T_4]), approximately 35% revert to euthyroidism, 50% continue to have subclinical hypothyroidism, and approximately 15% develop overt hypothyroidism (elevated serum TSH, subnormal free T_4) within 5 years. There are few reliable predictors of progression to hypothyroidism, so periodic monitoring of TSH levels is indicated in children with autoimmune thyroiditis.

Familial clusters of autoimmune thyroiditis are common, and the incidence in siblings or parents of affected children may be as high as 25%. The concurrence within families of patients with autoimmune thyroiditis and Graves disease reflects a fundamental pathophysiologic relationship among these autoimmune thyroid disorders.

Autoimmune thyroiditis is associated with other autoimmune disorders. Autoimmune thyroiditis occurs in 10% of patients with **type 1 autoimmune polyglandular syndrome (APS-1),** characterized by autoimmune

polyendocrinopathy, candidiasis, and ectodermal dysplasia **(APECED)**, a rare autosomal recessive disorder caused by pathogenic variants in the autoimmune regulator *(AIRE)* gene (see Chapter 608). Autoimmune thyroiditis occurs in 70% of patients with **type 2 autoimmune polyglandular syndrome (APS-2)**, including type 1 diabetes mellitus, autoimmune primary adrenal insufficiency, pernicious anemia, vitiligo, and alopecia. TPO-Abs are found in approximately 20% of White and 4% of Black children with type 1 diabetes mellitus. The onset of APS-2 typically occurs in late childhood or early adulthood. Its cause is unknown but may be related to predisposing genetic factors shared among these autoimmune conditions (see Chapter 608). Autoimmune thyroiditis has also been described in children with **immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome**, including early-onset diabetes and colitis (see Chapter 608).

Autoimmune thyroiditis is common in patients with celiac disease or certain chromosomal disorders, particularly Turner syndrome (8–30%) and trisomy 21 (7–10%). Males with Klinefelter syndrome also appear to be at increased risk for autoimmune thyroid disease.

Table 604.1 compares the characteristics of autoimmune thyroiditis to other forms of thyroiditis.

Laboratory and Imaging Findings

Thyroid function tests are often normal. Elevation of serum TSH indicates hypothyroidism, which may be subclinical (normal free T_4) or overt (low free T_4). TPO-Abs are present in most children with autoimmune thyroiditis. Tg-Abs are present in many adolescents but are somewhat less sensitive in young children. Testing for both antibodies will detect about 95% of children with autoimmune thyroiditis. Antibody levels are lower in children than in adults, so repeated measurements of borderline levels may be indicated. Measurement of thyroid autoantibody levels is useful only for diagnosing autoimmune thyroiditis; antibody levels do not correlate with thyroid function and should not be monitored routinely after the initial diagnosis. In adolescent females with overt hypothyroidism, measurement of TSH receptor antibodies may identify patients at future risk of having babies with transient congenital hypothyroidism caused by transplacental passage of TRBAbs.

Thyroid scintigraphy and ultrasonography usually are not necessary for the diagnosis of autoimmune thyroiditis. If performed, thyroid scintigraphy reveals decreased radioisotope uptake that is patchy and irregular. Thyroid ultrasonography shows diffusely heterogeneous echogenicity and frequently an increased number of hyperplastic, benign-appearing cervical lymph nodes. Thyroid ultrasound is indicated for patients with a palpable thyroid nodule or significant thyroid asymmetry.

Treatment

If hypothyroidism is overt (elevated TSH with low free T_4) or symptomatic, treatment with levothyroxine is indicated at doses specific to size and age. Goiter may decrease in size but can persist for years. In a euthyroid patient, treatment with levothyroxine is unlikely to significantly decrease the goiter's size, and doses of levothyroxine sufficient to suppress TSH should be avoided because of potential adverse effects. Because autoimmune thyroiditis is self-limited in some instances, the need for continued therapy may be reevaluated periodically, particularly after growth and pubertal development are complete. Untreated euthyroid patients should have periodic monitoring for risk of progression to hypothyroidism. There is some controversy about the management of patients with subclinical hypothyroidism. Subclinical hypothyroidism has not been demonstrated to have clinically significant adverse effects, but studies are small and of limited quality. Therefore observation without treatment is acceptable, but some clinicians prefer to treat until growth and puberty are complete and then reevaluate their thyroid function.

OTHER CAUSES OF THYROIDITIS

Painless thyroiditis (silent thyroiditis) is characterized by transient thyrotoxicosis, followed sometimes by hypothyroidism, and then recovery. It accounts for 1–5% of cases of thyrotoxicosis. It can also occur in the postpartum period and in response to certain types of drugs.

Drug-induced thyroiditis can be caused by medications including lithium, amiodarone, interferon-α, interleukin-2, and tyrosine kinase inhibitors. Patients taking lithium are susceptible to both lithium-induced hypothyroidism and painless thyroiditis. The antiarrhythmic drug amiodarone contains a high concentration of iodine and can cause two types of thyrotoxicosis. Type 1 is caused by increased synthesis of thyroid hormone (hyperthyroidism), typically occurs in patients with underlying thyroid autoimmunity, and is amenable to treatment with antithyroid drugs (methimazole). Type 2 is a destructive thyroiditis causing excessive release of preformed thyroid hormone, which can be treated with glucocorticoids (prednisone).

Fibrous thyroiditis (invasive or Riedel thyroiditis) is quite rare in children and is characterized by extensive fibrosis and macrophage and eosinophil infiltration of the thyroid gland. The thyroid becomes enlarged, hard, and affixed to surrounding structures. Thyroid function tests are normal, and a biopsy is required to confirm the diagnosis. Glucocorticoids may alleviate symptoms.

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Table 604.1 Characteristics of Thyroiditis Syndromes

CHARACTERISTIC	AUTOIMMUNE THYROIDITIS	PAINLESS THYROIDITIS	SUBACUTE THYROIDITIS	ACUTE INFECTIOUS THYROIDITIS	FIBROUS THYROIDITIS
Sex ratio (F:M)	4-6:1	2:1	5:1	1:1	3-4:1
Cause	Autoimmune	Autoimmune	Unknown (probably viral)	Infectious (bacterial)	Unknown
Pathologic findings	Lymphocytic infiltration, germinal centers, fibrosis	Lymphocytic infiltration	Giant cells, granulomas	Abscess formation	Dense fibrosis
Thyroid function	Usually euthyroidism; some hypothyroidism	Thyrotoxicosis, hypothyroidism, or both	Thyrotoxicosis, hypothyroidism, or both	Usually euthyroidism	Usually euthyroidism
TPO antibodies	Present, persistent	Present, persistent	Low titer, absent, or transient	Absent	Usually present
ESR	Normal	Normal	High	High	Normal
^{123}I uptake	Usually low	Low	Low	Normal	Low or normal

ESR, Erythrocyte sedimentation rate; ^{123}I, iodine 123; TPO, thyroid peroxidase.
Data from Farwell AP, Braverman LE. Inflammatory thyroid disorders. *Otolaryngol Clin North Am.* 1996;4:541–556.

Chapter 605

Goiter

Jessica R. Smith and Ari J. Wassner

A goiter is an enlargement of the thyroid gland. Average thyroid volume is approximately 1 mL at birth and increases with age and body mass index. For clinical assessment of thyroid size, the "rule of thumb" states that in older children (>5 years) each lobe of the thyroid gland is approximately the size of the distal phalanx of the child's thumb. Children with an enlarged thyroid can have normal thyroid function **(euthyroidism)**, underproduction of thyroid hormone **(hypothyroidism)**, or overproduction of thyroid hormone **(hyperthyroidism)**. Most goiters are discovered by the patient or a caregiver or on physical examination. Detection of a goiter should prompt an investigation of its cause and assessment of thyroid function.

Goiter may be congenital or acquired, endemic or sporadic. Goiter often results from increased pituitary secretion of thyroid-stimulating hormone (TSH) in response to decreased circulating levels of thyroid hormone. The most common causes of pediatric goiter are inflammation (autoimmune thyroiditis) and, in endemic areas, iodine deficiency (endemic goiter). Other causes include inborn errors in thyroid hormone synthesis (dyshormonogenesis), maternal ingestion of antithyroid drugs, goitrogens, abnormal activation of the TSH receptor by circulating antibodies (TRSAb) in Graves disease or by genetic gain-of-function pathogenic variants, or disorders of inappropriate TSH secretion. Thyroid enlargement can also result from thyroid nodules or infiltrative processes.

605.1 Congenital Goiter

Ari J. Wassner and Jessica R. Smith

Congenital goiter usually results from a defect in fetal thyroxine (T_4) synthesis that leads to neonatal hypothyroidism. This defect may be intrinsic to the fetal thyroid or may be caused by transplacental transfer from the mother of substances that decrease fetal thyroid hormone synthesis. Antithyroid drugs (methimazole or propylthiouracil) administered during pregnancy to treat maternal thyrotoxicosis cross the placenta and can interfere with fetal synthesis of thyroid hormone. The neonatal consequences are most severe when overtreatment with antithyroid drugs causes concomitant hypothyroidism in the mother, which reduces the supply of maternal thyroid hormone to the fetus. Fetal effects can occur even with low doses of antithyroid drugs; therefore infants born to women treated with such drugs in the third trimester should undergo serum thyroid studies at birth, even if they appear clinically euthyroid. Levothyroxine treatment may be indicated for severe hypothyroidism or to reduce the size of goiter that causes airway obstruction. Hypothyroidism caused by maternal antithyroid drugs is transient and resolves once the antithyroid drug has been excreted by the neonate, usually after 1-2 weeks. Like antithyroid drugs, other medications containing large amounts of iodine can cause congenital goiter, including amiodarone and some cough preparations.

In cases of congenital goiter and hypothyroidism in which no cause is identifiable from the maternal or medication history, an intrinsic defect in synthesis of thyroid hormone **(dyshormonogenesis)** should be suspected. Such disorders are caused by genetic defects in one of the proteins critical to thyroid hormone synthesis and are usually inherited in autosomal recessive fashion. Neonatal screening programs detect congenital hypothyroidism caused by such a defect in about 1 in 25,000 infants. Treatment with levothyroxine should be initiated immediately. If a specific defect is suspected, genetic testing to identify a mutation may be considered (see Chapter 603). Monitoring subsequent pregnancies with ultrasonography can be useful to detect fetal goiter (see Chapter 117).

Iodine deficiency is an important cause of congenital goiter that is rare in countries that have adopted universal salt iodization, but iodine deficiency persists in endemic areas (see Chapter 605.3). Severe maternal iodine deficiency early in pregnancy can cause neurologic damage during fetal development because maternal hypothyroidism reduces the transfer of maternal thyroid hormones that typically protect neurodevelopment in a fetus unable to synthesize its own thyroid hormone.

Goiter is almost always present in the infant with **neonatal Graves disease**. Thyroid enlargement results from transplacental passage of maternal TSH receptor-stimulating antibodies that promote thyroid hyperplasia (see Chapter 606.2). These goiters usually are not large, and the infant manifests clinical symptoms of hyperthyroidism. The diagnosis of maternal Graves disease is usually known but occasionally may be discovered by evaluating unexpected neonatal hyperthyroidism. Activating pathogenic variants of the TSH receptor are a rare cause of congenital goiter with hyperthyroidism.

A very large congenital goiter of any cause can lead to tracheal compression and respiratory distress that interferes with feeding and can even be fatal. Therefore intervening to reduce the size of a large fetal goiter may be necessary before delivery. Treatment should be directed at the underlying cause. Iodine deficiency should be treated if present. In pregnant women treated with antithyroid drugs, reducing the dose of maternal medication is appropriate. In severe cases, fetal goiter caused by fetal hypothyroidism (including dyshormonogenesis) may be reduced by intraamniotic injections of levothyroxine. If the fetal goiter is caused by fetal hyperthyroidism (e.g., fetal Graves disease), treatment with antithyroid drugs administered to the mother is indicated. Large obstructing fetal goiters are often managed with the ex utero intrapartum treatment (EXIT) procedure during elective delivery (see Chapter 117). When postnatal respiratory obstruction is severe, endotracheal intubation, hormone therapy, and occasionally partial thyroidectomy is indicated (Fig. 605.1).

When a palpable congenital goiter is lobulated, asymmetric, firm, or unusually large, a teratoma in or near the thyroid must be considered (see Chapter 607).

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605.2 Intratracheal Goiter

Ari J. Wassner and Jessica R. Smith

One of the many potential ectopic locations of thyroid tissue is within the trachea. When present, intraluminal thyroid tissue lies beneath the tracheal mucosa and is often continuous with the normally located extratracheal thyroid gland. Both eutopic and ectopic thyroid tissue are susceptible to goitrous enlargement. Therefore when airway obstruction is associated with a goiter, it must be ascertained whether the obstruction is extratracheal or intratracheal. If obstructive manifestations are mild, administration of levothyroxine usually decreases the size of the goiter. When symptoms are severe, surgical removal of the intratracheal goiter is indicated.

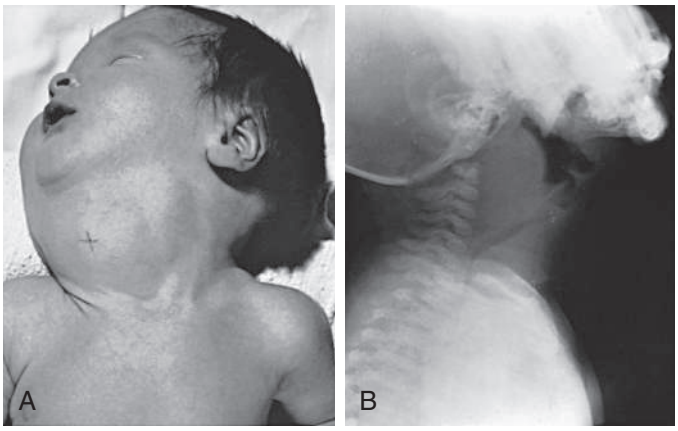

Fig. 605.1 Congenital goiter in infancy. **A,** Large congenital goiter in an infant born to a mother with thyrotoxicosis who had been treated with iodides and methimazole during pregnancy. **B,** A different infant, 6 wk old, with increasing respiratory distress and cervical mass since birth. Notice the anterior deviation and posterior compression of the trachea.

605.3 Endemic Goiter and Cretinism

Ari J. Wassner and Jessica R. Smith

ETIOLOGY

Goiter caused by iodine deficiency is termed *endemic goiter,* whereas *cretinism* refers to the clinical manifestations of severe hypothyroidism in early life. The association of dietary iodine deficiency with endemic goiter and cretinism is well established. The thyroid gland can overcome a moderate deficiency of iodine by increasing the efficiency of thyroid hormone synthesis. This increased activity is achieved by compensatory thyroid hypertrophy and hyperplasia (goiter). In cases of severe iodine deficiency, these compensatory mechanisms are insufficient, and hypothyroidism can result. The World Health Organization estimates that nearly 2 billion individuals have insufficient iodine intake, including one third of the world's school-age children. Thus despite significant progress in the global effort to reduce iodine deficiency, it remains a leading cause of preventable intellectual disability worldwide.

Because seawater is rich in iodine, endemic goiter is rare in coastal populations that consume much of their diet from the sea. In areas of iodine deficiency, iodized salt provides excellent prophylaxis, and endemic goiter has effectively disappeared in the United States and other countries that have introduced salt iodization programs. The U.S. recommended dietary allowance of iodine is:

- Infants under 6 months: 110 μg/day
- Infants 7-12 months: 130 μg/day
- Children 1-8 years: 90 μg/day
- Children 9-13 years: 120 μg/day
- Children 14 years and older: 150 μg/day
- Pregnant women: 220 μg/day
- Lactating women: 290 μg/day

Although the overall dietary iodine intake in the United States is considered adequate, recent data indicate that the median urinary iodine concentration among pregnant U.S. women has dropped to <150 μg/L (mild iodine deficiency). This highlights the re-emerging risk of iodine deficiency even in industrialized countries. These risks can be mitigated by the continued monitoring of iodine status, the adjustment of salt iodization levels, and the targeted supplementation of vulnerable subpopulations (e.g., promoting iodine-containing prenatal vitamins).

CLINICAL MANIFESTATIONS

In mild iodine deficiency, thyroid enlargement generally is not noticeable except when demand for thyroid hormone synthesis is increased, such as during rapid growth in adolescence and pregnancy. In regions of moderate iodine deficiency, goiter in school children can disappear with maturity and reappear during pregnancy or lactation. Iodine-deficient goiter is more common in girls than in boys. In areas of severe iodine deficiency, nearly half the population may have large goiters, and endemic cretinism is common (Fig. 605.2).

Serum T_4 levels are often low in individuals with endemic goiter, although clinical hypothyroidism is rare. Despite low serum T_4 levels, serum TSH concentrations are often normal or only mildly increased because of the elevated circulating levels of T_3 produced in response to iodine deficiency.

Endemic cretinism is the most severe consequence of iodine deficiency and occurs only in association with endemic goiter. The term *endemic cretinism* includes two distinct but overlapping syndromes (neurologic and myxedematous). The incidence of the two syndromes varies among different populations, but both syndromes are found in all endemic areas, and some individuals have intermediate or mixed features.

The **neurologic syndrome** is characterized by intellectual disability; deaf-mutism; disturbances in standing and gait; and pyramidal signs such as clonus of the foot, Babinski sign, and patellar hyperreflexia. Affected persons have a goiter but minimally impaired thyroid function and have normal pubertal development and adult stature. Persons with the **myxedematous syndrome** also have intellectual disability, deafness, and neurologic symptoms. In contrast to the neurologic type, they also have delayed growth and pubertal development and myxedema. Serum T_4 levels are low, TSH levels are markedly elevated, goiter is absent, and ultrasound demonstrates thyroid atrophy.

Fig. 605.2 A 14-yr-old male with a large nodular goiter was seen in 2004, in an area of severe iodine-deficiency disorders in northern Morocco. He had tracheal and esophageal compression and hoarseness, probably as a result of damage to the recurrent laryngeal nerves. *(From Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. Lancet. 2008;372:1251–1262, Fig. 2.)*

PATHOGENESIS

The pathogenesis of the **neurologic syndrome** is attributed to maternal iodine deficiency and hypothyroidism during pregnancy, leading to fetal and postnatal hypothyroidism. Maternal thyroid hormone is critical for early fetal neurodevelopment. Thyroid hormone receptors are expressed in the fetal brain as early as 7 weeks of gestation. Although the fetal thyroid gland does not produce significant amounts of thyroid hormone until midgestation, as early as 6 weeks there is measurable T_4 in the coelomic fluid that is of maternal origin. In addition, there is transplacental passage of maternal thyroid hormone into the fetus throughout gestation, which ameliorates the neurologic effects of fetal hypothyroidism in the second half of pregnancy. Thus maternal iodine deficiency affects fetal neurodevelopment throughout pregnancy. However, iodine intake after birth is often sufficient for the infant to maintain (near-)normal thyroid function.

The pathogenesis of the **myxedematous syndrome** and its persistent postnatal hypothyroidism is not well understood. Multiple environmental factors have been implicated (Table 605.1), as have thyroid autoimmunity and TSH receptor-blocking antibodies, but studies are conflicting, and the pathogenesis remains obscure.

TREATMENT

The optimal treatment of endemic goiter is prevention by ensuring iodine sufficiency in women before pregnancy. A single intramuscular injection of iodinated poppy seed oil administered to women prevents iodine deficiency during future pregnancies for approximately 5 years. This therapy is also effective in children younger than 4 years with myxedematous cretinism. However, older children and adults respond poorly, indicating a progressive inability of the thyroid gland to synthesize hormone, and these patients require treatment with levothyroxine. Large-scale prevention efforts include universal salt iodization in many countries, as well as

Table 605.1 Goitrogens and Their Mechanisms

GOITROGEN	MECHANISM
FOODS	
Cassava, lima beans, linseed, sorghum, sweet potato	Contain cyanogenic glucosides that are metabolized to thiocyanates that compete with iodine for uptake by the thyroid
Cruciferous vegetables (cabbage, kale, cauliflower, broccoli, turnips)	Contain glucosinolates; metabolites compete with iodine for uptake by the thyroid
Soy, millet	Flavonoids impair thyroid peroxidase activity
INDUSTRIAL POLLUTANTS	
Perchlorate	Competitive inhibitor of the sodium-iodide symporter, decreasing iodide transport into the thyroid
Others (e.g., disulfides from coal processes)	Reduce thyroidal iodine uptake
Smoking	Smoking during breastfeeding is associated with reduced iodine concentrations in breast milk; high serum concentration of thiocyanate from smoking might compete with iodine for active transport into the secretory epithelium of the lactating breast
NUTRIENTS	
Selenium deficiency	Accumulated peroxides can damage the thyroid, and deiodinase deficiency impairs thyroid hormone activation
Iron deficiency	Reduces heme-dependent thyroperoxidase activity in the thyroid and may blunt the efficacy of iodine prophylaxis
Vitamin A deficiency	Increases TSH stimulation and goiter through decreased vitamin A–mediated suppression of the pituitary TSH-β gene

TSH, Thyroid-stimulating hormone.
From Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet.* 2008;372:1251–1262, Table 1.

iodination of irrigation water in some areas. Nevertheless, political, economic, and practical obstacles have limited iodization efforts in many parts of the world.

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605.4 Acquired Goiter

Jessica R. Smith and Ari J. Wassner

Acquired goiter is usually sporadic and may develop from a variety of causes. The most common cause of acquired goiter is autoimmune thyroiditis (see Chapter 604). Other causes in children include painless sporadic thyroiditis and subacute thyroiditis (de Quervain disease; see Chapter 604). Ingestion of excess iodide or certain medications can cause goiter, as can congenital defects in thyroid hormone synthesis. The occurrence of goiter in siblings, onset in early life, and possible association with hypothyroidism are important clues to diagnosing congenital dyshormonogenesis.

IODIDE GOITER

Excessive iodine ingestion can result in a goiter. Large amounts of iodine are found in certain foods (such as seaweed) and some expectorants for chronic reactive airway disease or cystic fibrosis. Some children with iodine-induced goiter have underlying autoimmune thyroiditis or a subclinical congenital defect in thyroid hormone synthesis. In a normal thyroid gland, the acute intake of large doses of iodine inhibits thyroid hormone synthesis (Wolff-Chaikoff effect). However, this effect is short-lived and normally does not lead to hypothyroidism. If iodine administration continues, an autoregulatory mechanism limits iodide uptake by the thyroid, allowing thyroid hormone synthesis to resume. This "escape" from the Wolff-Chaikoff effect may not occur in individuals with underlying thyroid abnormalities (such as autoimmune thyroid disease or thyroid irradiation) or in neonates, potentially leading to hypothyroidism and iodine-induced goiter.

Iodine-Deficiency Goiter

Iodine deficiency is the most common cause of goiter worldwide, but salt iodization has nearly eradicated this entity in the United States and many other countries. A severely iodine-restricted diet can result in a goiter and hypothyroidism in children, adolescents, or neonates born to mothers with severe iodine deficiency (urine iodine concentration <50 mcg/L). Children with moderate or severe iodine deficiency and goiter have subclinical or mild hypothyroidism, but their serum T_3 concentrations may be normal or high because of preferential thyroidal T_3 secretion. Acquired iodine deficiency can be treated with either iodine or levothyroxine supplementation.

Goitrogens

Certain foods contain goitrogenic substances (see Table 605.1). When consumed alone, these substances are unlikely to cause goiter but can contribute to goiter formation when iodine intake is marginal.

Lithium carbonate can cause goiter and hypothyroidism in children. Lithium decreases T_4 and T_3 synthesis and release; the mechanism producing the goiter or hypothyroidism is similar to that described for iodide goiter. Lithium and iodide act synergistically to produce goiter, so their combined use should be avoided.

Amiodarone, a drug used to treat cardiac arrhythmias, can cause thyroid dysfunction with goiter because it is rich in iodine. Amiodarone can often cause hypothyroidism, particularly in patients with underlying autoimmune thyroid disease. In other patients, it can cause thyrotoxicosis through either transient thyroiditis or the Jod-Basedow effect.

SIMPLE GOITER (COLLOID GOITER)

Some children with euthyroid goiters have a simple goiter, a condition of unknown cause not associated with thyroid dysfunction and not caused by inflammation or neoplasia. Simple goiter is more common in girls, may be familial, and has its peak incidence during adolescence. Histologic examination of the thyroid either is normal or reveals variable follicular size, dense colloid, and flattened epithelium. The size of the goiter is variable. It can occasionally be firm, asymmetric, or nodular. Levels of TSH are normal, thyroid scintigraphy is normal, and thyroid antibodies are absent. Simple goiters usually decrease in size gradually over several years, without treatment. Patients should be reevaluated periodically because some have antibody-negative autoimmune thyroiditis and therefore are at risk for changes in thyroid function (see Chapter 604).

MULTINODULAR GOITER

Multinodular goiter is usually a firm goiter with a lobulated surface and one or more palpable nodules. Areas of cystic change, hemorrhage, and fibrosis may be present. The incidence of this condition has decreased markedly with the use of iodine-enriched salt. Ultrasonographic examination can reveal multiple nodules that are nonfunctioning on thyroid scintigraphy. Thyroid function is usually normal. Some children with autoimmune thyroiditis develop a multinodular goiter, and in such cases, thyroid antibodies may be present, and TSH may be elevated. If hypofunctioning nodules within a multinodular goiter grow to a significant size (≥1 cm) or have suspicious sonographic features, fine needle aspiration should be considered to rule out malignancy (see Chapter 607). Children with **McCune-Albright syndrome** or TSH receptor–activating mutations can develop a toxic multinodular goiter, characterized by suppressed TSH, hyperthyroidism, and multiple hyperfunctioning nodules.

TOXIC GOITER (HYPERTHYROIDISM)

See Chapter 606.

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Chapter 606

Thyrotoxicosis

Jessica R. Smith and Ari J. Wassner

Although the terms *hyperthyroidism* and *thyrotoxicosis* are often interchanged in the literature, they are not synonymous. **Hyperthyroidism** specifically refers to the synthesis and secretion of excess thyroid hormone from the thyroid gland; in contrast, **thyrotoxicosis** refers to any state of excess circulating thyroid hormone (and its clinical manifestations) regardless of its source. This distinction is physiologically and clinically relevant because different therapies may be indicated depending on the mechanism of thyroid hormone excess.

Graves disease is the most common cause of hyperthyroidism in children (Table 606.1). It is an autoimmune disorder that results in the production of thyrotropin (TSH) receptor–stimulating antibodies (TRSAbs) that bind and activate the G protein–coupled TSH receptor (TSHR) to cause increased thyroid hormonogenesis and diffuse glandular growth. In infants born to mothers with Graves disease, hyperthyroidism can be caused by transplacental passage of TRSAbs, but this is transitory and resolves when TRSBAbs are cleared from the neonate's circulation. Etiologies of nonautoimmune hyperthyroidism include hyperfunctioning thyroid nodules and germline gain-of-function pathogenic variants in the TSHR (either autosomal dominant or sporadic). Hyperthyroidism can also occur in patients with **McCune-Albright syndrome** because of an activating pathogenic variant of the stimulatory α-subunit of the G protein. These patients can also develop a multinodular goiter. Other rare causes of hyperthyroidism include iodine-induced hyperthyroidism, TSH-secreting adenomas, toxic multinodular goiters, and hyperfunctioning thyroid carcinoma. Thyrotoxicosis not caused by hyperthyroidism (i.e., not the result of overproduction of thyroid hormone by the gland) can be caused by thyroiditis (see Chapter 604) or ingestion of exogenous thyroid hormone. Choriocarcinoma, hydatidiform mole, and struma ovarii can cause hyperthyroidism but are rarely diagnosed in children.

Laboratory evaluation of primary thyrotoxicosis reveals suppression of serum TSH and elevation of serum total thyroxine (T_4) and/or total triiodothyronine (T_3) levels. Elevated T_4 and T_3 with normal or elevated TSH suggests hyperthyroidism caused by inappropriate TSH secretion, which may be caused by a dominant-negative pathogenic variant in thyroid hormone receptor-β *(THRB)* resulting in **resistance to thyroid hormone (RTH)**. TSH-secreting pituitary tumors are extremely rare in the pediatric population. Elevated T_4 and/or T_3 levels with normal TSH may also be caused by abnormalities of thyroid hormone–binding proteins such as **thyroxine-binding globulin** excess or **familial dysalbuminemic hyperthyroxinemia**. In such cases, free T_4 levels are normal, and patients are euthyroid.

606.1 Graves Disease

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EPIDEMIOLOGY

Graves disease occurs in approximately 0.02% of children (1:5,000) and is the most common cause of pediatric hyperthyroidism. It has a peak incidence in the 11- to 15-year-old age-group, and there is a 5:1 female:male ratio. Many children with Graves disease have a family history of autoimmune thyroid disease. Although rare in very young children, Graves disease has been reported between 6 weeks and 2 years of age in children born to mothers without a history of hyperthyroidism.

ETIOLOGY

Graves disease is a form of autoimmune thyroid disease characterized by infiltration of the thyroid gland by T-helper cells ($CD4^+$), cytotoxic T cells ($CD8^+$), and activated B lymphocytes. A postulated failure of T suppressor cells allows the expression of T helper cells sensitized to the TSH antigen to interact with B cells, which

Table 606.1 Pathogenic Mechanisms and Causes and Effects of Thyrotoxicosis

Thyrotoxicosis with hyperthyroidism (normal or high radioactive iodine uptake)	
EFFECT OF INCREASED THYROID STIMULATORS	
TSH-receptor antibody	Graves disease
Inappropriate TSH secretion	TSH-secreting pituitary adenoma; resistance to thyroid hormone β
Excess hCG secretion	Trophoblastic tumors (choriocarcinoma or hydatidiform mole); hyperemesis gravidarum
AUTONOMOUS THYROID FUNCTION	
Activating pathogenic variant in TSH receptor or $G_s\alpha$ protein	Solitary hyperfunctioning adenoma; multinodular goiter; familial nonautoimmune hyperthyroidism
Thyrotoxicosis without hyperthyroidism (low radioactive iodine uptake)	
INFLAMMATION AND RELEASE OF STORED HORMONE	
Autoimmune destruction of thyroid gland	Autoimmune thyroiditis; postpartum thyroiditis
Viral infection*	Subacute (painful) thyroiditis (de Quervain thyroiditis)
Toxic drug effects	Drug-induced thyroiditis (amiodarone, lithium, interferon-α)
Bacterial or fungal infection	Acute suppurative thyroiditis
Radiation	Radiation thyroiditis
EXTRATHYROIDAL SOURCE OF HORMONE	
Excess intake of thyroid hormone	Excess exogenous thyroid hormone (iatrogenic or factitious)
Ectopic hyperthyroidism (thyroid hormone produced outside the thyroid gland)	Struma ovarii; functional thyroid cancer
Ingestion of contaminated food	Hamburger thyrotoxicosis
EXPOSURE TO EXCESSIVE IODINE	
Jod-Basedow effect	Iodine-induced hyperthyroidism (radiocontrast agents or iodine in medications)

*Etiology is not definitive.
$G_s\alpha$, G protein alpha subunit; hCG, human chorionic gonadotropin; TSH, thyroid-stimulating hormone.
Modified from De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 1.

Table 606.2 Conditions Associated with Graves Disease

Type 1 diabetes mellitus
Celiac disease
Autoimmune adrenal insufficiency
Vitiligo
Psoriasis
Pernicious anemia
Alopecia areata
Myasthenia gravis
Rheumatoid arthritis
Trisomy 21
Turner syndrome

differentiate into plasma cells that produce TRSAbs. TRSAbs bind to and activate the TSHR, resulting in thyroid hyperplasia and unregulated thyroid hormone synthesis. Some patients with Graves disease also produce TSH receptor–blocking antibodies (TRBAbs) that bind to and block activation of the TSHR. In these cases, the clinical course of the disease correlates to the ratio between stimulating and blocking antibodies.

Ophthalmopathy may occur in Graves disease and appears to be caused primarily by autoimmunity to the TSHR, which is also expressed in orbital adipocytes and fibroblasts. TRSAb-mediated activation of these cells stimulates the synthesis of glycosaminoglycans and cytokines, resulting in retro-orbital inflammation and edema. Although 50–75% of children with Graves disease have some eye findings, the symptoms are much milder than in adults; significant ophthalmopathy is rare.

Graves disease is associated with specific human leukocyte antigen (HLA) haplotypes. It is also associated with other HLA-related disorders, such as autoimmune adrenal insufficiency, type 1 diabetes mellitus, myasthenia gravis, and celiac disease (Table 606.2). Systemic lupus erythematosus, rheumatoid arthritis, vitiligo, idiopathic thrombocytopenic purpura, and pernicious anemia have also been described in children with Graves disease. In family clusters, the condition associated most commonly with Graves disease is autoimmune thyroiditis. Polymorphisms in the *TSHR* gene and numerous immunomodulatory genes—including *FOXP3, IL2RA, CD40, CTLA4, PTPN22,* and *FCRL3*—have also been associated with increased susceptibility to Graves disease.

CLINICAL MANIFESTATIONS

The clinical course of Graves disease is variable, and children typically take longer to remit than adults. Because symptoms develop gradually, the interval between onset and diagnosis is typically 6-12 months and may be longer in prepubertal children than in adolescents.

Signs and symptoms of Graves disease in children are shown in Figure 606.1 and Table 606.3. Tremulousness, headaches, mood disturbances, behavioral swings, difficulties with sleep, decreased attention span, hyperactivity, and a decline in school performance are all common findings in childhood. Many hyperthyroid children are referred for evaluation of attention-deficit/hyperactivity disorder (ADHD). Children with hyperthyroidism may show acceleration in growth velocity and advanced skeletal maturation. The effect on growth may be more pronounced if hyperthyroidism presents earlier in childhood. The onset of puberty does not appear to be altered by hyperthyroidism, but postmenarchal females can develop secondary amenorrhea. There may also be an increase in appetite with either failure to gain weight or overt weight loss. Polyuria and more frequent defecation (although not usually frank diarrhea) contribute to changes in weight. Because of the increased risk

Fig. 606.1 A 15-yr-old female with classic Graves disease. Clinical features include a goiter and exophthalmos. She was treated with antithyroid drugs, to which she had a good response.

of comorbid autoimmune disorders, screening for type 1 diabetes, celiac disease, and inflammatory bowel disease should be considered in patients who present with these symptoms.

Most children with Graves disease have a diffuse goiter. The size of the thyroid is variable, but it is typically smooth and without nodules. A bruit can occasionally be auscultated over a markedly enlarged gland. Ocular manifestations can produce proptosis, pain, eyelid erythema, chemosis, decreased extraocular muscle function and decreased visual acuity (corneal or optic nerve involvement) (Table 606.4). In children with thyrotoxicosis and diffuse goiter, identifying these signs of ophthalmopathy on physical examination strongly suggests the diagnosis of Graves disease. However, stare and lid lag are eye findings caused by increased sympathetic activity and can be seen in thyrotoxicosis of any cause, not only Graves disease (Fig. 606.2). In general, ocular symptoms in children with Graves disease tend to be mild and improve with the restoration of euthyroidism.

Children with hyperthyroidism have an increase in cardiac output. Tachycardia, palpitations, increased systolic blood pressure, and a widened pulse pressure are common cardiac manifestations, whereas cardiac enlargement and insufficiency and atrial fibrillation are rare complications.

The skin is smooth and flushed, with excessive sweating. Occasionally, associated vitiligo or psoriasis can be present. Graves dermopathy, characterized by indurated, nonpitting edema often on the anterior shins (pretibial myxedema), is rare in children. Proximal muscular weakness may be present. Thyroid hormone stimulates bone resorption, leading to low bone density and increased fracture risk in patients with chronic hyperthyroidism. Bone density returns to normal with treatment.

Table 606.3 Clinical Manifestation of Thyrotoxicosis

	SYMPTOMS	SIGNS
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating, and polydipsia)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyperreflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension
Pulmonary	Dyspnea, shortness of breath	Tachypnea
Gastrointestinal	Hyperdefecation; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive		Menstrual disturbances
Ocular (Graves disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retro-orbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital edema; conjunctival injection and chemosis; ophthalmoplegia

From De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 2.

Table 606.4 Clinical Assessment of the Patient with Graves Ophthalmopathy

ACTIVITY MEASURES*
- Spontaneous retrobulbar pain
- Pain on attempted up or down gaze
- Redness of the eyelids
- Redness of the conjunctivae
- Swelling of the eyelids
- Inflammation of the caruncle and/or plica
- Conjunctival edema

SEVERITY MEASURES
- Lid aperture (distance between the lid margins in millimeters with the patient looking in the primary position, sitting relaxed, and with distant fixation)
- Swelling of the eyelids (absent/equivocal, moderate, severe)
- Redness of the eyelids (absent/present)
- Redness of the conjunctivae (absent/present)
- Conjunctival edema (absent, present)
- Inflammation of the caruncle or plica (absent, present)
- Exophthalmos (measured in millimeters using the same Hertel exophthalmometer and the same intercanthal distance for an individual patient)
- Subjective diplopia score†
- Eye muscle involvement (ductions in degrees)
- Corneal involvement (absent/punctate keratopathy/ulcer)
- Optic nerve involvement (best corrected visual acuity, color vision, optic disc, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

*Based on the classic features of inflammation in Graves ophthalmopathy.
†Subjective diplopia score: 0, no diplopia; 1, intermittent (i.e., diplopia in primary position of gaze, when tired or when first awakening); 2, inconstant (i.e., diplopia at extremes of gaze); 3, constant (i.e., continuous diplopia in primary or reading position). The clinical activity score (CAS) is the sum (1 point each) of all items present; a CAS ≥3/7 indicates active ophthalmopathy.
From Davies TF, Laurberg P, Bahn RS. Hyperthyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology,* 13th ed. Philadelphia: Elsevier; 2016: Table 12.4.

Thyroid storm is an extreme form of hyperthyroidism characterized by severely elevated thyroid hormone levels, hyperthermia, tachycardia, heart failure, altered mental status, and GI symptoms (Table 606.5). If untreated, there may be rapid progression to delirium, coma, and death. Precipitating events include trauma, infection, radioactive iodine (RAI) treatment, or surgery.

Fig. 606.2 Retraction of upper eyelids in the primary gaze (Dalrymple sign). *(From Kanski JJ. Systemic Diseases and the Eye: Signs and Differential Diagnosis. London: Mosby; 2001.)*

LABORATORY FINDINGS

In Graves disease, serum TSH is suppressed and free T_4 and T_3 are elevated. Most patients with Graves disease have measurable TRSAbs at diagnosis. TRSAbs can be measured either by a functional assay (thyroid-stimulating immunoglobulin [TSI]) that assesses the presence of antibodies capable of stimulating TSHR-mediated cyclic adenosine monophosphate (cAMP) generation, or by a competitive binding assay (thyrotropin-binding inhibitory immunoglobulin [TBII]) that assesses the presence of antibodies that bind to the TSHR, regardless of their effect on receptor activity. In a patient with thyrotoxicosis, both assays are highly sensitive and specific for Graves disease.

When the diagnosis cannot be established by history, physical examination, and laboratory evaluation, RAI uptake can be measured, preferably using ^{123}I. RAI uptake is elevated in Graves disease, whereas it is low in other causes of thyrotoxicosis like thyroiditis or exogenous thyroid hormone ingestion. If scintigraphy is also performed, the increased RAI uptake in Graves disease is present diffusely throughout the gland, whereas focally increased uptake is observed in hyperfunctioning thyroid nodules.

DIFFERENTIAL DIAGNOSIS

Elevated serum levels of T_4 or free T_4 and T_3 in association with suppressed levels of TSH are diagnostic of thyrotoxicosis (see Table 606.1).

Table 606.5 Diagnostic Criteria for Thyroid Storm

	POINTS
TEMPERATURE °F (°C)	
99-99.9 (37.2-37.7)	5
100-100.9 (37.8-38.2)	10
101-101.9 (38.3-38.8)	15
102-102.9 (38.9-39.4)	20
103-103.9 (39.4-39.9)	25
≥104.0 (>40.0)	30
CENTRAL NERVOUS SYSTEM EFFECTS	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
GASTROINTESTINAL-HEPATIC DYSFUNCTION	
Absent	0
Moderate (diarrhea, nausea/vomiting, abdominal pain)	10
Severe (unexplained jaundice)	20
CARDIOVASCULAR DYSFUNCTION	
Tachycardia	
90-109	5
110-119	10
120-129	15
130-139	20
≥140	25
Congestive Heart Failure	
Absent	0
Mild (pedal edema)	5
Moderate (bibasilar rales)	10
Severe (pulmonary edema)	15
Atrial Fibrillation	
Absent	0
Present	10
Precipitating History	
Absent	0
Present	10

In adults, a score ≥45 is highly suggestive of thyroid storm; a score of 25-44 is suggestive of impending thyroid storm; a score of <25 is unlikely to represent thyroid storm.
Data are from HB Burch, L Wartofsky. Life-threatening thyrotoxicosis. Thyroid storm. *Endocrinol Metab Clin North Am.* 1993;22:263–277. From De Leo S, Lee SY, Braverman LE. Hyperthyroidism. *Lancet.* 2016;388:906–916, Table 3.

The combination of diffuse goiter and prolonged thyrotoxicosis (>8 weeks) is most often caused by Graves disease; the presence of circulating TSHR antibodies or characteristic eye or skin changes is diagnostic.

If the etiology of thyrotoxicosis is unclear, ^{123}I radioiodine uptake can distinguish hyperthyroidism (increased uptake) from other causes of thyrotoxicosis, which will determine the appropriateness of antithyroid medication. If a discrete thyroid nodule is palpated, ^{123}I scintigraphy should be performed to assess for a hyperfunctioning nodule. Some children with toxic multinodular goiter may have a TSHR-activating pathogenic variant or McCune-Albright syndrome. If precocious puberty, polyostotic fibrous dysplasia, or café-au-lait macules are present, then McCune-Albright syndrome is likely.

Patients with thyroid hormone resistance have elevated levels of free T_4 and T_3, but levels of TSH are inappropriately elevated or normal. They must be differentiated from patients with TSH-secreting pituitary tumors who have elevated serum levels of the common α-subunit shared by TSH, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (hCG). Most other causes of elevated serum T_4 are uncommon but can result in an erroneous diagnosis. Patients with elevated thyroxine-binding globulin levels or familial dysalbuminemic hyperthyroxinemia have high serum T_4 but normal levels of free T_4 and TSH and are clinically euthyroid. Rare patients with pathogenic variants in *SLC16A2* (encoding the MCT8 thyroid hormone transporter) or *THRA* (encoding thyroid hormone receptor α) can present with high serum T_3, inappropriately normal or high TSH, and low or low-normal serum T_4 concentrations.

When thyrotoxicosis is caused by exogenous thyroid hormone, free T_4 and TSH levels are the same as those seen in Graves disease, but in contrast to Graves disease, thyroid size is small, serum thyroglobulin is very low, and ^{123}I radioiodine uptake is suppressed.

TREATMENT

Antithyroid Drugs

In most cases, antithyroid drugs (ATDs) are the preferred initial therapy for Graves disease in children. Alternative treatments include radioiodine ablation (in children older than 10 years of age) and thyroidectomy. Each therapeutic option has advantages and disadvantages (Table 606.6). Methimazole is the first-line ATD for children with Graves disease and functions by blocking the organification of iodide necessary to synthesize thyroid hormone. Methimazole has a long serum half-life (6-8 hours) that allows once- or twice-daily dosing. Propylthiouracil is similar to methimazole, but its use is not recommended in children because of its potential to cause liver failure. However, in rare instances of severe hyperthyroidism in which methimazole cannot be used, a short course of propylthiouracil may be offered to restore euthyroidism before definitive therapy.

Adverse reactions can occur with ATDs and range from mild to life-threatening. Minor adverse effects occur in approximately 10–20% of patients, and severe adverse effects occur in 2–5%. Reactions most commonly occur during the first 3 months of therapy but can occur at any time. Transient urticaria is common and may be managed with antihistamines or by a short period off therapy followed by restarting ATD. Agranulocytosis is a severe adverse reaction that occurs in 0.1–0.5% of patients and can lead to a fatal infection. Therefore during any episode of significant fever, pharyngitis, or oral ulcers, patients should stop taking methimazole and have an absolute neutrophil count checked. On the other hand, transient, asymptomatic granulocytopenia (<2,000/mm^3) is common in Graves disease; it is not a harbinger of agranulocytosis and is not a reason to discontinue treatment. Other severe reactions include hepatitis (0.2–1.0%), a lupus-like polyarthritis syndrome, glomerulonephritis, and antineutrophilic cytoplasmic antibody–positive vasculitis. Severe liver disease, including liver failure requiring transplantation, has been reported with propylthiouracil. The most common liver disease associated with methimazole is cholestatic jaundice, which is reversible when the drug is discontinued. Patients with severe adverse effects should be treated with radioiodine or thyroidectomy. Importantly, methimazole and propylthiouracil have been associated with congenital malformations in infants exposed to these drugs in utero. Methimazole exposure may be associated with aplasia cutis, omphalocele, choanal atresia,

Table 606.6 Treatments for Graves Disease

TREATMENT	ADVANTAGE	DISADVANTAGE	COMMENT
Antithyroid drugs	Noninvasive Less initial cost No risk of permanent hypothyroidism Possible remission	Remission rate 30–50% (with long-term treatment) Adverse drug reactions Drug compliance required	First-line treatment in children and adolescents
Radioactive iodine (^{131}I)	Cure of hyperthyroidism	Permanent hypothyroidism Might worsen ophthalmopathy Pregnancy must be deferred for 6-12 mo, mother cannot breastfeed; small potential risk of exacerbation of hyperthyroidism	No evidence for infertility or birth defects with currently recommended doses
Surgery	Rapid, effective (especially in patients with large goiter)	Most invasive therapy Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) Permanent hypothyroidism Pain, surgical scar	Useful when coexisting suspicious nodule is present or thyromegaly is massive Option for patients who do not desire radioiodine

Modified from Cooper DS. Hyperthyroidism. *Lancet.* 2003;362:459–468.

Table 606.7 Management of Thyroid Storm in Adolescents

GOAL	TREATMENT
Inhibition of thyroid hormone formation and secretion	Propylthiouracil 400 mg q8h PO/IV/NGT Saturated solution of potassium iodide, 3 drops every 8 hr
Sympathetic blockade	Propranolol 20-40 mg q4-6h or 1 mg IV slowly (repeat doses until heart rate slows); not indicated in patients with asthma or heart failure that is not rate related
Glucocorticoid therapy	Prednisone 20 mg bid
Supportive therapy	Intravenous fluids (depending on indication: glucose, electrolytes, multivitamins) Temperature control (cooling blankets, acetaminophen; avoid salicylates) O_2 if required Digitalis for heart failure and to slow ventricular response; pentobarbital for sedation Treatment of precipitating event (e.g., infection)

From Goldman L, Ausiello D, eds. *Cecil Textbook of Medicine,* 22nd ed. Philadelphia: WB Saunders; 2004:1401.

and urinary system malformations, whereas propylthiouracil may be associated with malformations of the head, neck, and urinary system.

The initial dosage of methimazole is 0.5-1.0 mg/kg/24 hr (max 40 mg/day) administered once or twice daily. Smaller initial dosages should be used in early childhood or for mild disease. Careful surveillance is required after treatment is initiated. Low serum free T_4 or elevated serum TSH indicates overtreatment and warrants a dose reduction. The clinical response becomes apparent in 3-4 weeks, and adequate control is typically evident within 2-4 months. The dose is slowly decreased to the minimal level required to maintain a euthyroid state.

Most studies report a remission rate of approximately 25% after 2 years of ATD treatment in children. However, extended treatment appears to be associated with higher remission rates of 30–50% after 4-10 years of drug treatment. Among patients who remit, relapse may occur, often within 6-12 months after therapy has been discontinued. In cases of relapse, ATD therapy may be resumed, or definitive therapy with radioiodine or thyroidectomy can be pursued. Rituximab has been used as an adjuvant therapy for difficult-to-treat Graves disease.

Thyroid hormones potentiate the actions of catecholamines, leading to symptoms of tachycardia, tremor, excessive sweating, lid lag, and stare. *To ameliorate cardiovascular symptoms, a β-adrenergic blocking agent such as propranolol or atenolol is a useful initial supplement to ATDs.* However, these agents do not alter thyroid function or treat Graves ophthalmopathy. Table 606.7 lists additional therapies for **thyroid storm**.

Definitive Therapy

Radioiodine ablation or thyroidectomy is indicated when medical management is not possible because of patient nonadherence or severe side effects of ATDs, when an adequate trial of medical management has failed to result in remission, or if the patient prefers definitive therapy.

Radioiodine ablation with ^{131}I is an effective therapy for Graves disease in children. In patients with severe hyperthyroidism, euthyroidism should be restored with methimazole before radioiodine ablation to deplete the gland of preformed hormone and reduce the risk of a thyrotoxic flare from radiation thyroiditis. If a patient is taking methimazole, it should be stopped 3-5 days before radioiodine administration. The goal of radioiodine ablation is to administer a sufficient dose of radioiodine to ensure complete ablation of thyroid tissue. Some centers measure radioiodine uptake before treatment and use this to calculate an ^{131}I dose that delivers an absorbed thyroid dose of >150 μCi/g thyroid tissue (based on thyroid gland mass estimated by clinical examination or ultrasound). Alternatively, an empiric fixed dose of ^{131}I (usually 10-15 mCi) can be offered. The theoretical advantage of calculated doses is that they define the lowest administered dose for each patient who achieves the therapeutic target. This benefit is most important in small children because the absorbed radiation dose to the bone marrow and other normal tissues is inversely proportional to body size. Based on this concept and theoretical modeling of radiation exposure, ^{131}I therapy should be avoided in children younger than 5 years of age. It should be used in children between 5 and 10 years of age if the administered dose is <10 mCi. Radioiodine ablation has a low failure rate (5–20%), and

patients with persistent hyperthyroidism more than 6 months after their first ^{131}I therapy can be offered retreatment.

Thyroidectomy is a safe procedure when performed by an experienced surgeon. Thyroid surgery should be performed only after the patient has been rendered euthyroid with methimazole. A saturated solution of potassium iodide (SSKI; 1-3 drops, 2-3 times per day) may be added for 7-14 days before surgery to decrease the vascularity of the gland. Complications of surgical treatment include hypoparathyroidism (transient or permanent) and paralysis of the vocal cords. Total or near-total thyroidectomy should be performed rather than a less extensive subtotal resection. Patients become hypothyroid postoperatively, and recurrence of hyperthyroidism is rare. Referral to a surgeon with extensive experience in thyroidectomy and a low personal complication rate is paramount.

Graves **ophthalmopathy** usually remits gradually and independently of hyperthyroidism, but control of ophthalmopathy is facilitated by maintaining consistent euthyroidism. Severe ophthalmopathy can require treatment with high-dose glucocorticoids, orbital radiotherapy, or orbital decompression surgery. Teprotumumab, a human monoclonal antibody against the insulin-like growth factor 1 receptor (IGF-1R) is effective in adults with ophthalmopathy. Cigarette smoking is a risk factor for thyroid eye disease and should be avoided or discontinued to avoid progression of eye involvement.

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Fig. 606.3 Twins with neonatal hyperthyroidism confirmed by abnormal thyroid function tests. Clinical features include lack of subcutaneous tissue owing to a hypermetabolic state and a wide-eyed, anxious stare. They were given the diagnosis of neonatal Graves disease, but, in fact, their mother did not have Graves disease; they had persistent, not transient, hyperthyroidism. At age 8 years, they were treated with radioiodine. They are now believed to have had some other form of neonatal hyperthyroidism, such as a constitutive activation of the thyroid-stimulating hormone receptor.

606.2 Congenital Hyperthyroidism

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Neonatal Graves disease is caused by transplacental passage of TRSAbs from mothers with a history of Graves disease. These mothers can have active Graves disease, Graves disease in remission, or a prior history of Graves disease treated with radioiodine ablation or thyroidectomy. Occasionally, there is a maternal history of autoimmune thyroiditis. High levels of TRSAb typically result in fetal and neonatal hyperthyroidism. However, if the mother has been treated with ATDs, the onset of hyperthyroidism may be delayed by 3-7 days postnatally until the ATD is metabolized by the neonate. If TRBAbs are also present, they may delay the onset of hyperthyroidism for several weeks or even cause neonatal hypothyroidism. Neonatal Graves disease typically remits spontaneously within 6-12 weeks but can persist longer, depending on the titer and rate of clearance of the TRSAbs (and TRBAbs, if present).

Neonatal hyperthyroidism occurs in approximately 2% of infants born to mothers with a history of Graves disease. Fetal tachycardia and goiter may suggest the diagnosis prenatally, and close ultrasound surveillance is recommended in mothers with uncontrolled hyperthyroidism, particularly in the third trimester. Elevated serum titers of TRSAb (more than 3 times the upper limit of normal) or a history of a prior child with neonatal thyroid dysfunction increases the likelihood of neonatal Graves disease.

CLINICAL MANIFESTATIONS

Many infants born with neonatal Graves disease are premature and have intrauterine growth restriction. Many infants also have a goiter, and tracheal compression can occur if the goiter is very large. Other signs and symptoms of neonatal Graves disease include stare, periorbital edema, retraction of the eyelids, hyperthermia, irritability, diarrhea, feeding difficulties, poor weight gain, tachycardia, heart failure, hypertension, hepatomegaly, splenomegaly, cholestasis, jaundice, thrombocytopenia, and hyperviscosity (Fig. 606.3). Laboratory evaluation shows suppressed serum TSH and elevated serum levels of T_4, free T_4, and T_3. TRSAbs are elevated at birth and typically resolve within 3 months of life. If symptoms and signs are not recognized and treated promptly, cardiac failure and death can occur. Permanent sequelae of neonatal hyperthyroidism can include craniosynostosis and developmental delay.

TREATMENT

Treatment should be initiated at the onset of symptoms to avoid short-term and long-term complications. Therapy consists of methimazole (0.5-1.0 mg/kg/24 hr given every 12 hr) and oral or intravenous administration of a nonselective β-adrenergic blocker such as propranolol to decrease sympathetic hyperactivity. In refractory cases, Lugol solution or potassium iodide (1-2 drops per day) can be added. The first dose of iodide should be given at least 1 hour after the first dose of ATD to prevent the iodide from being used for further thyroid hormone synthesis. If severe hyperthyroidism induces heart failure, parenteral fluid therapy, corticosteroids, and digitalization may be indicated. Once serum thyroid hormone levels begin to decrease, ATDs should be gradually tapered to keep the infant euthyroid. Occasionally, a block-and-replace method with concurrent ATD and thyroid hormone replacement therapy may be required to ensure euthyroidism.

Most cases of neonatal Graves disease remit by 3 months of age, but occasionally neonatal hyperthyroidism persists into childhood. Typically, there is a family history of hyperthyroidism. **Neonatal hyperthyroidism** *without* evidence for autoimmune disease in mother or infant may be caused by a gain-of-function pathogenic variant in the *TSHR* gene that results in constitutive activation of the receptor. This can be transmitted in an autosomal dominant manner or can occur sporadically. Neonatal hyperthyroidism has also been reported in patients with McCune-Albright syndrome because of an activating pathogenic variant of the G protein stimulatory α-subunit. Under these circumstances, hyperthyroidism recurs when ATDs are discontinued, and these children eventually must be treated with radioiodine or surgery.

PROGNOSIS

Advanced osseous maturation, microcephaly, and cognitive impairment occur when treatment of neonatal hyperthyroidism is delayed. Intellectual development is normal in most treated infants with neonatal Graves disease, although some have neurocognitive problems likely caused by in utero hyperthyroidism. Therefore neurocognitive development should be monitored throughout childhood. After the resolution of neonatal hyperthyroidism, some infants develop transient or permanent central hypothyroidism that requires thyroid hormone replacement, likely resulting from poorly understood changes in hypothalamic-pituitary-thyroid feedback caused by in utero hyperthyroidism.

Resistance to Thyroid Hormone

The actions of thyroid hormones are mediated by two thyroid hormone receptors (α and β), each with a unique tissue distribution. Inactivating pathogenic variants in each of these receptors gives rise to a distinct syndrome of resistance to thyroid hormone. Resistance to thyroid hormone β (RTHβ) is an *autosomal dominant* disorder caused by pathogenic variants in the *THRB* gene. Because this receptor mediates the normal feedback of thyroid hormone on the hypothalamus and pituitary, patients have elevated serum levels of T_4 and T_3, but serum TSH levels are inappropriately normal or elevated. Goiter is almost always present, but symptoms of thyroid dysfunction are variable among individuals. There may be clinical features of hypothyroidism such as developmental delay, growth retardation, delayed skeletal maturation, and some features of hyperthyroidism like tachycardia and hyperreflexia. Affected children have an increased prevalence of learning disabilities and ADHD. The clinical symptoms, goiter, and elevated thyroid hormone levels may be mistaken for Graves disease, but RTHβ is confirmed by the presence of normal or elevated (not suppressed) TSH levels. This condition must also be differentiated from a pituitary TSH-secreting tumor, which is not familial and in which serum levels of the common α-subunit are elevated.

More than 100 distinct variants in *THRB* have been identified in patients with RTHβ, and genotype-phenotype correlation is poor even among affected members of the same family. Nearly all mutations have a dominant-negative effect in which the variant receptor interferes with normal receptor action, leading to disease even in heterozygotes. Individuals carrying two mutant alleles are severely affected. A very rare *autosomal recessive* form of this disorder has been reported in individuals homozygous for a deletion of the *THRB* gene.

Treatment usually is not required unless growth and skeletal stunting are present. Different therapies, including levothyroxine and triiodothyroacetic acid, have been successful in some patients. Intermittent administration of T_3 may be useful for reducing goiter size. Symptoms of hyperthyroidism can be treated with β blockers, but ATDs or radioiodine ablation are generally not used because they increase TSH levels and goiter size.

Pathogenic variants in the *THRA* gene, which encodes thyroid hormone receptor α, have also been reported. *THRA* variants are dominant negative and cause RTHα in heterozygous individuals. Clinical symptoms are those of untreated primary hypothyroidism, including skeletal dysplasia with short stature and macrocephaly, developmental delay, constipation, bradycardia, and macrocytic anemia. Serum thyroid function tests show subtle abnormalities of low or low-normal T_4, high or high-normal T_3 (with elevated T_3/T_4 ratio), and normal TSH, as well as the unique finding of markedly low reverse T_3. Treatment has not been clearly established for RTHα.

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Chapter 607

Carcinoma of the Thyroid

Jessica R. Smith and Ari J. Wassner

Carcinoma of the thyroid is rare in childhood, with an annual incidence in children younger than 15 years of approximately 4-5 in 100,000 cases. The incidence of childhood thyroid cancer increases with age and peaks in adolescence. Females are more commonly affected than males. Compared to adults, childhood thyroid cancers are characterized by significantly higher rates of metastasis and recurrence. Despite often being metastatic at discovery, most pediatric thyroid cancers with adequate treatment have a favorable outcome.

PATHOGENESIS

The majority of differentiated thyroid cancers are of follicular cell origin; **papillary carcinoma** (85–90%) is the most common subtype. Although their histologic features are similar, papillary thyroid cancers of childhood are genetically distinct from their adult counterparts. About 70% of adults with papillary thyroid cancer exhibit pathogenic somatic variants in *BRAF* or *RAS*; pediatric papillary thyroid cancers are more commonly caused by somatic gene fusion events involving the oncogenic tyrosine kinases *RET* or *NTRK1/3*. **Follicular carcinoma** (8%) is the next most common type of childhood thyroid cancer and is also derived from thyroid follicular cells. **Medullary carcinoma** (4%), derived from thyroid C cells, and anaplastic thyroid cancers are relatively rare.

Up to 10% of cases of follicular cell–derived thyroid cancers may be familial. Genetic syndromes associated with an increased risk of thyroid neoplasia include ***PTEN* hamartoma tumor syndromes** (Cowden, Bannayan-Riley-Ruvalcaba, and Proteus syndromes) characterized by macrocephaly, mucocutaneous lesions (fibromas), and breast cancer and endometrial tumors; **familial adenomatous polyposis** (pathogenic variant in *APC*); and ***DICER1* syndrome**, which includes tumors of the lung, kidney, female reproductive tract, and other organs. The evaluation of a child with a thyroid nodule should include a medical and family history to assess for features of these syndromes. In addition, some families have a strong history of nonsyndromic nonmedullary thyroid cancer, but no specific genetic causes have been confirmed.

The thyroid gland of children is susceptible to radiation exposure, particularly in very young patients. Even a low dose (1 Gy) of radiation exposure results in a 7.7-fold increased relative risk of thyroid cancer. In past decades, irradiation of the cervical region for benign conditions (e.g., enlarged thymus or tonsils, adenitis) was a predominant cause of thyroid cancer in children. Currently, therapeutic irradiation for other regional neoplasms or bone marrow transplantation and the increased survival of these children have made this cause of thyroid cancer increasingly prevalent. Higher radiation dose, younger age at the time of treatment, and female sex are additional risk factors for the development of thyroid cancer. The relative risk of thyroid cancer is highest after radiation doses of 5-30 Gy, above which the excess risk declines but does not disappear. In studies of cancer survivors treated with radiation, ~10–30% develop benign thyroid nodules. There is an increased incidence of thyroid cancer beginning within 3-5 years after radiation treatment and peaking after 15-25 years.

Autoimmune thyroiditis and Graves disease may be associated with an increased risk of thyroid cancer, but data remain conflicting.

Therefore thyroid nodules detected in patients with these disorders should be evaluated for possible thyroid cancer. Thyroid cancer has been reported rarely in children with congenital goiter or ectopic thyroid tissue.

CLINICAL MANIFESTATIONS

Thyroid cancer usually presents as a *painless nodule* in the anterior neck. Rapid growth and large size, firmness, fixation to adjacent tissues, hoarseness, dysphagia, or neck lymphadenopathy should heighten the concern for thyroid cancer. Cervical lymph node metastasis is common, so any unexplained cervical lymphadenopathy warrants examination of the thyroid.

The lungs are the most common site of distant metastasis. Pulmonary metastases are usually asymptomatic, and pulmonary function testing may be normal even with widespread metastases. Radiologically, metastases may appear as diffuse miliary or nodular infiltrations, typically greatest in the posterior basal lung fields. Other sites of metastasis, including bones and brain, are rare in children. Almost all children with thyroid cancer are euthyroid, but rarely is the carcinoma functional and produces clinical and laboratory evidence of hyperthyroidism.

DIAGNOSIS

Patients usually present with a neck mass, and thyroid ultrasound demonstrates a thyroid nodule and/or diffuse infiltration of the thyroid. Although several imaging features (including calcifications, irregular margins, and the presence of abnormal lymph nodes) are significantly associated with thyroid cancer risk, the absence of these features does not exclude the possibility of thyroid cancer. The appropriate technique for evaluating sonographically suspicious nodules is fine needle aspiration (FNA), which can detect the characteristic nuclear abnormalities of papillary thyroid carcinoma, which is the most common form. In most cases, operative pathology is required to confirm the diagnosis of thyroid cancer and to determine the extent of disease.

TREATMENT

The primary therapy for thyroid cancer is surgical resection. Because intrathyroidal spread is common in papillary thyroid cancer, near-total thyroidectomy is recommended. Before surgery, neck ultrasonography should be performed to assess for abnormal lymph nodes, and suspicious lymph nodes may be biopsied preoperatively to determine the need for lymph node dissection. In patients with metastatic thyroid cancer, adjunctive therapy may be required with radioactive iodine (^{131}I) to ablate unresectable thyroid cancer and thyroid-stimulating hormone (TSH) suppression with supraphysiologic levothyroxine to reduce TSH-stimulated growth of residual cancer cells.

PROGNOSIS

Although regional and distant metastases are more common in the pediatric population than in adults, most children with thyroid cancer have an excellent prognosis. Long-term survival from pediatric thyroid cancer is >97%, although the disease may recur in up to 15–20%. Even in children with pulmonary metastasis at diagnosis, 30-year survival is 90%, and many patients who cannot achieve complete cure remain asymptomatic with stable or slowly progressive cancer burden over many years. For rare children with aggressive cancers that progress despite conventional therapy, targeted molecular therapies directed at the underlying genetic pathogenic variants are available and effective in many cases. Psychosocial supports, including access to social work and mental health professionals, are essential in caring for children with thyroid cancer.

Children with thyroid cancer require lifelong monitoring because of the risk of disease recurrence years or decades after initial treatment. For most patients, serum thyroglobulin is a sensitive and specific cancer marker. Circulating autoantibodies to thyroglobulin can confound the measurement of thyroglobulin levels and should be measured whenever serum thyroglobulin is assayed. Because most thyroid cancer recurrences occur in the thyroid bed or cervical lymph nodes, surveillance should include serial neck ultrasounds. Patients with a higher risk of recurrence or with distant metastases may require additional anatomic imaging (such as chest CT), whole-body radioactive iodine scanning (^{123}I), or combined anatomic and functional imaging (SPECT/CT).

MEDULLARY THYROID CARCINOMA

Medullary thyroid carcinoma (MTC) arises from the parafollicular cells (C cells) of the thyroid and accounts for approximately 4% of thyroid malignancies in children. In children, the majority of MTC cases are hereditary, as part of the syndrome of **multiple endocrine neoplasia type 2** (MEN2; see Chapter 609). Activating pathogenic variants in the *RET* proto-oncogene are responsible for most cases of MTC. These variants occur in the germline in patients with MEN2, but somatic *RET* changes are present in many sporadic cases of MTC.

The most common presentation of sporadic MTC is an asymptomatic thyroid nodule. When MTC occurs sporadically, it is usually unicentric, but in the familial form it may be multicentric. MTC begins as hyperplasia of the parafollicular cells (*C cell hyperplasia*), which is often present histologically in thyroid glands removed prophylactically from patients with MEN2. The diagnosis of MTC can also be made by cytology after FNA of a thyroid nodule. Because C cells produce calcitonin, a high calcitonin concentration in an FNA specimen or in a patient's serum can help confirm the diagnosis of MTC. The diagnosis warrants genetic testing for a germline *RET* variant, and in variant-positive patients, screening for pheochromocytoma and hyperparathyroidism should be obtained before anesthesia for thyroidectomy.

The most important treatment for MTC is surgical resection. Preoperative evaluation should include neck ultrasound to identify potential lymph node metastases. Baseline serum levels of calcitonin and carcinoembryonic antigen (CEA) should be measured preoperatively, and higher levels are correlated with a greater likelihood of metastatic disease. Surgical treatment includes total thyroidectomy and lymph node dissection of any involved lymph node compartments. Complete resection is often curative, but this can be difficult to achieve in patients with metastatic disease. Surveillance with neck ultrasound and serum levels of calcitonin and CEA can assess for the presence or progression of residual disease. Other treatment modalities for advanced or metastatic disease include specific *RET* inhibitors, external beam radiation, and radiofrequency ablation.

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607.1 Thyroid Nodules

Jessica R. Smith and Ari J. Wassner

The frequency of thyroid nodules increases with age. Sonographically detectable thyroid nodules are present in 19–67% of adults but in only 1–2% of children. Although the risk of malignancy in a thyroid nodule is higher in children (20–25%) than in adults (5–15%), the majority of thyroid nodules in children are benign.

Benign disorders that can present as a thyroid mass include benign adenomatous or colloid nodules and various congenital cysts (Table 607.1). A thyroid mass that appears suddenly or enlarges rapidly can indicate hemorrhage into a cyst, a benign adenoma, or an infectious process.

Evaluation of a child with a thyroid nodule should begin by measuring serum TSH. A low serum TSH suggests a possible hyperfunctioning (autonomous) thyroid nodule, which should be evaluated by scintigraphy (^{123}I or ^{99m}Tc-pertechnetate). Autonomous nodules generally are not malignant and do not require biopsy. Patients with a normal or elevated TSH should undergo neck ultrasound, and any sonographically suspicious nodule(s) of significant size should be evaluated by ultrasound-guided FNA

Table 607.1 Etiologic Classification of Solitary Thyroid Nodules

Lymphoid follicle, as part of autoimmune thyroiditis
Thyroid developmental anomalies
Intrathyroidal thyroglossal duct cyst
Intrathyroidal ectopic thymus
Thyroid abscess (acute infectious thyroiditis)
Simple cyst
Neoplasms
Benign
Colloid (adenomatous) nodule
Follicular adenoma
Hyperfunctioning (toxic) adenoma
Lymphohemangioma
Malignant
Papillary carcinoma
Follicular carcinoma
Anaplastic carcinoma
Medullary carcinoma
Nonthyroidal
Lymphoma
Teratoma

(Fig. 607.1). Thyroid cytology is evaluated using a standardized system, most commonly the Bethesda System for Reporting Thyroid Cytopathology. Cytology may be interpreted as benign, positive for papillary thyroid cancer, indeterminate, or nondiagnostic. The predictive value of cytology for thyroid cancer varies by category and to some degree among institutions. In general, cytology positive for papillary thyroid cancer confers a >98% likelihood of cancer, and near-total thyroidectomy is appropriate. For a nodule of indeterminate cytology, lobectomy is commonly performed for definitive diagnosis; this may be followed by completion thyroidectomy if pathology shows a significant thyroid cancer. Molecular testing for oncogenic mutations may inform the management of certain indeterminate cytology. Patients with cytologically benign nodules have a low likelihood of malignancy and should be monitored with serial neck ultrasound. Surgical resection may be offered for benign nodules that cause symptoms, including dysphagia, globus sensation, or undesired appearance.

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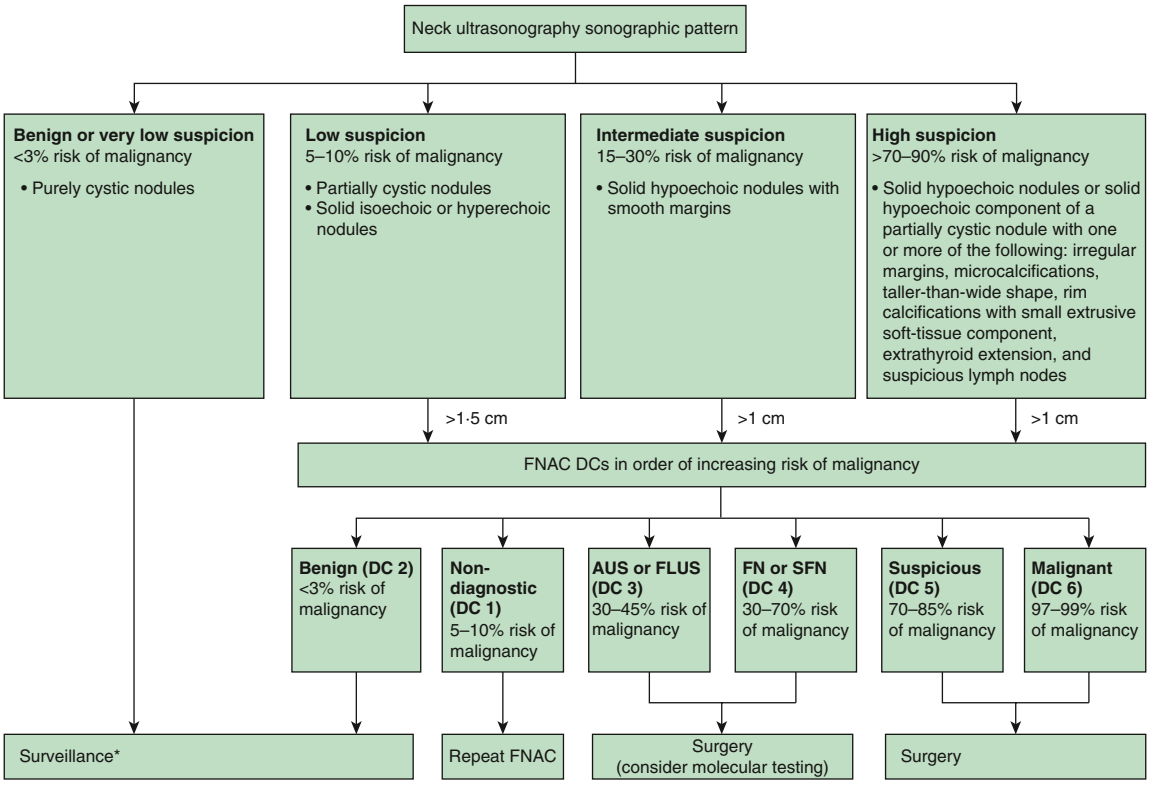

Fig. 607.1 Management algorithm for thyroid nodules based on sonographic patterns and cytology diagnostic categories of the Bethesda System. *Fine-needle aspiration can be considered (1) for nodules with a low-suspicion sonographic pattern and the largest diameter greater than 2 cm and (2) if there are suspicious clinical findings (e.g., firm mass, neck pain, cough, voice change, and a history of childhood neck irradiation or familial thyroid cancer), regardless of the sonographic appearances. AUS, Atypia of undetermined significance; DC, diagnostic category; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm; FNAC, fine needle aspiration cytology; SFN, suspicious for follicular neoplasm. *(From Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet. 2016;388:2783–2794, Fig. 2.)*

Chapter 608

Autoimmune Polyglandular Syndromes

Christina M. Astley, Jessica R. Smith, and Ari J. Wassner

An **autoimmune polyglandular syndrome (APS)** occurs when autoimmunity is directed at multiple glands and/or nonendocrine organs, sometimes associated with **immune dysregulation**. Endocrine glands and other organs commonly affected by APS have unique autoantigens that increase these tissues' susceptibility to damage by an untamed immune response. Most autoimmune endocrinopathies are caused by cell-mediated immunity from autoreactive T cells. Antibodies to one or more autoantigens are commonly associated with specific autoimmune manifestations and are markers of immune dysregulation. These autoantibodies are directly pathogenic in some nonendocrine tissues, but this is rarely the case in autoimmune endocrine disease. A notable exception is the autoantibodies in Graves disease that cause primary hyperthyroidism by activating the thyroid-stimulating hormone receptor (TSHR).

APS caused by monogenic disorders of immune dysregulation (including APS type 1 [**APS-1**]) have heritable lesions in key aspects of immune tolerance (Table 608.1). Polygenic disorders associated with APS (APS type 2 [**APS-2**]) and some chromosomal abnormalities (e.g., trisomy 21) also result in an aberrant immune response that causes multiorgan autoimmunity. Nongenetic factors (e.g., immune **checkpoint inhibitors** for cancer therapy) may lead to autoimmune polyglandular disease. Although APS is uncommon, patients can experience significant morbidity, particularly if the syndrome is not identified early and managed appropriately. There may be 1-2 decades between the presentations of the first and subsequent endocrinopathy. *The presence of hypoparathyroidism, primary adrenal insufficiency, neonatal type 1 diabetes mellitus, chronic mucocutaneous candidiasis, immune dysregulation, or a family history should raise particular suspicion for APS.*

MONOGENIC AUTOIMMUNE POLYGLANDULAR SYNDROMES

The number of recognized monogenic defects of immune regulation leading to APS continues to grow (see Table 608.1). The best-characterized monogenic APSs are caused by pathogenic genetic variants that primarily affect central immune tolerance **(APS-1)** or the development of regulatory T cells (immune dysregulation polyendocrinopathy enteropathy X-linked, or **IPEX**). Other monogenic APSs (the so-called IPEX-like disorders) are caused by defects in regulatory T-cell suppression or signaling.

AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE 1

APS-1 is an archetypal monogenic polyendocrinopathy syndrome. It is a rare, autosomal recessive disorder caused by loss-of-function variants in the autoimmune regulator gene *(AIRE)* on chromosome 21q22.3. *AIRE* plays a critical role in the presentation of self-antigens to developing T cells in the thymus, which normally leads to central immune tolerance by inducing apoptosis of T cells specific for these autoantigens (negative selection). *AIRE* also plays a role in the development of regulatory T cells (see Chapter 174). Therefore patients with APS-1 develop autoreactive T cells and autoantibodies directed at multiple tissues.

APS-1 is defined by the presence of at least two of three classic clinical features **(Whitaker triad)** of **chronic mucocutaneous candidiasis**, **hypoparathyroidism**, and primary **adrenal insufficiency**. These three manifestations tend to emerge over time—candidiasis before around 5 years of age, hypoparathyroidism around 10 years, and adrenal insufficiency around 15 years—but the precise order and age of onset of each component are variable. Most patients develop additional autoimmune manifestations over time, with skin and gastrointestinal disorders typically emerging before age 20 and other endocrine disorders after the second decade (see Table 608.1).

Nearly every endocrine gland may be affected by APS-1. The commonly affected glands include parathyroids and adrenals. Other glands affected, in decreasing order of frequency, are the ovaries, testes, thyroid, pancreatic β cells, and pituitary. A wide range of nonendocrine tissues can be affected, sometimes before the first endocrinopathy is detected. The commonly affected nonendocrine tissues are teeth and nails, and ectodermal dystrophy is present in most patients. For this reason, APS-1 has also been called **autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED)**. Other manifestations include gastrointestinal malabsorption, autoimmune hepatitis, pernicious anemia, vitiligo, and alopecia. APS-1 patients are at increased risk of infection, possibly related to a combination of cytokine autoantibodies, splenic dysfunction, and compromised gastrointestinal mucosal integrity. Mucocutaneous candidiasis is quite common and can lead to oral or esophageal cancer if not diagnosed and treated. Esophageal cancer, autoimmune hepatitis, adrenal crisis, and severe hypocalcemia are important causes of mortality in APS-1 patients. Therefore APS-1 patients require close clinical follow-up with a multidisciplinary team to manage disease manifestations. (Treatment of individual endocrinopathies and other manifestations are reviewed separately in the relevant chapters, including Chapters 280, 611, and 615).

The initial diagnosis of APS-1 generally is made clinically. Pathogenic *AIRE* variants can be detected in the majority of patients with clinical APS-1, and confirmation of the diagnosis by *AIRE* sequencing is indicated for any patient with known or suspected APS-1. APS-1 caused by pathogenic *AIRE* variants is more common in certain founder populations (e.g., Iranian Jews, Sardinians, Finns, and Norwegians reported a prevalence ranging from 1 in 9,000 to 1 in 90,000). Knowledge of the specific pathogenic variant facilitates clinical and genetic counseling, including testing of family members. *AIRE* variants with autosomal dominant inheritance and an atypical APS-2–like clinical presentation (especially with pernicious anemia or vitiligo) have been reported. APS-1 patients without identifiable *AIRE* variants may benefit from further evaluation (e.g., immune dysregulation gene panel, whole exome sequencing, imaging for thymoma).

The clinical presentation of APS-1 is variable, even within families with the same *AIRE* variant, making it difficult to predict the disease course for affected individuals. Therefore patients with APS-1 should have regular screening for the development of new clinical manifestations. The importance of screening is illustrated by unexplained deaths in APS-1 patients or their siblings, presumably the result of undiagnosed manifestations such as adrenal insufficiency.

Multiple autoantibodies may be detectable in patients with APS-1 (Table 608.2). Many of these autoantibodies are also present in the corresponding single-organ autoimmune disease, but autoantibodies to some antigens (e.g., NALP5, interleukin-17 family cytokine, and type 1 interferons) are unique to APS-1. Measuring organ-specific autoantibodies has variable utility for predicting the onset of endocrine gland failure or other APS-1 manifestations. Therefore clinical suspicion, laboratory screening, and education about symptoms of evolving endocrinopathies and/or other APS-1 manifestations are paramount regardless of autoantibody status.

IMMUNE DYSREGULATION-POLYENDOCRINOPATHY-ENTEROPATHY X-LINKED

IPEX is caused by loss-of-function variants in *FOXP3,* which is located on the X chromosome (Xp11.23) (see Chapter 174). The inactivation of *FOXP3* results in impaired peripheral immune tolerance caused by impaired development of regulatory T cells, leading to the emergence of autoreactive T cells. The endocrinopathies commonly associated with IPEX are early-onset type 1 diabetes mellitus and autoimmune thyroiditis. *Any diagnosis of type 1 diabetes mellitus*

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation

	EPIDEMIOLOGY AND GENETICS				ENDOCRINOPATHIES				
APS	GENETIC ABNORMALITY	INHERITANCE	ONSET	CLASSIC PHENOTYPE	ADRENAL INSUFFICIENCY	THYROID	TD1	HPT	GONADAL INSUFFICIENCY
MONOGENIC APS									
APS-1	*AIRE*	AR (AD rare)	Infancy	Candidiasis, hypoparathyroidism, Addison disease, ectodermal dystrophy	●●●●	●●	●●	●●●●	●●
IPEX	*FOXP3*	XL	Infancy	Enteropathy, type 1 diabetes in infancy, eczematous dermatitis		●●●●	●●●●		
CTLA4	*CLTA4*	AD	Infancy	Enteropathy, cytopenia, lymphocytic aggregates, hypogammaglobulinemia		●●	●		
LRBA	*LRBA*	AR	Infancy	Enteropathy, respiratory tract disease, organomegaly, hypogammaglobulinemia		●	●		
STAT1	*STAT1*	AD	Infancy	Candidiasis, recurrent infections, multiple autoimmunity, cerebral aneurysm	●	●●	●		
STAT5b	*STAT5b*	AR	Infancy	Enteropathy, respiratory tract disease, recurrent infections, growth failure		●●			
CD25	*IL2RA*	AR	Infancy	Enteropathy, type 1 diabetes in infancy, recurrent infections		●●●●	●●●●		
OTHER APS AND APS-LIKE CONDITIONS									
APS-2	*HLA, MICA, PTPN22, CTLA4, NALP1*	Polygenic	Adulthood	Addison disease, autoimmune thyroid disease, type 1 diabetes	●●●●	●●●	●●		●
Turner syndrome	*46, X* (most)	N/A	Congenital	Short stature, ovarian insufficiency, webbed neck, coarctation of the aorta		●●	●		●●●●
Klinefelter syndrome	*47, XXY* (most)	N/A	Congenital	Tall stature, testicular insufficiency, gynecomastia	●	●	●		●●●●
Down syndrome	Trisomy 21	N/A (most)	Congenital	Hypotonia, epicanthal folds, Brushfield spots, single palmar crease, developmental delay		●●	●		

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	NONENDOCRINE MANIFESTATIONS							
OTHER ENDOCRINE	**CANDIDA INFECTION**	**OTHER INFECTIONS**	**MALABSORPTION, ENTEROPATHY**	**GI AUTOIMMUNITY**	**AUTOIMMUNE HEPATITIS**	**VITILIGO**	**ECZEMA, ALLERGIC DISEASE**	**OTHER**
	●●●●	●●	●●	●●	●●	●●		Keratoconjunctivitis, periodic fever, asplenism
	●	●	●●●●		●		●●●●	Cytopenias, bacterial infections, nephritis
		●●●●	●●●●					Cytopenias, lung disease, psoriasis and skin disease
		●●●●	●●●	●		●	●	Respiratory infection, cytopenias, myasthenia gravis
	●●●●	●●●●	●●●●	●	●	●●	●●	Psoriasis, cytopenia, vascular, skin disease
GH resistance, hyperprolactinemia		●●●●	●●●●				●●●●	VZV infections, cytopenia
	●●●●	●●●●	●●●●				●●●●	EBV and CMV infections, cytopenia
			●	●●	●	●		
Short stature				●		●		Lymphedema, psoriasis, IBD
Tall stature, gynecomastia								Lupus, Sjogren syndrome, multiple sclerosis (rare)
Short stature				●				Congenital heart disease

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Continued

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	EPIDEMIOLOGY AND GENETICS				ENDOCRINOPATHIES				
APS	GENETIC ABNORMALITY	INHERITANCE	ONSET	CLASSIC PHENOTYPE	ADRENAL INSUFFICIENCY	THYROID	TD1	HPT	GONADAL INSUFFICIENCY
DiGeorge syndrome	*22q11.2 del*	AD	Congenital	Absent thymus, congenital heart disease, hypocalcemia, developmental delay		●	●	●●	
ROHHAD	None identified	N/A	Early childhood	Rapid-onset obesity, hypothalamic dysfunction, autonomic dysregulation, neuroblastic tumor					
Checkpoint inhibitor IRAE		N/A	Post-treatment	Oncology treatment, possible pre-existing autoimmunity	●	●	●		

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

before 6-9 months of age should prompt consideration of a monogenic APS or a genetic cause of β-cell dysfunction. Patients with IPEX often have autoimmune enteropathy and eczematous dermatitis. They may also have other autoimmunity (e.g., liver, kidney, cytopenias) and allergic dysregulation (e.g., food allergy, peripheral eosinophilia). Therapy for IPEX consists of immune modulation with immunosuppressants (e.g., glucocorticoids, tacrolimus), novel therapeutics (e.g., abatacept), or stem cell transplantation.

OTHER MONOGENIC IMMUNE DYSREGULATION DISORDERS

Several other disorders involve failure of peripheral tolerance and emergence of autoimmunity, often with some degree of immune dysregulation. These disorders include loss-of-function genetic variants in *IL2RA* (CD25), *LRBA, CTLA4, STAT5b,* and gain-of-function variants in *STAT1* and *STAT3* that are pathophysiologically similar to IPEX. Broadly, patients with these **IPEX-like disorders** are at high risk of type 1 diabetes mellitus and autoimmune thyroiditis (see Table 608.1). They also have multiple nonendocrine diseases, especially autoimmunity and immunodeficiency affecting the skin, lungs, and gastrointestinal tract. *STAT5b* participates in the IL2/STAT5 signal transduction axis necessary for growth hormone signaling and may also affect prolactin secretion. Therefore patients with **STAT5b** defects may have nonautoimmune growth hormone insensitivity and hyperprolactinemia in addition to immune dysregulation, hypergammaglobulinemia, and multiple autoimmunity. ***STAT1*** gain-of-function variants inhibit the normal production of Th17 cytokines, which leads to chronic mucocutaneous candidiasis. These patients also have increased risk of infection, squamous cell cancer, enteropathy, and arterial aneurysms. Patients with **CD25** defects are also at increased risk of infection because interleukin (IL)-2 signaling plays a role in Th17 responses. Many IPEX-like patients develop nonautoimmune endocrinopathies, including iatrogenic adrenal insufficiency, dysglycemia, hypocalcemia, poor bone health from high-dose glucocorticoid therapy, chronic inflammation/infection, and/or malabsorption/malnutrition.

POLYGENIC AUTOIMMUNE POLYGLANDULAR SYNDROME

APS-2 is a clinical syndrome defined by the presence of two or more syndrome-specific endocrinopathies: autoimmune primary adrenal insufficiency (Addison disease), autoimmune thyroid disease (Hashimoto thyroiditis or Graves disease), and/or type 1 diabetes mellitus. Some classification systems subdivide APS-2 according to the particular glands affected (e.g., subtype 2, 3, and 4 if adrenal, thyroid, or neither gland, respectively) or other autoimmune manifestations present (e.g., subtype 3A, 3B, and 3C if additional endocrine, gastrointestinal, or systemic autoimmunity are present, respectively). However, because there is no clear pathophysiologic distinction between these subtypes, they can be considered collectively as APS-2. When describing the characteristics of APS-2, it is important to recognize some degree of overlap between patients with clinical APS-2 and those with a single autoimmune endocrinopathy who may later develop another and be classified as APS-2.

Unlike monogenic APSs, which are rare diseases with early-childhood onset and a mendelian inheritance pattern, APS-2 is a common polygenic disease that usually manifests after the second decade in a patient with a personal or family history of autoimmune disease. APS-2 is most common in middle-age females (prevalence near 1 in 20,000). Primary gonadal insufficiency, vitiligo, alopecia, and chronic atrophic gastritis (with or without pernicious anemia) can occur. Autoimmune hypoparathyroidism and candidiasis are not typical of APS-2 and should prompt consideration of APS-1.

Addison disease is uncommon in the general population (prevalence near 1 in 10,000). However, patients with this condition are at high risk of developing additional endocrine autoimmunity constituting APS-2. Two thirds will have evidence of additional subclinical or clinical autoimmunity. Patients with Addison disease should have close follow-up, screening, and education about other autoimmune manifestations. About half of patients with Addison disease have autoimmune thyroid disease (**Schmidt syndrome**), and about 10% have type 1 diabetes mellitus **(Carpenter syndrome**). Less frequent comorbid autoimmune manifestations include Graves disease, ovarian insufficiency, alopecia, vitiligo, pernicious anemia, or celiac disease.

APS-2 develops less frequently in patients with type 1 diabetes mellitus than in those with Addison disease. Nevertheless, many patients with type 1 diabetes develop additional autoimmunity, and comorbid autoimmune thyroid and gastrointestinal disease are much more common (each about 20%) than comorbid adrenal disease (<1%). Because thyroxine and cortisol affect insulin sensitivity, metabolism, and appetite, unexplained hypoglycemia or deterioration in glycemic control may be the first clinical sign of APS-2 in a patient with preexisting type 1 diabetes mellitus. Unexplained hypoglycemia may also signal the onset of celiac disease. Indeed, **celiac disease** often precedes the onset of autoimmune endocrinopathies, including type 1 diabetes mellitus, hypothyroidism, and Addison disease.

The development of APS-2 in individuals with autoimmune thyroid disease is relatively infrequent. Nevertheless, the clinician should consider the possibility of adrenal insufficiency before treating

Table 608.1 Autoimmune Polyglandular Syndrome (APS) due to Monogenic Disorders of Immune Dysregulation—cont'd

	NONENDOCRINE MANIFESTATIONS							
OTHER ENDOCRINE	**CANDIDA INFECTION**	**OTHER INFECTIONS**	**MALABSORPTION, ENTEROPATHY**	**GI AUTOIMMUNITY**	**AUTOIMMUNE HEPATITIS**	**VITILIGO**	**ECZEMA, ALLERGIC DISEASE**	**OTHER**
Short stature								Thymic dysplasia/aplasia, congenital heart disease, T-cell deficiency, cytopenias
Hypothalamic dysfunction, hyperprolactinemia								Autonomic dysregulation, central hypoventilation
								Multiple nonendocrine IRAE

Inheritance
AR, Autosomal recessive; AD, autosomal dominant; XL, X-linked
●●●●, >75% (common); ●●●, 50–75%; ●●, 10–50%; ●, <10% (rare)
VZV, Varicella-zoster virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; IBD, inflammatory bowel disease; IRAE, immune-related adverse event; TD1, type 1 diabetes; HPT, hypoparathyroidism.

Table 608.2 Autoantibodies Present in Autoimmune Polyglandular Syndromes and in Isolated Autoimmune Endocrinopathies

TISSUE OR GLAND	AUTOANTIGEN	DISEASE MANIFESTATION	NOTE
AUTOIMMUNE ENDOCRINOPATHIES			
Adrenal	CYP21A2, CYP11A1, CYP17A1	Primary adrenal insufficiency	Of the adrenal autoantibodies, CYP21A2 is most strongly associated with adrenal insufficiency. Higher risk of progression to adrenal insufficiency in children with positive adrenal autoantibodies (over 80%) compared with adults (near 20%). Adrenal autoantibodies detected in 50% of pediatric hypoparathyroidism and 1% of pediatric type 1 diabetes
Thyroid	TPO, Tg	Autoimmune thyroiditis (hypothyroidism)	Frequently positive without clinical thyroid disease
	TSHR	Graves disease (hyperthyroidism)	Only endocrine autoantibody that directly causes autoimmune endocrinopathy
Pancreatic β cell	IA-2, GAD65, insulin, ZnT8	Type 1 diabetes mellitus	Risk of type 1 diabetes increases with the number of positive autoantibodies; IA-2, but not GAD65, autoantibodies associated with time to type 1 diabetes diagnosis in APS-1
Parathyroid	NALP5, CaSR	Hypoparathyroidism	NALP5 antibodies are present only in hypoparathyroidism caused by APS-1
Gonad	CYP11A1, CYP17A1, NALP5 and TSGA10	Gonadal insufficiency	CYP11A1 antibodies associated with gonadal insufficiency in APS-1
Pituitary	TDRD6	Hypophysitis	Poorly predictive of clinical pituitary disease
NONENDOCRINE DISEASE			
Cytokines	IFN-ω, IFN-α, IL-22, IL-17F	APS-1	IFN-ω autoantibodies are 100% sensitive and 99% specific for APS-1; IL-22 autoantibodies associated with time to diagnosis and diagnosis of candidiasis in APS-1
Gastric	IF, H+/K+ ATPase	Pernicious anemia, autoimmune gastritis	IF autoantibodies associated with time to B_{12} deficiency in APS-1
Small intestine	TTG, gliadin	Celiac disease	
Gastrointestinal	TPH, GAD65	Intestinal dysfunction	TPH autoantibodies associated with time to intestinal dysfunction in APS-1. Both autoantibodies associated with diagnosis of intestinal dysfunction in APS-1

Continued

Table 608.2 Autoantibodies Present in Autoimmune Polyglandular Syndromes and in Isolated Autoimmune Endocrinopathies—cont'd

TISSUE OR GLAND	AUTOANTIGEN	DISEASE MANIFESTATION	NOTE
Liver	CYP1A2, TPH, AADC	Autoimmune hepatitis	TPH autoantibodies associated with diagnosis of autoimmune hepatitis in APS-1
Skin melanocytes	Tyrosinase, SOX9, SOX10, AADC	Vitiligo	
Hair follicle	Tyrosine hydroxylase	Alopecia	
Lung	KCNRG, BPIFB1	Interstitial lung disease	Both autoantibodies present in 90–100% of APS-1 patients with interstitial lung disease and are associated with time to diagnosis

AADC, Aromatic L-amino acid decarboxylase; BPIFB1, bactericidal/permeability-increasing fold-containing B1; CaSR, calcium sensing receptor; CYP11A1, side chain cleavage enzyme; CYP17A1, 17-α-hydroxylase; CYP1A2, cytochrome P450 1A2; CYP21A2, 21-hydroxylase; GAD65, glutamic acid decarboxylase; IA-2, islet antigen-2; IF, intrinsic factor; IFN, interferon; IL, interleukin; KCNRG, potassium channel-regulating protein; NALP5, NACHT leucine-rich-repeat protein 5; TDRD6, Tudor domain containing protein 6; Tg, thyroglobulin; TPH, tryptophan hydroxylase; TPO, thyroid peroxidase; TSGA10, testis-specific gene 10 protein; TSHR, thyroid-stimulating hormone receptor; TTG, tissue transglutaminase; ZnT8, zinc transporter 8.

hypothyroidism in a patient with features suggestive of APS-2 because thyroid hormone replacement may precipitate **adrenal crisis** in this setting. Autoantibodies to specific tissues may be detectable and may prompt functional screening before the onset of overt clinical disease (see Table 608.2); however, the predictive value of these autoantibodies for the development of clinical disease is variable.

Aberrant T-cell responses probably play a role in the pathogenesis of multiple gland destruction present in APS-2. The risk of autoimmunity directed against the adrenal glands, thyroid gland, and islet cells appears to be shared across certain human leukocyte antigen (HLA) haplotypes and other immune-related genetic loci. However, the magnitude of this risk varies substantially for each endocrinopathy. The prevalence of HLA-D3 and HLA-D4 alleles is increased in patients with APS-2, and they appear to confer an increased risk for the development of this disease. Particular alleles of the major histocompatibility complex class I chain-related genes A and B (*MICA* and *MICB*) also are associated with APS-2. Polymorphisms in other genes (e.g., *PTPN22*, *CTLA4*) have been associated with individual autoimmune endocrinopathies that constitute APS-2, but the contribution of these genes to the pathogenesis of APS-2 itself is uncertain. Although not well defined, there are likely environmental factors that promote the development of autoimmunity in genetically susceptible individuals, and many of the risk factors associated with endocrine and nonendocrine autoimmunity overlap (see individual chapters on these diseases for more detailed discussions of risk factors). Next-generation immune therapies combined with an understanding of autoimmunity pathways may lead to targeted treatments to prevent new endocrinopathies (e.g., type 1 diabetes mellitus) among those at high risk.

CHROMOSOMAL ABNORMALITIES ASSOCIATED WITH AUTOIMMUNE POLYGLANDULAR SYNDROME

Many genetic syndromes involving chromosomal deletions, duplications, and other copy number variations are associated with an increased risk of autoimmunity, particularly endocrine autoimmunity affecting the thyroid and pancreatic β cells (see Table 608.1). Clinical practice guidelines for many of these genetic syndromes recommend routine screening for autoimmune and endocrine manifestations. Males with **Klinefelter syndrome** and females with **Turner syndrome** have an increased risk of autoimmunity in multiple systems, including autoimmune endocrine disease. The mechanism of autoimmunity in **trisomy 21** remains unclear, although differences in *AIRE* gene expression, HLA susceptibility, and autoantibody profiles have been described. Thymic dysplasia is a typical feature of **DiGeorge syndrome** (22q11.2 deletion), and the resulting **immune dysregulation** may play a role in the increased risk of autoimmunity in this disorder. Patients with genetic syndromes and chromosomal abnormalities may have nonautoimmune endocrinopathies such as abnormal growth, primary gonadal failure, and hypoparathyroidism.

Mitochondrial diseases such as Kearns-Sayre syndrome (progressive external ophthalmoplegia, retinal pigmentation, cardiac conduction defects) and MELAS (mitochondrial encephalomyopathy, lactic acidosis, strokelike episodes) have been associated with polyendocrinopathy syndromes, with some rare cases reported to be associated with autoimmunity. Endocrine manifestations of mitochondrial disease include diabetes mellitus, hypogonadism, adrenal insufficiency, hypoparathyroidism, and hypothyroidism. These manifestations may develop before neurologic and other organ injury and could be an early clue of mitochondrial dysfunction.

NONGENETIC AUTOIMMUNE CAUSES OF MULTIPLE ENDOCRINOPATHY

Rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation **(ROHHAD)** is a rare pediatric syndrome diagnosed by its cardinal clinical features (see Chapter 468.3). Children with ROHHAD abruptly develop rapid weight gain and associated autonomic deficits (e.g., ophthalmologic findings, gastrointestinal dysmotility, thermal dysregulation, bradycardia), central hypoventilation, and/or hypothalamic dysfunction. Patients have progressive dysfunction of hypothalamic-pituitary axes such as central hypothyroidism, growth hormone deficiency, hyperprolactinemia, and vasopressin dysregulation (see Chapter 468.3). It is hypothesized that ROHHAD is an autoimmune paraneoplastic neurologic syndrome based on the presence of cerebrospinal fluid inflammatory markers, response to immunosuppressive therapy in some patients, and identification of neuroblastic tumors in about half. Antineural autoantibody profiling and genetic testing have not yet identified the underlying cause of ROHHAD.

Novel immune-modulating biologic compounds are used increasingly in the treatment of malignancies and immune disorders. Monoclonal antitumor drugs that *inhibit immune checkpoints* such as CLTA4, PD1, and PD-L1 are associated with immune-related adverse effects (IRAEs). Clinically important IRAEs include acute onset of multiple autoimmune endocrinopathies, including hypophysitis with hypopituitarism (especially with CTLA4-directed therapies), thyroiditis with hyperthyroidism or hypothyroidism, type 1 diabetes mellitus, and primary adrenal insufficiency. Anti-CD52 antibodies used to treat multiple sclerosis have been linked to the development of Graves disease and other antibody-mediated autoimmune diseases (e.g., immune thrombocytopenic purpura). Preexisting autoimmunity may be a risk factor for developing autoimmune disease after exposure to a wide range of immunomodulatory therapies.

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Chapter 609

Multiple Endocrine Neoplasia Syndromes

Ari J. Wassner and Jessica R. Smith

Multiple endocrine neoplasia (MEN) syndromes are characterized by the development of tumors in two or more endocrine glands. These syndromes are divided clinically into two types based on the specific endocrine organs involved (Table 609.1). MEN type 1 is characterized by tumors of the parathyroid glands, anterior pituitary, and endocrine pancreas. In contrast, MEN type 2 is characterized by medullary thyroid cancer and pheochromocytoma. Both types of MEN are usually inherited in an autosomal dominant fashion, but sporadic cases can occur.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Multiple endocrine neoplasia type 1 (MEN1) most commonly presents in the fourth or fifth decade of life, but endocrine tumors can develop as early as 5 years of age. The endocrine tissues most frequently involved include the parathyroid glands, pituitary, and cells of the endocrine pancreas.

Primary hyperparathyroidism caused by a parathyroid adenoma or multigland hyperplasia is the most common manifestation of MEN1, with a lifetime cumulative incidence of 90–95%. In children with MEN1, hyperparathyroidism usually presents after 10 years of age and is often the first endocrine disorder to develop (in about 50% of cases). The diagnosis and management of hyperparathyroidism are discussed in Chapter 613. In patients with MEN1, bilateral surgical exploration is generally recommended over focused, minimally invasive approaches because of the tendency for multiple parathyroid glands to be hyperplastic. In such cases, subtotal (3- or 3.5-gland) parathyroidectomy may be required. MEN1 may be present in 15–70% of pediatric cases of primary hyperparathyroidism, and this syndrome should be considered in any child or adolescent with primary hyperparathyroidism, particularly if multigland hyperplasia is present.

Pituitary adenomas are the presenting feature of pediatric MEN1 in about 20% of cases and usually occur after age 10 years, although they have been reported in patients as young as 5 years. Although these adenomas most commonly secrete prolactin (60–70%), a few secrete growth hormone (5–10%) or adrenocorticotrophic hormone (5%), and the remainder are nonfunctioning (~25%). Diagnosis and management are similar to that of sporadic pituitary adenomas except that adenomas associated with MEN1 may be more locally aggressive and are more likely to cosecrete multiple pituitary hormones (see Chapter 598).

Patients with MEN1 can develop neoplasia of various **enteropancreatic endocrine** cells. Such tumors may occur in up to 70% of patients by adulthood but are found in only about 5–20% of affected children. Nonfunctioning pancreatic neuroendocrine tumors are the most common pancreatic lesions found in children with MEN1 and are usually detected by screening imaging. Insulinomas are the most common functional pancreatic tumor in children with MEN1, occurring in 3–10% of cases, and present with symptoms of hypoglycemia. These tumors may present before age 10 years but are more common in adolescence. Although gastrinomas represent over 50% of pancreatic tumors in adults with MEN1, they are rare in children (~2%) and occur after age 15 years. Rarer pancreatic tumors can secrete other hormones such as glucagon or vasoactive intestinal peptide (VIP).

MEN1 is also associated with several other rare tumors. Adrenocortical tumors in children with MEN1 may be benign or malignant, and they

Table 609.1 Clinical Manifestation of MEN Syndromes

SYNDROME	MEN 1	MEN 2		
		MEN 2A	MEN 2B	FAMILIAL MTC
Eponym	Wermer syndrome	Sipple syndrome	Gorlin syndrome	–
Gene	*MEN1* ~85%	*RET* ~100%	*RET* ~100%	*RET* ~100%
Prevalence	1/30,000	1/40,000	1/1,000,000	
Hyperparathyroidism	>90%	20–30%	–	–
Duodenopancreatic NETs: nonfunctioning 55%, gastrinoma 40%, insulinoma 10%, glucagonoma <1%, VIPoma <1%, somatostatinoma	30–80%	–	–	–
Pituitary adenoma	30–40%	–	–	–
Adrenal cortical tumor	20–40%	–	–	–
Pheochromocytoma	<1%	50%	50%	–
Medullary thyroid carcinoma (MTC)	–	100%	100%	100%
Thymic NET/bronchopulmonary NET/ gastric NET	2%/5%/30%		–	
Angiofibroma/collagenoma/lipoma	85%/70%/30%	–	–	–
Other tumors: meningioma 8%, ependymoma, melanoma, thyroid 25%	0–25%	–	–	–
Marfanoid habitus	–	–	75%	–
Mucosal neuroma	–	–	~100%	–
Cutaneous lichen amyloidosis	–	Up to 36%	–	–

MEN, Multiple endocrine neoplasia; NET, neuroendocrine tumor.
Modified from Al-Salameh, A, Baudry C, Cohen R. Update on multiple endocrine neoplasia type 1 and 2. *La Presse Médicale*. 2018;47(9):722–731, Table 1.

may be nonfunctional or hypersecrete cortisol, androgens, or aldosterone. Pheochromocytomas have been reported rarely. Meningiomas, carcinoid tumors, and neuroendocrine tumors of the thymus, bronchopulmonary tree, or stomach can also occur, usually in older adolescents. Older patients with MEN1 frequently manifest cutaneous angiofibromas or collagenomas, which are benign but may be a useful diagnostic clue.

The diagnosis of MEN1 can be made clinically based on the presence of at least two of the classical endocrine tumor types (parathyroid, pituitary, pancreas) or the presence of one of these tumors in a first-degree relative of a patient with known MEN1. Genetic testing should be used to confirm a clinical diagnosis of MEN1 or to diagnose the condition preclinically in a relative of an affected individual. The *MEN1* gene on chromosome 11q13 encodes the tumor suppressor menin. A single germline inactivating pathogenic variant in *MEN1* is inherited but is not sufficient to cause tumorigenesis; a second *somatic* variant that inactivates the remaining normal allele then leads to tumor formation in a specific tissue. MEN1 is generally inherited in an autosomal dominant fashion, although sporadic variants account for about 10% of cases. Over 1,000 *MEN1* variants have been described, including deletions and changes in noncoding regions; therefore genetic testing should include analysis for deletions in patients in whom MEN1 sequencing does not reveal a pathogenic variant. Children diagnosed with MEN1 should undergo routine age-based clinical, laboratory, and imaging surveillance for disease manifestations.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Multiple endocrine neoplasia type 2 (MEN2) is a rare genetic disorder that occurs in about 1 in 2 million individuals and is characterized by the development of **medullary thyroid carcinoma (MTC)** and **pheochromocytoma**. MEN2 is an autosomal dominant disorder caused by activating pathogenic variants in the *RET* proto-oncogene, a tyrosine kinase encoded on chromosome 10q11.2. The clinical features of the syndrome are related to the specific *RET* mutation present, although disease manifestations can vary even among family members carrying the same mutation.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2A

Multiple endocrine neoplasia type 2A (MEN2A) is characterized by MTC, pheochromocytoma, and primary hyperparathyroidism. At least 50 different *RET* pathogenic variants have been described in patients with MEN2A, the majority occurring in exons 10 or 11 (codons 609, 611, 618, 620, or 634) in the *RET* extracellular domain. Almost all patients with MEN2A develop MTC, but the occurrence of other manifestations is more variable. MTC, or its precursor C cell hyperplasia, is usually the first manifestation to occur, but the age at which it develops is variable. Pheochromocytomas are often bilateral and may be multiple, and they usually develop in the third decade or later but may occur in childhood. Hyperparathyroidism is caused by hyperplasia that may involve one or more parathyroid glands. Hyperparathyroidism occurs at an average age of about 30 years but can occur in childhood or adolescence. Variants in *RET* codon 634 confer a relatively high risk of pheochromocytoma and hyperparathyroidism compared to variants at other sites.

Additional clinical conditions associated with MEN2A include cutaneous lichen amyloidosis and Hirschsprung disease. **Cutaneous lichen amyloidosis** is a dermatologic lesion consisting of pruritic hyperpigmented papules that are usually distributed in the interscapular region and on extensor surfaces. These skin lesions may develop before MTC and may provide an early clue to the diagnosis of MEN2A. Some patients with **Hirschsprung** disease have variants in *RET,* particularly in exon 10. Although the *RET* variants that cause Hirschsprung disease are generally loss-of-function variants, some of these can nevertheless cause MEN2A. Therefore individuals with Hirschsprung disease who carry such *RET* pathogenic variants should be evaluated for MEN2A.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2B

Multiple endocrine neoplasia type 2B (MEN2B) is characterized by MTC and pheochromocytoma, but *not* hyperparathyroidism. Rather, the distinguishing features of MEN2B are the presence of **multiple neuromas** and a characteristic phenotype that includes **Marfan-like habitus**. Nearly all patients with MEN2B have a specific missense pathogenic variant (M918T) in the tyrosine kinase catalytic domain of *RET*. Although MEN2B can be inherited, about 75% of cases are caused by de novo variants.

MTC in MEN2B can develop early in childhood, including in infancy, and metastasis of MTC to local and distant sites is often present at diagnosis. Pheochromocytomas occur in about half of patients. The neuromas of MEN2B can occur throughout the digestive tract, most commonly on the tongue, buccal mucosa, lips, and conjunctivae. Diffuse proliferation of nerves and ganglion cells is found in mucosal, submucosal, myenteric, and subserosal plexuses throughout the digestive tract and may be associated with gastrointestinal symptoms. Peripheral neurofibromas and café-au-lait patches may be present. Affected individuals may be tall, with arachnodactyly and a Marfan-like appearance, including scoliosis, pectus excavatum, pes cavus, and muscular hypotonia. The eyelids may be thickened and everted, lips thickened, and jaw prognathic. Feeding difficulties, poor sucking, diarrhea, constipation, and failure to thrive can begin in infancy or early childhood, sometimes years before the appearance of neuromas or endocrine symptoms.

FAMILIAL MEDULLARY THYROID CARCINOMA

The familial occurrence of MTC without other clinical manifestations of MEN2 has been termed *familial medullary thyroid carcinoma* (FMTC). *RET* variants are commonly present in individuals with FMTC, and although some families appear to have truly isolated MTC, in other kindreds, the pattern of apparent FMTC may represent MEN2A in which other manifestations have not yet occurred or have not been diagnosed. FMTC is frequently regarded as a form of MEN2A, and evaluation for other manifestations of MEN2A is warranted in patients with FMTC.

MANAGEMENT OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

Genetic testing of affected family members often leads to the diagnosis of MEN2 in a child before the development of any disease manifestations. MTC is highly likely to develop in these individuals. Although thyroidectomy is curative if performed before the development of MTC or while it is still localized to the thyroid gland, the prognosis is poor once MTC has metastasized beyond the thyroid. Therefore prophylactic thyroidectomy is required in most individuals with MEN2. However, the timing of prophylactic thyroidectomy must be determined for each patient based on balancing the likelihood of developing metastatic MTC against the need to minimize the risks of surgery, which are higher in younger children.

Factors influencing the risk of MTC include the specific *RET* variants present, the history of MTC in the family, and serum levels of calcitonin. The first two factors are not entirely predictive, as MTC behavior can vary significantly even in family members with the same variant. Some *RET* variants are associated with earlier-onset MTC, and consensus guidelines categorize *RET* variants as highest risk (M918T, usually associated with MEN2B), high risk (codon 634 and 883 mutations), or moderate risk (other variants) for MTC. Patients at highest risk should undergo thyroidectomy within the first year of life. Those with high-risk variants should undergo thyroidectomy at 5 years of age or earlier if calcitonin levels begin to rise. Patients at moderate risk should be monitored by neck ultrasound and serum calcitonin levels beginning at age 5 years, and thyroidectomy should be performed if calcitonin levels rise. However, the timing of surgery may be influenced by other factors, including family history or desire to avoid prolonged monitoring by proceeding with thyroidectomy. For patients who do not wish to undergo prophylactic thyroidectomy, regular careful surveillance is mandatory. Thyroidectomy should be performed by an experienced thyroid surgeon, especially in the youngest patients, to minimize the risk of surgical complications. Prophylactic thyroidectomy reduces morbidity and mortality from MTC in patients with MEN2, many of whom are found to have C cell hyperplasia, or even MTC, at the time of prophylactic thyroidectomy. The management of MTC is described in detail in Chapter 607.

Screening for pheochromocytoma and hyperparathyroidism should be performed in children with MEN2. The age at which screening should commence depends on the specific RET variant (11 years for high and highest risk; 16 years for moderate risk). Management of pheochromocytoma (see Chapters 555.4 and 613) and hyperparathyroidism (see Chapter 621) are discussed elsewhere.

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Section 3

Disorders of the Parathyroid Gland

Chapter 610

Hormones and Peptides of Calcium Homeostasis and Bone Metabolism

Evan G. Graber and Daniel A. Doyle

Parathyroid hormone (PTH) and vitamin D are the principal regulators of calcium homeostasis (see Chapters 69 and 746). Calcitonin and PTH-related peptide (PTHrP) are important primarily in the fetus.

PARATHYROID HORMONE

PTH is an 84–amino acid chain (95 kDa), but its biologic activity resides in the first 34 residues. In the parathyroid gland, a pre–pro-PTH (115–amino acid chain) and a pro-PTH (90 amino acids) are synthesized. Pre–pro-PTH is converted to pro-PTH and pro-PTH to PTH. PTH (consisting of amino acids 1-84) is the major secretory product of the gland, but it is rapidly cleaved in the liver and kidney into smaller COOH-terminal, midregion, and NH_2-terminal fragments.

The occurrence of these fragments in serum has led to the development of a variety of assays. The 1-34 aminoterminal (N-terminus) fragments possess biologic activity but are present in low amounts in the circulation; assay of these fragments is most useful for detecting acute secretory changes. The carboxyterminal (C-terminus) and midregion fragments, although biologically inert, are cleared more slowly from the circulation and represent 80% of plasma immunoreactive PTH; concentrations of the C-terminal fragment are 50-500 times the level of the active hormone. The C-terminal assays are effective in detecting hyperparathyroidism, but because C-terminal fragments are removed from the circulation by glomerular filtration, these assays are less useful for evaluating the secondary hyperparathyroidism characteristic of renal disease. Only certain sensitive radioimmunoassays for PTH can differentiate the subnormal concentrations that occur in hypoparathyroidism from normal levels.

When serum levels of calcium fall, the signal is transduced through the calcium-sensing receptor, and secretion of PTH increases (Fig. 610.1). PTH stimulates activity of 1α-hydroxylase in the kidney, enhancing production of 1,25-dihydroxycholecalciferol, also written as $1,25(OH)_2D_3$. The increased level of $1,25(OH)_2D_3$ induces synthesis of a calcium-binding protein (calbindin-D) in the intestinal mucosa, with resultant absorption of calcium. PTH also mobilizes calcium by directly enhancing bone resorption, an effect that requires $1,25(OH)_2D_3$. The effects of PTH on bone and kidney are mediated through binding to specific receptors on the membranes of target cells and through activation of a transduction pathway involving a G-protein coupled to the adenylate cyclase system (see Chapter 594).

The calcium-sensing receptor regulates the secretion of PTH and the reabsorption of calcium by the renal tubules in response to alterations in serum calcium concentrations. The gene for the receptor is located on chromosome 3q13.3-q21 and encodes a cell surface protein that is expressed in parathyroid glands and kidneys and belongs to the family of G-protein–coupled receptors. In the normally functioning calcium-sensing receptor, hypocalcemia induces increased secretion of PTH and hypercalcemia depresses PTH secretion. Loss-of-function pathogenic variants cause an increased set point with respect to serum calcium, resulting in hypercalcemia and in the conditions of familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. There is a close genotype/phenotype relationship that determines severity of illness. Acquired hypocalciuric hypercalcemia may be a result of autoantibodies to the calcium-sensing receptor and manifests with hypercalcemia and hyperparathyroidism. Gain-of-function variants result in depressed secretion of PTH in response to hypocalcemia, leading to the syndrome of familial hypocalcemia with hypercalciuria (see Fig. 610.1).

PARATHYROID HORMONE–RELATED PEPTIDE

PTHrP is homologous to PTH only in the first 13 amino acids of its amino terminus, 8 of which are identical to PTH. Its gene is on the short arm of chromosome 12 and that of PTH is on the short arm of chromosome 11.

PTHrP, like PTH, activates PTH receptors in kidney and bone cells and increases urinary cyclic adenosine monophosphate and renal production of $1,25(OH)_2D_3$. It is produced in almost every type of cell of the body, including every tissue of the embryo at some stage of development. PTHrP is critical for normal fetal development. Inactivating variants of the receptor for PTH/PTHrP results in a lethal bone disorder characterized by short limbs and markedly advanced bone maturation known as **Blomstrand chondrodysplasia** (see Fig. 610.1). PTHrP appears to have a paracrine or autocrine role because serum levels are low except in a few clinical situations. Cord blood contains levels of PTHrP that are threefold higher than in serum from adults; it is produced by the fetal parathyroid glands and appears to be the main agent stimulating maternal-fetal calcium transfer. PTHrP appears to be essential for normal skeletal maturation of the fetus, which requires 30 g of calcium during a normal gestation. During pregnancy, maternal absorption of calcium increases from about 150 mg daily to 400 mg during the second trimester.

PTHrP levels are increased during lactation and in patients with benign breast hypertrophy. Breast milk and pasteurized bovine milk have levels of PTHrP that are 10,000 times higher than those of normal plasma. Most instances of the hormonal **hypercalcemia syndrome of malignancy** are caused by elevated concentrations of PTHrP.

VITAMIN D

See Chapter 69.

CALCITONIN

Calcitonin is a 32–amino acid polypeptide. Its gene is on chromosome 11p and is tightly linked to that of PTH. The gene for calcitonin encodes three peptides: calcitonin, a 21–amino acid carboxyterminal flanking peptide (katacalcin), and a calcitonin gene–related peptide. Katacalcin and calcitonin are cosecreted in equimolar amounts by the parafollicular cells (C cells) of the thyroid gland. Calcitonin appears to be of little consequence in children and adults because very high levels in patients with medullary carcinoma of the thyroid (a tumor arising from the C cells) do not cause hypercalcemia. In the fetus, circulating levels are high and appear to augment bone metabolism and skeletal growth; these high levels are probably stimulated by the normally high fetal calcium levels. Unlike the high levels in cord blood and circulating concentrations in young children, levels in older children and adults are low. Infants and children with congenital hypothyroidism (and presumed deficiency of C cells) have lower levels of calcitonin than normal children.

Its action appears to be independent of PTH and vitamin D. Its main biologic effect appears to be the inhibition of bone resorption by decreasing the number and activity of bone-resorbing osteoclasts. This action of calcitonin is the rationale for its use in treatment of Paget disease. Calcitonin is synthesized in other organs, such as the gastrointestinal tract, pancreas, brain, and pituitary. In these organs, calcitonin is thought to behave as a neurotransmitter to impose a local inhibitory effect on cell function.

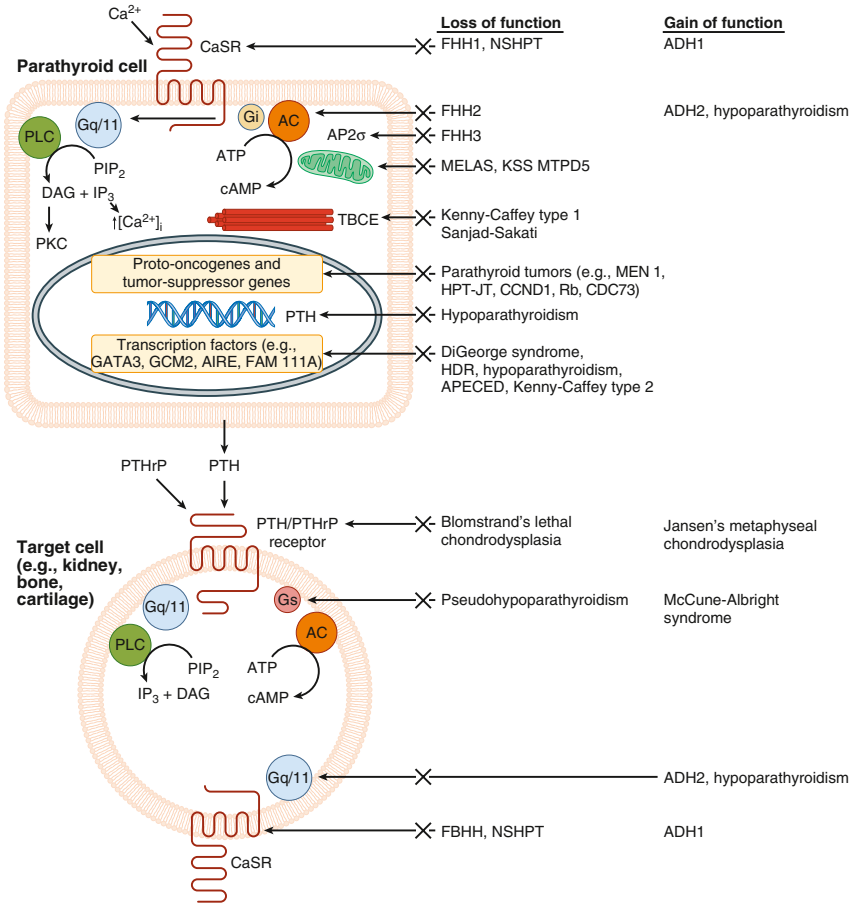

Fig. 610.1 Schematic representation of some of the components involved in calcium homeostasis. Alterations in extracellular calcium are detected by the calcium-sensing receptor *(CaSR)*, which is a 1078–amino acid, G protein–coupled receptor. The parathyroid hormone (PTH)/parathyroid hormone-related peptide (PTHrP) receptor, which mediates the actions of and PTHrP, is also a G protein–coupled receptor. Thus Ca^{2+}, PTH, and PTHrP involve G protein–coupled signaling pathways, and interaction with their specific receptors can lead to activation of Gs, Gi, and Gq, respectively. Gs stimulates adenylcyclase *(AC)*, which catalyzes the formation of cyclic adenosine monophosphate *(cAMP)* from adenosine triphosphate *(ATP)*. Gi inhibits AC activity. cAMP stimulates protein kinase A *(PKA)*, which phosphorylates cell-specific substrates. Activation of Gq stimulates phospholipase C *(PLC)*, which catalyzes the hydrolysis of the phosphoinositide *(PIP_2)* to inositol triphosphate *(IP_3)*, which then increases intracellular calcium, and diacylglycerol *(DAG)*, activating protein kinase C *(PKC)*. These proximal signals modulate downstream pathways, which results in specific physiologic effects. Loss of function in several genes, shown with their respective sites of action on the right, has been identified in specific disorders of calcium homeostasis. ADH, autosomal dominant hypocalcemia; APECED, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; FBHH, familial benign hypocalciuric hypercalcemia; FHH, familial hypocalciuric hypercalcemia; HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HPT-JT, hyperparathyroidism-jaw tumor syndrome; KSS, Kearns-Sayre syndrome; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MEN, multiple endocrine neoplasia; MTPD, mitochondrial trifunctional protein deficiency; NSHPT, neonatal severe hyperparathyroidism. TBCE, tubulin-specific chaperone E. *(From Thakkerf RV. The parathyroid glands, hypercalcemia and hypocalcemia. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine, 25th ed. Philadelphia: Elsevier; 2016: Fig. 245.2, p. 1651.)*

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Chapter 611

Hypoparathyroidism

Patrick C. Hanley and Daniel A. Doyle

Hypocalcemia is common in neonates between 12 and 72 hours of life, especially in premature infants, in infants with asphyxia, and in infants of diabetic mothers (**early neonatal hypocalcemia**; see Chapter 121.4; Table 611.1 and Fig. 611.1). After the second to third day and during the first week of life, the type of feeding also is a determinant of the level of serum calcium **(late neonatal hypocalcemia)**. The role played by the parathyroid glands in these hypocalcemic infants is unclear, although functional immaturity of the parathyroid glands is invoked as one pathogenetic factor. In a group of infants with **transient idiopathic hypocalcemia** (1-8 weeks of age), serum levels of parathyroid hormone (PTH) are significantly lower than those in unaffected infants. It is possible that the functional immaturity is a manifestation of a delay in development of the enzymes that convert glandular PTH to secreted PTH; other mechanisms are possible.

APLASIA OR HYPOPLASIA OF THE PARATHYROID GLANDS

Aplasia or hypoplasia of the parathyroid glands is often associated with **DiGeorge/velocardiofacial syndrome**. This syndrome occurs in 1 in 4,000 newborns. In 90% of patients, the condition is caused by a deletion of chromosome 22q11.2 with involvement of the *TBX1* gene. Approximately 25% of these patients inherit the chromosomal abnormality from a parent. Neonatal hypocalcemia occurs in 60% of affected patients, but it is transitory in the majority; hypocalcemia may recur or can have its onset later in life. Associated abnormalities of the third and fourth pharyngeal pouches are common; these include conotruncal defects of the heart in 25%, velopharyngeal insufficiency in 32%, cleft palate in 9%, renal anomalies in 35%, and aplasia of the thymus with severe immunodeficiency in 1%. This syndrome has also been reported in a small number of patients with a deletion of chromosome 10p13 thought to affect the *NEBL* gene, in infants of diabetic mothers, and in infants born to mothers treated with retinoic acid for acne early in pregnancy. Loss-of-function pathogenic variants in the *GCM2* gene, which is a key regulator of parathyroid gland development, leads to isolated parathyroid aplasia and hypoparathyroidism.

Table 611.1 Causes of Hypocalcemia

I. NEONATAL
A. Maternal Disorders
1. Diabetes mellitus
2. Toxemia of pregnancy
3. Vitamin D deficiency
4. High intake of alkali or magnesium sulfate
5. Use of anticonvulsants
6. Hyperparathyroidism

B. Neonatal Disorders
1. Low birthweight: prematurity, intrauterine growth restriction
2. Peripartum asphyxia, sepsis, critical illness
3. Hyperbilirubinemia, phototherapy, exchange transfusion
4. Hypomagnesemia, hypermagnesemia
5. Acute/chronic renal failure
6. Nutrients/medications: high phosphate intake, fatty acids, phytates, bicarbonate infusion, citrated blood, anticonvulsants, aminoglycosides
7. Hypoparathyroidism
8. Vitamin D deficiency or resistance
9. Osteopetrosis type II

II. HYPOPARATHYROIDISM
A. Congenital
1. Transient neonatal
2. Congenital hypoparathyroidism
   a. Familial isolated hypoparathyroidism
      (i) Autosomal recessive hypoparathyroidism *(GMC2, PTH)*
      (ii) Autosomal dominant hypoparathyroidism *(CASR, GNA11)*
      (iii) X-linked hypoparathyroidism *(SOX3)*
   b. DiGeorge syndrome types 1 and 2 *(TBX1, NEBL)*
   c. Sanjad-Sakati syndrome (short stature, retardation, dysmorphism; HRD) *(TBCE)*
   d. Kenny-Caffey syndrome type 1 (short stature, medullary stenosis, retardation) *(TBCE)*
   e. Kenny-Caffey syndrome type 2 (short stature, medullary stenosis) *(FAM111A)*
   f. Barakat syndrome (sensorineural deafness, renal dysplasia; HDR) *(GATA3)*
   g. Lymphedema-Hypoparathyroidism syndrome (nephropathy, mitral valve prolapse and brachytelephalangy).
   h. Mitochondrial disorders (Kearns-Sayre, Pearson, MELAS, trifunctional protein deficiency)
3. Insensitivity to PTH
   a. Blomstrand chondrodysplasia *(PTHR1)*
   b. Pseudohypoparathyroidism type IA *(GNAS)*
      (i) Pseudohypoparathyroidism type IB *(STX16, GNAS-A1)*
      (ii) Pseudohypoparathyroidism type IC *(GNAS)*
      (iii) Pseudohypoparathyroidism type II
      (iv) Pseudopseudohypoparathyroidism
   c. Acrodysostosis with hormone resistance *(PRKAR1A)*
   d. Hypomagnesemia
4. CaSR-activating mutation
   a. Sporadic
   b. Autosomal dominant (G protein subunit α11 mutation)

II. HYPOPARATHYROIDISM—cont'd
B. Acquired
1. Autoimmune polyglandular syndrome type I (*AIRE* gene mutation)
2. Activating antibodies to the CaSR
3. Postsurgical, radiation destruction
4. Infiltrative—excessive iron (hemochromatosis, thalassemia) or copper (Wilson disease) deposition; granulomatous inflammation, neoplastic invasion; amyloidosis, sarcoidosis
5. Hypomagnesemia/hypermagnesemia

III. VITAMIN D DEFICIENCY
IV. OTHER CAUSES OF HYPOCALCEMIA
A. Calcium Deficiency
1. Nutritional deprivation
2. Hypercalciuria

B. Disorders of Magnesium Homeostasis
1. Congenital hypomagnesemia
2. Acquired
   a. Acute renal failure
   b. Chronic inflammatory bowel disease, intestinal resection
   c. Diuretics

C. Hyperphosphatemia
1. Renal failure
2. Phosphate administration (intravenous, oral, rectal)
3. Tumor cell lysis
4. Muscle injuries (crush, rhabdomyolysis)

D. Miscellaneous
1. Hypoproteinemia
2. Hyperventilation
3. Drugs: furosemide, aminoglycosides, bisphosphonates, calcitonin, anticonvulsants, ketoconazole, antineoplastic agents (plicamycin, asparaginase, cisplatinum, cytosine arabinoside, doxorubicin), citrated blood products
4. Hungry bone syndrome
5. Acute and critical illness: sepsis, acute pancreatitis, toxic shock
   a. Organic acidemia: propionic, methylmalonic, isovaleric

CaSR, Ca^2-sensing receptor; HDR, hypoparathyroidism, sensorineural deafness, and renal anomaly; HRD, hypoparathyroidism, retardation, dysmorphism; MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episode; PTH, parathyroid hormone.
Modified from Root AW, Diamond Jr FB. Disorders of mineral homeostasis in children and adolescents. In: Sperling MA. *Pediatric Endocrinology*, 4th ed. Philadelphia: Elsevier; 2014: Table 18.2A.

X-LINKED RECESSIVE HYPOPARATHYROIDISM

Familial clusters of hypoparathyroidism with various patterns of transmission have been described. In two large North American pedigrees, this disorder appears to be transmitted by an X-linked recessive gene located on Xq26-q27, which has a key role in the development of the parathyroid glands. In these families, the onset of afebrile hypocalcemic seizures characteristically occurs in infants from 2 weeks to 6 months of age. The absence of parathyroid tissue after detailed examination of a male with this condition suggests a defect in embryogenesis.

AUTOSOMAL RECESSIVE HYPOPARATHYROIDISM WITH DYSMORPHIC FEATURES

Autosomal recessive hypoparathyroidism with dysmorphic features has been described in Middle Eastern children. Parental consanguinity occurred for most of several dozen affected patients. Profound hypocalcemia occurs early in life, and dysmorphic features include microcephaly, deep-set eyes, beaked nose, micrognathia, and large floppy ears. Intrauterine and postnatal growth restriction are severe, and cognitive impairment is common. The putative gene *(TBCE)* is on chromosome 1q42-43. In a few patients with autosomal recessive inheritance of isolated hypoparathyroidism, pathologic variants of the *PTH* gene have been found.

HYPOPARATHYROIDISM, SENSORINEURAL DEAFNESS, AND RENAL ANOMALY SYNDROME

Hypoparathyroidism, sensorineural deafness, and renal anomaly (HDR) occur owing to pathologic variants of the *GATA3* gene. The protein encoded by this gene is essential in the development of the

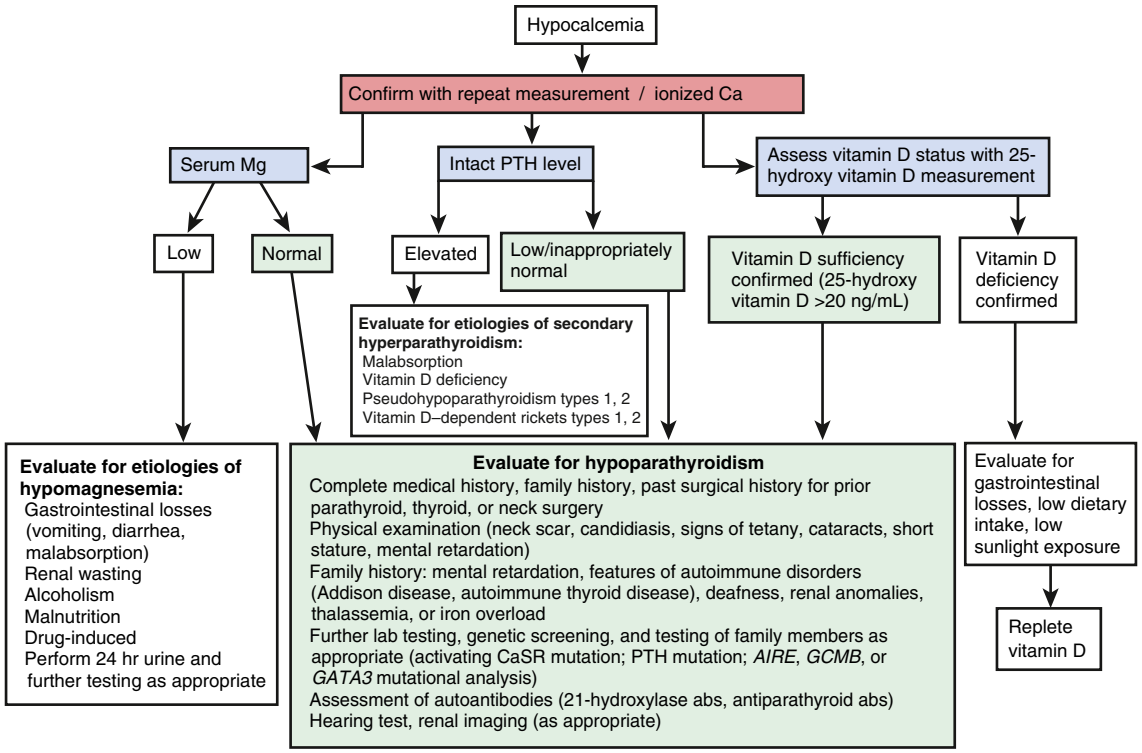

Fig. 611.1 Algorithm for the evaluation of hypocalcemia. Abs, autoantibodies; CaSR, Ca^2-sensing receptor; PTH, parathyroid hormone. *(From Bilezikian JP, Khan A, Potts Jr JT, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res. 2011;26:2317–2337, Fig. 1.)*

parathyroids, auditory system, and kidneys. The *GATA3* gene is located at chromosome 10p14 and is nonoverlapping with the DiGeorge critical region at 10p13 (see Fig. 610.1). Congenital ichthyosis and HDR have also been reported.

SUPPRESSION OF NEONATAL PARATHYROID HORMONE SECRETION BECAUSE OF MATERNAL HYPERPARATHYROIDISM OR MATERNAL FAMILIAL HYPOCALCIURIC HYPERCALCEMIA

Neonatal PTH secretion can be suppressed by maternal hyperparathyroidism, resulting in transient hypocalcemia in the newborn infant. It appears that neonatal hypocalcemia results from suppression of the fetal parathyroid glands by exposure to elevated levels of calcium in maternal and hence fetal serum. Tetany usually develops within 3 weeks but may be delayed by 1 month or more if the infant is breastfed. Seizures may occur within 1 week with familial hypocalciuric hypercalcemia (FHH1) because of maternal Ca^2-sensing receptor (CaSR) loss-of-function pathogenic variants. Hypocalcemia can persist for weeks or months. When the cause of hypocalcemia in an infant is unknown, measurements of calcium, phosphorus, and PTH should be obtained from the mother. Most affected mothers are asymptomatic, and the cause of their hyperparathyroidism is usually a parathyroid adenoma.

AUTOSOMAL DOMINANT HYPOPARATHYROIDISM

Patients with autosomal dominant hypoparathyroidism have an activating (gain-of-function) pathogenic variant of the Ca^{2+}-sensing receptor, forcing the receptor to an on state with subsequent depression of PTH secretion even during hypocalcemia. The patients have hypercalciuria. The hypocalcemia is usually mild and might not require treatment beyond childhood (see Fig. 610.1).

HYPOPARATHYROIDISM ASSOCIATED WITH MITOCHONDRIAL DISORDERS

Mitochondrial DNA pathogenic variants in Kearns-Sayre syndrome, MELAS (mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes) syndrome, and mitochondrial trifunctional protein–deficiency syndrome are associated with hypoparathyroidism. A diagnosis of mitochondrial cytopathy should be considered in patients with unexplained symptoms, such as ophthalmoplegia, sensorineural hearing loss, cardiac conduction disturbances, and tetany (see Fig. 610.1).

SURGICAL OR INFILTRATIVE HYPOPARATHYROIDISM

Removal or damage of the parathyroid glands can complicate thyroidectomy. Hypoparathyroidism has developed even when the parathyroid glands have been identified and left undisturbed at the time of operation. This may be the result of interference with the blood supply or of postoperative edema and fibrosis. Symptoms of tetany can occur abruptly postoperatively and may be temporary or permanent. In some instances, symptoms develop insidiously and go undetected until months after thyroidectomy. Occasionally, the first evidence of surgical hypoparathyroidism may be the development of cataract. The status of parathyroid function should be carefully monitored in all patients undergoing thyroidectomy.

Deposition of iron pigment or of copper in the parathyroid glands (thalassemia, Wilson disease) can also produce hypoparathyroidism.

AUTOIMMUNE HYPOPARATHYROIDISM

An autoimmune mechanism for hypoparathyroidism is strongly suggested by the finding of parathyroid antibodies and by its frequent association with other autoimmune disorders or organ-specific antibodies. Autoimmune hypoparathyroidism is often associated with Addison disease and chronic mucocutaneous candidiasis. The association of at least two of these three conditions has been classified as **autoimmune polyglandular disease type I** (see Chapter 608). It is also known as *autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy* (APECED). This syndrome is inherited in an autosomal recessive fashion and is not related to any single human leukocyte antigen–associated haplotype. Approximately one third of pediatric patients with this syndrome have all three components; 66% have only two of three conditions. The candidiasis almost always precedes the other disorders (70% of cases

occur in children *younger* than 5 years of age); the hypoparathyroidism (90% of cases occur *after* 3 years of age) usually occurs before Addison disease (90% of cases occur *after* 6 years of age). A variety of other disorders, including alopecia areata or totalis, malabsorption disorder, asplenia, pernicious anemia, gonadal failure, autoimmune hepatitis, vitiligo, dental enamel hypoplasia, nail dystrophy, keratoconjunctivitis, and insulin-dependent diabetes, occur at various times. Some of these associations might not appear until adult life. Autoimmune thyroid disease is a rare concomitant finding in pediatric patients.

Affected siblings can have the same or different constellations of disorders (hypoparathyroidism, Addison disease). The disorder is exceptionally prevalent among Finns and Iranian Jews. The gene for this disorder is designated *AIRE* (autoimmune regulator); it is located on chromosome 21q22. It appears to be a transcription factor that plays an essential role in the development of immunologic tolerance. Patients with Addison disease as part of polyendocrinopathy syndrome type I have demonstrated adrenal-specific autoantibody reactivity directed against the side-chain cleavage enzyme.

IDIOPATHIC HYPOPARATHYROIDISM

The term *idiopathic hypoparathyroidism* should be reserved for the small residuum of children with hypoparathyroidism for whom no causative mechanism can be defined. Most children in whom onset of hypoparathyroidism occurs after the first few years of life have an **autoimmune condition**. Autoantibodies to the extracellular domain of the Ca^2-sensing receptor have been identified in some patients with acquired hypoparathyroidism. One should always consider incomplete forms of DiGeorge syndrome or an activating Ca^2-sensing receptor pathogenic variant in the differential diagnosis.

Clinical Manifestations

There is a spectrum of parathyroid deficiencies with clinical manifestations varying from no symptoms to those of complete and long-standing deficiency. Mild deficiency may be revealed only by appropriate laboratory studies. Muscular pain and cramps are early manifestations; they progress to numbness, stiffness, and tingling of the hands and feet. There may be only a positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms. Seizures with or without loss of consciousness can occur at intervals of days, weeks, or months. These episodes can begin with abdominal pain, followed by tonic rigidity, retraction of the head, and cyanosis. Hypoparathyroidism is often mistaken for epilepsy. Headache, vomiting, increased intracranial pressure, and papilledema may be associated with seizures and might suggest a brain tumor.

In patients with long-standing hypocalcemia, the teeth erupt late and irregularly. Enamel formation is irregular, and the teeth may be unusually soft. The skin may be dry and scaly, and the nails might have horizontal lines. Mucocutaneous candidiasis, when present, antedates the development of hypoparathyroidism; the candidal infection most often involves the nails, the oral mucosa, the angles of the mouth, and less often, the skin; it is difficult to treat.

Cataracts in patients with long-standing untreated disease are a direct consequence of hypoparathyroidism; other autoimmune ocular disorders such as keratoconjunctivitis can also occur. Manifestations of Addison disease, lymphocytic thyroiditis, pernicious anemia, alopecia areata or totalis, hepatitis, and primary gonadal insufficiency may also be associated with those of hypoparathyroidism.

Permanent physical and mental deterioration occurs if initiation of treatment is long delayed.

Laboratory Findings

The serum calcium level is low (5-7 mg/dL), and the phosphorus level is elevated (7-12 mg/dL). Blood levels of ionized calcium (usually approximately 45% of the total) more nearly reflect physiologic adequacy but also are low. The serum level of alkaline phosphatase is normal or low, and the level of $1,25(OH)_2D_3$ is usually low, but high levels have been found in some children with severe hypocalcemia. The level of magnesium is normal but should always be checked in hypocalcemic patients. Levels of PTH are low relative to the calcium level when measured by immunometric assay. Radiographs of the bones occasionally reveal an increased density limited to the metaphyses, suggesting heavy metal poisoning, or an increased density of the lamina dura. Radiographs or CT scans of the skull can reveal calcifications in the basal ganglia. There is a prolongation of the QT interval on the electrocardiogram, which disappears when the hypocalcemia is corrected. The electroencephalogram usually reveals widespread slow activity; the tracing returns to normal after the serum calcium concentration has been within the normal range for a few weeks, unless irreversible brain damage has occurred or unless the parathyroid insufficiency is associated with epilepsy. When hypoparathyroidism occurs concurrently with Addison disease, the serum level of calcium may be normal, but hypocalcemia appears after effective treatment of the adrenal insufficiency.

Treatment

Emergency treatment of neonatal tetany consists of intravenous injections of 5-10 mL or 1-3 mg/kg of a 10% solution of calcium gluconate (elemental calcium 9.3 mg/mL) at the rate of 0.5-1.0 mL/min while the heart rate is monitored and a total dose not to exceed 20 mg of elemental calcium/kg. Additionally, 1,25-dihydroxycholecalciferol (calcitriol) should be given. The initial dosage is 0.25 μg/24 hr; the maintenance dosage ranges from 0.01-0.10 g/kg/24 hr to a maximum of 1-2 μg/24 hr. Calcitriol has a short half-life and should be given in two equally divided doses; it has the advantages of rapid onset of effect (1-4 days) and rapid reversal of hypercalcemia after discontinuation in the event of overdosage (calcium levels begin to fall in 3-4 days). Calcitriol is supplied as an oral solution.

An adequate intake of calcium should be ensured. Supplemental calcium can be given in the form of calcium gluconate or calcium glubionate to provide 800 mg of elemental calcium daily or 25-50 mg/kg day dosing of elemental calcium as needed. Foods with high phosphorus content such as milk, eggs, and cheese should be *reduced* in the diet. Other therapies used for some children with hypoparathyroidism in studies include hormone replacement with recombinant PTH 1-34 or recombinant PTH 1-84 given via a pump or subcutaneous injections in adult patients who do not respond to conventional therapy.

Clinical evaluation of the patient and frequent determinations of the serum calcium levels are indicated in the early stages of treatment to determine the requirement for calcitriol, calcium supplementation, or vitamin D_2. If hypercalcemia occurs, therapy should be discontinued and resumed at a lower dose after the serum calcium level has returned to normal. In long-standing cases of hypercalcemia, repair of cerebral and dental changes is not likely. Pigmentation, lowering of blood pressure, or weight loss can indicate adrenal insufficiency, which requires specific treatment. Patients with autosomal dominant hypocalcemic hypercalciuria can develop nephrocalcinosis and renal impairment if treated with vitamin D.

Differential Diagnosis

Magnesium deficiency must be considered in patients with unexplained hypocalcemia. Concentrations of serum magnesium <1.5 mg/dL (1.2 mEq/L) are usually abnormal (Table 611.2). Administration of calcium is ineffective, but administration of magnesium promptly corrects both calcium and magnesium levels. Oral supplements of magnesium are necessary to maintain levels of magnesium in the normal range.

Hypomagnesemia also occurs in malabsorption syndromes such as Crohn disease and cystic fibrosis. Patients with autoimmune polyglandular disease type I and hypoparathyroidism can also have concurrent

Table 611.2 Genetic Causes of Hypomagnesemia

CATEGORIES/NAMES OF DISORDERS*	GENE	INHERITANCE	DISTINCTIVE FINDINGS OTHER THAN HYPOMAGNESEMIA†
HYPERCALCIURIC HYPOMAGENESEMIAS			Hypercalciuria, nephrocalcinosis
FHHNC type 1	*CLDN16*	R	Polyuria/polydipsia, elevated serum iPTH, renal failure
FHHNC type 2	*CLDN19*	R	Same as FHHNC type 1, plus ocular abnormalities
ADHH Bartter syndrome type 5	*CASR*	D	Hypocalcemia with normal or low PTH
Bartter syndrome, type 3 (classical type)	*CLCNKB*	R	Gitelman-like phenotype possible, rarely nephrocalcinosis
GITELMAN-LIKE HYPOMAGNESEMIAS			Hypocalciuria, hypokalemia, metabolic alkalosis
Gitelman syndrome	*SLC12A3*	R	Chondrocalcinosis at older age
Bartter syndrome, type 4	*BSND*	R	Prenatal complications, renal failure early in life possible
EAST syndrome	*KCNJ10*	R	Sensorineural deafness, seizures, ataxia
IDH	*FXYD2*	D	
ADTKD/RCAD	*HNF1B*	D	Renal, genital, and pancreatic abnormalities and MODY5 in highly variable combination and presentation
HPABH4D/RCAD-like	*PCBD1*	R	MODY5-like
MITOCHONDRIAL HYPOMAGNESEMIAS			Variable
HHH	*MT-TI*	Mt	Hypertension and hypercholesterolemia
HUPRAS	*SARS2*	R	Hyperuricemia, pulmonary hypertension, renal failure, and alkalosis
KSS	Mitochondrial deletion	Mt	External ophthalmoplegia, retinopathy and cardiac conduction defects
OTHER HYPOMAGNESEMIAS			Variable
HSH	*TRPM6*	R	Neonatal presentation with severe hypomagnesemia
IRH	*EGF*	R	Intellectual disability
NISBD2	*EGFR*	R	Severe inflammation of skin and bowel from birth
HSMR	*CNNM2*	D/R	Intellectual disability, seizures
ADH/EA1	*KCNA1*	D	Episodic myokymia
KCS2	*FAM111A*	D	Impaired skeletal development and hypocalcemic hypoparathyroidism

*ADH, Autosomal dominant hypomagnesemia; ADHH, autosomal dominant hypocalcemia with hypocalciuria; ADTKD, autosomal dominant tubulointerstitial kidney disease; EA1, episodic ataxia type 1; EAST, epilepsy, ataxia, sensorineural deafness and tubulopathy; FHHNC, familial hypomagnesemia with hypocalcemia and nephrocalcinosis; HHH, hypertension, hypercholesterolemia and hypomagnesemia; HPABH4D, hyperphenylalaninemia BH4-deficient; HSH, hypomagnesemia with secondary hypocalcemia; HSMR, hypomagnesemia with seizures and mental retardation; HUPRAS, hyperuricemia, pulmonary hypertension, renal failure and alkalotic syndrome; IDH, isolated dominant hypomagnesemia; IRH, isolated recessive hypomagnesemia; KCS2, Kenny-Chaffey syndrome type 2; KSS, Kearns-Sayre syndrome; NISBD2, neonatal inflammatory skin and bowel disease type 2; RCAD, renal cysts and diabetes.

†iPTH, Intact parathyroid hormone; MODY5, maturity onset diabetes of the young type 5.

Modified from Viering DHHM, de Baaij JHF, Walsh SB. et al. Genetic causes of hypomagnesemia, a clinical overview. *Pediatr Nephrol.* 2017;32:1123–1135.

steatorrhea and low magnesium levels. Therapy with aminoglycosides causes hypomagnesemia by increasing urinary losses.

It is not clear how low levels of magnesium lead to hypocalcemia. Evidence suggests that hypomagnesemia impairs release of PTH and induces resistance to the effects of the hormone, but other mechanisms also may be operative.

Poisoning with inorganic phosphate leads to hypocalcemia and tetany. Infants administered large doses of inorganic phosphates, either as laxatives or as sodium phosphate enemas, have had sudden onset of tetany, with serum calcium levels <5 mg/dL and markedly elevated levels of phosphate. Symptoms are quickly relieved by intravenous administration of calcium. The mechanism of the hypocalcemia is not clear (see Chapter 73.6).

Hypocalcemia can occur early in treatment of acute lymphoblastic leukemia. Hypocalcemia is usually associated with hyperphosphatemia resulting from destruction of lymphoblasts.

Episodic symptomatic hypocalcemia occurs in **Kenny-Caffey syndrome**, which is characterized by medullary stenosis of the long bones, short stature, delayed closure of the fontanel, delayed bone age, and eye abnormalities. Idiopathic hypoparathyroidism and abnormal PTH levels have been found. Autosomal dominant and autosomal recessive modes of inheritance have been reported. Pathogenic variants of the *TBCE* gene (1q43-44) perturb microtubule organization in diseased cells in Kenny-Caffey syndrome type 1.

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Chapter 612

Pseudohypoparathyroidism

Patrick C. Hanley and Daniel A. Doyle

In pseudohypoparathyroidism (PHP, also known as *Albright hereditary osteodystrophy*), the parathyroid glands are normal or hyperplastic, and they can synthesize and secrete parathyroid hormone (PTH). Serum levels of immunoreactive PTH are elevated even when the patient is hypocalcemic and may be elevated when the patient is normocalcemic. Neither endogenous nor administered PTH raises the serum levels of calcium or lowers the levels of phosphorus. The genetic defects in the **hormone receptor adenylate cyclase system** are classified into various types depending on the phenotypic and biochemical findings (Table 612.1).

TYPE Ia

Type Ia accounts for the majority of patients with PHP. Affected patients have a genetic defect of the α subunit of the stimulatory guanine nucleotide-binding protein ($G_s\alpha$). This coupling factor is required for PTH bound to cell surface receptors to activate cyclic adenosine monophosphate (cAMP). Heterogeneous pathogenic variants of the $G_s\alpha$ gene have been documented; the gene is located on chromosome 20q13.2. Deficiency of the $G_s\alpha$ subunit is a generalized cellular defect and accounts for the association of other endocrine disorders with type Ia PHP. The defect is inherited as an autosomal dominant trait, and the paucity of father-to-son transmissions is thought to be a result of decreased fertility in males.

Tetany is often the presenting sign. Affected children have a short, stocky build and a round face. Brachydactyly with dimpling of the dorsum of the hand is usually present. The second metacarpal is involved least often. As a result, the index finger occasionally is longer than the middle finger. Likewise, the second metatarsal is only rarely affected. There may be other skeletal abnormalities such as short and wide phalanges, bowing, exostoses, and thickening of the calvaria. These patients often have obesity, calcium deposits, and metaplastic bone formation subcutaneously. Moderate degrees of cognitive impairment, calcification of the basal ganglia, and lenticular cataracts are common in patients whose disease is diagnosed late.

Some members of affected kindreds may have the usual anatomic stigmata of PHP type Ia, but serum levels of calcium and phosphorus are normal despite reduced $G_s\alpha$ activity; however, PTH levels may be slightly elevated. Such patients have been labeled as having **pseudopseudohypoparathyroidism (PPHP)**. Affected patients with PPHP have pathologic variants in the *GNAS* gene inherited in an autosomal dominant pattern. PPHP patients have inactivating *GNAS* variants encoding the $G_s\alpha$ subunit that are paternally inherited. The signs and symptoms of PPHP are similar to those of patients with PHP type Ia, except patients with PPHP do not have the characteristic PTH resistance seen in PHP type Ia.

Patients with **PHP type Ic** also have the usual anatomic stigmata of PHP along with the laboratory abnormalities associated with PTH resistance, including elevated phosphorus and PTH in the setting of hypocalcemia. PHP type Ic is differentiated from PHP type Ia and PPHP in that patients do not have abnormal $G_s\alpha$ activity.

Transition from normocalcemia to hypocalcemia often occurs with increasing age of the patient. These phenotypically similar but metabolically dissimilar patients may be in the same family and have the same pathogenic variants of $G_s\alpha$ protein. It is not known what other factors cause clinically overt hypocalcemia in some

Table 612.1 Clinical, Biochemical, and Genetic Features of Hypoparathyroid and Pseudohypoparathyroid Disorders

		PSEUDOHYPOPARATHYROIDISM				
	HYPOPARATHYROIDISM	**PHP 1a**	**PPHP**	**PHP 1b**	**PHP 1c**	**PHP 2**
AHO manifestations	No	Yes	Yes	No	Yes	No
Serum calcium	↓	↓	N	↓	↓	↓
Serum PO_4	↑	↑	N	↑	↑	↑
Serum PTH	↓	↑	N	↑	↑	↑
Response to PTH:						
Urinary cAMP* (Chase-Auerbach test)	↑	↓	↑	↓	↓	↑
Urinary PO_4 (Ellsworth-Howard test)	↑	↓	↑	↓	↓	↓
$G_s\alpha$ activity	N	↓	↓	N	N	N
Inheritance	AD, AR, X	AD	AD	AD	AD	Sporadic
Molecular defect	PTH, CaSR, GATA3, Gcm2, others	GNAS1	GNAS1	GNAS1†	?Adenyl cyclase	?cAMP targets
Other hormonal resistance	No	Yes	No	No	Yes	No

*Plasma cyclic adenosine monophosphate (cAMP) responses are similar to those of urinary cAMP.
†Involves deletions that are located upstream of GNAS1.
↓, Decreased; ↑, increased; ?, presumed, but not proved; AD, autosomal dominant; AHO, Albright hereditary osteodystrophy; AR, autosomal recessive; N, normal; PHP, pseudoparathyroidism; PPHP, pseudopseudoparathyroidism; PTH, parathyroid hormone; X, X-linked.
From Thakker RV. The parathyroid glands, hypercalcemia and hypocalcemia. In: Goldman L, Schafer AI, eds. *Goldman-Cecil Medicine*, 25th ed. Philadelphia: Elsevier; 2016: Table 245-8.

affected patients and not in others. There is evidence that the $G_s\alpha$ variant is paternally transmitted in PPHP and maternally transmitted in patients with type Ia disease. The gene may be imprinted in a tissue-specific manner and have different methylation patterns.

In addition to resistance to PTH, resistance to other G protein–coupled receptors for thyroid-stimulating hormone (TSH), gonadotropins, growth hormone–releasing hormone (GHRH), calcitonin, and glucagon can result in various metabolic effects. Clinical hypothyroidism is uncommon, but basal levels of TSH are elevated and thyrotropin-releasing hormone–stimulated TSH responses are exaggerated. Moderately decreased levels of thyroxine and increased levels of TSH have been demonstrated by newborn thyroid-screening programs, leading to the detection of type Ia PHP in infancy. In adults, gonadal dysfunction is common, as manifested by sexual immaturity, amenorrhea, oligomenorrhea, and infertility. Each of these abnormalities can be related to deficient synthesis of cAMP secondary to a deficiency of $G_s\alpha$, but it is not clear why resistance to other G protein–dependent hormones (corticotropin, vasopressin) are much less affected.

Serum levels of calcium are low, and those of phosphorus and alkaline phosphatase are elevated. Clinical diagnosis can be confirmed by demonstration of a markedly attenuated response in urinary phosphate and cAMP after intravenous infusion of the synthetic 1-34 fragment of human PTH (teriparatide acetate). Definitive diagnosis is established by demonstration of the pathogenic variant in the G protein gene.

Type Ia with Precocious Puberty

Two males have been reported with both type Ia PHP and gonadotropin-independent precocious puberty (see Chapter 600.7). They were found to have a temperature-sensitive variant of the G_s protein. Thus at normal body temperature (37°C), the G_s is degraded, resulting in PHP, but in the cooler temperature of the testes (33°C) the G_s variant results in constitutive activation of the luteinizing hormone receptor and precocious puberty.

TYPE Ib

Affected patients have normal levels of G protein activity and a normal phenotypic appearance. These patients have tissue-specific resistance to PTH but not to other hormones. Serum levels of calcium, phosphorus, and immunoreactive PTH are the same as those in patients with type Ia PHP. These patients also show no rise in cAMP in response to exogenous administration of PTH. Bioactive PTH is not increased. The pathophysiology of the disorder in this group of patients is caused by paternal uniparental isodisomy of chromosome 20q and resulting *GNAS1* methylation. This, along with the loss of the maternal *GNAS1* gene, leads to PTH resistance in the proximal renal tubules, which leads to impaired mineral ion homeostasis. Pathologic genetic deletions in the *STX16* gene are also associated with PHP type Ib.

ACRODYSOSTOSIS WITH HORMONE RESISTANCE

Patients with acrodysostosis resemble those with PHP type Ia, but defects in the $G_s\alpha$ subunit are not present. Instead, in one subgroup of patients there is a defect in the gene encoding *PRKAR1A,* the cAMP-dependent regulatory subunit of protein kinase A that confers resistance to multiple hormones, including PTH. Another subgroup has a defect in a phosphodiesterase gene *Pde4d.* This subgroup also carries the phenotype of PHP type Ia but rarely exhibits the hormone resistance. **Acroscyphodysplasia** is a distinctive form of metaphyseal dysplasia characterized by the distal femoral and proximal tibial epiphyses embedded in cup-shaped, large metaphyses known as *metaphyseal scypho* or *cup deformity* and is a phenotypic variation of PHP and acrodysostosis.

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Chapter 613

Hyperparathyroidism

Evan G. Graber and Daniel A. Doyle

Excessive production of parathyroid hormone (PTH) can result from a primary defect of the parathyroid glands such as an **adenoma** or hyperplasia **(primary hyperparathyroidism)**.

More often, the increased production of PTH is compensatory, usually aimed at correcting hypocalcemic states of diverse origins **(secondary hyperparathyroidism)**. In vitamin D–deficient rickets and the malabsorption syndromes, intestinal absorption of calcium is deficient, but hypocalcemia and tetany may be averted by increased activity of the parathyroid glands. In **pseudohypoparathyroidism**, PTH levels are elevated because a pathogenic variant in the $G_s\alpha$ protein interferes with response to PTH. Early in chronic renal disease, hyperphosphatemia results in a reciprocal fall in the calcium concentration with a consequent increase in PTH, but in advanced stages of renal failure, production of $1,25(OH)_2D_3$ is also decreased, leading to worsening hypocalcemia and further stimulation of PTH. In some instances, if stimulation of the parathyroid glands has been sufficiently intense and protracted, the glands continue to secrete increased levels of PTH for months or years after kidney transplantation, with resulting hypercalcemia.

ETIOLOGY

Childhood hyperparathyroidism is uncommon. Onset during childhood is usually the result of a single benign adenoma. It usually becomes manifested after 10 years of age. There have been some kindreds in which multiple members have hyperparathyroidism transmitted in an autosomal dominant fashion. Most of the affected family members are adults, but children have been involved in approximately 30% of the pedigrees. Some affected patients in these families are asymptomatic, and disease is detected only by careful study. In other kindreds, hyperparathyroidism occurs as part of the constellation known as the **multiple endocrine neoplasia** (MEN) syndromes (see Chapter 609) or of **hyperparathyroidism–jaw tumor syndrome**.

Neonatal severe hyperparathyroidism is rare. Symptoms develop shortly after birth and consist of anorexia, irritability, lethargy, constipation, and failure to thrive. Radiographs reveal subperiosteal bone resorption, osteoporosis, and pathologic fractures. Symptoms may be mild, resolving without treatment, or can have a rapidly fatal course if diagnosis and treatment are delayed. Histologically, the parathyroid glands show diffuse hyperplasia. Affected siblings have been observed in some kindreds, and parental consanguinity has been reported in several kindreds. Most cases have occurred in kindreds with the clinical and biochemical features of **familial hypocalciuric hypercalcemia**. Infants with neonatal severe hyperparathyroidism may be homozygous or heterozygous for the pathogenic variant in the Ca^{2+}-sensing receptor gene, whereas most persons with one copy of this variant exhibit autosomal dominant familial hypocalciuric hypercalcemia.

MEN type 1 (see Chapter 609) is an autosomal dominant disorder characterized by hyperplasia or neoplasia of the endocrine pancreas (which secretes gastrin, insulin, pancreatic polypeptide, and occasionally glucagon), the anterior pituitary (which usually secretes prolactin), and the parathyroid glands. In most kindreds, hyperparathyroidism is usually the presenting manifestation, with a prevalence approaching 100% by 50 years of age and occurring only rarely in children younger than 18 years of age. With genetic testing, it is possible to detect carriers of the gene with 99% accuracy at birth, avoiding unnecessary biochemical screening programs.

The gene for MEN type 1 is on chromosome 11q13; it appears to function as a tumor-suppressor gene and follows the two-hit hypothesis of tumor development. The first variant *(germinal)* is inherited and is recessive to the dominant allele; this does not result in tumor formation. A second variant *(somatic)* is required to eliminate the normal allele, which then leads to tumor formation.

Hyperparathyroidism–jaw tumor syndrome is an autosomal dominant (*CDC73*) disorder characterized by parathyroid adenomas and fibro-osseous jaw tumors. Affected patients can also have polycystic kidney disease, renal hamartomas, and Wilms tumor. Although the condition affects adults primarily, it has been diagnosed as early as age 10 years. **MEN type 2** may also be associated with hyperparathyroidism (see Chapter 609).

Transient neonatal hyperparathyroidism has occurred in a few infants born to mothers with hypoparathyroidism (idiopathic or surgical) or with pseudohypoparathyroidism. In each case, the maternal disorder had been undiagnosed or inadequately treated during pregnancy. The cause of the condition is chronic intrauterine exposure to hypocalcemia with resultant hyperplasia of the fetal parathyroid glands. In the newborn, manifestations involve the bones primarily, and healing occurs between 4 and 7 months of age.

CLINICAL MANIFESTATIONS

At all ages, the clinical manifestations of hypercalcemia of any cause include muscle weakness, fatigue, headache, hyporeflexia, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia and polyuria **(nephrogenic diabetes insipidus)**, weight loss, and fever. When hypercalcemia is of long duration, calcium may be deposited in the renal parenchyma (nephrocalcinosis), with progressively diminished renal function. Renal calculi can develop and can cause renal colic and hematuria. Osseous changes can produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors. Height can decrease from compression of vertebrae; the patient can become bedridden. Detection of completely asymptomatic patients is increasing with the advent of automated panel assays that include serum calcium determinations.

Abdominal pain is occasionally prominent and may be associated with **acute pancreatitis**. Parathyroid crisis can occur, manifested by serum calcium levels >15 mg/dL and progressive oliguria, azotemia, stupor, and coma. In infants, failure to thrive, poor feeding, and hypotonia are common. Cognitive impairment, convulsions, and blindness can occur as sequelae of long-standing hypercalcemia. Psychiatric manifestations include depression, confusion, dementia, stupor, and psychosis.

LABORATORY FINDINGS

The serum calcium level is elevated; 39 of 45 children with adenomas had levels >12 mg/dL. The hypercalcemia is more severe in infants with parathyroid hyperplasia; concentrations ranging from 15 to 20 mg/dL are common, and values as high as 30 mg/dL have been reported. Even when the total serum calcium level is borderline or only slightly elevated, ionized calcium levels are often increased. The serum phosphorus level is reduced to approximately 3 mg/dL or less, and the level of serum magnesium is low. The urine can have a low and fixed specific gravity, and serum levels of nonprotein nitrogen and uric acid may be elevated. In patients with adenomas who have skeletal involvement, serum phosphatase levels are elevated, but in infants with hyperplasia, the levels of alkaline phosphatase may be normal even when there is extensive involvement of bone.

The ECG may demonstrate a prolonged PR interval, short QT interval, widened QRS complex and bradycardia.

Serum levels of intact PTH are elevated, especially in relation to the level of calcium. Calcitonin levels are normal. Acute hypercalcemia can stimulate calcitonin release, but with prolonged hypercalcemia, hypercalcitoninemia does not occur.

The most consistent and characteristic radiographic finding is resorption of subperiosteal bone, best seen along the margins of the phalanges of the hands. In the skull, there may be gross trabeculation or a granular appearance resulting from focal rarefaction; the lamina dura may be absent. In more advanced disease, there may be generalized rarefaction, cysts, tumors, fractures, and deformities. Approximately 10% of patients have radiographic signs of rickets. Radiographs of the abdomen can reveal renal calculi or nephrocalcinosis.

DIFFERENTIAL DIAGNOSIS

Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism (Table 613.1 and Fig. 613.1). A low serum phosphorus level with hypercalcemia is characteristic of primary hyperparathyroidism; elevated levels of PTH are also diagnostic. With hypercalcemia of any cause except hyperparathyroidism and familial hypocalciuric hypercalcemia, PTH levels are suppressed. Pharmacologic doses of corticosteroids lower the serum calcium level to normal in patients with hypercalcemia from other causes but generally do not affect the calcium level in patients with hyperparathyroidism.

TREATMENT

When hyperparathyroidism is clearly established, imaging and possibly surgical exploration are indicated. All glands should be carefully inspected and if an adenoma is discovered, it should be removed. Very few instances of carcinoma are known in children. Most neonates with severe hypercalcemia require total parathyroidectomy; less severe hypercalcemia remits spontaneously in others. Still others have been treated successfully with bisphosphonates and calcimimetics. The patient should be carefully observed postoperatively for the development of hypocalcemia and tetany; intravenous administration of calcium gluconate may be required for a few days. The serum calcium level then gradually returns to normal, and, under ordinary circumstances, a diet high in calcium and phosphorus must be maintained for only several months after operation.

CT, real-time ultrasonography, and subtraction scintigraphy using sestamibi/technetium-pertechnetate alone and in combination have proved effective in localizing a single adenoma versus diffuse hyperplasia in 50–90% of adults. Parathyroid surgeons often rely on intraoperative selective venous sampling with intraoperative assay of PTH for localizing and removing the source of increased PTH secretion.

PROGNOSIS

The prognosis is good if the disease is recognized early and there is appropriate surgical treatment. When extensive osseous lesions are present, deformities may be permanent. A search for other affected family members is indicated.

613.1 Other Causes of Hypercalcemia

Evan G. Graber and Daniel A. Doyle

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FAMILIAL BENIGN HYPERCALCEMIA)

Patients with familial hypocalciuric hypercalcemia are usually asymptomatic, and the hypercalcemia is identified by chance during routine investigation for other conditions. Adults may have recurrent pancreatitis, chondrocalcinosis, or premature vascular calcification. The parathyroid glands are normal, PTH levels are inappropriately normal, and subtotal parathyroidectomy does not correct the hypercalcemia. Serum levels of magnesium are high-normal or mildly elevated. The ratio of calcium-to-creatinine clearance is usually decreased despite hypercalcemia.

The disorder is inherited in an autosomal dominant manner and is caused by a pathogenic variant *(CASR)* on chromosome 3q2 in ~65% of patients **(type 1)**. In **type 2**, there is a pathogenic variant in *GNA11,* and in **type 3**, the variant is on *AP2S1*. The disorder can be diagnosed early in childhood by serum and urinary calcium concentrations. Detection of other affected family members is important to avoid inappropriate parathyroid surgery. The defect in type 1 is an inactivating mutation in the Ca^{2+}-sensing receptor gene. This G-protein–coupled receptor senses the level of free Ca^{2+} in the blood and triggers the pathway to increase extracellular Ca^{2+} in the face of hypocalcemia. This receptor functions in the parathyroid and kidney to regulate calcium homeostasis; inactivating mutations lead to an increased set point with respect to serum Ca^{2+}, resulting in mild to moderate hypercalcemia in heterozygotes.

GRANULOMATOUS DISEASES

Hypercalcemia occurs in 30–50% of children with sarcoidosis and less often in patients with other granulomatous diseases such as tuberculosis. Levels of PTH are suppressed, and levels of $1,25(OH)_2D_3$ are elevated. The source of ectopic $1,25(OH)_2D_3$ is the activated macrophage, through stimulation by interferon-α from T lymphocytes, which are present in abundance in granulomatous lesions. Unlike renal tubular cells, the 1α-hydroxylase in macrophages is unresponsive to homeostatic regulation. Oral administration of prednisone lowers serum levels of $1,25(OH)_2D_3$ to normal and corrects the hypercalcemia.

Table 613.1 Causes of Hypercalcemia

I. NEONATE/INFANT
A. Maternal Disorders
1. Excessive vitamin D ingestion, hypoparathyroidism, pseudohypoparathyroidism
B. Neonate/Infant
1. Iatrogenic: excessive intake of calcium, vitamin D, vitamin A
2. Phosphate depletion
3. Subcutaneous fat necrosis
4. Williams syndrome (del7q11.23/WBSCR1)
5. Neonatal severe hyperparathyroidism *(CaSR)*
6. Metaphyseal chondrodysplasia, Murk-Jansen type *(PTH1R)*
7. Idiopathic infantile hypercalcemia *(CYP24A1)* (25-hydroxyvitamin D 24-hydroxylase)
8. Persistent parathyroid hormone–related protein
9. Lactase/disaccharidase deficiency *(LCT)*
10. Infantile hypophosphatasia *(TNSALP)*
11. Mucolipidosis type II *(GNPTAB)*
12. Blue diaper syndrome
13. Antenatal Bartter syndrome types 1 and 2 *(SLC12A1, KCNJ1)*
14. Distal renal tubular acidosis
15. IMAGe syndrome *(CDKN1C)*
16. Post bone marrow transplantation for osteopetrosis
17. Endocrinopathies: primary adrenal insufficiency, severe congenital hypothyroidism, hyperthyroidism

II. HYPERPARATHYROIDISM
A. Sporadic
1. Parathyroid hyperplasia, adenoma, carcinoma
B. Familial
1. Neonatal severe hyperparathyroidism *(CaSR)*
2. Multiple endocrine neoplasia, type 1 *(MEN1)*
3. Multiple endocrine neoplasia, type 2A *(RET)*
4. Multiple endocrine neoplasia, type 2B *(RET)*
5. Multiple endocrine neoplasia, type 4 *(CDKN1B)*
6. McCune-Albright syndrome *(GNAS)*
7. Familial isolated hyperparathyroidism 1 *(CDC73)*
8. Familial isolated hyperparathyroidism 2 (jaw tumor syndrome) *(CDC73)*
9. Familial isolated hyperparathyroidism 3
10. Jansen metaphyseal dysplasia *(PTH1R)*
C. Secondary/tertiary
1. Postrenal transplantation
2. Chronic hyperphosphatemia
D. Hypercalcemia of malignancy
1. Ectopic production of parathyroid hormone–related peptide
2. Metastatic dissolution of bone

III. FAMILIAL HYPOCALCIURIC HYPERCALCEMIA
A. Familial hypocalciuric hypercalcemia I (CaSR)
1. Loss-of-function mutations in *CaSR*
- Monoallelic: familial benign hypercalcemia
- Biallelic: neonatal severe hyperparathyroidism
B. Familial hypocalciuric hypercalcemia II (GNA11)
C. Familial hypocalciuric hypercalcemia III, Oklahoma variant (AP2S1)
D. CaSR-blocking autoantibodies

IV. EXCESSIVE CALCIUM OR VITAMIN D
A. Milk-alkali syndrome
B. Exogenous ingestion of calcium or vitamin D or topical application of vitamin D (calcitriol or analog)
C. Ectopic production of calcitriol associated with granulomatous diseases (sarcoidosis, cat scratch fever; tuberculosis, histoplasmosis, coccidioidomycosis, cryptococcosis, leprosy; human immunodeficiency virus; cytomegalovirus; chronic inflammatory bowel disease, Blau syndrome, granulomatosis with polyangiitis)
D. Neoplasia
1. Primary bone tumors
2. Metastatic tumors with osteolysis
3. Lymphoma, leukemia
4. Dysgerminoma
5. Pheochromocytoma
6. Langerhans cell histiocytosis
7. Tumors secreting parathyroid hormone–related peptide, growth factors, cytokines, prostaglandins, and osteoclast-activating factors
E. Williams-Beuren syndrome (del7q11.23)

V. IMMOBILIZATION
VI. OTHER CAUSES
A. Drugs: thiazides, lithium, vitamin A and analogs, calcium, alkali, antiestrogens, aminophylline, teriparatide, abaloparatide
B. Total parenteral nutrition
C. Endocrinopathies: hyperthyroidism, congenital hypothyroidism, Addison disease, pheochromocytoma
D. Vasoactive intestinal polypeptide–secreting tumor
E. Acute or chronic renal failure/administration of aluminum
F. Hypophosphatasia
G. Juvenile idiopathic arthritis: cytokine mediated
H. Late phase of rhabdomyolysis

IMAGe, intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, genital abnormalities; WBSCR1, Williams-Beuren syndrome chromosome region 1.
Adapted from Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. *Curr Opin Pediatr.* 2010;22:508–515; Benjamin RW, Moats-Staats BM, Calikoglu A, et al. Hypercalcemia in children. *Pediatr Endocrinol Rev.* 2008;5:778–784; Davies JH. A practical approach to the problems of hypercalcaemia. *Endocr Dev.* 2009;16:93–114.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia often occurs in adults with a wide variety of solid tumors but is identified much less often in children. It has been reported in infants with malignant rhabdoid tumors of the kidney or congenital mesoblastic nephroma and in children with neuroblastoma, medulloblastoma, leukemia, Burkitt lymphoma, dysgerminoma, and rhabdomyosarcoma. Serum levels of PTH are rarely elevated. In most patients, the hypercalcemia associated with malignancy is caused by elevated levels of parathyroid hormone–related peptide and not PTH. Rarely, tumors produce $1,25(OH)_2D_3$ or PTH ectopically.

MISCELLANEOUS CAUSES OF HYPERCALCEMIA

Hypercalcemia can occur in infants with **subcutaneous fat necrosis**. Levels of PTH are normal. In one infant, the level of $1,25(OH)_2D_3$ was elevated, and biopsy of the skin lesion revealed granulomatous infiltration, suggesting that the mechanism of the hypercalcemia was akin to that seen in patients with other granulomatous disease. In another infant, although the level of $1,25(OH)_2D_3$ was normal, PTH was suppressed, suggesting the hypercalcemia was not related to PTH. Treatment with prednisone is effective. Bisphosphonate therapy has also been effective in severe cases.

Hypophosphatasia, especially the severe infantile form, is usually associated with mild to moderate hypercalcemia (see Chapter 747). Serum levels of phosphorus are normal, and those of alkaline phosphatase are subnormal. The bones exhibit rachitic-like lesions on radiographs. Urinary levels of phosphoethanolamine, inorganic pyrophosphate, and pyridoxal 5′-phosphate are elevated; each is a natural substrate to a tissue-nonspecific (liver, bone, kidney) alkaline phosphatase enzyme. Missense variants of the tissue-nonspecific alkaline phosphatase enzyme gene result in an inactive enzyme in this autosomal recessive disorder.

Idiopathic hypercalcemia of infancy is manifested by failure to thrive and hypercalcemia during the first year of life, followed by spontaneous remission. Serum levels of phosphorus and PTH are normal. The condition has been defined as resulting from increased absorption of calcium from decreased degradation of $1,25(OH)_2D_3$. Pathogenic variants in the *CYP24A1* gene that encodes 25-hydroxyvitamin D 24-hydroxylase, the key enzyme in $1,25(OH)_2D_3$ degradation, cause excessive levels of the active vitamin D metabolite, which, in turn, causes hypercalcemia in a subset of infants who receive supplemental vitamin D. An excessive rise in the level of $1,25(OH)_2D_3$ in response to PTH administration has been reported years after the hypercalcemic phase.

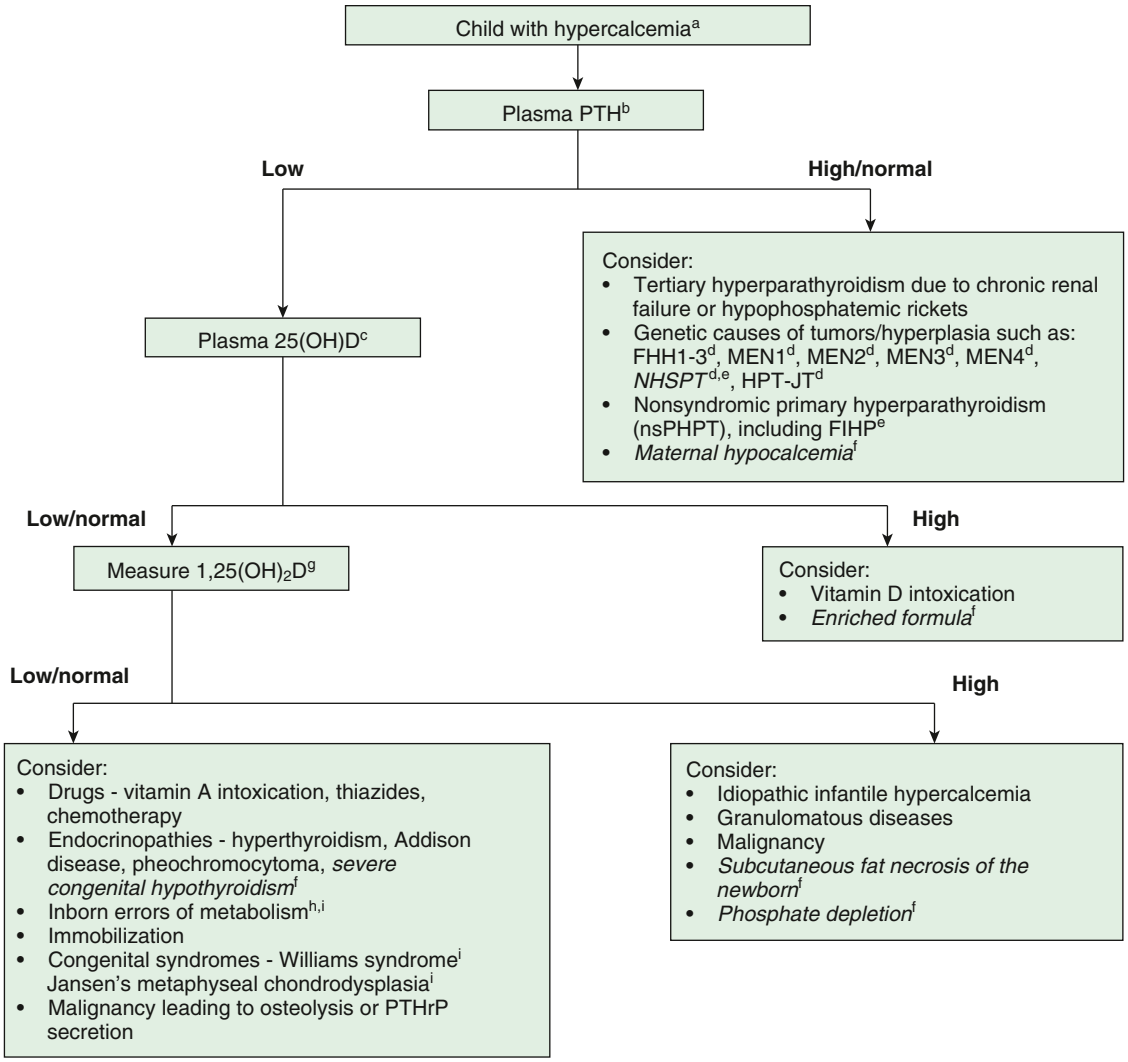

Fig. 613.1 Algorithm illustrating the clinical approach to investigation of causes of hypercalcemia in a child. [a]Confirm hypercalcemia, defined as plasma (or serum) adjusted calcium >10.5 mg/dL (2.60 mmol/L) or ionized calcium >5.25 mg/dL (1.32 mmol/L). [b]PTH, parathyroid hormone. [c]25(OH)D, 25-hydroxyvitamin D. [d]FHH1-3, familial hypocalciuric hypercalcemia types 1-3; MEN1, multiple endocrine neoplasia type 1; MEN2, multiple endocrine neoplasia type 2; MEN3, multiple endocrine neoplasia type 3; MEN4, multiple endocrine neoplasia type 4; NSHPT, neonatal severe primary hyperparathyroidism; HPT-JT, hyperparathyroid–jaw tumor syndrome. [e]FIHP, Familial isolated hyperparathyroidism. [f]Conditions affecting neonates (shown in italics). [g]1,25$(OH)_2$D, 1,25-dihydroxyvitamin D. [h]Inborn errors of metabolism, for example, hypophosphatasia, congenital lactase deficiency (CLD), and blue diaper syndrome. [i]These syndromes may be associated with dysmorphic features, for example, Williams syndrome, Jansen metaphyseal chondrodysplasia, and hypophosphatasia. PTHrP, parathyroid hormone-related peptide. *(From Stokes VJ, Nielsen MF, Hannan FM, Thaller RV. Hypercalcemic disorders in children. J Bone Miner Res. 2017;32:2157–2170, Fig. 2.)*

Approximately 15% of patients with **Williams syndrome** may exhibit hypercalcemia. Hypercalcemia is more common in patients <24 months of age. It is often transient and usually does not require treatment. The phenotype consists of feeding difficulties, slow growth, elfin facies (small mandible, prominent maxilla, upturned nose), renovascular disorders, and a gregarious "cocktail party" personality. Cardiac lesions include supravalvular aortic stenosis, peripheral pulmonic stenosis, aortic hypoplasia, coronary artery stenosis, and atrial or ventricular septal defects. **Nephrocalcinosis** can develop if hypercalcemia persists. The IQ score of 50-70 is curiously accompanied by enhanced quantity and quality of vocabulary, auditory memory, and social use of language. A contiguous gene deletion syndrome with a submicroscopic deletion at chromosome 7q11.23, which includes deletion of one elastin allele, occurs in 90% of patients and seems to account for the vascular problems. Definitive diagnosis can be established by specific fluorescence in situ hybridization. The hypercalcemia and central nervous system symptoms may be caused by deletion of adjacent genes. Hypercalcemia has been successfully controlled with either prednisone or calcitonin.

Hypervitaminosis D resulting in hypercalcemia from drinking milk that has been incorrectly fortified with excessive amounts of vitamin D has been reported. Not all patients with hypervitaminosis D develop hypercalcemia. Affected infants can manifest failure to thrive, nephrolithiasis, poor renal function, and osteosclerosis. Serum levels of 25(OH)D are a better indicator of hypervitaminosis D than levels of 1,25$(OH)_2D_3$ because 25(OH)D has a longer half-life.

Prolonged immobilization can lead to hypercalcemia and occasionally to decreased renal function, hypertension, and encephalopathy. Children who have hypophosphatemic rickets and undergo surgery with subsequent long-term immobilization are at risk for hypercalcemia and should therefore have their vitamin D supplementation decreased or discontinued.

Jansen-type metaphyseal chondrodysplasia is a rare genetic disorder characterized by short-limbed dwarfism and severe but asymptomatic hypercalcemia (see Chapter 735). Circulating levels of PTH and parathyroid hormone–related peptide are undetectable. These patients have an activating PTH–parathyroid hormone–related peptide receptor mutation that results in aberrant calcium homeostasis and abnormalities of the growth plate.

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Section 4

Disorders of the Adrenal Gland

Chapter 614

Physiology of the Adrenal Gland

614.1 Histology and Embryology

Perrin C. White

The adrenal gland is composed of two endocrine tissues: the medulla and the cortex. The chromaffin cells of the adrenal medulla are derived from neuroectoderm, whereas the cells of the adrenal cortex are derived from mesoderm. Mesodermal cells also contribute to the development of the gonads. The adrenal glands and gonads have certain common enzymes involved in steroid synthesis; an inborn error in steroidogenesis in one tissue can also be present in the other.

The adrenal cortex of the older child or adult consists of three zones: the **zona glomerulosa**, the outermost zone located immediately beneath the capsule; the **zona fasciculata**, the middle zone; and the **zona reticularis**, the innermost zone, lying next to the adrenal medulla. The zona fasciculata is the largest zone, constituting approximately 75% of the cortex; the zona glomerulosa constitutes approximately 15%; and the zona reticularis approximately 10%. Glomerulosa cells are small, with a lower cytoplasmic:nuclear ratio, an intermediate number of lipid inclusions, and smaller nuclei containing more condensed chromatin than the cells of the other two zones. The cells of the zona fasciculata are large, with a high cytoplasmic:nuclear ratio and many lipid inclusions that give the cytoplasm a foamy, vacuolated appearance. The cells are arranged in radial cords. The cells of the zona reticularis are arranged in irregular anastomosing cords. The cytoplasmic:nuclear ratio is intermediate, and the compact cytoplasm has relatively little lipid content.

The zona glomerulosa synthesizes **aldosterone**, the most potent natural **mineralocorticoid** in humans. The zona fasciculata produces **cortisol**, the most potent natural **glucocorticoid** in humans, and the zona fasciculata and zona reticularis synthesize the adrenal androgens.

The adrenal medulla consists mainly of neuroendocrine (chromaffin) cells and glial (sustentacular) cells with some connective tissue and vascular cells. Neuroendocrine cells are polyhedral, with abundant cytoplasm and small, pale-staining nuclei. Under the electron microscope, the cytoplasm contains many large secretory granules that contain catecholamines. Glial cells have less cytoplasm and more basophilic nuclei.

The adrenogonadal primordium differentiates from the coelomic mesothelium at 4 weeks of gestation at the urogenital ridge, just cephalad to the developing mesonephros. At 5-6 weeks, it develops into the steroidogenic cells of the gonads and adrenal cortex; the adrenal and gonadal cells separate, the adrenal cells migrate retroperitoneally, and the gonadal cells migrate caudad. At 6-8 weeks of gestation, the gland rapidly enlarges, the cells of the inner cortex differentiate to form the fetal zone, and the outer subcapsular rim remains as the definitive zone. The primordium of the adrenal cortex is invaded at this time by sympathetic neural elements of ectodermal origin that differentiate into the chromaffin cells capable of synthesizing and storing catecholamines. Catechol *O*-methyltransferase, which converts norepinephrine to epinephrine, is expressed later in gestation. By the end of the eighth week of gestation, the encapsulated adrenal gland is associated with the upper pole of the kidney. By 8-10 weeks of gestation, the cells of the fetal zone are capable of active steroidogenesis.

In the full-term infant, the combined weight of both adrenal glands is 7-9 g. At birth, the inner fetal zone of the cortex makes up approximately 80% of the gland and the outer definitive zone 20%. Within a few days the fetal cortex begins to involute, undergoing a 50% reduction by 1 month of age. Conversely, the adrenal medulla is relatively small at birth and undergoes a proportionate increase in size over the first 6 months after birth. By 1 year, the adrenal glands each weigh <1 g. Adrenal growth thereafter results in adult adrenal glands reaching a combined weight of 8 g. The zonae fasciculata and glomerulosa are fully differentiated by about 3 years of age. The zona reticularis is not fully developed until puberty.

Adrenocorticotropic hormone (ACTH) is essential for fetal adrenal growth and maturation; feedback regulation of ACTH by cortisol is apparently established by 8-10 weeks of gestation. Additional factors important in fetal growth and steroidogenesis include placental chorionic gonadotropins and a number of peptide growth factors produced by the placenta and fetus.

Many transcription factors are critical for the development of the adrenal glands. At least four, EMX2, LHX1 (also termed LIM1), WT1, and WNT4, are required for development of the adrenogonadal primordium. WT1 upregulates expression of steroidogenic factor-1 (SF-1, encoded by the *NR5A1* gene). NR5A1 is one of at least three transcription factors associated with **adrenal hypoplasia** in humans; the others are *NR0B1* (dosage-sensitive sex reversal, adrenal hypoplasia congenita, X chromosome; *DAX1*), and the *GLI3* oncogene. Disruption of *NR5A1,* encoded on chromosome 9q33, results in gonadal and often adrenal agenesis, absence of pituitary gonadotropes, and an underdeveloped ventral medial hypothalamus. In-frame deletions and frameshift and missense pathogenic variants of this gene are associated with **46,XX ovarian insufficiency** and **46,XY gonadal dysgenesis**. Pathogenic variants in the *NR0B1* gene, encoded on Xp21, result in **adrenal hypoplasia congenita** and **hypogonadotropic hypogonadism** (see Chapter 615.1). Pathogenic variants in *GLI3* on chromosome 7p13 cause **Pallister-Hall syndrome**, other features of which include hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, and postaxial polydactyly.

The postnatal adrenal cortex is not static but is continually regenerated from a population of stem or progenitor cells under the adrenal capsule. These cells move radially inward (i.e., centripetally) and can differentiate into zona glomerulosa or fasciculata cells as needed in response to the appropriate trophic stimuli (see Chapter 614.3). Several signaling pathways, including sonic hedgehog (SHH) and WNT, regulate this process. SHH expression is restricted to the peripheral cortical cells that do not express high levels of steroidogenic genes but give rise to the underlying differentiated cells of the cortex. Wnt/β-catenin signaling maintains the undifferentiated state and adrenal fate of adrenocortical stem/progenitor cells, in part through induction of its target genes *DAX1* and inhibin-α, respectively. Adrenal tumors can result from constitutive activation of the WNT signaling pathway (see Chapter 617).

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614.2 Adrenal Steroid Biosynthesis

Perrin C. White

Cholesterol is the starting substrate for all steroid biosynthesis (Fig. 614.1). Although adrenal cortex cells can synthesize cholesterol de novo from acetate, circulating plasma lipoproteins provide most of the cholesterol for adrenal cortex hormone formation. Receptors for both low-density lipoprotein and high-density lipoprotein cholesterol are expressed on the surface of adrenocortical cells; the receptor for high-density lipoprotein is termed *scavenger receptor class B, type I* (SR-BI). Patients with **homozygous familial hypercholesterolemia**

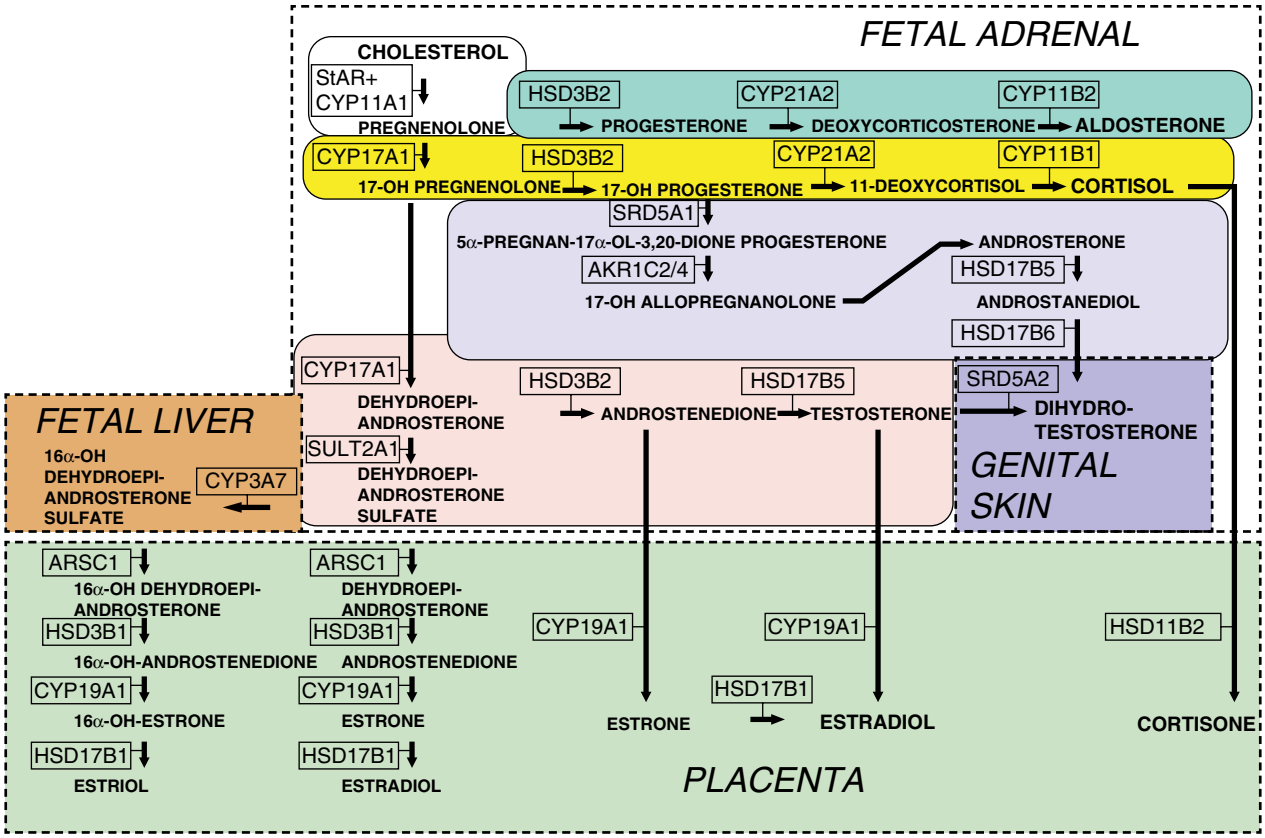

Fig. 614.1 Steroid biosynthesis and metabolism during gestation. Conversions within the fetal adrenal cortex, fetal liver *(brown rectangle),* male (i.e., testosterone-exposed) genital skin *(purple rectangle),* and placenta *(green rectangle)* are denoted by *arrows;* the enzyme mediating each conversion is also shown. Enzymatic conversions in the adrenal cortex are the same postnatally as prenatally, but cortisol and aldosterone biosynthesis (denoted by *yellow and turquoise boxes,* respectively) are more prominent, and normally little testosterone is synthesized *(pink rectangle).* A "backdoor pathway" *(lavender rectangle)* to convert 17-hydroxyprogesterone to dihydrotestosterone is active in the fetal adrenal and may assume particular importance in congenital adrenal hyperplasia (see Chapter 616). Many of the involved enzymes are cytochromes P450 (CYPs). The first step in all steroid biosynthesis is importation of cholesterol into mitochondria *(white rectangle)* mediated by the steroidogenic acute regulatory (StAR) protein. Adrenal enzymes include CYP11A1, cholesterol side-chain cleavage enzyme (P450scc in older terminology); HSD3B2, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 2; CYP17A1, 17β-hydroxylase/17,20-lyase (P450c17); CYP21A2, 21-hydroxylase (P450c21); CYP11B1, 11β-hydroxylase (P450c11); CYP11B2, aldosterone synthase (P450aldo; this enzyme mediates successive 11β-hydroxylase, 18-hydroxylase, and 18-oxidase reactions in the zona glomerulosa for the conversion of deoxycorticosterone to aldosterone); and AKR1C2/4, aldo-ketoreductases 1C2 and 1C4. Other enzymes important in the fetoplacental unit include ARSC1, arylsulfatase; CYP19, aromatase (P450arom); HSD3B1, 3β-hydroxysteroid dehydrogenase/Δ5,Δ4 isomerase type 1; HSD11B2, 11β-hydroxysteroid dehydrogenase type 2; HSD17B1, HSD17B5, and HSD17B6 are three different 17-hydroxysteroid dehydrogenase enzymes; SRD5A1 and SRD5A2, steroid 5α-reductase types 1 and 2, respectively; and SULT2A1, steroid sulfotransferase.

who lack low-density lipoprotein receptors have only mildly impaired adrenal steroidogenesis, suggesting that high-density lipoprotein is the more important source of cholesterol. Cholesterol is stored as cholesteryl esters in vesicles and subsequently hydrolyzed by cholesteryl ester hydrolases to liberate free cholesterol for steroid hormone synthesis.

The rate-limiting step of adrenal steroidogenesis is importation of cholesterol across the mitochondrial outer and inner membrane. This requires several proteins, particularly the steroidogenic acute regulatory (StAR) protein. The StAR protein has a very short half-life, and its synthesis is rapidly induced by trophic factors (corticotropin); it is the main short-term (minutes to hours) regulator of steroid hormone biosynthesis.

At the mitochondrial inner membrane, the side chain of cholesterol is cleaved to yield pregnenolone. This is catalyzed by the cholesterol side-chain cleavage enzyme (cholesterol desmolase, side-chain cleavage enzyme, P450scc, CYP11A1—the last term is the current systematic nomenclature), a cytochrome P450 (CYP) enzyme. Like other CYP enzymes, this is a membrane-bound hemoprotein with a molecular mass of approximately 50 kDa. It accepts electrons from a reduced nicotinamide adenine dinucleotide phosphate–dependent mitochondrial electron transport system consisting of two accessory proteins: adrenodoxin reductase (also called *ferredoxin reductase,* a flavoprotein) and adrenodoxin (or ferredoxin; a small protein containing nonheme iron). CYP enzymes use electrons and O_2 to hydroxylate the substrate and form H_2O. In the case of cholesterol side-chain cleavage, three successive oxidative reactions are performed to cleave the C20,22 carbon bond. Pregnenolone then diffuses out of mitochondria and enters the endoplasmic reticulum. The subsequent reactions that occur depend on the zone of the adrenal cortex.

ZONA GLOMERULOSA

In the zona glomerulosa, pregnenolone is converted to progesterone by 3β-hydroxysteroid dehydrogenase type 2, an oxidized nicotinamide adenine dinucleotide–dependent enzyme of the short-chain dehydrogenase type. Progesterone is converted to 11-deoxycorticosterone by steroid 21-hydroxylase (CYP21A2, P450c21), which is another CYP enzyme. Like other such enzymes in the endoplasmic reticulum, it uses an electron transport system with only one accessory protein: P450 oxidoreductase.

Deoxycorticosterone then reenters mitochondria and is converted to aldosterone by aldosterone synthase (CYP11B2, P450aldo), a CYP enzyme structurally related to cholesterol side-chain cleavage enzyme. Aldosterone synthase also carries out three successive oxidations: 11β-hydroxylation, 18-hydroxylation, and further oxidation of the 18-methyl carbon to an aldehyde.

ZONA FASCICULATA

In the endoplasmic reticulum of the zona fasciculata, pregnenolone and progesterone are converted by 17α-hydroxylase (CYP17A1, P450c17) to 17-hydroxypregenolone and 17-hydroxyprogesterone, respectively. This enzyme is not expressed in the zona glomerulosa, which consequently cannot synthesize 17-hydroxylated steroids. 17-Hydroxypregnenolone is converted to 17-hydroxyprogesterone and 11-deoxycortisol by the same 3β-hydroxysteroid and 21-hydroxylase enzymes, respectively, as are active in the zona glomerulosa. Thus inherited disorders in these enzymes affect both aldosterone and cortisol synthesis (see Chapter 616). Finally, 11-deoxycortisol reenters mitochondria and is converted to cortisol by steroid 11β-hydroxylase CYP11B1 (P450c11). This enzyme is closely related to aldosterone synthase but has low 18-hydroxylase and nonexistent 18-oxidase activity. Thus under normal circumstances the zona fasciculata cannot synthesize aldosterone.

ZONA RETICULARIS

In the zona reticularis and to some extent in the zona fasciculata, the 17-hydroxylase (CYP17A1) enzyme has an additional activity: cleavage of the 17,20 carbon-carbon bond. This converts 17-hydroxypregnenolone to dehydroepiandrosterone (DHEA). DHEA is converted to androstenedione by HSD3B2. This may be further converted in other tissues to testosterone and estrogens.

The Alternative or "Backdoor" Pathway to Dihydrotestosterone

In addition to the classic pathway via DHEA, androstenedione, and testosterone, the most potent endogenous androgen, 5-dihydrotestosterone (DHT), can also be synthesized via an alternative or "backdoor" pathway, which is physiologically active during the major period of human sexual differentiation in the 6th to 10th week of human fetal development and into the second trimester. To enter the alternative pathway, progesterone or 17-hydroxyprogesterone is 5α-reduced by steroid 5α-reductase type 1 (SRD5A1) to yield 5α-dihydroprogesterone and 17α-hydroxydihydroprogesterone. These three ketosteroids are subsequently 3α-reduced to allopregnanolone and 17α-hydroxyallopregnanolone by isoforms of the AKR1C enzyme family. CYP17A1 converts allopregnanolone to 17α-hydroxyallopregnanolone and then to androsterone by its 17,20-lyase activity. Androsterone can then be activated to DHT by sequential 17β-reduction and 3α-oxidase reactions.

FETOPLACENTAL UNIT

Steroid synthesis in the fetal adrenal varies during gestation (see Figs. 614.1 and 614.2). Shortly after the fetal adrenal gland forms (weeks 8-10), it efficiently secretes cortisol, which is able to negatively feed back on the fetal pituitary and hypothalamus to suppress ACTH secretion. This is a critical time for differentiation of the external genitalia in both sexes (see Chapter 616.1); to prevent virilization, the female fetus must not be exposed to high levels of androgens of adrenal origin, and placental aromatase activity must remain low during this time to minimize conversion of testosterone to estradiol in male fetuses, which would interfere with masculinization. After week 12, HSD3B activity in the fetal adrenal gland decreases and steroid sulfokinase activity increases. Major steroid products of the midgestation fetal adrenal gland are DHEA and DHEA sulfate (DHEAS) and, by 16α-hydroxylation in the liver, 16α-hydroxy DHEAS. Aromatase activity increases in the placenta at the same time, and steroid sulfatase activity is high as well. The placenta uses DHEA and DHEAS as substrates for estrone and estradiol synthesis and 16α-OH DHEAS as a substrate for estriol synthesis. Cortisol activity is low during the second trimester, which might serve to prevent premature secretion of surfactant by the developing fetal lungs; surfactant levels can affect the timing of parturition. As term approaches, fetal cortisol concentration increases because of increased cortisol secretion and decreased conversion of cortisol to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (HSD11B2). Low levels of aldosterone are produced in midgestation, but aldosterone secretory capacity increases near term.

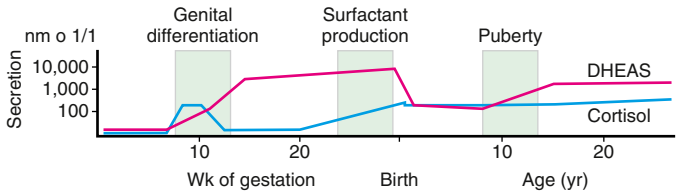

Fig. 614.2 Relative levels of cortisol and dehydroepiandrosterone sulfate (DHEAS) secretion by the fetal adrenal cortex during gestation and postnatally. Approximate times of several events are shown. Vertical axis is logarithmic, but values are approximate. Horizontal axis is not to scale.

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614.3 Regulation of the Adrenal Cortex

Perrin C. White

REGULATION OF CORTISOL SECRETION

Glucocorticoid secretion is regulated mainly by ACTH (corticotropin), a 39–amino acid peptide that is produced in the anterior pituitary (see Fig. 594.2). It is synthesized as part of a larger-molecular-weight precursor peptide known as *pro-opiomelanocortin*. This precursor peptide is also the source of β-lipotropin. ACTH and β-lipotropin are cleaved further to yield α- and β-melanocyte–stimulating hormone, corticotropin-like intermediate lobe peptide, γ-lipotropin, β- and γ-endorphin, and enkephalin (see Chapter 594).

ACTH is released in secretory bursts of varying amplitude throughout the day and night. The normal diurnal rhythm of cortisol secretion is caused by the varying amplitudes of ACTH pulses. Pulses of ACTH and cortisol occur every 30-120 minutes, are highest at about the time of waking, are low in late afternoon and evening, and reach their lowest point 1 or 2 hours after sleep begins.

Corticotropin-releasing hormone (CRH), synthesized by neurons of the parvicellular division of the hypothalamic paraventricular nucleus, is the most important stimulator of ACTH secretion. Arginine vasopressin (AVP) augments CRH action. Neural stimuli from the brain cause the release of CRH and AVP (see Chapter 594). AVP and CRH are secreted in the hypophyseal-portal circulation in a pulsatile manner. This pulsatile secretion appears to be responsible for the pulsatile (ultradian) release of ACTH. The circadian rhythm of ACTH release is probably induced by the corresponding circadian rhythm of hypothalamic CRH secretion, regulated by the suprachiasmatic nucleus with input from other areas of the brain. Cortisol exerts a negative feedback effect on the synthesis and secretion of ACTH, CRH, and AVP. ACTH inhibits its own secretion, a feedback effect mediated at the level of the hypothalamus. Finally, the adrenal cortex has intrinsic rhythmicity in its responses to the ACTH. Thus the secretion of cortisol is a result of the interaction of the hypothalamus, pituitary, and adrenal glands and other neural stimuli.

ACTH acts through a specific G protein–coupled receptor (also termed *melanocortin receptor-2,* encoded by the *MCR2* gene) to activate adenylate cyclase and increase levels of cyclic adenosine monophosphate. Cyclic adenosine monophosphate has short-term (minutes to hours) effects on cholesterol transport into mitochondria by increasing expression of StAR protein. The long-term effects (hours to days) of ACTH stimulation are to increase the uptake of cholesterol and the expression of genes encoding the enzymes required to synthesize cortisol. These transcriptional effects occur at least in part through increased activity of protein kinase A, which phosphorylates several transcriptional regulatory factors. MC2R trafficking and signaling are dependent on the MC2R accessory protein (MRAP). Pathogenic variants in either MC2R or MRAP can cause **familial glucocorticoid deficiency** (see Chapter 615).

REGULATION OF ALDOSTERONE SECRETION

The rate of aldosterone synthesis, which is normally 100- to 1,000-fold less than that of cortisol synthesis, is regulated mainly by the renin-angiotensin system and by potassium levels, with ACTH having only a short-term effect. In response to decreased intravascular volume, renin is secreted by the juxtaglomerular apparatus of the kidney. Renin is a proteolytic enzyme that cleaves angiotensinogen (renin substrate), an α_2-globulin produced by the liver, to yield the inactive decapeptide angiotensin I. Angiotensin-converting enzyme in the lungs and other tissues rapidly cleaves angiotensin I to the biologically active octapeptide angiotensin II. Cleavage of angiotensin II produces the heptapeptide angiotensin III. Angiotensins II and III are potent stimulators of aldosterone secretion; angiotensin II is a more potent vasopressor agent. Angiotensins II and III occupy a G protein–coupled receptor activating phospholipase C. This protein hydrolyzes phosphatidylinositol bisphosphate to produce inositol triphosphate and diacylglycerol, which raise intracellular calcium levels and activate protein kinase C and calmodulin-activated kinases. Similarly, increased levels of extracellular potassium depolarize the cell membrane and increase calcium influx through voltage-gated L-type calcium channels. Phosphorylation of transcriptional regulatory factors by calmodulin-activated kinases increases transcription of the aldosterone synthase (CYP11B2) enzyme required for aldosterone synthesis.

REGULATION OF ADRENAL ANDROGEN SECRETION

The mechanisms by which the adrenal androgens DHEA and androstenedione are regulated are not completely understood. **Adrenarche** is a maturational process in the adrenal gland that results in increased adrenal androgen secretion between the ages of 5 and 20 years. The process begins before the earliest signs of puberty and continues throughout the years when puberty is occurring. Histologically, it is associated with the appearance of the zona reticularis. Whereas ACTH stimulates adrenal androgen production acutely and clearly is the primary stimulus for cortisol release, additional factors have been implicated in the stimulation of the adrenal androgens. These include a relative decrease in expression of HSD3B2 in the zona reticularis and possibly increases in 17,20-lyase activity owing to phosphorylation of CYP17 or increased cytochrome b5 expression.

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614.4 Adrenal Steroid Hormone Actions

Perrin C. White

Steroid hormones act through several distinct receptors corresponding to the known biologic activities of the steroid hormones: glucocorticoid, mineralocorticoid, progestin, estrogen, and androgen. These receptors belong to a larger superfamily of nuclear transcription factors that include, among others, thyroid hormone and retinoic acid receptors. They have a common structure that includes a carboxyterminal ligand-binding domain and a midregion DNA-binding domain. The latter domain contains two zinc fingers, each of which consists of a loop of amino acids stabilized by four cysteine residues chelating a zinc ion.

Unliganded glucocorticoid and mineralocorticoid receptors are found mainly in the cytosol in complexes with other proteins. Hormone molecules diffuse through the cell membrane and bind receptors, changing their conformation and causing them to release their cytosolic binding proteins and translocate to the nucleus, where they bind DNA at specific hormone-response elements. Bound receptors can recruit other transcriptional coregulatory factors to DNA.

Whereas different steroids can share bioactivities because of their ability to bind to the same receptor, a given steroid can exert diverse biologic effects in different tissues. The diversity of hormonal responses is determined by the different genes that are regulated by each hormone in different tissues. Additionally, different combinations of coregulators are expressed in different tissues, allowing each steroid hormone to have many different effects. Moreover, enzymes can increase or decrease the affinity of steroids for their receptors and thus modulate their activity. 11β-Hydroxysteroid dehydrogenase type 1 (HSD11B1) converts cortisone, which is not a ligand for the glucocorticoid receptor, to cortisol, which is an active glucocorticoid. This increases local glucocorticoid concentrations in several tissues, especially the liver, where glucocorticoids maintain hepatic glucose output (see Chapter 615.4). Overexpression of this enzyme in adipose tissue can predispose to the development of obesity. Conversely, HSD11B2 oxidizes cortisol to cortisone, particularly in the kidney, preventing mineralocorticoid receptors from being occupied by high levels of cortisol (see Chapter 615.4).

Although corticosteroid receptors mainly act in the nucleus, some responses to both glucocorticoids and mineralocorticoids begin within minutes, an interval too short to be accounted for by increased gene transcription and protein synthesis. Such nongenomic effects can in some cases be mediated by cell membrane–associated isoforms of the classic glucocorticoid and mineralocorticoid receptors, which can couple to a variety of rapid intracellular signaling pathways such as G proteins. Direct interactions with other proteins, such as ion channels, have been documented as well, particularly in the nervous system.

ACTIONS OF GLUCOCORTICOIDS

Glucocorticoids are essential for survival. The term *glucocorticoid* refers to the glucose-regulating properties of these hormones. However, glucocorticoids have multiple effects on carbohydrate, lipid, and protein metabolism. They also regulate immune, circulatory, and renal function. They influence growth, development, bone metabolism, and central nervous system activity.

In stress situations, glucocorticoid secretion can increase up to 10-fold. This increase is believed to enhance survival through increased cardiac contractility, cardiac output, sensitivity to the pressor effects of catecholamines and other pressor hormones, work capacity of the skeletal muscles, and capacity to mobilize energy stores.

METABOLIC EFFECTS

The primary action of the glucocorticoids on carbohydrate metabolism is to increase glucose production by increasing hepatic gluconeogenesis. Glucocorticoids also increase cellular resistance to insulin, thereby decreasing entry of glucose into the cell. This inhibition of glucose uptake occurs in adipocytes, muscle cells, and fibroblasts. In addition to opposing insulin action, glucocorticoids can work in parallel with insulin to protect against long-term starvation by stimulating glycogen deposition and production in the liver. Both hormones stimulate glycogen synthetase activity and decrease glycogen breakdown. Glucocorticoid excess can cause hyperglycemia, and glucocorticoid deficiency can cause hypoglycemia.

Glucocorticoids increase free fatty acid levels by enhancing lipolysis, decreasing cellular glucose uptake, and decreasing glycerol production, which is necessary for reesterification of fatty acids. This increase in lipolysis is also stimulated through the permissive enhancement of lipolytic action of other factors such as epinephrine. This action affects adipocytes differently according to their anatomic locations. In the patient with glucocorticoid excess, fat is lost in the extremities, but it is increased in the trunk (centripetal obesity), neck, and face (moon facies). This may involve effects on adipocyte differentiation.

Glucocorticoids generally exert a catabolic or antianabolic effect on protein metabolism. Proteolysis in fat, skeletal muscle, bone, lymphoid, and connective tissue increases amino acid substrates that can be used in gluconeogenesis. Cardiac muscle and the diaphragm are almost entirely spared from this catabolic effect.

Circulatory and Renal Effects

Glucocorticoids have a positive inotropic influence on the heart, increasing the left ventricular work index. They have a permissive effect on the actions of epinephrine and norepinephrine on both the heart and the blood vessels. In the absence of glucocorticoids, decreased cardiac output and shock can develop; in states of glucocorticoid excess,

hypertension is often observed. This may be a result of activation of the mineralocorticoid receptor (see Chapter 615.4), which occurs when renal HSD11B2 is saturated by excessive levels of glucocorticoids.

Growth

In excess, glucocorticoids inhibit linear growth and skeletal maturation in children, apparently through direct effects on the epiphyses. However, glucocorticoids are also necessary for normal growth and development. In the fetus and neonate, they accelerate the differentiation and development of various tissues, including the hepatic and gastrointestinal systems, along with the production of surfactant in the fetal lung. Glucocorticoids are often given to pregnant women at risk for delivery of premature infants to accelerate these maturational processes.

Immunologic Effects

Glucocorticoids play a major role in immune regulation. They inhibit synthesis of glycolipids and prostaglandin precursors and the actions of bradykinin. They also block secretion and actions of histamine and proinflammatory cytokines (tumor necrosis factor-α, interleukin-1, and interleukin-6), thus diminishing inflammation. High doses of glucocorticoids deplete monocytes, eosinophils, and lymphocytes, especially T cells. They do so at least in part by inducing cell-cycle arrest in the G_1 phase and by activating apoptosis through glucocorticoid receptor–mediated effects. The effects on lymphocytes are primarily exerted on T-helper 1 cells and hence on cellular immunity, whereas the T-helper 2 cells are spared, leading to a predominantly humoral immune response. Pharmacologic doses of glucocorticoids can also decrease the size of immunologic tissues (spleen, thymus, and lymph nodes).

Glucocorticoids increase circulating polymorphonuclear cell counts, mostly by preventing their egress from the circulation. Glucocorticoids decrease diapedesis, chemotaxis, and phagocytosis of polymorphonuclear cells. Thus the mobility of these cells is altered such that they do not arrive at the site of inflammation to mount an appropriate immune response. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacterial, viral, fungal, and parasitic infections.

Effects on Skin, Bone, and Calcium

Glucocorticoids inhibit fibroblasts, leading to increased bruising and poor wound healing through cutaneous atrophy. This effect explains the thinning of the skin and striae that are seen in patients with Cushing syndrome.

Glucocorticoids have the overall effect of decreasing serum calcium and have been used in emergency therapy for certain types of hypercalcemia. This hypocalcemic effect probably results from a decrease in the intestinal absorption of calcium and a decrease in the renal reabsorption of calcium and phosphorus. Serum calcium levels, however, generally do not fall below normal because of a secondary increase in parathyroid hormone secretion.

The most significant effect of long-term glucocorticoid excess on calcium and bone metabolism is osteoporosis. Glucocorticoids inhibit osteoblastic activity by decreasing the number and activity of osteoblasts. Glucocorticoids also decrease osteoclastic activity but to a lesser extent, leading to low bone turnover with an overall negative balance. The tendency of glucocorticoids to lower serum calcium and phosphate levels causes secondary hyperparathyroidism. These actions decrease bone accretion and cause a net loss of bone mineral.

Central Nervous System Effects

Glucocorticoids readily penetrate the blood-brain barrier and have direct effects on brain metabolism. They decrease certain types of central nervous system edema and are often used to treat increased intracranial pressure. In large doses, they stimulate appetite and cause insomnia with a reduction in rapid eye movement sleep. There is an increase in irritability and emotional lability, with an impairment of memory and ability to concentrate. Mild to moderate glucocorticoid excess for a limited period often causes a feeling of euphoria or well-being, but glucocorticoid excess and deficiency can both be associated with clinical depression. *Glucocorticoid excess produces psychosis in some patients.*

Glucocorticoid effects in the brain are mediated largely through interactions with both the mineralocorticoid and glucocorticoid receptors (sometimes referred to in this context as *type I* and *type II corticosteroid receptors,* respectively). Activation of type II receptors increases sensitivity of hippocampal neurons to the neurotransmitter serotonin, which might help explain the euphoria associated with high doses of glucocorticoids. Glucocorticoids suppress release of CRH in the anterior hypothalamus, but they stimulate it in the central nucleus of the amygdala and lateral bed nucleus of the stria terminalis, where it can mediate fear and anxiety states. Glucocorticoids and other steroids might have nongenomic effects by modulating activities of both γ-aminobutyric acid and *N*-methyl-D-aspartate receptors.

ACTIONS OF MINERALOCORTICOIDS

The most important mineralocorticoids are aldosterone and, to a lesser degree, 11-deoxycorticosterone; corticosterone and cortisol are normally not important as mineralocorticoids unless secreted in excess. Mineralocorticoids have more limited actions than glucocorticoids. Their major function is to maintain intravascular volume by conserving sodium and eliminating potassium and hydrogen ions. They exert these actions in the kidney, gut, and salivary and sweat glands. Aldosterone can have distinct effects in other tissues. Mineralocorticoid receptors are found in the heart and vascular endothelium, and aldosterone increases myocardial fibrosis in heart failure.

Mineralocorticoids have their most important actions in the distal convoluted tubules and cortical collecting ducts of the kidney, where they induce reabsorption of sodium and secretion of potassium. In the medullary collecting duct, they act in a permissive fashion to allow vasopressin to increase osmotic water flux. Thus patients with mineralocorticoid deficiency can develop weight loss, hypotension, hyponatremia, and hyperkalemia, whereas patients with mineralocorticoid excess can develop hypertension, hypokalemia, and metabolic alkalosis (see Chapters 615, 616, and 620).

The mechanisms by which aldosterone affects sodium excretion are incompletely understood. Most effects of aldosterone are presumably the result of changes in gene expression mediated by the mineralocorticoid receptor, and indeed levels of subunits of both the Na^+, K^+-adenosine triphosphatase and the epithelial sodium channel increase in response to aldosterone. Additionally, aldosterone increases expression of the serum- and glucocorticoid-regulated kinase, which indirectly reduces turnover of epithelial sodium channel subunits and thus increases the number of open sodium channels.

The mineralocorticoid receptor has similar affinities in vitro for cortisol and aldosterone, yet cortisol is a weak mineralocorticoid in vivo. This discrepancy results from the action of HSD11B2, which converts cortisol to cortisone. Cortisone is not a ligand for the receptor, whereas aldosterone is not a substrate for the enzyme. Pharmacologic inhibition (as occurs with excessive consumption of licorice) or genetic deficiency of this enzyme allows cortisol to occupy renal mineralocorticoid receptors and produce sodium retention and hypertension; the genetic condition is termed **apparent mineralocorticoid excess syndrome**.

ACTIONS OF THE ADRENAL ANDROGENS

Many actions of adrenal androgens are exerted through their conversion to active androgens or estrogens such as testosterone, dihydrotestosterone, estrone, and estradiol. In males, <2% of the biologically important androgens are derived from adrenal production, whereas in females approximately 50% of androgens are of adrenal origin. The adrenal contribution to circulating estrogen levels is mainly important in pathologic conditions such as feminizing adrenal tumors. Adrenal androgens contribute to the physiologic development of pubic and axillary hair during normal puberty. They also play an important role in the pathophysiology of **congenital adrenal hyperplasia**, **premature**

adrenarche, **adrenal tumors,** and **Cushing syndrome** (see Chapters 616-619).

In humans, circulating levels of DHEA and DHEAS, the chief adrenal androgen precursors, reach a peak in early adulthood and then decline. This has led to speculation that some age-related physiologic changes might be reversed by DHEA administration, and beneficial effects have been suggested (but not proved) on insulin sensitivity, bone mineral density, muscle mass, cardiovascular risk, obesity, cancer risk, autoimmunity, and the central nervous system.

Synthetic Corticosteroids

Many synthetic analogs of cortisone and hydrocortisone are available. Prednisone and prednisolone are derivatives with an additional double bond in ring A. Similar to cortisone, prednisone is not an active steroid, but it is converted to prednisolone by HSD11B1 in the liver. Prednisone and prednisolone are 4-5 times as potent in antiinflammatory and carbohydrate activity but have slightly less effect on retention of water and sodium than cortisol. Halogenated derivatives have different effects. Betamethasone and dexamethasone have 25-40 times the glucocorticoid potency of cortisol but have little mineralocorticoid effect. These analogs are usually used in pharmacologic doses for their antiinflammatory or immunosuppressive properties. The antiinflammatory activity of fludrocortisone is about 15 times that of hydrocortisone, but fludrocortisone is more than 125 times as active a mineralocorticoid; it is used to treat aldosterone deficiency.

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614.5 Adrenal Medulla

Perrin C. White

The principal hormones of the adrenal medulla are the physiologically active catecholamines: dopamine, norepinephrine, and epinephrine (Fig. 614.3). Catecholamine synthesis also occurs in the brain, in sympathetic nerve endings, and in chromaffin tissue outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally 3-methoxy-4-hydroxymandelic acid, metanephrine, and normetanephrine. Urinary metanephrines and catecholamines are measured to detect pheochromocytomas of the adrenal medulla and sympathetic nervous system (see Chapter 621).

The proportions of epinephrine and norepinephrine in the adrenal gland vary with age. In early fetal stages, there is practically no epinephrine; at birth, norepinephrine remains predominant. However, in adults, norepinephrine accounts for only 10–30% of the pressor amines in the medulla.

The effects of catecholamines are mediated through a series of G protein–coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate and, by decreasing the peripheral vascular resistance, decreases the diastolic pressure. The hyperglycemic and calorigenic effects of norepinephrine are much less pronounced than are those of epinephrine.

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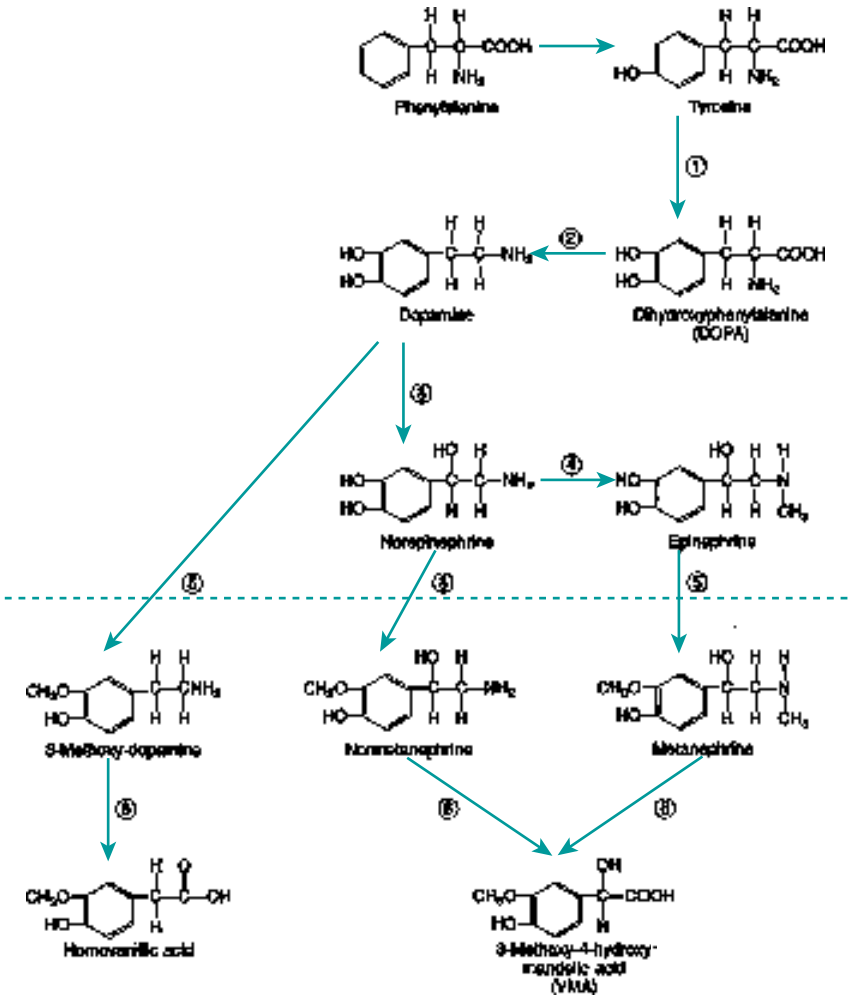

Fig. 614.3 Biosynthesis (above *dashed line*) and metabolism (below *dashed line*) of the catecholamines norepinephrine and epinephrine. Enzymes: *1*, tyrosine hydroxylase; *2*, dopa decarboxylase; *3*, dopamine β-oxidase; *4*, phenylethanolamine-*N*-methyltransferase; *5*, catechol *O*-methyltransferase; *6*, monoamine oxidase.

Chapter 615

Adrenocortical Insufficiency and Altered Sensitivity to Corticosteroids

Perrin C. White

In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone (Table 615.1). Acquired primary adrenal insufficiency is termed **Addison disease**. Dysfunction of the anterior pituitary gland or hypothalamus can cause a deficiency of corticotropin (adrenocorticotropic hormone [ACTH]) and lead to hypofunction of the adrenal cortex, termed *secondary adrenal insufficiency;* the term *tertiary adrenal insufficiency* is sometimes used to denote cases arising from hypothalamic dysfunction (Tables 615.2 and 615.3).

615.1 Primary Adrenal Insufficiency

Perrin C. White

Primary adrenal insufficiency in children is most frequently caused by genetic conditions that are often, but not always, manifested in infancy and, less often, by acquired problems such as autoimmune conditions (Table 615.4) or syndromes (Table 615.5). Susceptibility to autoimmune conditions often has a genetic basis, and so these distinctions are not absolute.

INHERITED ETIOLOGIES

Inborn Defects of Steroidogenesis

The most common causes of adrenocortical insufficiency in *infancy* are the salt-losing forms of congenital adrenal hyperplasia (CAH, see Chapter 616). Approximately 75% of infants with 21-hydroxylase deficiency, almost all infants with lipoid adrenal hyperplasia, and most infants with a deficiency of 3β-hydroxysteroid dehydrogenase manifest salt-losing symptoms in the newborn period because they are unable to synthesize either cortisol or aldosterone. Relatively mild pathogenic variants in *STAR* (which controls cholesterol importation into mitochondria) or *CYP11A1* (which encodes the cholesterol side-chain cleavage enzyme) can cause adrenal insufficiency manifesting in childhood.

Aside from CAH and autoimmune adrenalitis, a genetic cause can be identified in >65% of patients with primary adrenal insufficiency presenting in *childhood*. These can be grouped into several categories: (1) ACTH unresponsiveness (familial glucocorticoid deficiency); (2) adrenal hypoplasia congenita caused by pathogenic variants in orphan nuclear hormone receptors that affect expression of other genes; (3) defects in lipid metabolism, particularly adrenoleukodystrophy; (4) syndromes associated with intrauterine growth restriction, adrenal hypoplasia, and disorders of sexual development, such as IMAGe and MIRAGE syndromes (activating variants of *CDKN1C* and *SAMD9,* respectively), and type 2 IMAGe syndrome (*POLE1* gene); and (5) deficiency of mitochondrial reactive oxygen species detoxification (*NNT* and *TXNRD2* genes).

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is a form of chronic adrenal insufficiency characterized by isolated deficiency of glucocorticoids, elevated levels of ACTH, and generally normal aldosterone production, although salt-losing manifestations present in most other forms of adrenal insufficiency occasionally occur. Patients may have hypoglycemia, seizures, and increased pigmentation during the first decade of life. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa. Pathogenic variants in the gene for the ACTH receptor *(MCR2)* have been described in approximately 25% of these patients, most of which affect trafficking of receptor molecules from the endoplasmic reticulum to the cell surface. Another 10–20% of cases are caused by variants in *MRAP,* which encodes a melanocyte receptor accessory protein required for this trafficking.

Another syndrome of ACTH resistance occurs in association with achalasia and alacrima (**triple A** or **Allgrove syndrome**). These patients often have a progressive neurologic disorder that includes autonomic dysfunction, intellectual disability, motor neuropathy, and occasional deafness. This syndrome is autosomal recessive; the *AAAS* gene has been mapped to chromosome 12q13. The encoded protein, aladin, might help to regulate nucleocytoplasmic transport of other proteins.

Adrenal Hypoplasia Congenita

Adrenal hypoplasia congenita (AHC) is a relatively frequent cause of adrenal insufficiency in males, along with CAH, autoimmune disease, and adrenoleukodystrophy (ALD). AHC is predominantly a failure of development of the definitive zone of the adrenal cortex; the fetal zone may be relatively normal. Consequently, adrenal insufficiency generally becomes evident as the fetal zone involutes postnatally (see Chapter 614), with onset in infancy or in the first 2 years of life but occasionally in later childhood or even adulthood. In some cases, aldosterone deficiency becomes evident before cortisol deficiency.

The disorder is caused by pathogenic variants of *NR0B1 (DAX1)*, a member of the nuclear hormone receptor family, located on Xp21. Males with AHC often do not undergo puberty as a result of hypogonadotropic hypogonadism caused by the same variant of *NR0B1*. **Cryptorchidism**, sometimes noted in these males, is probably an early manifestation of hypogonadotropic hypogonadism, but often testicular function in infants is normal, with a typical or even an unusually prolonged testosterone surge in the first month of life.

AHC occasionally occurs as part of a *contiguous gene deletion* syndrome together with Duchenne muscular dystrophy, glycerol kinase deficiency, cognitive impairment, or a combination of these conditions.

The transcription factor NR5A1 (steroidogenic factor-1, SF-1) is required for adrenal and gonadal development (see Chapter 614). Males with heterozygous variants in *NR5A1* have impaired development of the testes despite the presence of a normal copy of the gene on the other chromosome and can appear to be female, similar to patients with lipoid adrenal hyperplasia (see Chapter 616). Rarely, such patients also have adrenal insufficiency.

Adrenal hypoplasia is also occasionally seen in patients with **Pallister-Hall syndrome** caused by pathogenic variants in *GLI3*.

Disorders of Lipid Metabolism

In **adrenal leukodystrophy (ALD)**, adrenocortical deficiency is associated with demyelination in the central nervous system (see Chapters 106.2 and 639.3). High levels of **very long-chain fatty acids** are found in tissues and body fluids, resulting from their impaired β-oxidation in the peroxisomes.

The most common form of ALD is an X-linked disorder with various presentations. The most common clinical picture is of a degenerative neurologic disorder appearing in childhood or adolescence and progressing to severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. Neurologic symptoms may be subtle at onset, sometimes consisting only of behavioral changes or deteriorating academic performance. Generalized but incomplete alopecia, resembling that of chemotherapy, is a characteristic but inconsistent finding. A milder form of X-linked ALD is **adrenomyeloneuropathy**, which begins in later adolescence or early adulthood. Patients may have evidence of adrenal insufficiency before, at the time of, or after neurologic symptoms develop, often with years

Table 615.1 Causes of Primary Adrenal Insufficiency

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ADRENAL DESTRUCTION		
Autoimmunity		
Autoimmune primary adrenal insufficiency and autoimmune polyendocrine syndrome type 2	*HLA-DR3, DR4, CTLA4, BACH2, PTPN22, GATA3, CLEC16, MIC-A, MIC-B, NALP1,* and *AIRE*	Hypothyroidism, hyperthyroidism, premature ovarian insufficiency, vitiligo, type 1 diabetes, pernicious anemia, other organ-specific autoimmune features
Autoimmune polyendocrine syndrome type 1	*AIRE* (240300)	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders, lymphomas (rarely)
Immunodeficiency 31C	*STAT1* (614162)	Chronic mucocutaneous candidiasis, susceptibility to *Staphylococcus aureus* and other bacterial, viral, and fungal infections, polyendocrinopathy (including hypothyroidism and type 1 diabetes), cerebral aneurysms
Peroxisomal Defects		
X-linked adrenoleukodystrophy	*ABCD1* (300100)	Progressive neurodegeneration, behavioral changes, cognitive decline, loss of speech, hearing, and vision, dementia, spasticity, seizures
Refsum disease	*PEX7* (266500)	Least severe form of peroxisome biosynthesis defects
Neonatal adrenoleukodystrophy (autosomal recessive)	*PEX1* (601539)	Craniofacial abnormalities, liver dysfunction, absence of peroxisomes
Zellweger syndrome	*PEX1* (214100)	Craniofacial abnormalities, hepatomegaly, severe intellectual disability and growth failure, hypotonia, deafness, blindness, genitourinary abnormalities, stippled epiphyses
Mitochondrial Defects		
Kearns-Sayre syndrome	Mitochondrial DNA deletions (530000)	External ophthalmoplegia, retinal degeneration, cardiac conduction defects, other endocrinopathies
Hemorrhage	—	Bilateral adrenal hemorrhage of the newborn baby, primary antiphospholipid syndrome, anticoagulation
Trauma or Surgery	—	Bilateral adrenalectomy
Infection	—	Septic shock, meningococcal sepsis (Waterhouse-Friderichsen syndrome), tuberculosis, fungal infections (e.g., histoplasmosis, cryptococcosis, coccidioidomycosis, and blastomycosis), African trypanosomiasis, cytomegalovirus, HIV-1, syphilis
Infiltration	—	Metastatic cancers, primary adrenal lymphoma, amyloidosis, sarcoidosis (rare), hemochromatosis
DRUGS	—	Ketoconazole, rifampicin, phenytoin, phenobarbital, aminoglutethimide, mitotane, abiraterone acetate, etomidate, suramin, mifepristone, nivolumab, pembrolizumab
IMPAIRED STEROIDOGENESIS		
Impaired Cholesterol Transport		
Steroidogenic acute regulatory protein (congenital lipoid adrenal hyperplasia)	*StAR* (201710)	46,XY DSD, gonadal insufficiency
Steroidogenic Enzyme or Cofactor Deficiency Causing Congenital Adrenal Hyperplasia		
3β-hydroxysteroid dehydrogenase type 2	*HSD3B2* (201810)	46,XX and 46,XY DSD, gonadal insufficiency
21-hydroxylase	*CYP21A2* (201 910)	46,XX DSD, hyperandrogenism
11β-hydroxylase	*CYP11B1* (202 010)	46,XX DSD, arterial hypertension
CYP17A1 deficiency	*CYP17A1* (202 110)	46,XY DSD, arterial hypertension, gonadal insufficiency
P450 oxidoreductase	*POR* (201 750)	46,XX and 46,XY DSD, gonadal insufficiency, bone malformation, dysfunction of all endoplasmic CYP450 enzymes
Steroidogenic Enzyme Deficiency (Noncongenital Adrenal Hyperplasia)		
P450 side-chain cleavage enzyme	*CYP11A1* (118 485)	46,XY DSD, gonadal insufficiency
Aldosterone synthase	*CYP11B2* (124 080)	Isolated mineralocorticoid deficiency
Defects of Cholesterol Synthesis or Metabolism		
Wolman disease (lysosomal acid lipase deficiency, and cholesterol ester storage disease)	*LIPA* (278 000)	Diffuse punctate adrenal calcification, xanthomatous changes in multiple organs, hypercholesterolemia, steatorrhea, poor prognosis

Continued

Table 615.1 Causes of Primary Adrenal Insufficiency—cont'd

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
Smith-Lemli-Opitz disease	*DHCR7* (270 400)	Intellectual disability, craniofacial malformations, limb abnormalities, growth failure
Abetalipoproteinemia	*MTP* (200 100)	Ataxia, retinopathy, acanthocytosis, fat malabsorption
ADRENAL DYSGENESIS		
X-linked adrenal hypoplasia congenital	*NROB1* (300 200)	Combined primary and secondary hypogonadism, Duchenne muscular dystrophy in contiguous gene syndrome
Adrenal hypoplasia steroidogenic factor-1 deficiency	*NR5A1* (184757)	46,XY DSD, gonadal insufficiency
IMAGe syndrome	*CDKN1C* (300 290)	Intrauterine growth restriction, metaphyseal dysplasia, adrenal insufficiency, genital anomalies
MIRAGE syndrome	*SMAD9* (617 053)	Myelodysplasia, infection, adrenal hypoplasia, growth restriction, genital anomalies, enteropathy
Pallister-Hall syndrome	*GLI3* (165 240)	Hypothalamic hamartoblastoma, hypopituitarism, imperforate anus, postaxial polydactyly
Meckel syndrome	*MKS1* (249 000)	CNS malformation, polycystic kidneys with fibrotic liver changes, polydactyly
Pseudotrisomy 13	(264 480)	Holoprosencephaly, severe facial anomalies, postaxial polydactyly, various other congenital defects, and normal chromosomes
Hydrolethalus syndrome	*HYLS1* (236 680)	Severe prenatal-onset hydrocephalus, polydactyly
Galloway-Mowat syndrome	*WDR73* (251 300)	Early-onset severe encephalopathy, intractable epilepsy, nephrotic syndrome, microcephaly, hiatal hernia
ACTH RESISTANCE		
Familial glucocorticoid deficiency type 1	*MC2R* (202 200)	Tall stature, isolated deficiency of glucocorticoids, generally normal aldosterone production
Familial glucocorticoid deficiency type 2	*MRAP* (607398)	Isolated deficiency of glucocorticoids, generally normal aldosterone production
IMPAIRED REDOX HOMEOSTASIS		
Triple A syndrome (Allgrove syndrome)	*AAAS* (231550)	Alacrimia, achalasia, neurologic impairment, deafness, intellectual disability, hyperkeratosis
Mitochondrial deficiency of free radical detoxification	*NNT* (614736) and *TRXR2* (606448)	*NNT*: hypoglycemia, hyperpigmentation, low cortisol concentration, increased ACTH concentration, isolated deficiency of glucocorticoids; *TRXR2*: isolated deficiency of glucocorticoids
MISCELLANEOUS		
Defects in DNA repair	*MCM4* (609981)	Natural killer cell deficiency, growth failure, increased chromosomal breakage
Bioinactive ACTH	*POMC* (201400)	—
Sphingosine-1-phosphate lyase 1	*SGPL1* (617575)	Steroid-resistant nephrotic syndrome, ichthyosis, primary hypothyroidism, cryptorchidism, immunodeficiency, neurologic defects

*www.omim.org
ACTH, Adrenocorticotropic hormone; DSD, disorder of sex development; OMIM, Online Mendelian Inheritance in Man.
Modified from Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 1.

separating their presentation. X-linked ALD is caused by pathogenic variants in *ABCD1* located on Xq28. The gene encodes a transmembrane transporter involved in the importation of very long-chain fatty acids into peroxisomes. Clinical phenotypes can vary even within families, perhaps owing to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency. Prenatal diagnosis by DNA analysis and family screening by very long-chain fatty acid assays and gene analysis are available. Females who are heterozygous carriers of the X-linked ALD gene can develop neurologic symptoms in midlife or later; adrenal insufficiency is rare. This condition is part of the newborn screening panel.

Neonatal ALD is a rare *autosomal recessive* disorder. Infants have neurologic deterioration and have or acquire evidence of adrenocortical dysfunction. Most patients have severe, progressive cognitive impairment and die before 5 years of age. This disorder is a subset of **Zellweger (cerebrohepatorenal) syndrome**, in which peroxisomes do not develop at all owing to pathogenic variants in any of several genes (*PEX5*, *PEX1*, *PEX10*, *PEX13*, and *PEX26*) controlling the development of peroxisomes.

Patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B–containing lipoproteins (such as low-density lipoprotein), and homozygous **familial hypercholesterolemia**, with impaired or absent low-density lipoprotein receptors, have mildly impaired adrenocortical function. Heterozygous familial hypercholesterolemia patients have normal adrenocortical function, which is unaffected by treatment with statin (HMG-CoA reductase inhibitor) drugs. Adrenal insufficiency has been reported in patients with **Smith-Lemli-Opitz syndrome**, an autosomal recessive disorder manifesting with facial anomalies, microcephaly, limb anomalies, and developmental delay (see Chapter 106.3), caused by pathogenic variants in the gene coding for sterol Δ^7-reductase on chromosome 11q12-q13.

Table 615.2 Causes of Secondary Adrenal Insufficiency in the Form of Pituitary Disorders

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ACQUIRED CAUSES		
Steroid withdrawal syndrome	*PDGFD*	Endogenous glucocorticoid hypersecretion caused by Cushing syndrome and exogenous glucocorticoid administration for more than 2 wk
Opioids	—	Hypogonadotropic hypogonadism
Tumor	—	Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, intrasellar or suprasellar metastases, adenoma, carcinoma
Trauma	—	Pituitary stalk lesions, battered child syndrome, vehicular trauma
Pituitary apoplexy (Sheehan syndrome)	—	High blood loss or hypotension
CONGENITAL CAUSES		
Aplasia or Hypoplasia		
PROP1 deficiency	*PROP1* (262600)	Additional deficiency of growth hormone, prolactin, thyroid-stimulating hormone, and luteinizing hormone or follicle-stimulating hormone, or both
LHX4 deficiency	*LHX4* (262700)	Additional deficiency of growth hormone and thyroid-stimulating hormone
SOX3 deficiency	*SOX3* (312000)	Additional deficiencies of pituitary hormones
Isolated ACTH Deficiency		
TBX19 deficiency	*TBX19* (201400)	Severe neonatal-onset adrenal insufficiency
Proopiomelanocortin	*POMC* (609734)	Adrenal insufficiency, early-onset obesity, red hair pigmentation
Proprotein convertase 1	*PCSK1* (600955)	Hypoglycemia, malabsorption, hypogonadotropic hypogonadism

*www.omim.org.
ACTH, Adrenocorticotropic hormone; OMIM, Online Mendelian Inheritance in Man.
From Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 2.

Table 615.3 Causes of Tertiary Adrenal Insufficiency

	GENE (OMIM*)	ASSOCIATED CLINICAL SIGNS AND SYMPTOMS
ACQUIRED CAUSES		
Steroid withdrawal syndrome	*PDGFD*	Endogenous glucocorticoid hypersecretion caused by Cushing syndrome and exogenous glucocorticoid administration for more than 2 wk
Opioids	—	Hypogonadotropic hypogonadism
Inflammatory disorders	—	Abscess, meningitis, encephalitis
Trauma	—	—
Radiation therapy	—	Craniospinal irradiation in leukemia and irradiation for tumors outside the hypothalamic-pituitary area
Surgery	—	—
Tumor	—	Craniopharyngioma, glioma, meningioma, ependymoma, germinoma, intrasellar or suprasellar metastases
Infiltrative diseases	—	Sarcoidosis, histiocytosis X, hemochromatosis
CONGENTIAL CAUSES		
Septo-optic dysplasia (de Morsier syndrome)	*HESX1* (182230)	Combined pituitary hormone deficiency, optic nerve hypoplasia, midline brain defects
Corticotropin-releasing hormone deficiency	—	—

*www.omim.org.
OMIM, Online Mendelian Inheritance in Man.
From Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613–629, Table 3.

This impairs the final step in cholesterol synthesis with marked elevation of 7-dehydrocholesterol and abnormally low cholesterol. **Wolman disease** is a rare autosomal recessive disorder caused by pathogenic variants in the gene encoding human lysosomal acid lipase on chromosome 10q23.2-23.3. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. Infants during the first or second month of life have hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the first year of life.

Multisystem Syndromes Associated with Growth Restriction

Pathogenic variants in genes that affect DNA replication may be associated with primordial dwarfism, immune deficiency, and adrenal insufficiency. Minichromosome maintenance-deficient 4 homolog *(MCM4)* functions to integrate several protein kinase signals that regulate progression of DNA replication through the S phase. Homozygous deficiency of MCM4 causes a primary **immunodeficiency syndrome** characterized by severe intrauterine and extrauterine growth

Table 615.4 Frequencies of Etiologies of Primary Adrenal Insufficiency

ETIOLOGY	%	AGE AT DIAGNOSIS
Congenital adrenal hyperplasia	59	Infancy
Autoimmune	16	Childhood to adolescence
APECED (autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy)	6	Childhood to adolescence
Adrenoleukodystrophy	4	Childhood to adolescence
Other genetic causes	14*	
Hemorrhage	1	Infancy

*See Table 615.5.
Data from Perry R, Kecha O, Paquette J, et al. Primary adrenal insufficiency in children: twenty years' experience at the Sainte-Justine Hospital, Montreal. *J Clin Endocrinol Metab.* 2005;90:3243–3250; Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood. J Clin Endocrinol Metab. 2011;96:E925–E928.

Table 615.5 Other Genetic Etiologies for Primary Adrenal Insufficiency

GENE	FUNCTION	SYNDROME	FREQUENCY* %
MC2R	Melanocortin (ACTH) receptor	Familial glucocorticoid deficiency type 1	22
MRAP	Melanocortin receptor accessory protein	Familial glucocorticoid deficiency type 2	4
NROB1	DAX1 orphan nuclear receptor	X-linked adrenal hypoplasia congenita	6†
NR5A1	SF-1 orphan nuclear receptor	Gonadal dysgenesis	<1
STAR	Steroidogenic acute regulatory protein	Nonclassic lipoid adrenal hyperplasia	8
CYP11A1	Cholesterol side-chain cleavage enzyme	Nonclassic lipoid adrenal hyperplasia	8
NNT	Nicotinamide nucleotide transhydrogenase	Familial glucocorticoid deficiency type 4	8
AAAS	Aladin (nuclear transport protein)	Triple A syndrome	5
SAMD9	Factor inhibiting cell proliferation	MIRAGE syndrome	3
CDKN1C	Cyclin-dependent kinase inhibitor	IMAGE syndrome	1
POLE	Subunit of DNA polymerase	IMAGE syndrome type 2	rare

*Frequencies are from 95 Turkish and 155 United Kingdom patients in whom congenital adrenal hyperplasia, autoimmune etiologies, and metabolic disorders (e.g., adrenoleukodystrophy) had been excluded.
†Many cases of X-linked adrenal hypoplasia congenita had already been identified, so this frequency is an underestimate.

restriction, microcephaly, decreased numbers of natural killer (NK) cells, recurrent viral infections, and adrenal insufficiency. It is relatively frequent (1 in 2,506) in the Irish Traveller population.

MIRAGE syndrome is a form of syndromic adrenal hypoplasia, characterized by myelodysplasia, infections, restriction of growth, adrenal hypoplasia, genital abnormalities, and enteropathy. It is often fatal within the first decade of life, usually because of invasive infection. It is caused by pathogenic variants in *SAMD9* on chromosome 7q21, which encodes a protein that inhibits cell proliferation. Disease-causing variants are heterozygous and usually arise de novo. When expressed in cultured cells, the abnormal proteins strongly inhibit cell proliferation. There is a risk that affected cells will attempt to escape growth inhibition by selectively losing chromosome 7 carrying the variant causing haploinsufficiency of *SAMD9*. This can cause myelodysplastic syndrome.

IMAGE syndrome consists of intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies. Two forms have been identified: an autosomal dominant form caused by pathogenic variants in *CDKN1C* and an autosomal recessive form caused by variants in *POLE*. Adrenal insufficiency in cases associated with *CDKN1C* variants tends to present in early infancy, whereas in cases caused by *POLE* variants, it is manifested during early childhood. The recessive form is also associated with immunodeficiency and is therefore sometimes termed *IMAGEI syndrome.*

The *CDKN1C* gene product, also called *p57(KIP2),* binds G1 cyclin/CDK complexes and thus inhibits cell proliferation. It is located in the imprinted region of chromosome 11p15 and is preferentially expressed from the maternal allele. Inactivating variants in this gene cause some cases of Beckwith-Wiedemann syndrome (see Chapter 113), which is associated with macrosomia and tumor risk. Variants that interfere with binding of CDKN1C to DNA polymerase delta auxiliary protein enhance the growth inhibitory effect of CDKN1C (gain of function) and cause IMAGE syndrome when maternally inherited. Thus both genes involved in IMAGE syndrome have roles in DNA replication and repair.

Deficiency of Mitochondrial Reactive Oxygen Species Detoxification

Nicotinamide nucleotide transhydrogenase *(NNT)* is a mitochondrial protein that catalyzes transfer of a hydride ion between nicotinamide adenine dinucleotide, NAD(H), and oxidized nicotinamide dinucleotide phosphate, NADP(H). Its deficiency manifests generally in infancy or early childhood, and most patients have both mineralocorticoid and glucocorticoid deficiencies. A pathogenic variant in *TXNRD2* has been identified in a single kindred with glucocorticoid deficiency.

Type 1 Autoimmune Polyendocrinopathy Syndrome

Although autoimmune Addison disease most often occurs sporadically, it can occur as a component of two syndromes, each consisting of a constellation of autoimmune disorders (see Chapter 608). **Type 1 autoimmune polyendocrinopathy syndrome (APS-1)**, also known as *autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy* (APECED) syndrome, is inherited in a mendelian autosomal recessive manner, whereas APS-2 has complex inheritance. Patients with APS-1

may have autoantibodies to the adrenal cytochrome P450 enzymes CYP21A2, CYP17A1, and CYP11A1. The presence of such antibodies indicates a high likelihood of the development of Addison disease or, in female patients, ovarian failure. Adrenal failure can evolve rapidly in APS-1; death in patients with a previous diagnosis and unexplained deaths in siblings of patients with APS-1 have been reported, indicating the need to closely monitor patients with APS-1 (or any child with unexplained hypoparathyroidism) and to thoroughly evaluate apparently unaffected siblings of patients with this disorder.

Corticosteroid-Binding Globulin Deficiency and Decreased Cortisol-Binding Affinity

Corticosteroid-binding globulin deficiency (*SERPINA6* pathogenic variant) and decreased cortisol-binding affinity result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of corticosteroid-binding globulin deficiency.

ACQUIRED ETIOLOGIES

Autoimmune Addison Disease

The most common cause of Addison disease is autoimmune destruction of the glands. The glands may be so small that they are not visible at autopsy, and only remnants of tissue are found in microscopic sections. Usually, the medulla is not destroyed, and there is marked lymphocytic infiltration in the area of the former cortex. In advanced disease, all adrenocortical function is lost, but early in the clinical course, isolated cortisol deficiency can occur. Most patients have **antiadrenal cytoplasmic antibodies** in their plasma; 21-hydroxylase (CYP21A2) is the most commonly occurring biochemically defined autoantigen.

Addison disease can occur as a component of two autoimmune polyendocrinopathy syndromes. Type 1 (APS-1) was discussed previously. **Type 2 autoimmune polyendocrinopathy (APS-2)** consists of Addison disease associated with autoimmune thyroid disease **(Schmidt syndrome)** or type 1 diabetes **(Carpenter syndrome)** (see Chapter 608). Frequencies of the human leukocyte antigen (HLA)-D3 and HLA-D4 alleles are increased in these patients and appear to confer an increased risk for development of this disease; particular alleles at the major histocompatibility complex class I chain–related genes A and B (*MICA* and *MICB*) also are associated with this disorder. Polymorphisms in genes involved in other autoimmune disorders have been inconsistently associated with primary adrenal insufficiency, and their contribution to its pathogenesis must be regarded as uncertain. These include the class II, major histocompatibility complex, transactivator *(CIITA),* C-type lectin domain family 16, member A (*CLEC16A*), and protein tyrosine phosphatase, nonreceptor type 22 *(PTPN22).* The disorder is most common in middle-age females and can occur in many generations of the same family. Antiadrenal antibodies, specifically antibodies to the CYP21A2, CYP17A1, and CYP11A1 enzymes, are also found in these patients. Autoimmune adrenal insufficiency may also be seen in patients with celiac disease and mitochondrial gene mutations.

Adrenal insufficiency remains a risk among patients previously treated with a prolonged course of steroids when stressed with an infection or trauma. Despite being "tapered or weaned" from the steroids, subclinical adrenal insufficiency may develop weeks to months later if stressed (see Chapter 615.2).

Infection

Tuberculosis was a common cause of adrenal destruction in the past but is currently much less prevalent. The most common infectious etiology for adrenal insufficiency is meningococcemia (see Chapter 237); adrenal crisis from this cause is referred to as **Waterhouse-Friderichsen syndrome**. Patients with AIDS can have a variety of subclinical abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, but frank adrenal insufficiency is rare. However, drugs used in the treatment of AIDS can affect adrenal hormone homeostasis.

Drugs

Ketoconazole, an antifungal drug, can cause adrenal insufficiency by inhibiting adrenal enzymes. Mitotane (o,p′-DDD), used in the treatment of adrenocortical carcinoma and refractory Cushing syndrome (see Chapters 617 and 619), is cytotoxic to the adrenal cortex and can also alter extraadrenal cortisol metabolism. Signs of adrenal insufficiency occur in a substantial percentage of patients treated with mitotane. **Etomidate**, used in the induction and maintenance of general anesthesia, inhibits 11β-hydroxylase (CYP11B1), and a single induction dose can block cortisol synthesis for 4-8 hours or longer. This may be problematic in severely stressed patients, particularly if repeated doses are used in a critical care setting. Abiraterone acetate, an androgen biosynthesis inhibitor that is used to treat metastatic prostate carcinoma, inhibits cortisol biosynthesis but leaves corticosterone biosynthesis unimpaired. This drug is not currently encountered in pediatric practice. **Immune checkpoint inhibitors** may rarely cause primary adrenal insufficiency. Although not themselves a cause of adrenal insufficiency, rifampicin and anticonvulsive drugs such as phenytoin and phenobarbital reduce the effectiveness and bioavailability of corticosteroid replacement therapy by inducing steroid-metabolizing enzymes in the liver.

Hemorrhage into Adrenal Glands

Hemorrhage into adrenal glands can occur in the neonatal period as a result of a difficult labor (especially breech presentation), or its etiology might not be apparent (Fig. 615.1). An incidence rate of 3 in 100,000 live births has been suggested. The hemorrhage may be sufficiently extensive to result in death from exsanguination or hypoadrenalism. An abdominal mass, anemia, unexplained jaundice, or scrotal hematoma may be the presenting sign. Often, the hemorrhage is asymptomatic initially and is identified later by calcification of the adrenal gland. Fetal adrenal hemorrhage has also been reported. Postnatally, adrenal hemorrhage most often occurs in patients being treated with anticoagulants. It can also occur as a result of child abuse.

CLINICAL MANIFESTATIONS

Primary adrenal insufficiency leads to cortisol and often aldosterone deficiencies. The signs and symptoms of adrenal insufficiency are most easily understood in the context of the normal actions of these hormones (see Chapter 614; Table 615.6).

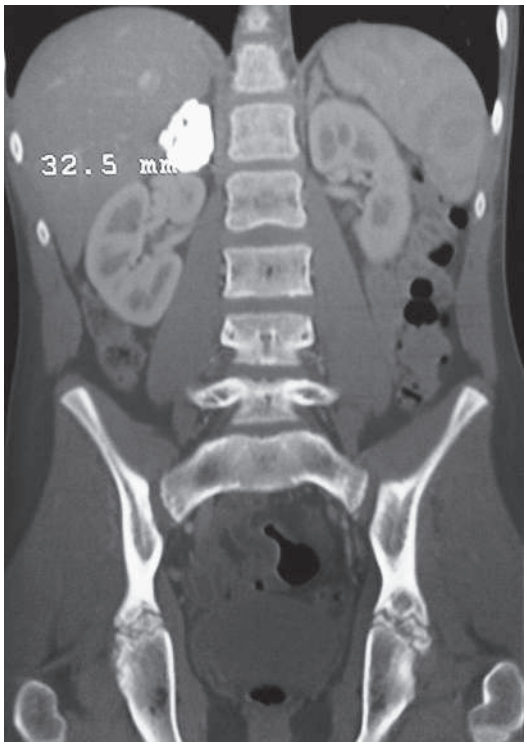

Fig. 615.1 Contrast-enhanced coronal CT confirming intraadrenal localization of a round hyperdense lesion compatible with a large calcification. *(From Llano JP, Beaufils E, Nicolino M. Uncommon cause of large paravertebral calcification in a child. J Pediatr. 2013;162:881, Fig. 2.)*

Table 615.6 Clinical Manifestations and Biochemical Findings in Adrenal Insufficiency

	PATHOPHYSIOLOGIC MECHANISM	PREVALENCE (%)*
SYMPTOMS		
Fatigue	Glucocorticoid deficiency	90
Anorexia, weight loss	Glucocorticoid deficiency	90
Nausea, vomiting	Glucocorticoid deficiency, mineralocorticoid deficiency	90
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency	20
Myalgia or joint pain	Glucocorticoid deficiency	
SIGNS		
Low blood pressure, orthostatic hypotension	Mineralocorticoid deficiency, glucocorticoid deficiency	70-100
Skin or mucosal hyperpigmentation (primary adrenal insufficiency only)	Excess of proopiomelanocortin-derived peptides	70
LABORATORY FINDINGS		
Hyponatremia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to decreased free water excretion)	90
Hyperkalemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency	50
Hypoglycemia	Glucocorticoid deficiency	30
Ketosis	Glucocorticoid deficiency	30
Low random cortisol level	Glucocorticoid deficiency	80
Eosinophilia, lymphocytosis	Glucocorticoid deficiency	
High ACTH level (primary adrenal insufficiency only)	Glucocorticoid deficiency	100
High plasma renin activity (primary adrenal insufficiency only)	Mineralocorticoid deficiency	100

*Prevalence data are for primary insufficiency only. Blanks indicate that no pediatric prevalence data are available.
Data from Hsieh S, White PC. Presentation of primary adrenal insufficiency in childhood J Clin Endocrinol Metab. 2011;96:E925–E928.

Cortisol deficiency decreases cardiac output and vascular tone; moreover, catecholamines such as epinephrine have decreased inotropic and pressor effects in the absence of cortisol. These problems are initially manifested as orthostatic hypotension in older children and can progress to frank shock in patients of any age. They are exacerbated by aldosterone deficiency, which causes hypovolemia owing to decreased resorption of sodium in the distal nephron.

Hypotension and decreased cardiac output decrease glomerular filtration and thus decrease the ability of the kidney to excrete free water. Vasopressin (AVP) is secreted by the posterior pituitary in response to hypotension and as a direct consequence of lack of inhibition by cortisol. These factors decrease plasma osmolality and lead to hyponatremia. Hyponatremia is also caused by aldosterone deficiency and may be much worse when both cortisol and aldosterone are deficient.

In addition to hypovolemia and hyponatremia, aldosterone deficiency causes hyperkalemia by decreasing potassium excretion in the distal nephron. Cortisol deficiency alone does not cause hyperkalemia.

Cortisol deficiency decreases negative feedback on the hypothalamus and pituitary, leading to increased secretion of ACTH. Hyperpigmentation is caused by ACTH and other peptide hormones (γ-melanocyte–stimulating hormone) arising from the ACTH precursor, proopiomelanocortin. In patients with a fair complexion, the skin can have a bronze cast. Pigmentation may be more prominent in skin creases, mucosa, and scars. In dark-skinned patients, it may be most readily appreciated in the gingival and buccal mucosa.

Hypoglycemia is a feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to use fatty acids as an alternative energy source. Ketosis may cause or be aggravated by anorexia, nausea, and vomiting, all of which occur frequently.

The clinical presentation of adrenal insufficiency depends on the age of the patient, whether both cortisol and aldosterone secretion are affected, and to some extent on the underlying etiology. The most common causes in early infancy are inborn errors of steroid biosynthesis, sepsis, AHC, and adrenal hemorrhage. Infants have a relatively greater requirement for aldosterone than do older children, possibly owing to immaturity of the kidney and to the low sodium content of human breast milk and infant formula. Hyperkalemia, hyponatremia, and hypoglycemia are prominent presenting signs of adrenal insufficiency in infants. Ketosis is not consistently present because infants generate ketones less well than do older children. Hyperpigmentation is not usually seen because this takes weeks or months to develop, and orthostatic hypotension is obviously difficult to demonstrate in infants.

Infants can become ill very quickly. There may be only a few days of decreased activity, anorexia, and vomiting before critical electrolyte abnormalities develop.

In older children with Addison disease, symptoms include muscle weakness, malaise, anorexia, vomiting, weight loss, and orthostatic hypotension. These may be of insidious onset. It is not unusual to elicit, in retrospect, an episodic history spanning years with symptoms being noticeable only during intercurrent illnesses. Such patients can present with acute decompensation **(adrenal crisis)** during relatively minor infectious illnesses. *Some of these patients have been initially misdiagnosed with chronic fatigue syndrome, postmononucleosis syndrome, chronic Lyme disease, or psychiatric disorders (depression or anorexia nervosa).*

Hyperpigmentation is often, but not necessarily, present. **Hyponatremia** is present at diagnosis in almost 90% of patients. **Hyperkalemia** tends to occur later in the course of the disease in older children than in infants and is present in only half of patients at diagnosis. *Normal potassium levels must never be presumed to rule out primary adrenal insufficiency.*

Hypoglycemia and ketosis are common. The clinical presentation can be easily confused with gastroenteritis or other acute infections. Chronicity of symptoms can alert the clinician to the possibility of Addison disease, but this diagnosis should be considered in any child with

orthostatic hypotension, hyponatremia, hypoglycemia, and ketosis. Salt craving is seen in primary adrenal insufficiency with mineralocorticoid deficiency. Fatigue, myalgias, fever, eosinophilia, lymphocytosis, hypercalcemia, and anemia may be noted with glucocorticoid deficiency.

LABORATORY FINDINGS

Hypoglycemia, ketosis, hyponatremia, and hyperkalemia have been discussed. An electrocardiogram is useful for quickly detecting hyperkalemia in a critically ill child. Acidosis is often present, and the blood urea nitrogen level is elevated if the patient is dehydrated.

Cortisol levels are sometimes at the low end of the normal range but are invariably low when the patient's degree of illness is considered. ACTH levels are high in primary adrenal insufficiency but can take time to be reported by the laboratory. Similarly, aldosterone levels may be within the normal range but inappropriately low considering the patient's hyponatremia, hyperkalemia, and hypovolemia. Plasma renin activity is elevated. Blood eosinophils may be increased in number, but this is rarely useful diagnostically.

Urinary excretion of sodium and chloride is increased and urinary potassium is decreased, but these are difficult to assess in random urine samples. Accurate interpretation of urinary electrolytes requires more prolonged (24 hours) urine collections and knowledge of the patient's sodium and potassium intake.

The most definitive test for adrenal insufficiency is measurement of serum levels of cortisol before and after administration of ACTH; resting levels are low and do not increase normally after administration of ACTH. Occasionally, normal resting levels that do not increase after administration of ACTH indicate an absence of adrenocortical reserve. A low initial level followed by a significant response to ACTH can indicate secondary adrenal insufficiency. Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 minutes after giving 0.250 mg of cosyntropin (ACTH 1-24) by rapid intravenous infusion. Aldosterone will transiently increase in response to this dose of ACTH and may also be measured. A low-dose test (1 μg ACTH 1-24/1.73 m^2) is a more sensitive test of pituitary-adrenal reserve but has somewhat lower specificity (more false-positive tests).

DIFFERENTIAL DIAGNOSIS

Upon presentation, Addison disease often needs to be distinguished from more acute illnesses such as gastroenteritis with dehydration or sepsis. Additional testing is directed at identifying the specific cause for adrenal insufficiency. When CAH is suspected, serum levels of cortisol precursors (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test (see Chapter 616) (Fig. 615.2). Elevated levels of very long-chain fatty acids are diagnostic of ALD (see Chapter 639.3). Many genetic etiologies for primary adrenal insufficiency may be identified by direct genetic testing, but it can take weeks for results to become available. The presence of antiadrenal antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders. In children, hypoparathyroidism is a commonly associated disorder, and it is suspected if hypocalcemia and elevated phosphate levels are present.

Ultrasonography, CT, or MRI can help to define the size of the adrenal glands, but this is not usually necessary.

TREATMENT

Treatment of acute adrenal insufficiency must be immediate and vigorous. If the diagnosis of adrenal insufficiency has not been established, a blood sample should be obtained before therapy to determine electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma renin activity. If the patient's condition permits, an ACTH stimulation test can be performed while initial fluid resuscitation is underway. An intravenous solution of 5% glucose in 0.9% saline should be administered to correct hypoglycemia, hypovolemia, and hyponatremia. Hypotonic fluids (e.g., 5% glucose in water or 0.2% saline) must be avoided because they can precipitate or exacerbate hyponatremia. If hyperkalemia is severe, it can require treatment with intravenous calcium and/or bicarbonate, intrarectal potassium-binding resin (sodium polystyrene sulfonate, Kayexalate), or intravenous infusion of glucose and insulin. A water-soluble form of hydrocortisone, such as hydrocortisone sodium succinate, should be given intravenously. As much as 10 mg for infants, 25 mg for toddlers, 50 mg for older children, and 100 mg for adolescents should be administered as a bolus and a similar total amount then given in divided doses at 6-hour intervals for the first 24 hours. These doses may be reduced during the next 24 hours if progress is satisfactory. Adequate fluid and sodium repletion is achieved by intravenous saline administration, aided by the mineralocorticoid effect of high doses of hydrocortisone.

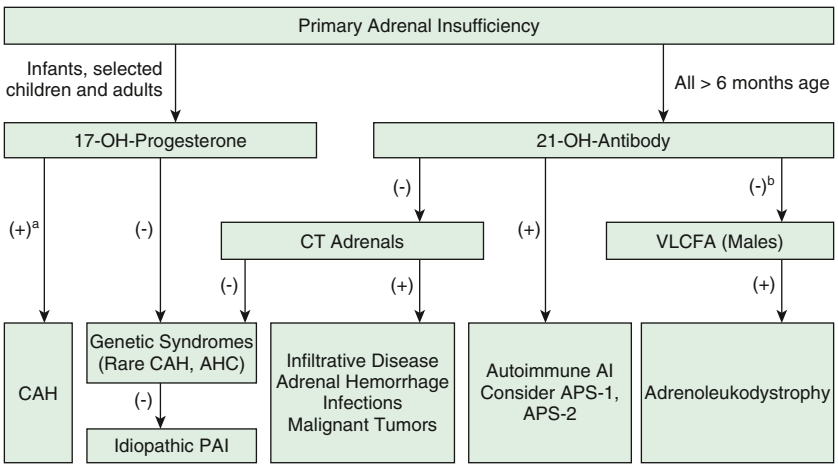

Fig. 615.2 Algorithm for the diagnostic approach to the patient with primary adrenal insufficiency (PAI). The most common causes of PAI are autoimmune destruction of the adrenal cortex in adults and congenital adrenal hyperplasia (CAH) in children. These etiologies can be screened for using 21-hydroxylase antibodies and a baseline serum 17-hydroxyprogesterone level, respectively. Males with negative 21-hydroxylase antibodies should be tested for adrenoleukodystrophy with plasma VLCFAs. If these diagnoses are excluded, a CT scan of the adrenals may reveal evidence of adrenal infiltrative processes or metastases, but this is of low yield in children and adolescents. The individual's clinical picture and family history may render some steps in the algorithm redundant or suggest specific genetic syndromes. The latter includes subtypes of autoimmune polyglandular syndromes or specific rare genetic disorders where adrenal failure is part of a broader phenotype. AHC, Adrenal hypoplasia congenita; AI, adrenal insufficiency; APS-1, type 1 autoimmune polyendocrinopathy syndrome; VLCFA, very long-chain fatty acid. [a]17-OH-progesterone >1,000 ng/dL is diagnostic for 21-OH deficiency. [b]VLCFA should be measured in the initial evaluation of preadolescent boys. *(Adapted from Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment, and follow-up of patients with primary adrenal insufficiency. J Intern Med. 2014;275:104–115.)*

Caution should be exercised in the rare patient with concomitant adrenal insufficiency and hypothyroidism, because thyroxine can increase cortisol clearance. Thus an adrenal crisis may be precipitated if hypothyroidism is treated without first ensuring adequate glucocorticoid replacement.

After the acute manifestations are under control, most patients require chronic replacement therapy for their cortisol and aldosterone deficiencies. Hydrocortisone (cortisol) may be given orally in daily doses of 10 mg/m^2/24 hr in three divided doses; some patients require 15 mg/m^2/24 hr to minimize fatigue, especially in the morning. Dividing the hydrocortisone into four doses daily may yield more physiologic drug profiles, but adherence to such frequent dosing may be problematic. Timed-release preparations of hydrocortisone are available in Europe and are undergoing clinical trials in the United States as of 2021. Subcutaneous infusion of hydrocortisone with a pump has also been examined in clinical trials; although this has the advantage that it can very closely mimic normal diurnal variation in cortisol secretion, it is expensive and has not yet entered routine clinical practice. Equivalent doses (20–25% of the hydrocortisone dose) of prednisone or prednisolone may be divided and given twice daily. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency; in CAH, levels of precursor hormones are used instead. Blood samples for monitoring should be obtained at a consistent time of day and in a consistent relation to (i.e., before or after) the hydrocortisone dose. Normalizing ACTH levels is unnecessary and can require excessive doses of hydrocortisone; in general, morning ACTH levels high in the normal range to 3-4 times normal are satisfactory. Because untreated or severely undertreated patients can acutely decompensate during relatively minor illnesses, assessment of symptoms (or lack thereof) should not be used as a substitute for biochemical monitoring. During situations of stress, such as periods of infection or minor operative procedures, the dose of hydrocortisone should be increased twofold to threefold. Major surgery under general inhalation anesthesia requires high intravenous doses of hydrocortisone similar to those used for acute adrenal insufficiency.

If aldosterone deficiency is present, fludrocortisone, a synthetic mineralocorticoid, is given orally in doses of 0.05-0.2 mg daily. Measurements of plasma renin activity are useful in monitoring the adequacy of mineralocorticoid replacement. Chronic overdosage with glucocorticoids leads to obesity, short stature, and osteoporosis, whereas overdosage with fludrocortisone results in hypertension and occasionally hypokalemia.

Replacement of dehydroepiandrosterone (DHEA) in adults remains controversial; prepubertal children do not normally secrete large amounts of DHEA. Many adults with Addison disease complain of having decreased energy, and replacing DHEA can improve this problem, particularly in women in whom adrenal androgens represent approximately 50% of total androgen secretion.

Additional therapy might need to be directed at the underlying cause of the adrenal insufficiency regarding infections and certain metabolic defects. Previous therapeutic approaches to ALD included administration of glycerol trioleate and glycerol trierucate (Lorenzo's oil), bone marrow transplantation, and lovastatin (see Chapter 639.3). Introducing a normal *ABCD1* gene into autologous stem cells with a lentiviral vector (officially termed *elivaldogene autotemcel*) has shown excellent results in preventing neurologic progression, but it remains investigational as of 2021.

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615.2 Secondary and Tertiary Adrenal Insufficiency

Perrin C. White

ABRUPT CESSATION OF ADMINISTRATION OF CORTICOSTEROIDS

Secondary adrenal insufficiency most commonly occurs when the HPA axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly. Patients at risk for this problem include those with leukemia, asthma (particularly when patients are transitioned from oral to inhaled corticosteroids), and collagen vascular disease or other autoimmune conditions and those who have undergone tissue transplants or neurosurgical procedures. The maximal duration and dosage of glucocorticoid that can be administered before encountering this problem is not known, but it is assumed that high-dose glucocorticoids (the equivalent of >10 times physiologic cortisol secretion) can be administered for less than 1 week without requiring a subsequent taper of dose. On the other hand, when high doses of dexamethasone are given to children with leukemia, it can take 6 months or longer after therapy is stopped before tests of adrenal function return to normal. Signs and symptoms of adrenal insufficiency are most likely in patients who are subsequently subjected to stresses such as severe infections or additional surgical procedures.

Corticotropin (Adrenocorticotropic Hormone) Deficiency

Pituitary or hypothalamic dysfunction can cause corticotropin deficiency (see Chapter 595), usually associated with deficiencies of other pituitary hormones such as growth hormone and thyrotropin. Destructive lesions in the area of the pituitary, such as craniopharyngioma and germinoma, are the most common causes of corticotropin deficiency. In many cases the pituitary or hypothalamus is further damaged during surgical removal or radiotherapy of tumors in the midline of the brain. Traumatic brain injury (see Chapter 750) frequently causes pituitary dysfunction, especially in the first days after the injury. However, corticotropin deficiency is difficult to detect in that period owing to frequent use of high doses of dexamethasone to minimize brain swelling, and permanent corticotropin deficiency is unusual after traumatic brain injury. In rare instances, autoimmune hypophysitis is the cause of corticotropin deficiency.

Congenital lesions of the pituitary also occur. The pituitary alone may be affected, or additional midline structures may be involved, such as the optic nerves or septum pellucidum. The latter type of abnormality is termed **septo-optic dysplasia**, or de Morsier syndrome (see Chapter 631.9). More severe developmental anomalies of the brain, such as anencephaly and holoprosencephaly, can also affect the pituitary. These disorders are usually sporadic, although a few cases of autosomal recessive inheritance have occurred. Isolated deficiency of corticotropin has been reported, including in several sets of siblings. Patients with multiple pituitary hormone deficiencies caused by pathogenic variants in the *PROP1* gene may develop progressive ACTH/cortisol deficiency. Isolated deficiency of corticotropin-releasing hormone has been documented in an Arab kindred as an autosomal recessive trait.

Up to 60% of children with **Prader-Willi syndrome** (see Chapter 99.8) have some degree of secondary adrenal insufficiency as assessed by provocative testing with metyrapone, although diurnal cortisol levels are normal. The clinical significance of this finding is uncertain, but it might contribute to the relatively high incidence of sudden death with infectious illness that occurs in this population. Although it is not yet a standard of care, some endocrinologists advocate treating patients who have Prader-Willi syndrome with hydrocortisone during febrile illness.

CLINICAL PRESENTATION

Aldosterone secretion is unaffected in secondary adrenal insufficiency because the adrenal gland is, by definition, intact and the renin-angiotensin system is not involved. Thus signs and symptoms are those of cortisol deficiency. Newborns often have hypoglycemia. Older children can have orthostatic hypotension or weakness. Hyponatremia may be present.

When secondary adrenal insufficiency is the consequence of an inborn or acquired anatomic defect involving the pituitary, there may be signs of associated deficiencies of other pituitary hormones. The penis may be small in male infants if gonadotropins are also deficient. Infants with secondary hypothyroidism are often jaundiced. Children with associated growth hormone deficiency grow poorly after the first year of life.

Some children with pituitary abnormalities have hypoplasia of the midface. Children with optic nerve hypoplasia can have obvious visual impairment. They usually have a characteristic wandering nystagmus, but this is often not apparent until several months of age.

LABORATORY FINDINGS

Because the adrenal glands themselves are not directly affected, the diagnosis of secondary adrenal insufficiency is sometimes challenging. The most commonly used test to diagnose secondary adrenal insufficiency is **low-dose ACTH stimulation testing** (1 μg/1.73 m^2 of cosyntropin given intravenously), the rationale being that there will be some degree of atrophy of the adrenal cortex if normal physiologic ACTH stimulation is lacking. Thus this test may be falsely negative in cases of acute compromise of the pituitary (e.g., injury or surgery). Such circumstances rarely pose a diagnostic dilemma; in general, this test provides excellent sensitivity and specificity. Although assays vary somewhat, a threshold cortisol level of 18-20 μg/dL 30 minutes after cosyntropin administration may be used to dichotomize normal and abnormal responses.

There seems to be little reason to use stimulation with corticotropin-releasing hormone instead of ACTH; although the corticotropin-releasing hormone test has the theoretical advantage of testing the ability of the anterior pituitary to respond to this stimulus by secreting ACTH (thus distinguishing secondary and tertiary adrenal insufficiency), in practice it does not provide improved sensitivity and specificity, and the agent is not as widely available.

TREATMENT

Iatrogenic secondary adrenal insufficiency (caused by chronic glucocorticoid administration) is best avoided by use of the smallest effective doses of systemic glucocorticoids for the shortest period. When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than the physiologic replacement (~10 mg/m^2/24 hr of hydrocortisone) and further tapering over several weeks can allow the adrenal cortex to recover without the patient developing signs of adrenal insufficiency. Patients with anatomic lesions of the pituitary should be treated indefinitely with glucocorticoids. Mineralocorticoid replacement is not required. In patients with panhypopituitarism, treating cortisol deficiency can increase free water excretion, thus unmasking central diabetes insipidus. Electrolytes must be monitored carefully when initiating cortisol therapy in panhypopituitary patients.

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615.3 Adrenal Insufficiency in the Critical Care Setting

Perrin C. White

Critical illness–related corticosteroid insufficiency (CIRCI) is encountered in up to 20–50% of critically ill pediatric patients, often as a transient condition. In many cases, it is considered functional or relative in nature, meaning that cortisol levels are within normal limits but cannot increase sufficiently to meet the demands of critical illness. The causes are heterogeneous (see Chapter 615.1). They include adrenal hypoperfusion from shock, particularly septic shock, as is often seen in meningococcemia. Inflammatory mediators during septic shock, particularly interleukin-6, can suppress ACTH secretion, directly suppress cortisol secretion, or both. Etomidate, used as sedation for intubation, inhibits steroid 11β-hydroxylase and thus blocks cortisol biosynthesis. Neurosurgical patients with closed head trauma or with tumors that involve the hypothalamus or pituitary might have ACTH deficiency in the context of panhypopituitarism. Some children have been previously treated with systemic corticosteroids (e.g., children with leukemia) and have suppression of the HPA axis for that reason. In the intensive care nursery, premature infants have not yet developed normal cortisol biosynthetic capacity and thus may not be able to secrete adequate amounts of this hormone when ill.

Additionally, plasma clearance of cortisol is markedly reduced during critical illness, owing to decreased activity of cortisol-metabolizing enzymes in the liver and kidney. Although this may help defend plasma levels of cortisol in the context of decreased cortisol secretion, the inflammation associated with sepsis may increase glucocorticoid resistance through activation of mitogen-activated protein kinases (MAPKs) and decreased activity of their regulators, dual-specific phosphatases (DUSPs).

CLINICAL MANIFESTATIONS

Cortisol is required for catecholamines to have their normal pressor effects on the cardiovascular system (see Chapters 614.4 and 614.5). Accordingly, adrenal insufficiency is often suspected in hypotensive patients who do not respond to intravenous pressor agents. Patients may be at increased risk for hypoglycemia or a presentation resembling the syndrome of inappropriate antidiuretic hormone secretion, but these conditions commonly occur in the context of sepsis, and the contribution of adrenal insufficiency may be difficult to distinguish.

LABORATORY FINDINGS

Although low random cortisol levels in severely stressed patients are certainly abnormal, very high levels are also associated with a poor outcome in such patients; the latter situation presumably reflects a maximally stimulated adrenal cortex with diminished reserve. ACTH (cosyntropin) stimulation testing is generally considered the best way to diagnose adrenal insufficiency in this setting (see Chapter 615.1); evidence suggests that the low-dose (1 μg/1.73 m^2) test may be superior to the 250-μg standard dose test, although this remains controversial. In general, a peak cortisol level <18 μg/dL or an increment of <9 μg/dL from baseline is considered suggestive for adrenal insufficiency in this context. In evaluating cortisol levels, cortisol in the circulation is mostly bound to cortisol-binding globulin; in hypoproteinemic states, total cortisol levels may be decreased, whereas free cortisol levels might be normal. It may be prudent to measure free cortisol before initiating treatment when total cortisol is low and albumin is <2.5 g/dL, but such measurements are not readily available in all institutions.

TREATMENT

It is likely that stress doses of hydrocortisone (e.g., 100 mg/m^2/day) improve responses to pressor agents in patients with shock *and* documented adrenal insufficiency (Waterhouse-Friderichsen syndrome). In adults with sepsis, corticosteroids probably reduce intensive care unit (ICU) and hospital length of stay and 28-day and hospital mortality, but there are limited data regarding treatment efficacy in critically ill children. The Surviving Sepsis Guidelines suggest using IV hydrocortisone (or not using it) to treat pediatric septic shock only if fluids and vasopressor therapy are unable to restore hemodynamic stability. This is a weak recommendation with low-quality evidence.

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615.4 Altered End-Organ Sensitivity to Corticosteroids

Perrin C. White

Diseases can result from altered actions of hormones at their physiologic targets. These may be caused by abnormal metabolism of hormones, mutations in hormone receptors, or defects in cellular effectors (such as ion channels) that are targets of hormone action.

GENERALIZED GLUCOCORTICOID RESISTANCE

Patients with generalized glucocorticoid resistance have target-tissue insensitivity to glucocorticoids. The condition is usually inherited in an autosomal dominant manner, but sporadic cases occur. Impairment of normal negative feedback of cortisol at the levels of the hypothalamus and pituitary activates the HPA axis, with consequent increases in ACTH and cortisol concentrations. Generalized glucocorticoid resistance is caused by pathogenic variants in the glucocorticoid receptor *(NR3C1)*. Most variants are heterozygous; glucocorticoid receptors usually bind DNA as dimers, and three out of four dimers will contain at least one abnormal receptor molecule when a heterozygous variant is present.

Clinical Manifestations

The excess ACTH secretion causes adrenal hyperplasia with increased production of adrenal steroids with mineralocorticoid activity, including cortisol, deoxycorticosterone, and corticosterone, and also androgens and precursors, including androstenedione, DHEA, and DHEA sulfate. The high cortisol concentrations do not cause Cushing syndrome (see Chapter 619) because of the insensitivity to glucocorticoids; conversely, most signs and symptoms of adrenal insufficiency are absent except for the frequent occurrence of chronic fatigue and occasional anxiety (neonatal hypoglycemia was reported in one very unusual patient with a homozygous null variant). The mineralocorticoid and androgen receptors are normally sensitive to their ligands. Signs of **mineralocorticoid excess**, such as hypertension and hypokalemic alkalosis, are frequently noted. The increased concentrations of adrenal androgens may cause ambiguous genitalia in females and gonadotropin-independent precocious puberty in children of either gender; acne, hirsutism, and infertility in both sexes; menstrual irregularities in females; and oligospermia in males. Testicular adrenal rest tumors and ACTH-secreting pituitary adenomas occasionally occur.

Laboratory Findings

The diagnosis of generalized glucocorticoid resistance is suggested by elevated serum cortisol concentrations and increased 24-hour urinary free cortisol excretion in the absence of Cushing syndrome. Levels of other adrenal steroids are also increased. Plasma concentrations of ACTH may be normal or high. The circadian pattern of ACTH and cortisol secretion is preserved, although at higher-than-normal concentrations, and there is resistance of the HPA axis to dexamethasone suppression. Sequencing of the *NR3C1* gene can confirm the diagnosis.

Differential Diagnosis

Generalized glucocorticoid resistance should be distinguished from relatively mild cases of Cushing syndrome (whether caused by a pituitary adenoma or adrenal tumor, see Chapter 619); the latter is more likely to be associated with excessive weight gain or poor linear growth. Adrenocortical tumors may secrete mineralocorticoids such as deoxycorticosterone and also androgens, but ACTH levels are often suppressed and, of course, the tumor can usually be visualized with appropriate imaging techniques. CAH (see Chapter 616), particularly 11β-hydroxylase deficiency, may present with hypertension and signs of androgen excess, but in that condition cortisol levels are low and levels of cortisol precursors (17-hydroxyprogesterone, 11-deoxycortisol) are elevated. Obese patients may be hypertensive and have hyperandrogenism, but cortisol secretion should be readily suppressed by dexamethasone.

Treatment

The goal of treatment is to suppress the excess secretion of ACTH, thereby suppressing the increased production of adrenal steroids with mineralocorticoid and androgenic activity. This requires administration of high doses of a pure glucocorticoid agonist such as dexamethasone (typically ~20-40 μg/kg/day) with careful titration to suppress endogenous corticosteroid secretion without causing signs of glucocorticoid excess such as excessive weight gain or suppression of linear growth.

CORTISONE REDUCTASE DEFICIENCY

Levels of active glucocorticoids in target tissues are modulated by two isozymes of 11β-hydroxysteroid dehydrogenase. The HSD11B2 isozyme converts cortisol to an inactive metabolite, cortisone; the two steroids differ in the presence of an 11β-hydroxyl versus an 11-oxo group, respectively. Pathogenic variants in this enzyme cause the syndrome of **apparent mineralocorticoid excess**. Conversely, the HSD11B1 isozyme converts cortisone to cortisol, and so it is sometimes referred to as *cortisone reductase*. This isozyme is expressed at high levels in glucocorticoid target tissues, particularly the liver, where it ensures adequate levels of active glucocorticoids (cortisol and corticosterone) to meet metabolic demands without requiring excessive adrenal cortisol secretion.

The HSD11B1 isozyme is located in the endoplasmic reticulum (i.e., it is a microsomal enzyme) and functions as a dimer. It accepts electrons from reduced nicotine–adenine dinucleotide phosphate, which is generated within the endoplasmic reticulum by hexose-6-phosphate dehydrogenase, an enzyme distinct from cytoplasmic glucose-6-phosphate dehydrogenase.

Apparent cortisone reductase deficiency is caused by homozygous pathogenic variants in hexose-6-phosphate dehydrogenase that prevent generation of reduced nicotine–adenine dinucleotide phosphate within the endoplasmic reticulum and thus starve HSD11B1 of its essential cofactor for the reductase reaction. Very rare patients have been reported to have heterozygous variants in *HSD11B1* itself and thus have "true" cortisone reductase deficiency; because the enzyme functions as a homodimer, heterozygous variants are able to impair three fourths of all dimers.

Clinical Manifestations

Because circulating cortisone is not converted to cortisol, the circulating half-life of cortisol is decreased, and the adrenal cortex must secrete additional cortisol to compensate. This leads to adrenocortical overactivity analogous to, but generally much milder than, that seen in generalized glucocorticoid resistance. This is usually not severe enough to cause hypertension, presenting instead with mild to moderate signs of androgen excess such as hirsutism, oligomenorrhea or amenorrhea, and infertility in females and precocious pseudopuberty (axillary and pubic hair and penile enlargement, but not testicular enlargement) in males.

Laboratory Findings

The ratio of cortisol to cortisone in blood is lower than usual. The same is true of urinary metabolites, typically measured as a ratio of the sum of the tetrahydrocortisol and allotetrahydrocortisol excretion to that of tetrahydrocortisone. These determinations are best accomplished by gas chromatography followed by mass spectrometry and are available in specialized reference laboratories. Absolute levels of cortisol and ACTH are within normal limits.

Differential Diagnosis

Cortisone reductase deficiency should be distinguished from and is much less common than other causes of androgen excess such as polycystic ovarian syndrome and nonclassical CAH as a result of 21-hydroxylase deficiency.

Treatment

Treatment is aimed at decreasing adrenal overactivity and thus reducing secretion of androgens. This can be accomplished by administration of hydrocortisone.

ALTERED END-ORGAN SENSITIVITY TO MINERALOCORTICOIDS

Pseudohypoaldosteronism

Pseudohypoaldosteronism type 1 (PHA1) is a monogenic disease in which aldosterone action is deficient and patients are thus unable

to resorb urinary sodium or excrete potassium properly. There are two forms. A relatively mild autosomal dominant form is caused by pathogenic variants in *NR3C2* encoding the human mineralocorticoid receptor. A heterozygous variant is sufficient to cause disease because the mineralocorticoid receptor interacts with DNA as a dimer, and three fourths of the dimers are defective in individuals carrying heterozygous variants (assuming mutant protein is synthesized). A more severe autosomal recessive form is usually the result of homozygous pathogenic variants in the α *(SCNN1A),* β *(SCNN1B),* or γ *(SCNN1G)* subunits of the epithelial Na^+ channel; one reported case of severe autosomal recessive disease was caused by homozygous variants in *NR3C2*.

PHA1 should not be confused with **pseudohypoaldosteronism type 2**, a rare mendelian syndrome characterized by hyperkalemia and, in contrast to PHA1, by hypertension from excessive renal sodium reabsorption. This disorder is caused by variants in the renal regulatory kinases WNK1 and WNK4 or components of an E3 ubiquitin ligase complex, Kelch-like 3 (KLHL3) and Cullin 3 (CUL3).

Transient or "secondary" (nongenetic) pseudohypoaldosteronism can occur in infants, mainly male, with urinary tract malformations and/or urinary tract infections.

Clinical Manifestations

Infants with PHA1 present with hyperkalemia, hyponatremia, hypovolemia, hypotension, and failure to thrive. In more severe (usually autosomal recessive) cases, salt loss is not confined to the kidney, but instead occurs from most epithelia. Mothers may report that the skin of their affected infants tastes salty. Some infants suffer from *cystic fibrosis–like pulmonary symptoms*. It is often difficult to control electrolyte abnormalities in patients with the autosomal recessive form, leading to frequent hospitalizations and a need for close clinical monitoring.

It is noteworthy that signs and symptoms of aldosterone deficiency tend to remit as the patients get older, particularly in the autosomal dominant form. This is similar to what is seen in actual aldosterone deficiency, as occurs in the salt-losing forms of CAH or aldosterone synthase deficiency. The kidney matures after early infancy to become more efficient at excreting potassium, and although breast milk and infant formula are low in sodium, the normal adult Western diet is relatively high in sodium, thus compensating for the renal salt wasting.

Laboratory Findings

Infants have marked hyperkalemia and hyponatremia. Both plasma renin and aldosterone are markedly elevated. Levels of cortisol and ACTH are normal. If hypovolemia is severe, patients may develop prerenal azotemia. With severe hyperkalemia, the electrocardiogram may include tall-peaked T waves or ventricular tachycardia.

Differential Diagnosis

PHA in infants should be distinguished from other causes of hyperkalemia and hyponatremia. These include renal failure of any cause, CAH, aldosterone synthase deficiency, and other causes of adrenocortical insufficiency such as AHC. Patients with renal failure will have elevated blood urea nitrogen and creatinine, but these may also be seen in severely dehydrated patients with PHA or adrenal insufficiency. Patients with any form of adrenal insufficiency in this clinical context will have low or low-normal aldosterone levels (with elevated plasma renin), in contrast to the elevated aldosterone levels seen in PHA. Patients with CAH have elevated levels of steroid precursors such as 17-hydroxyprogesterone (in patients with 21-hydroxylase deficiency), and patients with most forms of adrenal insufficiency have elevated ACTH levels.

Treatment

Infants must be given sodium supplementation (initially IV and then oral or enteral), typically approximately 8 mEq/kg/day. Potassium levels in the infant formula often need to be reduced, which may be accomplished by mixing the formula with polystyrene resin (Kayexalate) and then decanting the formula before feeding. Fludrocortisone, a synthetic mineralocorticoid, may be efficacious in milder autosomal dominant cases if administered in high doses (titrating up to ~0.5 mg daily). Significant electrolyte abnormalities require treatment with IV normal saline and rectal polystyrene resin. Severe hyperkalemia may require glucose and insulin infusions to keep it under control.

Secondary PHA owing to urinary tract infections or malformations generally resolves when the underlying condition is treated.

ACTIVATING PATHOGENIC VARIANTS IN THE MINERALOCORTICOID RECEPTOR

In contrast to PHA1, the S810L (serine-810 to leucine) variant of *NR3C2* causes autosomal dominant, severe, early-onset hypertension. This variant alters the ligand specificity of the mineralocorticoid receptor so that it is activated by cortisone and so HSD11B2 cannot protect it. It is also activated by progesterone, and consequently the hypertension is *exacerbated by pregnancy*. Conversely, the glucocorticoid and progesterone receptor antagonist mifepristone (RU-486) antagonizes the mutant receptor and might be useful therapeutically in nonpregnant individuals.

APPARENT MINERALOCORTICOID EXCESS

The syndrome of apparent mineralocorticoid excess is an autosomal recessive disorder caused by pathogenic variants in *HSD11B2* encoding the type 2 isozyme of 11β-hydroxysteroid dehydrogenase. The mineralocorticoid receptor has nearly identical affinities for aldosterone (the main mineralocorticoid hormone) and cortisol, yet cortisol is normally only a weak mineralocorticoid in vivo. This is because HSD11B2 is expressed along with the mineralocorticoid receptor in most target tissues such as the renal cortical collecting duct epithelium. It converts cortisol to cortisone, which is not an active steroid, thus preventing it from occupying the mineralocorticoid receptor. In contrast, aldosterone is not a substrate for the enzyme because its 11β-hydroxyl group forms a hemiketal with the 18-aldehyde group of the steroid and is thus not accessible to the enzyme. Thus in the absence of HSD11B2, cortisol efficiently occupies the mineralocorticoid receptor, and because cortisol concentrations are normally far higher than those of aldosterone, this results in signs and symptoms of mineralocorticoid excess.

A similar clinical picture occurs with excessive consumption of licorice or licorice-flavored chewing tobacco; licorice contains compounds, including glycyrrhetinic and glycyrrhizic acids, that inhibit HSD11B2. Carbenoxolone, an antihypertensive drug that is not marketed in the United States, has similar effects.

Clinical Manifestations

Affected infants often have some degree of intrauterine growth restriction, with birthweights of 2 kg typical for term infants. Infants and children often fail to thrive. Severe hypertension (to ~200/120 mm Hg) is almost always present. In some patients, the hypertension tends to be labile or paroxysmal with severe emotional stress as a precipitating factor. Complications of hypertension have included cerebrovascular accidents. Several patients have died during infancy or adolescence, either from electrolyte imbalances leading to cardiac arrhythmias or from vascular sequelae of hypertension. Hypokalemic alkalosis can eventually cause nephrocalcinosis (often visible on renal ultrasound) and nephrogenic diabetes insipidus leading to polyuria and polydipsia. Deleterious effects on muscle range from elevations in serum creatine phosphokinase to rhabdomyolysis. Electrocardiograms show left ventricular hypertrophy.

Laboratory Findings

Hypokalemia and alkalosis are common but not consistently present. Sodium levels are generally in the upper part of the reference range. Aldosterone and renin levels are very low because the

hypertension and hypervolemia are independent of aldosterone concentrations. Serum cortisol and ACTH levels are generally within normal limits. The serum half-life of cortisol is increased, but the test for this requires a radioactive tracer and is not clinically available. Total urinary excretion of cortisol metabolites is markedly decreased. The urinary ratio of free cortisol to free cortisone is elevated, as is the ratio of urinary tetrahydrocortisol plus allotetrahydrocortisol to tetrahydrocortisone.

Differential Diagnosis

The differential diagnosis includes other forms of severe childhood hypertension such as renal artery anomalies, but relatively few conditions present with suppressed renin and aldosterone levels. **Liddle syndrome** has a similar presentation but no abnormalities in the steroid profile, typically has an autosomal dominant mode of inheritance, and does not respond to treatment with mineralocorticoid receptor antagonists. Hypertensive forms of CAH (see Chapter 616) also have suppressed renin and aldosterone levels, but they present with signs of androgen excess (11β-hydroxylase deficiency) or androgen deficiency (17α-hydroxylase deficiency); the latter can be difficult to appreciate in young children. The steroid profiles in CAH differ from those seen in apparent mineralocorticoid excess syndrome.

Patients with severe Cushing syndrome may have high enough cortisol levels to overwhelm renal HSD11B2, leading to severe hypertension with alterations in urinary cortisol-to-cortisone ratios. This occurs most often in patients with ectopic ACTH syndrome. This generally does not present a diagnostic dilemma because other signs of Cushing syndrome are present, including high cortisol levels.

Treatment

Treatment includes a low-salt diet, potassium supplementation, and mineralocorticoid receptor blockade with spironolactone or eplerenone; a sodium channel blocker, such as amiloride or triamterene, may work at least as well. In principle, suppression of cortisol secretion with dexamethasone (which does not bind the mineralocorticoid receptor) should work, but in practice it is much less effective than mineralocorticoid receptor blockade.

LIDDLE SYNDROME

Liddle syndrome is a form of hypertension and hypokalemia that is clinically similar to the syndrome of apparent mineralocorticoid excess, but it is inherited in an autosomal dominant manner. It is caused by an activating pathogenic variant in the β *(SCNN1B)* or γ *(SCNN1G)* subunits of the epithelial sodium channel. Most of these mutations prevent the channel subunits from being ligated to ubiquitin and targeted to the proteasome for degradation, a process that is normally regulated indirectly by aldosterone. The net effect is to increase the number of open channels at the apical surface of epithelial cells of the renal collecting duct, thus facilitating sodium resorption and potassium excretion.

Clinical Manifestations, Laboratory Findings, and Differential Diagnosis

Liddle syndrome is characterized by severe early-onset hypertension and by hypokalemia, which may not be persistent. Aldosterone and renin levels are suppressed, but all steroid hormone levels are normal.

The differential diagnosis is the same as that for apparent mineralocorticoid excess.

Treatment

The mainstays of treatment are a low-salt diet, potassium supplementation, and a sodium channel blocker such as amiloride or triamterene. Mineralocorticoid receptor antagonists such as spironolactone are ineffective.

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Chapter 616

Congenital Adrenal Hyperplasia and Related Disorders

Perrin C. White and Ming Yang

Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of cortisol biosynthesis (normal adrenal steroidogenesis is discussed in Chapter 614). Cortisol deficiency increases secretion of corticotropin (adrenocorticotropic hormone [ACTH]), which, in turn, leads to adrenocortical hyperplasia and overproduction of intermediate metabolites. Depending on the enzymatic step that is deficient, there may be signs, symptoms, and laboratory findings of mineralocorticoid deficiency or excess; incomplete virilization or precocious puberty in affected males; and virilization or sexual infantilism in affected females (Figs. 616.1 and 616.2, Table 616.1).

616.1 Congenital Adrenal Hyperplasia Caused by 21-Hydroxylase Deficiency

Perrin C. White and Ming Yang

More than 90% of CAH cases are caused by 21-hydroxylase deficiency. This P450 enzyme (CYP21A2, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone to yield 11-deoxycorticosterone and 11-deoxycortisol, respectively (see Fig. 614.1 in Chapter 614). These conversions are required for synthesis of aldosterone and cortisol, respectively. Both hormones are deficient in the most severe,

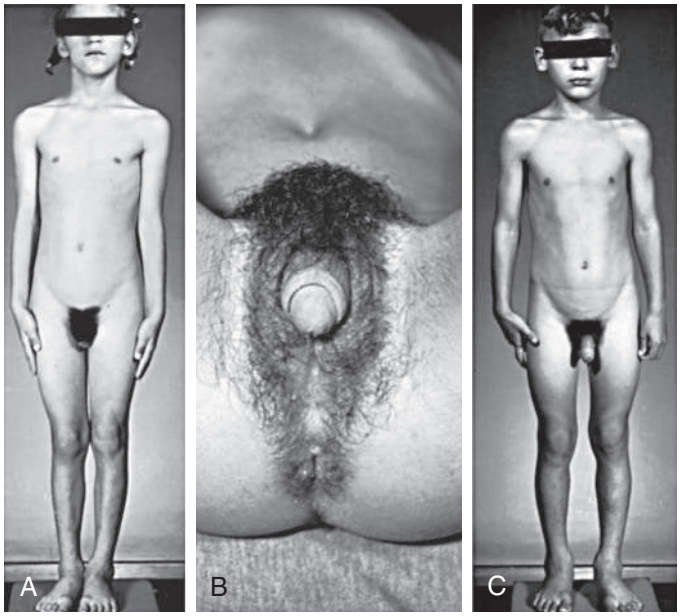

Fig. 616.1 **A,** A 6-yr-old female with congenital virilizing adrenal hyperplasia. The height age was 8.5 yr, and the bone age was 13 yr. **B,** Notice the clitoral enlargement and labial fusion. **C,** Her 5-yr-old brother was not considered to be abnormal by the parents. The height age was 8 yr, and the bone age was 12.5 yr.

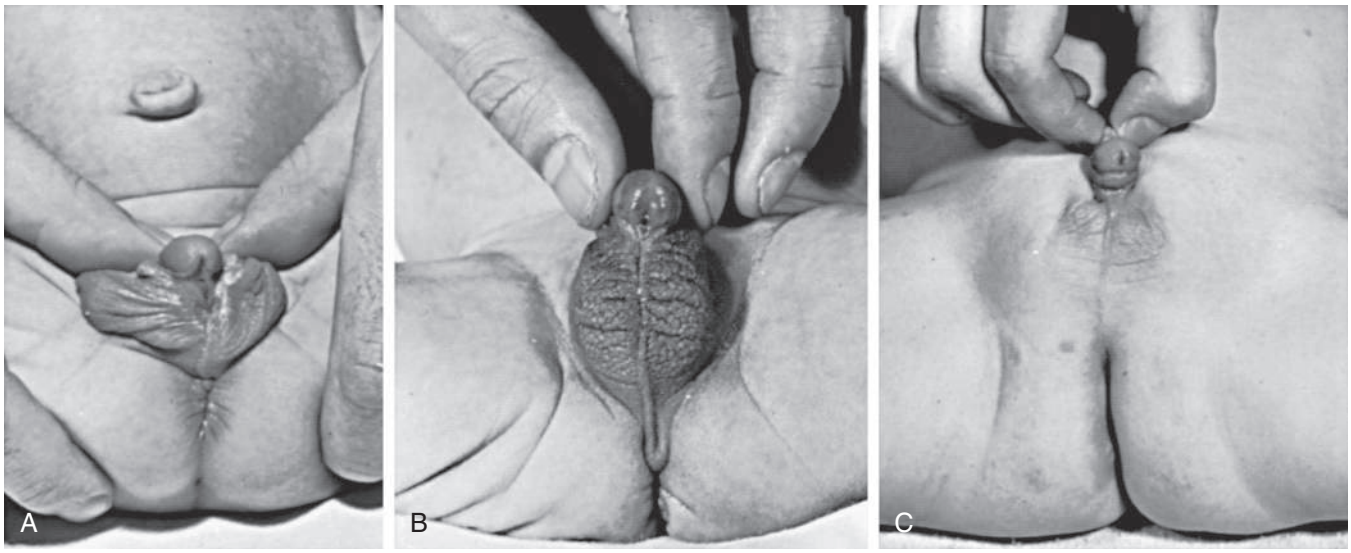

Fig. 616.2 Three virilized females with untreated congenital adrenal hyperplasia. All were erroneously assigned male sex at birth, and each had a normal female sex-chromosome complement. Infants A and B had the salt-wasting form and received the diagnosis early in infancy. Infant C was referred at 1 yr of age because of bilateral cryptorchidism. Notice the completely penile urethra; such complete masculinization in females with adrenal hyperplasia is rare; most of these infants have the salt-wasting form.

salt-wasting form of the disease. Slightly less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin; this is termed **simple virilizing disease**. These two forms are collectively termed **classic 21-hydroxylase deficiency**. Patients with **nonclassic** disease have relatively mildly elevated levels of androgens and may be asymptomatic or have signs of androgen excess at any time after birth. Clinical presentation is dependent, in part, on the genotype (Table 616.2).

EPIDEMIOLOGY

Classic 21-hydroxylase deficiency occurs in approximately 1 in 14,000-18,000 births in most populations. Approximately 70% of affected infants have the salt-losing form, whereas 30% have the simple virilizing form of the disorder. In the United States, CAH is less common in African Americans compared with White children (1:42,000 vs 1:15,500). Nonclassic disease has a prevalence of approximately 1 in 1,000 in the general population but occurs more frequently in specific ethnic groups such as Ashkenazi Jews and Hispanics.

GENETICS

There are two steroid 21-hydroxylase genes—*CYP21P (CYP21A1P, CYP21A)* and *CYP21 (CYP21A2, CYP21B)*—which alternate in tandem with two genes for the fourth component of complement (C4A and C4B) in the human leukocyte antigen (HLA) major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. Many other genes are in this cluster. *CYP21* is the active gene; *CYP21P* is 98% identical in DNA sequence to *CYP21* but is a pseudogene because of at least 10 different pathogenic variants. Although almost 300 variants have been reported, more than 90% of abnormal alleles causing 21-hydroxylase deficiency are the result of recombinations between *CYP21* and *CYP21P.* Approximately 20% are deletions generated by unequal meiotic crossing-over between *CYP21* and *CYP21P,* whereas the remainder are nonreciprocal transfers of deleterious variants from *CYP21P* to *CYP21,* a phenomenon termed *gene conversion.*

The deleterious variants in *CYP21P* have different effects on enzymatic activity when transferred to *CYP21.* Several variants completely prevent synthesis of a functional protein, whereas others are missense variants that yield enzymes with 1–50% of normal activity. Disease severity correlates well with the variants carried by an affected individual; patients with salt-wasting disease usually carry variants on both alleles that result in no enzymatic activity. Patients are frequently compound heterozygotes for different types of variants (i.e., one allele is less severely affected than the other), in which case the severity of disease expression is largely determined by the activity of the less severely affected of the two alleles.

Closely adjacent to, but on the opposite DNA strand from, *CYP21* is the tenascin-X *(TNX)* gene, which encodes a connective tissue protein. Rarely, deletions of *CYP21* extend into *TNX*. Such patients may have a contiguous gene syndrome (see Chapter 99.1) consisting of CAH and **Ehlers-Danlos syndrome** (see Chapter 744).

PATHOGENESIS AND CLINICAL MANIFESTATIONS

Aldosterone and Cortisol Deficiency

Because both cortisol and aldosterone require 21-hydroxylation for their synthesis, both hormones are deficient in the most severe, salt-wasting form of the disease. This form constitutes approximately 70% of cases of classic 21-hydroxylase deficiency. The signs and symptoms of cortisol and aldosterone deficiency, and the pathophysiology underlying them, are essentially those described in adrenal insufficiency (see Chapter 615). These include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, and hyperkalemia. These problems typically first develop in affected infants at approximately 10-14 days of age. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks.

CAH differs from other causes of primary adrenal insufficiency in that precursor steroids accumulate proximal to the blocked enzymatic conversion. Because cortisol is not synthesized efficiently, ACTH levels are high, leading to hyperplasia of the adrenal cortex and levels of precursor steroids that may be hundreds of times normal. In the case of 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of aldosterone deficiency in untreated patients.

It is not unusual for children with classic CAH to require hospitalization for intercurrent illnesses during childhood. This is most likely to occur in the first 2 years of life and to be precipitated by gastroenteritis, because such illnesses may cause fluid and electrolyte losses, and vomiting may interfere with medication dosing. Children requiring high fludrocortisone doses are most likely to be hospitalized, presumably because those patients have the greatest propensity to salt wasting.

Prenatal Androgen Excess

The most important problem caused by accumulation of steroid precursors is that 17-hydroxyprogesterone is shunted into the pathway for androgen biosynthesis, leading to high levels of androstenedione that

Table 616.1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ACTH ↑↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classic form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑↑ Baseline and ACTH-stimulated Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH ↑ DOC, corticosterone Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids

Table 616.1 Diagnosis and Treatment of Congenital Adrenal Hyperplasia—cont'd

DISORDER	AFFECTED GENE AND CHROMOSOME	SIGNS AND SYMPTOMS	LABORATORY FINDINGS	THERAPEUTIC MEASURES
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑ LH, ↓ estradiol (after puberty)	Estrogen replacement
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH ↑ Pregnenolone, ↑ progesterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in males and females	↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Maternal virilization Antley-Bixler syndrome	Decreased ratio of estrogens to androgens	

↓, Decreased; ↑, increased; ↑↑, markedly increased; ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DOC, 11-deoxycorticosterone; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table 616.2 Genotype-Phenotype Correlations in Congenital Adrenal Hyperplasia Owing to 21-Hydroxylase Deficiency

VARIANT GROUP	A	B	C
Enzymatic activity, % normal	Nil	1–2%	20–50%
CYP21 variants (phenotype generally corresponds to the least affected allele)	Gene deletion Exon 3 del 8 bp Exon 6 cluster Q318X R356W Intron 2 splice*	I172N	P30L V281L P453S
Severity	Salt wasting	Simple virilizing	Nonclassic
Aldosterone synthesis	Low	Normal	Normal
Age at diagnosis (without newborn screening)	Infancy	Infancy (females) Childhood (males)	Childhood to adulthood, or asymptomatic
Virilization	Severe	Moderate to severe	None to mild
Incidence	1/20,000	1/50,000	1/500

*This variant is associated with both salt-wasting and simple virilizing disease.

are converted outside the adrenal gland to testosterone. This problem begins in affected fetuses by 8-10 weeks of gestation and leads to abnormal genital development in females (see Figs. 616.1 and 616.2).

The external genitalia of males and females normally appear identical early in gestation (see Chapter 622). Affected females who are exposed in utero to high levels of androgens of adrenal origin have masculinized external genitalia (see Figs. 616.1 and 616.2). This is manifested by enlargement of the clitoris and by partial or complete labial fusion. The vagina usually has a common opening with the urethra (urogenital sinus). The clitoris may be so enlarged that it resembles a penis; because the urethra opens below this organ, some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism. The severity of virilization is usually greatest in females with the salt-losing form of 21-hydroxylase deficiency (see Table 616.2). The internal genital organs are normal because affected females have normal ovaries and not testes and thus do not secrete antimüllerian hormone.

Prenatal exposure of the brain to high levels of androgens may influence subsequent sexually dimorphic behaviors in affected females. Females may demonstrate aggressive play behavior, tend to be interested in masculine toys such as cars and trucks, and often show decreased interest in playing with dolls. Women may have decreased interest in maternal roles. There is an increased frequency of homosexuality in affected females. Nonetheless, most function heterosexually and do not have gender identity confusion or dysphoria. It is unusual

for affected females to assign themselves a male role except in some with the severest degree of virilization.

Male infants appear normal at birth. The diagnosis may not be made in males until signs of adrenal insufficiency develop. Because patients with this condition can deteriorate quickly, infant males are more likely to die than infant females. For this reason, all 50 American states and many countries have instituted newborn screening for this condition (see Chapter 616.2).

Postnatal Androgen Excess

Untreated or inadequately treated children of both sexes develop additional signs of androgen excess after birth. Males with the simple virilizing form of 21-hydroxylase deficiency often have a delayed diagnosis because they appear normal and rarely develop adrenal insufficiency.

Signs of androgen excess include **rapid somatic growth** and **accelerated skeletal maturation**. Affected patients are tall in childhood, but premature closure of the epiphyses causes growth to stop relatively early, and adult stature is stunted (see Fig. 616.1). Muscular development may be excessive. Pubic and axillary hair may appear, and acne and a deep voice may develop. The penis, scrotum, and prostate may become enlarged in affected males; however, the testes are usually prepubertal in size so that they appear small relative to the enlarged penis. Occasionally, ectopic adrenocortical cells in the testes of patients become hyperplastic similarly to the adrenal glands, producing **testicular adrenal rest tumors** (see Chapter 624). The clitoris may become further enlarged in affected females (see Fig. 616.1). Although the internal genital structures are female, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

Similar but usually milder signs of androgen excess may occur in **nonclassic 21-hydroxylase deficiency** (see Table 616.2). In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Males and females may present with precocious pubarche and early development of pubic and axillary hair. Hirsutism, acne, menstrual disorders, and infertility may develop later in life, but many females and males are completely asymptomatic.

Adrenomedullary Dysfunction

Development of the adrenal medulla requires exposure to the extremely high cortisol levels normally present within the adrenal gland. Thus patients with classic CAH have abnormal adrenomedullary function, as evidenced by blunted epinephrine responses, decreased blood glucose, and lower heart rates with exercise. Ability to exercise is unimpaired, and the clinical significance of these findings is uncertain. Adrenomedullary dysfunction may exacerbate the cardiovascular effects of cortisol deficiency in untreated or undertreated patients.

LABORATORY FINDINGS

See Table 616.1.

Patients with salt-losing disease have typical laboratory findings associated with cortisol and aldosterone deficiency, including hyponatremia, hyperkalemia, metabolic acidosis, and, often, hypoglycemia, but these abnormalities can take 10-14 days or longer to develop after birth. Blood levels of 17-hydroxyprogesterone are markedly elevated. However, levels of this hormone are high during the first 2-3 days of life even in unaffected infants and especially if they are ill or premature. After infancy, once the circadian rhythm of cortisol is established, 17-hydroxyprogesterone levels vary in the same circadian pattern, being highest in the morning and lowest at night. Blood levels of cortisol are usually low in patients with the salt-losing type of disease. They are often normal in patients with simple virilizing disease but inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-hydroxyprogesterone, levels of androstenedione and testosterone are elevated in affected females; testosterone is not elevated in affected males because normal infant males have high testosterone levels compared with those seen later in childhood. Levels of urinary 17-ketosteroids and pregnanetriol are elevated but are now rarely used clinically because blood samples are easier to obtain than 24-hour urine collections. ACTH levels are elevated but have no diagnostic utility over 17-hydroxyprogesterone levels. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low for the renin level. However, renin levels are high in normal infants in the first few weeks of life.

Diagnosis of 21-hydroxylase deficiency is most reliably established by measuring 17-hydroxyprogesterone before and 30 or 60 minutes after an intravenous bolus of 0.125-0.25 mg of cosyntropin (ACTH 1-24). Nomograms exist that readily distinguish between unaffected individuals and patients with nonclassic and classic 21-hydroxylase deficiency. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-hydroxyprogesterone levels than genetically unaffected individuals, but there is significant overlap between subjects in these two categories. However, in infants with frank electrolyte abnormalities or circulatory instability, it may not be possible or necessary to delay treatment to perform this test, as levels of precursors will be sufficiently elevated on a random blood sample to make the diagnosis.

Genotyping is clinically available and may help to confirm the diagnosis. Because the gene conversions that generate most pathogenic alleles may transfer more than one variant, at least one parent should also be genotyped to determine which variants are on each allele.

DIFFERENTIAL DIAGNOSIS

Disorders of sexual development are discussed more generally in Chapter 628. The initial step in evaluating an infant with ambiguous genitalia is a thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads usually indicate the presence of testicular tissue and that the infant is a genetic male), and look for any other anatomic abnormalities. Ultrasonography is helpful in demonstrating the presence or absence of a uterus and can often locate the gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These results are all likely to be available before the results of hormonal testing and together allow the clinical team to advise the parents as to the genetic sex of the infant and the anatomy of internal reproductive structures. Injection of contrast medium into the urogenital sinus of a virilized female demonstrates a vagina and uterus; surgeons use this information to formulate a plan for surgical management.

PRENATAL DIAGNOSIS

Prenatal diagnosis of 21-hydroxylase is possible late in the first trimester by analysis of DNA obtained by chorionic villus sampling or during the second trimester by amniocentesis. This is usually done because the parents already have an affected child. Most often, the *CYP21A2* gene is analyzed for frequently occurring pathogenic variants; less common variants may be detected by DNA sequencing. Cell-free fetal DNA may be an adjunctive noninvasive testing method to help guide decision-making for possible prenatal treatment with dexamethasone, given that prenatal sex typing can be performed as early as 6-9 weeks. As of 2021, cell-free fetal DNA testing for this disorder is not yet available as part of routine clinical care.

NEWBORN SCREENING

Because 21-hydroxylase deficiency is often undiagnosed in affected males until they have severe adrenal insufficiency, all states in the United States and many other countries have instituted newborn screening programs. These programs analyze 17-hydroxyprogesterone levels in dried blood obtained by heelstick and absorbed on filter paper cards; the same cards are screened in parallel for other congenital conditions, such as hypothyroidism and phenylketonuria. Potentially affected infants are typically quickly recalled for additional testing (electrolytes and repeat 17-hydroxyprogesterone determination) at approximately 2 weeks of age. Infants with salt-wasting disease often have abnormal electrolytes by this age but are usually not severely ill. Screening programs are effective in preventing many cases of adrenal crisis in affected males. The nonclassic form of the disease is not

reliably detected by newborn screening, but this is of little clinical significance because adrenal insufficiency does not occur in this type of 21-hydroxylase deficiency.

The main difficulty with current newborn screening programs is that to reliably detect all affected infants, the cutoff 17-hydroxyprogesterone levels for first-tier screening are set so low that there is a very high frequency of false-positive results (i.e., the test has a low positive predictive value of as little as 1%). This problem is worst in premature infants. Positive predictive value can be improved by using cutoff levels based on gestational age and by using more specific second-tier screening methods such as liquid chromatography followed by tandem mass spectrometry.

TREATMENT

Glucocorticoid Replacement

Cortisol deficiency is treated with glucocorticoids. Treatment also suppresses excessive production of androgens by the adrenal cortex and thus minimizes problems such as excessive growth and skeletal maturation and virilization. This often requires larger glucocorticoid doses than are needed in other forms of adrenal insufficiency, typically 12-15 mg/m^2/24 hr of hydrocortisone daily administered orally in 3 divided doses. Affected infants usually require dosing at the high end of this range. Double or triple doses are indicated during periods of stress, such as infection or surgery. Glucocorticoid treatment must be continued indefinitely in all patients with classic 21-hydroxylase deficiency but may not be necessary in patients with nonclassic disease unless signs of androgen excess are present. Therapy must be individualized. It is desirable to maintain linear growth along percentile lines; crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles often indicates overtreatment with glucocorticoids. Overtreatment is also suggested by excessive weight gain. Pubertal development should be monitored by periodic examination, and skeletal maturation is evaluated by serial radiographs of the hand and wrist for bone age. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning, before taking the morning medications, or at a consistent time in relation to medication dosing. Desirable 17-hydroxyprogesterone levels are in the high-normal range or several times normal; low-normal levels can usually be achieved only with excessive glucocorticoid doses. Hydrocortisone is the preferred glucocorticoid in growing children because its shorter half-life minimizes adverse side effects such as growth suppression, which is seen with longer half-life glucocorticoids. It is available as tablets, immediate-release granules, and a custom-compounded suspension. Use of continuous subcutaneous pump infusion devices to deliver hydrocortisone in a pattern more closely approximating the normal diurnal rhythm variation in cortisol secretion has been studied but has not entered clinical practice. Clinical trials for delayed-release hydrocortisone tablets are currently underway in the pediatric population.

Menarche occurs at the appropriate age in most females in whom good control has been achieved; it may be delayed in females with suboptimal control. Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3-7 years of age, at which time skeletal maturation may be 5 years or more in advance of chronological age. In some children, especially if the bone age is 12 years or more, spontaneous central (i.e., gonadotropin-dependent) puberty may occur when treatment is instituted, because therapy with hydrocortisone suppresses production of adrenal androgens and thus stimulates release of pituitary gonadotropins if the appropriate level of hypothalamic maturation is present. This form of superimposed true precocious puberty may be treated with a gonadotropin hormone–releasing hormone analog such as leuprolide (see Chapter 600.1).

Males with 21-hydroxylase deficiency who have had inadequate corticosteroid therapy may develop **testicular adrenal rest tumors**, which may regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow Doppler examination help to define the character and extent of disease. Testis-sparing surgery to resect steroid-unresponsive tumors may be required in adult men to preserve fertility.

Mineralocorticoid Replacement

Patients with salt-wasting disease (i.e., aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Infants may have very high mineralocorticoid requirements in the first few months of life, usually 0.1-0.3 mg daily in 2 divided doses, but occasionally up to 0.4 mg daily, and often require sodium supplementation (sodium chloride 8 mmol/kg) in addition to the mineralocorticoid. Older infants and children are usually maintained with 0.05-0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even when these patients have normal aldosterone levels in the absence of mineralocorticoid replacement. Therapy is evaluated by monitoring of vital signs; tachycardia and hypertension are signs of overtreatment with mineralocorticoids. Serum electrolytes should be measured frequently in early infancy as therapy is adjusted. Plasma renin activity is a useful way to determine adequacy of therapy; it should be maintained in or near the normal range but not suppressed.

Additional approaches to improve outcome have been proposed but have not yet become the standard of care. These include an antiandrogen such as flutamide to block the effects of excessive androgen levels and/or an aromatase inhibitor such as anastrozole or letrozole, which blocks conversion of androgens to estrogen and thus retards skeletal maturation, a process that is sensitive to estrogens in both males and females. Aromatase inhibitors generally should not be used in pubertal females, except in combination with a gonadotropin-releasing hormone agonist because this will expose the ovaries to excessive levels of gonadotropins. Growth hormone, with or without gonadotropin–releasing hormone agonists, has been suggested to improve adult height. Corticotropin-releasing hormone receptor antagonists such as crinecerfont and tildacerfont are in phase 2-3 studies as of 2021; they may reduce ACTH secretion, thus suppressing secretion of abnormal steroids at lower glucocorticoid doses than otherwise necessary. This strategy may reduce the adverse effects of high glucocorticoid doses. Abiraterone acetate, a CYP17A1 inhibitor that suppresses secretion of androgens and estrogens and is used for treatment of prostate cancer, may also permit reductions in glucocorticoid dosing and is in early-phase trials for CAH as of 2021.

Surgical Management of Ambiguous Genitals

Significantly virilized females usually undergo surgery between 2 and 6 months of age. If there is severe clitoromegaly, the clitoris is reduced in size, with partial excision of the corporal bodies and preservation of the neurovascular bundle; however, moderate clitoromegaly may become much less noticeable without surgery as the patient grows. Vaginoplasty and correction of the urogenital sinus usually are performed at the time of clitoral surgery; revision in adolescence is often necessary.

Risks and benefits of surgery should be fully discussed with parents of affected females. There is limited long-term follow-up of functional outcomes in patients who have undergone modern surgical procedures. It appears that female sexual dysfunction increases in frequency and severity in those with the most significant degrees of genital virilization and with the degree of enzymatic impairment (prenatal androgen exposure) caused by each patient's pathogenic variant (see Table 616.2). Sex assignment of infants with disorders of sexual differentiation (including CAH) is usually based on expected sexual functioning and fertility in adulthood, with early surgical correction of the external genitalia to conform with the sex assignment. The majority of females with CAH identify as female gender and are heterosexual. Gender dysphoria is not common with CAH; it occurs mostly in females with the salt-wasting form of the disease and the greatest degree of virilization.

Lay and medical opponents of genital surgery for other disorders of sexual differentiation raise the concern that it ignores any prenatally influenced gender role effects from androgen exposure and precludes the patient from having any decision as to the patient's own preferred sexual identity and what surgical correction of the genitals should be performed. They advocate that treatment should be aimed primarily at educating the patient, family, and others about the medical condition

and its treatment. They propose that surgery should be delayed until the patient decides on what, if any, surgery should be performed. There have not been any studies comparing early with late surgery. Not all lay groups support delaying surgery, and many agree with appropriate surgery during infancy. Severely virilized genotypic (XX) females raised as males have generally functioned well in the male gender as adults.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsutism, obesity, amenorrhea), bilateral laparoscopic adrenalectomy (with hormone replacement) may be an alternative to standard medical hormone replacement therapy, but because the adrenal glands have been removed, patients treated in this way may be more susceptible to acute adrenal insufficiency if treatment is interrupted. Moreover, they may exhibit signs of elevated ACTH levels such as abnormal pigmentation. There have also been reports of development of adrenal rest tumors in women after adrenalectomy, which defeats the purpose of adrenalectomy and allows the recurrence of androgen excess.

Prenatal Treatment

Besides genetic counseling, the main goal of prenatal diagnosis is to facilitate prenatal treatment of affected females. Mothers with pregnancies at risk may be given dexamethasone, a steroid that readily crosses the placenta, in an amount of 20 μg/kg pre-pregnancy maternal weight daily in 2 or 3 divided doses. This suppresses secretion of steroids by the fetal adrenal, including secretion of adrenal androgens. If started by 6 weeks of gestation, it ameliorates virilization of the external genitals in affected females. Chorionic villus biopsy is then performed to determine the sex and genotype of the fetus; therapy is continued only if the fetus is an affected female. DNA analysis of fetal cells isolated from maternal plasma for sex determination and *CYP21* gene analysis may permit earlier identification of the affected female fetus. Treatment should be considered only in affected female fetuses. Children exposed to this therapy have slightly lower birthweights. Reports of failure to thrive, stroke-like events, and midline defects have been observed in treated cases. Effects on personality or cognition, such as increased shyness, have been suggested but not consistently observed. At present there is insufficient information to determine whether the long-term risks are acceptable, particularly in the males and unaffected females who derive no direct benefit from the treatment. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae. Consensus statements from professional societies recommend that prenatal treatment be carried out only under institutional protocols, but it is sometimes offered as an option outside the research setting by some high-risk obstetricians.

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616.2 Congenital Adrenal Hyperplasia Caused by 11β-Hydroxylase Deficiency

Perrin C. White and Ming Yang

Deficiency of 11β-hydroxylase is caused by a pathologic variant in the *CYP11B1* gene located on chromosome 8q21-q22. *CYP11B1* mediates 11-hydroxylation of 11-deoxycortisol to cortisol. Because 11-deoxycortisol is not converted to cortisol, levels of corticotropin are high. In consequence, precursors—particularly 11-deoxycortisol and deoxycorticosterone—accumulate and are shunted into androgen biosynthesis in the same manner as occurs in 21-hydroxylase deficiency. The adjacent *CYP11B2* gene encoding aldosterone synthase is generally unaffected in this disorder, so patients are able to synthesize aldosterone normally.

EPIDEMIOLOGY

11β-Hydroxylase deficiency accounts for approximately 5% of cases of adrenal hyperplasia; its incidence in the general population has been estimated as 1 in 250,000 to 1 in 100,000. The disorder occurs relatively frequently in Israeli Jews of North African origin (1 in 5,000-7,000 live births). In this ethnic group, almost all alleles carry an Arg448 to His (R448H) variant in *CYP11B1,* but many other variants have been identified. This disorder presents in a classic, severe form and very rarely in a nonclassic, milder form.

CLINICAL MANIFESTATIONS

Although cortisol is not synthesized efficiently, aldosterone synthetic capacity is normal, and some corticosterone is synthesized from progesterone by the intact aldosterone synthase enzyme. Thus it is unusual for patients to manifest signs of adrenal insufficiency such as hypotension or hypoglycemia. On the contrary, approximately 65% of patients become *hypertensive,* although this can take several years to develop. Hypertension is probably a consequence of elevated levels of deoxycorticosterone, which has mineralocorticoid activity. Infants may transiently develop signs of mineralocorticoid deficiency after treatment with hydrocortisone is instituted. This is presumably from sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity.

All signs and symptoms of androgen excess that are found in 21-hydroxylase deficiency may also occur in 11β-hydroxylase deficiency.

LABORATORY FINDINGS

Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated. Because deoxycorticosterone and some metabolites have mineralocorticoid activity, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. *Hypokalemic alkalosis occasionally occurs.*

TREATMENT

Patients are treated with hydrocortisone in doses similar to those used for 21-hydroxylase deficiency. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

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616.3 Congenital Adrenal Hyperplasia Caused by 3β-Hydroxysteroid Dehydrogenase Deficiency

Perrin C. White and Ming Yang

Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) occurs in less than 2% of patients with adrenal hyperplasia. This enzyme is required for conversion of Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-hydroxyprogesterone, and androstenedione). Thus deficiency of the enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA (see Fig. 614.1 in Chapter 614). The 3β-HSD isozyme expressed in the adrenal cortex and gonad is encoded by the *HSD3B2* gene located on chromosome 1p13.1. More than 30 pathogenic variants in *HSD3B2* have been described in patients with 3β-HSD deficiency.

CLINICAL MANIFESTATIONS

Because cortisol and aldosterone are not synthesized in patients with the classic form of the disease, infants are prone to **salt-wasting crises**. Because androstenedione and testosterone are not synthesized, *males*

are incompletely virilized; varying degrees of hypospadias may occur, with or without bifid scrotum or cryptorchidism. Because DHEA levels are elevated and this hormone is a weak androgen, females are mildly virilized, with slight to moderate clitoral enlargement. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsutism, irregular menses, and polycystic ovarian disease occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. However, a persistent defect of testicular 3β-HSD is demonstrated by the high Δ5:Δ4 steroid ratio in testicular effluent.

LABORATORY FINDINGS

The hallmark of this disorder is the marked elevation of the Δ5 steroids (such as 17-hydroxypregnenolone and DHEA) preceding the enzymatic block. Patients may also have elevated levels of 17-hydroxyprogesterone because of the extraadrenal 3β-HSD activity that occurs in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. The ratio of 17-hydrox ypregnenolone:17-hydroxyprogesterone is markedly elevated in 3β-HSD deficiency, in contrast to the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

DIFFERENTIAL DIAGNOSIS

It is not unusual for children with premature adrenarche, or females with signs of androgen excess, to have mild to moderate elevations in DHEA levels. It has been suggested that such individuals have *nonclassic 3β-HSD deficiency*. Variants in *HSD3B2* are usually not found in such individuals, and a nonclassic form of this deficiency may be quite rare. The activity of 3β-HSD in the adrenal zonae fasciculata and reticularis, relative to CYP17A1 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in preteenage children or women usually represent a normal variant.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of 25 mg of a depot form of testosterone every 4 weeks early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

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616.4 Congenital Adrenal Hyperplasia Caused by 17-Hydroxylase Deficiency

Perrin C. White and Ming Yang

Less than 1% of CAH cases are caused by 17-hydroxylase deficiency, but the condition is apparently more common in Brazil and China. A single polypeptide, CYP17A1, catalyzes two distinct reactions: 17-hydroxylation of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively, and the 17,20-lyase reaction–mediating conversion of 17-hydroxypregnenolone to DHEA and, to a lesser extent, 17-hydroxyprogesterone to Δ4-androstenedione. DHEA and androstenedione are steroid precursors of testosterone and estrogen (see Fig. 614.1 in Chapter 614). The enzyme is expressed in both the adrenal cortex and the gonads and is encoded by a gene on chromosome 10q24.3. Most pathogenic variants affect both the hydroxylase and lyase activities, but rare variants can affect either activity alone.

Pathogenic variants in genes other than *CYP17A1* can have the same phenotype as 17,20-lyase deficiency (i.e., deficient androgen synthesis with normal cortisol synthesis). These include an accessory electron transfer protein, cytochrome-b_5, (CYB5) and variants in two aldo-keto reductases AKR1C2 and AKR1C4. These AKR1C isozymes normally catalyze 3α-HSD activity, which allows synthesis of the potent androgen dihydrotestosterone through an alternative backdoor biosynthetic pathway that does not include testosterone as an intermediate (see Chapter 614).

CLINICAL MANIFESTATIONS AND LABORATORY FINDINGS

Patients with 17-hydroxylase deficiency cannot synthesize cortisol, but their ability to synthesize corticosterone is intact. Because corticosterone is an active glucocorticoid, patients do not develop adrenal insufficiency. Deoxycorticosterone, the immediate precursor of corticosterone, is synthesized in excess. This can cause **hypertension**, **hypokalemia**, and suppression of renin and aldosterone secretion, as occurs in 11β-hydroxylase deficiency. However, in contrast to 11β-hydroxylase deficiency, patients with 17-hydroxylase deficiency are unable to synthesize sex hormones. *Affected males are incompletely virilized* and present as phenotypic females (but the gonads are usually palpable in the inguinal region or the labia) or with sexual ambiguity. Affected females usually present with *failure of sexual development* at the expected time of puberty. 17-Hydroxylase deficiency in females must be considered in the differential diagnosis of primary hypogonadism (see Chapter 626). Levels of deoxycorticosterone are elevated, and renin and aldosterone are consequently suppressed. Cortisol and sex steroids are unresponsive to stimulation with ACTH and human chorionic gonadotropin, respectively.

Patients with isolated 17,20-lyase deficiency have deficient androgen synthesis with normal cortisol synthesis and therefore do not become hypertensive.

TREATMENT

Patients with 17-hydroxylase deficiency require glucocorticoid replacement with hydrocortisone to suppress secretion of deoxycorticosterone and thus control hypertension. Additional antihypertensive medication may be required. Females require estrogen replacement at puberty. Genetic males may require either estrogen or androgen supplementation depending on the sex of rearing. Because of the possibility of malignant transformation of abdominal testes, genetic males with severe 17-hydroxylase deficiency being reared as females require gonadectomy at or before adolescence.

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616.5 Lipoid Adrenal Hyperplasia

Perrin C. White and Ming Yang

Lipoid adrenal hyperplasia is a rare disorder, most frequently found in Japanese persons. Patients with this disorder exhibit marked accumulation of cholesterol and lipids in the adrenal cortex and gonads associated with severe impairment of all steroidogenesis. Lipoid adrenal hyperplasia is usually caused by pathogenic variants in the gene for steroidogenic acute regulatory protein (StAR), a mitochondrial protein that promotes the movement of cholesterol from the outer to the inner mitochondrial membrane. However, pathogenic variants in *CYP11A1* (which encodes the cholesterol side-chain cleavage enzyme) have been reported in more than 30 patients. A milder, nonclassic form of StAR deficiency has been reported.

Some cholesterol is able to enter mitochondria even in the absence of StAR, so it might be supposed that this disorder would not completely impair steroid biosynthesis. However, the accumulation of cholesterol in the cytoplasm is cytotoxic, eventually leading to death of all steroidogenic cells in which StAR is normally expressed. This occurs prenatally in the adrenals and testes. The ovaries do not

normally synthesize steroids until puberty, so cholesterol does not accumulate, and the ovaries can retain the capacity to synthesize estrogens until adolescence.

Although estrogens synthesized by the placenta are required to maintain pregnancy, the placenta does not require StAR for steroid biosynthesis. Variants of StAR are not prenatally lethal.

CLINICAL MANIFESTATIONS

Patients with lipoid adrenal hyperplasia are usually unable to synthesize any adrenal steroids. Thus affected infants are likely to be confused with those with adrenal hypoplasia congenita. Salt-losing manifestations are typical, and many infants die in early infancy. Genetic males are unable to synthesize androgens and thus are **phenotypically female** but with gonads palpable in the labia majora or inguinal areas. Genetic females appear normal at birth and may undergo feminization at puberty with menstrual bleeding. They, too, progress to hypergonadotropic hypogonadism when accumulated cholesterol damages granulosa (i.e., steroid synthesizing) cells in the ovary.

LABORATORY FINDINGS

Adrenal and gonadal steroid hormone levels are low in lipoid adrenal hyperplasia, with a decreased or absent response to stimulation (ACTH, human chorionic gonadotropin). Plasma renin levels are increased.

Imaging studies of the adrenal gland demonstrating massive adrenal enlargement in the newborn help to establish the diagnosis of lipoid adrenal hyperplasia.

TREATMENT

Patients require glucocorticoid and mineralocorticoid replacement. Genetic males are usually assigned a female sex of rearing; thus both genetic males and females require estrogen replacement at the expected age of puberty.

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616.6 Deficiency of P450 Oxidoreductase (Antley-Bixler Syndrome)

Perrin C. White and Ming Yang

P450 oxidoreductase (*POR*; gene located on chromosome 7q11.3) is required for the activity of all microsomal cytochrome P450 enzymes (see Chapter 614), including the adrenal enzymes CYP17 and CYP21. Complete *POR* deficiency abolishes all microsomal P450 activity. This is embryonically lethal in mice and presumably also in humans. Patients with pathogenic variants that decrease but do not abolish *POR* activity have partial deficiencies of 17-hydroxylase and 21-hydroxylase activities in the adrenals. A single recurrent variant A287P (alanine-287 to proline) is found on approximately 40% of alleles.

Deficiency of 17-hydroxylase leads to incomplete masculinization in males; 21-hydroxylase deficiency may lead to virilization in females. In addition, aromatase *(CYP19)* activity in the placenta is decreased, leading to unopposed action of androgens produced by the fetal adrenal. This exacerbates virilization of female fetuses and may **virilize the mother** of an affected fetus as well. Although it is puzzling that affected females could be virilized despite a partial deficiency in *CYP17* (which is required for androgen biosynthesis), an alternative (backdoor) biosynthetic pathway is used in which 17-hydroxyprogesterone is converted to 5α-pregnane-3α,17α-diol-20-one, a metabolite that is a much better substrate for the 17,20-lyase activity of *CYP17* than the usual substrate, 17-hydroxypregnenolone (see Chapter 614). The metabolite is then converted in several enzymatic steps to dihydrotestosterone, a potent androgen.

Because many other P450 enzymes are affected, patients may have other congenital anomalies collectively referred to as **Antley-Bixler syndrome**. These include craniosynostosis; brachycephaly; frontal bossing; severe midface hypoplasia with proptosis and choanal stenosis or atresia; humeroradial synostosis; medial bowing of ulnas; long, slender fingers with camptodactyly; narrow iliac wings; anterior bowing of femurs; and malformations of the heart and kidneys.

EPIDEMIOLOGY

More than 130 cases of *POR* deficiency have been reported. Although the prevalence is not known with certainty, it might be the second most common cause of CAH in some populations such as Korea and Japan.

LABORATORY FINDINGS

Serum steroids that are not 17- or 21-hydroxylated are most increased, including pregnenolone and progesterone. 17-Hydroxy and 21-deoxysteroids are also increased, including 17-hydroxypregnenolone, 17-hydroxyprogesterone, and 21-deoxycortisol. Urinary steroid metabolites may be determined by quantitative mass spectrometry. Metabolites excreted at increased levels include pregnanediol, pregnanetriol, pregnanetriolone, and corticosterone metabolites. Urinary cortisol metabolites are decreased. Genetic analysis demonstrates pathogenic variants in *POR*.

DIFFERENTIAL DIAGNOSIS

This disorder must be distinguished from other forms of CAH, particularly 21-hydroxylase deficiency in females, which is far more common and has similar laboratory findings. Suspicion for *POR* deficiency may be raised if the mother is virilized or if the associated abnormalities of Antley-Bixler syndrome are present. Conversely, virilization of both the mother and her daughter can result from a luteoma of pregnancy, but in this case postnatal abnormalities of corticosteroid biosynthesis should not be observed. Antley-Bixler syndrome may also occur without abnormalities of steroid hormone biosynthesis, resulting from pathogenic variants in the fibroblast growth factor receptor FGFR2.

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616.7 Aldosterone Synthase Deficiency

Perrin C. White and Ming Yang

This is an autosomal recessive disorder in which conversion of corticosterone to aldosterone is impaired; a group of Iranian Jewish patients has been the most thoroughly studied. Most cases result from pathogenic variants in *CYP11B2* coding for aldosterone synthase; however, linkage to *CYP11B2* has been excluded in other kindreds. When not caused by *CYP11B2* variants, the disorder has been termed **familial hyperreninemic hypoaldosteronism type 2**; the causative gene or genes have not yet been identified.

Aldosterone synthase mediates the three final steps in the synthesis of aldosterone from deoxycorticosterone (11β-hydroxylation, 18-hydroxylation, and 18-oxidation). Although 11β-hydroxylation is required to convert deoxycorticosterone to corticosterone, this conversion can also be catalyzed by the related enzyme, CYP11B1, located in the fasciculata, which is unaffected in this disorder. For the same reason, these patients have normal cortisol biosynthesis.

The disease has been classified into two types, termed **corticosterone methyloxidase deficiency types I and II**. They differ only in levels of the immediate precursor of aldosterone, 18-hydroxycorticosterone; levels are low in type I deficiency and elevated in type II deficiency.

CLINICAL MANIFESTATIONS

Infants with aldosterone synthase deficiency may have severe electrolyte abnormalities with **hyponatremia**, **hyperkalemia**, and

metabolic acidosis. Because cortisol synthesis is unaffected, infants rarely become as ill as untreated infants with salt-losing forms of CAH such as 21-hydroxylase deficiency. Thus some infants escape diagnosis. Later in infancy or in early childhood they may exhibit failure to thrive and poor growth. Adults often are asymptomatic, although they may develop electrolyte abnormalities when depleted of sodium through procedures such as bowel preparation for a barium enema.

LABORATORY FINDINGS

Infants have elevated plasma renin activity. Aldosterone levels are decreased; they may be at the lower end of the normal range but are always inappropriately low for the degree of hyperkalemia or hyperreninemia. Corticosterone levels are often elevated.

Some, but not all, patients have marked elevation of 18-hydroxycorticosterone; however, low levels of this steroid do not exclude the diagnosis. In those kindreds in which 18-hydroxycorticosterone levels are elevated in affected individuals, this biochemical abnormality persists in adults even when they have no electrolyte abnormalities.

DIFFERENTIAL DIAGNOSIS

It is important to distinguish aldosterone synthase deficiency from primary adrenal insufficiency in which both cortisol and aldosterone are affected (including salt-wasting forms of CAH), because the latter condition is usually associated with a much greater risk of shock and hyponatremia. This becomes apparent after the appropriate laboratory studies. **Adrenal hypoplasia congenita** may initially present with aldosterone deficiency; all male infants with apparently isolated aldosterone deficiency should be carefully monitored for subsequent development of cortisol deficiency. **Pseudohypoaldosteronism** (see Chapter 615.4) may have similar electrolyte abnormalities and hyperreninemia, but aldosterone levels are high, and this condition usually does not respond to fludrocortisone treatment.

TREATMENT

Treatment consists of giving enough fludrocortisone (0.05-0.2 mg daily) or sodium chloride, or both, to return plasma renin levels to normal. With increasing age, salt-losing signs usually improve, and drug therapy can often be discontinued.

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616.8 Glucocorticoid-Remediable Aldosteronism

Perrin C. White

Glucocorticoid-remediable aldosteronism (glucocorticoid-suppressible hyperaldosteronism, familial hyperaldosteronism type I) is an autosomal dominant form of *low-renin hypertension* in which hyperaldosteronism is rapidly suppressed by glucocorticoid administration. This unusual effect of glucocorticoids suggests that aldosterone secretion in this disorder is regulated by ACTH instead of by the renin-angiotensin system. In addition to abnormally regulated secretion of aldosterone, there is marked overproduction of 18-hydroxycortisol and 18-oxocortisol. The synthesis of these steroids requires both 17-hydroxylase (CYP17A1) activity, which is expressed only in the zona fasciculata, and aldosterone synthase (CYP11B2) activity, which is normally expressed only in the zona glomerulosa. These features imply that aldosterone synthase is being expressed in a manner similar to the closely related enzyme steroid 11-hydroxylase *(CYP11B1)*. The disorder is caused by unequal meiotic crossing-over events between the *CYP11B1* and *CYP11B2* genes, which are closely linked on chromosome 8q24. An additional "chimeric" gene is produced, having regulatory sequences of *CYP11B1* juxtaposed with coding sequences of *CYP11B2*. This results in the inappropriate expression of a *CYP11B2*-like enzyme with aldosterone synthase activity in the adrenal fasciculata.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension, typically approximately 30 mm Hg higher than unaffected family members of the same age. Others have more symptomatic hypertension with headache, dizziness, and visual disturbances. A strong family history of early-onset hypertension or early strokes may alert the clinician to the diagnosis. Some patients have chronic hypokalemia, but this is not a consistent finding and is usually mild.

LABORATORY FINDINGS

Patients have elevated plasma and urine levels of aldosterone and suppressed plasma renin activity. *Hypokalemia is not consistently present.* Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol are markedly increased. The hybrid *CYP11B1/CYP11B2* gene can be readily detected by molecular genetic methods.

DIFFERENTIAL DIAGNOSIS

This condition should be distinguished from primary aldosteronism based on bilateral hyperplasia or an aldosterone-producing adenoma (see Chapter 620). Most cases of primary aldosteronism are sporadic, although several affected kindreds have been reported. Patients with primary aldosteronism may also have elevated levels of 18-hydroxycortisol and 18-oxocortisol, and these biochemical tests should be used cautiously when attempting to distinguish primary and glucocorticoid-suppressible aldosteronism. By definition, a therapeutic trial of dexamethasone should suppress aldosterone secretion only in glucocorticoid-remediable aldosteronism, and genetic testing should identify the hybrid gene if it is present.

TREATMENT

Glucocorticoid-remediable aldosteronism is managed by daily administration of a glucocorticoid, usually dexamethasone 25 μg/kg/day in divided doses. If necessary, effects of aldosterone can be blocked with a potassium-sparing diuretic such as spironolactone, eplerenone, or amiloride. Hypertension resolves in patients in whom the hypertension is not severe or of long standing. If hypertension is long standing, additional antihypertensive medication may be required, such as a calcium channel blocker.

GENETIC COUNSELING

Because of the autosomal dominant mode of inheritance, at-risk family members should be investigated for this easily treated cause of hypertension.

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Chapter 617

Adrenocortical Tumors and Masses

Perrin C. White

Adrenocortical tumors are rare in childhood, with an incidence of 0.3-0.5 cases per 1 million child-years. They occur in all age-groups but most commonly in children younger than 6 years of age and are slightly more frequent (1.6-fold) in females. In 2–10% of cases, the tumors are bilateral. Almost half of childhood adrenocortical tumors are carcinomas. Pathogenic variants in many genes can influence the risk of developing adrenal tumors (Table 617.1).

Tumors may be associated with hemihypertrophy, usually occurring during the first few years of life. They are also associated with other congenital defects, particularly genitourinary tract and central nervous system abnormalities and hamartomatous defects.

Many adrenocortical tumors secrete sex hormones, cortisol, or aldosterone; these are discussed in Chapters 618, 619, and 620, respectively.

617.1 Adrenocortical Carcinoma

Perrin C. White

ETIOLOGY

The incidence of adrenocortical carcinoma is increased in several familial cancer syndromes resulting from abnormalities in genes that encode transcription factors implicated in cell proliferation, differentiation, senescence, apoptosis, and genomic instability. These include tumor protein 53 *(TP53)*, menin (the *MEN1* gene involved in multiple endocrine neoplasia type 1; 1–2% of MEN1 patients develop adrenocortical carcinoma), the *APC* gene involved in familial adenomatous polyposis coli, and the *PRKAR1A* gene encoding a cyclic adenosine monophosphate–dependent protein kinase regulatory subunit (also see Chapter 619).

Germline pathogenic variants in *TP53* (on chromosome 17p13.1) occur in 50–80% of children with adrenocortical carcinoma. They have been found in patients with isolated adrenal carcinoma and in patients with familial clustering of unusual malignancies (choroid plexus tumors, sarcomas, early-onset breast cancers, brain cancers, and leukemias); this latter condition is termed **Li-Fraumeni syndrome**. A 15-fold increased incidence of childhood adrenocortical tumors is found in southern Brazil, associated with an R337H variant in *TP53*.

Overexpression of insulin-like growth factor (IGF) 2 (encoded by *IGF2,* on chromosome 11p15.5) occurs in 80% of sporadic childhood adrenocortical tumors and in those associated with **Beckwith-Wiedemann syndrome**, in which there is loss of the normal imprinting of genes in this chromosomal region, including *H19, CDKN1C, KCNQ1,* and *KCNQ1OT1*. However, whereas 5–10% of patients with Beckwith-Wiedemann syndrome develop tumors, <1% develop an adrenocortical carcinoma. Further implicating IGFs in pathogenesis, many pediatric adrenocortical tumors overexpress the IGF receptor, IGF1R.

Pathogenic variants in the *MENIN* gene on chromosome 11q13 cause **multiple endocrine neoplasia type 1**. Approximately 10% of MEN1 patients have adrenocortical tumors, of which ~14% are malignant. Adrenocortical carcinomas also occur in patients with **Lynch syndrome**, a hereditary cancer syndrome (mainly colorectal and endometrial cancer) caused by pathogenic variants in genes involved in DNA mismatch repair, including *MLH1, MSH2, MSH6,* and *PMS2,* or loss of expression of *MSH2* caused by deletion in the *EPCAM* gene. Occasional adrenocortical carcinomas occur in patients with familial adenomatous polyposis, neurofibromatosis type 1, Werner syndrome, and Carney complex.

In adult adrenocortical carcinoma samples, *somatic* pathogenic variants are detected in nine genes (*ZNRF3, CTNNB1, TP53, CDKN2A, RB1, MEN1, DAXX, MED12,* and *TERT*), most frequently (21%) in *ZNRF3*. This gene encodes a cell surface transmembrane E3 ubiquitin ligase that acts as a negative feedback regulator of Wnt/β-catenin signaling. There are also tumor-specific differences in DNA methylation and in micro-RNA (miRNA) expression that have prognostic significance in adults, but there are no corresponding data in children.

CLINICAL MANIFESTATIONS

Symptoms of endocrine hyperfunction are present in 80–90% of children with adrenal tumors. Tumors that secrete cortisol and aldosterone are discussed in Chapters 619 and 621. Other tumors are detected because of symptoms related to local tumor growth, such as abdominal pain, or as incidental findings on abdominal imaging.

Tumors can usually be detected by ultrasonography, CT, or MRI. Preoperatively, the presence of metastatic disease should be determined by MRI or CT of the chest, abdomen, and pelvis. Because these tumors are metabolically active, ^{18}F-fluorodeoxyglucose positron emission tomography (PET)/CT has very good sensitivity and specificity in distinguishing benign from malignant lesions, but it cannot distinguish adrenocortical carcinomas from other metabolically active tumors such as metastases, lymphoma, or pheochromocytoma. Radiochemical imaging of these tumors by PET may be improved with ^{11}C-metomidate or single photon emission CT or MRI with ^{123}I-iodometomidate.

PATHOLOGIC FINDINGS

Most pediatric adrenocortical tumors would be classified as malignant by the criteria used to classify adult tumors. Size is a useful prognostic factor, with tumors weighing less than 200 g, 200-400 g, and >400 g being classified, respectively, as low, intermediate, and high risk (>10 cm diameter has also been suggested as a high-risk category). Incomplete resection and gross local invasion or metastasis are also associated with a poor prognosis. However, most tumors occurring in children younger than 4 years of age have a favorable prognosis. Tumors associated with Cushing syndrome may have a poor prognosis, whereas the presence of germline *TP53* variants may be more favorable.

DIFFERENTIAL DIAGNOSIS

For functioning tumors, the differential diagnoses are those of the main presenting signs and symptoms. The differential diagnosis for Cushing syndrome is discussed in Chapter 619. For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 616) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for hormonally

Table 617.1 Genes Involved in Adrenal Neoplasia

SYNDROME	ADRENAL NEOPLASIA TYPE	GENE	OTHER PHENOTYPE
Li-Fraumeni syndrome	Adrenocortical carcinoma	*TP53*	Sarcoma, choroid plexus tumor, brain cancer, early breast cancer, leukemia, lymphoma
Multiple endocrine neoplasia type 1	Diffuse hyperplasia, nodular hyperplasia, adrenal adenoma, adrenocortical carcinoma	*MENIN*	Foregut neuroendocrine tumors, pituitary tumors, parathyroid hyperplasia or tumors, collagenoma, angiofibroma
Lynch syndrome	Adrenocortical carcinoma	*MSH2, MSH6, MLH1, PMS2*	Colorectal cancer, endometrial cancer, sebaceous neoplasms, ovarian cancer, pancreatic cancer, brain cancer
Beckwith-Wiedemann syndrome	Adrenal adenoma, adrenocortical carcinoma	*IGF2, CDKN1C, H19* methylation changes on 11p15	Macrosomia, hemihypertrophy, macroglossia, omphalocele, ear pits; Wilms tumor, hepatoblastoma
Familial adenomatous polyposis coli	Bilateral macronodular adrenal hyperplasia, aldosterone-producing adenoma, adrenocortical carcinoma	*APC*	Intestinal polyps, colon cancer, duodenal carcinoma, thyroid cancer, desmoid tumor, supernumerary teeth, congenital hypertrophy of the retina, osteoma, epidermoid cysts
Neurofibromatosis type 1	Adrenocortical carcinoma, pheochromocytoma	*NF1*	Malignant peripheral nerve sheet tumor, café-au-lait spots, neurofibroma, optic glioma, Lisch nodule, skeletal abnormalities
ADRENAL ADENOMA AND CARCINOMA			
Carney complex	Primary pigmented nodular adrenal disease, adrenocortical carcinoma	*PRKAR1A*	Large-cell calcifying Sertoli cell tumors, thyroid adenoma, myxoma, somatotroph pituitary adenoma, lentigines
	Primary pigmented nodular adrenal disease	*PDE8B* or *PDE11A*	
Overexpression of steroidogenic factor-1	Adrenal adenoma, adrenocortical carcinoma	Somatic amplification of *NR5A1*	
McCune-Albright syndrome	Nodular hyperplasia, cortisol-secreting adenoma	Activating somatic mosaic variant of *GNAS*	Hyperfunction of bone (producing fibrous dysplasia), gonads, thyroid, and pituitary
	Cortisol-secreting adenomas	Activating somatic variant in *PRKACA*	
Somatic pathogenic variants	Adrenocortical carcinoma	*CDKN2A, CTNNB1, DAXX, MED12, MEN1, RB1,TERT, or TP53*	
PRIMARY ALDOSTERONISM			
Genetic causes of excess cortisol and aldosterone secretion	Hypertrophy of zona glomerulosa, aldosterone-producing adenoma	Germline or somatic activating variant in *KCNJ5*	
	Aldosterone-producing adenoma	Germline variants in *CYP11B2, CLCN2, or CACNA1H*	
	Aldosterone-producing adenoma	Germline and somatic activating variants in *CACNA1D*	
	Aldosterone-producing adenoma	Somatic variants in *ATP1A1, ATP2B3, CTNNB1, or APC*	
Pheochromocytoma			
von Hippel-Landau syndrome	Pheochromocytoma	*VHL*	Retinal and central nervous system hemangioblastomas, renal clear cell carcinomas
Multiple endocrine neoplasia syndromes *MEN2A* and *MEN2B*	Pheochromocytoma	*RET*	Medullary thyroid carcinoma and parathyroid tumors; type 2B also may include multiple mucosal neuromas and intestinal ganglioneuromas, a marfanoid habitus, and other skeletal abnormalities
	Pheochromocytoma, often malignant	*SDHB, SDHD, SDHC, SDHA, SDHAF2, MAX, TMEM127*	Paragangliomas, sometimes associated with gastrointestinal stromal tumors and/or pulmonary chondromas (Carney-Stratakis dyad or triad)

inactive adrenocortical adenomas includes pheochromocytomas (see Chapter 621), adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma (very rare in children). Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Not infrequently, a low level of autonomous cortisol secretion is detected that does not cause clinically apparent symptoms; this condition is sometimes referred to as *subclinical Cushing syndrome.*

TREATMENT

Functioning adrenocortical tumors should be removed surgically. There are no data on which to base a recommendation regarding nonfunctioning childhood incidentalomas; in adults, such tumors may be closely observed with imaging and repeat biochemical studies if smaller than 4 cm in diameter, but it is not certain that this is prudent in children. Adrenalectomy should be performed transperitoneally to minimize the risk of surgical rupture of the capsule and consequent dissemination of malignant cells. Some adrenocortical neoplasms are highly malignant and metastasize widely, but less malignant, encapsulated tumors (stage I-II) are often curable if they can be resected without tumor spillage. Postoperatively, patients should be closely monitored biochemically, with frequent determinations of adrenal androgen levels and imaging studies. Recurrent symptoms or biochemical abnormalities should prompt a careful search for metastatic disease. Metastases primarily involve liver, lung, and regional lymph nodes. Most metastatic recurrences appear within 1 year of tumor resection. Repeat surgical resection of metastatic lesions should be performed if possible and adjuvant therapy instituted. Radiation therapy has not been generally helpful. Antineoplastic agents such as cisplatin, doxorubicin and etoposide, ifosfamide and carboplatin, and 5-fluorouracil and leucovorin have had limited use in children, toxicity is high, and in adults with metastatic disease, progression-free survival is only a few months. Therapy with o,p′-DDD (mitotane), an adrenolytic agent, may relieve the symptoms of hypercortisolism or virilization in recurrent disease. In adults, treatment with mitotane plus local or regional treatment (surgery or radiotherapy) is associated with improved survival. Other agents that interfere with adrenal steroid synthesis, such as ketoconazole, aminoglutethimide, and metyrapone, may also relieve symptoms of steroid excess but do not improve survival.

A neoplasm of one adrenal gland may produce atrophy of the other because excessive production of cortisol by the tumor suppresses adrenocorticotropic hormone stimulation of the normal gland. Consequently, **adrenal insufficiency** may follow surgical removal of the tumor. This situation can be avoided by giving 10-25 mg of hydrocortisone every 6 hours, starting on the day of operation and gradually decreased postoperatively. Adequate quantities of water, sodium chloride, and glucose also must be provided.

617.2 Adrenal Incidentaloma

Perrin C. White

Adrenal masses are discovered with increasing frequency in patients undergoing abdominal imaging for reasons unrelated to the adrenal gland. There are no published data on the frequency of the occurrence of such tumors in childhood. They are likely to be infrequent, being found in approximately 7% of autopsies of persons older than age 70 years but in <1% of those younger than age 30 years. They are detected in 1–4% of abdominal CT examinations in adults.

The unexpected discovery of such a mass presents the clinician with a dilemma in terms of diagnostic steps to undertake and treatment interventions to recommend. The differential diagnosis of adrenal incidentaloma includes benign lesions such as cysts, hemorrhagic cysts, hematomas, and myelolipomas. These lesions can usually be identified on CT or MRI. If the nature of the lesion is not readily apparent, additional evaluation is required. Included in the differential diagnosis of lesions requiring additional evaluation are benign adenomas, pheochromocytomas, adrenocortical carcinoma, and metastasis from an extraadrenal primary carcinoma. Benign, hormonally inactive adrenocortical adenomas make up the majority of incidentalomas. Careful history, physical examination, and endocrine evaluation must be performed to seek evidence of autonomous cortisol, androgen, mineralocorticoid, or catecholamine secretion. Functional tumors require removal. If the adrenal mass is nonfunctional but is larger than 4-6 cm, recommendations are to proceed with surgical resection of the mass. Lesions of 3 cm or less should be followed clinically with periodic reimaging. Treatment must be individualized; nonsecreting adrenal incidentalomas may enlarge and become hyperfunctioning. Nuclear scan, and occasionally fine-needle aspiration, may be helpful in defining the mass.

617.3 Adrenal Calcification

Perrin C. White

Calcification within the adrenal glands may occur in a wide variety of situations, some serious and others of no obvious consequence. Adrenal calcifications are often detected as incidental findings in radiographic studies of the abdomen in infants and children. The physician may elicit a history of anoxia or trauma at birth. Hemorrhage into the adrenal gland at or immediately after birth is probably the most common factor that leads to subsequent calcification (see Fig. 615.1). Although it is advisable to assess the adrenocortical reserve of such patients, there is rarely any functional disorder.

Neuroblastomas, ganglioneuromas, adrenocortical carcinomas, pheochromocytomas, and cysts of the adrenal gland may be responsible for calcifications, particularly if hemorrhage has occurred within the tumor. Calcification in such lesions is almost always unilateral.

In the past, tuberculosis was a common cause of both calcification within the adrenals and Addison disease. Calcifications may also develop in the adrenal glands of children who recover from Waterhouse-Friderichsen syndrome; such patients are usually asymptomatic. Infants with Wolman disease, a rare lipid disorder caused by a deficiency of lysosomal acid lipase, have extensive bilateral calcifications of the adrenal glands (see Chapter 106.4).

Chapter 618

Virilizing and Feminizing Adrenal Tumors

Perrin C. White

Virilization is the most common presenting symptom in children with adrenocortical tumors (see Chapter 617), occurring in 50–80%. In males, the clinical picture is similar to that of simple virilizing congenital adrenal hyperplasia: accelerated growth velocity and muscle development, acne, penile enlargement, and the precocious development of pubic and axillary hair. In females, virilizing tumors of the adrenal gland cause masculinization of a previously normal female with clitoral enlargement, growth acceleration, acne, deepening of the voice, and premature pubic and axillary hair development.

Conversely, adrenal tumors can occasionally (<10%) secrete high levels of estrogens because of overexpression of CYP19 (aromatase). Gynecomastia in males or premature thelarche in females is often the initial manifestation. Growth and development may be otherwise normal, or concomitant virilization may occur.

In addition to virilization, 15–40% of children with adrenocortical tumors also have Cushing syndrome (see Chapter 619). Whereas isolated virilization occurs relatively frequently, children with adrenal tumors usually do not have Cushing syndrome alone.

LABORATORY FINDINGS

Serum levels of dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione are usually elevated, often markedly. Serum levels of testosterone are often increased, usually because of peripheral conversion of androstenedione, but infants with predominantly testosterone-secreting adenomas have been reported. Levels of estrone and estradiol are elevated in tumors from patients with feminizing signs. Urinary 17-ketosteroids (sex steroid metabolites) are also increased but are no longer routinely measured. Many adrenocortical tumors have a relative deficiency of 11β-hydroxylase activity and secrete increased amounts of deoxycorticosterone; these patients are hypertensive, and their tumors are often malignant.

DIFFERENTIAL DIAGNOSIS

For virilizing signs, the differential includes virilizing forms of adrenal hyperplasia (see Chapter 616) and factitious exposure to androgens, such as topical testosterone preparations. The differential diagnosis for adrenal tumors is discussed in Chapter 617.

TREATMENT

Functioning adrenocortical tumors should be removed surgically (see Chapter 617).

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Chapter 619

Cushing Syndrome

Perrin C. White

Cushing syndrome is the result of abnormally high blood levels of cortisol or other glucocorticoids. This can be iatrogenic or the result of endogenous cortisol secretion, a result of either an adrenal tumor or of hypersecretion of corticotropin (adrenocorticotropic hormone [ACTH]) by the pituitary (Cushing disease), or by a tumor (Table 619.1).

Table 619.1 Etiologic Classification of Adrenocortical Hyperfunction

EXCESS ANDROGEN
Congenital adrenal hyperplasia
21-Hydroxylase (CYP21A2) deficiency
11β-Hydroxylase (CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase (HSD3B2) defect (deficiency or dysregulation)
Tumor
EXCESS CORTISOL (CUSHING SYNDROME)
Bilateral adrenal hyperplasia
Adenoma
Hypersecretion of corticotropin (Cushing disease)
Ectopic secretion of corticotropin
Exogenous corticotropin
Adrenocortical nodular dysplasia
Pigmented nodular adrenocortical disease (Carney complex)
Tumor
McCune-Albright syndrome
EXCESS MINERALOCORTICOID
Primary hyperaldosteronism
Aldosterone-secreting adenoma
Bilateral micronodular adrenocortical hyperplasia
Glucocorticoid-suppressible aldosteronism
Tumor
Deoxycorticosterone excess
Congenital adrenal hyperplasia
• 11β-Hydroxylase (CYP11B1)
• 17α-Hydroxylase (CYP17A1)
Tumor
Apparent mineralocorticoid excess (deficiency of 11β-hydroxysteroid dehydrogenase type 2 [HSD11B2])
EXCESS ESTROGEN
Tumor

ETIOLOGY

The most common cause of Cushing syndrome is prolonged exogenous administration of glucocorticoid hormones, especially at the high doses used to treat lymphoproliferative disorders. This rarely represents a diagnostic challenge, but management of hyperglycemia, hypertension, weight gain, linear growth retardation, and osteoporosis often complicates therapy with corticosteroids.

Endogenous Cushing syndrome is most often caused in infants by a functioning adrenocortical tumor (see Chapter 617). Patients with these tumors often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone.

Although extremely rare in infants, the most common etiology of endogenous Cushing syndrome in children older than 7 years of age is **Cushing disease**, in which excessive ACTH secreted by a **pituitary adenoma** causes bilateral adrenal hyperplasia. Such adenomas are often too small to detect by imaging techniques and are termed **microadenomas**. They consist principally of chromophobe cells and frequently show positive immunostaining for ACTH and its precursor, proopiomelanocortin. Although most such tumors are sporadic, a small number occur in kindreds with **familial isolated pituitary adenoma syndrome**. This syndrome, which is caused by pathogenic variants in the *AIP* gene, accounts for perhaps 2% of pituitary adenomas; more commonly tumors with *AIP* variants secrete growth hormone or prolactin, and only rarely do they secrete ACTH. Similarly, multiple endocrine neoplasia type 1 (MEN1) patients who have pathogenic variants in the *MEN1* gene may develop pituitary tumors, but these are typically prolactinomas. Other genes have also been implicated (Fig. 619.1).

ACTH-dependent Cushing syndrome may also result from ectopic production of ACTH, although this is uncommon in children. Ectopic ACTH secretion in children is associated with islet cell carcinoma of the pancreas, neuroblastoma or ganglioneuroblastoma, hemangiopericytoma, Wilms tumor, and thymic carcinoid. Hypertension is more

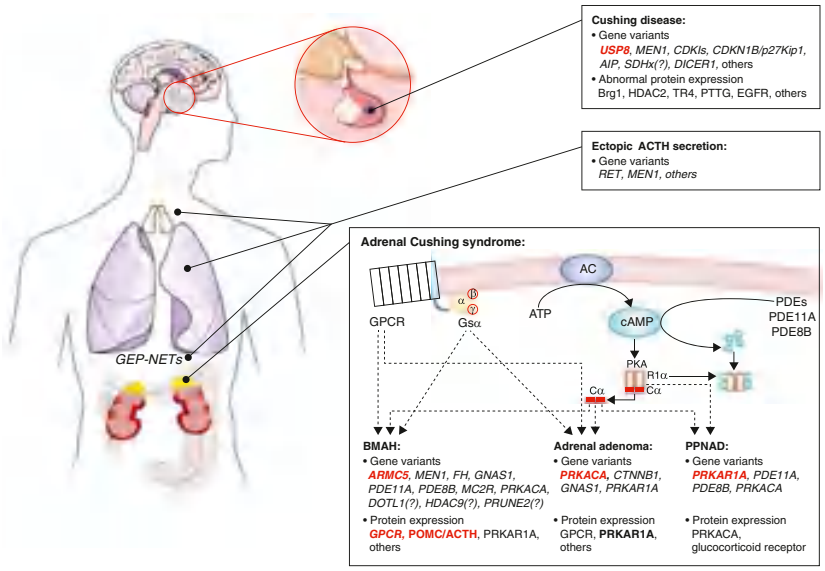

Fig. 619.1 Summary of genetic and molecular mechanisms implicated in Cushing syndrome. For each cause, the various pathogenic variants or abnormal protein expression believed to play a part in the pathophysiology is shown. The most frequent mechanisms are highlighted in red; the well-characterized mechanisms are highlighted in bold characters, and other potential mechanisms are in normal characters; a question mark shows an unconfirmed association or genetic predisposition. Please refer to the text for explanation of the various genetic defects under each diagnostic category. AC, Adenylate cyclase; ACTH, adrenocorticotropic hormone; BMAH, bilateral macronodular adrenal hyperplasia; Cα, catalytic subunit of PKA; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; GPCR, G protein–coupled receptor; PDEs, phosphodiesterases; PKA, protein kinase A; PPNAD, primary pigmented nodular adrenocortical disease; R1α, type 1α regulatory subunit of PKA. *(From Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. Lancet. 2015;386:913–927. Fig. 1.)*

common in ectopic ACTH syndrome than in other forms of Cushing syndrome, because very high cortisol levels may overwhelm type 2 11β-hydroxysteroid dehydrogenase in the kidney (see Chapter 615) and thus have an enhanced mineralocorticoid (salt-retaining) effect.

Several syndromes are associated with the development of multiple autonomously hyperfunctioning nodules of adrenocortical tissue, rather than single adenomas or carcinomas (see Chapter 617). In many cases they are caused by pathogenic variants in genes in the cyclic adenosine monophosphate (cAMP)–mediated signaling pathway by which ACTH normally regulates cortisol secretion. **Primary pigmented nodular adrenocortical disease (PPNAD)** is a distinctive form of ACTH-independent Cushing syndrome. It may occur as an isolated event or, more commonly, as a familial disorder with other manifestations. The adrenal glands are small and have characteristic multiple small (<4 mm in diameter), pigmented (black) nodules containing large cells with cytoplasm and lipofuscin; there is cortical atrophy between the nodules. This adrenal disorder occurs as a component of **Carney complex**, an autosomal dominant disorder also consisting of centrofacial lentigines and blue nevi; cardiac and cutaneous myxomas; pituitary, thyroid, and testicular tumors; and pigmented melanotic schwannomas. Carney complex is inherited in an autosomal dominant manner, although sporadic cases occur. Genetic loci for Carney complex have been mapped to the gene for the type 1α regulatory subunit of protein kinase A *(PRKAR1A)* on chromosome 17q22-24 and less frequently to chromosome 2p16. Patients with Carney complex and *PRKAR1A* variants generally develop PPNAD as adults, and those with the disorder mapping to chromosome 2 (and most sporadic cases) develop PPNAD less frequently and later. Conversely, children presenting with PPNAD as an isolated finding rarely have pathogenic variants in *PRKAR1A,* or subsequently develop other manifestations of Carney complex. Some patients with isolated PPNAD have pathogenic variants in *PDE8B* or *PDE11A* encoding different phosphodiesterase isozymes. In contrast, activating *somatic* variants have been documented in the PRKACA catalytic subunit of protein kinase A in cortisol-secreting adenomas.

ACTH-independent Cushing syndrome with nodular hyperplasia and adenoma formation occurs rarely in cases of **McCune-Albright syndrome**, with symptoms beginning in infancy or childhood. McCune-Albright syndrome is caused by *somatic* variants of *GNAS* encoding the G protein, $G_s\alpha$, through which the ACTH receptor (MCR2) normally signals. When the variant is present in adrenal tissue, cortisol and cell division are stimulated independently of ACTH. Other tissues in which activating mutations may occur are bone (producing fibrous dysplasia), gonads, thyroid, and pituitary. Clinical manifestations depend on which tissues are affected.

The genes causing nodular adrenocortical hyperplasia that have been identified mainly produce overactivity of the ACTH signaling pathway either by constitutively activating $G_s\alpha$ (McCune-Albright syndrome), by reducing the breakdown of cAMP and thus increasing its intracellular levels (variants of *PDE8B* or *PDE11A*), by disrupting the regulation of the cAMP-dependent enzyme protein kinase A (PRKAR1A mutations), or via microduplications encompassing *PRKACA*. Additionally, *ARMC5,* a tumor-suppressor gene, is abnormal in approximately 40% of cases of primary bilateral macronodular adrenocortical hyperplasia. Adrenocortical lesions, including diffuse hyperplasia, nodular hyperplasia, adenoma, and rarely carcinoma, may occur as part of MEN1 syndrome (see Chapter 617), an autosomal dominant disorder in which there is homozygous inactivation of the menin (MEN1) tumor-suppressor gene on chromosome 11q13.

CLINICAL MANIFESTATIONS

Signs of Cushing syndrome have been recognized in infants younger than 1 year of age. The disorder appears to be more severe and the clinical findings more dramatic in infants than in older children. The face is rounded, with prominent cheeks and a flushed appearance (moon facies). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently; accordingly, there may be hirsutism on the face and trunk, pubic hair, acne, deepening of the voice, and enlargement of the clitoris in females. Growth is impaired, with length falling below the third percentile, except when significant virilization produces normal or even accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature (Table 619.2). Gradual onset of obesity and deceleration or cessation of growth may be the only early manifestations. Older children most often have more severe obesity of the face and trunk compared with the extremities. However, obesity of the neck and upper back ("buffalo hump") is a nonspecific finding to which excessive importance should not be attached. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in females past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures.

Table 619.2	Presenting Signs and Symptoms of Cushing Syndrome in Children
Dermatologic	Facial plethora, acne, acanthosis nigricans, easy bruising, supratemporal and supraclavicular fat pads, moon facies, fungal infection, hirsutism, fine downy hair, violaceous striae (unusual in children <7 yr age)
Neurologic	Headaches
Cardiovascular	Hypertension, coagulopathy
Growth	Growth deceleration with concomitant weight gain, central obesity
Gonadal	Amenorrhea, virilization, gynecomastia
Other	Nephrolithiasis, bone fractures, impaired glucose tolerance, type 2 diabetes
Psychologic	Depression, anxiety, mood swings, irritability, fatigue

From Lodish MB, Keil MF, Stratakis CA. Cushing's syndrome in pediatrics: an update. *Endocrinol Metab Clin N Am.* 2018;47:451–462. Table 1.

LABORATORY FINDINGS

Cortisol levels in blood are normally highest at 8 AM and decrease to less than 50% of peak levels by midnight, except in infants and young children, in whom a diurnal rhythm is not always established. In patients with Cushing syndrome, this circadian rhythm is lost; *midnight cortisol levels >4.4 μg/dL strongly suggest the diagnosis*. It is difficult to obtain diurnal blood samples as part of an outpatient evaluation, but cortisol can be measured in *saliva samples,* which can be obtained at home at the appropriate times of day. Elevated nighttime salivary cortisol levels raise suspicion for Cushing syndrome.

Urinary excretion of free cortisol is increased. This is best measured in a 24-hour urine sample and is expressed as a ratio of micrograms of cortisol excreted per gram of creatinine. This ratio is independent of body size and completeness of the urine collection.

A single-dose dexamethasone suppression test is often helpful; a dose of 25-30 μg/kg (maximum: 2 mg) given at 11 PM results in a plasma cortisol level of less than 5 μg/dL at 8 AM the next morning in normal individuals but not in patients with Cushing syndrome. It is prudent to measure the dexamethasone level in the same blood sample to ensure the adequacy of dosing.

A glucose tolerance test is often abnormal but is of no diagnostic utility. Levels of serum electrolytes are usually normal, but potassium may be decreased, especially in patients with tumors that secrete ACTH ectopically.

After the diagnosis of Cushing syndrome has been established, it is necessary to determine whether it is caused by a pituitary adenoma, an ectopic ACTH-secreting tumor, or a cortisol-secreting adrenal tumor (Fig. 619.2). ACTH concentrations are usually suppressed in patients with cortisol-secreting tumors and are very high in patients with ectopic ACTH-secreting tumors, but may be normal in patients with ACTH-secreting pituitary adenomas. After an intravenous bolus of corticotropin-releasing hormone, patients with ACTH-dependent Cushing syndrome have an exaggerated ACTH and cortisol response, whereas those with adrenal tumors show no increase in ACTH and cortisol. The two-step dexamethasone suppression test consists of administration of dexamethasone, 30 and 120 μg/kg/24 hr in four divided doses, on consecutive days. In children with pituitary Cushing syndrome, the larger dose, but not the smaller dose, suppresses serum levels of cortisol. Typically, patients with ACTH-independent Cushing syndrome do not show suppressed cortisol levels with dexamethasone.

CT detects virtually all adrenal tumors larger than 1.5 cm in diameter. MRI may detect ACTH-secreting pituitary adenomas, but many are too small to be seen; the addition of gadolinium contrast increases the sensitivity of detection. Bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after corticotropin-releasing hormone administration may be required to localize the tumor when a pituitary adenoma is not visualized; this is not routinely available in many centers, and moreover may be of decreased specificity in children.

DIFFERENTIAL DIAGNOSIS

Cushing syndrome is frequently suspected in children with obesity, particularly when striae and hypertension are present. Children with simple obesity are usually tall, whereas those with Cushing syndrome are short or have a decelerating growth rate. Although urinary excretion of cortisol is often elevated in simple obesity, salivary nighttime levels of cortisol are usually normal, and cortisol secretion is normally suppressed by oral administration of low doses of dexamethasone.

Elevated levels of cortisol and ACTH without clinical evidence of Cushing syndrome occur in patients with generalized glucocorticoid resistance (see Chapter 615.4). Affected patients may be asymptomatic or exhibit hypertension, hypokalemia, and precocious pseudopuberty; these manifestations are caused by increased mineralocorticoid and adrenal androgen secretion in response to elevated ACTH levels. Mutations in the glucocorticoid receptor have been identified.

TREATMENT

Transsphenoidal pituitary microsurgery is the treatment of choice in *pituitary* Cushing disease in children. The overall success rate with follow-up of less than 10 years is 60–80%. Low postoperative serum or urinary cortisol concentrations predict long-term remission in most cases. Relapses are treated with reoperation or pituitary irradiation.

Cyproheptadine, a centrally acting serotonin antagonist that blocks ACTH release, has been used to treat Cushing disease in adults; remissions are usually not sustained after discontinuation of therapy. This agent is rarely used in children. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide, etomidate) have been used preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. Mifepristone, a glucocorticoid receptor antagonist, has been used in a limited number of cases. Pasireotide, a somatostatin analog, can inhibit ACTH secretion and is approved for use in adults with persistent disease after surgery or in whom surgery is contraindicated.

If a pituitary adenoma does not respond to treatment or if ACTH is secreted by an ectopic metastatic tumor, the adrenal glands may need to be removed. This can often be accomplished laparoscopically. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyperpigmentation; this condition is termed **Nelson syndrome**, which occurs in ~25% of adults who have undergone adrenalectomy for Cushing syndrome.

Several drugs that inhibit adrenocortical function may be an alternative to adrenalectomy. FDA-approved agents include mitotane (which is toxic to adrenocortical cells) and osilodrostat (a cortisol synthesis inhibitor); levoketoconazole, a stereoisomer of ketoconazole, inhibits several steroidogenic enzymes and is in an advanced stage of development.

Management of patients undergoing adrenalectomy requires adequate preoperative and postoperative replacement therapy with a corticosteroid. Tumors that produce corticosteroids usually lead to atrophy of the normal adrenal tissue, and replacement with cortisol (10 mg/m^2/24 hr in three divided doses after the immediate postoperative period) is required until there is recovery of the hypothalamic-pituitary-adrenal axis. Postoperative complications may include sepsis, pancreatitis, thrombosis, poor wound healing, and sudden collapse, particularly in infants with Cushing syndrome. Substantial catch-up growth, pubertal progress, and increased bone density occur, but bone density remains abnormal and adult height is often compromised. The management of adrenocortical tumors is discussed in Chapter 617.

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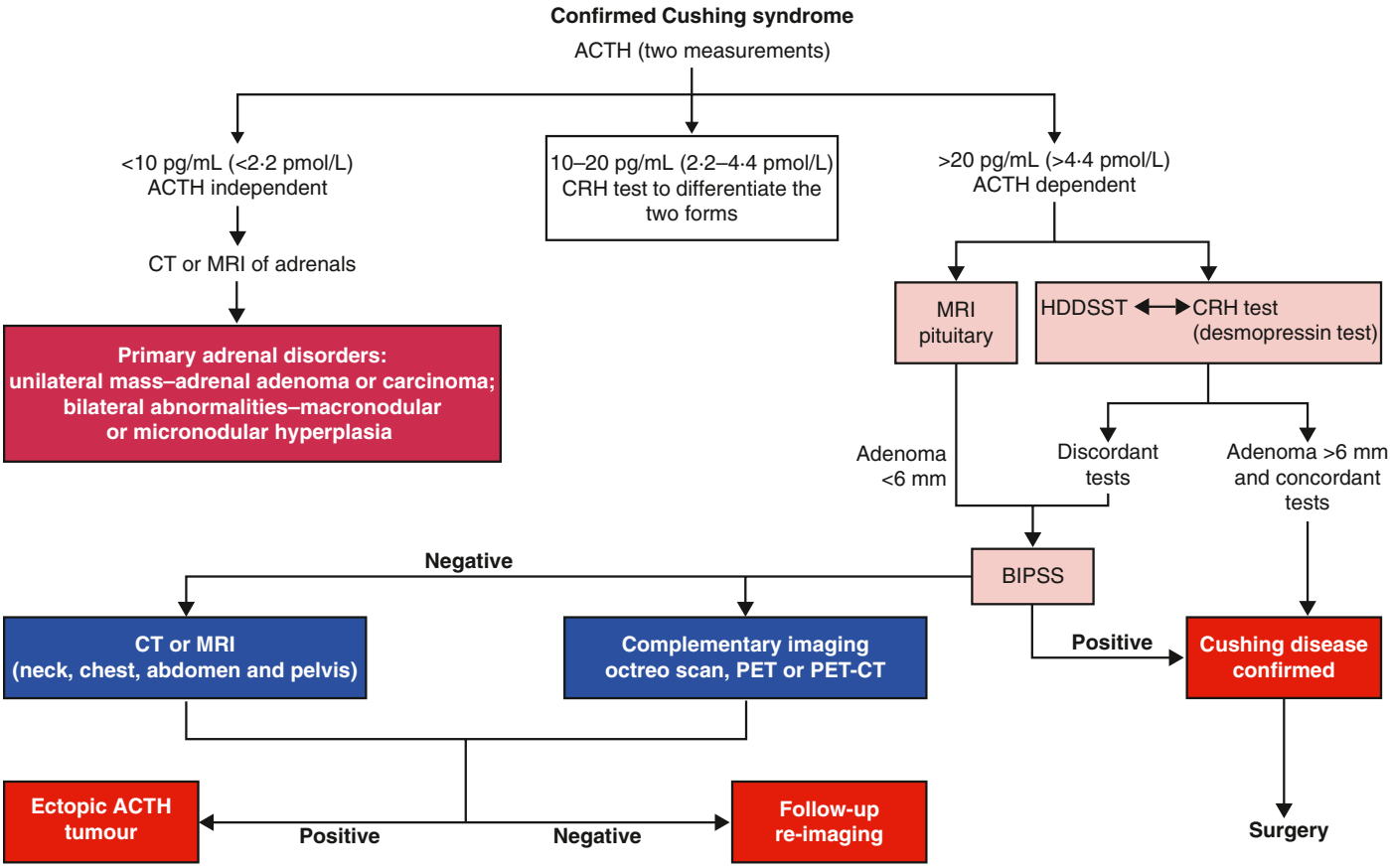

Fig. 619.2 Clinical decision-making algorithm for the differential diagnosis of confirmed Cushing syndrome of different causes. ACTH, Adrenocorticotropic hormone; BIPSS, bilateral inferior petrosal sinus sampling; CRH, corticotropin-releasing hormone; HDDSST, high-dose dexamethasone suppression test. *(From Lacroix A, Feelders RA, Stratakis CA, et al. Cushing's syndrome. Lancet. 2015;386:913–927. Fig. 3.)*

Chapter 620

Primary Aldosteronism

Perrin C. White

Primary aldosteronism encompasses disorders caused by excessive aldosterone secretion independent of the renin-angiotensin system. These disorders are characterized by hypertension, hypokalemia, and suppression of the renin-angiotensin system.

Aldosterone-secreting adenomas are unilateral and have been reported in children as young as 3.5 years of age. They are rarely malignant. Bilateral micronodular adrenocortical hyperplasia tends to occur in older ages. Primary aldosteronism caused by unilateral adrenal hyperplasia may also occur. Glucocorticoid-suppressible hyperaldosteronism is discussed in Chapter 616.8.

EPIDEMIOLOGY

These conditions are thought to be rare in children, but they may account for 5–10% of cases of hypertension in adults. Although usually sporadic, kindreds with several affected members have been reported. Genetic linkage to chromosome 7p22 was reported in some kindreds, but the involved gene has not yet been identified. Pathogenic variants in *KCNJ5* on chromosome 11q24 (encoding G protein–gated inward rectifier potassium channel 4) have been identified in several kindreds; these variants (*G151R* and *G151E*) altered channel selectivity, producing increased Na^+ conductance and membrane depolarization, which increase aldosterone production and proliferation of adrenal glomerulosa cells. Such variants have been identified in a subset of sporadic aldosterone-producing adenomas. Germline variants have also been reported in *CYP11B2* (encoding aldosterone synthase), *CLCN2* (encoding voltage-gated chloride channel ClC-2), and *CACNA1H* (encoding a subunit of the T-type voltage-gated calcium channel CaV3.2). Germline and somatic variants have also been reported in *CACNA1D* encoding a voltage-sensitive calcium channel and *somatic* variants in *ATP1A1* and *ATP2B3,* respectively, encoding sodium-potassium and calcium ATPases. Most aldosterone-producing adenomas have pathogenic variants that activate the Wnt/β-catenin signaling pathway, either in β-catenin *(CTNNB1)* itself, or in *APC,* which regulates this pathway.

CLINICAL MANIFESTATIONS

Some affected children have no symptoms, the diagnosis being established after incidental discovery of moderate hypertension. Others have severe hypertension (up to 240/150 mm Hg), with headache, dizziness, and visual disturbances. If present, chronic hypokalemia may lead to polyuria, nocturia, enuresis, and polydipsia. Muscle weakness and discomfort, tetany, intermittent paralysis, fatigue, and growth failure affect children with severe hypokalemia.

LABORATORY FINDINGS

Hypokalemia occurs frequently. Serum pH and carbon dioxide and sodium concentrations may be elevated and serum chloride and magnesium levels decreased. Serum levels of calcium are normal, even in children who manifest tetany. The urine is neutral or alkaline, and urinary potassium excretion is high. Plasma levels of aldosterone may be normal or elevated. Aldosterone concentrations in 24-hour urine collections are always increased. Plasma levels of renin are persistently low.

The diagnostic test of choice for primary aldosteronism is controversial. Both renin and aldosterone levels may vary by time of day, posture, and sodium intake, making it difficult to establish consistent reference ranges. It is desirable to establish a consistent sampling protocol, for example, at midmorning after the patient has been sitting for 15 minutes. If possible, antihypertensive drugs or other medications that can affect aldosterone or renin secretion should be avoided for several weeks before testing, including diuretics, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine, and nonsteroidal anti-inflammatory agents. Patients taking these agents may need to be changed to α-adrenergic blockers or calcium channel blockers that have smaller effects on the biochemical measurements. The ratio of plasma aldosterone concentration to renin activity is always high, and this represents a cost-effective screening test for primary aldosteronism. Aldosterone does not decrease with administration of saline solution or fludrocortisone, and renin does not respond to salt and fluid restriction. Urinary and plasma levels of 18-oxocortisol and 18-hydroxycortisol may be increased but not to the extent seen in glucocorticoid-suppressible hyperaldosteronism.

DIFFERENTIAL DIAGNOSIS

Primary aldosteronism should be distinguished from glucocorticoid-remediable aldosteronism (also termed **glucocorticoid-suppressible hyperaldosteronism**, see Chapter 616.8), which is specifically treated with glucocorticoids. An autosomal dominant pattern of inheritance should raise suspicion for the latter disorder. **Glucocorticoid-remediable aldosteronism** is diagnosed by dexamethasone suppression tests or by specific genetic testing.

Patients with primary aldosteronism should be evaluated by computed tomography (CT). It does not reliably distinguish aldosterone-producing adenomas, which tend to be small, from bilateral hyperplasia, but it can exclude the presence of large tumors that might otherwise raise concern for adrenocortical carcinomas. Adrenal venous sampling can accurately determine if excess aldosterone secretion is originating in one gland or both, but it is invasive and may not be available in all centers. Positron emission tomography with ^{11}C-metomidate is a non-invasive alternative.

TREATMENT

The treatment of an aldosterone-producing adenoma is laparoscopic adrenalectomy; successful enucleation of aldosterone-producing adenomas has also been reported. Hyperaldosteronism caused by bilateral adrenal hyperplasia is treated with the mineralocorticoid antagonist spironolactone (1-3 mg/kg/day to a maximum of 100 mg/day) or eplerenone (25-100 mg/day in 2 divided doses), often normalizing blood pressure and serum potassium levels. There is greater experience with spironolactone, but this agent has antiandrogenic properties that may be unacceptable in pubertal males. Eplerenone is a more specific antimineralocorticoid that is safe in children, but there is little specific experience with primary aldosteronism in the pediatric age-group. As an alternative, an epithelial sodium channel blocker, such as amiloride, may be used, with other antihypertensive agents added as necessary. In patients whose condition cannot be controlled medically, unilateral adrenalectomy may be considered.

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Chapter 621

Pheochromocytoma

Perrin C. White

See also Chapter 555.4.

Pheochromocytomas are catecholamine-secreting tumors arising from chromaffin cells. The most common site of origin (approximately 90%) is the adrenal medulla; however, tumors may develop anywhere along the abdominal sympathetic chain and are likely to be located near the aorta at the level of the inferior mesenteric artery or at its bifurcation. They also appear in the periadrenal area, urinary bladder or ureteral walls, thoracic cavity, and cervical region. Ten percent occur in children, presenting most frequently between 6 and 14 years of age. Tumors vary from 1 to 10 cm in diameter; they are found more often on the right side than on the left. In more than 20% of affected children, the adrenal tumors are bilateral; in 30–40% of children, tumors are found in both adrenal and extraadrenal areas or only in an extraadrenal area.

Most pheochromocytomas are associated with germline pathogenic variants (see Table 555.2 in Chapter 555.4). They may be associated with genetic syndromes such as **von Hippel-Lindau disease, multiple endocrine neoplasia** (MEN) syndromes MEN2A and MEN2B, and less often, in association with **neurofibromatosis (type 1)** or **tuberous sclerosis**. The classic features of von Hippel-Landau syndrome, which occurs in 1 in 36,000 individuals, include retinal and central nervous system hemangioblastomas, renal clear cell carcinomas, and pheochromocytomas, but kindreds differ in their propensity to develop pheochromocytoma; in some kindreds, pheochromocytoma is the only tumor to develop. Germline variants in the *VHL* tumor-suppressor gene on chromosome 3p25-26 have been identified in patients with this syndrome. Variants of the *RET* protooncogene on chromosome 10q11.2 have been found in families with MEN2A and MEN2B. Patients with MEN2 are at risk of developing medullary thyroid carcinoma and parathyroid tumors; approximately 50% develop pheochromocytoma, with patients carrying variants at codon 634 of the *RET* gene being at particularly high risk. Variants are present in the *NF1* gene on chromosome 17q11.2 in neurofibromatosis type 1 patients (see Table 555.2 in Chapter 555.4).

Pheochromocytomas may occur in kindreds along with paragangliomas, particularly at sites in the head and neck. Such families typically carry pathogenic variants in *SDHB, SDHD,* and rarely the *SDHC* encoding subunits of the mitochondrial enzyme succinate dehydrogenase. Approximately 50% of tumors with *SDHB* variants are malignant. The *VHL* and the various *SDH* gene products participate in the *pseudohypoxia* signaling pathway (pseudohypoxia is a decrease in the ratio of the cytosolic oxidized to reduced forms of nicotinamide adenine dinucleotide [NAD (+)/NADH]) and thus represent a common pathogenetic pathway. In rare cases, individuals with germline variants in SDH genes develop pheochromocytomas and/or paragangliomas along with pituitary adenomas, which is termed the **3P association (3Pas)**.

Pheochromocytomas and paragangliomas can occur in association with **gastrointestinal stromal tumors** (GISTs; the association is termed the *Carney-Stratakis dyad*) and/or pulmonary chondromas (Carney-Stratakis triad) and adrenocortical tumors. These associations have heterogenous genetic etiologies but often involve variants in SDH genes.

CLINICAL MANIFESTATIONS

Pheochromocytomas detected by surveillance of patients who are known carriers of variants in tumor-suppressor genes may be asymptomatic. Particularly in adults, some are diagnosed on abdominal CT or MRI performed for another purpose (see Chapter 617). Otherwise, patients are detected owing to hypertension, which results from excessive secretion of metanephrines, epinephrine and norepinephrine. All

patients have hypertension at some point. Paroxysmal hypertension should particularly suggest pheochromocytoma as a diagnostic possibility, but in contrast to adults, the hypertension in children is more often sustained rather than paroxysmal. When there are paroxysms of hypertension, the attacks are usually infrequent at first, but become more frequent and eventually give way to a continuous hypertensive state. Between attacks of hypertension, the patient may be free of symptoms. During attacks, the patient complains of headache, palpitations, abdominal pain, and dizziness; pallor, vomiting, and sweating also occur. Seizures and other manifestations of hypertensive encephalopathy may occur. In severe cases, precordial pains radiate into the arms; pulmonary edema and cardiac and hepatic enlargement may develop. Symptoms may be exacerbated by exercise or with the use of nonprescription medications containing stimulants such as pseudoephedrine. Patients have a good appetite but because of the hypermetabolic state may not gain weight, and severe cachexia may develop. Polyuria and polydipsia can be sufficiently severe to suggest diabetes insipidus. Growth failure may be striking. The blood pressure may range from 180 to 260 mm Hg systolic and from 120 to 210 mm Hg diastolic, and the heart may be enlarged. Ophthalmoscopic examination may reveal papilledema, hemorrhages, exudate, and arterial constriction. The differential diagnosis is noted in Table 555.3.

LABORATORY FINDINGS

The urine may contain protein, a few casts, and occasionally glucose. Gross hematuria suggests that the tumor is in the bladder wall. Polycythemia is occasionally observed.

Pheochromocytomas produce norepinephrine and epinephrine. Normally, norepinephrine in plasma is derived from both the adrenal gland and adrenergic nerve endings, whereas epinephrine is derived primarily from the adrenal gland. In contrast to adults with pheochromocytoma in whom both norepinephrine and epinephrine are elevated, children with pheochromocytoma predominantly excrete norepinephrine in the urine (see Fig. 614.3 in Chapter 614). Daily urinary excretion of these compounds by unaffected children increases with age. Although urinary excretion of vanillylmandelic acid (3-methoxy-4-hydroxymandelic acid), the major metabolite of epinephrine and norepinephrine, is increased, vanilla-containing foods and fruits can produce falsely elevated levels of this compound, which therefore is no longer routinely measured.

Elevated levels of free catecholamines and metanephrines can also be detected in plasma. The consensus is to measure plasma free metanephrines and urinary fractionated metanephrines. The patient should be instructed to abstain from caffeinated drinks and to avoid acetaminophen, which can interfere with plasma normetanephrine immunoassays. If possible, the blood sample should be obtained from an indwelling intravenous catheter to avoid acute stress associated with venipuncture.

Most tumors in the area of the adrenal gland are readily localized by CT or MRI (Fig. 621.1), but extraadrenal tumors may be difficult to detect. ^{123}I or ^{131}I-metaiodobenzylguanidine (MIBG) is taken up by chromaffin tissue anywhere in the body and is useful for localizing small tumors. PET-CT with ^{18}F-fluorodeoxyglucose or ^{68}Ga-DOTA(0)-Tyr(3)-octreotate (a somatostatin receptor ligand) is highly sensitive and a more favored imaging approach (Fig. 621.2 and Fig. 555.2) for difficult-to-localize tumors. Venous catheterization with sampling of blood at different levels for catecholamine determinations is now only rarely necessary for localizing the tumor.

DIFFERENTIAL DIAGNOSIS

Various causes of hypertension in children must be considered, such as renal or renovascular disease; coarctation of the aorta; hyperthyroidism; Cushing syndrome; deficiencies of 11β-hydroxylase, 17α-hydroxylase, or 11β-hydroxysteroid dehydrogenase (type 2 isozyme); primary aldosteronism; adrenocortical tumors; and, rarely, essential hypertension (see Chapter 494). A nonfunctioning kidney may result from compression of a ureter or of a renal artery by a pheochromocytoma. Paroxysmal hypertension may be associated with porphyria or familial dysautonomia. Cerebral disorders and hyperthyroidism must also be considered in the differential diagnosis. Hypertension in patients with neurofibromatosis may be caused by renal vascular involvement or by concurrent pheochromocytoma.

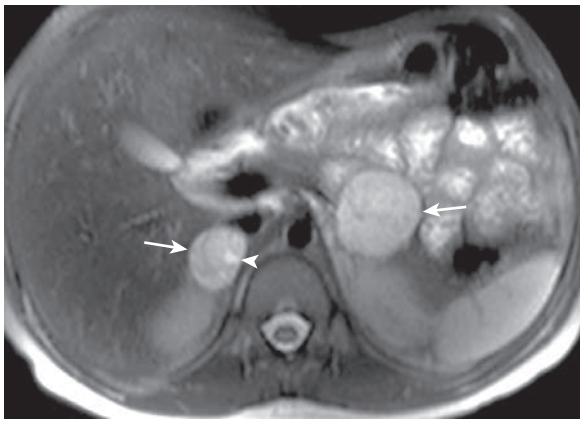

Fig. 621.1 Bilateral pheochromocytoma in an 11-yr-old child with von Hippel-Lindau disease and arterial hypertension. An axial fat-suppressed T2 weighted magnetic resonance image shows bilateral adrenal masses *(arrows)*, larger on the left. The masses are hyperintense with small cystic change on the right medially. *(From Navarro OM, Daneman A. Acquired conditions. In: Coley B, ed. Caffey's Pediatric Diagnostic Imaging, 12th ed. Philadelphia: Elsevier; 2013: Fig. 123.9.)*

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma frequently produce catecholamines, but urinary levels of most catecholamines are higher in patients with pheochromocytoma, although levels of dopamine and homovanillic acid are usually higher in neuroblastoma. Secreting neuroendocrine tumors often produce hypertension, excessive sweating, flushing, pallor, rash, polyuria, and polydipsia. Chronic secretory diarrhea may be associated with these tumors, particularly with ganglioneuroma.

TREATMENT

These tumors must be removed surgically, but careful preoperative, intraoperative, and postoperative management is essential. Manipulation and excision of these tumors result in marked increases in catecholamine secretion that increase blood pressure and heart rate. Therefore preoperative α- *and β-adrenergic blockade* are required. Whereas phenoxybenzamine has been most often used, it may not be covered by insurance, and selective α_1-blockers, such as doxazosin, as well as calcium channel blockers like amlodipine, have also been used. Because these tumors are often multiple in children, a thorough transabdominal exploration of all the usual sites offers the best opportunity to find them all. Appropriate choice of anesthesia and *expansion of blood volume with appropriate fluids before and during surgery* are critical to avoid a precipitous drop in blood pressure during operation or within 48 hours postoperatively. Surveillance must continue postoperatively.

Because bilateral and recurrent pheochromocytomas occur frequently, some have advocated for adrenal cortex–sparing surgery to reduce the probability of causing Addison disease. However, this approach increases the risk of tumor recurrence.

Although these tumors often appear malignant histologically, the only accurate indicators of malignancy are the presence of metastatic disease or local invasiveness that precludes complete resection, or both. Approximately 10% of all adrenal pheochromocytomas are malignant. Such tumors are rare in childhood; pediatric malignant pheochromocytomas occur more frequently in extraadrenal sites and are often associated with pathogenic variants in *SDHB* encoding a subunit of succinate dehydrogenase. Prolonged follow-up is indicated, particularly in patients with germline mutations in risk loci, because functioning tumors at other sites may be manifested many years after the initial operation. Examination of relatives of affected patients may reveal other individuals harboring unsuspected tumors that may be asymptomatic.

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Fig. 621.2 Paraganglioma in a 30-yr-old woman who presented with refractory hypertension. **A,** Axial T2-weighted MRI shows homogeneously T2-hyperintense left periaortic mass just above the level of the aortic bifurcation (Zuckerkandl organ), illustrating the "light bulb" T2-bright appearance of pheochromocytomas and paragangliomas. **B,** Axial contrast-enhanced T1-weighted MRI demonstrates heterogeneous enhancement within the mass. **C,** ^{123}I-MIBG fused SPECT/CT axial image shows diffuse uptake within the tumor, compatible with paraganglioma. *(From Ho LM. Adrenal glands. In: Haaga JR, Boll DT, eds. CT and MRI of the Whole Body, 6th ed. Philadelphia: Elsevier; 2017: Fig. 53-18.)*

Section 5

Disorders of the Gonads

Chapter 622

Development and Function of the Gonads

Patricia A. Donohoue

GENETIC CONTROL OF EMBRYONIC GONADAL DIFFERENTIATION

Gonadal differentiation is a complex, multistep process that requires the sequential action and interaction of multiple gene products. Early in the first trimester, the undifferentiated, bipotential fetal gonad begins as a thickening of the urogenital ridge, near the developing kidney and adrenal cortex. At 6 weeks of gestation, the gonad contains germ cells, stromal cells that will become Leydig cells in the testes or theca, interstitial, or hilar cells in the ovaries, and supporting cells that will develop into Sertoli cells in the testes or granulosa cells in the ovaries. In males, the *SRY* gene (**s**ex-determining **r**egion on the **Y** chromosome) is transiently expressed, followed by a sequential upregulation of a number of testis-specific genes. In the absence of *SRY,* the bipotential gonad will be able to develop into an ovary. Ovarian development is also characterized by expression of ovary-specific genes during the same period. One such gene is *R-spondin1*. During the gestation period of 6-9 weeks, a number of genes are upregulated to the same degree in both the testis and the ovary, including *WNT4* and *CTNNB1*.

A chromosome complement of 46,XX is necessary for the development of normal ovaries. Both the long and short arms of the X chromosome contain genes for normal ovarian development. The DSS (**d**osage **s**ensitive/**s**ex reversal) locus associated with the *DAX1* (**D**SS **a**drenal hypoplasia on the **X** chromosome) gene, which is defective in 46,XY patients with X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism, is a member of the nuclear receptor superfamily and acts as a repressor of male gene expression. The *DAX1* gene product acts by binding to a related nuclear receptor SF-1 (**s**teroidogenic **f**actor-1, also known as *NR5A1*). In vitro, the signaling gene *WNT4* stimulates expression of *DAX1,* resulting in the suppression of androgen synthesis in XX females. The WNTs are ligands that activate receptor-mediated signal transduction pathways and are involved in modulating gene expression as well as cell behavior, adhesion, and polarity. Once developed, the ovary requires FAX12 to preserve its differentiation and stability. A key to its role in humans was elucidated by a loss-of-function pathogenic variant of *WNT4* that was found in an 18-year-old 46,XX woman. She had an absence of müllerian-derived structures (uterus and fallopian tubes), unilateral renal agenesis, and clinical signs of androgen excess.

Pathogenic variants of the Wilms tumor 1 *(WT1)* gene may also affect sex differentiation. *WT1* pathogenic variants are associated with **Denys-Drash syndrome** (early-onset renal failure, abnormal external genitalia in genetic males, and Wilms tumor). Haploinsufficiency of a three–amino acid (KTS) form of *WT1* has been implicated in the gonadal dysgenesis of patients with **Fraser syndrome** (late-onset progressive glomerulopathy and 46,XY gonadal dysgenesis). Variants in the *FOXL2* and *SF-1* genes are associated with ovarian failure. Pathogenic variants of the *R-spondin1* gene has been described in individuals with 46,XX disorder of sex development (DSD). Other autosomal genes also play a role in normal ovarian organogenesis and testicular development. Several conditions of gonadal dysgenesis are associated with gross abnormalities of both autosomes and sex chromosomes. A deletion affecting the short arm of the X chromosome produces the typical somatic anomalies of Turner syndrome.

Development of the testis requires the short arm of the Y chromosome; this contains the *SRY* gene, which is required for testicular differentiation. During male meiosis, the Y chromosome must segregate from the X chromosome so that both X and Y chromosomes do not occur in the same spermatozoa. The major portion of the Y chromosome is composed of Y-specific sequences that do not pair with the X chromosome. However, a minor portion of the Y chromosome shares sequences with the X chromosome, and pairing does occur in this region. The genes and sequences in this area recombine between the sex chromosomes, behaving like autosomal genes. Therefore the term *pseudoautosomal region* is used to describe this portion of the chromosome, and the term indicates genetic behavior of these genes relative to pairing and recombinational events. The *SRY* gene is localized to the 35-kb portion proximal to the pseudoautosomal region of the Y chromosome. It contains a high-mobility group (HMG) nonhistone protein (HMG box), supporting SRY's role as a transcriptional regulator of other genes involved in sex differentiation. The gonadal ridge forms at around 33 days of gestation. SRY is detected at 41 days, peaks at 44 days when testis cords are first visible, and persists into adulthood.

Other genes that are found on autosomes are important in this process. *SOX9,* an *SRY*-related gene containing a region homologous with the HMG box 9 of *SRY,* is located on chromosome 17. Pathogenic variants of this gene result in **XY sex reversal** and **campomelic dysplasia**. *SF-1 (NR5A1)* on chromosome 9q33 is important

in adrenal and gonadal development, as well as the development of gonadotropin-releasing hormone–secreting neurons in the hypothalamus. *WTI,* especially the KST isoform on chromosome 11p13, is needed for early gonadal, adrenal, and renal development. Fibroblast growth factor-9, GATA-4, XH-2, and SOY9 are also important.

When genetic recombination events on sex chromosomes extend beyond the pseudoautosomal region, X- and Y-specific DNA may be transferred between the chromosomes. Such aberrant recombinations result in X chromosomes carrying *SRY,* resulting in **XX males**, or Y chromosomes that have lost *SRY,* resulting in **XY females**. SRY acts as a transcriptional regulator to increase cellular proliferation, attract interstitial cells from adjacent mesonephros into the genital ridge, and stimulate testicular Sertoli cell differentiation. Sertoli cells act as an organizer of steroidogenic and germ cell lines and produce **antimüllerian hormone** (AMH) that causes the female duct system to regress. Table 622.1 lists additional genes involved in sex development that, if abnormal, result in DSD.

Table 622.1 Pathogenic Genes in Disorders of Sex Development

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
46,XY DSD								
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: SINGLE-GENE DISORDERS								
WT1	TF	607102	11p13	AD	Dysgenetic testis	±	Female or ambiguous	Wilms tumor, renal abnormalities, gonadal tumors (WAGR, Denys-Drash, and Frasier syndromes)
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis; ovotestis	±	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis; mothers who carry SF-1 mutation have premature ovarian insufficiency
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	±	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	±	Female or ambiguous	Camptomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)
DHH	Signaling molecule	605423	12q13.1	AR	Dysgenetic testis	±	Female	The severe phenotype of one patient included minifascicular neuropathy; other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodeling)	300032	Xq13.3	X	Dysgenetic testis	–	Female, ambiguous or male	α-Thalassemia, intellectual disability
ARX	TF	3003382	Xp22.13	X	Dysgenetic testis	–	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Gata4	TF	615542	8p23.1	AD in XY subjects	Dysgenetic testes	_	Ambiguous	Congenital heart disease
DISORDERS OF GONADAL (TESTICULAR) DEVELOPMENT: CHROMOSOMAL CHANGES INVOLVING KEY CANDIDATE GENES								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	±	Female or ambiguous	Intellectual disability
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	±	Female or ambiguous	
WNT4	Signaling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Intellectual disability

Table 622.1 Pathogenic Genes in Disorders of Sex Development—cont'd

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
DISORDERS IN HORMONE SYNTHESIS OR ACTION								
LHGCR	G-protein receptor	152790	2p21	AR	Testis	–	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	–	Variable	Smith-Lemli-Opitz syndrome: coarse facies, 2nd-3rd toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
StAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	–	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	–	Female or ambiguous	Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	–	Ambiguous	CAH, primary adrenal failure, partial androgenization caused by ↑ DHEA
CYP17	Enzyme	202110	10q24.3	AR	Testis	–	Female ambiguous or micropenis	CAH, hypertension caused by ↑ corticosterone and 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	–	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley-Bixler skeletal dysplasia
HSD17B3	Enzyme	605573	9q22	AR	Testis	–	Female or ambiguous	Partial androgenization at puberty, ↑ androstenedione: testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	–	Ambiguous or micropenis	Partial androgenization at puberty, ↑ testosterone:DHT ratio
AKR1C4	Enzyme	600451	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20 lyase deficiency; dose effect with *AKR1C2* variant is possible
AKR1C2	Enzyme	600450	10p15.1	Unclear	Testis	–	Ambiguous or micropenis	DHT deficiency in patients once thought to have 17,20 lyase deficiency; dose effect with *AKR1C2* variant is possible
AMH	Signaling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent müllerian duct syndrome (PMDS); male
AHM receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	–	Normal male	External genitalia, bilateral cryptorchidism

Continued

Table 622.1 Pathogenic Genes in Disorders of Sex Development—cont'd

GENE	PROTEIN	OMIM #	LOCUS	INHERITANCE	GONAD	MÜLLERIAN STRUCTURES	EXTERNAL GENITALIA	ASSOCIATED FEATURES/VARIANT PHENOTYPES
Androgen receptor	Nuclear receptor TF	3130700	Xq11-12	X	Testis	–	Female, ambiguous, micropenis, or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility
46,XX DSD								
DISORDERS OF GONADAL (OVARIAN) DEVELOPMENT								
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguous	
R-spondin1	TF	610644	1p34.3	AR	Ovotestis	±	Male or ambiguous	Palmoplantar hyperkeratosis and certain malignancies
ANDROGEN EXCESS								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenization caused by ↑ DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt-losing forms associated with adrenal failure to simple virilizing forms with compensated adrenal function, ↑ 17-hydroxyprogesterone
CYP11B1	Enzyme	20210	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension caused by ↑ 11-deoxycortisol and 11-deoxycorticosterone
POR (P450 oxidoreductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; associated with Antley-Bixler skeletal dysplasia
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal virilization during pregnancy, absent breast development at puberty, except in partial cases
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (patient heterozygous for a variant in *CYP21*)

ACTH, Adrenocorticotropin; AD, autosomal dominant (often de novo mutation); AR, autosomal recessive; CAH, congenital adrenal hyperplasia; ND, not determined; *OMIM #*, Online Mendelian Inheritance in Man number; TF, transcription factor; WAGR, Wilms, aniridia, genital anomalies, and retardation; X, X-chromosomal; Y, Y-chromosomal. Chromosomal rearrangements likely to include key genes are included.

From Lee PA, Houk CP, Ahmed SF, et al. International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. Pediatrics. 2006;118:e488–e500; with additional data from Baxter RM, Arboleda VA, Lee H, et al. Exome sequencing for the diagnosis of 46,XY disorders of sex development. J Clin Endocrinol Metab. 2015;100:e333–e344; and Lourenco D, Brauner R, Rybczynska M, et al. Loss-of-function mutation in *GATA4* causes anomalies of human testicular development. PNAS. 2011;108:1597–1602.

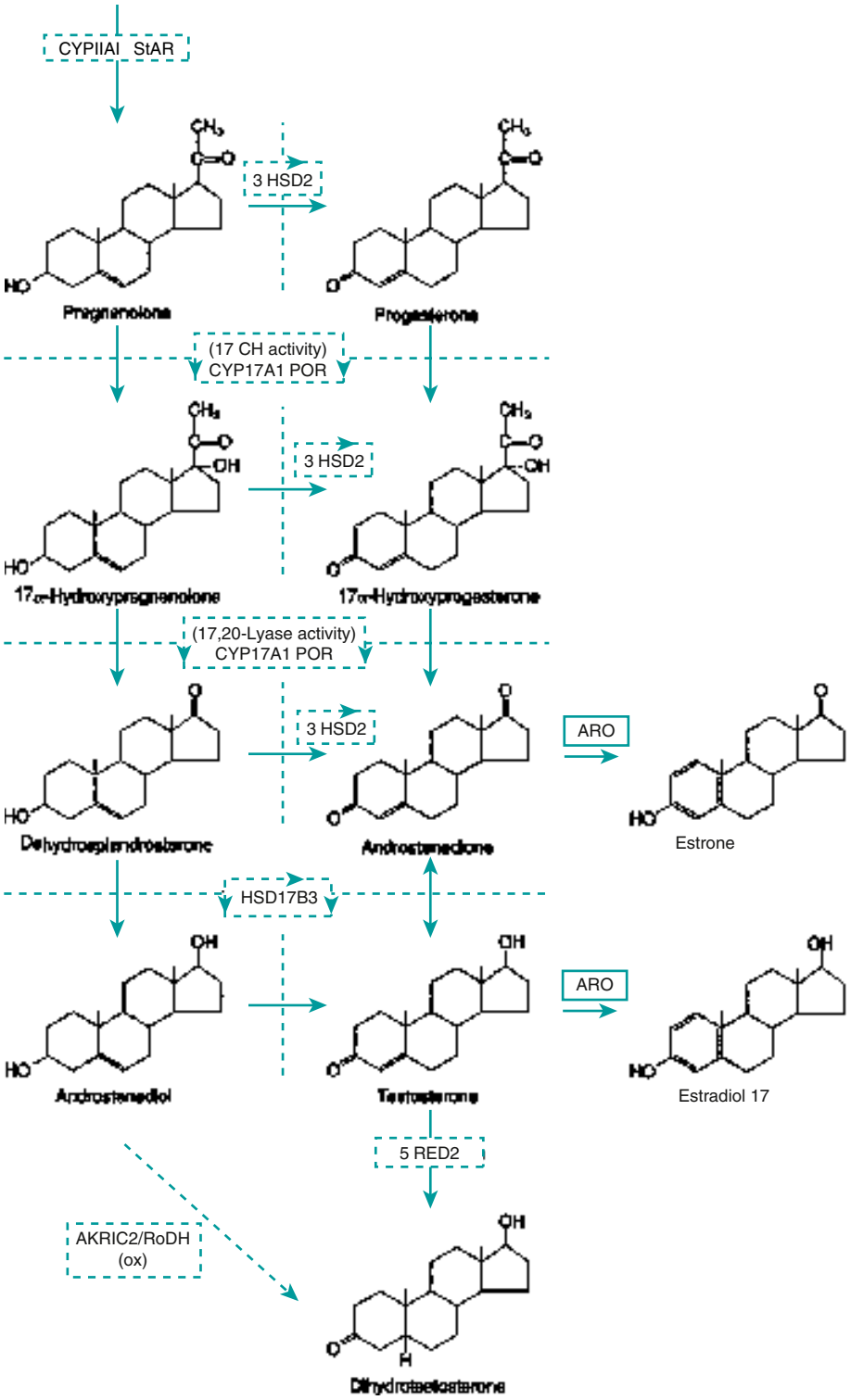

Fig. 622.1 Biosynthesis of sex steroids. *Dashed lines* indicate enzymatic defects associated with 46,XY disorders of sex development. 3β-HSD2, 3β-hydroxysteroid dehydrogenase type 2; 5RED2, 5α-reductase type 2; AKR1C2/RoDH (Ox), one of the enzymes in the alternative androgen biosynthetic pathway; ARO, aromatase; CYP17A1, the enzyme that catalyzes both 17α-hydroxylase (17-OH) and 17,20-lyase activities; HSD17B3, the enzyme that catalyzes the 17-ketoreductase reaction; POR, P450 oxidoreductase; StAR, steroidogenic acute regulatory protein.

Development of the ovary was once thought to be a passive process in the absence of SRY. Although the morphologic changes in the developing ovary are less marked than in the testis, sequentially expressed genes and pathways are required for complete ovarian development along with maintenance of ovarian integrity postnatally. One of these genes is *R-spondin1,* which if abnormal can result in testicular or ovotesticular development in 46,XX individuals. Some peptides in the Wnt-signaling pathway may antagonize testicular development, thus allowing for ovarian differentiation. This effect may be mediated by β-catenin signaling, which is required for suppressing testicular features. Once developed, the ovary requires FAX12 to preserve its differentiation and stability.

FUNCTION OF THE TESTES

Levels of placental chorionic gonadotropin peak at 8-12 weeks of gestation and stimulate the fetal Leydig cells to secrete testosterone, the main hormonal product of the testis (Fig. 622.1). By way of two different biosynthetic pathways, the more potent metabolite of testosterone, dihydrotestosterone (DHT), is produced. In the originally described

pathway, testosterone is converted by the enzyme 5α-reductase to DHT. In another pathway, DHT is produced from androstanediol. The early fetal period of DHT production and action is critical for normal and complete virilization of the XY fetus. Defects in this process lead to different forms of atypical male development (see Chapter 628.2). After virilization occurs, fetal levels of testosterone decrease but are maintained at lower levels in the latter half of pregnancy by luteinizing hormone (LH) secreted by the fetal pituitary; this LH-mediated testosterone secretion is required for continued penile growth and to some degree also for testicular descent.

As part of the normal transition from intrauterine to extrauterine life, perhaps related to the sudden withdrawal of maternal and placental hormones, newborns and young infants experience a transient surge of gonadotropins and sex steroids. This is the so-called **minipuberty**.

In males, LH and testosterone peak at 1-2 months of age and then decline to reach prepubertal levels by 4-6 months of age. Follicle-stimulating hormone (FSH), along with inhibin B, peak at 3 months and decline to prepubertal levels by 9 and 15 months, respectively. The LH rise is more dominant than that of FSH.

The neonatal surge may be important for postnatal maturation of the gonads, stabilization of male external genitalia, and perhaps also for gender identity and sexual behaviors. The postnatal surge in LH and testosterone is absent or blunted in infants with hypopituitarism, cryptorchidism, and complete androgen insensitivity syndrome. The development of nocturnal pulsatile secretion of LH marks the beginning of puberty.

Within specific target cells, 6–8% of testosterone is converted by 5α-reductase to DHT, the more potent androgen (see Fig. 622.1), and approximately 0.3% is acted on by aromatase to produce estradiol. Approximately half of circulating testosterone is bound to sex hormone–binding globulin and half to albumin; only 2% circulates in the free form. Plasma levels of sex hormone–binding globulin are low at birth, rise rapidly during the first 10 days of life, and then remain stable until the onset of puberty. Thyroid hormone may play a role in this physiologic increase because neonates with athyreosis (absence of the thyroid gland) have very low levels of sex hormone–binding globulin.

AMH (previously referred to as *müllerian inhibitory substance*), **inhibin**, and **activin** are members of the transforming growth factor-β (TGF-β) superfamily of growth factors. This group, which has more than 45 members, also includes bone morphogenetic proteins. Members of the TGF-β superfamily are involved in the regulation of developmental processes and multiple diverse human disease states, including chondrodysplasias and cancer.

AMH, a homodimeric glycoprotein hormone encoded by a gene on chromosome 19, is the earliest secreted product of the Sertoli cells of the fetal testis. Produced as a prohormone, its carboxyterminal fragment is cleaved to make it active. *AMH* transcription is initiated by *SOX9* acting through the HMG box, and its expression is upregulated by SF-1 binding to its promoter and further interacting with *SOX9, WT1,* and *GATA4.* AMH binds to two distinct serine/threonine receptors, each having a single transmembrane domain. The activated type 1 receptor signals to the SMAD family of intracellular mediators.

The gene for the AMH receptor (on chromosome 12) is expressed in Sertoli cells. In the female, it is expressed in fetal müllerian duct cells and in fetal and postnatal granulosa cells. During sex differentiation in males, AMH causes involution of the müllerian (paramesonephric) ducts, which are embryologic precursors of the cervix and uterus. It works in concert with SF-1 to cause involution of the fallopian tubes.

AMH is secreted in males by Sertoli cells during both fetal and postnatal life. In females, it is secreted by granulosa cells from 36 weeks of gestation to menopause but at lower levels. The serum concentration of AMH in males is highest at birth, whereas in females it is highest at puberty. After puberty, both sexes have similar serum concentrations of AMH. Its role in postnatal life is not yet fully characterized.

Inhibin is another glycoprotein hormone secreted by the Sertoli cells of the testes and granulosa and theca cells of the ovary. Inhibin A consists of an α-subunit disulfide linked to the β-A subunit, whereas inhibin B consists of the same α subunit linked to the β-B subunit. Activins are dimers of the B subunits, either homodimers (BA/BA, BB/BB) or heterodimers (BA/BB). Inhibins selectively inhibit, whereas activins stimulate pituitary FSH secretion. By means of immunoassays specific for inhibin A or B, it has been shown that inhibin A is absent in males and is present mostly in the luteal phase in women. Inhibin B is the principal form of inhibin in males and in females during the follicular phase. Inhibin B may be used as a marker of Sertoli cell function in males. FSH stimulates inhibin B secretion in females and males, but only in males is there also evidence for gonadotropin-independent regulation. Levels of inhibin B are potentially informative in children with various forms of gonadal and pubertal disorders. In males with delayed puberty, inhibin B may be a useful screening test to differentiate between constitutional delay of puberty and hypogonadotropic hypogonadism. In hypogonadotropic hypogonadism, the serum inhibin B level is very low to undetectable.

Like inhibin and activin, follistatin (a single-chain glycosylated protein) is produced by gonads and other tissues such as the hypothalamus, kidney, adrenal gland, and placenta. Follistatin inhibits FSH secretion principally by binding activins, thereby blocking the effects of activins at the level of both ovary and pituitary.

Many additional peptides act as mediators of the development and function of the testis. They include neurohormones such as growth hormone–releasing hormone, gonadotropin-releasing hormone, corticotropin-releasing hormone, oxytocin, arginine vasopressin, somatostatin, substance P, and neuropeptide Y; growth factors such as insulin-like growth factors (IGFs) and IGF-binding proteins, TGF-β, and fibroblast, platelet-derived, and nerve growth factors; vasoactive peptides; and immune-derived cytokines such as tumor necrosis factor and interleukins 1, 2, 4, and 6.

Clinical patterns of pubertal changes vary widely (see Chapter 599). In 95% of males, enlargement of the genitals begins between 9.5 and 13.5 years of age, reaching maturity at 13-17 years of age. In a minority of normal males, puberty begins after 15 years of age. In some males, pubertal development is completed in less than 2 years, but in others it may take longer than 4.5 years. Pubertal development and the adolescent growth spurt occur at an older age in males than in females by approximately 2 years.

The median age of sperm production (spermarche) is 14 years. This event occurs in midpuberty as judged by pubic hair, testis size, evidence of growth spurt, and testosterone levels. Nighttime levels of FSH are in the adult male range at the time of spermarche; the first conscious ejaculation occurs at about the same time.

FUNCTION OF THE OVARIES

In the normal female, the undifferentiated gonad can be identified histologically as an ovary by 10-11 weeks of gestation, after the upregulation of *R-spondin1*. Oocytes are present from the fourth month of gestation and reach a peak of 7 million by 5 months of gestation. For normal maintenance, oocytes need granulosa cells to form primordial follicles. Functional FSH (but not LH) receptors are present in oocytes of primary follicles during follicular development. Two normal X chromosomes are needed for maintenance of oocytes. In contrast to somatic cells, in which only one X chromosome is active, both X chromosomes are active in germ cells. At birth, the ovaries contain approximately 1 million active follicles, which decrease to 0.5 million by menarche. Thereafter, they decrease at a rate of 1,000/month and at an even higher rate after the age of 35 years.

The hormones of the fetal ovary are provided for the most part by the fetoplacental unit. As in males, peak gonadotropin secretion occurs in fetal life and then again at 2-3 months of life, with the lowest levels at about 6 years of age. In contrast to males, the FSH surge predominates over LH in females. FSH peaks around 3-6 months of age and declines by 12 months, but remains detectable for 24 months. Under LH influence, estradiol peaks at 2-6 months of age. The inhibin B response is variable, peaking between 2 and 12 months and remaining above prepubertal levels until 24 months.

In both infancy and childhood, gonadotropin levels are higher in females than in males.

The most important estrogens produced by the ovary are estradiol-17β (E_2) and estrone (E_1); estriol is a metabolic product of these two, and all three estrogens may be found in the urine of mature females. Estrogens also arise from androgens produced by the adrenal gland and both the female and male gonads (see Fig. 622.1). This conversion explains why in certain types of DSD in males, feminization occurs at puberty. In 17-ketosteroid reductase deficiency, for example, the enzymatic block results in markedly increased secretion of androstenedione, which is converted in the peripheral tissues to estradiol and estrone. These estrogens, in addition to those directly secreted by the testis, result in gynecomastia. Estradiol produced from testosterone in complete androgen insensitivity syndrome causes complete feminization in these XY individuals.

Estrogen regulates a host of functionally different activities in multiple tissues. There are at least two distinct estrogen receptors with different expression patterns. The ovary also synthesizes progesterone, the main progestational steroid; the adrenal cortex and testis also synthesize progesterone, where it is a precursor for other adrenal and testicular hormones.

A host of other hormones with autocrine, paracrine, and intracrine effects have been identified in the ovary. They include inhibins, activins, relaxin, and the growth factors IGF-1, TGF-α and TGF-β, and cytokines.

Plasma levels of estradiol increase slowly but steadily with advancing sexual maturation and correlate well with clinical evaluation of pubertal development, skeletal age, and rising levels of FSH. Levels of LH do not rise until secondary sexual characteristics are well developed. Estrogens, like androgens, inhibit secretion of both LH and FSH (negative feedback). In females, estrogens also provoke the surge of LH secretion that occurs in the midmenstrual cycle and stimulates ovulation. The capacity for this positive feedback is another maturational milestone of puberty.

The average age at menarche in American females is approximately 12.5-13 years, but the range of normal is wide, and 1–2% of normal females have not menstruated by 16 years of age. The age at onset of pubertal signs varies, with studies suggesting earlier ages than previously thought, especially in the US Black population (see Chapter 599). Menarche generally correlates closely with skeletal age. Maturation and closure of the epiphyses is estrogen-dependent, as demonstrated by a very tall 28-year-old, normally masculinized male with continued growth as a result of incomplete closure of the epiphyses, who had complete estrogen insensitivity caused by an estrogen receptor defect.

DIAGNOSTIC TESTING

In male infants, measurements of LH, FSH, and testosterone can detect pituitary and testicular defects. Leydig cell integrity in childhood can be determined by the testosterone response after human chorionic gonadotropin administration. One protocol is to inject 5,000 IU IM daily for 3 days; other protocols are available. The integrity and maturity of the hypothalamic-pituitary-gonadal axis in males and females can be assessed by measuring serial sex steroid, LH, and FSH levels after the subcutaneous administration of the gonadotropin-releasing hormone analog leuprolide. An ultrasensitive LH assay has been shown to differentiate between males with delayed puberty and those with complete, but not partial, hypogonadotropic hypogonadism.

The normal range for inhibin B levels has been established in infant males. Inhibin B may be a marker of spermatogenesis and also of tumors such as granulosa cell tumors. Inhibins may be involved in tumor suppression. Estrogen receptor assays may be clinically useful in the management of various ovarian cancers. AMH measurements are useful in the evaluation of children with nonpalpable gonads and DSD.

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Chapter 623

Hypofunction of the Testes

Omar Ali and Patricia A. Donohoue

Testicular hypofunction during fetal life can be a component of some types of **disorders of sex development** (see Chapter 628.2) and may lead to varying degrees of ambiguous genitalia. After birth, neonates undergo *minipuberty* with relatively high levels of gonadotropins and sex steroids, but this phenomenon is transient, and its absence does not appear to lead to any obvious clinical findings. Because prepubertal children normally do not produce significant amounts of testosterone and are not yet producing sperm, there are no discernible effects of testicular hypofunction in this age-group. Testicular hypofunction from the age of puberty onward may lead to testosterone deficiency, infertility, or both. Such hypofunction may be primary in the testes **(primary hypogonadism)** or secondary to deficiency of pituitary gonadotropic hormones **(secondary hypogonadism)**. Insults to the testes (primary hypogonadism) tend to affect sperm counts more than testosterone secretion, as the seminiferous tubules take up much more of the testicular volume than Leydig cells do, so sperm production is usually affected more than testosterone production. On the other hand, hypogonadotropic hypogonadism tends to affect both testosterone and sperm production.

Both types of hypogonadism may be caused by inherited genetic defects or acquired causes, and in some cases the etiology may be unclear, but the level of the lesion (primary or secondary) is usually well defined; patients with primary hypogonadism have elevated levels of gonadotropins (hypergonadotropic); those with secondary hypogonadism have inappropriately low or absent levels (hypogonadotropic). Table 623.1 details the etiologic classification of male hypogonadism (see also Fig. 600.6).

623.1 Hypergonadotropic Hypogonadism in the Male (Primary Hypogonadism)

Omar Ali and Patricia A. Donohoue

Complete absence or severe dysfunction of the testes in the first trimester will lead to a lack of male sex differentiation and the fetus will have a female phenotype or pronounced ambiguous genitalia (see Chapter 628). If testicular function is present, sex differentiation is normally complete by the 14th week of intrauterine life. *Testicular dysfunction after this stage will lead to hypergonadotropic hypogonadism, and this can occur for a variety of reasons;* genetic or chromosomal anomalies may lead to testicular hypofunction that does not become apparent until the time of puberty, when these males may have delayed or incomplete pubertal development. In other cases, normally developed testes may be damaged by infarction, trauma, radiation, chemotherapy, infections, infiltration, or other causes after sexual differentiation has occurred. In some cases, genetic defects may predispose to atrophy or maldescent; torsion or infarction may lead to progressive testicular damage and atrophy after a period of normal development. If testicular compromise is global, both testosterone secretion and fertility (sperm production) are likely to be affected. Even when the primary defect is in testosterone production, low levels of intratesticular testosterone will frequently lead to infertility. The reverse is not necessarily true. Defects in sperm production and in the storage and transit of sperm may not be associated with low testosterone levels; infertility may thus be seen in patients with normal testosterone levels, normal libido, and normal secondary sexual characteristics.

Table 623.1 Etiologic Classification of Male Hypogonadism

HYPERGONADOTROPIC HYPOGONADISM (PRIMARY HYPOGONADISM; TESTES)
Congenital
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) resistance
Pathogenic variants in steroid synthetic pathways
Gonadal dysgenesis
Klinefelter syndrome (47,XXY)
Noonan syndrome (RASopathy genes)
Cystic fibrosis (infertility)
Acquired
Cryptorchidism (some cases)
Vanishing testes
Chemotherapy
Testicular radiation
Infection (e.g., mumps)
Infarction (testicular torsion)
Trauma
HYPOGONADOTROPIC HYPOGONADISM (SECONDARY HYPOGONADISM; HYPOTHALAMIC-PITUITARY)
Congenital
Genetic defects causing Kallmann syndrome and/or normosmic hypogonadotropic hypogonadism (HH)
Other genetic disorders associated with HH: leptin gene, leptin receptor, DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), SF-1 (steroidogenic factor-1)
Inherited syndromes: Prader-Willi, Bardet-Biedl, Laurence-Moon-Biedl, Alström
Isolated HH at pituitary level (gonadotropin-releasing hormone receptor, FSH and LH β-subunit)
Multiple pituitary hormone deficiencies: septo-optic dysplasia (*HESX-1* in some cases) and other disorders of pituitary organogenesis (e.g., *PROP1, LHX3, LHX4, SOX-3*)
Idiopathic
Acquired
Anorexia nervosa
Drug use
Malnutrition
Chronic illness, especially Crohn disease
Hyperprolactinemia
Pituitary tumors
Pituitary infarction
Infiltrative disorders (e.g., histiocytosis, sarcoidosis)
Hemosiderosis and hemochromatosis
Cranial radiation

Various degrees of primary hypogonadism occur in a significant percentage of patients with chromosomal aberrations, as in **Klinefelter syndrome**, **males with more than one X chromosome**, and **XX males**. These chromosomal anomalies are also associated with other characteristic findings. Noonan syndrome is also associated with cryptorchidism and infertility, but other (nongonadal) features dominate its clinical picture (see Chapters 100 and 101).

CONGENITAL ANORCHIA OR TESTICULAR REGRESSION SYNDROME

Males in whom the external genitalia have developed normally (or nearly normally) and paramesonephric (müllerian) duct derivatives (uterus, fallopian tubes) are absent have had testicular function for at least some part of gestation. If their testes cannot be palpated at birth, they are said to have **cryptorchidism**. In most such cases, the testes are undescended or retractile, but in some cases no testes are found in any location, even after extensive investigation. This syndrome of absence of testes in a phenotypic male with a normal 46,XY karyotype (indicating that there was some period of testicular function in intrauterine life) is known as *vanishing testes, congenital anorchia,* or testicular regression syndrome.

Testicular regression syndrome is not uncommon. Cryptorchidism occurs in 1.5–9% of male births; in 10–20% of these cases, the testes are impalpable. Of children with impalpable testes, up to 50% may have no detectable testes after extensive investigation. Most cases appear to be sporadic and are thought to be the result of torsion or vascular accidents. The incompletely descended testis may be more prone to torsion, and this may be one of the causes of vanishing testes. Most cases are sporadic, but in a subset of patients, testicular regression syndrome occurs in monozygotic twins or in families with other affected individuals, suggesting a genetic etiology. Some cases are associated with micropenis, and in these cases the testicular loss probably occurred after the 14th week but well before the time of birth, or this may indicate a preexisting dysfunction of male hormonal development. Low levels of testosterone (<10 ng/dL) and markedly elevated levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are found in the early postnatal months; thereafter levels of gonadotropins tend to decrease even in agonadal children, rising to very high levels again as the pubertal years approach. Stimulation with human chorionic gonadotropin (hCG) fails to evoke an increase in the level of testosterone. *Serum levels of antimüllerian hormone (AMH) are undetectable or low.* All patients with undetectable testes should be tested for AMH and should undergo an hCG stimulation test. If the results indicate that no testicular tissue is present (absent AMH and no rise in testosterone after hCG stimulation), then the diagnosis of testicular regression syndrome is confirmed. If testosterone secretion is demonstrated, then imaging with abdominal magnetic resonance imaging (MRI) and/or surgical exploration is indicated. A small fibrotic nodule may be found at the end of the spermatic cord in many cases of testicular regression syndrome. There is no possibility of normal fertility in these patients.

Treatment of male hypogonadism (primary or secondary) is discussed in Chapter 623.2.

Chemotherapy and Radiation-Induced Hypogonadism

Testicular damage is a frequent consequence of chemotherapy and radiotherapy for cancer. The frequency and extent of damage depend on the agent used, total dose, duration of therapy, and posttherapy interval of observation. Another important variable is age at therapy; it has been suggested that prepubertal testes are less prone to damage than pubertal testes, though the evidence is not conclusive. Chemotherapy is most damaging if more than one agent is used, and alkylating agents and platinum-containing agents are the ones most likely to lead to testicular damage. Although many chemotherapeutic agents produce azoospermia and infertility, Leydig cell damage (leading to low testosterone levels) is less common. In many cases the damage is transient and sperm counts recover after 12-24 months. The use of alkylating agents such as cyclophosphamide in prepubertal children may not impair pubertal development, even though there may be biopsy evidence of germ cell damage. Cisplatin causes transient azoospermia or oligospermia at lower doses, whereas higher doses (400-600 mg/m^2) can cause permanent infertility. Interleukin 2 can depress Leydig cell function, whereas interferon-α does not seem to affect gonadal function. Both chemotherapy and radiotherapy are associated with an increase in the percentage of abnormal gametes, but data concerning the outcomes of pregnancies after such therapy have *not* shown any increase in genetically mediated birth defects, possibly because of selection bias against abnormal sperm.

Radiation damage is dose dependent. Temporary oligospermia can be seen with doses as low as 0.1 Gy, with permanent azoospermia seen with doses greater than 2 Gy. Recovery of spermatogenesis can be seen 5 years (or more) after irradiation, with higher doses leading to slower recovery. Leydig cells are more resistant to irradiation. Mild damage as determined by elevated LH levels can be seen with up to 6 Gy; doses greater than 30 Gy cause hypogonadism in most patients. Whenever possible, testes should be shielded from irradiation. Testicular function should be carefully evaluated in adolescents after multimodal treatment for cancer in childhood. Replacement therapy with testosterone and counseling concerning fertility may be indicated. The storage of sperm before chemotherapy or radiation treatment in pubertal

and postpubertal males is an option. Even in those cases where sperm counts are abnormal, recovery is possible, though the chances of recovery decline with increasing dose of radiation. If sperm counts remain low, fertility is still possible in some cases with testicular sperm extraction and intracytoplasmic sperm injection.

Sertoli Cell–Only Syndrome

Small testes and azoospermia are seen in patients with the extremely rare Sertoli cell–only syndrome (**SCO**, **germ cell aplasia**, or **Del Castillo syndrome**). These patients have no germ cells in the testes but usually have normal testosterone production and present as adults with infertility. Typically, patients have small testes and elevated FSH levels with normal LH and testosterone. They may have gynecomastia because of FSH stimulation of aromatase activity. Inhibin B levels may be decreased when compared with individuals with normal spermatogenesis. Most cases are sporadic and idiopathic, but large deletions involving the azoospermia factor (AZF) region of the Y chromosome (Yq11) may be found in some cases. Y chromosome microdeletions are also occasionally identified as a cause of SCO syndrome.

Other Causes of Testicular Hypofunction

Atrophy of the testes may follow damage to the vascular supply because of manipulation of the testes during surgical procedures for correction of cryptorchidism or because of bilateral torsion of the testes. **Cryptorchidism** is a common condition (found in 3% of male children at birth, decreasing to 1% by age 6 months), and guidelines stress the importance of treatment before age 12 months (or even earlier) to maximize future fertility. But a small percentage of cases will develop fertility issues even when surgical treatment is successful and is completed within the first year of life. These cases may represent intrauterine damage, surgical damage, or genetic defects in testicular development and are therefore included among the causes of testicular hypofunction.

Acute orchitis is common in pubertal or adult males with mumps and may lead to subfertility in ~10% of cases, though infertility is rare. Testosterone secretion usually remains normal. The incidence of mumps orchitis in postpubertal males has increased in some areas because of a decrease in measles, mumps, and rubella vaccination uptake. **Autoimmune polyendocrinopathy** may be associated with primary hypogonadism (associated with anti-P450scc antibodies), but this appears to be more common in females.

Testicular Dysgenesis Syndrome

The incidence of testicular cancer has increased in many developed societies, and the incidence of cryptorchidism, hypospadias, low sperm counts, and sperm abnormalities also appears to have increased in some, but not all, studies. It has been proposed that all these trends are linked by prenatal testicular dysgenesis. The hypothesis is that some degree of testicular dysgenesis develops in intrauterine life from genetic and environmental factors and is associated with an increased risk of cryptorchidism, hypospadias, hypofertility, and testicular cancer. The environmental influences that have been implicated in this syndrome include environmental chemicals that act as endocrine disruptors, such as bisphenol A and phthalates (components of many types of plastics), several pesticides, phytoestrogens or mycoestrogens, and other chemicals. The fact that these lesions can be reproduced in some animal models by environmental chemicals has led to efforts to remove these chemicals from products used by infants and pregnant mothers and from the environment in general. Nonetheless the evidence is only suggestive and not conclusive.

CLINICAL MANIFESTATIONS

Primary hypogonadism may be suspected at birth if the testes and penis are abnormally small. Normative data are available for different populations. The condition is often not noticed until puberty, when secondary sex characteristics fail to develop. Facial, pubic, and axillary hair are scant or absent; there is neither acne nor regression of scalp hair; and the voice remains high pitched. The penis and scrotum remain infantile and may be almost obscured by pubic fat; the testes are small or not palpable. Fat accumulates in the region of the hips and buttocks and sometimes in the breasts and on the abdomen. The epiphyses close later than normal; therefore the extremities are long. The span may be several inches longer than the height, and the distance from the symphysis pubis to the soles of the feet (lower segment) is much greater than that from the symphysis to the vertex (upper segment). The proportions of the body are described as **eunuchoid**. The ratio of the upper to lower segment is considerably less than 0.9. Many individuals with milder degrees of hypogonadism may be detected only by appropriate studies of the pituitary-gonadal axis. Examination of the testes should be performed routinely by the pediatrician; testicular volumes as determined by comparison with standard orchidometers or by measurement of linear dimensions should be recorded.

DIAGNOSIS

Levels of serum FSH and, to a lesser extent, of LH are elevated to greater than age-specific normal values in early infancy (when minipuberty normally occurs and the gonadotropins are normally disinhibited). This is followed by a time when even agonadal children may not exhibit significant elevation in gonadotropins, indicating that the gonadotropins are also suppressed at this stage by some mechanism independent of feedback inhibition by gonadal hormones. In the latter half of childhood and several years before the onset of puberty, this inhibition is released and gonadotropin levels again rise above age-based normal levels in subjects with primary hypogonadism. These elevated levels indicate that even in the prepubertal child there is an active hypothalamic-gonadal feedback relationship. After the age of 11 years, FSH and LH levels rise significantly, reaching the agonadal range. Measurements of random plasma testosterone levels in prepubertal males are not helpful because they are low in normal prepubertal children, rising during puberty to attain adult levels. During puberty, these levels, when measured in an early morning blood sample, correlate better with testicular size, stage of sexual maturity, and bone age than with chronological age. In patients with primary hypogonadism, testosterone levels remain low at all ages. There is an attenuated rise or no rise at all after administration of hCG, in contrast to normal males in whom hCG produces a significant rise in plasma testosterone at any stage of development.

AMH is secreted by the Sertoli cells, and this secretion is suppressed by testosterone. AMH levels are elevated in prepubertal males and suppressed at the onset of puberty. Males with primary hypogonadism continue to have elevated AMH levels in puberty. Detection of AMH may be used in the prepubertal years as an indicator of the presence of testicular tissue (e.g., in patients with bilateral cryptorchidism). Inhibin B is also secreted by the Sertoli cells, is present throughout childhood, and rises at the onset of puberty (more in males than in females). It may be used as another marker of the presence of testicular tissue in bilateral cryptorchidism and as a marker of spermatogenesis (e.g., in delayed puberty, cancer survivors, and patients with Noonan syndrome). Bone age x-rays are useful to document delayed bone age in patients with constitutional growth delay as well as primary hypogonadism.

NOONAN SYNDROME

The term *Noonan syndrome* has been applied to males and females with normal karyotypes who have certain phenotypic features that occur also in females with Turner syndrome (although the genetic causes are completely distinct) (see Chapter 101). Males with this syndrome frequently have cryptorchidism and small testes. Testosterone secretion may be low or normal, but spermatogenesis may be affected even in those with normal testosterone (and normal secondary sexual characteristics). Serum inhibin-B is a useful marker of Sertoli cell function in these patients. Puberty is delayed, and adult height is achieved by the end of the second decade; the syndrome is discussed in detail in Chapter 101. Patients with significant hypogonadism will need treatment as discussed in Chapter 623.2.

KLINEFELTER SYNDROME

See also Chapter 99.4.

Klinefelter syndrome is the most common sex chromosomal aneuploidy in males, with an incidence of 0.1–0.2% in the general population

(1 in 500-1,000) and rising to 4% among infertile males and 10–11% in those with oligospermia or azoospermia. Approximately 80% of them have a 47,XXY chromosome complement, whereas mosaics and higher degrees of poly-X are seen in the remaining 20%. Even with as many as four X chromosomes, the Y chromosome determines a male phenotype. The chromosomal aberration most often results from meiotic nondisjunction of an X chromosome during parental gametogenesis; the extra X chromosome is maternal in origin in 54% and paternal in origin in 46% of patients. A national study in Denmark revealed a prenatal prevalence of 213 per 100,000 male fetuses, but in adult men the prevalence was only 40 per 100,000, suggesting that 25% of adult males with Klinefelter syndrome were diagnosed. The incidence of Klinefelter syndrome increases with maternal age and possibly also with paternal age.

Clinical Manifestations

In patients who do not have a prenatal diagnosis, the diagnosis is rarely made before puberty because of the paucity or subtlety of clinical manifestations in childhood. Behavioral or psychiatric disorders may be apparent long before defects in sexual development. These children tend to have learning disabilities and deficits in executive function (concept formation, problem solving, task switching, and planning), and the condition should be considered in males with psychosocial, learning, or school adjustment problems. Affected children may be anxious, immature, or excessively shy and tend to have difficulty in social interactions throughout life. In a prospective study, a group of children with 47,XXY karyotypes identified at birth exhibited relatively mild deviations from normal during the first 5 years of life. None had major physical, intellectual, or emotional disabilities; some were inactive, with poorly organized motor function and mild delay in language acquisition. Problems often first become apparent after the child begins school. Full-scale IQ scores may be normal, with verbal IQ being somewhat decreased. Verbal cognitive defects and underachievement in reading, spelling, and mathematics are common. By late adolescence, many males with Klinefelter syndrome have generalized learning disabilities, most of which are language based. Despite these difficulties, most complete high school.

The patients tend to be tall and slim and have a specific tendency to have long legs (disproportionate to the arms and longer than those seen with other causes of hypogonadism), but body habitus can vary markedly. The testes tend to be small for age, but this sign may become apparent only after puberty, when normal testicular growth fails to occur. The phallus tends to be smaller than average, and cryptorchidism is more common than in the general population. Bone mineral density may be low in adults with Klinefelter syndrome, and this correlates with lower testosterone levels.

Pubertal development may be delayed, although some children undergo apparently normal or nearly normal virilization. Despite normal testosterone levels, serum LH and FSH concentrations and their responses to gonadotropin-releasing hormone (GnRH) stimulation are elevated starting at around 13 years of age. Approximately 50–80% of adults have **gynecomastia**; they have sparser facial hair. The most common testicular lesions are spermatogenic arrest and Sertoli cell predominance. The sperm have a high incidence of sex chromosomal aneuploidy. Azoospermia and infertility are usual, although rare instances of fertility are known. It is now clear that germ cell numbers and sperm counts are higher in early puberty and decline with age. Testicular sperm extraction followed by intracytoplasmic sperm injection can result in the birth of healthy infants, with success rates declining with increasing age. In nonmosaic Klinefelter patients, most testicular sperm (94%) have a normal pattern of sex chromosome segregation, indicating that meiotic checkpoints can remove most aneuploid cells. Antisperm antibodies have been detected in 25% of tested specimens.

There is an increased incidence in adulthood of central adiposity, metabolic syndrome, pulmonary disease, varicose veins, and cancer of the breast. Among 93 unselected **male breast cancer** patients, 7.5% were found to have Klinefelter syndrome. Mediastinal germ cell tumors have been reported; some of these tumors produce hCG and cause precocious puberty in young males. They may also be associated with leukemia, lymphoma, and other types of hematologic neoplasia. The highest cancer risk (relative risk: 2.7) occurs in the 15- to 30-year age-group. A large cohort study in Britain demonstrated an overall significantly increased standardized mortality ratio, with increases in deaths from diabetes, epilepsy, peripheral and intestinal vascular sufficiency, pulmonary embolism, and renal disease. Mortality from ischemic heart disease was decreased. In adults, structural brain abnormalities correlate with cognitive deficits.

Patients with Klinefelter syndrome also have an increased risk of *autoimmune disorders*. It seems that the presence of one or more X chromosomes changes the risk of autoimmune disorders, which are similar to those seen in XX females. These patients have an increased incidence of rheumatoid arthritis, Sjogren syndrome, systemic lupus erythematosus (SLE), and other autoimmune disorders.

In adults with XY/XXY mosaicism, the features of Klinefelter syndrome are decreased in severity and frequency. Children with mosaicism have a better prognosis for virilization, fertility, and psychosocial adjustment.

Klinefelter Variants and Other Poly-X Syndromes

When the number of X chromosomes exceeds two, the clinical manifestations, including intellectual disability and impairment of virilization, are more severe. Height decreases with increasing number of X chromosomes. The **XXYY** variant is the most common variant (1 in 18,000-40,000 male births). In most, intellectual disability occurs with IQ scores between 60 and 80, but 10% have IQs greater than 110. The XXYY male phenotype is not distinctively different from that of the XXY patient except that XXYY adults tend to be taller than the average XXY patient. The **49,XXXXY** variant is sufficiently distinctive to be detected in childhood. Its incidence is estimated to be 1 in 80,000-100,000 male births. The disorder arises from sequential nondisjunction in meiosis. Affected patients are severely cognitively impaired and have short necks and typical coarse facies. The eyes are wide set, with a mild upward slant of the fissures as well as epicanthus and strabismus; the nose is upturned, wide, and flat; also noted is a large open mouth and large malformed ears. The testes are small and may be undescended, the scrotum is hypoplastic, and the penis is very small. Defects suggestive of Down syndrome (short, incurved terminal fifth phalanges, single palmar creases, and hypotonia) and other skeletal abnormalities (including defects in the carrying angle of the elbows and restricted supination) are common. The most frequent radiographic abnormalities are radioulnar synostosis or dislocation, elongated radius, pseudoepiphyses, scoliosis or kyphosis, coxa valga, and retarded bone age. Most patients with such extensive changes have a 49,XXXXY chromosome karyotype; several mosaic patterns have also been observed: 48,XXXY/49,XXXXY; 48,XXXY/49,XXXXY/50,XXXXXY; and 48,XXXY/49,XXXXY/50,XXXXYY. Prenatal diagnosis of a 49,XXXXY infant has been reported. The fetus had intrauterine growth restriction, edema, and cystic hygroma colli.

The **48,XXXY** variant is relatively rare. The characteristic features are generally less severe than those of patients with 49,XXXXY and more severe than those of 47,XXY patients. Mild intellectual disability, delayed speech and motor development, and immature but passive and pleasant behavior are associated with this condition.

Very few patients have been described with 48,XYYY and 49,XXYYY karyotypes. Dysmorphic features and cognitive impairment are common to both.

Laboratory Findings

Most males with Klinefelter syndrome go through life undiagnosed. The chromosomes should be examined in all patients suspected of having Klinefelter syndrome, particularly those attending child guidance, psychiatric, and cognitive disability clinics. In infancy, inhibin B and AMH levels are normal but testosterone levels are lower than in controls. Before 10 years of age, males with 47,XXY Klinefelter syndrome have normal basal plasma levels of FSH and LH. Responses to gonadotropin-stimulating hormone and to hCG are normal. The testes show normal growth early in puberty, but by midpuberty the testicular growth stops, gonadotropins become elevated, and testosterone levels

are slightly low. Inhibin B levels are normal in early puberty, decrease in late puberty, and are low in adults with the syndrome. Elevated levels of estradiol, resulting in a high ratio of estradiol to testosterone, account for the development of gynecomastia during puberty. Sex hormone–binding globulin levels are elevated, further decreasing free testosterone levels. A long androgen receptor polyglutamine (CAG) repeat length is associated with the more severe phenotype, including gynecomastia, small testes, and short penile length.

Testicular biopsy before puberty may reveal only deficiency or absence of germinal cells. After puberty, the seminiferous tubular membranes are hyalinized and there is adenomatous clumping of Leydig cells. Sertoli cells predominate. Azoospermia is characteristic, and infertility is the rule.

Management

Males known to have Klinefelter syndrome should be monitored closely for speech, learning, and behavioral problems; they should be referred for early evaluation and treatment as needed. Testosterone, LH, and FSH levels should be checked at 11-12 years of age; replacement therapy with testosterone is recommended once FSH and LH begin to rise above normal. Fasting glucose, lipids, and hemoglobin A_{1C} should also be obtained, as these children are at risk for central adiposity and metabolic syndrome. A baseline dual-energy x-ray absorptiometry scan to assess bone density is also recommended by some authorities. Although testosterone treatment will normalize testosterone levels, stimulate the development of secondary sexual characteristics, increase bone and muscle mass, and improve body composition, it will *not* improve fertility (and will, in fact, suppress spermatogenesis). There is some evidence that it also improves mood and may have a positive effect on cognition and social functioning, but the findings are not conclusive at this time. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are not frequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly or subcutaneously every 3-4 weeks, with 50-mg increments every 6-12 months until a maintenance dose for adults (200-250 mg every 3-4 weeks) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization. The various transdermal preparations differ somewhat, and standard references should be consulted for recommendations regarding dosage and mode of application.

Gynecomastia may be treated with aromatase inhibitors (which will also increase endogenous testosterone levels), but medical treatment is not always successful and plastic surgery may be needed. Fertility is usually not an issue in the pediatric age-group, but adults can father children using testicular sperm extraction followed by intracytoplasmic sperm injection. Because sperm counts decrease rapidly after the onset of puberty in children with Klinefelter syndrome, sperm banking during early puberty is an option that can be discussed with a fertility specialist. Sperm counts can be stimulated using hCG treatment before testicular sperm extraction. Therapy, counseling, and psychiatric services should be provided as needed for learning difficulties and psychosocial disabilities.

XX MALES

This disorder is thought to occur in 1 in 20,000 newborn males. Affected individuals have a male phenotype, small testes, a small phallus, and no evidence of ovarian or müllerian duct tissue. They therefore appear to be *distinct from* those with the **ovotesticular disorder of sexual development**. Undescended testes and hypospadias occur in a minority of patients. Infertility occurs in practically all cases, and the histologic features of the testes are essentially the same as in Klinefelter syndrome. Patients with the condition usually come to medical attention in adult life because of hypogonadism, gynecomastia, or infertility. Hypergonadotropic hypogonadism occurs secondary to testicular failure. A few cases have been diagnosed perinatally as a result of discrepancies between prenatal ultrasonography and karyotype findings.

In 90% of XX males with normal male external genitalia, one of the X chromosomes carries the *SRY* (sex-determining region on the Y chromosome) gene. The exchange from the Y to the X chromosome occurs during paternal meiosis, when the short arms of the Y and X chromosomes pair. XX males inherit one maternal X chromosome and one paternal X chromosome containing the translocated male-determining gene. A few cases of 46,XX males with 9P translocations have also been identified. Most XX males who are identified before puberty have hypospadias or a micropenis; this group of patients may lack Y-specific sequences, suggesting other mechanisms for virilization. Fluorescent in situ hybridization and primed in situ labeling have been used to identify small *SRY* DNA segments. Yp fragment abnormalities may result in sexually ambiguous phenotypes.

45,X MALES

In a few male patients recognized with a 45,X karyotype, Yp sequences are translocated to an autosomal chromosome. In one instance, the terminal short arm of the Y chromosome was translocated onto an X chromosome. In another, *SRY/autosomal* translocation was postulated. A male with the 45,X karyotype and Leri-Weill dyschondrosteosis, *SHOX* gene loss, and an SRY to Xp translocation has also been described.

47,XXX MALES

A Japanese male with poor pubic hair development, hypoplastic scrotal testes (4 mL), normal penis and normal height, gynecomastia, and severe cognitive impairment had 47,XXX karyotype caused by an abnormal X-Y interchange during paternal meiosis and X-X nondisjunction during maternal meiosis.

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623.2 Hypogonadotropic Hypogonadism in the Male (Secondary Hypogonadism)

Omar Ali and Patricia A. Donohoue

In hypogonadotropic hypogonadism (HH), lack of gonadal function is secondary to deficiency of one or both gonadotropins: FSH or LH. The primary defect may lie either in the anterior pituitary or in the hypothalamus. Hypothalamic etiologies result in deficiency of GnRH. The testes are normal but remain in the prepubertal state because stimulation by gonadotropins is lacking. The disorder may be recognized in infancy but is much more commonly recognized because of marked pubertal delay. Rarely, patients with a milder inherited form of HH may go through puberty and may present with hypogonadism as adults.

HH may be genetic or acquired (Table 623.2). Several different genes can cause inherited forms of HH; the affected genes may be upstream of GnRH, at the level of GnRH receptors, or at the level of gonadotropin production. In addition, various genetic defects in transcription factors—such as POUF-1, LHX-3, LHX-4, and HESX-1—lead to defects in pituitary development and multiple pituitary hormone deficiencies, including deficiency of gonadotropins. Acquired pituitary gonadotropin deficiency may develop from various lesions in the hypothalamic-pituitary region (e.g., tumors, infiltrative disease, autoimmune disease, trauma, stroke).

ISOLATED GONADOTROPIN DEFICIENCY

Isolated gonadotropin deficiency in which other pituitary hormone levels are normal is more likely to be from defects in the secretion of GnRH from the hypothalamus rather than defects in gonadotropin synthesis in the pituitary. It affects approximately 1 in 10,000 males and 1 in 50,000 females and encompasses a heterogeneous group of entities. Many cases are associated with anosmia, and this combination of anosmia and HH defines **Kallmann syndrome**.

Table 623.2 Forms of Congenital Hypogonadotropic Hypogonadism and Differential Diagnosis

FORMS OF CHH
GnRH Deficiency and Defective Sense of Smell
Kallmann syndrome
Isolated GnRH Deficiency (Normal Sense of Smell)
Normosmic CHH
Complex Syndromes Including CHH or KS
Combined pituitary hormone deficiency
Septo-optic dysplasia
CHARGE syndrome
Adrenal hypoplasia congenita with HH
Waardenburg syndrome
Bardet-Biedl syndrome
Gordon Holmes syndrome
Others
DIFFERENTIAL DIAGNOSIS
Functional Causes
Malnutrition and/or malabsorption
Any chronic disease (e.g., IBD or asthma)
Celiac disease
Eating disorders
Excessive exercise
Systemic Causes
Hemochromatosis
Sarcoidosis
Histiocytosis
Thalassemia
Acquired Causes
Hyperprolactinemia
Pituitary adenomas and/or brain tumors
Rathke cleft cyst
Pituitary apoplexy
Radiation (brain or pituitary)
Medication induced (such as by steroids, opiates, or chemotherapy)

CHARGE, Coloboma, heart defects, atresia of choanae, retardation of growth and/or development, genital and/or urinary defects, ear anomalies or deafness; CHH, congenital hypogonadotropic hypogonadism; GnRH, gonadotropin-releasing hormone; HH, hypogonadotropic hypogonadism; IBD, inflammatory bowel disease; KS, Kallmann syndrome.

From Boehm U, Bouloux PM, Dattani MT, et al. European consensus statement on congenital hypogonadotropic hypogonadism—pathogenesis, diagnosis and treatment. Nat Rev. 2015;11:547–564. Box 2.

Kallmann syndrome is the most common form of HH and is genetically heterogeneous, with autosomal recessive, X-linked, and autosomal dominant forms of inheritance. Clinically it is characterized by its association with anosmia or hyposmia; 85% of cases appear to be autosomal and 15% are X-linked, but a specific genetic defect may not be identified in more than half of the cases of HH. There is a wide spectrum of severity and associated features in patients with Kallmann syndrome, and the same genetic pathogenic variants may be associated with different phenotypes, even within the same family. Some kindreds contain anosmic individuals *with or without* hypogonadism; others contain hypogonadal individuals who are anosmic. Cleft lip and palate, hypotelorism, median facial clefts, sensorineural hearing loss, unilateral renal aplasia, neurologic deficits, and other findings occur in some affected patients.

The **X-linked** form (*ANOS1*, formerly known as *KAL1*) is caused by variants of *ANOS1* at Xp22.3. This leads to failure of olfactory axons and GnRH-expressing neurons to migrate from their common origin in the olfactory placode to the brain. The *ANOS1* gene product anosmin-1, an extracellular 95-kDa matrix glycoprotein, facilitates neuronal growth and migration. The *ANOS1* gene is also expressed in various parts of the brain, facial mesenchyme, and mesonephros and metanephros, thus explaining some of the associated findings in patients with Kallmann syndrome, such as synkinesia (mirror movements), hearing loss, midfacial defects, and renal agenesis.

When Kallmann syndrome is caused by terminal or interstitial deletions of the Xp22.3 region, it may be associated with other contiguous gene syndromes, such as steroid sulfatase deficiency, chondrodysplasia punctata, X-linked ichthyosis, or ocular albinism.

The **autosomal dominant** form of Kallmann syndrome (sometimes referred to as *KAL2*) occurs in up to 10% of patients and is caused by a loss-of-function pathogenic variant in the fibroblast growth factor receptor 1 *(FGFR1)* gene. Cleft lip and palate are associated with this form, but not with the X-linked form. Oligodontia and hearing loss may occur with both KAL1 and KAL2.

A variety of other genes—including *SOX10, FGF8, PROK2/PROKR2, NELF, CHD7* (responsible for CHARGE [coloboma of the eye, heart anomaly, choanal atresia, retardation, and genital and ear anomalies] syndrome, which includes hypogonadism in its phenotype), *HS6ST1, WDR11,* and *SEMA3A*—are associated with defects in neuronal migration that can result in Kallmann syndrome.

Hypogonadotropic Hypogonadism Without Anosmia

A specific genetic defect is not found in most cases of *normosmic idiopathic hypogonadotropic hypogonadism (IHH)*, but the list of genes associated with this disorder is growing; pathogenic variants in *KISS1/KISS1R, TAC3/TACR3,* and *GNRH1/GNRHR* lead to abnormalities in the secretion and action of GnRH and are seen exclusively in patients with normosmic IHH. Variants in *FGFR1, FGF8, PROKR2, CHD7,* and *WDR11* more commonly present with anosmia/hyposmia (Kallmann syndrome) but are also associated with normosmic IHH in some cases. It appears that kisspeptin (the gene product of the *KISS1* gene) and its G protein–coupled receptor (GPCR54) play an important role in triggering puberty in humans and act downstream of the leptin receptor in this pathway. Rare cases of leptin deficiency and leptin receptor defects are also associated with HH. In addition, starvation and anorexia are associated with hypogonadism, most likely acting via the leptin pathway.

There are no known human variants of the *GnRH* gene, but several families with variants in the GnRH *receptor* have been described. These variants account for 2–14% of IHH without anosmia. The severity of the defect is variable, and many patients will respond to high-dose GnRH with increased gonadotropin secretion, indicating that the receptor defect is partial.

Variants in gonadotropin genes are extremely rare. Variants in the common α-subunit are not known in humans. Variants in the LH-β subunit have been described in a few individuals and may lead to low, absent, or elevated LH levels, depending on the variant. This leads to testosterone deficiency (diminished Leydig cell function), but because intratesticular testosterone is critical for spermatogenesis, this also leads to diminished sperm counts. Defects in the FSH-β subunit may be the cause of azoospermia in a few rare cases. Interestingly these patients may also have testosterone deficiency, indicating that Sertoli cells also play a role in supporting normal Leydig cell function.

Children with **X-linked adrenal hypoplasia congenita (AHC)** have associated HH because of impaired GnRH secretion. In these patients, there is a pathogenic variant of *DAX1* at Xp21.2-21.3. This region of the X chromosome includes genes for glycerol kinase, Duchenne muscular dystrophy, and ornithine transcarbamoyltransferase (OTC); these genes may be affected as part of a contiguous gene deletion syndrome that includes AHC, glycerol kinase deficiency, Duchenne muscular dystrophy, and OTC deficiency. Most males with *DAX1* variants develop HH in adolescence, although a patient with adult-onset adrenal insufficiency and partial HH and two females with HH and delayed puberty have also been described, the latter as part of extended families including males with classic HH. The *DAX1* gene defect is, however, rare in patients with delayed puberty or HH without at least a family history of adrenal failure (see Chapter 616).

It should be noted that genotype-phenotype correlations in IHH appear to be complex, and pedigrees with digenic or oligogenic inheritance have been described. The same genetic defect may be associated with Kallmann syndrome, normosmic IHH, additional birth defects,

delayed normal puberty, or an apparently normal phenotype. This variability has been observed more frequently in kindreds with pathogenic variants in *FGF8/FGFR1* and in *PROK2/PROKR2* ligand-receptor pairs and may result from other interacting genes, epigenetic effects, or environmental factors.

OTHER DISORDERS WITH HYPOGONADOTROPIC HYPOGONADISM

HH has been observed in a few patients with **polyglandular autoimmune syndrome**, in some with elevated melatonin levels, and in those with a variety of other syndromes, such as **Bardet-Biedl, Prader-Willi, multiple lentigines, and several ataxia syndromes**. In rare cases, HH is associated with complex chromosomal abnormalities.

HYPOGONADOTROPIC HYPOGONADISM ASSOCIATED WITH OTHER PITUITARY HORMONE DEFICIENCIES

Defects in pituitary transcription factors such as PROP-1, HESX-1, LHX-4, SOX-3, and LHX-3 lead to multiple pituitary deficiencies including HH. Most of these present with multiple pituitary hormone deficiency in infancy, but some cases (especially with *PROP-1* pathogenic variants) may present with hypogonadism or hypoadrenalism in adult life. Growth hormone is almost always affected in multiple pituitary hormone deficiency, but thyroid-stimulating hormone and adrenocorticotropic hormone may be spared in some cases. In patients with organic lesions in or near the pituitary, the gonadotropin deficiency is usually pituitary in origin.

DIAGNOSIS

Levels of gonadotropins and gonadal steroids are normally elevated for up to 6 months after birth (minipuberty); if the diagnosis of HH is suspected in early infancy, these levels will be found to be inappropriately low. By the second half of the first year of life, these normally decline to nearly undetectable levels and remain suppressed until late childhood. Routine laboratory tests cannot distinguish HH from normal suppression of gonadotropins in this age-group. At the normal age of puberty, these patients fail to show clinical signs of puberty or a normal increase in LH and FSH levels. *Children with constitutional delay of growth and puberty will have the same clinical picture and similar laboratory findings (these cases are far more common than true HH, especially in males), and their differentiation from patients with HH is extremely difficult.* Dynamic testing with GnRH or hCG may *not* be able to distinguish these groups in a reliable manner. A testosterone level greater than 50 ng/dL (1.7 nmol/L) generally indicates that normal puberty is likely, but a lower level does not reliably distinguish these groups. At least one study showed that an inhibin B level of <35 pg/mL in Tanner stage 1 and <65 pg/mL in Tanner stage 2 may be able to distinguish IHH from constitutional delay in males, but no single test will reliably distinguish these conditions in all patients.

Insulin-like growth factor-1, thyroid-stimulating hormone, free thyroxine, and morning cortisol levels should be checked to assess the status of other anterior pituitary hormones; dynamic testing for growth hormone deficiency and adrenal insufficiency may be necessary if these are abnormal or equivocal. HH is very likely if the patient has evidence of another pituitary deficiency, such as a deficiency of growth hormone, particularly if it is associated with adrenocorticotropic hormone deficiency. **Hyperprolactinemia** is a known cause of delayed puberty and should be excluded by determination of serum prolactin levels in all patients. The presence of *anosmia* usually indicates permanent gonadotropin deficiency, but occasional instances of markedly delayed puberty (18-20 years of age) have been observed in anosmic individuals. Although anosmia may be present in the family or in the patient from early childhood, its existence is rarely volunteered, and direct questioning is necessary in all patients with delayed puberty. Formal olfactometry, such as the University of Pennsylvania Smell Identification Test, is advisable to determine if partial degrees of hyposmia are present, because IHH patients display a broad spectrum of olfactory function.

In the absence of family history, it may not be possible to make the diagnosis of HH with certainty, but the diagnosis will become more and more likely as puberty is delayed further beyond the normal age. If pubertal delay persists beyond age 18 years with low 8 AM testosterone levels and inappropriately low gonadotropins (normal values are inappropriately low in this setting), then the patient can be presumptively diagnosed with HH. *An MRI of the brain is indicated* to look for tumors and other anomalies in the hypothalamic-pituitary region. Genetic testing for pituitary transcription factors and several of the genes involved in isolated HH is also available and should be performed when possible. A renal ultrasound is recommended in patients with Kallmann syndrome because of its association with unilateral renal agenesis. Some authorities also recommend obtaining a baseline bone-density evaluation.

TREATMENT

Constitutional delay of puberty should be ruled out before a diagnosis of HH is established and treatment is initiated. Testicular volume of less than 4 mL by 14 years of age occurs in approximately 3% of males, but most of these are cases of constitutional delay of puberty, and true HH is a rare condition. Although constitutional delay is a benign condition that will (by definition) resolve spontaneously, even relatively moderate delays in sexual development and growth may result in significant psychologic distress and require attention. Initially an explanation of the variations characteristics of puberty and reassurance suffice for the majority of males. If by 15 years of age no clinical evidence of puberty is apparent and the testosterone level is <50 ng/dL, a brief course of testosterone may be recommended. Various regimens are used, including testosterone enanthate or cypionate 100 mg intramuscularly once monthly for 4-6 months or 150 mg once monthly for 3 months. Some practitioners use oral oxandrolone in a dose of 1.25-2.5 mg daily for 6-12 months, which has the theoretical advantage that it is not aromatized and may have less effect on bone age advancement (though definitive evidence of advantage is lacking). Oral oxandrolone may cause hepatic dysfunction, and liver function tests should be monitored if it is used. Treatment is not necessary in all cases of constitutional delay, but if used it is usually followed by normal progression through puberty, and this may differentiate constitutional delay in puberty from isolated gonadotropin deficiency. The age of initiation of this treatment must be individualized.

If puberty fails to progress spontaneously after a short course of testosterone has been attempted, then HH becomes the likely diagnosis and necessitates continuous use of testosterone for normal pubertal development. At this point the patient should undergo an MRI scan and genetic testing to try to make a specific diagnosis. Once a diagnosis of HH has been made, treatment with testosterone will induce secondary sexual characteristics but will *not* stimulate testicular growth or spermatogenesis. Treatment with gonadotropins (either as a combination of hCG and human menopausal gonadotropins or as GnRH pulse therapy) will lead to testicular development, including spermatogenesis, but it is much more complex to manage, so in most cases testosterone treatment is still the best option. Either long-acting testosterone injections or a daily application of testosterone gel may be used (testosterone patches have a high incidence of skin rash and are infrequently used in pediatrics). Testosterone enanthate or cypionate ester may be used in a starting dose of 25-50 mg injected intramuscularly or subcutaneously every 3-4 weeks, with 50-mg increments every 6-9 months until a maintenance dose for adults (200-250 mg every 3-4 weeks) is achieved. At that time, testosterone patches or testosterone gel may be substituted for the injections. Depending on patient and physician preference, transdermal testosterone may also be used as initial treatment instead of injections. For older males, larger initial doses and increments can achieve more rapid virilization.

Treatment with gonadotropins is more physiologic but is expensive and complex, so it is less commonly used in adolescence. This treatment may be attempted in adult life when fertility is desired. The treatment schedule varies from 1,250 to 5,000 IU hCG in combination with 12.5-150 IU human menopausal gonadotropins 3 times per week intramuscularly. It may require up to 2 years of treatment to achieve

adequate spermatogenesis in adults. Recombinantly produced gonadotropins (LH and FSH) are also able to stimulate gonadal growth and function but are much more expensive. Treatment with GnRH (when available) is the most physiologically appropriate, but it requires the use of a subcutaneous infusion pump to deliver appropriately pulsed therapy because continuous exposure to GnRH will suppress gonadotropins rather than stimulate them. In some cases, patients with GnRH defects also have pituitary or testicular dysfunction (a dual defect) and may fail to respond adequately to GnRH or gonadotropin treatment. The rare patient with isolated LH deficiency can be treated effectively using hCG injections.

It has been found that up to 10% of patients diagnosed with HH (with or without anosmia) may exhibit spontaneous reversal of hypogonadism with sustained normal gonadal function after treatment has been discontinued; this may even occur in patients with known genetic variants in various genes, including *FGFR1, PROK2, GNRH, CHD7,* and *TAC/TACR3*. Such recovery is more likely in patients who show an increase in testicular volume during treatment or when treatment has been discontinued. A brief trial of interruption of treatment is justified in patients with idiopathic HH. However, the recovery of gonadal function may not be lifelong.

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Chapter 624

Pseudoprecocity Resulting from Tumors of the Testes

Omar Ali and Patricia A. Donohoue

Testicular tumors are relatively rare tumors in childhood, accounting for only 2–4% of all childhood cancers. 35% of prepubertal tumors are malignant, but in pubertal children most tumors are malignant (98% of painless testicular masses in pubertal males are malignant). Testicular tumors are discussed further in Chapter 552. Tumors that cause masculinization or feminization are rare and are derived from Leydig cells (producing androgens) or Sertoli cells (producing feminization). In addition, *enlargement* of the testes can be seen in congenital adrenal hyperplasia (CAH, caused by adrenal rests), in fragile X syndrome, and in cases where one testis is lost and the other hypertrophies to compensate.

Leydig cell tumors of the testes are rare causes of precocious pseudopuberty (gonadotropin-independent puberty) and cause asymmetric enlargement of the testes. Leydig cells are sparse before puberty, and tumors derived from them are more common in the adult. However, rare cases do occur in children; the youngest reported case was in a 1-year-old male. Although up to 10% of adult tumors may be malignant, metastasizing malignant tumors have not been reported in children, and pediatric Leydig cell tumors are usually unilateral and benign. Some tumors may be the result of somatic activating pathogenic variants of the luteinizing hormone receptor.

The clinical manifestations are those of puberty in the male; onset usually occurs at 5-9 years of age. Unilateral pubarche caused by local hormone action has been described. Gynecomastia may occur. The tumor of the testis can usually be readily felt; the contralateral unaffected testis is normal in size for the age of the patient.

Plasma levels of testosterone are markedly elevated, and follicle-stimulating hormone and luteinizing hormone levels are suppressed. Ultrasonography may aid in the detection of small nonpalpable tumors. Fine-needle aspiration biopsy may help define the diagnosis.

Treatment consists of surgical removal of the affected testis. These tumors are generally resistant to chemotherapy. Progression of virilization ceases after removal of the tumor, and partial reversal of the signs of precocity may occur.

Testicular adrenal rests may develop into tumors that mimic Leydig cell tumors. **Testicular adrenal rest tumors (TARTs)** are usually bilateral and occur in children with inadequately controlled CAH, usually of the salt-losing variety, during adolescence or young adult life. The stimulus for the growth of the adrenal rests is inadequate corticosteroid suppressive therapy causing excess adrenocorticotropic hormone secretion; treatment with adequate doses may result in their regression if they have not become quite large. These tumors are histologically similar to primary Leydig cell tumors, but definite evidence of their origin may be achieved by demonstrating their 21-hydroxylase activity. Misdiagnosis of these tumors as primary Leydig cell tumors may lead to unnecessary orchiectomy and should be avoided. Treatment is frequently unsatisfactory; improving the control of CAH will lower adrenocorticotropic hormone (ACTH) levels and prevent further growth of TARTs but may not shrink existing masses. Surgical removal can relieve pain (and is indicated if severe pain is present) but will not necessarily restore fertility. Sperm banking is recommended in adults with TARTs because these treatment modalities may not reverse their effect on fertility.

Fragile X syndrome (see Chapter 59) is caused by the amplification of a polymorphic CGG repeat in the 5′ untranslated region of *FMRI* at Xp17.3. The gene encodes an RNA-binding protein that is highly expressed in the brain and the testis. In otherwise normal individuals, 6-50 CGG repeats are present in the gene; the presence of 50-200 repeats is associated with mild intellectual disability and other abnormalities, and the presence of more than 200 repeats (fragile X pathogenic variant) is associated with the classic fragile X syndrome. 50 to 200 repeats are present in 1 in 1,000 White males, and pathogenic variants are found in 1 in 4,000-8,000. A cardinal characteristic of the condition is testicular enlargement *(macroorchidism)*, reaching 40-50 mL after puberty. Although the condition has been recognized in a child as young as 5 months of age, affected males younger than 6 years of age rarely have testicular enlargement; by 8-10 years of age, most have testicular volumes greater than 3 mL. The testes are enlarged bilaterally, are not nodular, and are histologically normal. Results of hormonal studies are normal. Direct DNA analysis searching for CGG repeat sequences permits definitive diagnosis.

Large-cell calcifying Sertoli cell tumors of the testes (usually associated with **Carney complex**) and **sex cord tumors with annular tubules** (frequently associated with **Peutz-Jeghers syndrome**) are extremely rare Sertoli cell tumors that may be a cause of breast development in young males. These tumors often occur bilaterally, are multifocal, and are detectible by ultrasonography. Excessive production of aromatase (P450arom), the enzyme that converts testosterone to estradiol, causes feminization of these males. Because these tumors are usually benign, they may be left in place if they are not causing pain; the gynecomastia can be treated with aromatase inhibitors.

Other causes of testicular enlargement are also present. In males with unilateral cryptorchidism, the contralateral testis is approximately 25% larger than normal for age. Testicular enlargement has also been noted in males with Henoch-Schönlein purpura and lymphangiectasia. Epidermoid and dermoid cysts of the testes have been reported but are rare.

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Chapter 625

Gynecomastia

Omar Ali and Patricia A. Donohoue

Gynecomastia, the proliferation of mammary glandular tissue in the male, is a common condition. True gynecomastia (the presence of glandular breast tissue) must be distinguished from pseudogynecomastia, which is the result of accumulation of adipose tissue in the area of the breast that is commonly seen in overweight males. True gynecomastia is characterized by the presence of a palpable fibroglandular mass at least 0.5 cm in diameter that is located concentrically beneath the nipple and areolar region.

PHYSIOLOGIC FORMS OF GYNECOMASTIA

Gynecomastia occurs in many newborn males as a result of normal stimulation by maternal estrogen; the effect usually disappears in a few weeks. It is then extremely rare in prepubertal males, in whom it should always be investigated to identify the cause, but it again becomes common during normal puberty.

Neonatal Gynecomastia

Transient gynecomastia occurs in 60–90% of male newborns secondary to exposure to estrogens during pregnancy. Breast development may be asymmetric, and galactorrhea is seen in approximately 5%. Most cases resolve within 4-8 weeks of birth, but a few can last as long as 12 months. No treatment is necessary.

Pubertal Gynecomastia

During early to mid-puberty, up to 70% of males develop various degrees of subareolar hyperplasia of the breasts. Incidence peaks at the same time as peak height velocity, which is around 14 years of age, at Tanner stage 3-4 and at a testicular volume of 5-10 mL. Physiologic pubertal gynecomastia may involve only one breast, and it is not unusual for both breasts to enlarge at disproportionate rates or at different times. Tenderness of the breast is common but transient. Spontaneous regression may occur within a few months; it rarely persists longer than 2 years. Significant psychosocial distress may be present, especially in obese males with relatively large breasts.

The cause is thought to be an imbalance between estrogen and androgen action at the level of breast tissue. Testing usually fails to reveal any significant difference in circulating estrogen and androgen levels between affected and unaffected males, but minor degrees of imbalance in free hormone levels may still be present. Other hormones, including leptin, insulin-like growth factor 1 (IGF-1), and luteinizing hormone, may directly stimulate breast development and may play a role in pubertal gynecomastia. Some cases may be caused by an increased sensitivity to estrogens and/or relative androgen resistance in the affected tissue. As androgen levels continue to rise in later puberty, *most cases resolve and no specific treatment is needed.*

Pathologic Gynecomastia

Monogenic forms of gynecomastia are extremely rare. Familial gynecomastia has occurred in several kindreds as an X-linked or autosomal dominant sex-limited trait. Some of these cases were found to be caused by constitutive activation of the P450 aromatase enzyme *(CYP19A1),* leading to increased peripheral conversion of C-19 steroids to estrogens (increased aromatization). A report of this syndrome in a father and his son and daughter suggests autosomal dominant inheritance.

Exogenous sources of estrogens are an important cause of gynecomastia in prepubertal children. Very small amounts of estrogens can cause gynecomastia in male children, and accidental exposure may occur by inhalation, percutaneous absorption, or ingestion. Common sources of estrogens include oral contraceptive pills and oral and transdermal estrogen preparations. Gynecomastia has been reported in workers involved in the manufacture of estrogens and even in the children of such workers. Gynecomastia can also occur secondary to exposure to medications that decrease the level of androgens (especially free androgens), increase estradiol, or displace androgens from breast androgen receptors. Spironolactone, alkylating agents, anabolic steroids, human chorionic gonadotropin, ketoconazole, cimetidine, and androgen inhibitors such as flutamide are all associated with the occurrence of gynecomastia. Antipsychotic medications may also cause gynecomastia by inducing hyperprolactinemia and hypogonadism. Weaker associations are seen with a large number of other medications and drugs, including opiates, alcohol, and marijuana, although the association with marijuana may not be as strong as previously thought. Lavender, tea tree oils, and excessive consumption of soy are also implicated as possible causes of prepubertal gynecomastia. An increased incidence of gynecomastia has also been reported in cancer survivors, in whom the mechanisms include the antiandrogenic or hypogonadotropic effects of cytotoxic drugs and radiotherapy.

Klinefelter syndrome and other causes of *male hypogonadism* are strongly associated with gynecomastia. Significant gynecomastia is seen in 50% of adolescents with Klinefelter syndrome; it is also seen in other conditions characterized by male undervirilization, including partial androgen insensitivity syndrome and 17-ketosteroid reductase deficiency. Gynecomastia has also been observed in children with congenital virilizing adrenal hyperplasia caused by 11β-hydroxylase deficiency and with Leydig and Sertoli cell tumors of the testis or with feminizing tumors of the adrenal gland. Patients with Klinefelter syndrome may also develop gynecomastia because of estrogen-secreting germ cell tumors of the mediastinum. The finding of such a tumor should prompt a karyotype; conversely, the finding of elevated β-human chorionic gonadotropin (HCG) in a patient with Klinefelter syndrome should lead to imaging of the mediastinum to look for a possible germ cell tumor there. The testes may not be enlarged in patients with Sertoli or Leydig cell tumors, and the tumor is frequently multifocal and bilateral. Excessive aromatase production and/or excessive estrogen production accounts for the gynecomastia. Feminizing Sertoli cell tumors are also a feature of Peutz-Jeghers syndrome and Carney complex. When gynecomastia is associated with galactorrhea, a prolactinoma should be considered. Hyperprolactinemia can also cause gynecomastia indirectly by inducing hypogonadism. Hyperthyroidism alters the ratio of androgen to estrogen by increasing bound androgen and decreasing the free testosterone; this may result in gynecomastia in up to 40% of cases. Gynecomastia is also seen in malnourished patients after restoration of normal nutrition (refeeding syndrome), in whom it may result from hepatic dysfunction or abnormal activation of the gonadotropin axis.

EVALUATION OF GYNECOMASTIA

In pubertal cases a detailed history and physical examination may be all that is needed to exclude rare pathologic causes. Historical evaluation should include family history of male relatives with gynecomastia, history of liver or renal disease, use of medications or drugs of abuse, and exposure to herbal and cosmetic products that may contain phytoestrogens. Physical examination should include special attention to the breasts (looking for overlying skin changes, fixation, local lymphadenopathy, and nipple discharge) as well as a testicular exam. No laboratory evaluation is indicated in routine cases with no other associated abnormality; however, all prepubertal cases and pubertal cases with suspicious features should be investigated. *Suspicious features include diameter >4 cm, rapid progression, persistence for more than 2 years, and persistence after age 17.*

Initial laboratory evaluation should include thyroid function tests (to rule out hyperthyroidism), testosterone, estradiol, HCG, luteinizing hormone, follicle-stimulating hormone, and prolactin levels. Because of circadian variation, these hormone levels should ideally be obtained in the morning. Liver and kidney function should also be evaluated. Most cases of hyperprolactinemia are associated with galactorrhea, but hyperprolactinemia can also cause gynecomastia without associated galactorrhea by suppressing gonadotropins and

inducing some degree of hypogonadism. A karyotype should be checked in all cases where history, examination, or laboratory tests suggest the possibility of Klinefelter syndrome. Gonadotropin levels can be a useful screen for Klinefelter syndrome and will be elevated in pubertal males with this condition. If they are elevated, a karyotype should be performed.

TREATMENT

Treatment in cases of benign pubertal gynecomastia usually consists of reassuring the boy and his family of the physiologic and transient nature of the phenomenon. When the enlargement is striking and persistent and causes serious emotional disturbance to the patient, specific treatment may be justified. Unfortunately, medical treatment is generally ineffective in long-standing cases. Early cases respond better to medical treatment, but it is then harder to justify, as most cases will resolve spontaneously. Agents that have been used for medical treatment include androgens, aromatase inhibitors, and estrogen antagonists. The effectiveness of synthetic androgens is variable and side effects are a concern, so these are rarely used in pediatrics. Aromatase inhibitors have a physiologic rationale, but placebo-controlled trials have been disappointing. Estrogen antagonists like tamoxifen and raloxifene are more effective, with raloxifene being the superior agent in at least one well-designed trial. If medical treatment is attempted, it should be in early cases (<12 months standing) using raloxifene (in a dose of 60 mg/day) or tamoxifen (10-20 mg/day) for 3-9 months, with the understanding that success rates are generally low in severe cases and that mild cases will likely resolve on their own without treatment.

In those cases where breast development is excessive (Tanner stages 3-5), causes significant psychologic distress, or fails to regress in 18-24 months, surgical removal of the enlarged breast tissue may be indicated, particularly in males who have completed or nearly completed pubertal development. Careful examination and laboratory testing to exclude nonphysiologic causes are advisable before proceeding to surgery.

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Chapter 626

Hypofunction of the Ovaries

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can be either primary or central in etiology. It may be caused by congenital failure of development, postnatal injury (primary or hypergonadotropic hypogonadism), or lack of central stimulation by the pituitary and/or hypothalamus (secondary or tertiary hypogonadotropic hypogonadism). **Primary ovarian insufficiency** (hypergonadotropic hypogonadism), also termed *premature ovarian failure* (POF), is characterized by the arrest of normal ovarian function before 40 years of age. Certain genetic pathogenic variants have been identified that can result in primary ovarian insufficiency. Hypofunction of the ovaries because of a lack of central stimulation (hypogonadotropic hypogonadism) can be associated with other processes, such as multiple pituitary hormone deficiencies and some chronic diseases. Table 626.1 details the etiologic classification of ovarian hypofunction (see also Fig. 600.7).

626.1 Hypergonadotropic Hypogonadism in the Female (Primary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

A diagnosis of hypergonadotropic hypogonadism before puberty is difficult. Except in the case of Turner syndrome, most affected patients have no prepubertal clinical manifestations.

TURNER SYNDROME

The term *Ullrich-Turner syndrome* is frequently used in Europe but is infrequently used in the United States, where the condition is called just *Turner syndrome* (see Chapter 99.4). The syndrome is defined as the combination of the characteristic phenotypic features accompanied by a complete or partial absence of the second X chromosome with or without mosaicism.

Pathogenesis

Half the patients with Turner syndrome have a 45,X chromosomal complement. Approximately 15% of patients are mosaics for 45,X and a normal cell line (45,X/46,XX). Other mosaics with isochromosomes, 45,X/46,X,i(Xq); with rings, 45,X/46,X,r(X); or with fragments, 45,X/46fra, occur less often. Mosaicism is commonly detected when more than one tissue is examined. The single X chromosome is of maternal origin in nearly 80% of 45,X patients. The mechanism of chromosome loss is unknown, and the risk for the syndrome does not increase with maternal age. The genes involved in the Turner phenotype are X-linked genes that escape inactivation. A major locus involved in the control of linear growth has been mapped within the pseudoautosomal region of the X chromosome (PAR1). *SHOX,* a homeobox-containing gene of 170 kb of DNA within the PAR1, is thought to be important for controlling growth in children with Turner syndrome, with Leri-Weill syndrome, and, rarely, patients with idiopathic short stature. Genes for the control of normal ovarian function are postulated to be on Xp and perhaps two supergenes on Xq.

Turner syndrome occurs in approximately 1 in 1,500-2,500 liveborn females. The frequency of the 45,X karyotype at *conception* is approximately 3%. However, 99% of these are spontaneously aborted, accounting for 5–10% of all abortuses. Mosaicism (45,X/46,XX) occurs in a proportion higher than that seen with any other aneuploid state, but the mosaic Turner constitution is rare among the abortuses; these findings indicate preferential survival for mosaic forms.

The normal fetal ovary contains approximately 7 million oocytes, but these begin to disappear rapidly after the fifth month of gestation. At birth, there are only 2 million (1 million active follicles); by menarche, there are 400,000-500,000; and at menopause, 10,000 remain. In the absence of one X chromosome, this process is accelerated, and nearly all oocytes are gone by 2 years of age. In aborted 45,X fetuses, the number of primordial germ cells in the gonadal ridge appears to be normal, suggesting that the normal process of oocyte loss is accelerated in patients with Turner syndrome. Eventually, the ovaries are described as streaks and consist only of connective tissue, with very few germ cells present.

Clinical Manifestations

Many patients with Turner syndrome are recognizable at birth because of a characteristic edema of the dorsa of the hands and feet and loose skinfolds at the nape of the neck. Low birthweight and decreased birth length are common (see Chapter 99.4). Clinical manifestations in childhood include webbing of the neck, a low posterior hairline, small mandible, prominent ears, epicanthal folds, high arched palate, a broad chest presenting the illusion of widely spaced nipples, cubitus valgus, and hyperconvex fingernails. The diagnosis is often first suspected at puberty when breast development fails to occur.

Short stature, the cardinal finding in virtually all females with Turner syndrome, may be present with few other clinical manifestations. The linear growth deceleration begins in infancy and early childhood, gets progressively more pronounced in later childhood and adolescence,

Table 626.1 Etiologic Classification of Ovarian Hypofunction

HYPOGONADOTROPIC HYPOGONADISM

Hypothalamic

Genetic defects
- Kallmann syndrome: *KAL1, FGFR1, FGF8, PROK2, PROKR2, CHD7, WDR11, NELF, SEMA3A*
- Other gene defects: leptin, leptin receptor, KISS-1 (deficiency of kisspeptin), *DAX-1, TAC3* (deficiency of neurokinin B), *TACR3, SEMA7A*
- Inherited syndromes: Prader-Willi, Bardet-Biedl, and others
- Marked constitutional growth delay

Acquired defects (reversible)
- Anorexia nervosa
- Drug use
- Malnutrition
- Chronic illness, especially Crohn disease
- Hyperprolactinemia

Pituitary

Genetic defects
- Isolated gonadotropin deficiency (GnRH receptor, FSH, and LH β-subunit)
- Septo-optic dysplasia (*HESX-1* defect in some cases)
- Disorders of pituitary organogenesis (*PROP1, LHX3, LHX4, SOX-3*)

Acquired defects
- Hyperprolactinemia
- Pituitary tumors
- Pituitary infarction
- Infiltrative disorders (histiocytosis, sarcoidosis)
- Hemosiderosis and hemochromatosis
- Radiation

HYPERGONADOTROPIC HYPOGONADISM

Genetic
- Follicle-stimulating hormone and luteinizing hormone resistance
- Pathogenic variants in steroidogenic pathways
- 46,XX gonadal dysgenesis
- Turner syndrome and its variants
- Noonan syndrome (RASopathy genes)
- *SF-1* pathogenic variants
- Galactosemia
- Fragile X–associated disorders
- Bloom syndrome
- Werner syndrome
- Ataxia-telangiectasia
- Fanconi anemia

Acquired
- Chemotherapy
- Radiation
- Autoimmune ovarian failure from autoimmune polyendocrine syndromes 1 and 2

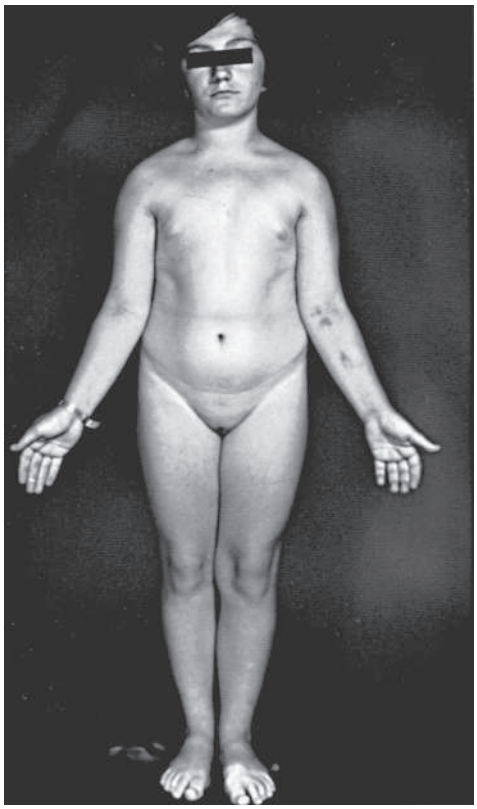

Fig. 626.1 Turner syndrome in a 15-yr-old female exhibiting failure of sexual maturation, short stature, cubitus valgus, and a goiter. There is no webbing of the neck. Karyotyping revealed 45,X/46,XX chromosome complement.

and results in significant adult short stature. Sexual maturation (breast development) fails to occur at the expected age; however, signs of adrenarche (pubic hair) are normally present. Among untreated patients with Turner syndrome, the mean adult height is 143-144 cm in the United States and most of Northern Europe, but 140 cm in Argentina and 147 cm in Scandinavia (Fig. 626.1). The height is well correlated with the midparental height (average of the parents' heights adjusted for child's sex). Specific growth curves for height have been developed for females with Turner syndrome.

Associated **cardiac defects** are common. In females with Turner syndrome, life-threatening consequences of X chromosome haploinsufficiency involve the cardiovascular system. There is a four- to fivefold increase in the rate of premature mortality secondary to congenital heart disease and premature coronary heart disease in adults with Turner syndrome. Clinically silent cardiac defects, mainly bicuspid aortic valve, are present in patients with Turner syndrome. Regardless of age, all patients with Turner syndrome need comprehensive cardiovascular evaluation by a cardiologist specializing in congenital heart disease at the time of diagnosis. Complete cardiologic evaluation, including echocardiography, reveals isolated nonstenotic bicuspid aortic valves in one third to half of the patients. In later life, bicuspid aortic valve disease can progress to dilation of the aortic root or aortic dissection. Less frequent defects include aortic coarctation (20%), aortic stenosis, mitral valve prolapse, and anomalous pulmonary venous drainage. In one study, 38% of patients with 45,X chromosomes had cardiovascular malformations compared with 11% of those with mosaic monosomy X; the most common were aortic valve abnormalities and aortic coarctation. Webbed neck in patients with or without recognized chromosome syndromes is associated with both flow-related and non–flow-related heart defects. Among patients with Turner syndrome, those with webbed necks have a much greater chance of having coarctation of the aorta than do those without webbed necks. Transthoracic echocardiogram in young females is adequate if cardiac anatomy is clearly seen; otherwise, magnetic resonance angiographic screening studies should be considered in asymptomatic individuals with Turner syndrome. During adolescence, and certainly before pregnancy (when possible) is contemplated, repeat cardiac evaluation should be considered even in those without prior findings of cardiac abnormalities. Blood pressure should be routinely monitored even in the absence of cardiac or renal lesions, especially in those with suggestions of aortic root dilation. Cardiac MRI is a valuable tool to detect and monitor aortic root dilation.

Renal ultrasound should be performed in all females with Turner syndrome at diagnosis. One fourth to one third of patients have **renal malformations** on ultrasonographic examination (50% of those with 45,X karyotypes). The more serious defects include pelvic kidney, horseshoe kidney, double collecting system, the complete absence of one kidney, and ureteropelvic junction obstruction. Some of the malformations may increase the risk of hypertension and urinary tract

infection. Idiopathic hypertension is also common. Females with Turner syndrome who had normal baseline renal ultrasound findings did not develop the renal disease during a follow-up period averaging 6 years.

When the ovaries are examined by ultrasonography, there are no age-related differences in detecting ovarian tissue; 27–46% of patients have detectable ovaries at various ages; 76% of those with X mosaicism and 26% of those with 45,X karyotypes have detectable ovaries.

Sexual maturation usually fails to occur, but 10–20% of females have spontaneous breast development, and a small percentage may have menstrual periods. Primary gonadal failure is associated with early onset of adrenarche (elevation in dehydroepiandrosterone sulfate) but delayed pubarche (pubic hair development). Spontaneous pregnancies have been reported in menstruating patients with Turner syndrome. Premature menopause, increased risk of miscarriage, and offspring with increased risk of trisomy 21 have been reported. A woman with a 45,X/46,X,r(X) karyotype treated with hormone replacement therapy had three pregnancies, resulting in a normal 46,XY male infant, a spontaneous abortion, and a healthy term female with Turner syndrome 45,X/46,Xr(X).

Antithyroid antibodies (thyroid peroxidase and/or thyroglobulin antibodies) occur in 30–50% of patients. The prevalence increases with advancing age. **Autoimmune thyroid disease**, with or without a goiter, occurs in 10–30% of patients. Age-dependent abnormalities in carbohydrate metabolism characterized by abnormal glucose tolerance and insulin resistance and, only rarely, frank type 2 diabetes occur in older patients with Turner syndrome. Impaired insulin secretion has been described in 45,X women. Cholesterol levels are elevated in adolescence, regardless of body mass index or karyotype.

Inflammatory bowel disease (both Crohn disease and ulcerative colitis), gastrointestinal bleeding because of abnormal mesenteric vasculature, and delayed gastric emptying time have all been reported. Screening for celiac disease is recommended because the risk of celiac disease is increased in Turner syndrome, with 4–6% of individuals affected. Although autoimmune diseases have been associated with Turner syndrome, the prevalence of type 1 diabetes with Turner syndrome is not very high.

Chronic liver disease may develop in adults with Turner syndrome. Its pathogenesis is poorly defined.

Sternal malformations can be detected by lateral chest radiography. An increased carrying angle at the elbow is usually not clinically significant. Scoliosis occurs in approximately 10% of adolescent females. Congenital hip dysplasia occurs more commonly than in the general population. Reported eye findings include anterior segment dysgenesis and keratoconus. Pigmented nevi become more prominent with age; melanocytic nevi are common. Essential hyperhidrosis, torus mandibularis, and alopecia areata occur rarely.

Recurrent bilateral otitis media develops in approximately 75% of patients. Sensorineural hearing deficits are common, and the frequency increases with age. Problems with gross and fine motor sensory integration, failure to walk before 15 months of age, and early language dysfunction often raise questions about developmental delay, but intelligence is normal in most patients. However, cognitive impairment does occur in patients with 45,X/46,X,r(X); the ring chromosome is unable to undergo inactivation and leads to two functional X chromosomes.

Special attention should be given to psychosocial development in females with Turner syndrome. In general, behavior is normal in females with Turner syndrome, but they are at an increased risk for social isolation, immaturity, and anxiety. Other conditions, such as dyslexia, nonverbal learning disability, and attention-deficit disorder, have been reported in females with Turner syndrome. In adults, deficits in perceptual spatial skills are more common than they are in the general population. Some unconfirmed data suggest the existence of an imprinted X-linked locus that affects cognitive function such as verbal and higher-order executive function skills. These functions are apparently better when the X is paternal in origin.

The prevalence of mosaicism depends in large part on the techniques used for studying chromosomal patterns. The use of fluorescent in situ hybridization and reverse transcription–polymerase chain reaction (PCR) has increased the reported prevalence of mosaic patterns to as high as 60–74%.

Mosaicism involving the Y chromosome occurs in 5%. A population study using PCR with five different primer sets found Y chromosome material in 12.2%. **Gonadoblastoma** among Y-positive patients occurred in 7–10%. Therefore the recommendation is that prophylactic gonadectomy be performed even in the absence of MRI or CT evidence of tumors. The recommended timing of this procedure is at the time of diagnosis, but this may need to be reevaluated in the future. The gonadoblastoma locus on the Y chromosome (GBY) maps close to the Y centromere. The presence of only the SRY (sex-determining region on the Y chromosome) locus is not sufficient to confer increased susceptibility for the development of gonadoblastoma. Routine PCR for Y chromosome detection for the purpose of assigning gonadoblastoma risk is not indicated. High-throughput quantitative genotyping may provide an effective and inexpensive method for the identification of X chromosome abnormalities and Y chromosome material identification.

In patients with 45,X/46,XX mosaicism, the clinical abnormalities are attenuated and fewer; short stature is as frequent as it is in the 45,X patient and may be the only manifestation of the condition other than ovarian failure (see Fig. 626.1).

Laboratory Findings

Chromosomal analysis must be considered routinely in females who have unexpected short stature based on parental heights. Turner syndrome is detected in ~5% of females referred to an endocrinology service because of short stature. Patients with a marker chromosome in some or all cells should be tested for DNA sequences at or near the centromere of the Y chromosome for GBY.

Ultrasonography of the heart, kidneys, and ovaries is indicated after the diagnosis is established. The most common skeletal abnormalities are shortening of the fourth metatarsal and metacarpal bones, epiphyseal dysgenesis in the joints of the knees and elbows, Madelung deformity, scoliosis, and, in older patients, inadequate osseous mineralization.

Plasma levels of gonadotropins, particularly follicle-stimulating hormone (FSH), are markedly elevated to greater than those of age-matched controls during infancy; at 2-3 years of age, a progressive decrease in levels occurs until they reach a nadir at 6-8 years of age, and by 10-11 years of age, they rise to adult agonadal levels.

Thyroid peroxidase antibodies should be checked to detect autoimmune thyroiditis if the thyroid-stimulating hormone (TSH) level is abnormal. Annual or biannual TSH levels are recommended. Females with Turner syndrome should be screened for celiac disease by measuring tissue transglutaminase immunoglobulin A antibodies. Initial testing should be done around age 4 years and repeated every 2-5 years. Extensive studies have failed to establish that growth hormone deficiency plays a primary role in the pathogenesis of the growth disorder. Defects in normal secretory patterns of growth hormone are seen in adolescents because of a lack of gonadal steroids, but not in younger females with Turner syndrome.

Treatment

Treatment with recombinant human growth hormone increases height velocity and ultimate stature in most, but not all, children with Turner syndrome. Many females achieve heights of greater than 150 cm with early initiation of treatment. In one clinical trial, 99 patients with Turner syndrome who started receiving growth hormone at a mean age of 10.9 years at doses between 0.27 and 0.36 mg/kg/wk achieved a mean height of 149 cm, with nearly one third reaching heights greater than 152.4 cm (60 in). In the Netherlands, higher doses of growth hormone (up to 0.63 mg/kg/wk in the third year of treatment) resulted in 85% of the subjects reaching adult heights in the normal range for the Dutch reference population. Growth hormone treatment should be initiated in early childhood and/or when there is evidence of height velocity attenuation on specific Turner syndrome growth curves. Growth hormone therapy does not significantly aggravate carbohydrate tolerance and does not result in marked adverse events in patients with Turner syndrome. Serum levels of insulin-like growth factor 1 should be monitored if the patient is receiving high doses of growth hormone. If the insulin-like growth

factor 1 levels are significantly elevated, the dose of growth hormone may need to be reduced. Treatment with growth hormone can cause excessive growth of the hands and feet in some females with Turner syndrome.

Oxandrolone has also been used to treat the short stature associated with Turner syndrome, either alone or in combination with growth hormone. This nonaromatizable synthetic anabolic steroid has weak androgenic effects, and patients should be monitored for signs of pubarche and hepatotoxicity. The latter is rare.

Replacement therapy with estrogens is indicated, but there is variation among pediatric endocrinologists about the optimal age at which to initiate treatment. The psychologic preparedness of the patient to accept therapy must be considered. The improved growth achieved by females treated with growth hormone in childhood permits initiation of estrogen replacement at 12-13 years. Delaying estrogen therapy to optimize height potential until 15 years of age, as previously recommended, seems unwarranted. This change to starting earlier estrogen therapy was considered because of the psychologic importance of age-appropriate pubertal maturation. In addition, delaying estrogen therapy could be deleterious for bone health and potentially other aspects of the child's health. Low-dose estrogen replacement at 12 years of age permits a normal pace of puberty without interfering with the positive effect of growth hormone on the final adult height. Estrogen therapy improves verbal and nonverbal memory in females with Turner syndrome. In young women with age-appropriate pubertal development who achieve normal height, health-related quality-of-life questionnaires have yielded normal results.

Many forms of estrogen are available. Oral estrogens had been mostly used in the past. Transdermal patches are increasing in popularity. This is because transdermal patches bypass the first-pass hepatic metabolism, requiring only a small amount of estrogen to attain adequate function. Many treatment protocols have been developed, and several are as follows. For oral preparations, a conjugated estrogen (Premarin), 0.15-0.625 mg daily, or micronized estradiol (Estrace), 0.5 mg given daily for 3-6 months, is usually effective in inducing puberty. The recommendations for transdermal patch therapy are 6.25 μg daily, gradually increased over 2 years to the adult dose of 100-200 μg daily. The estrogen may be cycled (taken on days 1-23) or not. A progestin (Provera) is added (taken on days 10-23) in a dose of 5-10 mg daily. In the week after the progestin, withdrawal bleeding usually occurs. Combination oral contraceptive pills may also be used for hormone replacement therapy.

Prenatal chromosome analysis for advanced maternal age has revealed a frequency of 45,X/46,XX that is 10 times higher than when diagnosed postnatally. Most of these patients have no clinical manifestations of Turner syndrome, and levels of gonadotropins are normal. Awareness of this mild phenotype is important in counseling patients.

Psychosocial support for these females is an integral component of treatment. A comprehensive psychologic education evaluation is recommended either at the time of Turner syndrome diagnosis, depending on the patient's age, when any of the components of behavior or cognition become obvious, or immediately preceding school entry. In addition to the healthcare team, the Turner Syndrome Society, which has local chapters in the United States and similar groups in Canada and other countries, provides a valuable support system for these patients and their families.

Successful pregnancies have been carried to term using ovum donation and in vitro fertilization. Adolescents with few signs of spontaneous puberty may have ovaries with follicles. There remains a future possibility of using cryopreserved ovarian tissue with immature oocytes before the regression of the ovaries for future pregnancies. In adult women with Turner syndrome, there seems to be a high prevalence of undiagnosed bone mineral density, lipid, and thyroid abnormalities. Glucose intolerance diminished first-phase insulin response, elevated blood pressure, and lowered fat-free mass are common. Glucose tolerance worsens, but fat-free mass and blood pressure and general physical fitness improve with sex hormone replacement. The neurocognitive profile of adult women is unaffected by estrogen status.

XX GONADAL DYSGENESIS

Some phenotypically and genetically normal females have gonadal lesions identical to those in 45,X patients but without somatic features of Turner syndrome; their condition is termed **pure gonadal dysgenesis** or pure **ovarian dysgenesis**.

The disorder is rarely recognized in prepubertal children because the external genitals are normal, no other abnormalities are visible, and growth is normal. At pubertal age, sexual maturation fails to take place. Plasma gonadotropin levels are elevated. Delay of epiphyseal fusion may result in a *eunuchoid* habitus. Pelvic ultrasonography reveals streak ovaries.

Affected siblings, parental consanguinity, and failure to uncover mosaicism suggest female-limited autosomal recessive inheritance. The disorder appears to be especially frequent in Finland (1 in 8,300 liveborn females). In this population, several pathogenic variants in the FSH receptor gene (on chromosome 2p) are demonstrated as the cause of the condition. In contrast, FSH receptor gene variants are not detected in Mexican women with 46,XX gonadal dysgenesis. In some patients, XX gonadal dysgenesis has been associated with sensorineural deafness (**Perrault syndrome**). A patient with this condition and concomitant growth hormone deficiency and virilization has also been reported. There may be distinct genetic forms of this disorder. **Müllerian agenesis**, or **Mayer-Rokitansky-Küster-Hauser** syndrome, which is second to gonadal dysgenesis as the most common cause of primary amenorrhea, occurring in 1 in 4,000-5,000 females, has been reported in association with 46,XX gonadal dysgenesis in a 17-year-old adolescent with primary amenorrhea and lack of breast development. One case of dysgerminoma with syncytiotrophoblastic giant cells was reported. An 18-year-old woman with primary amenorrhea and an absence of müllerian-derived structures, unilateral renal agenesis, and clinical signs of androgen excess—a phenotype resembling Mayer-Rokitansky-Küster-Hauser syndrome—was found to have a loss-of-function variant in *WNT4*. Treatment consists of estrogen replacement therapy.

45,X/46,XY GONADAL DYSGENESIS

45,X/46,XY gonadal dysgenesis, also called **mixed gonadal dysgenesis**, has extreme postnatal phenotypic variability that may extend from a Turner-like syndrome to a male phenotype with a penile urethra; it is possible to delineate three major clinical phenotypes. Short stature is a major finding in all affected children. Ninety percent of prenatally diagnosed cases have a normal male phenotype.

Some patients have no evidence of virilization; they have a female phenotype and often have the somatic signs of Turner syndrome. The condition is discovered prepubertally when chromosomal studies are made in short females or later when chromosomal studies are made because of failure of sexual maturation. Fallopian tubes and uterus are present. The gonads consist of intraabdominal undifferentiated streaks; chromosomal study of the streak often reveals an XY cell line. The streak gonad differs somewhat from that in females with Turner syndrome; in addition to wavy connective tissue, there are often tubular or cordlike structures, occasional clumps of granulosa cells, and, frequently, mesonephric or hilar cells.

Some children have mild virilization manifested only by prepubertal clitoromegaly. Normal müllerian structures are present, but at puberty virilization occurs. These patients usually have an intraabdominal testis, a contralateral streak gonad, and bilateral fallopian tubes.

Many 45,X/46,XY children present with frank ambiguity of the genitals in infancy (Fig. 626.2). A testis and vas deferens are found on one side in the labioscrotal fold, and a streak gonad is identified on the contralateral side. Despite the presence of a testis, fallopian tubes are often present bilaterally. An infantile or rudimentary uterus is often present.

Other genotypes and phenotypes have been described in mixed gonadal dysgenesis. Approximately 25% of 200 analyzed patients have a dicentric Y chromosome (45,X/46,X,dic Y). In some patients the Y chromosome may be represented by only a fragment (45,X/45,X +fra); application of Y-specific probes can establish the origin of the fragment. It is unclear why the same genotype (45,X/46,XY) can result in

Fig. 626.2 A 45,X/46XY neonate with sex chromosome disorder of sex development was noted at birth to have male-appearing external genitalia with a phallus measured at 2.5 × 1.2 cm and penoscrotal hypospadias. The left gonad was palpable in an incompletely fused scrotum, whereas the right gonad was not palpable. Gonadal biopsy revealed a testis on the left side and streak gonad on the right. The diagnosis was mixed gonadal dysgenesis. *(From Remeithi SA, Wherret DK. Disorders of sexual development. In: Martin RJ, Fanaroff AA, Walsh MC, eds. Fanaroff and Martin's Neonatal-Perinatal Medicine, 10th ed. Philadelphia: Elsevier; 2015: Fig. 98–13)*

diverse phenotypes. Pathogenic variants in *SRY* have been described in some patients.

Children with a female phenotype present no problem in gender of rearing. Patients who are only slightly virilized are usually assigned a female gender of rearing before a diagnosis is established. Patients with ambiguity of the genitals are often clinically indistinguishable from patients with various types of 46,XY disorders of sex development (46,XY DSD). In some instances, there may need to be careful consideration regarding gender of rearing. Factors that may influence this decision include short stature, the need for surgical genital reconstruction, the presence of müllerian structures, and the need for gonadectomy because of predisposition of the gonad to the development of malignancy. In some patients followed to adulthood, the putative normal testis proves to be dysgenetic with eventual loss of Leydig and Sertoli cell function (see Chapter 623). In an analysis of 22 patients with mixed gonadal dysgenesis, no significant associations or correlations were found between internal and external phenotypes or endocrine function and gonadal morphologic features. The appearance of the external genitalia determined the gender of rearing. In 11 patients, basal and human chorionic gonadotropin–stimulated testosterone levels were lower than in control subjects.

Gonadal tumors, usually **gonadoblastomas**, occur in approximately 25% of these children. A gonadoblastoma locus has been localized to a region near the centromere of the Y chromosome (GBY). These germ cell tumors are preceded by the changes of carcinoma in situ. Accordingly, both gonads should be removed in all patients reared as females, and the undifferentiated gonad should be removed in the patients reared as males.

There is no correlation among the proportion of 45,X/46,XY cell lines in either blood or fibroblasts with the phenotype. In the past, all patients came to clinical attention because of their abnormal phenotypes. However, 45,X/46,XY mosaicism is found in approximately 7% of fetuses, with true chromosome mosaicism encountered prenatally. Of 76 infants with 45,X/46,XY mosaicism diagnosed prenatally, 72 had a normal male phenotype, 1 had a female phenotype, and only 3 males had hypospadias. Of 12 males whose gonads were examined, only 3 were abnormal. These data must be considered when counseling a family in which a 45,X/46,XY infant is discovered prenatally.

XXX, XXXX, AND XXXXX FEMALES

XXX Females

The 47,XXX (trisomy) chromosomal constitution is the most frequent extra X chromosome abnormality in females, occurring in almost 1 in 1,000 liveborn females. In 68%, this condition is caused by maternal meiotic nondisjunction, but paternal sex chromosome errors cause most 45,X and half of 47,XXY constitutions. The phenotype is that of a normal female; affected infants and children are not recognized based on the genital appearance.

Sexual development and menarche are normal. Most pregnancies have resulted in normal infants. By 2 years of age, delays in speech and language become evident, and some see a lack of coordination, poor academic performance, and immature behavior. These females tend to be tall, manifest behavior disorders, and often require special education classes. Using high-resolution MRI, 47,XXX subjects have lower amygdala volumes than euploid controls; 47,XXY subjects had even lower amygdala volumes. In a review of 155 females, 62% were physically normal. There is marked variability within the syndrome, and a small proportion of affected females are well coordinated, socially outgoing, and academically superior.

XXXX and XXXXX Females

The great majority of females with these rare karyotypes have intellectual disabilities. Commonly associated defects are epicanthal folds, hypertelorism, clinodactyly, transverse palmar creases, radioulnar synostosis, and congenital heart disease. Sexual maturation is often incomplete and may not occur at all. Nevertheless, three women with tetra-X syndrome gave birth, but no pregnancies were reported in 49,XXXXX women. Most 48,XXXX women tend to be tall, with an average height of 169 cm, whereas short stature is a common feature of the 49,XXXXX phenotype.

NOONAN SYNDROME

Females with Noonan syndrome show certain anomalies also seen in females with 45,X Turner syndrome, but they have normal 46,XX chromosomes (see Chapter 101.1). The most common abnormalities are the same as those described for males with Noonan syndrome (see Chapter 623). Short stature is one of the cardinal signs of this syndrome. The phenotype differs from Turner syndrome in several respects. Cognitive impairment is often present, the cardiac defect is most often pulmonary valvular stenosis or an atrial septal defect rather than an aortic defect, normal sexual maturation usually occurs but is delayed by 2 years on average, and POF has been reported. The FDA approves growth hormone therapy for use in Noonan syndrome patients with short stature.

OTHER OVARIAN DEFECTS

Some young women with no chromosomal abnormalities are found to have streak gonads that may contain only occasional or no germ cells. Gonadotropins are increased. Cytotoxic drugs, especially alkylating agents such as cyclophosphamide and busulfan, procarbazine, etoposide, and exposure of the ovaries to irradiation for the treatment of malignancy are frequent causes of ovarian failure. Young women with Hodgkin disease demonstrate that combination chemotherapy and pelvic irradiation may be more deleterious than either therapy alone. Teenagers are more likely than older women to retain or recover ovarian function after irradiation or combined chemotherapy; normal pregnancies have occurred after such treatment. Treatment regimens may result in some ovarian damage in most females treated for cancer. The median lethal dose for the human oocyte is estimated to be approximately 4 Gy; doses as low as 6 Gy have produced primary amenorrhea. Ovarian transposition before abdominal and pelvic irradiation

in childhood can preserve ovarian function by decreasing the ovarian exposure to less than 4-7 Gy.

Autoimmune ovarian failure occurs in 60% of children older than 13 years of age with type I autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, mucocutaneous candidiasis). This condition, also known as *polyglandular autoimmune disease type 1,* is rare worldwide but not in Finland, where, as a result of a founder gene effect, it occurs in 1 in 25,000 people. Affected females may not develop sexually; secondary amenorrhea may occur in young women. The ovaries may have lymphocytic infiltration or appear simply as streaks. Most affected patients have circulating steroid cell antibodies and autoantibodies to 21-hydroxylase. Among patients with polyglandular autoimmune syndromes, 5% have hypogonadism.

The condition also occurs in young women as an isolated event or in association with other autoimmune disorders, leading to secondary amenorrhea (POF). It occurs in 0.2–0.9% of women younger than 40 years of age. POF is a heterogeneous disorder with many causes: chromosomal, genetic, enzymatic, infectious, and iatrogenic. When associated with autoimmune adrenal disease, steroid cell autoantibodies are usually present. These antibodies react with P450scc, 17α-OH, or 21-OH enzymes. Steroid cell autoantibodies are rarely found when associated with an entire host of endocrine and nonendocrine autoimmune diseases and not adrenal autoimmunity. A second autoimmune disorder, often subclinical, is found in 10–39% of adult patients with POF, including autoimmune thyroid disease, type 1 diabetes, systemic lupus erythematosus (SLE), inflammatory bowel disease, immune thrombocytopenia or hemolytic anemia, celiac disease, myasthenia gravis, and rheumatoid arthritis. One 17-year-old with idiopathic thrombocytopenic purpura and 47,XXX chromosomes had autoimmune POF. Patients with POF do not have the neurocognitive defects found in Turner syndrome patients.

Galactosemia, particularly the classical form of the disease, usually results in ovarian damage, beginning during intrauterine life. Levels of FSH and luteinizing hormone (LH) are elevated early in life. Ovarian damage may be caused by deficient uridine diphosphate-galactose (see Chapter 107.2). **Denys-Drash syndrome** caused by a *WT1* pathogenic variant can result in ovarian dysgenesis.

Ataxia-telangiectasia may be associated with ovarian hypoplasia and elevated gonadotropins; the cause is unknown. Gonadoblastomas and dysgerminomas have occurred in a few females.

Hypergonadotropic hypogonadism occurs as a result of resistance of the ovary to both endogenous and exogenous gonadotropins **(Savage syndrome)**. This condition also occurs in women with POF. Antiovarian antibodies or FSH receptor abnormalities may cause this condition. The FSH receptor gene variants have been reported as an autosomal recessive condition (see Chapter 622). A few females with 46,XX chromosomes presenting in primary amenorrhea with elevated gonadotropin levels were found to have inactivating variants of the LH receptor gene. This suggests that LH action is needed for normal follicular development and ovulation. Other genetic defects associated with ovarian failure include pathogenic variants in *SF-1, FOXL2, GNAS, CYP17,* and *CYP19.*

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626.2 Hypogonadotropic Hypogonadism in the Female (Secondary Hypogonadism)

Alvina R. Kansra and Patricia A. Donohoue

Hypofunction of the ovaries can result from failure to secrete normal pulses of the gonadotropins LH and FSH. Hypogonadotropic hypogonadism (HH) may occur if the hypothalamic-pituitary-gonadal axis is interrupted either at the hypothalamic or pituitary level. The mechanisms that result in HH include failure of the hypothalamic LH–releasing hormone (also known as *gonadotropin-releasing hormone*) pulse generator or inability of the pituitary to respond with secretion of LH and FSH. It is often difficult to distinguish between marked constitutional delay and HH.

HYPOPITUITARISM

Hypogonadotropic hypogonadism is most commonly seen with multiple pituitary hormone deficiencies resulting from malformations (e.g., septo-optic dysplasia, other midline defects), pituitary transcription factor defects such as in PROP-1, or lesions of the pituitary that are acquired postnatally. Familial isolated gonadotropin deficiency associated with anosmia (Kallmann syndrome) may occur in females. Many other genetic causes for HH have been identified. A gene important in LH-releasing hormone secretion is named *KISS* (encoding the protein kisspeptin), which is suggested to play a significant role in the development of the LH-releasing hormone–secreting cells. Another set of genes implicated in HH are the genes for neurokinin B *(TAC3)* and its receptor *(TAC3R).*

In children with idiopathic hypopituitarism, the defect is usually found in the hypothalamus. In these patients, administration of gonadotropin-releasing hormone results in increased plasma levels of FSH and LH, establishing the integrity of the pituitary gland.

Hypogonadotropic hypogonadism is less common than hypergonadotropic hypogonadism. Ovarian function may be abnormal when associated with LH excess, a condition known as *polycystic ovarian syndrome* (polycystic ovary syndrome; see Chapter 589).

Isolated Deficiency of Gonadotropins

This heterogeneous group of disorders is evaluated more fully with the use of the gonadotropin-releasing hormone analog stimulation test rather than a single measurement of gonadotropin levels. In most children the pituitary gland is normal, and the defect causing gonadotropin deficiency resides in the hypothalamus. Patients with **hyperprolactinemia**, most often caused by a pituitary prolactin-secreting adenoma, often have suppression of gonadotropin secretion. If breast development has occurred, then galactorrhea and amenorrhea are frequently seen.

Several sporadic instances of anosmia with hypogonadotropic hypogonadism have been reported. **Anosmic** hypogonadal females have also been reported in kindreds with Kallmann syndrome, but hypogonadism more frequently affects the males in these families. Pathogenic variants in the gene for the β-subunit of FSH and LH have been reported.

Some autosomal recessive disorders, such as Laurence-Moon-Biedl, multiple lentigines, and Carpenter syndromes, appear in some instances to include gonadotropic hormone deficiency. Patients with Prader-Willi syndrome usually have some degree of HH. Females with severe thalassemia may have gonadotropin deficiency from pituitary damage caused by chronic iron overload secondary to multiple transfusions. Anorexia nervosa frequently results in HH. The rare patients described with leptin deficiency or leptin receptor defects have failure of pubertal maturation because of gonadotropin deficiency.

DIAGNOSIS

The diagnosis may be apparent in patients with other deficiencies of pituitary tropic hormones, but, as in males, it is difficult to differentiate isolated hypogonadotropic hypogonadism from physiologic delay of puberty. Repeated measurements of FSH and LH, particularly during sleep, may reveal the rising levels that herald the onset of puberty. Stimulation testing with gonadotropin-releasing hormone analog may help to establish the diagnosis. Morbidity for both men and women with hypogonadism includes infertility and an increased risk of osteoporosis.

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Chapter 627

Pseudoprecocity Resulting from Lesions of the Ovary

Alvina R. Kansra and Patricia A. Donohoue

Females with signs of early puberty may, in rare circumstances, have ovarian tumors or cysts that secrete estrogenic, androgenic, or both types of hormones. In these patients, the sex steroid production is not mediated by pituitary gonadotropin secretion; they produce pseudoprecocity.

Ovarian tumors are rare in the pediatric population, occurring at a rate of fewer than 3 in 100,000. Most ovarian masses are benign, but 10–30% may be malignant. If they occur before 8 years of age, they may cause signs of puberty. Ovarian malignancies, the most common genital neoplasms in adolescence, account for only 1% of childhood cancers. More than 60% are germ cell tumors, which are dysgerminomas that can secrete tumor markers and sex hormones (see Chapter 552). Five to 10% of germ cell tumors occur in phenotypic females, with abnormal gonads associated with the presence of a Y chromosome. The next most common are epithelial cell tumors (20%), and nearly 10% are sex cord/stromal tumors (granulosa, Sertoli cell, and mesenchymal tumors). Multiple tumor markers can be seen in ovarian tumors, including α-fetoprotein, human chorionic gonadotropin, carcinoembryonic antigen, oncoproteins, p105, p53, *KRAS* pathogenic variants, cyclin D_1, epidermal growth factor–related proteins and receptors, cathepsin B, and others. Variable levels of inhibin-activin subunit gene expression have been detected in ovarian tumors.

Functioning lesions of the ovary consist of benign cysts or malignant tumors. The majority synthesize estrogens; a few synthesize androgens. The most common estrogen-producing ovarian tumor causing precocious puberty is the granulosa cell tumor. Other tumors that can cause precocious puberty are thecomas, luteomas, mixed types, theca-lutein, follicular cysts, and other ovarian tumors (i.e., teratoma, choriocarcinoma, and dysgerminoma).

ESTROGENIC LESIONS OF THE OVARY

These lesions cause **isosexual** precocious sexual development but account for only a small percentage of all cases of precocity. Benign ovarian follicular cysts are the most common tumors associated with isosexual precocious puberty in females; they may rarely be gonadotropin dependent. Gonadotropin-independent follicular cysts that produce estrogen are often associated with **McCune-Albright syndrome**.

Juvenile Granulosa Cell Tumor

In childhood, the most common neoplasm of the ovary with estrogenic manifestations is the granulosa cell tumor, although it makes up only 1–10% of all ovarian tumors. These tumors have distinctive histologic features that differ from those encountered in older females (adult granulosa cell tumor). The cells have high mitotic activity, follicles are often irregular, Call-Exner bodies are rare, and luteinization is frequent. The tumor may be solid or cystic or both. It usually is benign. This tumor has been associated with multiple enchondromas **(Ollier disease)** and with multiple subcutaneous hemangiomas **(Maffucci syndrome)**.

Clinical Manifestations and Diagnosis

The juvenile granulosa cell tumor has been observed in newborns and may manifest with sexual precocity at 2 years of age or younger; about half these tumors occurred before 10 years of age. The mean age at diagnosis is 7.5 years. The tumors are almost always unilateral. The breasts become enlarged, rounded, and firm, and the nipples prominent. The external genitals resemble those of a normal girl at puberty, and the uterus is enlarged. A white vaginal discharge is followed by irregular or cyclic menstruation. However, ovulation does not occur. The presenting manifestation may be abdominal pain or swelling. Pubic hair is usually absent unless there is mild virilization.

A mass is readily palpable in the lower portion of the abdomen in most children by the time sexual precocity is evident. However, the tumor may be small and escape detection even on careful rectal and abdominal examination; ultrasonography may detect the tumors, but CT or MRI scans are most sensitive. Most tumors are diagnosed at very early stages of malignancy.

Plasma estradiol levels are markedly elevated. Plasma levels of gonadotropins are suppressed and do not respond to gonadotropin-releasing hormone analog stimulation. Levels of antimüllerian hormone, inhibin B, and α-fetoprotein may be elevated. Activating pathogenic variants of $G_S\alpha$ are seen in 30%, and GATA-4 expression is retained in the more aggressive tumors, whereas antimüllerian hormone levels are inversely proportional to tumor size. Bone age is moderately advanced. Several case reports showing the association of 45,X/46,XY karyotype and ambiguous genitalia with ovarian granulosa tumor have been published.

Treatment and Prognosis

The tumor should be removed as soon as the diagnosis is established. Prognosis is excellent because less than 5% of these tumors in children are malignant. However, advanced-stage tumors behave aggressively and require difficult decisions regarding surgical approaches and the use of irradiation and chemotherapy. In adults with granulosa cell tumors, p53 expression is associated with unfavorable prognosis. Vaginal bleeding immediately after removal of the tumor is common. Signs of precocious puberty abate and may disappear within a few months after the operation. The secretion of estrogens returns to normal.

Sex cord tumor with annular tubules is a distinctive tumor, thought to arise from granulosa cells, that occurs primarily in patients with **Peutz-Jeghers syndrome**. These tumors are multifocal, bilateral, and usually benign. The presence of calcifications aids ultrasonographic detection. Increased aromatase production by these tumors results in gonadotropin-independent precocious puberty. Inhibin A and B levels are elevated and decrease after tumor removal. In one study, 9 of 13 sex cord/stromal tumors exhibited follicle-stimulating hormone receptor pathogenic variants, suggesting a role for such mutation in the development of these tumors.

Chorioepithelioma has been reported only rarely. This highly malignant tumor is thought to arise from a preexisting teratoma. The usually unilateral tumor produces large amounts of human chorionic gonadotropin, which stimulates the contralateral ovary to secrete estrogen. Elevated levels of human chorionic gonadotropin are diagnostic.

Follicular Cyst

Small ovarian cysts (<0.7 cm in diameter) are common in prepubertal children. At puberty and in females with true isosexual precocious puberty, larger cysts (1-6 cm) are often seen; these are secondary to stimulation by gonadotropins. Similar larger cysts occur occasionally in young females with precocious puberty in the absence of luteinizing hormone and follicle-stimulating hormone. Surgical removal or spontaneous involution of these cysts results in regression of pubertal changes. The mechanism of production of these autonomously functioning cysts is unknown. Such cysts may form only once, or they may disappear and recur, resulting in waxing and waning of the signs of precocious puberty. They may be unilateral or bilateral. The sexual precocity that occurs in young females

with **McCune-Albright syndrome** is usually associated with autonomous follicular cysts caused by somatic-activating pathogenic variants of the $G_S\alpha$-protein occurring early in development (see Chapter 600.6). Gonadotropins are suppressed, and estradiol levels are often markedly elevated, but they may fluctuate widely and even temporarily may return to normal. Gonadotropin-releasing hormone analog stimulation fails to evoke an increase in gonadotropins. Ultrasonography is the method of choice for the detection and monitoring of such cysts. Aromatase inhibitors are shown to be the mainstay of therapy in females with McCune-Albright syndrome and persistent estradiol elevation. Estrogen receptor blockers have also been used. A short period of observation to ascertain the lack of spontaneous resolution is advisable before cyst aspiration or cystectomy is considered. Cystic neoplasms must be considered in the differential diagnosis.

ANDROGENIC LESIONS OF THE OVARY

Virilizing ovarian tumors are rare at all ages but particularly so in prepubertal females. **Arrhenoblastoma** has been reported as early as 14 days of age, but few cases have been reported in females younger than 16 years of age.

The **gonadoblastoma** occurs exclusively in dysgenetic gonads, particularly in phenotypic females who have a Y chromosome or a Y fragment in their genotype (46,XY; 45,X/46,XY; 45,X/46,X-fra). There is a gonadoblastoma locus on the Y chromosome (GBY). The tumors may be bilateral. Virilization occurs with some, but not all, tumors. The clinical features are the same as those seen in patients with virilizing adrenal tumors and include accelerated growth, acne, clitoral enlargement, and growth of sexual hair. A palpable, abdominal mass is found in about 50% of patients. Plasma levels of testosterone and androstenedione are elevated, and gonadotropins are suppressed. Ultrasonography, CT, and MRI usually localize the lesion. The dysgenetic gonad of phenotypic females with a Y chromosome or fragment of Y chromosome containing GBY should be removed prophylactically. *When a unilateral tumor is removed, the contralateral dysgenetic gonad should also be removed.* Association of gonadoblastoma and WAGR (Wilms tumor, aniridia, genitourinary anomalies, mental retardation) syndrome is also reported. In an immunohistochemical study of two gonadoblastomas, expressions of *WT1, p53,* and *MIS*, as well as inhibin, were all demonstrated.

Virilizing manifestations occur occasionally in females with **juvenile granulosa cell tumors**. Adrenal rests and hilum cell tumors rarely lead to virilization. Activating pathogenic variants of G protein genes have been described in ovarian (and testicular) tumors. $G_S\alpha$ variants, usually seen in gonadal tumors associated with **McCune-Albright syndrome**, were also noted in four of six Leydig cell tumors (three ovarian, one testicular). Two granulosa cell tumors and 1 thecoma of 10 ovarian tumors studied were found to have *GIP-2* variants.

Sertoli-Leydig cell tumors, rare sex cord/stromal neoplasms, constitute less than 1% of ovarian tumors. The average age at diagnosis is 25 years; less than 5% of these tumors occur before puberty. α-Fetoprotein levels may be mildly elevated. In one 12-month-old with Sertoli-Leydig cell tumor presenting with isosexual precocity, the only detectable tumor marker was the serum inhibin level, with elevations in both A and B subunits. Five-year survival rates are 70–90%.

Of 102 consecutive patients who underwent surgery because of ovarian masses over a 15-year period, the presenting symptoms were acute abdominal pain in 56% and abdominal or pelvic mass in 22%. Of nine children whose cause for surgery was presumed malignancy, three had dysgerminomas, two had teratomas, two had juvenile granulosa cell tumors, one had a Sertoli-Leydig cell tumor, and one had a yolk sac tumor.

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Chapter 628

Disorders of Sex Development

Patricia A. Donohoue

SEX DIFFERENTIATION

See also Chapter 622.

Differentiation and development of the gonads and genitalia are largely complete in the first half of gestation. In normal differentiation, the final form of all sexual structures is consistent with normal sex chromosomes (either XX or XY). A 46,XX complement of chromosomes, as well a genetic factors such as DAX1 (dosage-sensitive/sex-reversal adrenal hypoplasia on the X chromosome), the signaling molecule WNT-4, and R-Spondin1, are among the many needed for the development of normal ovaries. Development of the male phenotype is potentially more complex. It requires a Y chromosome and, specifically, an intact *SRY* (sex-determining region on the Y chromosome) gene, which, in association with genes such as *SOX9, SF-1* (steroidogenic factor-1), *WT1* (Wilms tumor 1), and others (see Chapter 622), directs the undifferentiated gonad to become a testis. Aberrant recombinations may result in X chromosomes carrying *SRY,* resulting in XX males, or Y chromosomes that have lost *SRY,* resulting in XY females.

Antimüllerian hormone (AMH) causes the müllerian (paramesonephric) ducts to regress; in its absence, they persist as the uterus, fallopian tubes, cervix, and upper vagina. AMH activation in the testes probably requires the *SF-1* gene. By about 8 weeks of gestation, the Leydig cells of the testis begin to produce testosterone. During this critical period of male differentiation, testosterone secretion is stimulated by placental human chorionic gonadotropin (hCG), which peaks at 8-12 weeks. In the latter half of pregnancy, lower levels of testosterone are maintained by luteinizing hormone (LH) secreted by the fetal pituitary. Testosterone produced locally initiates development of the ipsilateral wolffian (mesonephric) duct into the epididymis, vas deferens, and seminal vesicle. Complete development of the external genitalia also requires dihydrotestosterone (DHT), the more active metabolite of testosterone. DHT is produced largely from circulating testosterone and is necessary to fuse the genital folds to form the penis and scrotum. DHT is produced from testosterone via the action of the enzyme 5α-reductase. DHT is also produced through an alternative biosynthetic pathway from androstanediol, and this pathway must be intact for normal and complete prenatal virilization to occur. Figure 628.1 illustrates the production of steroid hormones in various glands and the integrated pathways to the synthesis of DHT. A functional androgen receptor, produced by an X-linked gene, is required for testosterone and DHT to induce these androgen effects.

In the XX fetus with normal long and short arms of the X chromosome, the bipotential gonad develops into an ovary by about the 10th to 11th week. This occurs only in the absence of SRY, testosterone, and AMH and requires a normal gene in the dosage-sensitive/sex-reversal locus *DAX1,* the WNT-4 molecule, and R-Spondin1. A female external phenotype develops in the absence of fetal gonads. However, the male phenotype development requires androgen production and action. Estrogen is unnecessary for normal prenatal sexual differentiation, as demonstrated by 46,XX patients with aromatase deficiency.

Chromosomal aberrations may result in ambiguity of the external genitalia. Conditions of aberrant sex differentiation may also occur with the XX or XY genotype. The appropriate term for what was previously called *intersex* is **disorders of sex development (DSD)**. This term defines a condition "in which development of chromosomal, gonadal, or anatomic sex is atypical." It is increasingly preferable to use the term *atypical genitalia* rather than *ambiguous genitalia.* Tables 628.1 and 628.2 compare previous

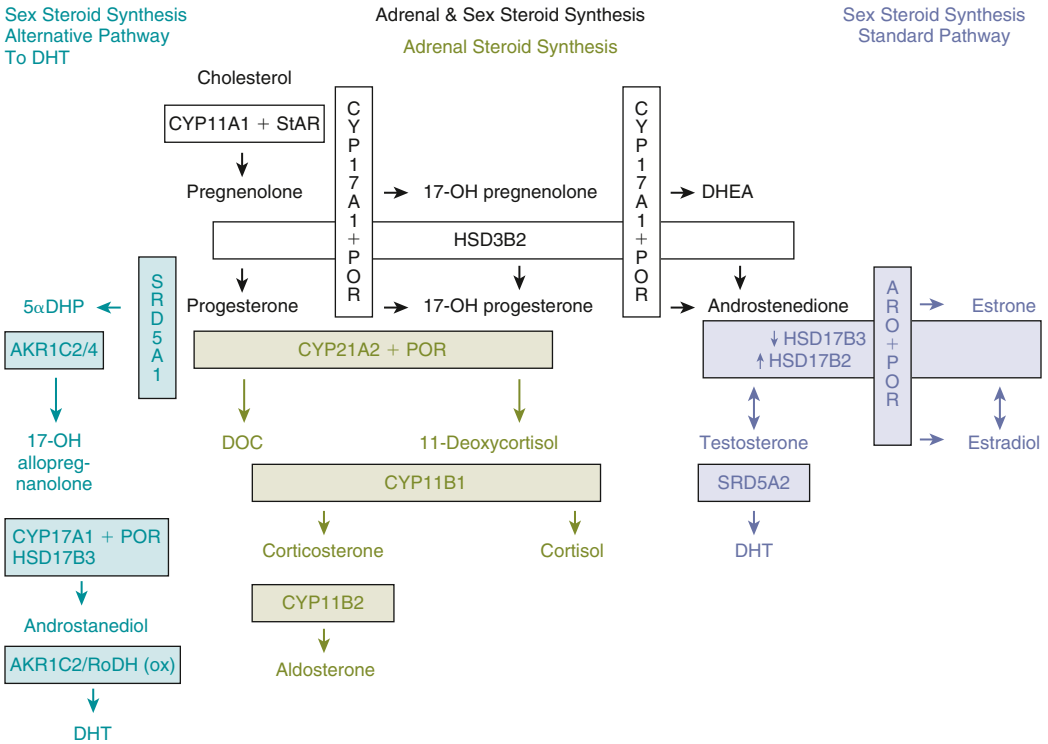

Fig. 628.1 Steroidogenic pathways enzyme names and activities. CYP11A1: cholesterol side-chain cleavage. Enzyme activities include 20-hydroxylase, 22-hydroxylase, and 20,22-lyase. CYP17A1: activities include 17α-hydroxylase and 17,20-lyase. 3βHSD2 (HSD3B2): activities include 3β-hydroxysteroid dehydrogenase (type 2) and D5D4-isomerase. CYP21A2: activity is 21-hydroxylase. CYP11B1: activity is 11β-hydroxylase. CYP11B2: activities include 18-hydroxylase (CMOI) and 18-dehydrogenase (CMOII). SRD5A1: activity is 5α-reductase type 1. SRD5A2: activity is 5α-reductase type 2. HSD17B2: activity is 17β-hydroxysteroid dehydrogenase type 2. HSD17B3: activity is 17β-hydroxysteroid dehydrogenase type 3. AKR1C2/4: activities are 3α-reductase types 1 and 3. AKR1C2/RoDH (ox): activities are 3α-reductase and 3-hydroxyepimerase. ARO, aromatase; CMOI, corticosterone methyl oxidase type 1; CMOII, corticosterone methyl oxidase type 2; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; 5αDH*P*, 5α dihydroprogesterone. *(Adapted from Kim MS, Donohoue PA. Adrenal disorders. In Kappy MS, Allen DB, Geffner ME, eds. Pediatric Practice Endocrinology, 2nd ed. New York: McGraw Hill, 2014; and Flück CE, Meyer-Böni M, Pandey AV, et al. Why boys will be boys: two pathways of fetal testicular androgen biosynthesis are needed for male sexual differentiation. Am J Hum Genet. 2011;89:201–218.)*

Table 628.1 Revised Nomenclature

PREVIOUS	CURRENTLY ACCEPTED
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite	46,XY DSD
Undervirilization of an XY male	46,XY DSD
Undermasculinization of an XY male	46,XY DSD
46,XY intersex	46,XY DSD
Female pseudohermaphrodite	46,XX DSD
Overvirilization of an XX female	46,XX DSD
Masculinization of an XX female	46,XX DSD
46,XX intersex	46,XX DSD
True hermaphrodite	Ovotesticular DSD
Gonadal intersex	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

From Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics*. 2006;118:e488–e500. Table 1.

terms with their revised etiologic classification nomenclature. Table 622.1 in Chapter 622 lists some of the many genes that may be abnormal in various forms of DSD. Gender fluidity (nonconformity) has become a socially and, in New York State, legally accepted concept and is often expressed by self-identified people as intersex. New York State has an intersex category on its birth certificate. Partial androgen insensitivity, 5α-reductase deficiency, and mixed gonadal dysgenesis are often associated with gender dissatisfaction, and an intersex designation may help with future self-identification once the child is mature.

The definition of atypical or ambiguous genitalia, in a broad sense, is any case in which the external genitalia do not appear completely male or completely female. Although there are standards for genital size dimensions, variations in size of these structures do not always constitute ambiguity.

Development of the external genitalia begins with the potential to be either male or female (Fig. 628.2). Virilization of a female, the most common form of DSD, results in varying phenotypes (Fig. 628.3) that develop from the basic bipotential genital appearances of the embryo (see Fig. 628.2).

DIAGNOSTIC APPROACH TO THE PATIENT WITH ATYPICAL OR AMBIGUOUS GENITALIA

The appearance of the external genitalia is rarely diagnostic of a particular disorder and thus does not often allow distinction among the various forms of DSD. The most common forms of 46,XX DSD are *virilizing forms of congenital adrenal hyperplasia*. It is important to note that in 46,XY DSD, the specific diagnosis is not found in up to 50% of cases; partial androgen insensitivity syndrome (PAIS) and

Table 628.2 Etiologic Classification of Disorders of Sex Development

46,XX DSD
Androgen Exposure
Fetal/fetoplacental source
21-Hydroxylase (P450c21 or CYP21) deficiency
11β-Hydroxylase (P450c11 or CYP11B1) deficiency
3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency
Cytochrome P450 oxidoreductase (POR deficiency)
Aromatase (P450arom or CYP19) deficiency
Glucocorticoid receptor gene pathogenic variant
Maternal source
Virilizing ovarian tumor
Virilizing adrenal tumor
Androgenic drugs
Disorder of Ovarian Development
XX gonadal dysgenesis
Testicular DSD (SRY+, SOX9 duplication)
Undetermined Origin
Associated with genitourinary and gastrointestinal tract defects
46,XY DSD
Defects in Testicular Development
Denys-Drash syndrome (pathogenic variant in *WT1*)
WAGR syndrome (Wilms tumor, aniridia, genitourinary malformation, retardation)
Deletion of 11p13
Campomelic syndrome (autosomal gene at 17q24.3-q25.1) and SOX9 pathogenic variant
XY pure gonadal dysgenesis (Swyer syndrome)
Pathogenic variant in SRY
XY gonadal agenesis
Unknown cause
Deficiency of Testicular Hormones
Leydig cell aplasia
Pathogenic variant in LH receptor
Lipoid adrenal hyperplasia (P450scc or CYP11A1) deficiency; pathogenic variant in StAR (steroidogenic acute regulatory protein)
3β-HSD II deficiency
17-Hydroxylase/17,20-lyase (P450c17 or CYP17) deficiency
Persistent müllerian duct syndrome because of antimüllerian hormone gene variants or receptor defects for antimüllerian hormone
Defect in Androgen Action
Dihydrotestosterone deficiency because of 5α-reductase II pathogenic variants or AKR1C2/AKR1C4 variants
Androgen receptor defects:
Complete androgen insensitivity syndrome
Partial androgen insensitivity syndrome (Reifenstein and other syndromes)
Smith-Lemli-Opitz syndrome (defect in conversion of 7-dehydrocholesterol to cholesterol, DHCR7)
OVOTESTICULAR DSD
XX
XY
XX/XY chimeras
SEX CHROMOSOME DSD
45,X (Turner syndrome and variants)
47,XXY (Klinefelter syndrome and variants)
45,X/46,XY (mixed gonadal dysgenesis, sometimes a cause of ovotesticular DSD)
46,XX/46,XY (chimeric, sometimes a cause of ovotesticular DSD)

DSD, Disorders of sex development.
Data from Lee PA, Houk CP, Ahmed SF, et al. Consensus statement on management of intersex disorders. *Pediatrics.* 2006;118:e488–e500.

pure gonadal dysgenesis are common identifiable etiologies in XY DSD. At one center with a large experience, the etiologies of DSD in 250 patients older than 25 years were compiled. The six most common diagnoses accounted for 50% of the cases. These included virilizing congenital adrenal hyperplasia (14%), androgen insensitivity syndrome (AIS; 10%), mixed gonadal dysgenesis (8%), clitoral/labial anomalies (7%), hypogonadotropic hypogonadism (6%), and 46,XY small-for-gestational-age males with hypospadias (6%). Potential diagnostic clues are noted in Tables 628.3 and 628.4.

The potential of not finding a diagnosis in patients with DSD and the resulting lack of specific management emphasizes the need for thorough diagnostic evaluations. These include biochemical characterization of possible steroidogenic enzymatic defects in each patient with genital ambiguity. The parents need counseling about the potentially complex nature of the baby's condition and guidance as to how to deal with their well-meaning but curious friends and family members. The evaluation and management should be carried out by a multidisciplinary team of experts that includes pediatric endocrinology, pediatric surgery/urology, pediatric radiology, newborn medicine, genetics, and psychology. Once the sex of rearing has been agreed on by the family and team, treatment can be organized. Genetic counseling should be offered when the specific diagnosis is established.

After a complete history and physical exam, the common diagnostic approach includes multiple steps, described in the following outline. These steps are usually performed simultaneously rather than waiting for results of one test before performing another, because of the sensitive and sometimes urgent nature of the condition. Careful attention to the presence of physical features other than the genitalia is crucial to determine if a diagnosis of a particular multisystem syndrome is possible (see Chapters 628.1, 628.2, and 628.3). Table 628.5 summarizes many of the features of commonly encountered causes of DSD. Exome sequencing or molecular testing using specific DSD DNA panels are quite useful in the diagnostic evaluation, especially in 46,XY DSD, and may become first-line diagnostic tests.

Diagnostic tests include the following:

1. Blood karyotype, with rapid determination of sex chromosomes (in many centers this is available within 24-48 hours)
2. Other blood tests
   a. Screen for congenital adrenal hyperplasia: cortisol biosynthetic precursors and adrenal androgens (particularly 17-hydroxyprogesterone and androstenedione for 21-hydroxylase deficiency, the most common form). In the United States, all 50 states have a newborn screen for 21-hydroxylase deficiency.
   b. Screen for androgen biosynthetic defects with serum levels of androgens and their precursors.
   c. Assess for gonadal response to gonadotropin stimulation to screen for the presence and function of testicular gonadal tissue: obtain serum levels of testosterone and DHT before and after IM injections of hCG.
   d. Molecular genetic analyses for SRY, other Y-specific loci, and when needed, other single-gene defects associated with DSD.
   e. Gonadotropin (LH and follicle-stimulating hormone [FSH]) levels.
3. The internal anatomy of patients with ambiguous genitalia can be defined with one or more of the following studies:
   a. Voiding cystourethrogram
   b. Endoscopic examination of the genitourinary tract
   c. Pelvic ultrasound; renal and adrenal ultrasound
   d. Pelvic MRI
   e. Exploratory laparoscopy to locate and characterize/biopsy the gonads

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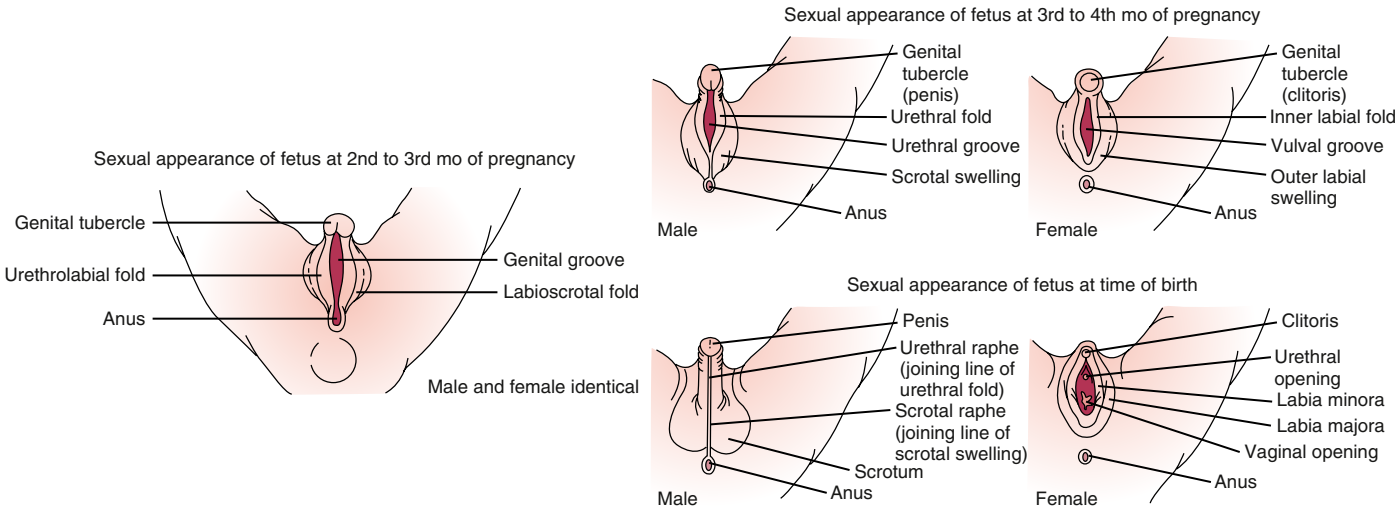

Fig. 628.2 Schematic demonstration of differentiation of normal male and female genitalia during embryogenesis. *(From Zitelli BJ, Davis HW. Atlas of Pediatric Physical Diagnosis, 4th ed. St. Louis: Mosby, 2002: p. 328.)*

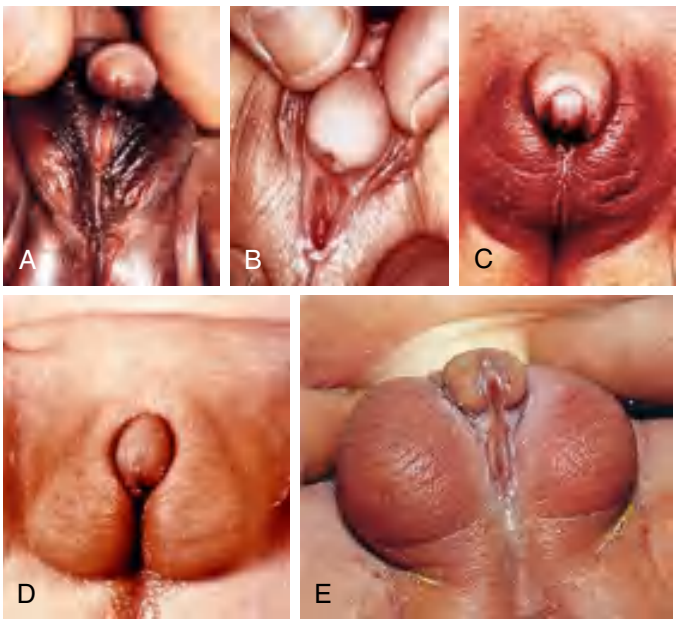

Fig. 628.3 Examples of atypical genitalia. These cases include ovotesticular disorder of sexual development (**A**) and congenital virilizing adrenal hyperplasia (**B-E**). (**B-D**, *Courtesy D. Becker, MD, Pittsburgh. From Zitelli BJ, Davis HW. Atlas of Pediatric Physical Diagnosis, 4th ed. St. Louis: Mosby, 2002: p. 329.)*

628.1 46,XX DSD

Patricia A. Donohoue

The genotype is XX and the gonads are ovaries, but the external genitalia are virilized. There is no significant prenatal AMH production because the gonads are ovaries. Thus the uterus, fallopian tubes, and cervix develop. The varieties and causes of this condition are relatively few. Most instances result from exposure of the female fetus to excessive *exogenous* or *endogenous* androgens during intrauterine life. The changes consist principally of virilization of the external genitalia (clitoral hypertrophy and labioscrotal fusion).

CONGENITAL ADRENAL HYPERPLASIA

See Chapter 616.1.

Table 628.3 Associations of Genital Abnormalities

ABNORMAL CHARACTERISTICS	EXAMPLES OF ASSOCIATED DISORDERS
MALE-APPEARING GENITALIA	
Micropenis	Growth hormone or luteinizing hormone deficiency Testosterone deficiency (in second and third trimesters) Partial androgen insensitivity Syndrome: idiopathic
Hypospadias (more severe)	Disorders of gonadal development 46,XX DSD Ovotesticular DSD 46,XX or 46,XY DSD Syndrome: idiopathic
Impalpable gonads	Anorchia Persistent müllerian duct syndrome 46,XX DSD with 21- or 11β-hydroxylase deficiency Cryptorchidism
Small gonads	47,XXY, 46,XX DSD Dysgenetic or rudimentary testes
Inguinal mass (uterus or tube)	Persistent müllerian duct syndrome, dysgenetic testes
FEMALE-APPEARING GENITALIA	
Clitoromegaly	XX with 21- or 11β-hydroxylase or 3β-hydroxy dehydrogenase deficiency Other 46,XX DSD Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD Tumor infiltration of clitoris Syndrome: idiopathic
Posterior labial fusion	As for clitoromegaly
Palpable gonad(s)	Gonadal dysgenesis, dysgenetic testes, ovotesticular DSD 46,XY DSD
Inguinal hernia or mass	As for palpable gonad(s)

DSD, Disorders of sex development.
From Al Remeithi S, Wherrett DK. Disorders of sex development. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine*, 10th ed. Philadelphia: Elsevier; 2015: Table 98.3.

Table 628.4 Key Points in Evaluation of Infants with Disorders of Sexual Development

Identification of syndromic features in physical exam	• Craniosynostosis and other synostosis in POR deficiency • Cleft palate and second to third toe syndactyly in Smith-Lemli-Opitz (SLO) syndrome • Pierre Robin sequence or campomelia for *SOX9* pathogenic variants • Kidney abnormalities or dysfunction in *WTI* or *WNT4* pathogenic variants • Cardiac abnormalities in Turner syndrome, mixed gonadal dysgenesis or *GATA4* pathogenic variants • Adrenal insufficiency in cases of *SLO*, *NR5A1 (SF-1)* pathogenic variants • POR deficiency or congenital adrenal hyperplasia or hypoplasia forms • Polyneuropathy in *DHH* pathogenic variants • Chondrodysplasia in *HHAT* pathogenic variants • Blepharophimosis/ptosis in *FOXL2* pathogenic variants
Evaluation of internal genitalia to conclude about exposure to AMH using pelvic ultrasound or MRI	*Normal Uterus In:* 46,XY complete gonadal dysgenesis (CGD) 46,XX CGD 46,XX with androgen exposure (i.e., virilizing forms of CAH) Turner syndrome *Abnormal Uterus In:* 46,XY PGD (partial gonadal dysgenesis) Mixed gonadal dysgenesis *Absent Uterus In:* 46,XY DSD with androgen synthesis defects and androgen action defects 46,XX testicular DSD

POR, P450 oxidoreductase; AMH, anti-Mullerian hormone; CAH, congenital adrenal hyperplasia.
Modified from Rodriguez-Buritica D. Overview of genetics of disorders of sexual development. Curr Opin Pediatr. 2015;27:675–684. Table 1.

This is the most common cause of atypical genitalia and of 46,XX DSD. Females with the 21-hydroxylase and 11-hydroxylase defects are the most highly virilized, although minimal virilization also occurs with the type II 3β-hydroxysteroid dehydrogenase defect (see Fig. 628.3). Female patients with salt-losing congenital adrenal hyperplasia (CAH) caused by 21-hydroxylase deficiency tend to have more virilization than do patients with the non–salt-losing form. Masculinization may be so complete that a penile urethra results, and the patient may appear to be a male with bilateral cryptorchidism.

AROMATASE DEFICIENCY

In 46,XX females, the rare condition of aromatase deficiency during fetal life leads to 46,XX DSD and results in hypergonadotropic hypogonadism at puberty because of ovarian failure to synthesize estrogen.

Examples of this condition include two 46,XX infants who had enlargement of the clitoris and posterior labial fusion at birth. In one instance, maternal serum and urinary levels of estrogen were very low and serum levels of androgens were high. Cord serum levels of estrogen were also extremely low, and levels of androgen were elevated. The second patient also had virilization of unknown cause since birth, but the aromatase deficiency was not diagnosed until 14 years of age, when she had further virilization and failed to go into puberty. At that time, she had elevated levels of gonadotropins and androgens but low estrogen levels, and ultrasonography revealed large ovarian cysts bilaterally. These patients demonstrate the important role of aromatase in the conversion of androgens to estrogens. Additional female and male patients with aromatase deficiency as a consequence of pathogenic variants in the *aromatase gene (CYP19)* are known. Two siblings with this gene defect were described, both of whom had tall stature because of a lack of estrogen-mediated epiphyseal fusion. The 28-year-old XX proband was 177.6 cm tall (+2.5 SD) after having received hormonal replacement therapy. Her 24-year-old brother was 204 cm tall (+3.7 SD) and had a bone age of 14 years. Low-dose estradiol replacement, carefully adjusted to maintain normal age-appropriate levels, may be indicated for affected females, even prepubertally.

CORTISOL RESISTANCE CAUSED BY A GLUCOCORTICOID RECEPTOR GENE PATHOGENIC VARIANT

A 9-year-old female with 46,XX DSD, thought to be caused by 21-hydroxylase deficiency (CAH) since the age of 5 years, had elevated cortisol levels both at baseline and after dexamethasone, hypertension, and hypokalemia, suggestive of the diagnosis of generalized glucocorticoid resistance. A novel homozygous variant in exon 5 of the glucocorticoid receptor was demonstrated. In this Brazilian family, the condition was autosomal recessive. Virilization occurs because of excess adrenocorticotropic hormone (ACTH) stimulation of adrenal steroid production because the glucocorticoid receptor defect is also present in the pituitary gland, which senses inadequate cortisol effect to provide negative feedback.

P450 Oxidoreductase Deficiency

Cytochrome P450 oxidoreductase (POR), encoded by a gene on 7q11.2, is a cofactor required for normal enzymatic activity of the microsomal 21- and 17-hydroxylases. POR deficiency thus causes partial combined P450C17 and P450C21 steroidogenic defects. Females are born with ambiguous genitalia, but as opposed to classic CAH, the virilization does not progress postnatally and androgen levels are normal or low. Males may be born undervirilized. Both may exhibit bony abnormalities seen in **Antley-Bixler syndrome**. Conversely, in a series of Antley-Bixler syndrome patients, those with ambiguous genitalia and disordered steroidogenesis had cytochrome POR deficiency. Those without genital ambiguity with normal steroidogenesis had *FGFR2* pathogenic variants. The cardinal features of Antley-Bixler syndrome include craniosynostosis, severe midface hypoplasia, proptosis, choanal atresia/stenosis, frontal bossing, dysplastic ears, depressed nasal bridge, radiohumeral synostosis, long bone fractures and femoral bowing, and urogenital abnormalities.

VIRILIZING MATERNAL TUMORS

Rarely, the female fetus has been virilized by a *maternal* androgen-producing tumor. In a few cases, the lesion was a benign adrenal adenoma, but all others were ovarian tumors, particularly androblastomas, luteomas, and Krukenberg tumors (Table 628.6). **Maternal virilization** may be manifested by enlargement of her clitoris, acne, deepening of the voice, decreased lactation, hirsutism, and elevated levels of androgens. In the infant, there is enlargement of the clitoris of varying degrees, often with labial fusion. Mothers of children with unexplained 46,XX DSDs should undergo physical examination and measurements of their own levels of plasma testosterone, dehydroepiandrosterone (DHEA) sulfate, and androstenedione.

EXPOSURE TO ANDROGENIC DRUGS BY WOMEN DURING PREGNANCY

Testosterone and 17-methyltestosterone have been reported to cause 46,XX DSDs in some instances (see Table 628.6). The greatest number of cases has resulted from the use of certain progestational compounds

Table 628.5 Atypical Genitalia: Steps in Establishing the Diagnosis

	21-OH DEFICIENCY	GONADAL DYSGENESIS WITH Y CHROMOSOME	OVOTESTICULAR DSD	PARTIAL ANDROGEN INSENSITIVITY	BLOCK IN TESTOSTERONE SYNTHESIS
CLINICAL FEATURE					
Palpable gonad(s)	–	±	±	+	+
Uterus present*	+	+	Usually	–	–
Increased skin pigmentation	±	–	–	–	–
Sick baby	±	–	–	–	±
Dysmorphic features	–	±	–	–	–
DIAGNOSTIC CONSIDERATIONS					
Serum 17-OHP	Elevated	Normal	Normal	Normal	Normal
Electrolytes	Possibly abnormal	Normal	Normal	Normal	Possibly abnormal
Karyotype	46,XX	45,X/46,XY or others	46,XX most common	46,XY	46,XY
Testosterone response to hCG	NA	Positive	Normal or reduced	Positive response	Reduced or absent
Gonadal biopsy	NA	Dysgenetic gonad	Ovotestis	Normal testis with ± Leydig cell hyperplasia	Normal testis
Other testing				Genital skin fibroblast culture AR assay, OR blood DNA screening for AR gene variants	Measure testosterone precursors

*As determined by ultrasound, MRI, or rectal examination.
AR, Androgen receptor; DSD, disorder of sex development; hCG, human chorionic gonadotropin; 21-OH, 21-hydroxylase; 17-OHP, 17-hydroxyprogesterone; NA, not applicable.
Adapted from Donohoue PA, Saenger PH. Ambiguous genitalia. In Finberg L, Kleinman RE, eds. Saunders Manual of Pediatric Practice, Philadelphia: WB Saunders, 2002: p. 874.

Table 628.6 Sources of Maternal-Derived Androgens

ENDOGENOUS
Benign
Luteoma of pregnancy
Adrenal adenoma
Hyperreactio luteinalis
Thecoma/fibroma
Stromal hyperthecosis
Brenner tumor
Serous cystadenoma
Mature cystic teratoma (dermoid cyst)
Malignant
Metastatic carcinomas (Krukenberg tumor)
Sex-cord stromal tumors—granulosa cell and Sertoli-Leydig tumors
Adrenal cortical carcinoma
Cystadenocarcinoma
Hilar cell tumor
EXOGENOUS
Synthetic Androgens
Danazol
Progestins (medroxyprogesterone acetate)
Potassium-sparing diuretics

From Auchus RJ, Chang AY. 46,XX DSD: the masculinised female. *Best Pract Res Clin Endocrinol Metab*. 2010;24:219–242. Table 2.

for the treatment of threatened abortion. These progestins have since been replaced by nonvirilizing ones.

Infants with virilization and 46,XX chromosomes and caudal anomalies have been reported for whom no virilizing agent could be identified. In such instances, the disorder is usually associated with other congenital defects, particularly of the urinary and gastrointestinal tracts. Y-specific DNA sequences, including *SRY*, are absent. In one case, a scrotal raphe and elevated testosterone levels were found, but the cause remains unknown.

SF-1 Pathogenic Variants

In a worldwide study of patients with **46,XX ovotesticular DSD**, a specific variant in *SF-1* was identified: p.Arg92Trp. Functional studies showed that the variant probably interfered with inhibition of testicular development. In one family with a maternally transmitted variant, the mother had early menopause. Multiple other *SF-1* variants have been reported to cause isolated ovarian insufficiency, some associated with 46,XY DSDs in their offspring.

46,XX Testicular DSD

In this condition, also known as **XX male**, the gonads are testicular and virilization is typically incomplete. Infertility and/or gonadal failure may develop after childhood. Many cases are caused by translocation of *SRY* sequences onto one of the X chromosomes, often paired with duplication of *SOX-9*. The appropriate sex of rearing may be difficult to determine.

46,XX Gonadal Dysgenesis

These females typically present at puberty with normal female genitalia and lack of breast development and hypergonadotropic hypogonadism. Normal müllerian structures are present, but ovaries are absent or streaked.

Undetermined/Unknown

Rarely, 46,XX DSDs can be associated with other congenital anomalies, especially those of the GU or GI tract, and are thus multifactorial in

origin. These include cloacal exstrophy and **MURCS association** (müllerian hypoplasia, renal agenesis, and cervicothoracic somite abnormalities). Isolated deficiency of müllerian development is known as **Meyer-Rokitansky-Küster-Hauser syndrome**.

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628.2 46,XY DSD

Patricia A. Donohoue

In this condition the genotype is XY but the external genitalia are either not completely virilized, are ambiguous (atypical), or are completely female. When gonads can be found, they typically contain *testicular* elements; their development ranges from rudimentary to normal. Because the process of normal virilization in the fetus is so complex, it is not surprising that there are many varieties and causes of 46,XY DSD. The etiology is not identified in up to 50% of cases.

DEFECTS IN TESTICULAR DIFFERENTIATION

The first step in male differentiation is conversion of the bipotential gonad into a testis. In the XY fetus, if there is a deletion of the short arm of the Y chromosome or of the *SRY* gene, male differentiation does not occur. The phenotype is female; müllerian (paramesonephric) ducts are well developed because of the absence of AMH, and gonads consist of undifferentiated streaks. By contrast, even extreme deletions of the long arm of the Y chromosome (Yq−) have been found in normally developed males, most of whom are azoospermic and have short stature. This indicates that the long arm of the Y chromosome normally has genes that prevent these manifestations. In many syndromes in which the testes fail to differentiate, Y chromosomes are morphologically normal on karyotyping.

Wilms Tumor-Suppressor Gene Pathogenic Variants: Denys-Drash, Frasier, and WAGR Syndromes

Denys-Drash syndrome: The constellation of nephropathy with atypical (ambiguous) genitalia and bilateral Wilms tumor is the major phenotype of this syndrome. Most reported cases have been 46,XY. Müllerian ducts are often present, indicating a global deficiency of fetal testicular function. Patients with a 46,XX karyotype have normal external genitalia. The onset of proteinuria in infancy progresses to nephrotic syndrome and end-stage renal failure by 3 years of age, with focal or diffuse mesangial sclerosis being the most consistent histopathologic finding. Wilms tumor usually develops in children younger than 2 years of age and is frequently bilateral. Gonadoblastomas have also been reported.

Several pathogenic variants in *WT1,* located on chromosome 11p13, have been found. *WT1* functions as a tumor suppressor gene and a transcription factor and is expressed in the genital ridge and fetal gonads. Nearly all reported variants are near or within the zinc finger–coding region. One report found a zinc finger domain variant in the *WT1* alleles of a patient with no GU abnormalities, suggesting that some cases of sporadic Wilms tumor may carry the *WT1* pathogenic variant.

Frasier syndrome: Different pathogenic variants in *WT1,* constitutional heterozygote variants at intron 9, have been described in Frasier syndrome, a condition of nonspecific focal and segmental glomerulosclerosis, 46,XY gonadal dysgenesis, and frequent gonadoblastoma, but *without* Wilms tumor.

WAGR syndrome: This acronym refers to a contiguous gene syndrome consisting of Wilms tumor, aniridia, GU malformations, and retardation (WAGR). These children have a deletion of one copy of chromosome 11p13, which may be visible on karyotype analysis. The deleted region encompasses the aniridia gene *(PAX6)* and the Wilms tumor suppressor gene *(WT1).* Only the 46,XY patients have genital abnormalities, ranging from cryptorchidism to severe deficiency of virilization. Gonadoblastomas have developed in the dysgenetic gonads. Wilms tumor usually occurs by 2 years of age. Some cases also had unexplained obesity, raising the question of an obesity-associated gene in this region of chromosome 11 and naming the syndrome *WAGRO.*

Campomelic Syndrome

See Chapter 735.

This form of **short-limbed skeletal dysplasia** is characterized by anterior bowing of the femur and tibia, small, bladeless scapulae, small thoracic cavities, and 11 pairs of ribs, along with malformations of other organs. It is usually lethal in early infancy. Approximately 75% of reported 46,XY patients exhibit a completely **female phenotype**; the external and internal genitalia are female. Some 46,XY patients have ambiguous genitalia. The gonads appear to be ovaries but histologically may contain elements of both ovaries and testes.

The gene responsible for the condition is *SOX9* and is on 17q24-q25. This gene is structurally related to *SRY* and directly regulates development of the type II collagen gene *(COL2A1)*. The same variants may result in different gonadal phenotypes. Gonadoblastoma was reported in a patient with this condition. The inheritance is autosomal dominant.

SF-1 (Also Known as *Ad4BP* and *NR5A1*) Defects and 46,XY DSD

Adrenal insufficiency and 46,XY gonadal dysgenesis have been described in patients with pathogenic variants in *SF-1*. In some of these patients, if the mother shares the *SF-1* variant, she has premature ovarian insufficiency. *SF-1*–related 46,XY DSD may also occur in the absence of adrenal insufficiency and may resemble PAIS.

46,XY sex reversal has also been described in patients with deletions of parts of autosomal loci on chromosomes 2q, 9p, and 10q.

XY Pure Gonadal Dysgenesis (Swyer Syndrome)

The designation *pure* distinguishes this condition from forms of gonadal dysgenesis that are of chromosomal origin and associated with somatic anomalies. Affected patients have normal stature and a female phenotype, including vagina, uterus, and fallopian tubes, but at pubertal age, breast development and menarche fail to occur. None of the other phenotypic features associated with 45,X (Turner syndrome) are present. Patients present at puberty with hypergonadotropic primary amenorrhea. Familial cases suggest an X-linked or a sex-limited dominant autosomal transmission. Most of the patients examined have had pathogenic variants in *SRY*. The gonads consist of almost totally undifferentiated streaks despite the presence of a cytogenetically normal Y chromosome. The primitive gonad cannot accomplish any testicular function, including suppression of müllerian (paramesonephric) ducts. There may be hilar cells in the gonad capable of producing some androgens; accordingly, some virilization, such as clitoral enlargement, may occur at the age of puberty. The streak gonads may undergo neoplastic changes, such as gonadoblastomas and dysgerminomas, and should be removed as soon as the diagnosis is established, regardless of the age of the patient.

Pure gonadal dysgenesis also occurs in XX individuals.

XY Gonadal Agenesis Syndrome (Embryonic Testicular Regression Syndrome)

In this rare syndrome, the external genitalia are slightly ambiguous but more nearly female. Hypoplasia of the labia; some degree of labioscrotal fusion; a small, clitoris-like phallus; and a perineal urethral opening are present. No uterus, no gonadal tissue, and usually no vagina can be found. At the age of puberty, no sexual development occurs and gonadotropin levels are elevated. Most children have been reared as females. In several patients with XY gonadal agenesis in whom no gonads could be found on exploration, significant rises in testosterone followed stimulation with hCG, indicating

Leydig cell function somewhere. Siblings with the disorder are known.

It is presumed that testicular tissue was active long enough during fetal life for AMH to inhibit development of müllerian ducts but not long enough for testosterone production to result in virilization. In one patient, no deletion of the Y chromosome was found by means of Y-specific DNA probes. Testicular degeneration seems to occur between the 8th and 12th fetal week. Regression of the testis before the 8th week of gestation results in Swyer syndrome; between the 14th and 20th weeks of gestation, it results in the rudimentary testis syndrome; and after the 20th week, it results in anorchia.

In **bilateral anorchia**, sometimes referred to as *vanishing testes syndrome,* testes are absent, but the male phenotype is complete; it is presumed that tissue with fetal testicular function was active during the critical period of genital differentiation but that sometime later it was damaged. Bilateral anorchia in identical twins and unilateral anorchia in identical twins and in siblings suggest a genetic predisposition. Coexistence of anorchia and gonadal agenesis syndrome in a sibship is evidence for a relationship between the disorders. A retrospective review of urologic explorations revealed absent testes in 21% of 691 testes. Of those, 73% had blind-ending cord structures with the suggested site of the vanishing testes being the inguinal canal (59%), abdomen (21%), superficial inguinal ring (18%), and scrotum (2%). It was suggested that the presence of cord structures on laparoscopy should prompt inguinal exploration because viable testicular tissue was found in four of these children.

DEFICIENCY OF TESTICULAR HORMONE PRODUCTION

Several genetic defects have been delineated in the enzymatic synthesis of testosterone by the fetal testis, and a defect in Leydig cell differentiation has been described. These defects produce 46,XY males with inadequate masculinization. Because levels of testosterone are normally low before puberty, an hCG stimulation test may be needed in children to assess the ability of the testes to synthesize testosterone.

Leydig Cell Aplasia

Patients with aplasia or hypoplasia of the Leydig cells usually have female phenotypes, but there may be mild virilization. Testes, epididymis, and vas deferens are present; the uterus and fallopian tubes are absent because of normal production of AMH. There is no breast development at puberty, but pubic hair development may be normal because of the production of adrenal androgens. Plasma levels of testosterone are low and do not respond to hCG; LH levels are elevated. The Leydig cells of the testes are absent or markedly deficient. The defect may involve a lack of functional receptors for LH. In children, hCG stimulation is necessary to differentiate the condition from the AISs. There is male-limited autosomal recessive inheritance. The human LH/chorionic gonadotropin (CG) receptor is a member of the G-protein–coupled superfamily of receptors that contains seven transmembrane domains. Several inactivating pathogenic variants of the LH/CG receptor have been described in males with hypogonadism suspected of having Leydig cell hypoplasia or aplasia.

High serum LH and low FSH were noted in one male with hypogonadism owing to a pathogenic variant in the gene for the β-subunit of FSH (see Table 622.1).

Lipoid Adrenal Hyperplasia

See Chapter 616.

This is the most severe form of CAH; enlarged adrenal glands result from accumulation of cholesterol and cholesterol esters. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane, where the P450 side-chain cleavage enzyme (P450scc; CYP11A1) acts. Cholesterol transport into mitochondria is mediated by the steroidogenic acute regulatory protein (StAR). StAR is a 30-kDa protein essential for steroidogenesis and is encoded by a gene on chromosome 8p11.2. The mitochondrial content of StAR increases between 1 and 5 hours after ACTH stimulation, long after the acute ACTH-induced increase in steroidogenesis. This has led some to suggest that extramitochondrial StAR might also be involved in the acute response to ACTH. Most patients with lipoid CAH have pathogenic variants in the gene encoding *StAR,* and a few have variants in *CYP11A1*.

All serum steroid levels are low or undetectable, whereas ACTH and plasma renin levels are quite elevated. The phenotype is female in both genetic females and males. Genetic males have no müllerian structures because the testes can produce normal AMH but no steroid hormones. These children present with acute adrenal crisis and salt wasting in infancy. Most patients are 46,XY. In a few patients, ovarian steroidogenesis is present at puberty.

The regulatory role of StAR-independent steroidogenesis is illustrated by 46,XX 4-month-old twins with lipoid adrenal hyperplasia. One died at 15 months because of cardiac complications related to coarctation of the aorta. The adrenal glands had characteristic lipid deposits. The surviving twin had spontaneous puberty with feminization at 11.5 years and menarche at 13.8 years. When restudied at the age of 15 years, a homozygous frameshift-inactivating variant in *StAR* was discovered. This supports the hypothesis that StAR-independent steroidogenesis was able to proceed until enough intracellular lipid accumulated to damage steroidogenic activity. Partial defects in only partially virilized males and delayed onset of salt wasting have been described. Complete *CYP11A1* defects may be incompatible with life because only this enzyme can convert cholesterol to pregnenolone, which then becomes progesterone, a hormone essential for the maintenance of normal mammalian pregnancy. Heterozygous variants in *CYP11A1* were described in a 4-year-old with 46,XY sex reversal and late-onset form of lipoid adrenal hyperplasia. At 6-7 weeks of gestation, when maternal corpus luteum progesterone synthesis stops, the placenta, which does not express StAR, produces progesterone by StAR-independent steroidogenesis using the CYP11A1 enzyme system.

3β-Hydroxysteroid Dehydrogenase Deficiency

Males with this form of CAH (see Chapter 616) have various degrees of hypospadias, with or without bifid scrotum and cryptorchidism, and, rarely, a complete female phenotype. Affected infants usually develop salt-losing manifestations shortly after birth. Incomplete defects, occasionally seen in males with premature pubarche, as well as late-onset nonclassic forms, have been reported. These children have pathogenic variants of the gene for type II 3β-hydroxysteroid enzyme, resulting in impairment of steroidogenesis in the adrenals and gonads; the impairment may be unequal between adrenals and gonads. Normal pubertal changes in some males could be explained by the normally present type I 3β-hydroxysteroid dehydrogenase present in many peripheral tissues. Infertility is frequent. There is no correlation between degree of salt wasting and degree of phenotypic abnormality.

Deficiency of 17-Hydroxylase/17,20-Lyase

A single enzyme (CYP17A1) encoded by a single gene on chromosome 10q24.3 has both 17-hydroxylase and 17,20-lyase activities in adrenal and gonadal tissues (see Chapter 616). Many different pathogenic gene variants have been reported. Genetic males usually have a complete female phenotype or, less often, various degrees of undervirilization, from labioscrotal fusion to perineal hypospadias and cryptorchidism. Pubertal development fails to occur in both genetic sexes.

In the classical disorder, there is decreased synthesis of cortisol by the adrenals and of sex steroids by the adrenals and gonads. Levels of the steroid precursor with mineralocorticoid activity, deoxycorticosterone and corticosterone, are markedly increased and lead to the hypertension and hypokalemia characteristic of this form of 46,XY

DSD. Although levels of cortisol are low, the elevated ACTH and corticosterone levels prevent symptomatic cortisol deficiency. The renin-aldosterone axis is suppressed because of the strong mineralocorticoid effect of elevated deoxycorticosterone. Virilization does not occur at puberty; levels of testosterone are low and those of gonadotropins are increased. Because fetal production of AMH is normal, no müllerian duct remnants are present. In XY phenotypic females, gonadectomy and replacement therapy with hydrocortisone and sex steroids are indicated.

The defect follows autosomal recessive inheritance. Affected XX females are usually not detected until young adult life, when they fail to experience normal pubertal changes and are found to have hypertension and hypokalemia. This condition should be suspected in patients presenting with primary amenorrhea and hypertension whose chromosomal complement is either 46,XX or 46,XY.

Some patients originally described as having isolated 17,20 lyase deficiency were subsequently shown to have a defect in the production of DHT because of deficiency of enzymes in the alternative pathway of DHT synthesis.

Deficiency of 17-Ketosteroid Reductase

This enzyme, also called *17β-hydroxysteroid dehydrogenase,* catalyzes the final step in testosterone biosynthesis. It is necessary to convert androstenedione to testosterone, DHEA to androstenediol, and estrone to estradiol. Deficiency of 17-ketosteroid reductase in the fetal testis causes the male fetus to have complete or near-complete female phenotype. Müllerian ducts are absent, and a shallow vagina is present. The diagnosis is based on the ratio of androstenedione to testosterone. In prepubertal children, stimulation with hCG may be necessary to make the diagnosis.

The defect is inherited in an autosomal recessive fashion. At least four different types of 17β-hydroxysteroid dehydrogenase are recognized, each coded by genes on different chromosomes. Type III is the enzyme responsible for testicular production of testosterone. This defect is more common in a highly inbred Arab population in Gaza than it is in other populations. The gene for the disorder is at 9q22 and is expressed only in the testes, where it converts androstenedione to testosterone. Most patients are diagnosed at puberty because of virilization and the failure to menstruate. Testosterone levels at puberty may approach normal, presumably as a result of peripheral conversion of androstenedione to testosterone; at this time, some patients may spontaneously adopt a male gender role.

Type I 17β-hydroxysteroid dehydrogenase, encoded by a gene on chromosome 17q21, converts estrone to estradiol and is found in the placenta, ovary, testis, liver, prostate, adipose tissue, and endometrium. Type II, whose gene is on chromosome 16q24, reverses the reactions of types I and III (converting testosterone to androstenedione and estrone to estradiol, respectively). Type IV is similar in action to type II. A late-onset form of 17-ketosteroid reductase deficiency presents as gynecomastia in young adult males.

Persistent Müllerian Duct Syndrome

In this disorder, there is persistence of müllerian (paramesonephric) duct derivatives in otherwise completely virilized males. Cases have been reported in siblings and identical twins. Cryptorchidism is present in 80% of affected males, and during surgery for this or inguinal hernia, the condition is discovered when a fallopian tube and uterus are found. The degree of müllerian development is variable and may be asymmetric. Testicular function is normal in most, but testicular degeneration has been reported. Some affected males acquire testicular tumors after puberty. In a study of 38 families, 16 families had defects in the AMH gene, located on the short arm of chromosome 19. Affected patients had low AMH levels. In 16 families with high AMH levels, the defect was in the AMH type II receptor gene, with 10 of 16 having identical 27-bp deletions on exon 10 in at least one allele.

Fig. 628.4 5α-Reductase deficiency. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*

Treatment consists of removal of as many of the müllerian structures as possible without causing damage to the testis, epididymis, or vas deferens.

DEFECTS IN ANDROGEN ACTION

Dihydrotestosterone Deficiency

Decreased production of DHT in utero results in marked ambiguity of external genitalia of affected males. Biosynthesis and peripheral action of testosterone are normal.

The phenotype commonly associated with this condition results in males who have a small phallus, bifid scrotum, urogenital sinus with perineal hypospadias, and a blind vaginal pouch (Fig. 628.4). Testes are in the inguinal canals or labioscrotal folds and are normal histologically. There are no müllerian structures. Wolffian (mesonephric) structures—the vas deferens, epididymis, and seminal vesicles—are present. Most affected patients have been identified initially as females but at puberty, *virilization occurs;* the phallus enlarges, the testes descend and grow normally, and spermatogenesis occurs. There is no gynecomastia. Beard growth is scanty, acne is absent, the prostate is small, and recession of the temporal hairline fails to occur. Virilization of the wolffian duct is caused by the action of testosterone itself, although masculinization of the urogenital sinus and external genitals depends on the action of DHT during the critical period of fetal masculinization. Growth of facial hair and of the prostate also appears to be DHT dependent.

The adult height reached is close to that of the father and other male siblings. There is significant phenotypic heterogeneity. This has led to a classification of such patients into five types of **steroid 5α-reductase deficiency (SRD)**.

Several different gene defects of *SRD5A2* (the 5α-reductase type 2 gene leading to SRD) have been identified, located on the short arm of chromosome 2, in patients from throughout the world. Familial clusters have been reported from the Dominican Republic, Turkey, Papua New Guinea, Brazil, Mexico, and the Middle East. There is no reliable correlation between genotype and phenotype.

The disorder is inherited as an autosomal recessive trait but is limited to males; normal homozygous females with normal fertility indicate that in females DHT has no clinically significant role in sexual differentiation or in ovarian function later in life. The clinical diagnosis

should be made as early as possible in infancy. It is important to distinguish this from PAIS because patients with PAIS are far less sensitive to androgen than are patients with SRD. The biochemical diagnosis of SRD is based on finding normal serum testosterone levels, normal or low DHT levels with markedly increased basal and especially hCG-stimulated testosterone:DHT ratios (>17), and high ratios of urinary etiocholanolone to androsterone. Children with androgen insensitivity have normal hepatic 5α reduction and thus a normal ratio of tetrahydrocortisol to 5α-tetrahydrocortisol, as opposed to those with SRD.

It is important to note that many, but not all, children with SRD reared as females in childhood have changed to a male role around the time of puberty. It appears that exposures to testosterone in utero, neonatally, and at puberty have variable contributions to the formation of male gender identity. Infants with this condition should be reared as males whenever practical. Treatment of male infants with DHT results in phallic enlargement.

Another cause of DHT deficiency is a block in an alternative pathway of DHT synthesis. Patients previously thought to have 46,XY DSD because of isolated 17,20-lyase deficiency have subsequently been characterized as having pathogenic variants in *AKR1C2* (3α-reductase type 3) or both *AKR1C2* and *AKR1C4* (3α-reductase type 4) (see Fig. 628.1). These findings showed that both the classical and alternative pathways to DHT must be intact for normal prenatal virilization.

Androgen Insensitivity Syndromes

The AISs are the most common forms of male DSDs, occurring with an estimated frequency of 1/20,000 genetic males. This group of heterogeneous X-linked recessive disorders is caused by more than 150 different pathogenic variants in the androgen receptor gene, located on Xq11-12: single point variants result in amino acid substitutions or premature stop codons, frameshift and premature terminations, gene deletions, and splice-site variants.

Clinical Manifestations

The clinical spectrum of patients with AISs, all of whom have a 46,XY chromosomal complement, range from phenotypic females (in *complete* AIS), to males with various forms of ambiguous genitalia and undervirilization (*partial* AIS, or clinical syndromes such as **Reifenstein syndrome**), to phenotypically normal-appearing males with infertility. In addition to normal 46,XY chromosomes, the presence of testes and normal or elevated testosterone and LH levels are common to all such children (Figs. 628.5 and 628.6).

In **complete androgen insensitivity syndrome (CAIS)**, an extreme form of failure of virilization, genetic males appear female at birth and are invariably reared accordingly. The external genitalia are female. The vagina ends blindly in a pouch, and the uterus is absent because of the normal production and effect of AMH by the testes. In ~30% of patients, unilateral or bilateral fallopian tube remnants are found. The testes are usually intraabdominal but may descend into the inguinal canal; they consist largely of seminiferous tubules. At puberty, there is normal development of breasts and the habitus is female, but menstruation does not occur and sexual hair is absent. Adult heights are commensurate with those of normal males despite profound congenital deficiency of androgenic effects.

The testes of affected adult patients produce normal male levels of testosterone, which are converted to normal levels of DHT. Failure of normal male differentiation during fetal life reflects a defective response to androgens at that time. The absence of androgenic effects is caused by a striking resistance to the action of endogenous or exogenous testosterone at the cellular level.

Prepubertal phenotypic females with this disorder are often detected when inguinal masses prove to be testes or when a testis is unexpectedly found during herniorrhaphy. Approximately 1–2% of females with an inguinal hernia prove to have this disorder. In infants, elevated LH levels should suggest the diagnosis. In older children and adults, amenorrhea is the usual presenting symptom. In prepubertal children, the condition must be differentiated from other types of XY undervirilized males in which there is complete feminization. These include XY gonadal dysgenesis **(Swyer syndrome)**, true agonadism, Leydig cell aplasia including LH receptor defects, and 17-ketosteroid reductase deficiency. All these conditions, unlike CAIS, are characterized by low

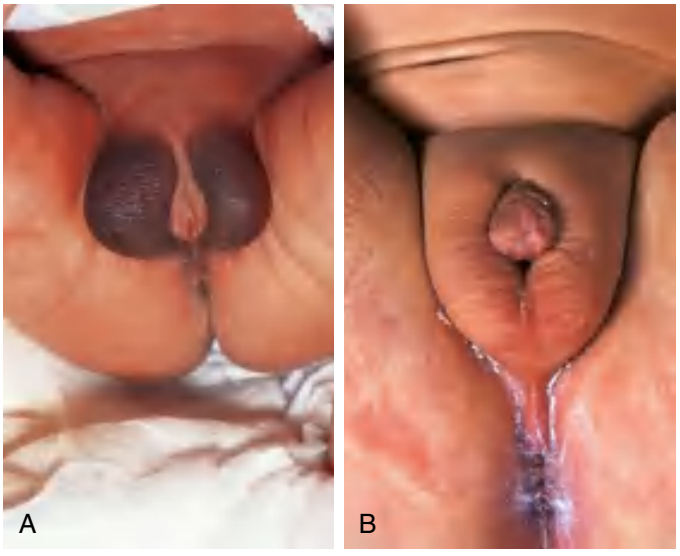

Fig. 628.5 A, Partial androgen insensitivity with descended testes in bifid labioscrotal folds. B, Less severe partial androgen insensitivity with severe hypospadias and maldescent of testes. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*

Fig. 628.6 Partial androgen insensitivity syndrome at adolescence, male sex of rearing. Note gynecomastia from peripheral aromatase conversion of testosterone to estrogen. Abundant pubic hair implies only partial resistance. *(From Wales JKH, Wit JM, Rogol AD. Pediatric Endocrinology and Growth, 2nd ed. Philadelphia: Saunders, 2003: p. 165.)*

Table 628.7 Causes of a Partial Androgen Insensitivity Syndrome–Like Phenotype

DEFECTS IN ANDROGEN PRODUCTION
Partial gonadal dysgenesis
Pathogenic variants in *SRY, NR5A1, WT1*
Pathogenic variants of the luteinizing hormone receptor
Biosynthetic enzyme deficiencies
17,20-Lyase deficiency
P450 oxidoreductase deficiency
17β-hydroxysteroid dehydrogenase deficiency type 3
5α-Reductase deficiency type 2
GENETIC
Klinefelter syndrome
Smith-Lemli-Opitz syndrome
Denys-Drash syndrome
Frasier syndrome
PAIS
Pathogenic variants of the androgen receptor gene
Normal androgen receptor gene with fetal growth restriction

NR5A1, Nuclear receptor subfamily 5 A1; PAIS, partial androgen insensitivity syndrome; SRY, sex-determining region Y; WT1, Wilms tumor 1.

From Hughes IA, Davies JD, Bunch TI, et al. Androgen insensitivity syndrome. *Lancet.* 2012;380:1419–1428. Panel 1.

levels of testosterone as neonates and during adult life and by failure to respond to hCG during the prepubertal years.

Although patients with CAIS have unambiguously female external genitals at birth, those with **PAIS** have a wide variety of phenotypic presentations, ranging from **perineoscrotal hypospadias**, bifid scrotum, and cryptorchidism to extreme undervirilization appearing as clitoromegaly and labial fusion. Some forms of PAIS are known as specific syndromes. Patients with **Reifenstein syndrome** have incomplete virilization characterized by hypogonadism, severe hypospadias, and gynecomastia (see Fig. 628.6). **Gilbert-Dreyfus** and **Lubs syndromes** are also classified as PAISs. In all cases, abnormalities in the androgen receptor gene have been identified. Table 628.7 lists other causes of a PAIS-like syndrome.

Diagnosis

The diagnosis of patients with PAIS may be particularly difficult in infancy. The postnatal surge in testosterone and LH is diminished in those with CAIS but not in those with PAIS. In some, especially those sufficiently virilized in infancy, the diagnosis is not suspected until puberty, when there is inadequate virilization with lack of facial hair or voice change and the appearance of gynecomastia. Azoospermia and infertility are common. Androgen receptor defects are recognized in adults who have a small phallus and testes and infertility. A single–amino acid substitution in the androgen receptor was reported in a large Chinese family in whom some affected members were fertile whereas others had gynecomastia and/or hypospadias.

Treatment and Prognosis

In patients with CAIS whose sexual orientation is unambiguously female, the testes should be removed because they have malignant potential. Historically, they were removed as soon as they were discovered. However, there is a trend to allow the testes to remain because they are the source of estradiol (through conversion from testosterone), and this results in normally timed puberty with the individual's endogenous hormones. Careful monitoring for testicular masses should be performed, and removal of the testes is advised in early adulthood. Laparoscopic removal of Y chromosome–bearing gonads has been performed in patients with AIS and in those with gonadal dysgenesis. In ~30% of patients, malignant tumors, usually seminomas, develop by 50 years of age. Several teenage females developed seminomas. Replacement therapy with estrogens is indicated at the age of puberty in those whose testes were removed in childhood.

Normal breasts develop in affected females who have not had their testes removed by the age of puberty. The absence of androgenic activity in addition to the production of estradiol contributes to the feminization of these women.

The psychosexual and surgical management of patients with PAIS is extremely complex and depends in large part on the presenting phenotype. Osteopenia is recognized as a late feature of AIS.

Molecular analyses have suggested that phenotype may depend in part on somatic mosaicism of the androgen receptor gene. The presence of mosaicism shifts the phenotype to a higher degree of virilization than expected from the genotype of the mutant allele alone.

Genetic counseling is difficult in families with androgen receptor gene variants. In addition to lack of genotype-phenotype correlations, there is a high rate (27%) of de novo pathogenic variants in families.

Sex hormone–binding globulin reduction after exogenous androgen administration (stanozolol) correlates with the severity of the receptor defect and may become a useful clinical tool. Successful therapy with supplemental androgens has been reported in patients with PAIS and various variants of the androgen receptor in the DNA-binding domain and the ligand-binding domain.

Pathogenic variants in androgen receptors are also reported in patients with **spinal and bulbar muscular atrophy** in whom clinical manifestations including testicular atrophy, infertility, gynecomastia, and elevated LH, FSH, and estradiol levels usually manifest between the third and fifth decades of life.

UNDETERMINED CAUSES

Other XY undervirilized males display great variability of the external and internal genitalia and various degrees of phallic and müllerian development. The testes may be histologically normal or rudimentary, or there may only be one. No recognized cause is identified in up to 50% of children with 46,XY DSDs. Some ambiguity of the genitalia is associated with a wide variety of chromosomal aberrations, which must always be considered in the differential diagnosis, the most common being 45,X/46,XY syndrome (see Chapter 626.1). It may be necessary to karyotype several tissues to establish mosaicism. Other complex genetic syndromes, many resulting from single-gene variants, are associated with varying degrees of ambiguity of the genitalia, particularly in the male. These entities must be identified by the associated extragenital malformations.

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder caused by pathogenic variants in the sterol Δ7-reductase gene located on chromosome 11q12-q13. It is characterized by prenatal and postnatal growth restriction, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the second to third toes, and severe cognitive impairment (see Chapter 106.3). Its incidence is 1 in 20,000-30,000 live births in populations of Northern and Central European origin; 70% are male. Genotypic males usually have genital ambiguity and, occasionally, partial sex reversal with female genital ambiguity or complete sex reversal with female external genitalia. Müllerian duct derivatives are usually absent. Affected 46,XX patients have normal genitalia. Two types of Smith-Lemli-Opitz syndrome have been recognized: the **classical form (type I)** described earlier and the acrodysgenital syndrome, which is usually lethal within 1 year and is associated with severe malformations, postaxial polydactyly, and extremely abnormal external genitalia **(type II)**. Pyloric stenosis is associated with Smith-Lemli-Opitz syndrome type I and Hirschsprung disease with type II. Cleft palate, skeletal abnormalities, and one case of a lipoma of the pituitary gland have been seen in **type II** cases. Some authors believe in a spectrum of disease severity rather than in the previous classification. Low plasma cholesterol with elevated 7-dehydrocholesterol, its precursor, are found in types I and II, and the levels do not correlate with severity. Maternal apolipoprotein E values do seem to correlate with severity. The most common prenatal expression of Smith-Lemli-Opitz syndrome is intrauterine growth retardation (see Chapter 106.3 for treatment).

46,XY DSD subjects also have been described in siblings with α-thalassemia/mental retardation syndrome.

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628.3 Ovotesticular DSD

Patricia A. Donohoue

In ovotesticular DSD, both ovarian and testicular tissues are present, either in the same or in opposite gonads. Affected patients have ambiguous genitalia, varying from normal female genitalia with only slight enlargement of the clitoris to almost normal male external genitalia (see Fig. 628.3A).

Approximately 70% of all patients have a 46,XX karyotype. Ninety-seven percent of affected patients of African descent are 46,XX. Less than 10% of persons with ovotesticular DSD are 46,XY. Approximately 20% have 46,XX/46,XY mosaicism. Half of these are derived from more than one zygote and are chimeras (chi 46,XX/46,XY). The presence of paternal and both maternal alleles for some blood groups is demonstrated. An ovotesticular DSD chimera, 46,XX/46,XY, was reported as resulting from embryo amalgamation after in vitro fertilization. Each embryo was derived from an independent, separately fertilized ovum.

Examination of 46,XX ovotesticular DSD patients with Y-specific probes has detected less than 10% with a portion of the Y chromosome, including the *SRY* gene. Ovotesticular DSD is usually sporadic, but several siblings have been reported. The cause of many cases of ovotesticular DSD is unknown.

The most frequently encountered gonad in ovotesticular DSD is an ovotestis, which may be bilateral. If unilateral, the contralateral gonad is usually an ovary but may be a testis. The ovarian tissue is normal, but the testicular tissue is dysgenetic. The presence and function of testicular tissue can be determined by measuring basal and hCG-stimulated testosterone levels along with AMH levels. Patients who are highly virilized and have had adequate testicular function with no uterus are usually reared as males. If a uterus exists, virilization is often mild and testicular function minimal; assignment of female sex may be indicated. Selective removal of gonadal tissue inconsistent with sex of rearing may be indicated. In a few families, 46,XY ovotesticular DSD subjects and 46,XX males have been described in the same sibship.

Defects in R-Spondin1, encoded by the *RSPO1* gene, have been described in 46,XX ovotesticular DSD. Defects in SF-1 have been described in both XX and XY ovotesticular DSD.

Pregnancies with living offspring have been reported in 46,XX ovotesticular DSD individuals reared as females, but very few males with ovotesticular DSD have fathered children. Approximately 5% of patients will develop gonadoblastomas, dysgerminomas, or seminomas.

DIAGNOSIS AND MANAGEMENT OF DISORDERS OF SEX DEVELOPMENT

In the neonate, ambiguity of the genitals requires immediate attention to decide on the sex of rearing as early in life as possible. The family of the infant needs to be informed of the child's condition as early, completely, compassionately, and honestly as possible. Caution must be used to avoid feelings of guilt, shame, and discomfort. Guidance needs to be provided to alleviate both short-term and long-term concerns and to allow the child to grow up in a completely supportive environment. The initial care is best provided by a team of professionals that includes neonatologists and pediatric specialists, endocrinologists, radiologists, surgeons/urologists, psychologists, and geneticists, all of whom remain focused foremost on the needs of the child. Management of the potential psychologic upheaval that these disorders can generate in the child or the family is of paramount importance and requires physicians and other healthcare professionals with sensitivity, training, and experience in this field.

While awaiting the results of chromosomal analysis, pelvic ultrasonography is indicated to determine the presence of a uterus and ovaries. Presence of a uterus and absence of palpable gonads usually suggest a virilized XX female; however, as described previously, these structures may also be found in 46,XY DSD. A search for the source of virilization should be undertaken; this includes studies of adrenal hormones to rule out varieties of congenital adrenal hyperplasia, and studies of androgens and estrogens occasionally may be necessary to rule out aromatase deficiency. Virilized XX females are generally (but not always) reared as females even when highly virilized.

The absence of a uterus, with or without palpable gonads, often indicates an undervirilized male and an XY karyotype. Measurements of levels of gonadotropins, testosterone, AMH, and DHT are necessary to determine whether testicular production of androgen is present and is normal. Undervirilized males who are totally feminized may be reared as females. Certain significantly feminized infants, such as those with 5α-reductase deficiency, may be reared as males because these children virilize normally at puberty. Sixty percent of individuals with 5α-reductase deficiency assigned as female in infancy live as males as adults. An infant with a comparable degree of feminization resulting from an androgen receptor defect, such as CAIS, may be successfully reared as a female.

When receptor disorders are suspected in the XY male with a small phallus (micropenis), a course of three monthly IM injections of testosterone enanthate (25-50 mg) may assist in the differential diagnosis of androgen insensitivity and in the treatment of the small phallus.

In some mammals, the female exposed to androgens prenatally or in early postnatal life exhibits nontraditional sexual behavior in adult life. Most, but not all, females who have undergone fetal masculinization from CAH or from maternal progestin therapy have female sexual identity, although during childhood they may appear to prefer male playmates and activities over female playmates and feminine play with dolls in mothering roles.

In the past it was thought that surgical treatment of ambiguous genitalia to create a female appearance, particularly when a vagina is present, was more successful than construction of male genitalia. Considerable controversy exists regarding these decisions. Sexual functioning is to a large extent more dependent on neurohormonal and behavioral factors than the physical appearance and functionality of the genitalia. Similarly, controversy exists regarding the timing of the performance of invasive and definitive procedures, such as surgery. Whenever possible without endangering the physical or psychologic health of the child, an expert multidisciplinary team should consider deferring elective surgical repairs and gonadectomies until the child can participate in the informed consent for the procedure. One study of children (59 males and 18 females) with gender dysphoria but without documentation of genomic or enzymologic abnormalities indicated that most of these children no longer have gender dysphoria after completion of puberty. Among those who do, homosexuality and bisexuality are the most frequent diagnoses.

For patients with DSD who have Y-chromosome material and intraabdominal gonads, gonadectomy is generally recommended because of the risk of gonadal tumors, many of which are malignant.

The pediatrician, pediatric endocrinologist, and psychologist, along with the appropriate additional specialists, should provide ongoing compassionate, supportive care to the patient and the patient's family throughout childhood, adolescence, and adulthood. Support groups are available for families and patients with many of the conditions discussed.

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Section 6

Diabetes Mellitus in Children

Chapter 629

Diabetes Mellitus

629.1 Classification of Diabetes Mellitus

David R. Weber

Diabetes mellitus (DM) is a common chronic metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. The major forms of diabetes are differentiated by insulin deficiency versus insulin resistance: **type 1 diabetes mellitus (T1DM)** results from deficiency of insulin secretion because of pancreatic β-cell damage; **type 2 diabetes mellitus (T2DM)** is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment. T1DM is the most common endocrine metabolic disorder of childhood and adolescence, with important consequences for physical and emotional development. Individuals with T1DM confront serious lifestyle alterations, including an absolute daily requirement for exogenous insulin, the need to monitor their own glucose level, and the need to pay attention to dietary intake. Morbidity and mortality stem from a constant potential for acute metabolic derangements and from long-term complications. Potential acute complications include the development of hypoglycemia related to insulin excess or hyperglycemic ketoacidosis from insulin deficiency. Long-term complications typically manifest in adulthood and are related to the adverse effects of chronic hyperglycemia and associated metabolic abnormalities on tissues and organ systems. This can result in microvascular diseases such as retinopathy, nephropathy, and neuropathy and macrovascular complications such as ischemic heart disease and arterial obstruction with gangrene of the extremities.

DM is not a single entity, but rather a heterogeneous group of disorders in which there are distinct genetic patterns and other etiologic and pathophysiologic mechanisms that lead to impairment of glucose tolerance through deficient insulin production or action. The American Diabetes Association (ADA) has proposed a diabetes classification system that includes four categories: type 1 diabetes, type 2 diabetes, other specific types, and gestational diabetes. An expanded list of diabetes etiologies is provided in Table 629.1. The current criteria for the diagnosis of diabetes are provided in Table 629.2. A thorough clinical history and physical exam are often sufficient to determine the etiology; however, in some cases additional testing may be required.

TYPE 1 DIABETES MELLITUS

Formerly called *insulin-dependent diabetes mellitus* (IDDM) or *juvenile diabetes,* T1DM is characterized by low or absent levels of endogenously produced insulin and by dependence on exogenous insulin to prevent development of ketoacidosis, an acute life-threatening complication of T1DM. The natural history includes four distinct stages: (1) preclinical β-cell autoimmunity with progressive defect of insulin secretion, (2) onset of clinical diabetes, (3) transient remission honeymoon period, and (4) established diabetes during which there may occur acute and/or chronic complications and decreased life expectancy. The onset occurs predominantly in childhood, with a median age of 7-15 years, but it may present at any age. The incidence of T1DM varies markedly across the world but has increased in nearly all parts of the world over recent decades (Fig. 629.1). Both genetic susceptibility and environmental factors contribute to the pathogenesis. Susceptibility to T1DM is genetically controlled by alleles of the major histocompatibility complex (MHC) class II genes expressing human leukocyte antigens (HLAs). Autoantibodies to β-cell antigens, including islet cell cytoplasm (ICA), insulin autoantibody (IAA), glutamic acid decarboxylase (GAD), islet antigen 2 (IA-2A, formerly ICA512), and zinc transporter 8 (ZnT8A), are detected in serum from affected subjects. These can be detected months to years before the clinical onset of T1DM. In some children and adolescents with apparent T1DM, the β-cell destruction is not immune mediated. This subtype of diabetes occurs in patients of African or Asian origin and is distinct from known causes of β-cell destruction such as drugs or chemicals, viruses, mitochondrial gene defects, pancreatectomy, and ionizing radiation. These individuals may have ketoacidosis, but they have extensive periods of remission with variable insulin deficiency, similar to patients with T2DM. Patients with T1DM require lifelong treatment with insulin.

TYPE 2 DIABETES MELLITUS

Formerly known as *adult-onset diabetes mellitus* or *non–insulin-dependent diabetes mellitus,* T2DM develops because of insulin resistance and progressive non-autoimmune β-cell failure. There is a strong heritable component to T2DM, although the genetic basis remains poorly understood. Population-based studies have linked T2DM risk with polymorphisms in a large number of genes related to insulin secretion, insulin action, energy expenditure, and birthweight; however, the collective contribution of these variants to overall T2DM risk remains low at <20%. Although T2DM has long been the most prevalent form of diabetes in adults, the rise in childhood obesity over the past few decades has led to a markedly increased incidence of this disease in children and adolescents. Pediatric T2DM accounts for most of the new cases of diabetes in high-risk populations such as obese adolescents of Black or Hispanic population ancestry (see Chapter 65). *Childhood-onset T2DM differs from adult disease in that it is associated with a more rapid decline in β-cell function and the earlier development of T2DM-related complications.*

The presentation of T2DM is typically more insidious than that with T1DM. In contrast to patients with T1DM, who are usually ill at the time of diagnosis and whose presentation rarely spans more than a few weeks, children with T2DM often seek medical care because of excessive weight gain and fatigue as a result of insulin resistance and/or the incidental finding of glycosuria during routine physical examination. A history of polyuria and polydipsia is not always a cardinal clinical feature in these patients. **Acanthosis nigricans** (dark pigmentation of skin creases in the nape of the neck especially), a sign of insulin resistance, is present in the majority of patients with T2DM and is accompanied by a relative hyperinsulinemia at the time of the diagnosis. However, as the disease progresses, β-cell function becomes increasingly impaired such that children with advanced T2DM often present in diabetic ketoacidosis (DKA).

Healthy lifestyle interventions and treatment with metformin remain the cornerstones of T2DM treatment in children and adolescents. Liraglutide (a glucagon-like peptide-1 receptor agonist) is approved in children ≥10 years and may have an additional benefit of slowing weight gain. Insulin therapy is required for patients who present with severe hyperglycemia and for those patients in whom hyperglycemia worsens in spite of lifestyle modification and noninsulin pharmacologic management.

OTHER SPECIFIC TYPES OF DIABETES

Monogenic Diabetes

The term *monogenic diabetes* is used to refer to a heterogeneous group of single-gene disorders resulting in impaired insulin secretion. This category encompasses **maturity-onset diabetes of the young (MODY)** and **transient and permanent neonatal diabetes (TND or PND)**. Characteristics of monogenic diabetes can include age of onset before 6 months (for TND or PND), development of hyperglycemia before 25 years of age, and strong family history of diabetes. Monogenic etiologies are estimated to comprise anywhere from 1% to 10% of all diabetes cases, with the uncertainty related to the clinical difficulty in differentiating these cases from T1DM and T2DM. Monogenic forms of diabetes may present with hyperglycemia, and consequent polyuria and polydipsia, or may be diagnosed simply by routine screening. Extrapancreatic manifestations vary by genetic defect (see Table 629.1 and Chapter 629.4) and can include hepatic, renal, and central nervous system (CNS) manifestations. Treatment is guided by genetic diagnosis and clinical course, with

Table 629.1 Etiologic Classifications of Diabetes Mellitus

I. TYPE 1 DIABETES (B-CELL DESTRUCTION ULTIMATELY LEADING TO COMPLETE INSULIN DEFICIENCY)
- *A. Immune Mediated*
- *B. Idiopathic*

II. TYPE 2 DIABETES (VARIABLE COMBINATIONS OF INSULIN RESISTANCE AND INSULIN DEFICIENCY)
- *A. Typical*
- *B. Atypical*

III. OTHER SPECIFIC TYPES
- *A. Genetic Defects Of β-Cell Function (Monogenic Diabetes)*
  1. Neonatal diabetes
     a. Pathogenic variants leading to transient neonatal diabetes (*KCNJ11, ABCC8, 6q24 overexpression, INS, ZFP57, SLC2A2 HNF1β*)
     b. Pathogenic variants leading to permanent neonatal diabetes (*KCNJ11, ABCC8, INS, GATA6, EIF2AK3, GCK, PTF1A, FOXP3, GLIS3, PDX1, SLC2A2, SLC19A2, GATA4, NEUROD1, NEUROG3, NKX2-2, RFX5, IER3IP1, MNX1*)
  2. MODY (maturity-onset diabetes of the young) syndromes
     a. MODY 1 chromosome 20, *HNF4α*
     b. MODY 2 chromosome 7, *GCK*
     c. MODY 3 chromosome 12q24.2, *HNF1α, TCF-1*
     d. MODY 4 chromosome 13q12.1, *IPF-1 (PDX1)*
     e. MODY 5 chromosome 17, *HNF1β, TCF-2*
     f. MODY 6 chromosome 2q32, *NEUROD1*
     g. MODY 7 chromosome 2p25, *KLF11*
     h. MODY 8 chromosome 9q34, *CEL*
     i. MODY 9 chromosome 7q32, *PAX4*
     j. MODY 10 chromosome 11p15.5, *INS*
     k. MODY 11 chromosome 8p23, *BLK*
     l. MODY 12 chromosome 11p15, *ABCC8*
     m. MODY 13 chromosome 11p15, *KCNJ11*
     n. MODY 14 chromosome 3p14, *APPL1*
  3. Mitochondrial DNA pathogenic variants (includes one form of Wolfram syndrome, Pearson syndrome, Kearns-Sayre, and maternally inherited diabetes and deafness)
  4. Wolfram syndrome—DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness):
     a. WFS1-Wolframin—chromosome 4p
     b. Wolfram locus 2—chromosome 4q22-24
     c. Wolfram mitochondrial
  5. Thiamine-responsive megaloblastic anemia and diabetes
- *B. Genetic Defects of Insulin Action*
  1. Type A insulin resistance
  2. Donohue syndrome
  3. Rabson-Mendenhall syndrome
  4. Lipoatrophic diabetes syndromes
- *C. Other Genetic Syndromes Associated With Diabetes (Insulin Resistance Or Deficiency)*
  1. Down syndrome
  2. Turner syndrome
  3. Klinefelter syndrome
  4. Prader-Willi syndrome
  5. Bardet-Biedl syndrome
  6. Alström syndrome
  7. Werner syndrome
  8. Friedreich ataxia
- *D. Other Autoimmune Syndromes Associated With Diabetes*
  1. IPEX (immunodysfunction, polyendocrinopathy, enteropathy, X-linked)
  2. Autoimmune polyendocrinopathy syndromes (APS)
     a. APS-1 (APCED)
     b. APS-2
  3. Stiff person syndrome
  4. Anti-insulin receptor antibodies
- *E. Drug Or Chemical Induced*
  1. Antirejection—cyclosporine, sirolimus
  2. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
  3. l-Asparaginase
  4. β-Adrenergic blockers
  5. Vacor (rodenticide)
  6. Phenytoin (Dilantin)
  7. α-Interferon
  8. Diazoxide
  9. Nicotinic acid
  10. Pentamidine
  11. Immune checkpoint inhibitors (immune mediated)
- *F. Diseases of Exocrine Pancreas*
  1. Cystic fibrosis
  2. Trauma/pancreatectomy
  3. Pancreatitis/ionizing radiation
  4. Hemochromatosis
  5. Fibrocalculous pancreatopathy
- *G. Infections*
  1. Congenital rubella
  2. Cytomegalovirus
  3. Hemolytic-uremic syndrome
- *H. Endocrinopathies Associated With Diabetes*
  1. Cushing (hypercortisolism)
  2. Acromegaly (growth hormone excess)
  3. Pheochromocytoma
  4. Glucagonoma
  5. Somatostatinoma
  6. Aldosteronoma

IV. GESTATIONAL DIABETES

Modified from Sperling MA, Tamborlane WV, Battelino T, et al. Diabetes mellitus. In: Sperling MA. *Pediatric Endocrinology*, 4th ed. Philadelphia: Elsevier; 2014: Box 19-1.

some forms being responsive to oral sulfonylureas and others requiring insulin replacement. *Children diagnosed with diabetes before 6 months of age should have genetic testing for TND/PND, and older individuals with diabetes not characteristic of T1DM or T2DM in the setting of a family history of diabetes should have genetic testing for monogenic forms of diabetes.* A comparison of the four types of diabetes is noted in Table 629.3.

OTHER ETIOLOGIES OF DIABETES

Examples include diabetes secondary to exocrine pancreatic diseases (cystic fibrosis), other endocrine diseases (Cushing syndrome), infection, and ingestion of certain drugs or poisons (the rodenticide Vacor). In organ transplantation survivors, there is a linkage between cyclosporine and tacrolimus and post-transplantation DM, ascribed to a number of mechanisms. Certain genetic syndromes, including those with abnormalities of the insulin receptor or the immune system, are also included in this category.

PREDIABETES

The term *prediabetes* is used to identify individuals with abnormalities in blood glucose homeostasis who are at increased risk for the development of diabetes (see Table 629.2). Prediabetes is defined by **impaired fasting glucose** (IFG, fasting glucose 100-125 mg/dL

Table 629.2 Diagnostic Criteria for Dysglycemia and Diabetes Mellitus

DYSGLYCEMIA	DIABETES MELLITUS
IMPAIRED FASTING GLUCOSE	
Fasting (at least 8 hr) plasma glucose 100-125 mg/dL (5.6-7.0 mmol/L)	Fasting (at least 8 hr) plasma glucose ≥126 mg/dL (7.0 mmol/L) *Or*
IMPAIRED GLUCOSE TOLERANCE	
2-hr plasma glucose during OGTT ≥140 mg/dL (7.8 mmol/L), but <200 mg/dL (11.1 mmol/L)	2-hr plasma glucose during OGTT ≥200 mg/dL (11.1 mmol/L) *Or*
PREDIABETES	
Hemoglobin A_{1c} 5.7–6.4% (39-47 mmol/mol)	Hemoglobin A_{1c} ≥6.5% (48 mmol/mol) *Or* Symptoms* of diabetes mellitus plus random or casual plasma glucose ≥200 mg/dL (11.1 mmol/L)†

*Symptoms include polyuria, polydipsia, and unexplained weight loss with glucosuria and ketonuria.
†Results should be confirmed by repeat testing if in absence of unequivocal hyperglycemia.
OGTT, Oral glucose tolerance test.
Adapted from the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1999;20(Suppl 1):S5; with data from American Diabetes Association. Standards in Medical Care of Diabetes – 2017. *Diabetes Care.* 2017;40(Suppl 1):S11–S24.

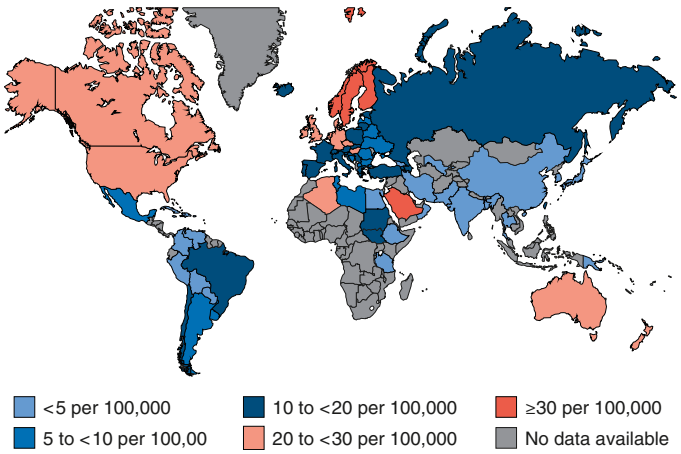


Fig. 629.1 Map of age-sex standardized incidence rates (per 100,000) from publications of type 1 diabetes in children age under 15 yr. *(From Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107842. Fig 1.)*

[5.6-6.9 mmol/L]), **impaired glucose tolerance** (IGT, 2 hours postprandial glucose 140-199 mg/dL [7.8-11 mmol/L]), or hemoglobin A_{1c} (HbA_{1c}) values of 5.7–6.4% (39-47 mmol/mol). A fasting glucose concentration of 99 mg/dL (5.5 mmol/L) is the upper limit of normal. This choice is near the level above which acute-phase insulin secretion is lost in response to intravenous administration of glucose and is associated with a progressively greater risk of the development of microvascular and macrovascular complications. Many individuals with IFG are euglycemic in their daily lives and may have normal or nearly normal HbA_{1c} levels. Individuals with IFG often manifest hyperglycemia only when challenged with the oral glucose load used in the standardized oral glucose tolerance test (OGTT).

Prediabetes is not a clinical entity, but rather a risk factor for future diabetes and cardiovascular disease. This may be observed as an intermediate stage in any of the disease processes listed in Table 629.1. Prediabetes is often associated with **insulin resistance syndrome** (also known as **metabolic syndrome**), which consists of insulin resistance, compensatory hyperinsulinemia to maintain glucose homeostasis, obesity (especially abdominal or visceral obesity), dyslipidemia of the high-triglyceride or low- or high-density lipoprotein type, or both in addition to hypertension. Insulin resistance is directly involved in the pathogenesis of T2DM.

629.2 Type 1 Diabetes Mellitus (Immune Mediated)

David R. Weber

EPIDEMIOLOGY

T1DM accounts for approximately 10% of all cases of diabetes in all ages, affecting up to 2 million people in the United States and more than 15 million people in the world; approximately 15,000 youths are diagnosed with T1DM each year. Although T1DM accounts for most cases of diabetes in childhood, it is not limited to this age-group; new cases continue to present in adult life, and up to 50% of individuals with T1DM present as adults. The incidence of T1DM is highly variable among different racial and ethnic groups (see Fig. 629.1). The overall age-adjusted incidence of T1DM varies from <5 in 100,000 per year in parts of Asia, Africa, and South America to more than 30 in 100,000 per year in Northern Europe. The incidence of T1DM is increasing in most (but not all) populations, and this increase appears to be most marked in populations where the incidence of autoimmune diseases was historically low. Data from Western European diabetes centers suggest that the annual rate of increase in T1DM incidence is 2–5%, whereas some Central and Eastern European countries demonstrate an even more rapid increase—up to 9%. Data from the United States have shown that the incidence of T1DM in children increased by 1.9% per year from 2002 to 2015 from 19.5/100,000 to 22.3/100,000. Steeper increases in annual incidence were seen in people of Asian/Pacific Islander (4.4%), Hispanic (4%), and Black (2.7%) versus those of White (0.7%) racial/ethnic background.

Females and males are almost equally affected, with a modest male preponderance in some populations (Western European/United States and a female preponderance in others (Japanese); there is no apparent correlation with socioeconomic status. Peaks of presentation occur in two age-groups: at 5-7 years of age and at the time of puberty. The first peak may correspond to the time of increased exposure to infectious agents coincident with the beginning of school; the second peak may correspond to the pubertal growth spurt induced by gonadal steroids and the increased pubertal growth hormone secretion (which antagonizes insulin). The understanding of the cause of diabetes or of its increased incidence remains elusive. A growing number of cases are presenting between 1 and 2 years of age, especially in high-risk groups; the average age of presentation is older in low-risk populations. Low-risk groups that migrate to a high-risk country seem to acquire the increased risk of that country. There can be marked differences in incidence rates in various ethnic groups within the same country; incidence rates (per 100,000) in the 10- to 14-year-old age-group in the United States range from a low of 7.1 in Native Americans to 17.6 in Hispanics, 19.2 in Black Americans, and 32.9 in Whites.

GENETICS

There is a clear familial clustering of T1DM, with prevalence in siblings approaching 8%, whereas the prevalence in the general population in the United States is only 0.4%. Risk of T1DM is also increased when a parent has T1DM, and this risk differs between the two parents; the risk is 3–4% if the mother is affected but 5–6% when the father is affected. In monozygotic twins, the concordance rate ranges from 30% to 65%, whereas dizygotic twins have a concordance rate of 6–10%.

Table 629.3 Key Features of Diabetes in Pediatric Patients

	TYPE 1 DIABETES	TYPE 2 DIABETES	MONOGENIC DIABETES (MATURITY-ONSET DIABETES IN THE YOUNG)	NEONATAL DIABETES
Age at diagnosis	6 mo-18 yr	Puberty; rarely younger than 10 yr	Younger than 25 yr	Younger than 6 mo
Causes and genetic factors	Autoimmune; genetic predisposition (HLA and other genes)	Obesity; genetic and ethnic predisposition	Autosomal dominant; *HNF1A, HNF4A, GCK, HNF1B* (see Table 629.1)	*KCNJ11, ABCC8, INS* (see Table 629.1)
Associated features	Lean or mildly overweight at diagnosis, often with weight loss; thyroid autoimmunity; celiac disease	Obesity; acanthosis nigricans; polycystic ovarian syndrome; hypertension; hyperlipidemia; fatty liver disease; family history	Lean or weight loss at diagnosis; *GCK* variants are asymptomatic	Failure to thrive
Diabetic ketoacidosis at presentation	Yes; about 25%	Yes; 5–20%	No	Yes; frequency not described
Treatment	Insulin	Lifestyle modification; metformin; liraglutide; insulin; bariatric surgery	Sulfonylurea; no treatment for *GCK* variants	Sulfonylurea for *KCJN11* and *ABCC8* variants; insulin for other variants

Adapted from Cameron FJ, Wherrett DK. Care of diabetes in children and adolescents: controversies, changes, and consensus. Lancet. 2015;385:2096–2104. Table 1.

Because the concordance rate of dizygotic twins is higher than the sibling risk, factors other than the shared genotypes (e.g., the shared intrauterine environment) may play a role in increasing the risk in dizygotic twins. Furthermore, the genetic susceptibility for T1DM in the parents of an affected child is estimated at 3%. It should be kept in mind that although there is a large genetic component in T1DM, 85% of newly diagnosed patients with T1DM do not have an affected family member.

Monogenic Type 1 Diabetes Mellitus

Classic single-gene defects are an extremely rare cause of autoimmune-mediated T1DM. **IPEX (immune dysfunction, polyendocrinopathy, enteropathy, X-linked) syndrome** is caused by pathogenic variants in *FOXP3* and other genes. The *FOXP3* is a gene involved in immune system responses. A member of the FOX protein family, *FOXP3* appears to function as the master regulator in the development and function of regulatory T cells. These variants lead to the lack of a major population of regulatory T lymphocytes, with resulting overwhelming autoimmunity and development of diabetes (as early as 2 days of age) in approximately 80% of the children with this disorder.

Wolfram syndrome (DIDMOD: diabetes insipidus, diabetes mellitus, optic atrophy, deafness) is an autosomal recessive disease caused predominantly by pathogenic variants in *WFS1* and is a progressive neurodegenerative disease. Case definition requires the presence of T1DM and optic atrophy. This syndrome may be present in ~5% of patients with T1DM.

Autoimmune polyendocrinopathy syndrome type 1 (APS-1) is caused by pathogenic variants in *AIRE* leading to abnormalities in expression of peripheral antigens within the thymus and/or abnormalities of negative selection in the thymus. This results in widespread autoimmunity. Approximately 18% of children with this syndrome develop T1DM.

Genes Altering the Risk of Autoimmune Type 1 Diabetes Mellitus

The risk of developing T1DM is modified by the influence of several risk loci. The genomic region with by far the greatest contribution to the risk of T1DM is the MHC on chromosome 6p21. Outside of the MHC, genome-wide association studies have identified T1DM to be associated with at least 100 different single-nucleotide polymorphisms, from which about 50 genes have emerged as potentially causal. Notable high-risk loci include *INS*, *PTPN22*, *IL2RA*, *CTLA4*, *IFIH1*, *ERBB3*, and *BAD*. The contribution of each non-MHC locus to T1DM risk is small, making individual variants less useful for predicting the genetic risk of T1DM in a patient. The known functions of these genes suggest the primary etiologic pathways of diabetes, namely, HLA class II and class I molecules binding, T- and β-cell activation, innate pathogen viral responses, chemokine and cytokine signaling, and T-regulatory and antigen-presenting cell functions.

Major Histocompatibility Complex/Human Leukocyte Antigen–Encoded Susceptibility to Type 1 Diabetes Mellitus

The MHC is a large genomic region that contains a number of genes related to immune system function in humans. These genes are further divided into HLA classes I, II, III, and IV. Class II genes are the ones most strongly associated with risk of T1DM, but some of the risk associated with various HLA types is a result of variation in genes in HLA classes other than class II. Overall, genetic variation in the HLA region can explain 40–50% of the genetic risk of T1DM.

Some of the known associations include the HLA DR3/4-DQ2/8 genotype; compared to a population prevalence of T1DM of approximately 1 in 300, DR3/4-DQ2/8 newborns from the general population have a 1 in 20 genetic risk. This risk of development of T1DM is even higher when the high-risk HLA haplotypes are shared with a sibling or parent with T1DM. If one sibling has T1DM and shares the same high-risk DR3/4-DQ2/8 haplotype with another sibling, the risk of autoimmunity in the other sibling is 50%. Moreover, this risk approaches 80% when siblings share both HLA haplotypes identical by descent. This is known as the *relative paradox* and points to the existence of other shared genetic risk factors (most likely in the extended HLA haplotype).

With advances in genotyping, further discrimination is possible and we can identify more specific risk ratios for specific haplotypes. For example, the DRB1*0401-DQA1*0301g-DQB1*0302 haplotype has an odds ratio (OR) of 8.39, whereas the DRB1*0401-DQA1*0301g-DQB1*0301 haplotype has an OR of 0.35, implicating the DQB1*0302 allele as a critical susceptibility allele. There are some dramatically protective DR-DQ haplotypes (e.g., DRB1*1501-DQA1*0102-DQB1*0602 [OR = 0.03], DRB1*1401-DQA1*0101-DQB1*0503 [OR = 0.02], and DRB1*0701-DQA1*0201-DQB1*0303 [OR = 0.02]). The DR2 haplotype (DRB1*1501-DQA1*0102-DQB1*0602) is dominantly protective and is present in 20% of the general population but is seen in only 1% of patients with T1DM.

Role of Aspartate at Position 57 in DQB1

DQB1*0302 (high risk for diabetes) differs from DQB1*0301 (protective against diabetes) only at position 57, where it lacks an aspartic acid

residue. The DQB1*0201 allele (increased risk for diabetes) also lacks aspartic acid at position 57, and it has been proposed that the presence of aspartate at this position alters the protein-recognition and protein-binding characteristics of this molecule. Although the absence of aspartate at this position appears to be important in most studies on White individuals, it does not have the same role in Korean and Japanese populations. Moreover, certain low-risk DQB1 genotypes also lack aspartic acid at position 57, including DQB1*0302/DQB1*0201 (DR7) and DQB1*0201 (DR3)/DQB1*0201 (DR7). Thus the presence of aspartate at this position is usually, but not always, protective in White populations but not necessarily in other populations.

Role of Human Leukocyte Antigen Class I

Although the alleles of class II HLA genes appear to have the strongest associations with diabetes, recent genotyping studies and analyses of pooled data have identified associations with other elements in the HLA complex, especially HLA-A and HLA-B. The most significant association is with HLA-B39, which confers high risk for T1DM in three different populations, makes up the majority of the signal from HLA-B, and is associated with a lower age of onset of the disease.

Non-MHC/HLA Genes Associated with T1DM Risk

The second locus found to be associated with risk of T1DM was localized to a region upstream of the *INS*. Susceptibility in this region has been primarily mapped to a variable number of tandem repeats approximately 500 base pairs (bp) upstream of the insulin gene. This highly polymorphic region consists of anywhere from 30 to several hundred repeats of a 14- to 15-bp unit sequence (ACAGGGGTCTGGGG). The high-risk allele has been found to be associated with lower insulin and messenger RNA (mRNA) production in the thymus, suggesting a possible mechanism for decreased immune tolerance to insulin. A number of candidate genes linked to T1DM susceptibility have also been associated with increased risk of *other* autoimmune disease. These include the genes *PTPN22, IL2RA, CTLA4,* and *IFIH1,* which are involved in immune system regulation. Others, such as *ERBB3* and *BAD,* are thought to be associated with cell apoptosis.

ENVIRONMENTAL FACTORS

That ~45–70% of monozygotic twins are discordant for T1DM, the variation seen in urban and rural areas populated by the same ethnic group, the change in incidence that occurs with migration, the increase in incidence that has been seen in almost all populations in the last few decades, and the occurrence of seasonality all provide evidence that environmental factors also play a significant role in the causation of T1DM.

Viral Infections

It is possible that various viruses play a role in the pathogenesis of T1DM, but no single virus, and no single pathogenic mechanism, stands out in the environmental etiology of T1DM. Instead, a variety of viruses and mechanisms may contribute to the development of diabetes in genetically susceptible hosts. Invoked mechanisms involve direct infection of β cells by viruses resulting in lysis and release of self-antigens, direct viral infection of antigen-presenting cells causing increased expression of cytokines, and molecular mimicry, which is the notion that viral antigens exhibit homology to self-epitopes.

The clearest evidence of a role for viral infection in human T1DM is seen in congenital rubella syndrome. Prenatal infection with rubella is associated with β-cell autoimmunity in up to 70%, with development of T1DM in up to 40% of infected children. The time lag between infection and development of diabetes may be as large as 20 years. T1DM after congenital rubella is more likely in patients who carry the higher-risk genotypes. Interestingly, there appears to be no increase in risk of diabetes when rubella infection develops after birth or when live-virus rubella immunization is used.

Studies have shown an increase in evidence of enteroviral infection in patients with T1DM and an increased prevalence of enteroviral RNA in prenatal blood samples from children who subsequently develop T1DM. It has been reported that mumps infection leads to the development of β-cell autoimmunity with high frequency and to T1DM in some cases. Although mumps may play a role in some cases, the fact that T1DM incidence has increased steadily in several countries after universal mumps vaccination was introduced and that the incidence is extremely low in several populations where mumps is still prevalent indicates that mumps alone is not a major causal factor in diabetes.

The Hygiene Hypothesis: Possible Protective Role of Infections

Although some viral infections may increase the risk of T1DM, infectious agents may also play a protective role against diabetes. The hygiene hypothesis states that T1DM risk is increased in industrialized countries, where the observation that there are fewer infections implies that the immune system is less well trained for its main task, namely host defense. Some call this theory the *microbial deprivation hypothesis*. The hygiene hypothesis states that lack of exposure to childhood infections may increase an individual's chances of developing autoimmune diseases, including T1DM. Rates of T1DM and other autoimmune disorders are generally lower in underdeveloped nations with a high prevalence of childhood infections and tend to increase as these countries become more developed. The incidence of T1DM differs almost sixfold between Russian Karelia and Finland, even though both are populated by genetically related populations and are adjacent to each other and at the same latitude. The incidence of autoimmunity in the two populations varies inversely with immunoglobulin (Ig) E antibody levels, and IgE is involved in the response to parasitic infestation. All these observations suggest that decreased exposure to certain parasites and other microbes in early childhood may lead to an increased risk of autoimmunity in later life, including autoimmune diabetes. Nonetheless, retrospective case-control studies have been equivocal at best, and direct evidence of protection by childhood infections is still lacking.

Gastrointestinal Microbiome

There is emerging evidence that the intestinal microbiome is altered in T1DM; however, a cause-and-effect relationship has yet to be established. Human studies have found that the intestinal microbiome in T1DM has decreased diversity of microbial species and contains fewer butyrate-producing organisms compared to healthy controls. Butyrate is a short-chain fatty acid that is thought to be antiinflammatory and may have a role in protecting the intestinal epithelium, either directly or indirectly, through an effect to increase mucin production. Theoretically, a disruption in epithelial integrity (the so-called *leaky gut*) could trigger inflammation and an enhanced autoimmune response because of increased entry of pathogenic or dietary antigens into the bloodstream. Early, small-scale prospective studies in infants and children at high risk for T1DM have shown an imbalance favoring species including *Bacteroides dorei* and *Bacteroides vulgatus* among individuals who went on to develop T1DM autoantibodies or disease compared with those who did not. A larger study across six different study sites in The Environmental Determinants of Diabetes in the Young (TEDDY) study identified significant geographic differences in fecal microbiome composition, highlighting the challenges in this field of study.

Diet

Dietary exposure may modify T1DM risk; a definitive link between any single dietary exposure and T1DM development has not been found. The majority of interventional studies have not shown an effect of delayed gluten exposure or the use of hydrolyzed formula to reduce the risk for development of T1DM autoantibodies of disease. A meta-analysis of both interventional and observational studies concluded that there was no association between early exposure of gluten or milk protein and risk of T1DM. Some, but not all, studies have suggested that breastfeeding lowers the risk of T1DM. The potential mechanism for a protective effect of breast milk is not well understood but could be related to a beneficial effect of breast milk on the infant immune system or an indirect effect such as reduced exposure to other dietary antigens early in life. Timing of solid food introduction may modify T1DM risk, as seen in a report from the Diabetes Autoimmunity Study in the

Young (DAISY), which found that both early (before 4 months of age) and late (after 6 months of age) introduction of solid foods predicted development of T1DM.

Other dietary factors that have been suggested at various times as playing a role in T1DM risk include omega-3 fatty acids, vitamin D, ascorbic acid, zinc, and vitamin E. Vitamin D is biologically plausible (it has a role in immune regulation), and deficiency is more common in northern countries like Finland where T1DM incidence is highest; however, most observational studies have failed to find associations between vitamin D level or supplementation and T1DM risk. Interventional studies to assess the effect of vitamin D supplementation on T1DM risk are lacking.

PATHOGENESIS AND NATURAL HISTORY OF TYPE 1 DIABETES MELLITUS

In T1DM, a genetically susceptible host develops autoimmunity against the host's own β cells. What triggers this autoimmune response is complex and multifactorial. In some (but not all) patients, this immune-mediated process results in progressive destruction of β cells until a critical mass of β cells is lost and insulin deficiency develops. Insulin deficiency, in turn, leads to the onset of clinical signs and symptoms of T1DM. At the time of diagnosis, if viable β cells are still present and produce some insulin, there may be a partial remission of the disease (**honeymoon period**), but over time, more β-cell mass is destroyed, despite any regeneration and/or persistence of β cells, and the patient becomes totally dependent on exogenous insulin for survival (Fig. 629.2). Over time, some of these patients develop secondary complications of diabetes that appear, in part, to be related to how well-controlled the diabetes has been. The natural history of T1DM involves some or all of the following stages, with two distinct identifiable stages before onset of symptoms:

1. Persistence of one or more islet autoantibodies with normoglycemia and presymptomatic; can last years to decades (onset of autoimmune islet disease AID])
2. β-cell autoimmunity with dysglycemia and presymptomatic; shorter
3. Onset of symptomatic disease; usually quite brief, weeks, rarely months
4. Transient remission, usually within weeks of onset, may last 6-12 months ("honeymoon")
5. Established disease, lifelong
6. Development of complications, quite variable

Initiation of Autoimmunity

Genetic susceptibility to T1DM is determined by several genes, with the largest contribution coming from variants in the HLA system. Nonetheless even with the highest-risk haplotypes, most carriers will not develop T1DM. In monozygotic twins, the concordance of the development of T1DM is reported to be 30–65%. The observed rise in incidence of T1DM, and particularly so in younger children with an essentially genetically stable patient population, implies that something has accordingly changed in the environment. A number of factors, including maternal and intrauterine environmental influences, route of neonatal delivery, foods and diet in infancy, viral infections, lack of exposure to certain infections and antibiotic use, host microbiome, and even psychologic stress, are implicated in the pathogenesis of T1DM, but their exact role and the mechanism by which they trigger or aggravate autoimmunity remain uncertain. What is clear is that markers of autoimmunity are much more prevalent than clinical T1DM, indicating that initiation of autoimmunity is a necessary, but not a sufficient, condition for T1DM. Although no conclusive triggering factor has been identified, it seems that in most cases of T1DM that are diagnosed in childhood, the onset of autoimmunity occurs very early in life. In most children diagnosed before age 10 years, the first signs of autoimmunity appear before age 2 years. Development of autoimmunity is associated with the appearance of several autoantibodies. IAAs are usually the first to appear in young children, followed by GAD, and later by IA-2 and ZnT8 antibodies. The earliest antibodies are predominantly of the IgG_1 subclass. Not only is there spreading of autoimmunity to more antigens (IAA, GAD, IA-2A, ZnT8) but there is also epitope spreading within one antigen. Initial GAD antibodies tend to be against the middle region or the carboxyl-terminal region, whereas amino terminal antibodies usually appear later and are less common in children.

Preclinical Autoimmunity with Progressive Loss of β-Cell Function

In nearly all patients, the appearance of autoimmunity is followed by progressive or eventual destruction of β cells (Figs. 629.3 and 629.4).

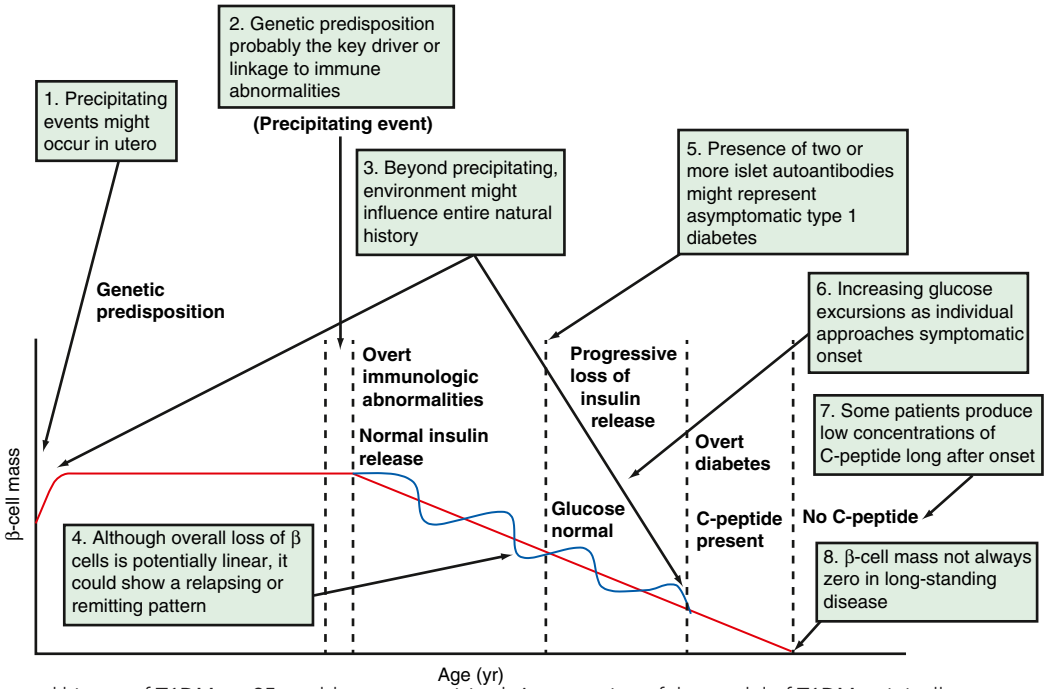
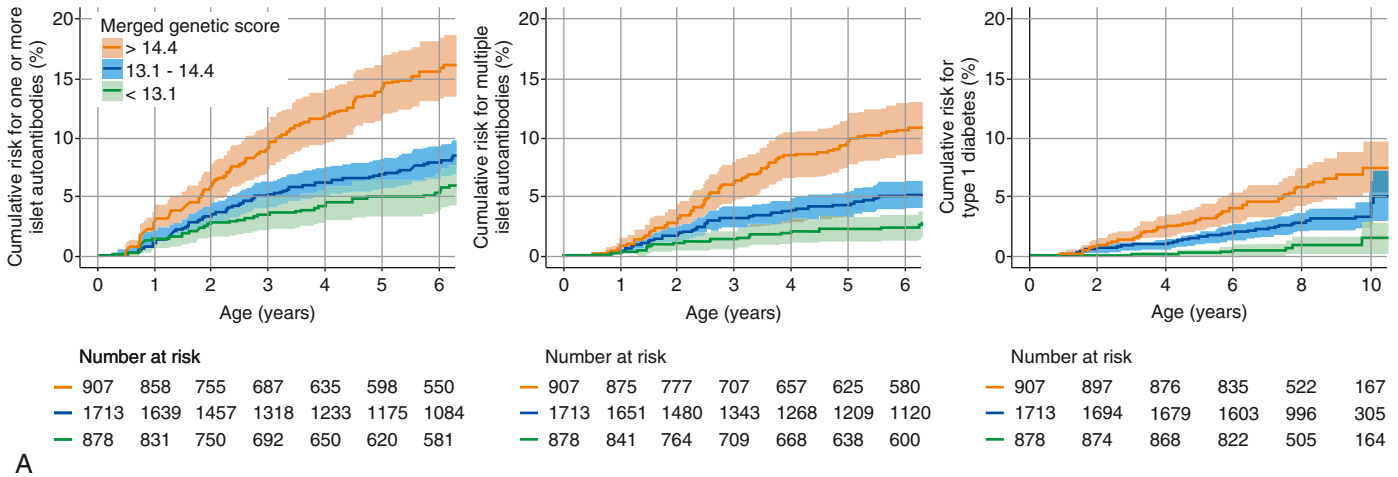
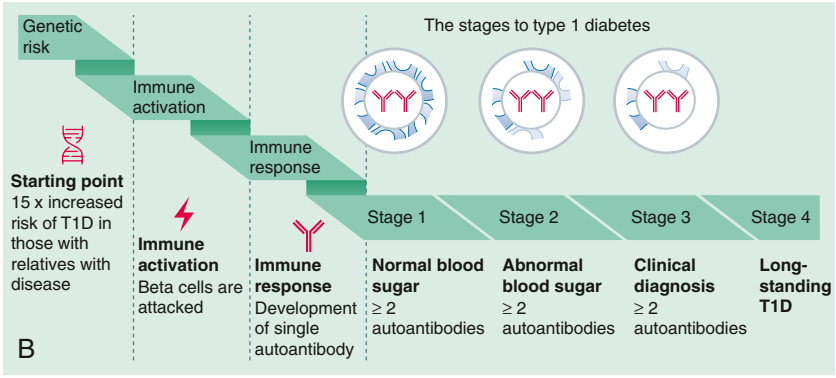


Fig. 629.2 The natural history of T1DM—a 25-yr-old concept revisited. A re-creation of the model of T1DM, originally proposed in 1986, is shown in *black*. Additions and conjectures based on recent knowledge gains are shown in *green boxes*. *(From Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–78. Fig. 4.)*



A



B

Fig. 629.3 Contributing factors and disease progression in type 1 diabetes. **A,** Cumulative risks of one or more islet autoantibodies, multiple islet autoantibodies, and type 1 diabetes development in TEDDY children with the HLA DR3/DR4-DQ8 or DR4-DQ8/DR4-DQ8 genotype stratified by their merged score. The cumulative risk of developing one or more islet autoantibodies *(left graph)*, multiple islet autoantibodies *(middle graph)*, and type 1 diabetes (*right graph, y* axis) is shown relative to age in yr (*x* axis) and was calculated using the Kaplan ± Meier method. Curves are shown for children with genetic scores in the upper *(orange line)*, lower *(green line)*, and two middle *(blue line)* quartiles. The shaded areas represent the 95% confidence interval of the cumulative risk. The numbers at risk indicate the number of children included in the analysis at each age. **B,** Type 1 diabetes progression and stages of type 1 diabetes. Stage 1 is the start of type 1 diabetes, marked by individuals having two or more diabetes-related autoantibodies and normal blood sugar concentrations. In stage 2, individuals have dysglycemia without symptoms. Stage 3 is the time of clinical diagnosis. T1D, type 1 diabetes. *(**A** from Bonifacio E, Beyerlein A, Hippich M, et al. Genetic scores to stratify risk of developing multiple islet autoantibodies and type 1 diabetes: A prospective study in children. PLoS Med. 2018;15:e1002548. Fig. 4; **B** from Greenbaum CJ, Speake C, Krischer J, et al. Strength in numbers: opportunities for enhancing the development of effective treatments for type 1 diabetes—the TrialNet experience. Diabetes. 2018;67:1216–1225.)*

Antibodies are a marker for the presence of autoimmunity, but the actual damage to the β cells is primarily T-cell mediated (see Fig. 629.4). Histologic analysis of the pancreas from patients with recent-onset T1DM reveals insulitis, with an infiltration of the islets of Langerhans by mononuclear cells, including T and B lymphocytes, monocytes/macrophages, and natural killer cells. The process in human T1DM is not necessarily linear, and there may be an undulating downhill course, with remissions and relapses, in the development of T1DM.

Role of Autoantibodies

Even though T1DM does not occur as a direct consequence of autoantibody formation, the risk of developing clinical disease increases dramatically with an increase in the number of antibodies; only 15% of children with one antibody will progress to diabetes in 10 years, but this risk increases to 70% when two antibodies are present and 90% when three are present. The risk of progression also varies with the intensity of the antibody response, and those with higher antibody titers are more likely to progress to clinical disease. Another factor that appears to influence progression of β-cell damage is the age at which autoimmunity develops; children in whom IAAs appeared within the first 2 years of life rapidly developed anti–islet cell antibodies and progressed to diabetes more frequently than children in whom the first antibodies appeared between ages 5 and 8 years.

Role of Genetics in Disease Progression

In a large study of *healthy* children, the appearance of single antibodies is relatively common and usually transient and does not correlate with the presence of high-risk HLA alleles; those carrying high-risk HLA alleles are more likely to develop multiple antibodies and progress to disease. Similarly, the appearance of antibodies is more likely to predict diabetes in those with a family history of diabetes versus those with no family history of T1DM. Environmental factors may induce transient autoimmunity in many children, but those with genetic susceptibility are more likely to see progression of autoimmunity and eventual development of diabetes.

Role of Environmental Factors

Environmental factors may also act as accelerators of T1DM after the initial appearance of autoimmunity. This is evident from the fact that the incidence of T1DM can vary several-fold between populations that have the same prevalence of autoimmunity. The incidence of T1DM in Finland is almost fourfold higher than in Lithuania, but the incidence of autoimmunity is similar in both countries.

The fact that all children with evidence of autoimmunity and of autoreactive T cells do not progress to diabetes indicates that there are checkpoints at which the autoimmune process can be halted or reversed before it progresses to full-blown diabetes.

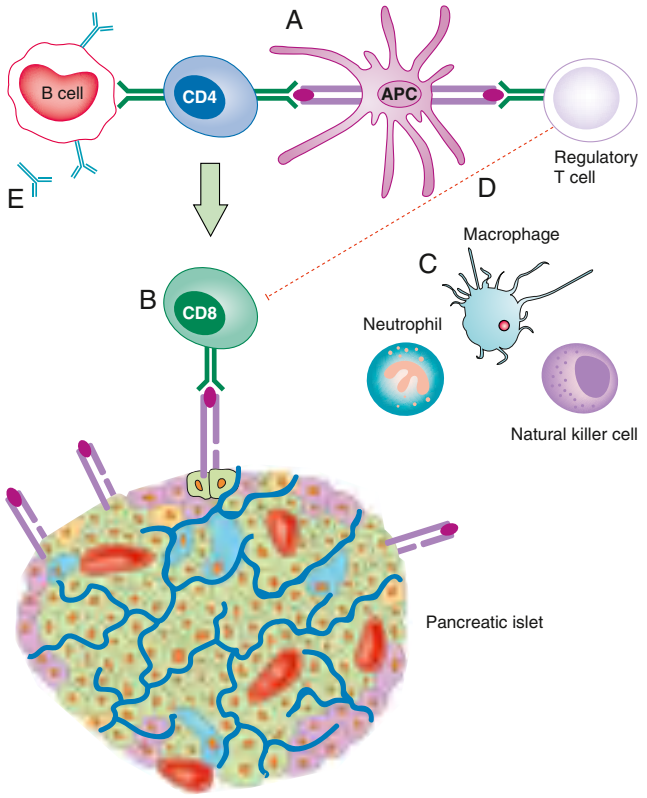


Fig. 629.4 The immunopathogenesis of type 1 diabetes. The development of type 1 diabetes is thought to be initiated by the presentation of β-cell peptides by antigen-presenting cells *(APCs)*. APCs bearing these autoantigens migrate to the pancreatic lymph nodes, where they interact with autoreactive $CD4^+$ T lymphocytes, which in turn mediate the activation of autoreactive $CD8^+$ T cells *(A)*. These activated $CD8^+$ T cells return to the islet and lyse β cells expressing immunogenic self-antigens on major histocompatibility complex class I surface molecules *(B)*. β-Cell destruction is further exacerbated by the release of proinflammatory cytokines and reactive oxygen species from innate immune cells (macrophages, natural killer cells, and neutrophils) *(C)*. This entire process is amplified by defects in regulatory T lymphocytes, which do not effectively suppress autoimmunity *(D)*. Activated T cells within the pancreatic lymph node also stimulate B lymphocytes to produce autoantibodies against β-cell proteins. These autoantibodies can be measured in circulation and are considered a defining biomarker of type 1 diabetes *(E)*. *(From DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391:2449–2458. Fig. 3.)*

Onset of Clinical Disease

Patients with progressive β-cell destruction will eventually present with clinical T1DM. It was thought that 90% of the total β-cell mass is destroyed by the time clinical disease develops, but other studies have revealed that this is not always the case. It appears that β-cell destruction is more rapid and more complete in younger children, whereas in older children and adults, the proportion of surviving β cells is greater (10–20% in autopsy specimens), and some β cells (about 1% of the normal mass) survive up to 30 years after the onset of diabetes. Because autopsies are usually done only on patients who died of DKA, these figures may underestimate the actual β-cell mass present at diagnosis. Functional studies indicate that up to 40% of the insulin secretory capacity may be preserved in adults at the time of presentation of T1DM. Ultrasensitive assays indicate that C-peptide production is measurable decades after the onset of T1DM. The fact that newly diagnosed diabetic individuals may still have a significant surviving β-cell mass is important because it raises the possibility of *secondary* prevention of T1DM. Similarly, the existence of viable β cells years or decades after initial presentation indicates that even patients with long-standing diabetes may be able to exhibit some recovery of β-cell function if the autoimmune destructive process could be halted and if islet cell regeneration could occur.

PREDICTION

Autoimmunity precedes clinical T1DM, and indicators of autoimmune responses may be useful markers for disease prediction. Individuals at risk for T1DM can be identified by a combination of genetic, immunologic, and metabolic markers. The most informative genetic locus, HLA class II, confers about half of the total genetic risk but has a low positive predictive value (PPV) when used in the general population. Autoantibodies provide a practical readout of β-cell autoimmunity, are easily sampled in venous blood, and have become the mainstay of T1DM prediction efforts. By comparison, and even though T lymphocytes mediate β-cell destruction, T cells are rare in blood, and assays of their function have been difficult to standardize and validate. In the first-degree relatives of patients with T1DM, the number of positive autoantibodies can help estimate the risk of developing T1DM: low risk (single autoantibodies: PPV of 2–6%), moderate risk (2 autoantibodies: PPV of 21–40%), and high risk (>2 autoantibodies: PPV of 59–80%) over a 5-year period. In children carrying the T1DM highest-risk genotype (HLA-DQB1*0201-DQA1*05/DQB1*0302-DQA1*03), insulitis is almost 10 times more frequent (PPV 21%) than in children with other genotypes (PPV 2.2%). But although autoantibodies are useful for the prediction of T1DM in the relatives of patients with T1DM, outside of that obvious population, the screening of the general population would be required to identify healthy subjects at risk of T1DM. Indeed, ~90% of individuals with new-onset T1DM have no family background of T1DM. Screening the general population is difficult to justify, in part, because the observed autoantibody prevalence greatly exceeds the low disease prevalence in nonrelatives, leading to high false-positive rates.

PREVENTION

Strategies for the prevention of T1DM are focused primarily on slowing progression of β-cell loss after the onset of autoimmune islet disease through targeted immunosuppression of autoreactive regulatory T cells. Numerous compounds are under investigation for this purpose, including agents that could modulate regulatory T cells via stimulating interleukin (IL)-2, tumor necrosis factor (TNF)-α signaling, or CTLA signaling and by inhibiting IL-17 or T-cell receptor (TCR) signaling. Teplizumab, a humanized anti-CD3 monoclonal antibody that inhibits TCR signaling, has been shown to delay the onset of clinical diabetes in high-risk children and young adults. It is approved for use in the United States for patients 8 years and older with stage 2 T1DM, defined by at least two positive pancreatic islet cell autoantibodies and dysglycemia without hyperglycemia.

PATHOPHYSIOLOGY OF T1DM

Insulin performs a critical role in the storage and retrieval of cellular fuel. Its secretion in response to feeding is exquisitely modulated by the interplay of neural, hormonal, and substrate-related mechanisms to permit controlled disposition of ingested foodstuff as energy for immediate or future use. Insulin levels must be lowered to then mobilize stored energy during the fasted state. Thus in normal metabolism, there are regular swings between the postprandial, high-insulin anabolic state and the fasted, low-insulin catabolic state that affect liver, muscle, and adipose tissue (Table 629.4). T1DM is a progressive low-insulin catabolic state in which feeding does not reverse, but rather exaggerates, these catabolic processes. With moderate insulinopenia, glucose use by muscle and fat decreases and postprandial hyperglycemia appears. At even lower insulin levels, the liver produces excessive glucose via glycogenolysis and gluconeogenesis, and fasting hyperglycemia begins. Hyperglycemia produces an osmotic diuresis (glycosuria) when the renal threshold is exceeded (180 mg/dL; 10 mmol/L). The resulting loss of calories and electrolytes, as well as the worsening dehydration, produces a physiologic stress with hypersecretion of stress hormones (epinephrine, cortisol, growth hormone, and glucagon). These hormones, in turn, contribute to the metabolic decompensation by further impairing insulin secretion (epinephrine), by antagonizing its action (epinephrine, cortisol, growth hormone), and by promoting

Table 629.4 Influence of Feeding (High Insulin) or of Fasting (Low Insulin) on Some Metabolic Processes in Liver, Muscle, and Adipose Tissue*

	HIGH PLASMA INSULIN (POSTPRANDIAL STATE)	LOW PLASMA INSULIN (FASTED STATE)
Liver	Glucose uptake	Glucose production
	Glycogen synthesis	Glycogenolysis
	Absence of gluconeogenesis	Gluconeogenesis
	Lipogenesis	Absence of lipogenesis
	Absence of ketogenesis	Ketogenesis
Muscle	Glucose uptake	Absence of glucose uptake
	Glucose oxidation	Fatty acid and ketone oxidation
	Glycogen synthesis	Glycogenolysis
	Protein synthesis	Proteolysis and amino acid release
Adipose tissue	Glucose uptake	Absence of glucose uptake
	Lipid synthesis	Lipolysis and fatty acid release
	Triglyceride uptake	Absence of triglyceride uptake

*Insulin is considered to be the major factor governing these metabolic processes. Diabetes mellitus may be viewed as a permanent low-insulin state that, if untreated, results in exaggerated fasting.

glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis (glucagon, epinephrine, growth hormone, and cortisol) while decreasing glucose use and glucose clearance (epinephrine, growth hormone, cortisol).

The combination of insulin deficiency and elevated plasma values of the counterregulatory hormones is also responsible for accelerated lipolysis and impaired lipid synthesis, with resulting increased plasma concentrations of total lipids, cholesterol, triglycerides, and free fatty acids. The hormonal interplay of insulin deficiency and glucagon excess shunts the free fatty acids into ketone body formation; the supranormal rate of formation of these ketone bodies, principally β-hydroxybutyrate and acetoacetate, exceeds the capacity for peripheral use and renal excretion. Accumulation of these keto acids results in metabolic acidosis (DKA) and compensatory rapid, deep, nondyspneic breathing to excrete excess CO_2 (Kussmaul respiration). Acetone, formed by nonenzymatic conversion of acetoacetate, is responsible for the characteristic fruity odor of the breath. Ketones are excreted in the urine in association with cations and thus further increase losses of water and electrolyte and bicarbonate regenerating ability. With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen use, consciousness becomes impaired, and the patient ultimately becomes comatose.

CLINICAL MANIFESTATIONS

The classic clinical manifestations of new-onset diabetes in children reflect the hyperglycemic and catabolic physiologic state and include polyuria, polydipsia, polyphagia, and weight loss. Other common symptoms include fatigue, weakness, and a general feeling of malaise. Patients presenting with more advanced disease will exhibit signs of **DKA**, including dehydration, nausea, vomiting, lethargy, altered mental status, and in extreme cases, coma. If the diagnosis is not recognized, the progression of symptoms follows a predictable course from early intermittent polyuria, to sustained polyuria and weight loss, followed by development of DKA. In most cases, this initial progression occurs over a period of weeks rather than months.

Initially, when only insulin reserve is limited, occasional asymptomatic postprandial hyperglycemia occurs. When insulin secretory capacity declines, blood glucose levels begin to rise. When the blood glucose increases above the renal threshold, intermittent polyuria and/or nocturia begins. With further β-cell loss, chronic hyperglycemia causes a more persistent diuresis, which often includes nocturnal enuresis in younger children. Female patients may develop vulvovaginal candidiasis from the chronic glycosuria. Eventually, daily losses of water and glucose may be as high as 5 L and 250 g, respectively, representing 1,000 calories, or 50%, of the average daily caloric intake. These losses trigger compensatory polydipsia and polyphagia; however, progressive dehydration and weight loss will inevitably ensue unless treatment is initiated.

When the disease continues to progress, ketoacids begin to accumulate. At this stage in the disease, rapid clinical deterioration is possible. Ketoacids produce abdominal pain, anorexia, nausea, and emesis and thereby impede the patient's ability to maintain sufficient oral replacement of urinary water losses. Dehydration accelerates, as manifested by weakness, orthostasis, and further weight loss. As in any hyperosmotic state, the degree of dehydration may be clinically underestimated because intravascular volume is conserved at the expense of intracellular volume. Signs and symptoms of advanced ketoacidosis include Kussmaul respirations (deep, heavy, nonlabored, rapid breathing), fruity breath odor (acetone), prolonged corrected Q-T interval, diminished neurocognitive function, and coma. Approximately 20–40% of children with new-onset diabetes progress to DKA before diagnosis; data from the United States suggest that the prevalence of DKA at onset of T1DM is increasing.

Clinical progression typically happens more quickly in younger children, owing to either more aggressive autoimmune destruction of β-cells and/or to lower β-cell mass. Disease onset in infancy is associated with a greater likelihood of DKA at presentation. Weight loss in younger children and individuals with more rapidly progressive disease will be composed mostly of acute fluid loss, whereas weight loss in adolescents and individuals with slowly progressive disease will also include significant fat and lean mass deficits as a result of prolonged starvation. In any child, the progression of symptoms may be accelerated by the stress of an intercurrent illness or trauma, when counterregulatory (stress) hormones counter the limited insulin secretory capacity.

DIAGNOSIS

The diagnosis of T1DM is usually straightforward (see Table 629.2). Although most symptoms are nonspecific, the most important clue is an inappropriate polyuria in any child with signs of dehydration and poor weight gain. Hyperglycemia can be identified quickly from capillary blood by use of a glucometer; glycosuria and ketonuria can readily be determined by urine dipstick. Nonfasting blood glucose greater than 200 mg/dL (11.1 mmol/L) with typical symptoms is diagnostic with or without ketonuria. In the obese child, T2DM must be considered (see Chapter 629.3). Once hyperglycemia is confirmed, it is prudent to determine whether DKA is present (especially if ketonuria is found) by checking a venous blood sample for bicarbonate and pH and also to evaluate for electrolyte abnormalities—even if signs of dehydration are minimal. A baseline HbA_{1c} will be confirmatory and allows an estimate of the duration of hyperglycemia and provides an initial value by which to compare the effectiveness of subsequent therapy. Falsely low HbA_{1c} levels are noted in hemolytic anemias (sickle cell anemia, others), pure red cell aplasia, blood transfusions, and anemias associated with hemorrhage, cirrhosis, myelodysplasias, or renal disease treated with erythropoietin.

Testing for autoimmunity (T1DM autoantibodies) (see Chapter 629.1) should be considered in cases where the differentiation between T1DM and T2DM is not apparent and in cases where there is a strong family history suggestive of monogenic and syndromic diabetes. The presence of other autoimmune diseases associated with T1DM should be sought at or shortly after diagnosis, including celiac disease (by tissue transglutaminase immunoglobulin A [IgA] and total IgA) and autoimmune hypothyroidism (by thyroid-stimulating hormone [TSH] and free or total thyroxine). Because significant physiologic perturbations can affect thyroid and celiac screening tests, individuals with

only mild abnormalities should have tests repeated *after* several weeks before instituting therapy. In addition, because there is an increased risk of cardiovascular disease associated with diabetes, it is also recommended to obtain a fasting lipid profile in children ≥10 years of age once glucose control has been established.

Rarely, a child has transient hyperglycemia with glycosuria while under substantial physical stress or illness. This usually resolves permanently during recovery from the stressors. **Stress-produced hyperglycemia** can reflect a limited insulin reserve temporarily revealed by elevated counterregulatory hormones. A child with temporary hyperglycemia should therefore be monitored for the development of symptoms of persistent hyperglycemia and be tested with an HbA_{1c} if such symptoms occur. Formal testing in a child who remains clinically asymptomatic is not necessary.

Routine screening procedures, such as postprandial determinations of blood glucose or screening OGTTs, have yielded low detection rates in healthy, asymptomatic children, even among those considered at risk, such as siblings of diabetic children. Accordingly, such screening procedures are not recommended in children.

TREATMENT

Therapy is tailored to the degree of insulinopenia at presentation. Most children with new-onset T1DM have mild to moderate symptoms, have minimal dehydration with no history of emesis, and have not progressed to ketoacidosis. They can be started on subcutaneous insulin therapy directly. About 20–40% of children with new-onset diabetes present in DKA, which can be arbitrarily classified as mild, moderate, or severe (Table 629.5), and the range of symptoms depends on the degree of ketoacidosis. Cardinal biochemical abnormalities include elevations in blood and urine ketones, an increased anion gap, a decreased serum bicarbonate (or total CO_2) and pH, and an elevated effective serum osmolality. Hyponatremia is commonly present with hyperglycemia and is the result of an osmotic dilution as water shifts into the extracellular fluid. Potassium and phosphate depletion is common after prolonged polyuria but may be masked by acidosis, which leads to extracellular shifting of these ions.

Treatment of Diabetic Ketoacidosis

Severe insulinopenia (or lack of effective insulin action) results in a physiologic cascade of events in three general pathways:

1. Excessive glucose production coupled with reduced glucose use raises serum glucose. This triggers an osmotic diuresis, with urinary loss of fluid and electrolytes, dehydration, and activation of the renin-angiotensin-aldosterone axis with accelerated potassium loss. When glucose elevation and dehydration are severe and persist for several hours, the risk of cerebral edema increases.
2. Increased catabolic processes result in cellular losses of sodium, potassium, and phosphate.
3. Increased release of free fatty acids from peripheral fat stores supplies substrate for hepatic ketoacid production. When ketoacids accumulate, buffer systems are depleted, and a metabolic acidosis ensues.

Therapy must address both the initiating event in this cascade (insulinopenia) and the subsequent physiologic disruptions.

Reversal of DKA is associated with inherent risks that include hypoglycemia, hypokalemia, and cerebral edema. Any protocol must be used with caution and close monitoring of the patient. Adjustments based on sound medical judgment may be necessary for any given level of DKA (Figs. 629.5 and 629.6).

Dehydration and Hyperglycemia

Judicious fluid resuscitation is the first step in the medical management of DKA. Correction of fluid deficits must be tempered by the potential risk of cerebral edema. It is prudent to approach any child in any hyperosmotic state with cautious rehydration. The effective serum osmolality ($E_{osm} = 2 \times [Na_{uncorrected}] + [glucose]$) is an accurate index of tonicity of the body fluids, reflecting intracellular and extracellular hydration better than measured plasma osmolality. It is calculated with sodium and glucose in mmol/L. This value is usually elevated at the beginning of therapy and should steadily normalize. A rapid decline, or a slow decline to a subnormal range, may indicate an excess of free water entering the vascular space and an increasing risk of cerebral edema. Therefore patients should not be allowed oral fluids until rehydration is well underway and significant electrolyte shifts are no longer likely. Limited ice chips may be given as a minimal oral intake. All fluid intake and output should be closely monitored.

Calculation of fluid deficits using clinical signs is difficult in children with DKA because intravascular volume is better maintained in the hypertonic state. For any degree of tachycardia, delayed capillary refill, decreased skin temperature, or orthostatic blood pressure change, the child with DKA will be more dehydrated than the child with a normotonic fluid deficit. Typically, an initial intravenous bolus of 10-20 mL/kg of glucose-free isotonic sodium salt solution such as Ringer lactate or 0.9% sodium chloride is given over 1 to 2 hours. Further fluid boluses should be given only for hemodynamically unstable patients. This bolus is given as isotonic saline because the patient is inevitably hypertonic, keeping most of the initial infusion in the intravascular space. Subsequent fluid replacement then consists of 0.45% or 0.9% sodium chloride infused at a rate calculated to replace the fluid deficit (after subtracting initial fluid bolus) over 24-48 hours plus maintenance. The fluid deficit can be calculated empirically if a recent weight is available, estimated at 5–10% of body weight based upon clinical severity, or by assuming a standard water deficit (85 mL/kg). Practically, this is generally equivalent to a rate of ~1.5 times maintenance, which can be substituted for simplicity in most situations.

The optimal fluid protocol to prevent CNS complications (cerebral edema) of DKA remains uncertain. When children with DKA were randomly assigned to one of four treatment arms consisting of fast or slow fluid deficit repletion of 0.9% or 0.45% sodium chloride, there were no differences in short- or long-term neurocognitive outcomes among any of the treatment arms. In general, after reestablishing the intravascular volume and avoiding rapid declines of blood glucose levels and hyponatremia, fluid replacement rates or fluid composition may subsequently be administered per protocol (see Fig. 629.5). *It is possible that cerebral injury preceded therapy and is the result of DKA and not rates or composition of IV fluids.*

Insulin must be given to promote movement of glucose into cells, to subdue hepatic glucose production, and to halt the movement of fatty acids from the periphery to the liver. An initial IV insulin bolus does not speed recovery and may increase the risk of hypokalemia and hypoglycemia. *Therefore insulin infusion is typically begun without an insulin bolus at*

Table 629.5 Classification of Diabetic Ketoacidosis

	NORMAL	MILD	MODERATE	SEVERE*
HCO_2 (mEq/L, venous)†	20-28	16-20	10-15	<10
pH (venous)†	7.35-7.45	7.25-7.35	7.15-7.25	<7.15
Clinical	No change	Oriented, alert but fatigued	Kussmaul respirations; oriented but sleepy; arousable	Kussmaul or depressed respirations; sleepy to depressed sensorium to coma

*Severe hypernatremia (corrected Na >150 mEq/L) would also be classified as severe diabetic ketoacidosis.
†HCO_2 and pH measurement are method dependent; normal ranges may vary.

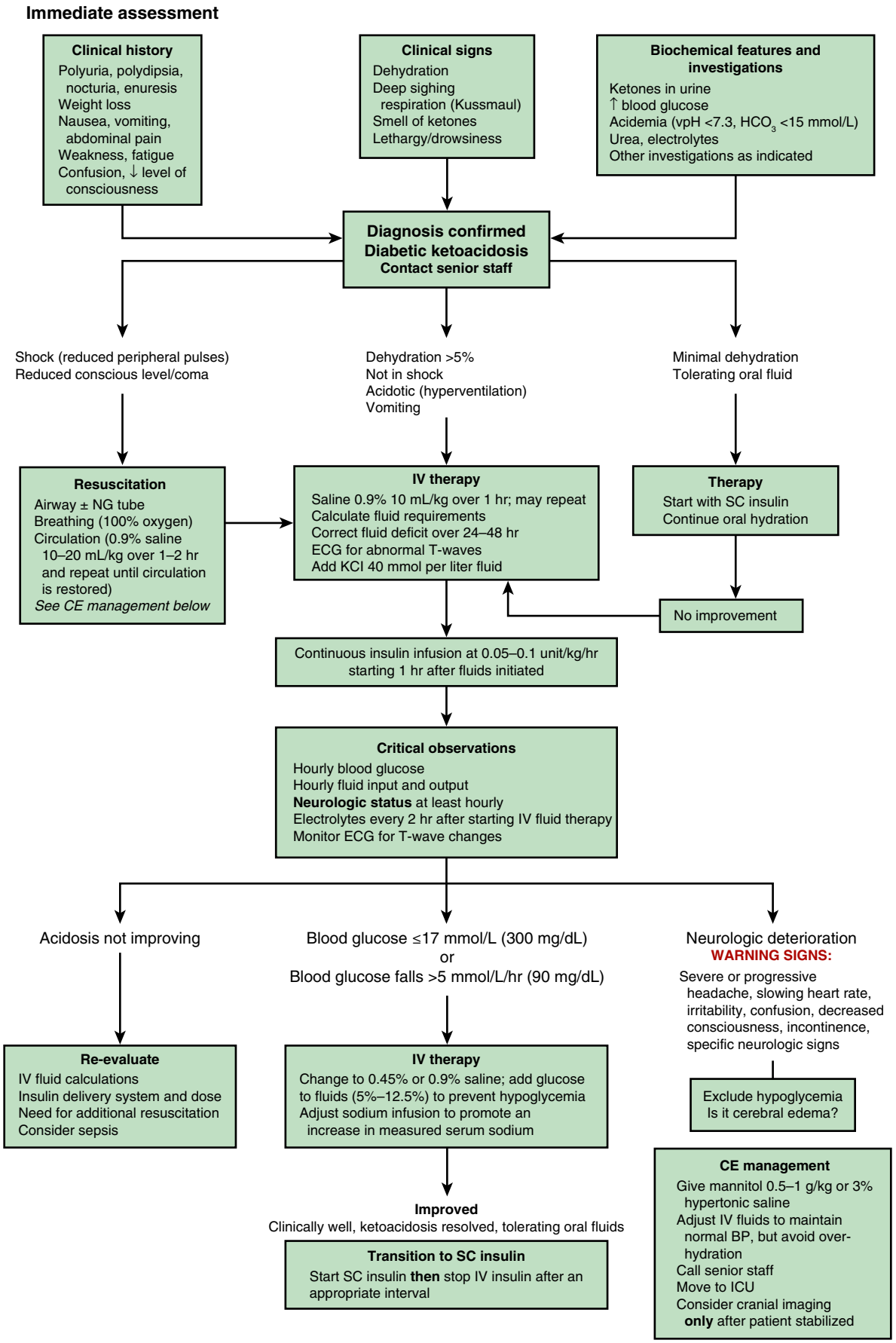


Fig. 629.5 Algorithm for the management of diabetic ketoacidosis. CE, cerebral edema; ECG, electrocardiogram; KCl, potassium chloride; SC, subcutaneous. *(Adapted from Pinhas-Hamiel O, Sperling M. Diabetic ketoacidosis. In: Hochberg Z, ed. Practical Algorithms in Pediatric Endocrinology. 3rd ed. Basel, Switzerland: Karger; 2017:112–113.)*

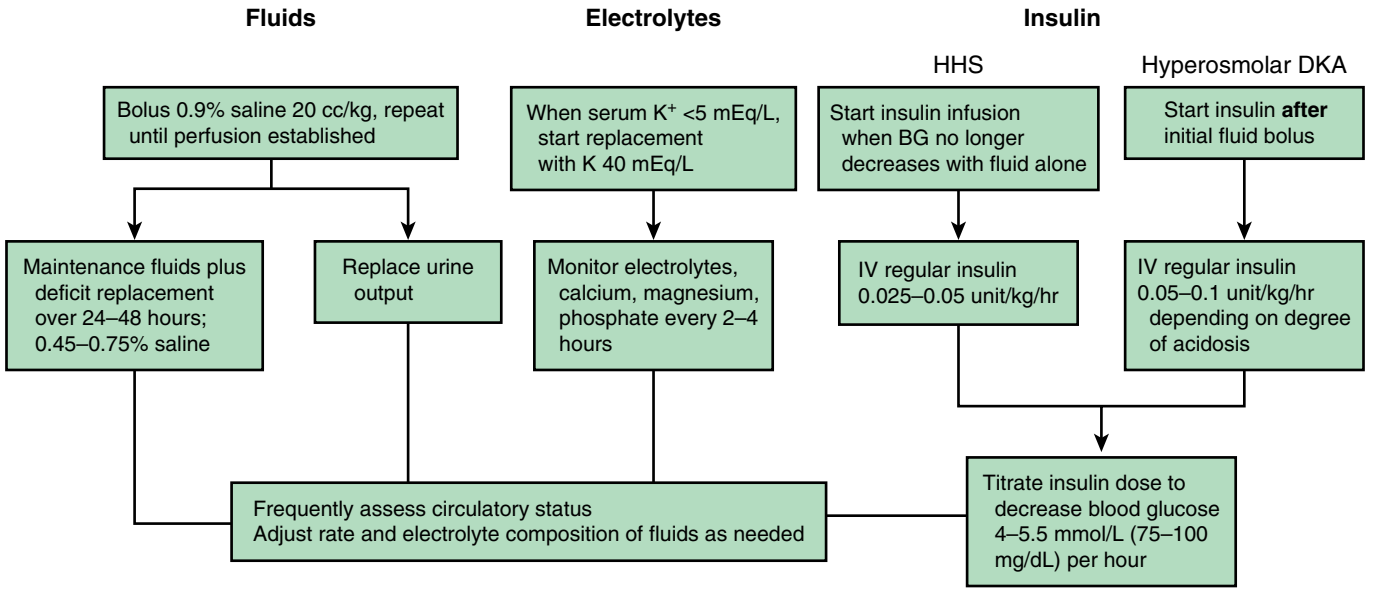


Fig. 629.6 Algorithm for the treatment of hyperglycemic hyperosmolar syndromes (HHS). BG, blood glucose. *(From Zeitler P, Haqq A, Rosenbloom A, Glaser N. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2011;158(1):9–14, 14.e1–2.)*

a rate of 0.05 to 0.1 units/kg/hr after initial fluid resuscitation is complete. This approximates maximal insulin output in normal subjects during an OGTT. Rehydration alone also lowers glucose levels by improving renal perfusion and enhancing renal excretion. The combination of these therapies usually causes a rapid initial decline in serum glucose levels. Persistent decreases in serum glucose of >100 mg/dL/hr may increase the risk of cerebral edema; therefore careful monitoring of serum glucose and adjustment of the dextrose concentration of the IV fluids is essential. The dextrose concentration of the IV fluids should be 5% (D5) once serum glucose falls below ~300 mg/dL and 10% once glucose is below 200 mg/dL. The use of a two-bag system is the preferred approach for managing the dextrose concentrations of the infused IV fluid during DKA. A two-bag system consists of two IV bags of identical electrolyte concentrations, where one bag contains 0% dextrose and the other contains 10% dextrose. The fluids are administered via a Y-site and can be easily titrated to infuse fluids ranging from 0% to 10% dextrose.

Once the blood glucose level decreases below ~180 mg/dL (10 mmol/L), the osmotic diuresis stops and rehydration accelerates without further increase in the infusion rate. Repair of hyperglycemia occurs well before correction of acidosis. Therefore insulin is still needed to control fatty acid release and ketosis after normal glucose levels are reached. If serum glucose levels fall below 100 mg/dL despite an infusion of D10-containing IV fluids, the glucose infusion rate can be increased by increasing dextrose to 12.5% or by increasing the infusion rate. Alternatively, the IV insulin rate can be decreased if ketosis continues to improve.

The initial serum sodium is usually normal or low because of the osmolar dilution caused by hyperglycemia and the effect of an elevated sodium-free lipid fraction. An estimate of the reconstituted, or "true," serum sodium for any given glucose level above 100 mg/dL (5.6 mmol/L) is calculated as follows:

$$\left[Na^+\right] + \left(\begin{array}{l}1.6\,\text{mEq/L}\,Na^+ \text{ for every } 100\,\text{mg/dL glucose in}\\ \text{excess of } 100\end{array}\right)$$

or

$$\left[Na^+\right] + \left(\frac{1.6\,\text{mEq}}{\text{L}\,Na^+ \text{ for every } 5.6\,\text{mmol}\ \text{L glucose}} \text{ in excess of } 5.6\right)$$

The sodium should *increase* by approximately 1.6 mmol/L for each 100 mg/dL *decline* in the glucose. The corrected sodium is usually normal or slightly elevated and indicates moderate hypernatremic dehydration. If the corrected value is greater than 150 mmol/L, severe hypernatremic dehydration may be present and may require *slower* fluid replacement. The sodium should steadily increase with therapy. *Declining sodium may indicate excessive free water accumulation and increased risk of cerebral edema.*

Both the metabolic shift to a catabolic predominance and the acidosis move potassium and phosphate from the cell to the serum. The osmotic diuresis, the kaliuretic effect of the hyperaldosteronism, and the ketonuria then accelerate renal losses of potassium and phosphate. Sodium is also lost with the diuresis, but free water losses are greater than isotonic losses. With prolonged illness and severe DKA, total body losses can approach 10-13 mEq/kg of sodium, 5-6 mEq/kg of potassium, and 4-5 mEq/kg of phosphate. These losses continue for several hours during therapy until the catabolic state is reversed and the diuresis is controlled. For example, 50% of infused sodium may be lost in the urine during IV therapy. Even though the sodium deficit may be repaired within 24 hours, intracellular potassium and phosphate may not be completely restored for several days.

Although patients with DKA have a total body potassium deficit, the initial serum level is often normal or elevated. This is caused by the movement of potassium from the intracellular space to the serum, both as part of the ketoacid buffering process and as part of the catabolic shift. These effects are reversed with therapy, and potassium returns to the cell. Improved hydration increases renal blood flow, allowing for increased excretion of potassium in the elevated aldosterone state. The net effect is often a dramatic decline in serum potassium levels, especially in severe DKA. This can precipitate changes in cardiac conductivity, flattening of T waves, and prolongation of the QRS complex and can cause skeletal muscle weakness or ileus. The risk of myocardial dysfunction is increased with shock and acidosis. Potassium levels must be closely followed and electrocardiographic monitoring continued until DKA is substantially resolved. Potassium should be added to the IV fluids once serum potassium declines below 5.5 mEq/L and titrated. A 1:1 mixture of potassium chloride (or acetate) and potassium phosphate is typically used. Rarely, the IV insulin must be temporarily held if serum potassium levels drop below 3 mEq/L. It is unclear whether phosphate deficits contribute to symptoms of DKA such as generalized muscle weakness. In pediatric patients, a deficit has not been shown to compromise oxygen delivery via a deficiency of 2,3-diphosphoglycerate. In most cases, the inclusion of potassium phosphate as outlined earlier will be sufficient; however, additional IV supplementation with potassium phosphate can be used if needed.

Pancreatitis (usually mild) is occasionally seen with DKA, especially if prolonged abdominal distress is present; serum amylase and lipase may be elevated. If the serum lipase is not elevated, the amylase is likely nonspecific or salivary in origin. Serum creatinine adjusted for age may be falsely elevated owing to interference by ketones in the autoanalyzer methodology. An initial elevated value rarely indicates renal failure and should be rechecked when the child is less ketonemic. Blood urea nitrogen may be elevated with prerenal azotemia and should be rechecked as the child is rehydrated. Mildly elevated creatinine or blood urea nitrogen is not a reason to withhold potassium therapy if good urinary output is present.

Ketoacid Accumulation

Low insulin infusion rates (0.02-0.05 units/kg/hr) are usually sufficient to stop peripheral release of fatty acids, thereby eliminating the flow of substrate for ketogenesis. Ketogenesis continues until fatty acid substrates already in the liver are depleted, but this production declines much more quickly without new substrate inflow. Bicarbonate buffers, regenerated by the distal renal tubule and by metabolism of ketone bodies, steadily repair the acidosis once ketoacid production is controlled. *Bicarbonate therapy may increase the risk of hypokalemia and cerebral edema; it should be considered only in rare situations with severe acidosis unresponsive to standard DKA management.*

There should be a steady increase in pH and serum bicarbonate as therapy progresses. Kussmaul respirations should abate and abdominal pain resolve. Persistent acidosis may indicate inadequate insulin or fluid therapy, infection, or rarely lactic acidosis. Urine ketones may be positive after ketoacidosis has resolved because the nitroprusside reaction routinely used to measure urine ketones by dipstick measures only acetoacetate. During DKA, most excess ketones are β-hydroxybutyrate, which increases the normal ratio to acetoacetate from 3:1 to as high as 8:1. With resolution of the acidosis, β-hydroxybutyrate converts to acetoacetate, which is excreted into the urine and detected by the dipstick test. Therefore persistent ketonuria may not accurately reflect the degree of clinical improvement and should not be relied on as an indicator of therapeutic failure. β-Hydroxybutyrate can be measured from serum and even by bedside capillary ketometer and is used in some protocols to monitor the resolution of DKA and help determine when to transition from IV to subcutaneous insulin administration.

All patients with known diabetes presenting in DKA should be checked for precipitating events (infection, poor compliance, trauma) that may have triggered the metabolic decompensation.

Diabetic Ketoacidosis Protocol

See Figure 629.5.

Even though DKA can be of variable severity, a common approach to all cases simplifies the therapeutic regimen and can be safely used for most children. Fluids are best calculated based on weight, not body surface area (m^2), because heights are rarely available for the acutely critically ill child. Children with milder DKA recover in 10-20 hours (and need less total IV fluid before switching to oral intake), whereas those with more severe DKA may require up to 36 hours with this protocol. Any child can be transitioned to oral intake and subcutaneous insulin when DKA has resolved (total CO_2 >15 mEq/L; pH >7.30; sodium is stable between 135 and 145 mEq/L; anion gap closed; no emesis). A dose of long-acting insulin is given (or continuous subcutaneous infusion is started via pump) and the insulin drip is discontinued approximately 30 minutes later. Typically, transition is timed to occur around mealtime so that short-acting insulin can be given as well. Frequent (every 2-3 hours) short-acting insulin bolusing may need to be given until ketosis resolves.

A flow sheet is mandatory for accurate monitoring of changes in acidosis, electrolytes, fluid balance, and clinical status, especially if the patient is transferred from the emergency department to an inpatient setting with new caretakers. This flow sheet is best implemented by a central computer system, which allows for rapid update and wide availability of results, as well as rule-driven highlighting of critical values. A paper flow sheet suffices if it stays with the patient, is kept current, and is reviewed frequently by the physician. Any flow sheet should include columns for serial electrolytes, pH, glucose, and fluid balance. Blood glucose should be tested every hour and electrolytes should be tested every 1-2 hours for children with severe DKA and every 3-4 hours for those with mild to moderate DKA.

Cerebral Edema

Cerebral edema is an important cause of morbidity and mortality in children and adolescents with T1DM. Despite the clinical significance of this complication, its etiology remains incompletely understood. A case control study of DKA suggested that baseline acidosis and abnormalities of sodium, potassium, and blood urea nitrogen concentrations were important predictors of risk of cerebral edema. Early bolus administration of insulin and high volumes of fluid were also identified as risk factors. The incidence of cerebral edema in children with DKA has not changed over the past 15-20 years, despite the widespread introduction of gradual rehydration protocols during this interval. Radiographic imaging is frequently unhelpful in making the diagnosis of cerebral edema. Consequently, each patient must be closely monitored (see Fig. 629.5). For all but the mildest cases, this includes frequent neurologic checks for any signs of increasing intracranial pressure, such as a change of consciousness, depressed respiration, worsening headache, bradycardia, apnea, pupillary changes, papilledema, ptosis, posturing, and seizures. In the event of the development of cerebral edema, immediate interventions should include elevation of the head of the bed, reduction in IV fluid rate, and administration of mannitol (typically 1 g/kg infused intravenously over 20 minutes). Children with moderate to severe DKA have a higher overall risk of cerebral edema and should be treated in a hospital environment where appropriate monitoring can occur.

Nonketotic Hyperosmolar Coma

This syndrome is characterized by severe hyperglycemia (blood glucose >800 mg/dL; 44 mmol/L), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Respirations are usually shallow, but coexistent metabolic (lactic) acidosis may be manifested by Kussmaul breathing. Serum osmolarity is commonly 350 mOsm/kg or greater. This condition is uncommon in children, although it may be increasing in frequency with the rise in the incidence of T2DM. Among adults, mortality rates are high, possibly in part because of delays in recognition and institution of appropriate therapy. In children, there has been a high incidence of preexisting neurologic injury. Profound hyperglycemia may develop over a period of days, and initially, the obligatory osmotic polyuria and dehydration may be partially compensated for by increasing fluid intake. In some cases, consumption of excessive sugar-sweetened beverages may further exacerbate hyperglycemia. With progression of disease, thirst becomes impaired, possibly because of alteration of the hypothalamic thirst center by hyperosmolarity and, in some instances, because of a preexisting defect in the hypothalamic osmoregulating mechanism.

The low production of ketones is attributed mainly to the hyperosmolarity, which in vitro blunts the lipolytic effect of epinephrine and the antilipolytic effect of residual insulin; blunting of lipolysis by the therapeutic use of β-adrenergic blockers may contribute to the syndrome. Depression of consciousness is closely correlated with the degree of hyperosmolarity in this condition and in DKA. Hemoconcentration may also predispose to cerebral arterial and venous thromboses before therapy is initiated.

Treatment of nonketotic hyperosmolar coma is directed at rapid repletion of the vascular volume deficit with normal saline and very slow correction of the hyperosmolar state (see Fig. 629.6). The fluid deficit should be estimated at 12–15% of body weight. Additional normal saline boluses may be required to reduce tachycardia and poor perfusion. One-half isotonic saline (0.45% NaCl; may use normal saline) is administered at a rate estimated to replace 50% of the volume deficit in the first 12 hours, and the remainder is administered during the ensuing 24 hours. The rate of infusion and the saline concentration are titrated to result in a slow decline of serum osmolality. When

the blood glucose concentration approaches 300 mg/dL, the hydrating fluid should be changed to 5% dextrose in 0.45% NaCl. Approximately 20 mEq/L of potassium chloride should be added to each of these fluids to prevent hypokalemia. Serum potassium and plasma glucose concentrations should be monitored at 2-hour intervals for the first 12 hours and at 4-hour intervals for the next 24 hours to permit appropriate adjustments of administered potassium and insulin.

Insulin can be given by continuous intravenous infusion only after serum glucose levels no longer decline with fluid administration. The IV insulin should be initiated at a low dose of 0.025-0.05 units/kg/hr and titrated to achieve a slow decline in serum glucose of 50-75 mg/dL/hr (2.8-4.2 mmol/L/hr). The presence of ketosis or more severe acidosis may necessitate earlier insulin initiation.

INITIATION OF SUBCUTANEOUS INSULIN THERAPY

Excellent diabetes control involves many goals: to maintain blood glucose and HbA_{1c} levels as close to normal without causing hypoglycemia, to eliminate polyuria and nocturia, to prevent ketoacidosis, to permit normal growth and development, and to avoid development of diabetes-related complications—all while minimizing the impact on lifestyle. The specific components of therapy include initiation and adjustment of insulin, extensive teaching of the child and caretakers, and reestablishment of the life routines. Each aspect should be addressed early in the overall care.

Insulin Therapy

Insulin therapy is initiated at the time of diagnosis for all patients with T1DM. The starting dose may range from 0.4 to 1.2 units/kg/day and is calculated based on a number of factors, including age, pubertal stage, and presence or absence of DKA. Typically, prepubertal children presenting without DKA can be started on a dose of 0.4-0.6 units/kg/day. Overweight pubertal adolescents presenting with DKA may need up to 1-1.2 units/kg/day. Insulin requirements in infancy vary tremendously, from <0.2 units/kg/day to >1 unit/kg day. Table 629.6 shows typical starting ranges for total daily insulin dose (units/kg/day) in children.

The precise optimal insulin dose can only be determined empirically, after beginning with the previously mentioned starting doses, with frequent self-monitored blood glucose levels and insulin adjustment by the diabetes team. Many children with new-onset diabetes have some residual β-cell function (the honeymoon period), which is associated with reduced exogenous insulin needs shortly after starting treatment. Residual β-cell function usually fades within a few months and is reflected as a steady increase in insulin requirements and wider glucose excursions.

The initial insulin schedule should be directed toward the optimal degree of glucose control in an attempt to duplicate the activity of the β cell. There are inherent limits to our ability to mimic the β cell. Exogenous insulin does not have a first pass to the liver, whereas 50% of pancreatic portal insulin is taken up by the liver, a key organ for the disposal of glucose. Absorption of an exogenous dose continues despite hypoglycemia, whereas endogenous insulin secretion ceases and serum levels quickly lower with a normally rapid clearance. The absorption rate from an injection varies by injection site and patient activity level, whereas endogenous insulin is secreted directly into the portal circulation. Despite these fundamental physiologic differences, acceptable glucose control can be obtained with insulin analogs used in a **basal-bolus regimen**. Basal-bolus regimens can be accomplished with multiple daily injections (MDIs), where a slow-onset, long-duration background insulin is given once or twice daily for between-meal glucose control (basal) and a rapid-onset insulin is given with meals to provide carbohydrate coverage and correct hyperglycemia. Alternatively, an **insulin pump** can be used, where a rapid-onset insulin is used to provide both basal (via continuous infusion) and bolus (at mealtimes and as needed for hyperglycemia) coverage. The doses of short-acting insulin include two components: **carbohydrate ratio** (typically expressed as 1 unit of insulin for a set number of grams of carbohydrates) and **insulin sensitivity factor** (ISF), also referred to as the *correction factor,* and typically expressed as 1 unit of insulin will decrease blood sugar by a set number of mg/dL to achieve a target blood glucose level). Target blood glucose levels should be individualized according to factors including age, duration of diabetes, history of hypoglycemia, time of day, and physical activity, but will generally range between 90 and 180 mg/dL. Formulas for calculating the basal dose, carbohydrate ratio, and ISF from the total daily insulin dose are provided in Table 629.6

Table 629.6 Approach to Calculating Initial Subcutaneous Insulin Doses at Diagnosis of Type 1 Diabetes (or Type 2 Diabetes Requiring Intensive Insulin Therapy) for Patients Starting on a Basal-Bolus Regimen

CALCULATE *TOTAL DAILY DOSE* (TDD) OF INSULIN*	
Minimum starting dose:	0.2 units/kg/day
Add to the minimum dose as follows:	
- Initial blood glucose >200 mg/dL	+ 0.2 units/kg/day
- Ketosis at presentation	+ 0.2 units/kg/day
- Acidosis (by pH or serum bicarbonate)	+ 0.2 units/kg/day
- Puberty (Tanner stage 2 or greater)†	+ 0.2 units/kg/day
CALCULATE DOSES OF *BASAL* AND *BOLUS* INSULIN‡	
Basal dose (long-acting insulin)	x = 50% of TDD (x = daily dose of basal insulin, typically given as one dose before bedtime)
Carbohydrate coverage (short-acting insulin)	y = 450 / TDD (1 unit of insulin for every "y" grams of carbohydrates consumed at snacks/meals)
Insulin sensitivity factor (short-acting insulin)	z = 1800 / TDD (1 unit of insulin will lower blood glucose by "z" mg/dL)

*Patients with obesity or severe insulin resistance may require an additional 0.2 units/kg/day (or more) of insulin.
†For example, a prepubertal child presenting with hyperglycemia only with a blood glucose of 325 mg/dL would be started on a TDD of insulin of 0.4 units/kg/day, whereas a pubertal adolescent presenting in DKA would be started on 1 units/kg/day.
‡Other equations for calculating basal and bolus insulin doses have been proposed and can be found in the literature. All equations provide only an estimate of insulin requirements. All patients need frequent monitoring of blood glucose after initiation of insulin, and most will require dose adjustments.

All preanalog insulins form hexamers, which must dissociate into monomers subcutaneously before being absorbed into the circulation. Thus a detectable effect for **regular insulin** is delayed by 30-60 minutes after injection. This, in turn, requires delaying the meal 30-60 minutes after the injection for optimal effect—a delay rarely attained in a busy child's life. Regular insulin has a wide peak and a long tail for bolus insulin. This profile limits postprandial glucose control, produces prolonged peaks with excessive hypoglycemic effects between meals, and increases the risk of nighttime hypoglycemia. **Neutral protamine Hagedorn** (**NPH**, also known as *insulin isophane*) is an intermediate-acting insulin with inherent limitations as a basal insulin because it does not achieve a peakless background insulin level. This produces a significant hypoglycemic effect during the midrange of the duration. Thus it is often difficult to predict its interaction with fast-acting insulins. When regular insulin is combined with NPH, the composite insulin profile poorly mimics normal endogenous insulin secretion. Lente and ultralente insulins were other intermediate-acting insulins that have since been discontinued.

Lispro, **aspart**, and **glulisine insulin** are rapid-onset analogs that are absorbed much more quickly because they do not form hexamers. They provide discrete pulses, with onset of action in as little as 10 minutes, with little, if any, overlap and short tail effect. This allows better control of postmeal glucose increase and reduces between-meal or nighttime hypoglycemia. Other ultra-fast-acting insulin analogs are being developed that promise even faster onset of action, a feature that

may make these insulins especially useful in insulin pumps and closed-loop systems.

The **long-acting analogs glargine**, **detemir**, and **degludec** are designed to provide longer duration of action, ranging from ~20 hours (glargine) to ~40 hours (degludec). Glargine forms a precipitate after subcutaneous injection, detemir binds to circulating albumin, and degludec forms dihexamers—all of which lead to stabilization of the hexameric structure, slower disassociation into insulin monomers, and prolonged duration of action. The result is a flatter 24-hour profile, making it easier to predict the combined effect of a rapid bolus (lispro, aspart, or glulisine) on top of the basal insulin and thereby create a more physiologic pattern of insulin effect. Postprandial glucose elevations are better controlled, and between-meal and nighttime hypoglycemia are reduced. An illustration of the insulin effect profiles of the currently available short- and long-acting insulins is provided in Figures 629.7 and 629.8.

At diagnosis, the basal dose of long-acting insulin is typically calculated to provide around 50% of the total daily dose, with the remainder provided with bolus doses of short-acting insulin at mealtimes (calculations used to determine insulin doses are provided in Table 629.6). Over time the ratio of basal to bolus will typically shift downward and will be affected by the magnitude of carbohydrate intake (especially during adolescence). Some infants and toddlers may do well with a higher percentage of their daily insulin provided as basal. There is considerable individual variability in the duration of action of long-acting insulins, and some younger children and obese adolescents will require twice-daily dosing of glargine. Both long- and short-acting insulins are available for administration via multidose insulin pens, which are generally easier to use compared with a traditional syringe and vial approach.

Some families may be unable to administer four daily injections. In these cases, a compromise may be needed. A three-injection regimen combining NPH with a rapid analog bolus at breakfast, a rapid-acting analog bolus at supper, and glargine at bedtime may provide fair glucose control and eliminate the need for an injection at school. Further compromise to a two-injection regimen may occasionally be needed and frequently involves use of premixed insulin preparations that include both rapid- and intermediate-acting insulins (e.g., 70/30). For this regimen, 70% of the total daily dose (TDD) is typically provided with breakfast and 30% of TDD with dinner. An illustration of commonly used insulin regimens is shown in Figure 629.8.

Insulin Pump Therapy

Continuous subcutaneous insulin infusion (CSII) via battery-powered pumps provides a closer approximation of normal plasma insulin profiles and increased flexibility regarding timing of meals and snacks compared with conventional insulin injection regimens. Insulin pump models can be programmed with a patient's personal insulin dose algorithms, including the ISF and carbohydrate ratios for premeal glucose levels. At mealtimes, the patient enters the blood glucose level (or it is automatically transmitted from a linked glucometer) and the carbohydrate content of the meal, and the pump computer will calculate the proper insulin bolus dose. Although CSII frequently improves metabolic control, this may not always be the case. The degree of glycemic control is mainly dependent on how closely patients adhere to the principles of diabetes self-care, regardless of the type of intensive insulin regimen. One benefit of pump therapy may be a reduction in severe hypoglycemia and associated seizures. Randomized trials comparing multiple daily insulin regimens using glargine insulin and CSII in children with T1DM demonstrate similar metabolic control and frequency of hypoglycemic events. Most patients will initiate therapy with insulin pens; timing of transition to an insulin pump can be individualized per patient preference as soon as 6-12 months after diagnosis.

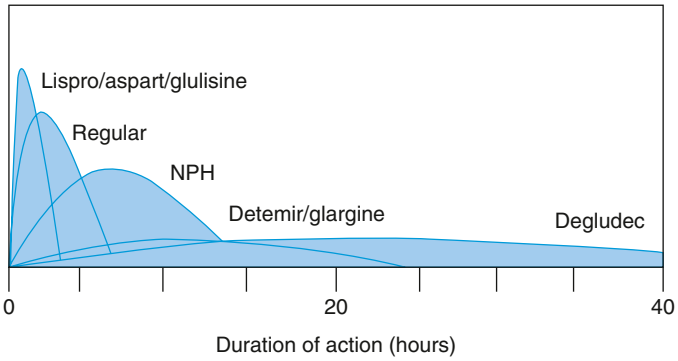


Fig. 629.7 Approximate insulin effect profiles. The following relative peak effect and duration units are used: lispro/aspart/glulisine, peak 20 for 4 hr; regular, peak 15 for 7 hr; neutral protamine Hagedorn *(NPH)* peak 12 for 12 hr; detemir/glargine, peak 5 for 20-24 hr; degludec peak 5 for 42 hr.

Continuous Glucose Monitoring Systems

Continuous glucose monitoring systems (CGMs) consist of a subcutaneous glucose sensor that continuously measures interstitial fluid glucose levels and a receiver to collect and display glucose data. CGMs reduce, but do not eliminate, the need for finger stick blood glucose checking, as calibrations with capillary blood glucose readings are required at least every 12 hours. CGMs report blood glucose levels to the patient/caregiver in real time and can be integrated with smartphones/watches for remote monitoring. To avoid hypoglycemia, the CGM system sounds an alarm once a critical low blood sugar threshold is reached. Additional alerts can be set to notify users of hyperglycemia or rapid rates of change in glucose levels. Short-term studies indicate clinical benefits of these devices as compared to conventional methods of blood glucose monitoring when used by motivated and well-informed patients. CGMs also allow for the determination of **time in range**, where the amount of time in and out of the target glycemic range *(defined by international consensus as glucose between 70 and 180 mg/dL)* can be determined and tracked. Glycemic control has been traditionally monitored by HbA_{1c}, which provides an estimate of average blood glucose over the prior 2 to 3 months. Time in range allows for a more granular assessment of glucose excursions within and between days and may prove to be a more clinically significant metric of diabetes control. A limitation of CGM-only systems is that they require the user to respond to the alert, interpret the data, and intervene to prevent hypoglycemic or hyperglycemic episodes. This limitation is mitigated when the CGM is combined with an insulin pump in a closed-loop system.

Closed-Loop Systems

A closed-loop system allows for direct communication between the continuous glucose sensor and insulin pump for automatic adjustment of insulin infusion rates in response to glucose levels (Fig. 629.9). A fully closed-loop system would be completely independent of the user and theoretically could improve glycemic control through the early identification and response to glucose perturbation and by minimizing the opportunity for human error in insulin dosing. Both single-hormone (insulin only) and bihormone (insulin and glucagon) systems are undergoing clinical investigation.

Several hybrid closed-loop systems with integrated insulin pumps and continuous glucose sensors have gained regulatory approval and entered clinical practice. There is emerging evidence from short-term clinical trials that the use of hybrid closed-loop systems can improve time in range and reduce hyperglycemia and hypoglycemia compared to sensor-augmented systems. Current issues hampering full implementation of this technology include limitations in the accuracy and precision of interstitial fluid glucose sensing, the need for short-acting insulins with more rapid onset of action, and complexity of day-to-day use.

Adjunct Pharmacotherapy

Pramlintide acetate, a synthetic injectable analog of amylin, may be of therapeutic value combined with insulin therapy. However, it has not

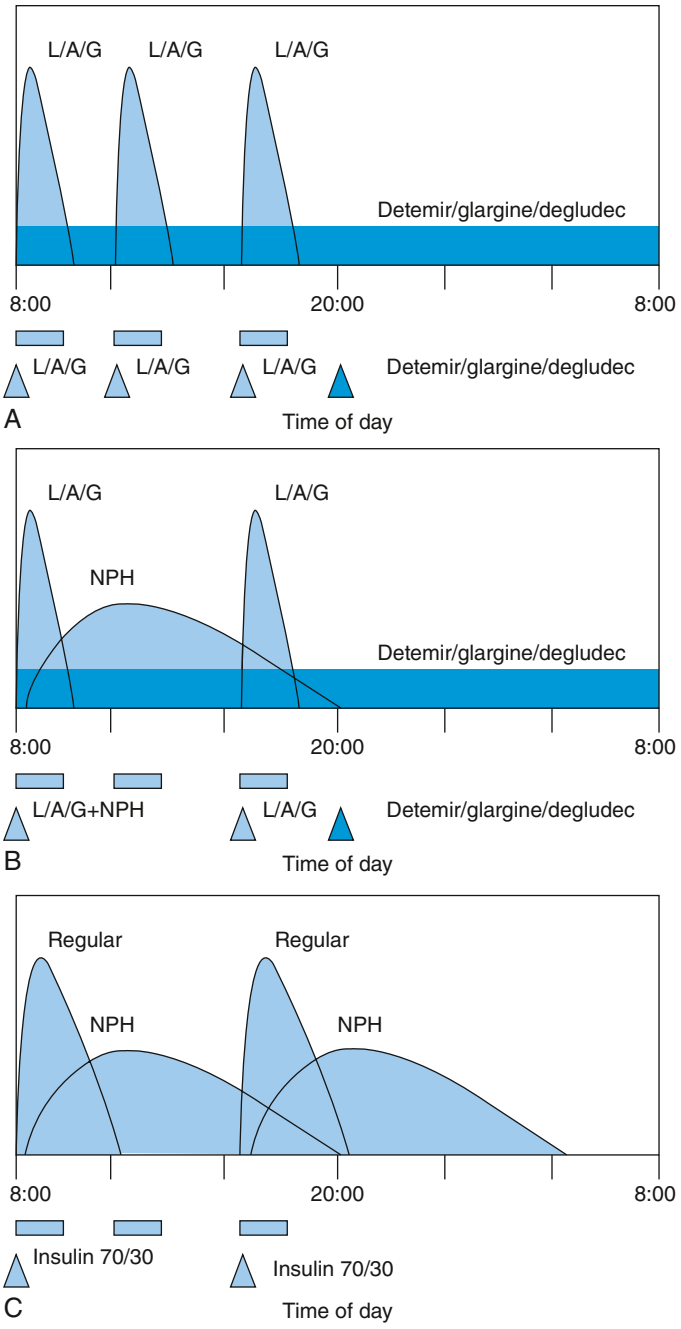


Fig. 629.8 Approximate composite insulin effect profiles of various insulin dosing strategies. Meals are shown as *rectangles* below the time axis. Injections are shown as labeled *triangles;* L/A/G, lispro, aspart, glulisine. All profiles are idealized using average absorption and clearance rates. In typical clinical situations, these profiles vary among patients. A given patient has varying rates of absorption depending on the injection site, physical activity, and other variables. **A,** Basal-bolus regimen: A short-acting insulin (Lantus/aspart/glulisine) is injected before meals, and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Additional short-acting insulin is given to cover between-meal snacks as needed (not shown). For patients on insulin pumps, the composite insulin profile is similar; however, the basal insulin coverage is provided by a continuous infusion of short-acting insulin. **B,** Thrice-daily injection regimen: A short-acting insulin (Lantus/aspart/glulisine) and neutral protamine Hagedorn *(NPH)* are injected with breakfast (the two types of insulin can be drawn up into one syringe for administration with a single injection), a short-acting insulin is injected with dinner, and a long-acting basal insulin (glargine/detemir/degludec) is injected at bedtime. Because NPH is not a peakless insulin, this regimen is associated with greater risk of hypoglycemia compared with the basal-bolus regimen show in Figure 629.6A but does offer the advantage of eliminating the need for an injection at lunchtime. **C,** Twice-daily injection regimen: The use of a premixed insulin containing a short- and an intermediate-acting insulin that is given twice daily is sometimes necessary for families who are unable to manage more complex dosing regimens. Insulin 70/30 is one such product that combines regular and NPH insulins. This produces the least physiologic profile, with large excesses before lunch and during the early night, combined with poor coverage before supper and breakfast.

gained widespread use. Metformin, an oral antihyperglycemic commonly used to treat T2DM, is sometimes used clinically as an adjunct therapy in T1DM patients with evidence of significant insulin resistance (i.e., obesity, insulin requirements >1.2 units/kg/day, acanthosis nigricans on exam). A clinical trial investigating the addition of metformin in overweight adolescents with T1DM did not find a sustained effect of metformin to lower HbA_{1c} but did show a reduction in daily insulin dose and body mass index (BMI). Reports from observational studies are likewise mixed. These agents would typically not be started at diagnosis of T1DM.

Basic and Advanced Diabetes Education

Therapy consists not only of initiation and adjustment of insulin dose but also of education of the patient and family. Teaching is most efficiently provided by experienced diabetes educators and dietitians. In the acute phase, the family must learn the basics, which includes monitoring the child's blood glucose and urine and/or blood ketones, preparing and injecting the correct insulin dose subcutaneously at the proper time, recognizing and treating low blood glucose reactions, and having a basic meal plan. Most families are trying to adjust psychologically to the new diagnosis of diabetes in their child and thus have a limited ability to retain new information. Written materials covering these basic topics help the family during the first few days.

Children and their families are also required to complete advanced self-management classes to facilitate implementation of flexible insulin management. These educational classes will help patients and their families acquire skills for managing diabetes during athletic activities and sick days. Likewise, further patient and caregiver education with a diabetes educator familiar with diabetes technology is imperative when adding a CGM or transitioning to an insulin pump.

Nutritional Management

Nutrition plays an essential role in the management of patients with T1DM. This is of critical importance during childhood and adolescence, when appropriate energy intake is required to meet the needs for energy expenditure, growth, and pubertal development. There are no special nutritional requirements for the diabetic child other than those for optimal growth and development. Nutritional requirements for the child are outlined on the basis of age, sex, weight, activity, and food preferences. Cultural ethnic considerations must also be integrated into the nutrition plan.

Total recommended caloric intake is based on size or surface area and can be obtained from standard tables (Tables 629.7 and 629.8). The caloric mixture should comprise approximately 55% carbohydrate, 30% fat, and 15% protein, but must be individualized to meet specific patient needs. Approximately 70% of the carbohydrate content should be derived from complex carbohydrates such as starch; intake of sucrose and highly refined sugars should be limited. Complex carbohydrates require prolonged digestion and absorption and thereby raise plasma glucose levels slowly, whereas glucose from refined sugars, including carbonated beverages, is rapidly absorbed and may cause wide swings in the metabolic pattern. The consumption of sugar-sweetened beverages, including soda and juice, should be discouraged. Priority should be given to total calories and total carbohydrates consumed rather than the source. Carbohydrate counting has become a mainstay in the nutrition education and management of patients with T1DM. Patients and their families are provided with information regarding the carbohydrate contents of different foods and food label reading. This allows patients to adjust their insulin dosage to their mealtime carbohydrate

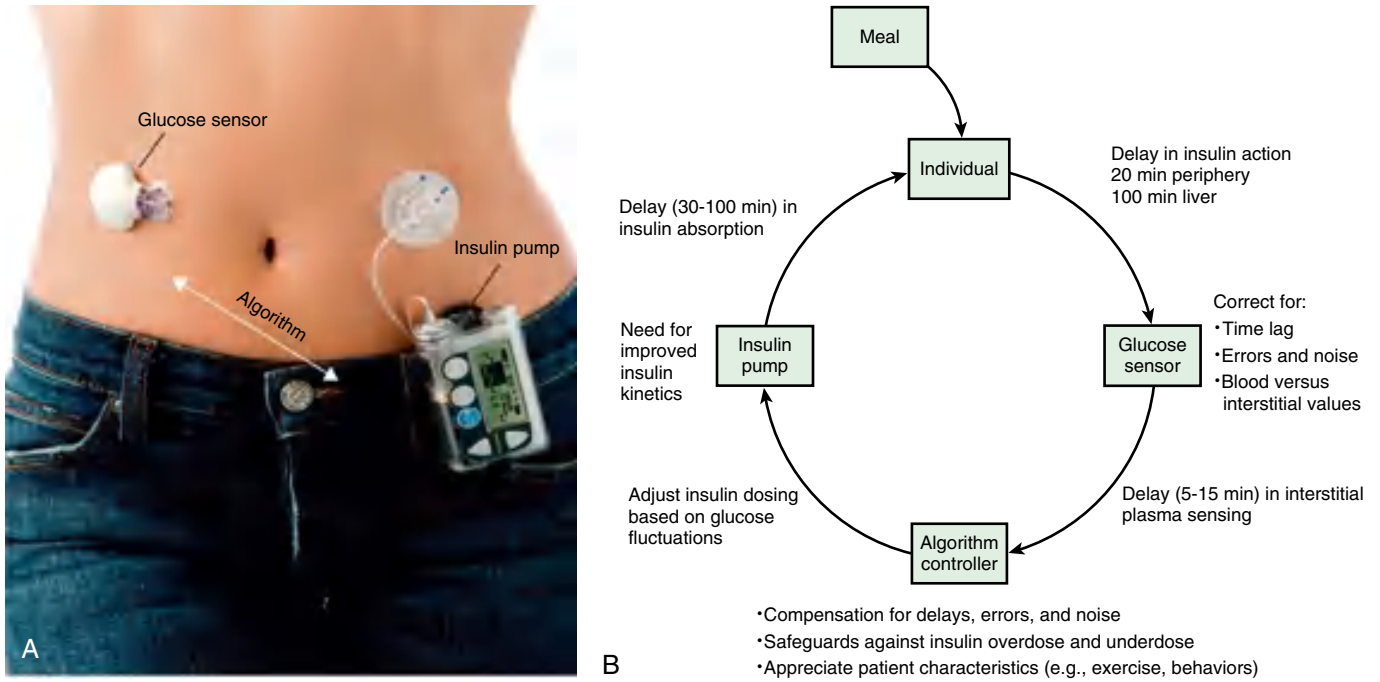


Fig. 629.9 Closed-loop system for T1DM (artificial pancreas). **A,** Prototype of a closed-loop system. **B,** Components of a closed-loop system. Three potential delays in the system include glucose sensing in interstitial fluid, insulin absorption (depends on use of rapid vs regular insulin), and insulin action in peripheral tissues and liver. *(From Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014;383:69–78. Fig. 5.)*

Table 629.7 Calorie Needs for Children and Young Adults

AGE	KCAL REQUIRED/KG BODY WEIGHT*
CHILDREN	
0-12 mo	120
1-10 yr	100-75
YOUNG WOMEN	
11-15 yr	35
≥16 yr	30
YOUNG MEN	
11-15 yr	80-55 (65)
16-20 yr	
Average activity	40
Very physically active	50
Sedentary	30

*Gradual decline in calories per unit weight as age increases.
Numbers in parentheses are means.
From *Nutrition Guide for Professionals. Diabetes education and meal planning.* Alexandria, VA, and Chicago, IL: The American Diabetes Association and The American Dietetic Association, 1988.

intake. The use of carbohydrate counting and insulin-to-carbohydrate ratios as a part of an MDI regimen allows for less rigid meal planning. Flexibility in the use of insulin in relation to carbohydrate content of food improves the quality of life.

Diets with high fiber content are useful in improving control of blood glucose. Daily recommended fiber intake can be determined using the equation:

$$\text{Age in years} + 5 = \text{grams of fiber per day}$$

Moderate amounts of sucrose consumed with fiber-rich foods such as whole-grain bread may have no more glycemic effect than their low-fiber, sugar-free equivalents. Saturated fat intake may increase in patients with T1DM who reduce carbohydrate consumption to avoid taking insulin doses by ingesting carbohydrate-free foods. Total energy from fat should not exceed 35%, and education should be provided such that <10% of total energy should come from saturated and trans fats. Dietary fats derived from animal sources should be reduced and replaced by polyunsaturated fats from vegetable sources. Substituting vegetable oil for animal oils or butter in cooking and lean cuts of meat, poultry, and fish for fatty meats can help to achieve these goals. The intake of cholesterol is also reduced by these measures. These simple measures may reduce serum low-density lipoprotein cholesterol, a predisposing factor to atherosclerotic disease. Table 629.8 summarizes typical nutritional guidelines for T1DM.

Each child and family can and should select a diet based on personal taste with the help of the physician or dietitian (or both). Emphasis should be placed on lifestyle changes to promote adherence to a healthy, balanced diet on a daily basis. Occasional excesses (treats) are permissible but should be limited just as for any child without diabetes. Adjustments in meal planning must constantly be made to meet the needs and the desires of each child. A consistent eating pattern with appropriate supplements for exercise, the pubertal growth spurt, and pregnancy in an adolescent with diabetes is important for metabolic control.

Monitoring

Success in the daily management of the child with diabetes can be measured by the competence acquired by the family, and subsequently by the child, in assuming responsibility for daily self-care. Their initial and ongoing instruction in conjunction with their supervised experience can lead to a sense of confidence in adjusting an insulin dosage for dietary deviations, for unusual physical activity, and for some intercurrent illnesses. Such acceptance of responsibility should make them relatively independent of the physician for their ordinary care. The physician must maintain ongoing interested supervision and shared responsibility with the family and the child.

Self-monitoring of blood glucose is an essential component of managing diabetes. Effective monitoring often also includes other factors that influence blood glucose such as insulin dose, physical activity,

Table 629.8 Summary of Nutrition Guidelines for Children and/or Adolescents with Type 1 Diabetes Mellitus

NUTRITION CARE PLAN		
Promotes optimal compliance.		
Incorporates goals of management: normal growth and development, control of blood glucose, maintenance of optimal nutritional status, and prevention of complications. Uses staged approach.		
NUTRITION RECOMMENDATIONS AND DISTRIBUTION		
NUTRIENT	% OF CALORIES	RECOMMENDED DAILY INTAKE
Carbohydrate	Will vary	High fiber, especially soluble fiber; optimal amount unknown
Fiber		>20 g/day
Protein	12–20	
Fat	<30	
Saturated	<10	
Polyunsaturated	6–8	
Monounsaturated	Remainder of fat allowance	
Cholesterol		300 mg
Sodium		Avoid excessive; limit to 3,000-4,000 mg if hypertensive
ADDITIONAL RECOMMENDATIONS		
Energy: If using measured diet, reevaluate prescribed energy level at least every 3 mo.		
Protein: High-protein intakes may contribute to diabetic nephropathy. Low intakes may reverse preclinical nephropathy. Therefore 12–20% of energy is recommended; lower end of range is preferred. In guiding toward the end of the range, a staged approach is useful.		
Alcohol: Safe use of moderate alcohol consumption should be taught as routine anticipatory guidance as early as junior high school.		
Snacks: Snacks vary according to individual needs (generally three snacks per day for children; midafternoon and bedtime snacks for junior high children or teens).		
Alternative sweeteners: Use of a variety of sweeteners is suggested.		
Educational techniques: No single technique is superior. Choice of educational method used should be based on patient needs. Knowledge of variety of techniques is important. Follow-up education and support are required.		
Eating disorders: Best treatment is prevention. Unexplained poor control or severe hypoglycemia may indicate a potential eating disorder.		
Exercise: Education is vital to prevent delayed or immediate hypoglycemia and to prevent worsened hyperglycemia and ketosis.		

From Connell JE, Thomas-Doberson D. Nutritional management of children and adolescents with insulin-dependent diabetes mellitus: a review by the Diabetes Care and Education Dietetic Practice Group. J Am Diet Assoc. 1991;91:1556.

dietary changes, hypoglycemia, and illness. A record of these items may be valuable in interpreting the self-monitoring of blood glucose, prescribing appropriate adjustments in insulin doses, and teaching the family. If there are discrepancies in the self-monitoring of blood glucose and other measures of glycemic control (such as the HbA_{1c}), the clinician should attempt to clarify the situation in a manner that does not undermine their mutual confidence.

Daily blood glucose monitoring is accomplished using blood test strips or a CGM. Test strips are impregnated with glucose oxidase that permit blood glucose measurement from a drop of blood. A portable calibrated reflectance meter can approximate the blood glucose concentration accurately. Glucometers contain a memory chip enabling recall of each measurement and the ability to calculate measurement average over a given interval and display the pattern on a computer screen. Such information is a useful educational tool for verifying degree of control and modifying recommended regimens. A small, spring-loaded device that automates capillary bloodletting (lancing device) in a relatively painless fashion is commercially available. Parents and patients should be taught to use these devices and measure blood glucose at least 4 times daily—before breakfast, lunch, and supper and at bedtime. When insulin therapy is initiated and when adjustments are made that may affect the overnight glucose levels, self-monitoring of blood glucose should also be performed at midnight and 3 AM to detect nocturnal hypoglycemia. Standard blood glucose targets are 90-130 mg/dL before meals and 90-150 mg/dL before bedtime; however, glycemic goals must be individualized to the patient based on age, hypoglycemia risk, and other factors.

Glucose measurements that are consistently at or outside these limits, in the absence of an identifiable cause such as exercise or dietary indiscretion, are an indication for a change in the insulin dose. If the fasting blood glucose is high, the evening dose of long-acting insulin (or the early morning/overnight basal rate for insulin pump users) is increased by 10–20% and/or additional fast-acting insulin coverage for a bedtime snack may be considered. If the noon glucose level exceeds set limits, the morning fast-acting insulin-to-carbohydrate ratio is increased by 10–20%. If the presupper glucose is high, the noon fast-acting insulin-to-carbohydrate ratio is increased by 10–20%. If the prebedtime glucose is high, the presupper fast-acting insulin-to-carbohydrate ratio is increased by 10–15%. The ISF can be increased by 10–20% if it is found that insulin corrections given for hyperglycemia do not normalize glucose levels as expected. Similarly, reductions in the insulin type and dose should be made if the corresponding blood glucose measurements are consistently below desirable limits.

A minimum of four daily blood glucose measurements (or CGM use) should be performed. However, some children and adolescents may need to have more frequent blood glucose monitoring based on their level of physical activity and history of frequent hypoglycemic reactions. Families should be encouraged to become sufficiently knowledgeable about managing diabetes.

The FDA has approved the use of CGMs to replace finger stick blood glucose checking for the monitoring and treatment of diabetes in children 2 years of age and older. CGMs are minimally invasive and entail the placement of a small, subcutaneous catheter that can be easily worn by adults and children. The system provides information that allows the patient and healthcare team to adjust the insulin regimen and the nutrition plan to improve glycemic control. CGMs can be helpful in detecting asymptomatic nocturnal hypoglycemia and in lowering HbA_{1c} values without increasing the risk for severe hypoglycemia. Although there are potential pitfalls in CGM use, including suboptimal compliance, human error, incorrect technique, and sensor

failure, the implementation of CGMs in ambulatory diabetes practice allows the clinician to diagnose abnormal glycemic patterns in a more precise manner. In many cases, CGMs are now factory calibrated and nearly eliminate the need for finger sticks. For these reasons, CGMs are increasingly replacing finger stick blood testing as the primary means of glucose monitoring in many patients with T1DM.

Glycosylated Hemoglobin (HbA_{1c})

A reliable index of long-term glycemic control is provided by measurement of glycosylated hemoglobin. HbA_{1c} represents the fraction of hemoglobin to which glucose has been nonenzymatically attached in the bloodstream. The formation of glycosylated hemoglobin is a slow reaction that is dependent on the prevailing concentration of blood glucose; it continues irreversibly throughout the red blood cell's life span of approximately 120 days. The higher the blood glucose concentration and the longer the red blood cell's exposure to it, the higher the fraction of glycosylated hemoglobin, which is expressed as a percentage of total hemoglobin. Because a blood sample at any given time contains a mixture of red blood cells of varying ages, exposed for varying times to varying blood glucose concentrations, an HbA_{1c} measurement reflects the average blood glucose concentration from the preceding 2-3 months. For some patients, it may be helpful to translate HbA_{1c} into estimated average glucose (eAG) using the following equation:

$$eAG = 28.7 * HbA_{1c} - 46.7$$

When measured by standardized methods to remove labile forms, HbA_{1c} is not influenced by an isolated episode of hyperglycemia.

HbA_{1c} measurements should be obtained three to four times a year to obtain a profile of long-term glycemic control. The lower the HbA_{1c} level, the more likely it is that microvascular complications such as retinopathy and nephropathy will be less severe, delayed in appearance, or even avoided altogether. Depending on the method used for determination, HbA_{1c} values may be spuriously elevated in thalassemia (or other conditions with elevated hemoglobin F) and spuriously lower in sickle cell disease (or other conditions with high red blood cell turnover). Fructosamine can be used instead of HbA_{1c} in these patients. Although values of HbA_{1c} may vary according to the method used for measurement, in individuals without diabetes, the HbA_{1c} is usually less than 6%. The HbA_{1c} target should be individualized, but the general recommendation of the ADA and the International Society for Pediatric and Adolescent Diabetes is that children, adolescents, and young adults with T1DM should aim to achieve an HbA_{1c} of <7%.

Exercise

Regular, daily exercise with the goal of 60 minutes of moderate- to vigorous-intensity aerobic activity daily, with vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week is recommended for all children with T1D. A potential complication of exercise in patients with diabetes is the development of hypoglycemia during or within the hours after exercise. Patients and families should be educated on the risk of hypoglycemia and taught strategies to ameliorate this risk, including frequent glucose monitoring before, during, and after exercise; modifying diet and insulin doses around times of exercise; and ensuring access to fast-acting carbohydrates during exercise to treat hypoglycemia should it develop. Regular exercise also improves glucoregulation by increasing glucose use by muscles and increasing the insulin receptor number. In patients who are in poor metabolic control, vigorous exercise may precipitate ketoacidosis because of the exercise-induced increase in the counterregulatory hormones.

Benefits of Improved Glycemic Control

The Diabetes Control and Complications Trial (DCCT) established conclusively the association between higher glucose levels and long-term microvascular complications. Intensive management produced dramatic reductions of retinopathy, nephropathy, and neuropathy by 47–76%. The data from the adolescent cohort demonstrated the same degree of improvement and the same relationship between the outcome measures of microvascular complications.

The beneficial effect of intensified treatment was determined by the degree of blood glucose normalization independently of the type of intensified treatment used. Frequent blood glucose monitoring was considered an important factor in achieving better glycemic control for the intensively treated adolescents and adults. Patients who were intensively treated had individualized glucose targets, frequent adjustments based on ongoing capillary blood glucose monitoring, and a team approach that focused on the person with diabetes as the prime initiator of ambulatory care. Care was constantly adjusted toward reaching normal or near-normal glycemic goals while avoiding or minimizing severe episodes of hypoglycemia. Teaching emphasized a preventive approach to blood glucose fluctuations with constant readjustment to counterbalance any high or low blood glucose readings. Target blood glucose goals were adjusted upward if hypoglycemia could not be prevented.

Total duration of diabetes contributes to development and severity of complications. Nonetheless, many professionals have concerns about applying the results of the DCCT to preschool-age children, who often have hypoglycemia unawareness with unique safety issues, and to prepubertal school-age children, who were not included in the DCCT. The follow-up study to the DCCT, called Epidemiology of Diabetes Interventions and Complications (EDIC), assessed the incidence and predictors of cardiovascular disease events such as heart attack, stroke, or needed heart surgery, as well as diabetic complications related to the eye, kidney, and nerves. The EDIC demonstrated that intensive blood glucose control reduced the risk of any cardiovascular disease event by 42%. In addition, intensive therapy reduced the risk of nonfatal heart attack, stroke, or death from cardiovascular causes by 57%.

Hypoglycemic Reactions

Hypoglycemia is the major limitation to tight control of glucose levels. Once injected, insulin absorption and action are independent of the glucose level, thus creating a unique risk of hypoglycemia from an unbalanced insulin effect. Insulin analogs may help reduce, but cannot eliminate, this risk. Most children with T1DM can expect mild hypoglycemia each week, moderate hypoglycemia a few times each year, and severe hypoglycemia every few years. These episodes are usually not predictable, although exercise, delayed meals or snacks, and wide swings in glucose levels increase the risk. Infants and toddlers are at higher risk for hypoglycemia because they have more variable meals and activity levels, are unable to recognize early signs of hypoglycemia, and are limited in their ability to seek a source of oral glucose to reverse the hypoglycemia. The very young have an increased risk of permanently reduced cognitive function as a long-term sequela of severe hypoglycemia. For these reasons, a more relaxed degree of glucose control may be tolerated in infants and young children.

Hypoglycemia can occur at any time of the day or night. Early symptoms and signs (mild hypoglycemia) may occur with a sudden decrease in blood glucose to levels that do not meet standard criteria for hypoglycemia in children without diabetes. The child may show pallor, sweating, apprehension or fussiness, hunger, tremor, and tachycardia, all as a result of the surge in catecholamines as the body attempts to counter the excessive insulin effect. Behavioral changes such as tearfulness, irritability, and aggression are more prevalent in children. As glucose levels decline further, cerebral glucopenia occurs with drowsiness, personality changes, mental confusion, and impaired judgment (moderate hypoglycemia), progressing to inability to seek help and seizures or coma (severe hypoglycemia). Prolonged severe hypoglycemia can result in a depressed sensorium or strokelike focal motor deficits that persist after the hypoglycemia has resolved. Although permanent sequelae are rare, severe hypoglycemia is frightening for the child and family and can result in significant reluctance to attempt even moderate glycemic control afterward.

Important counterregulatory hormones in children include growth hormone, cortisol, epinephrine, and glucagon. The latter two seem more critical in the older child. Many older patients with long-standing T1DM lose their ability to secrete glucagon in response to hypoglycemia. In the young adult, epinephrine deficiency may also develop as part of a general autonomic neuropathy. This substantially increases the

risk of hypoglycemia because the early warning signals of a declining glucose level are as a result of catecholamine release. Recurrent hypoglycemic episodes associated with tight metabolic control may aggravate partial counterregulatory deficiencies, producing a syndrome of hypoglycemia unawareness and reduced ability to restore euglycemia (hypoglycemia-associated autonomic failure). Avoidance of hypoglycemia allows some recovery from this unawareness syndrome.

The most important factors in the management of hypoglycemia are an understanding by the patient and family of the symptoms and signs of the reaction and an anticipation of known precipitating factors such as gym or sports activities. Tighter glucose control increases the risk. Families should be taught to look for typical hypoglycemic scenarios or patterns in the home blood glucose log, so that they may adjust the insulin dose and avert predictable episodes. A source of emergency glucose should be available at all times and places, including at school and during visits to friends. If possible, it is important to document the hypoglycemia before treating, because some symptoms may not always be from hypoglycemia. Any child suspected of having a moderate to severe hypoglycemic episode should be treated before testing. It is important not to give too much glucose in response to hypoglycemia; 15 g should be given as juice or a sugar-containing beverage or candy, and the blood glucose checked 15-20 minutes later.

Patients, parents, and teachers should also be instructed in the administration of **glucagon** when the child cannot take glucose orally. Glucagon is available for intramuscular or subcutaneous injection and as a nasal powder. A glucagon kit should be kept at home and school. The intramuscular dose of glucagon is 0.5 mg if the child weighs less than 20 kg and 1.0 mg if more than 20 kg; the subcutaneous dose (via prefilled device) is 0.5 mg if less than 45 kg and 1.0 mg if more than 45 kg; the intranasal dose is 3 mg. Glucagon produces a brief release of glucose from the liver. Glucagon often causes emesis, which precludes giving oral supplementation if the blood glucose declines after the glucagon effects have waned. Caretakers must then be prepared to take the child to the hospital for IV glucose administration, if necessary. Mini-dose glucagon (10 μg/yr of age up to a maximum of 150 μg subcutaneously) is effective in treating hypoglycemia in children with blood glucose less than 60 mg/dL who fail to respond to oral glucose and remain symptomatic. Glucagon is reconstituted as per standard instructions, then drawn up for subcutaneous injection using a standard insulin syringe, whereby 1 unit is the equivalent of 10 mcg of glucagon.

Dawn Phenomenon and Somogyi Phenomenon

There are several reasons that blood glucose levels increase in the early morning hours before breakfast. The most common is a simple decline in insulin levels. This usually results in routinely elevated morning glucose. The **dawn phenomenon** is thought to be mainly caused by overnight growth hormone secretion and increased insulin clearance. It is a normal physiologic process seen in most adolescents without diabetes, who compensate with more insulin output. A child with T1DM cannot compensate. The dawn phenomenon is usually recurrent and modestly elevates most morning glucose levels. Rarely, high morning glucose is caused by the **Somogyi phenomenon**, a theoretical rebound from late-night or early-morning hypoglycemia thought to be from an exaggerated counterregulatory response. It is unlikely to be a common cause, in that most children remain hypoglycemic (do not rebound) once nighttime glucose levels decline. CGMs may help clarify a child's ambiguously elevated morning glucose levels.

Behavioral/Psychologic Aspects and Eating Disorders

Diabetes in a child affects the lifestyle and interpersonal relationships of the entire family. Feelings of anxiety and guilt are common in parents. Similar feelings, coupled with denial and rejection, are equally common in children, particularly during the rebellious teenage years. Family conflict has been associated with poor treatment adherence and poor metabolic control among youths with T1DM. On the other hand, it has been shown that shared responsibility is consistently associated with better psychologic health, good self-care behavior, and good metabolic control, whereas responsibility assumed by either the child or parent alone does not have outcomes that are equally successful. In some cases, links of shared responsibility to health outcomes were stronger among older adolescents. However, no specific personality disorder or psychopathology is characteristic of diabetes; similar feelings are observed in families with children who have other chronic diseases.

COGNITIVE FUNCTION

There is evidence that children with T1DM are at higher risk of developing small differences in cognitive abilities compared to healthy age-matched peers. Evidence suggests that early-onset diabetes (younger than 7 years) is associated with cognitive difficulties compared to late-onset diabetes and healthy controls. The cognitive difficulties observed were primarily learning and memory skills (both verbal and visual) and attention/executive function skills. It is likely that the impact of diabetes on pediatric cognition appears shortly after diagnosis. Indeed, it has been observed that early-onset diabetes and longer duration of diabetes in some children with diabetes adversely affect their school performance and educational achievements.

COPING STYLES

Children and adolescents with T1DM are faced with a complex set of developmental changes and shifting burdens of the disease. Adjustment problems might affect psychologic well-being and the course of the disease by affecting self-management and leading to poor metabolic control. Coping styles refer to typical habitual preferences for ways of approaching problems and might be regarded as strategies that people generally use to cope across a wide range of stressors. Problem-focused coping refers to efforts directed toward rational management of a problem, and it is aimed at changing the situation causing distress. On the other hand, emotion-focused coping implies efforts to reduce emotional distress caused by the stressful event and to manage or regulate emotions that might accompany or result from the stressor. In adolescents with diabetes, avoidance coping and venting emotions have been found to predict poor illness-specific self-care behavior and poor metabolic control. Patients who use more mature defenses and exhibit greater adaptive capacity are more likely to adhere to their regimen. Coping strategies seem to be age dependent, with adolescents using more avoidance coping than younger children with diabetes.

NONADHERENCE

Family conflict, anger, sadness, or denial and feelings of anxiety or loss of control find expression in nonadherence to instructions regarding nutritional and insulin therapy and in noncompliance with self-monitoring. When adolescents externalize behavior problems, such behaviors interfere with adherence and may result in deterioration of glycemic control. Such externalizing behaviors are common, whereas repeated omission of insulin resulting in ketoacidosis in the same individual is less common, and episodes of deliberate overdosage with insulin resulting in hypoglycemia are even less prevalent. They may, however, be pleas for psychologic help or be manipulative attempts to escape an environment perceived as undesirable or intolerable; occasionally, they may be manifestations of suicidal intent. Frequent admissions to the hospital for ketoacidosis or hypoglycemia should arouse suspicion of an underlying emotional conflict. Overprotectiveness on the part of parents is common and often is not in the best interest of the adolescent patient. Feelings of being different or of being alone, or both, are common and must be acknowledged. Tailoring the insulin administration and the timing of meals and blood sugar tests may support individual lifestyle choices. Aggregating what they know about diabetes, families and patients worry about the risk of complications from diabetes and about the decreased life span. Unfortunately, misinformation abounds about the risks of the development of diabetes in siblings or offspring and of pregnancy in young diabetic women. Even appropriate information may cause further anxiety.

All of these issues must be spoken about at the outset, and many of these problems can be averted through continued empathic counseling based on correct information, focusing on normality and on planning to be a productive member of society. Recognizing the potential

impact of these problems and that feelings of isolation and frustration tend to be lessened by the sharing of common problems, peer discussion groups have been organized in many locales. Summer camps for diabetic children afford an excellent opportunity for learning and sharing under expert supervision. Education about the pathophysiology of diabetes, insulin dose, technique of administration, nutrition, exercise, and hypoglycemic reactions can be reinforced by medical and paramedical personnel. The presence of numerous peers with similar problems offers new insights to the diabetic child. Residential treatment for children and adolescents with difficult-to-manage T1DM is rarely available.

ANXIETY AND DEPRESSION

It has been shown that there are significant correlations between poor metabolic control and depressive symptoms, a high level of anxiety, or a previous psychiatric diagnosis. In a similar way, poor metabolic control is related to higher levels of personal, social, school maladjustment, or family environment dissatisfaction. It is estimated that 20–26% of adolescent patients may develop major depressive disorder. The prevalence of depression is twofold greater than controls in children with diabetes and threefold greater in adolescents. Additionally, the prevalence of psychopathology is greater in people with diabetes. The course characteristics of depression in young diabetic subjects and psychiatric control subjects appear to be similar. However, eventual propensity of diabetic youths for more protracted depressions is greater. There is also a higher risk of recurrence among young diabetic females. On balance, anxiety and depression play an important and complex role in T1DM; their relationship to metabolic control does not yet appear clear. Therefore the healthcare providers managing a child or adolescent with diabetes should be aware of their pivotal role as counselor and advisor and should closely monitor the mental health of patients with diabetes. Accordingly, the recommendation is screening for anxiety and/or depression in subjects exhibiting symptoms, using a validated screening tool, followed by the appropriate referral to mental health providers when warranted.

FEAR OF SELF-INJECTING AND SELF-TESTING

Extreme fear of self-injecting insulin *(injection phobia)* is likely to compromise glycemic control and emotional well-being. Likewise, fear of finger pricks of CGM and pump site insertions can be a source of distress and may seriously hamper self-management. Children and adolescents may either omit insulin dosing or refuse to rotate their injection sites because repeated injection in the same site is associated with less pain sensation. Failure to rotate injection sites results in subcutaneous scar formation **(lipohypertrophy)**. Insulin injection into the lipohypertrophic skin is usually associated with poor insulin absorption, consequent frustration with lack of expected glucose control, and/or insulin leakage with resultant suboptimal glycemic control. Children and adolescents with injection phobia and fear of self-testing can be counseled by a trained behavioral therapist and benefit from such techniques as desensitization and biofeedback to attenuate pain sensation and psychologic distress associated with these procedures.

EATING DISORDERS

Treatment of T1DM involves constant monitoring of food intake. In addition, improved glycemic control is sometimes associated with increased weight gain. These factors, along with individual, familial, and socioeconomic factors, can lead to an increased incidence of both nonspecific and specific eating disorders, which can disrupt glycemic control and increase the risk of long-term complications. Eating disorders and subthreshold eating disorders are almost twice as common in adolescent females with T1DM as in their nondiabetic peers. There is less information regarding the prevalence of eating disorders among male adolescents with T1DM. The prevalence of eating disorders identified in females with T1DM has ranged from 9% to 32% in different studies. Other studies have found that approximately 11% of T1DM adolescent females take less insulin than prescribed to lose weight. Among adolescent females with T1DM and an eating disorder, the misuse of insulin to lose weight is not uncommon.

When behavioral/psychologic problems and/or eating disorders are assumed to be responsible for poor adherence with the medical regimen, referral for psychologic evaluation and management is indicated. Behavioral therapists and psychologists usually form part of the pediatric diabetes team in most centers and can help assess and manage emotional and behavioral disorders in diabetic children. Evaluation of nurse-delivered motivational enhancement with and without cognitive-behavioral therapy in adults revealed that combined therapy resulted in modest improvement in glycemic control. However, motivational enhancement therapy alone did not improve glycemic control. Whereas in some studies the effect of therapist-delivered motivational enhancement therapy on glycemic control in adolescents with T1DM lasted only as long as intensive individualized counseling continued, in other studies, motivational interviewing was shown to be an effective method of facilitating changes in a teenager's behavior with T1DM, with corresponding improvement in glycemic control.

Management During Infections

Although infections are no more common in diabetic children than in nondiabetic ones, they can disrupt glucose control and may precipitate DKA. In addition, the child with diabetes is at increased risk of dehydration if hyperglycemia causes an osmotic diuresis or if ketosis causes emesis. Counterregulatory hormones associated with stress blunt insulin action and elevate glucose levels. If anorexia occurs from ketosis, lack of caloric intake increases the risk of hypoglycemia. Although children younger than 3 years of age tend to become hypoglycemic and older children tend toward hyperglycemia, the overall effect is unpredictable. Therefore frequent blood glucose monitoring, monitoring of urine and/or blood ketones, and adjustment of insulin doses are essential elements of **sick day guidelines** (Table 629.9).

The overall goals are to maintain hydration, control glucose levels, and avoid ketoacidosis. This can usually be done at home if proper sick day guidelines are followed and with telephone contact with healthcare providers. The development of ketones in a patient on insulin pump therapy may be a sign of infusion failure and the infusion set should be changed. The family should seek advice if home treatment does not

Table 629.9 Guidelines for Sick Day Management

	GLUCOSE TESTING AND EXTRA RAPID-ACTING INSULIN		
URINE KETONE STATUS	**INSULIN**	**CORRECTION DOSES***	**COMMENT**
Negative or small†	q2h	q2h for glucose >250 mg/dL	Check ketones every other void
Moderate to large‡	q1h	q1h for glucose >250 mg/dL	Check ketones each void; go to hospital if emesis occurs

*Give insulin based on individualized dosing schedule. Also give usual dose for carbohydrate intake if glucose >150 mg/dL.
†For home serum ketones <1.5 mmol/L per commercial kit.
‡For home serum ketones >1.5 mmol/L.
Basal insulin: glargine or detemir basal insulin should be given at the usual dose and time. NPH and lente should be reduced by half if blood glucose <150 mg/dL and the oral intake is limited.
Oral fluids: sugar-free if blood glucose >250 mg/dL (14 mmol/L); sugar-containing if blood glucose <250 mg/dL.
Call physician or nurse if blood glucose remains elevated after three extra doses, if blood glucose remains <70 mg/dL and child cannot take oral supplement, if dehydration occurs.

control ketosis, hyperglycemia, or hypoglycemia or if the child shows signs of dehydration or has persistent vomiting. A child with significant ketosis and emesis should be seen in the emergency department for a general examination, to evaluate hydration, and to determine whether ketoacidosis is present by checking serum electrolytes, glucose, pH, and total CO_2. A child whose blood glucose declines to less than 50-60 mg/dL (2.8-3.3 mmol/L) and who cannot maintain oral intake may need IV glucose, especially if further insulin is needed to control ketosis.

Management During Surgery

Surgery can disrupt glucose control in the same way as intercurrent infections can. Stress hormones associated with the underlying condition and with the surgery itself cause insulin resistance. This increases glucose levels, exacerbates fluid losses, and may initiate DKA. On the other hand, caloric intake is usually restricted, which decreases glucose levels. The net effect is as difficult to predict as during an infection. Vigilant monitoring and frequent insulin adjustments are required to maintain euglycemia and avoid ketosis.

For most elective and other smaller surgical procedures, patients can simply be continued on their typical home basal regimens. This includes injection of the usual dose of long-acting insulin at the usual time for patients on shots. Patients on pumps can simply wear the pump during the surgery, if approved by hospital policy. Blood sugar should be monitored hourly during the procedure and perioperatively; hyperglycemia can be corrected using the standard home ISF, and IV dextrose can be provided as needed for hypoglycemia. For major procedures, trauma, or situations where a prolonged period of decreased oral intake is expected postoperatively, it is advisable to manage insulin requirements with an IV insulin drip (Table 629.10). IV insulin is typically started at a dose of 0.03 units/kg/hr for patients who are euglycemic at the time of surgery. Serum glucose levels should be followed every hour operatively and perioperatively, and the insulin dose and/or the dextrose concentration of the IV fluids can be adjusted as needed. In patients who are found to be hyperglycemic preoperatively (serum glucose >250 mg/dL), it is advisable to check for ketones before starting surgery. If significant ketosis is identified, surgery should be delayed (if possible) until the ketosis can be treated and resolved. Postoperatively, the patient should not be discharged until blood glucose levels are stable and oral intake is tolerated.

LONG-TERM COMPLICATIONS: RELATION TO GLYCEMIC CONTROL

Complications of DM include microvascular complications, such as retinopathy and nephropathy; macrovascular complications, including coronary artery disease, cerebrovascular disease, and peripheral vascular disease; peripheral and autonomic neuropathies; and diabetic osteopathy manifesting as increased risk for osteoporosis and fracture.

Diabetic Retinopathy

Diabetic retinopathy is the leading cause of blindness in the United States in adults age 20-65 years. The risk of diabetic retinopathy after 15 years' duration of diabetes is 98% for individuals with T1DM and 78% for those with T2DM. Rates for diabetic retinopathy range from close to 15% to up to 30%. Lens opacities (caused by glycation of tissue proteins and activation of the polyol pathway) are present in at least 5% of those younger than age 19 years. Metabolic control has an impact on the development of this complication, as prevalence rates are substantially higher with increased duration of diabetes and higher HbA_{1c}, hypertension, and high cholesterol levels. Independent of duration, the prevalence of diabetic retinopathy is higher in T1DM. Genetic factors may have a role, because only 50% of patients develop proliferative retinopathy. The earliest clinically apparent manifestations of diabetic retinopathy are classified as nonproliferative or background diabetic retinopathy—microaneurysms, dot and blot hemorrhages, hard and soft exudates, venous dilation and beading, and intraretinal microvascular abnormalities. These changes do not impair vision. The more severe form is proliferative diabetic retinopathy, which manifests by neovascularization, fibrous proliferation, and preretinal and vitreous hemorrhages. Proliferative retinopathy, if not treated, is relentlessly progressive and impairs vision, leading to blindness. The mainstay of treatment is panretinal laser photocoagulation. In advanced diabetic eye disease—manifested by severe vitreous hemorrhage or fibrosis, often with retinal detachment—vitrectomy is an important therapeutic modality. Eventually, the eye disease becomes quiescent, a stage termed *involutional retinopathy.* A separate subtype of retinopathy is diabetic maculopathy, which is manifested by severe macular edema impairing central vision. Focal laser photocoagulation may be effective in treating diabetic maculopathy.

Diabetic patients should have an initial dilated and comprehensive examination by an ophthalmologist shortly after the diagnosis of diabetes is made in patients with T2DM and within 3-5 years after the onset of T1DM (but not before age 10 years). Any patients with visual symptoms or abnormalities should be referred for ophthalmologic evaluation. Subsequent evaluations for both T1DM and T2DM patients should be repeated every 1-2 years as recommended by an eye care professional experienced in the diagnosis and management of diabetic retinopathy (Table 629.11).

Diabetic Nephropathy

Diabetic nephropathy is the leading known cause of end-stage renal disease (ESRD) in the United States. Most ESRD from diabetic nephropathy is preventable. Diabetic nephropathy affects 20–30% of patients with T1DM and 15–20% of T2DM patients 20 years after onset. The mean 5-year life expectancy for patients with diabetes-related ESRD is less than 20%. The increased mortality risk in long-term T1DM may be the result of nephropathy, which may account for approximately 50% of deaths. The risk of nephropathy increases with the duration of diabetes (up until 25-30 years' duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension. Only 30–40% of patients affected by T1DM eventually experience ESRD. The glycation of tissue proteins results in glomerular basement membrane thickening. The course of diabetic nephropathy is slow. An increased urinary albumin excretion rate of 30-300 mg/24 hr (20-200 μg/min)—**microalbuminuria**—can be detected and constitutes an early stage of nephropathy from intermittent to persistent (incipient), which is commonly associated with glomerular hyperfiltration and blood pressure elevation. As nephropathy evolves to an early overt stage with proteinuria (albumin excretion rate >300 mg/24 hr or >200 μg/min), it is accompanied by hypertension. Advanced-stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and hypertension. Progression to ESRD is recognized by the appearance of uremia, nephrotic syndrome, and the need for renal replacement (transplantation or dialysis).

Screening for diabetic nephropathy is a routine aspect of diabetes care. The ADA recommends yearly screening for individuals with T2DM and yearly screening for those with T1DM after 5 years' duration of disease with a random spot urine sample for albumin-to-creatinine ratio. Abnormal results should be confirmed by two

Table 629.10 Guidelines for Intravenous Insulin Coverage During Surgery

BLOOD GLUCOSE LEVEL (mg/dL)	INSULIN INFUSION (units/kg/hr)	BLOOD GLUCOSE MONITORING
<120	0.00	1 hr
121-200	0.03	2 hr
200-300	0.06	2 hr
300-400	0.08	1 hr*
400	0.10	1 hr*

*Check urine ketones.
An infusion of 5% glucose and 0.45% saline solution with 20 mEq/L of potassium acetate is given at 1.5 times the maintenance rate.

Table 629.11 Screening Guidelines

	INITIAL TESTING	FREQUENCY	TEST
Thyroid disease	At diagnosis	Every 1-2 yr or sooner if symptoms	TSH, thyroid antibodies
Celiac	At diagnosis	Within 2 yr and again at 5 yr or sooner if symptoms	IgA and TTG
Hypertension	At diagnosis	Each visit	Elevated BP based on ≥90th% for age, sex, height on three separate occasions
Dyslipidemia	≥10 yr of age at diagnosis once glucose control established	If abnormal annually; every 5 yr if initially normal	Goal LDL-C <100 mg/dL
Nephropathy	At puberty or age ≥10 yr whichever comes first, if T1DM ≥5 yr	Annually	Albuminuria; urine albumin-to-creatinine ratio
Retinopathy	T1DM ≥3-5 yr when ≥10 yr or puberty, whichever comes first	Annually	Dilated eye exam
Neuropathy	At puberty or ≥10 year, whichever earlier if T1DM >5 yr	Annually	Foot exam

BP, Blood pressure; IgA, immunoglobulin A; LDL, low density lipoprotein; TSH, thyroid-stimulating hormone; TTG, tissue transglutaminase.
Data from American Diabetes Association. Children and adolescents: standards of medical care in diabetes—2018. Diabetes Care. 2018;41(Suppl 1):S126–S136.

additional specimens on separate days because of the high variability of albumin excretion in patients with diabetes. Short-term hyperglycemia, strenuous exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness can cause transient elevation in urinary albumin excretion. There is marked day-to-day variability in albumin excretion, so at least two of three collections done in a 3- to 6-month period should show elevated levels before microalbuminuria is diagnosed and treatment is started. Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys: (1) meticulous control of hyperglycemia, (2) aggressive control of systemic blood pressure, (3) selective control of arteriolar dilation by use of angiotensin-converting enzyme inhibitors (thus decreasing transglomerular capillary pressure), and (4) dietary protein restriction (because high protein intake increases the renal perfusion rate). Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy.

DIABETIC NEUROPATHY

Both the peripheral and autonomic nervous systems can be involved; diabetic neuropathy can develop in both children and adolescents. The etiology of diabetic neuropathy remains incompletely understood, and the impact of hyperglycemia on its development remains uncertain. Observational studies done in the years before the era of intensive insulin therapy for T1DM reported a higher incidence of neuropathy compared with more recent studies. However, several studies have found that the development of preclinical and symptomatic peripheral diabetic neuropathy in childhood is not strongly associated with either glycemic control or duration of disease. The polyol pathway, nonenzymatic glycation, and/or disturbances of myoinositol metabolism, affecting one or more cell types in the multicellular constituents of the peripheral nerve, have been hypothesized to have an inciting role. Other factors, such as possible direct neurotrophic effects of insulin, insulin-related growth factors, nitric oxide, and stress proteins, may also contribute to the development of neuropathy. Using quantitative sensory testing, abnormal cutaneous thermal perception is a common finding in both upper and lower limbs in neurologically asymptomatic young diabetic patients. Heat-induced pain threshold in the hand is correlated with the duration of the diabetes. There is no correlation between quantitative sensory testing scores and metabolic control. Subclinical motor nerve impairment as manifested by reduced sensory nerve conduction velocity and sensory nerve action potential amplitude have been detected in as many as 10–58% of children with diabetes. An early sign of autonomic neuropathy, such as decreased heart rate variability, may present in adolescents with a history of long-standing disease and poor metabolic control. A number of therapeutic strategies have been attempted with variable results. These treatment modalities include (1) improvement in metabolic control, (2) use of aldose reductase inhibitors to reduce by-products of the polyol pathway, (3) use of α-lipoic acid (an antioxidant) that enhances tissue nitric oxide and its metabolites, (4) use of anticonvulsants (e.g., lorazepam, valproate, gabapentin, carbamazepine, pregabalin, phenytoin, tiagabine, and topiramate) for treatment of neuropathic pain, and (5) use of antidepressants (amitriptyline, imipramine, and selective serotonin reuptake inhibitors). Additional medications include antiarrhythmics such as lidocaine, topical analgesics, and nonsteroidal antiinflammatory drugs.

Skeletal Effects of Type 1 Diabetes Mellitus

The skeleton is adversely affected by diabetes, with T1DM patients at greater risk for skeletal complications than those with T2DM. T1DM is associated with an increased risk of fracture that first becomes evident in childhood and persists across the entire life span. This includes a dramatically increased hip fracture risk in adults, ranging from two- to sevenfold higher than patients without diabetes, depending on the population studied. Most, but not all, studies have shown T1DM to be associated with low bone mineral density. This differs from T2DM, where bone density is normal or even above average because of increased mechanical loading in association with obesity. The deficits in bone density do not appear to be sufficient to explain the degree of increased fracture risk, leading to the hypothesis that bone quality may be impaired as well. The mechanism(s) underlying diabetic-related osteopathy is poorly understood and presumed to be multifactorial. Most, but not all, studies show an association between poor glycemic control and adverse skeletal outcomes, suggesting a role for hyperglycemia and/or insulin deficiency. Chronic exposure to hyperglycemia may weaken bone strength through the accumulation of advanced glycation end products (AGEs) in bone. Other factors hypothesized to impair bone health in diabetes include chronic inflammation, abnormalities in the growth hormone-insulin-like growth factor 1 (IGF-1) axis, and abnormalities in bone mineral metabolism including excess urinary calcium loss. There are no standard guidelines for bone health screening in children. Assessment of bone density by dual-energy x-ray absorptiometry (DXA) and markers of bone mineral metabolism is recommended in adults with fracture history and other risk factors for osteoporosis. Dietary education should reinforce the importance of meeting the recommended daily allowance (RDA) for calcium and vitamin D intake from diet and supplements.

Other Complications

Mauriac syndrome is a rare complication related to chronic underinsulinization that is characterized by growth failure and hepatomegaly

caused by excess glycogen accumulation in the liver. It has become much less common since longer-acting insulins have become available. Clinical features of Mauriac syndrome include moon face, protuberant abdomen, proximal muscle wasting, and enlarged liver from fat and glycogen infiltration.

The syndrome of **limited joint mobility** is frequently associated with the early development of diabetic microvascular complications, such as retinopathy and nephropathy, which may appear before 18 years of age. The prevalence of limited joint mobility has significantly decreased, which is attributed to the improved overall metabolic control of children and adolescents with T1DM.

PROGNOSIS

T1DM is a serious, chronic disease. It has been estimated that the average life span of individuals with diabetes is approximately 10 years shorter than that of people without diabetes, but with improved care, that figure is lessening consistently. Although most children with T1DM eventually attain a height within the normal adult range, puberty may be delayed, and the final height may be less than the genetic potential. From studies in identical twins, it is apparent that despite seemingly satisfactory control, the affected twin manifests delayed puberty and a substantial reduction in height when the onset of disease occurs before puberty. These observations indicate that, in the past, conventional criteria for judging control were inadequate and that adequate control of T1DM was almost never achieved by routine means.

The changing pattern of metabolic control is having a profound influence on reducing the incidence and the severity of certain complications. For example, after 20 years of diabetes, there was a decline in the incidence of nephropathy in T1DM in Sweden among children whose disease was diagnosed in 1971–1775 compared with in the preceding decade. In addition, in most patients with microalbuminuria in whom it was possible to obtain good glycemic control, microalbuminuria disappeared. This improved prognosis is directly related to metabolic control.

PANCREAS AND ISLET TRANSPLANTATION AND REGENERATION

In an attempt to cure T1DM, transplantation of a segment of the pancreas or of isolated islets has been performed in adults. These procedures are both technically demanding and associated with the risks of disease recurrence and complications of rejection or its treatment by immunosuppression. Long-term complications of immunosuppression include the development of malignancy. Some antirejection drugs, notably cyclosporine and tacrolimus, are toxic to the islets of Langerhans, impairing insulin secretion and even causing diabetes. Hence, segmental pancreas transplantation is generally only performed in association with transplantation of a kidney for a patient with ESRD caused by diabetic nephropathy in which the immunosuppressive regimen is indicated for the renal transplantation. Several thousand such transplants have been performed in adults. With experience and better immunosuppressive agents, functional survival of the pancreatic graft may be achieved for up to several years, during which time patients may be in metabolic control with no or minimal exogenous insulin and reversal of some of the microvascular complications. However, because children and adolescents with DM are not likely to have ESRD from their diabetes, pancreas transplantation as a primary treatment in children cannot be recommended.

Islet cell transplantation is challenging because of limited survival of the transplanted cells and because of rejection. An islet transplantation strategy (Edmonton protocol) infused isolated pancreatic islets into the portal vein of adults with T1DM, along with immunosuppressive medications that had lower side effect profiles than other drugs. Although lasting insulin independence was initially low, engraftment and insulin independence have improved over the last decade, and over a thousand patients have undergone the procedure. There has been improved islet engraftment using improved induction and maintenance immunosuppression. Still, in 5-year follow-up studies, only ~10% maintain insulin independence, with an average duration of insulin independence of ~15 months. Long-term challenges remain the toxicity of immunosuppression, the limited procurement of viable tissue, and funding and limitations of engraftment itself.

629.3 Type 2 Diabetes Mellitus

David R. Weber

Formerly known as *non–insulin-dependent diabetes* or *adult-onset diabetes,* T2DM is a heterogeneous disorder, characterized by peripheral insulin resistance and failure of the β cell to keep up with increasing insulin demand. Patients with T2DM have relative rather than absolute insulin deficiency. Generally, they are not ketosis prone, but ketoacidosis is the initial presentation in 5–10% of affected subjects (Table 629.12).

NATURAL HISTORY

T2DM is a heterogenous, polygenic disease aggravated by environmental factors, including low physical activity and excessive caloric intake. Most patients are obese, although the disease can occasionally be seen in normal-weight individuals. People of Asian ancestry appear to be at risk for T2DM at lower degrees of total adiposity. Obesity, in particular central obesity, is associated with the development of insulin resistance (Fig. 629.10). In addition, patients who are at risk for developing T2DM exhibit decreased glucose-induced insulin secretion. Obesity does not lead to the same degree of insulin resistance in all individuals, and even those who develop insulin resistance do not necessarily exhibit impaired β-cell function. Thus many obese individuals have some degree of insulin resistance but compensate for it by increasing insulin secretion.

Those individuals who are unable to adequately compensate for insulin resistance by increasing insulin secretion develop IGT and IFG, usually, although not always, in that order. Hepatic insulin resistance leads to excessive hepatic glucose output (failure of insulin to suppress hepatic glucose output), and skeletal muscle insulin resistance leads to decreased glucose uptake in a major site of glucose disposal. Over time hyperglycemia worsens, a phenomenon that has been attributed to the deleterious effect of chronic hyperglycemia (glucotoxicity) or chronic hyperlipidemia (lipotoxicity) on β-cell function and is often accompanied by increased triglyceride content and decreased insulin gene expression.

At some point, blood glucose elevation meets the criteria for a diagnosis of T2DM (see Table 629.2), but most patients with T2DM remain asymptomatic for months to years after this point because hyperglycemia is moderate and symptoms are not as dramatic as the polyuria and weight loss at presentation of T1DM. Weight gain may even continue. The prolonged hyperglycemia may be accompanied by the development of microvascular and macrovascular complications. Among the differences between T2DM in children and adults is a faster decline in β-cell function and insulin secretion, as well as faster development of diabetes complications in children.

In T2DM, insulin deficiency is rarely absolute, so patients usually do not need insulin to survive, at least early in the disease course. However, in some cases, the degree of hyperglycemia is such that exogenous insulin therapy is needed. DKA is uncommon in patients with T2DM but does occur and appears to be more common in children than in adults. Although it is generally believed that autoimmune destruction of pancreatic β-cells does not occur in T2DM, autoimmune markers of T1DM—namely, GAD, ICA512, and IAA—may be positive in ~30% of the cases of adolescent T2DM. The presence of these autoimmune markers does not rule out T2DM in children and adolescents. At the same time, because of the general increase in obesity, the presence of obesity does not preclude the diagnosis of T1DM. Although most newly diagnosed children and adolescents can be confidently assigned a diagnosis of T1DM or T2DM, a few exhibit features of both types and are difficult to classify.

EPIDEMIOLOGY

The prevalence of T2DM in children (10-19 years) has risen dramatically from 34 cases per 100,000 youth in 2001 to 67 cases per 100,000

Table 629.12 Characteristics at Presentation for Type 1, Type 2, and Monogenic Diabetes

	TYPE 1 DIABETES	TYPE 2 DIABETES	MATURITY-ONSET DIABETES OF THE YOUNG
Age of onset during childhood and adolescence	Any	Rarely before puberty	Any
Weight status	Any	Rarely with normal weight	Any
Symptomatic (polyuria, polydipsia, weight loss)	Nearly universal	Two thirds	Common
Duration of symptoms before presentation	<1 mo	Frequently >1 mo	Any
Diabetic ketoacidosis at presentation	Common	Rare (6–11%)	—
Family history of diabetes before age 40	Uncommon	Strong family history for type 2 diabetes	Very strong family history, classically in three generations
Acanthosis nigricans	Rare	Common (86%)	—
Ethnicity	Any	Predominantly Black or minority ethnicity	Any
Diabetes-associated antibodies (IA2, glutamate decarboxylase, insulin)	Positive in majority	Negative (<10%)	Negative (<1%)
Pathogenic variants in *HNF1A, GCK,* or *HNF4A*	Negative	Negative	Nearly universal
Complications at presentation	Very rare	Common	Rare

IA2, Tyrosine phosphatase-related islet antigen 2.
From Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet. 2017;389:2252–2260.

in 2017. Certain ethnic groups appear to be at higher risk; for example, Native Americans, Hispanic Americans, and Black Americans (in that order) have higher incidence rates than White Americans (Fig. 629.11). Although most children presenting with diabetes have T1DM, the percentage of children presenting with T2DM is increasing and represents up to 50% of the newly diagnosed children in some centers.

GENETICS

T2DM has a strong genetic component; concordance rates among identical twins are in the 40–80% range, but there is not a simple mendelian pattern. Twinning itself increases the risk of T2DM (because of intrauterine growth restriction), and this may distort estimates of genetic risk. Monozygotic twins have a lifetime concordance of T2DM of around 70%, indicating that shared environmental factors (including the prenatal environment) may have a role in the development of T2DM; dizygotic twins have a lifetime concordance of around 20–30%. The genetic basis for T2DM is complex and incompletely defined; no single identified defect predominates. Genome-wide association studies have identified certain genetic polymorphisms that are associated with increased T2DM risk in most populations studied; the most consistently identified are variants of *TCF7L2,* which may have a role in β-cell function. Other identified risk alleles include variants in *PPARG* and *KCNJ11-ABCC8.* These variants only explain a small portion (probably less than 20%) of the population risk of diabetes, and in many cases the mechanism by which these polymorphisms confer risk of T2DM is not clear.

EPIGENETICS AND FETAL PROGRAMMING

Low birthweight and intrauterine growth restriction are associated with increased risk of T2DM. This risk appears to be higher in low-birthweight infants who gain weight more rapidly in the first few years of life. These findings have led to the formulation of the *thrifty phenotype hypothesis,* which postulates that poor fetal nutrition programs these children to maximize storage of nutrients and makes them more prone to future weight gain and development of diabetes. Epigenetic modifications may play a role in this phenomenon, given that so few of the known T2DM genes are associated with low birthweight.

ENVIRONMENTAL AND LIFESTYLE-RELATED RISK FACTORS

Obesity is the most important lifestyle factor associated with development of T2DM. This, in turn, is associated with the intake of high-energy foods, physical inactivity, excess screen time, and low socioeconomic status. Maternal smoking also increases the risk of diabetes and obesity in the offspring. Increasingly, exposure to land pollutants and air pollutants is demonstrated to contribute to insulin resistance. The lipophilic nature of these organic pollutants and their consequent storage in adipose tissue may promote obesity and insulin resistance. In addition, sleep deprivation and psychosocial stress are associated with increased risk of obesity in childhood and with IGT in adults, possibly via overactivation of the hypothalamic-pituitary-adrenal axis. Many antipsychotics (especially the atypical antipsychotics like olanzapine and quetiapine) and antidepressants (both tricyclic antidepressants and newer antidepressants like fluoxetine and paroxetine) induce weight gain. In addition to the risk conferred by increased obesity, some of these medications may also have a direct role in causing insulin resistance, β-cell dysfunction, leptin resistance, and activation of inflammatory pathways.

CLINICAL FEATURES

In the United States, T2DM in children is more likely to be diagnosed in Native American, Hispanic American, and Black American youth, with the highest incidence being reported in Pima Indian youth. Although cases may be seen as young as 4 years of age, most are diagnosed in adolescence; the incidence increases with increasing age. Family history of T2DM is present in most cases. Patients are obese and present with mild symptoms of polyuria and polydipsia or are asymptomatic and T2DM is detected on screening tests. Presentation with DKA occurs in ~10% of cases. Physical examination frequently reveals the presence of acanthosis nigricans, most commonly on the neck and in other flexural areas. Other findings may include striae and an increased waist-to-hip ratio. Laboratory testing reveals elevated HbA_{1c} levels. Hyperlipidemia characterized by elevated triglycerides and low-density lipoprotein cholesterol levels is commonly seen in patients with T2DM at diagnosis. Lipid screening is indicated in all new cases of T2DM. The current recommendation is that blood pressure measurement, random urine

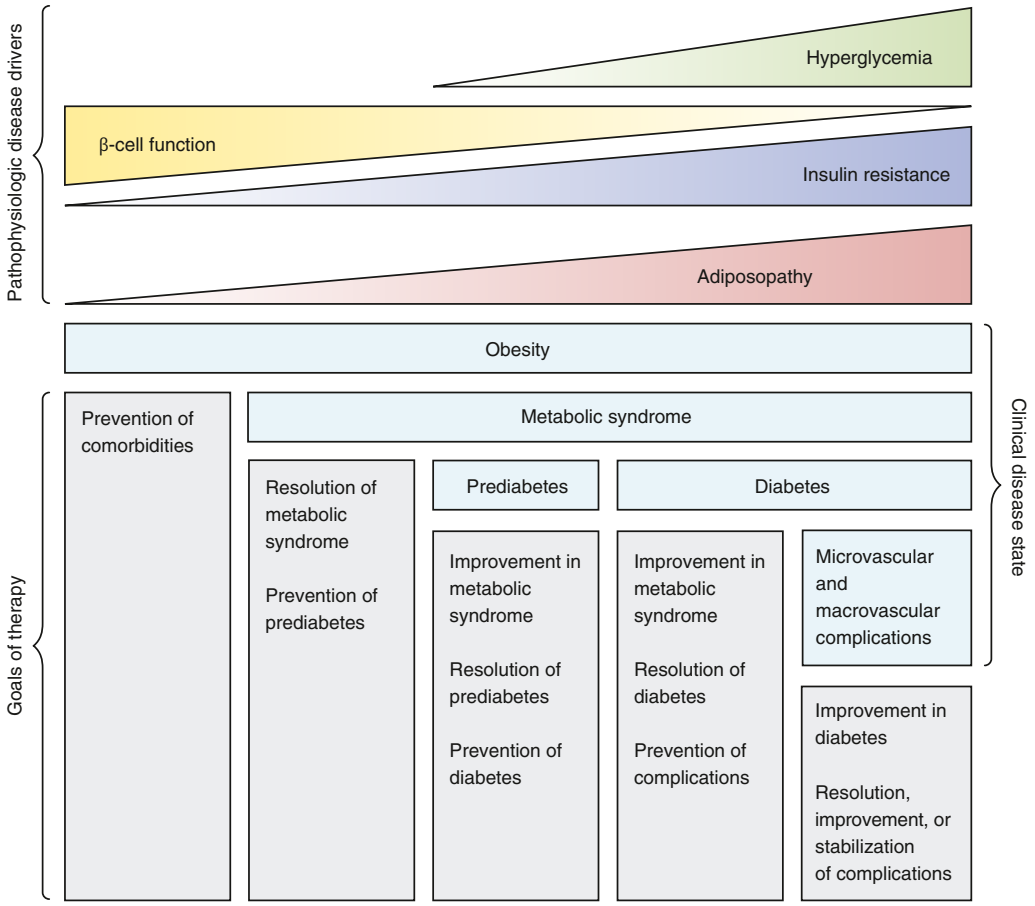


Fig. 629.10 The disease continuum for weight-related type 2 diabetes. *(From Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet. 2022;399:394–404.)*

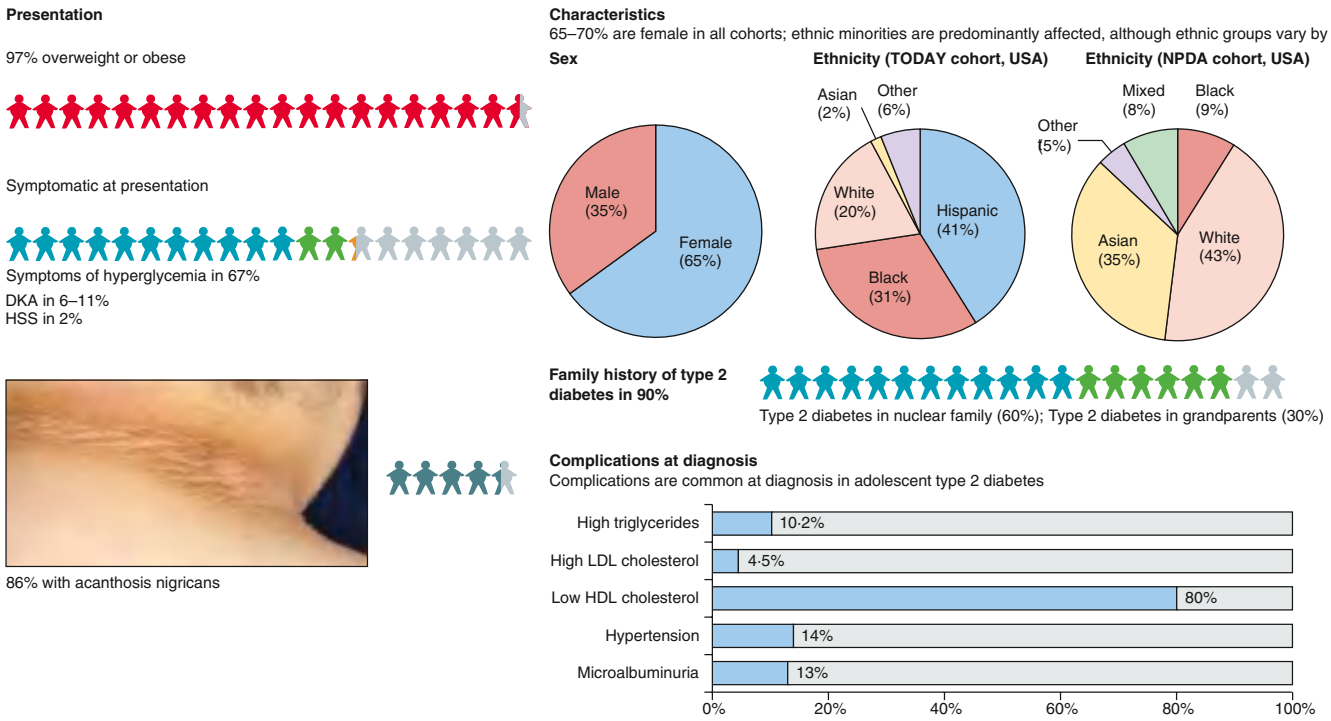


Fig. 629.11 Features of adolescent type 2 diabetes at diagnosis. DKA, diabetic ketoacidosis. HHS, hyperglycemic hyperosmolar syndrome; NPDA, National Diabetes Pediatric Audit; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth. *(From Viner R, White B, Christie D. Type 2 diabetes in adolescents: a severe phenotype posing major clinical challenges and public health burden. Lancet. 2017;389:2252–2260.)*

albumin-to-creatinine ratio, and a dilated eye examination should be performed at diagnosis.

Because hyperglycemia develops slowly and patients may be asymptomatic for months or years after they develop T2DM, screening is recommended in high-risk children (Table 629.13). All youth who are overweight and have at least one other risk factor should be tested for T2DM beginning at age 10 years or at the onset of puberty. Risk factors include family history of T2DM in first- or second-degree relatives, history of gestational diabetes in the mother, belonging to a high-risk racial or ethnic group (i.e., Native American, Black American, Hispanic, or Asian/Pacific Islander groups), and having signs of insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome). The current recommendation is to use the HbA_{1c} the screening tool; fasting plasma glucose is also acceptable. In borderline or asymptomatic cases, the diagnosis may be confirmed using a standard OGTT, but this test is not required if typical symptoms are present or fasting plasma glucose or HbA_{1c} is clearly elevated.

TREATMENT

T2DM is a progressive syndrome that gradually leads to complete insulin deficiency during the patient's life. A systematic approach for the treatment of T2DM should be implemented according to the natural course of the disease, including adding insulin when hyperglycemia cannot be controlled by lifestyle and noninsulin pharmacotherapy. Lifestyle modification (diet and exercise) is an essential part of the treatment regimen, and consultation with a dietitian is usually necessary (see Fig. 629.10). An oral agent monotherapy may not maintain lasting glucose control in close to half of those with T2DM.

Recommendations are to implement a comprehensive lifestyle modification plan designed to induce weight loss of 7–10%. There is no specific dietary or exercise regimen that has been conclusively shown to be superior, and practitioners recommend a low-calorie, low-fat diet and 30-60 minutes of physical activity at least 5 times a week. Screen time should be limited to 1-2 hours a day. Education is provided to diminish unhealthy habits such as skipping meals, heavy snacking, and excessive screen time. Adolescents may engage in non–appetite-based eating (i.e., emotional eating, television-cued eating, boredom) and cyclic dieting ("yo-yo" dieting). Treatment in these cases is frequently challenging and may not be successful unless the entire family buys into the need to change their unhealthy lifestyle.

Pharmacologic therapy should be initiated at diagnosis of T2DM. Noninsulin pharmacotherapies used in the treatment of T2DM are shown in Table 629.14; most of these are not approved for use in patients under the age of 18 years. Metformin is the first line of pharmacotherapy and should be started in all patients. Renal insufficiency and liver disease are contraindications to metformin use and may increase the risk of lactic acidosis. Patients with markedly elevated liver transaminases should undergo evaluation by a gastroenterologist/hepatologist before initiating therapy. The starting dose is 500-1000 mg/day, which should be increased over a few weeks to the full therapeutic dose of 2,000 mg daily. Patients who present with significant (HbA_{1c} >8.5%) or symptomatic (e.g., polyuria, polydipsia) hyperglycemia should be started on basal insulin with a long-acting insulin analog, typically at a dose of 0.5 units/kg/day. Those presenting in DKA will require initial treatment with insulin using protocols similar to those used for treating T1DM. Once blood glucose levels are under control, many cases can be managed with hypoglycemic agents and lifestyle interventions, but some patients will continue to require insulin therapy.

Ongoing care should include periodic review of weight and BMI, diet, and physical activity; blood glucose monitoring; and monitoring of HbA_{1c} at 3-month intervals. Frequency of home glucose monitoring can range from 3-4 times daily for those on multiple daily insulin injections to twice daily for those on a stable long-acting insulin regimen or metformin. Alternatively, blood glucose monitoring can be done by CGM. Patients who fail to achieve glycemic targets (typically HbA_{1c} <7%) with lifestyle modification and metformin alone will require escalation of therapy with the addition of basal insulin or liraglutide. Liraglutide is an injectable glucagon-like peptide-1 (GLP-1) analog approved by the FDA for use in children ≥10 years. A potential benefit of liraglutide over basal insulin is that it may promote weight loss. The typical starting dose is 0.6 mg/daily, increased as tolerated by 0.6 mg/day per week until a maximum dose of 1.8 mg is achieved. Gastrointestinal symptoms are the most common side effect. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN 2), based on animal data showing a dose- and duration-dependent effect to promote thyroid C-cell tumors in rodents.

Other agents such as thiazolidinediones, sulfonylureas, other GLP-1 analogs, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), pramlintide, and sodium-glucose transport protein inhibitors (SGLT2 inhibitors) are used with variable frequency in adults but are infrequently used in children. Sulfonylureas cause insulin release by closing the potassium channel (K_{ATP}) on β cells. They are occasionally used when metformin monotherapy is unsuccessful or contraindicated for some reason (use in certain forms of neonatal diabetes is discussed in the relevant section). Thiazolidinediones increase insulin sensitivity via activation of the peroxisome proliferator-activated receptor pathway, but use is limited because of concerns about adverse cardiac effects. Pramlintide is an analog of islet amyloid polypeptide (IAPP), which delays gastric emptying, suppresses glucagon, and possibly suppresses food intake. It is not approved for pediatric use and increases the risk of hypoglycemia when used with insulin or other hypoglycemic agents.

Incretins are gut-derived peptides like GLP-1, GLP-2, and GIP (glucose-dependent insulinotropic peptide, previously known as *gastric inhibitory protein*) that are secreted in response to meals and act to enhance insulin secretion and action, suppress glucagon production, and delay gastric emptying (among other actions). Other daily and weekly forms of GLP-1 agonists beyond liraglutide are commonly used in adults. DPP-4 inhibitors are oral agents that prolong the action of GLP-1 and are currently being studied for use in children. The SGLT-2 inhibitors act by blocking glucose reabsorption in the proximal renal tubule and are commonly used as second- or third-line agents in adults, with specific benefits in improving cardiorenal outcomes in patients with heart failure or declining renal function. SGLT-2 inhibitors are currently under evaluation for potential use in children. Adults with T2DM have been treated with *double incretion* therapy (tirzepatide) with the combination of a GLP-1 agonist and GIP.

Further rises in HbA_{1c} despite the addition of basal insulin and/or liraglutide will necessitate addition of short-acting insulin at mealtimes. Bariatric surgery is also used in adolescents with moderate to severe obesity and frequently leads to complete remission of T2DM. Guidelines for the routine use of bariatric surgery in adolescents continue to emerge, but expert opinion suggests that adolescents with BMI ≥35 or 120% of the 95th percentile for age and gender with a clinically significant complication (including T2DM) are potential candidates, provided there is access to a quality multidisciplinary center with pediatric experience.

Table 629.13 Testing for Type 2 Diabetes in Children

- **Criteria***

Overweight (body mass index >85th percentile for age and sex
Plus
One or more of the following risk factors:
- Family history of type 2 diabetes in first- or second-degree relative or gestational diabetes in the mother
- High risk racial/ethnic background (Native American, Black American, Hispanic, Asian/Pacific Islander)
- Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)

- **Age of initiation**: age 10 yr or at onset of puberty if puberty occurs at a younger age
- **Frequency:** every 1-2 yr, based upon clinical suspicion
- **Test:** fasting glucose, HbA_{1c}, or oral glucose tolerance teat

*Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

Table 629.14 Noninsulin Pharmacotherapies Used to Treat T2DM

MEDICATIONS	CLASS	MECHANISM OF ACTION	ROUTE	FDA-APPROVED AGE
Pramlintide	Amylin analogue	Increases satiety, slows gastric emptying, and suppresses postprandial glucagon secretion, resulting in decreased postmeal glucose excursions	Subcutaneous injection	>18 yr
Metformin	Biguanide	Improves hepatic insulin sensitivity. Increases GLP-1 and PYY	Oral	>10 yr
Alogliptin Linagliptin Saxagliptin Sitagliptin	DPP-4 inhibitors	Inhibits DPP-4 from degrading GLP-1 and GIP	Oral	>18 yr
Albiglutide Dulaglutide Exenatide Liraglutide Lixisenatide Semaglutide	Glucagon-like peptide agonists	Increase release of GLP-1, which stimulates release of insulin	Subcutaneous injection	>8 yr, with exception of liraglutide, which is >10 yr
Nateglinide Repaglinide	Meglitinides	Causes rapid secretion of insulin by acting on the ATP sensitive potassium channel of pancreatic beta cells	Oral	>18 yr
Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Sodium-glucose co-transporter 2 inhibitors	Promotes renal excretion of glucose at the level of the proximal tubule causing an osmotic diuresis	Oral	>18 yr
Gliclazide Glimepiride Glipizide Glyburide	Sulfonylureas	Increase insulin section via interaction with the K-ATP channel in β cells	Oral	>18 yr
Pioglitazone Rosiglitazone	Thiazolidinediones	Increase insulin sensitivity at adipose and muscle tissue	Oral	>18 yr

DPP-4, Dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1 agonist; PYY, peptide YY.

COMPLICATIONS

In one study of diabetes in youth, 92% of the patients with T2DM had two or more elements of **metabolic syndrome** (hypertension, hypertriglyceridemia, decreased high-density lipoprotein, increased waist circumference), including 70% with hypertension. In addition, the incidence of microalbuminuria and diabetic retinopathy appears to be higher in T2DM than it is in T1DM. In long-term follow-up from another study, the participants at a mean of age 26 years reported a cumulative incidence of hypertension of 68%, dyslipidemia 52%, diabetic kidney disease 55%, and nerve disease 32%.

Given the extremely high risk of diabetes-related comorbidities, routine screening for microalbuminuria, dyslipidemia, hypertension, and retinopathy should commence shortly after diagnosis. Sleep apnea and fatty liver disease are being diagnosed with increasing frequency and may necessitate referral to the appropriate specialists. Complications associated with all forms of diabetes and recommendations for screening are noted in Table 629.12; Table 629.15 lists conditions particularly associated with T2DM.

PREVENTION

The difficulties in achieving good glucose control and preventing diabetes complications make prevention a compelling strategy. This is particularly true for T2DM, which is linked to modifiable risk factors (obesity, a sedentary lifestyle). The Diabetes Prevention Program demonstrated that intensified lifestyle or drug intervention in individuals with IGT prevented or delayed the onset of T2DM. Lifestyle intervention reduced the diabetes incidence by 58%; metformin reduced the incidence by 31% compared with placebo. Lifestyle interventions are believed to have similar beneficial effects in obese adolescents with IGT.

629.4 Other Specific Types of Diabetes

David R. Weber

Most cases of diabetes in children and adults fall into the two broad categories of T1DM and T2DM, but between 1% and 10% of cases are caused by single-gene disorders. These disorders include hereditary defects of β-cell function and insulin action, as well as rare forms of mitochondrial diabetes.

GENETIC DEFECTS OF β-CELL FUNCTION

Transient Neonatal Diabetes Mellitus

Neonatal diabetes is transient in approximately 50% of cases, but after an interim period of normal glucose tolerance, 50–60% of these patients develop permanent diabetes (at an average age of 14 years). It remains to be determined whether this association of transient diabetes in the newborn followed much later in life by classic T1DM is a chance occurrence or causally related (Fig. 629.12).

The syndrome of **transient DM** in the newborn infant has its onset in the first week of life and persists several weeks to months before spontaneous resolution. Median duration is 12 weeks. It occurs most often in infants who are small for gestational age and is characterized by hyperglycemia and pronounced glycosuria, resulting in severe dehydration and, at times, metabolic acidosis, but with only minimal or no ketonemia or ketonuria. There may also be findings such as umbilical hernia or large tongue. Insulin responses to glucose or tolbutamide are low to absent; basal plasma insulin concentrations are normal. After spontaneous recovery, the insulin responses to these same stimuli are brisk and normal, implying a possible functional delay in β-cell maturation with spontaneous resolution. Occurrence of the syndrome in

Table 629.15 Monitoring for Complications and Comorbidities in T2DM

CONDITION	SCREENING TEST	COMMENT
Hypertension	Blood pressure	
Fatty liver	Aspartate aminotransferase, alanine aminotransferase, possibly liver ultrasound	
Polycystic ovary syndrome	Menstrual history, assessment for androgen excess with free/total testosterone, dehydroepiandrosterone sulfate	
Microalbuminuria	Urine albumin concentration and albumin-to-creatinine ratios	
Dyslipidemia	Fasting lipid profile (total, low-density lipoprotein, high-density lipoprotein cholesterol, triglycerides)	Obtain at diagnosis and every 2 yr
Sleep apnea	Polysomnography: Sleep study to assess overnight oxygen saturation, airflow, heart rate, electromyography, and eye movements	

consecutive siblings has been reported. About 70% of cases are the result of abnormalities of an imprinted locus on chromosome 6q24, resulting in overexpression of paternally expressed genes such as *PLAGL1/ZAC* and *HYMAI*. Most of the remaining cases are caused by pathogenic variants in K_{ATP} channels. Variants in K_{ATP} channels also cause many cases of permanent neonatal diabetes, but there is practically no overlap between the variants that lead to transient neonatal DM and those causing permanent neonatal DM. This syndrome of transient neonatal DM should be distinguished from the severe hyperglycemia that may occur in hypertonic dehydration that usually occurs in infants beyond the newborn period and responds promptly to rehydration with minimal or no requirement for insulin.

Administration of insulin is mandatory during the active phase of DM in the newborn. Rehydration and IV insulin are usually required initially; transition to subcutaneous insulin can occur once clinically stable. A variety of regimens, including intermediate- or long-acting insulin given in one to two daily doses or continuous insulin therapy with an insulin pump, have been used successfully. The starting dose is typically 1-2 units/kg/day but will need to be adjusted based upon blood glucose levels. Attempts at gradually reducing the dose of insulin may be made as soon as recurrent hypoglycemia becomes manifested or after 2 months of age.

Permanent Neonatal Diabetes Mellitus

Permanent DM in the newborn period is caused, in approximately 50% of the cases, by pathogenic variants in the *KCNJ11* and *ABCC8* genes (see Figs. 629.12 and 629.13). These genes code for the Kir6.2 and SUR1 subunits of the adenosine triphosphate–sensitive potassium channel, which is involved in an essential step in insulin secretion by the β cell. Some cases are caused by pancreatic agenesis because of homozygous pathogenic variants in *IPF-1* (where heterozygous variants cause MODY4); homozygous variants in the glucokinase gene (where heterozygous variants cause MODY2); and variants in the insulin gene (see Tables 629.1 and 629.12). Almost all these infants are small at birth because of the role of insulin as an intrauterine growth factor. Instances of affected twins and families with more than one affected infant have been reported. Infants with permanent neonatal DM may be initially euglycemic and typically present between birth and 6 months of life (mean age of presentation is 5 weeks), but rarely can present up to 1 year of age. There is a spectrum of severity, and up to 20% have neurologic features. The most severely affected patients have the syndrome of *d*evelopmental delay, *e*pilepsy, and *n*eonatal *d*iabetes (**DEND syndrome**).

Activating pathogenic variants in the *KCNJ11* gene (encoding the adenosine triphosphate–sensitive potassium channel subunit Kir6.2) are associated with both TND and PND, with variants associated with each phenotype. More than 90% of these patients respond to sulfonylureas (at higher doses than those used in T2DM), but patients with severe neurologic disease may be less responsive. Pathogenic variants in *ABCC8* (encoding the SUR1 subunit of this potassium channel) were thought to be less likely to respond to sulfonylureas (because this is the subunit that binds sulfonylurea drugs), but some of these variants are reported to respond; patients have been successfully switched from insulin to oral therapy. Several protocols for switching the patient from insulin to glyburide are available, and patients are usually stabilized on doses ranging from 1 to 2.5 mg/kg/day. Because approximately 50% of neonatal diabetics have potassium-channel variants that can be switched to sulfonylurea therapy, with dramatic improvement in glycemic control, neurologic outcomes, and quality of life, all patients with diabetes diagnosed before 6 months of age (and perhaps even those diagnosed before 12 months of age) in whom insulin dependence persists beyond 7-10 days should have genetic testing (Fig. 629.14).

Maturity-Onset Diabetes of Youth

Several forms of diabetes are associated with **monogenic defects in β-cell function**. Before these genetic defects were identified, this subset was diagnosed on clinical grounds and described by the term *MODY*. This subtype of DM consists of a group of heterogeneous clinical entities that are characterized by onset before 25 years, autosomal dominant inheritance, and a primary defect in insulin secretion. Strict criteria for the diagnosis of MODY include diabetes in at least three generations with autosomal dominant transmission and diagnosis before age 25 years in at least one affected subject. Pathogenic variants have been found in at least 14 different genes, accounting for the dominantly inherited monogenic defects of insulin secretion, for which the term MODY is used (Table 629.16). The ADA groups these disorders together under the broader category of *genetic defects of β-cell function*. Just three of them (MODY2, MODY3, and MODY5) account for 90% of the cases in this category in European populations, but the distribution may be different in other ethnic groups. Except for MODY2 (which is caused by variants in the enzyme glucokinase), all other forms are caused by genetic defects in various transcription factors (see Table 629.16).

MODY2

This is the second most common form of MODY and accounts for approximately 15–30% of all patients diagnosed. Glucokinase plays an essential role in β-cell glucose sensing, and heterozygous pathogenic variants in this gene lead to mild reductions in pancreatic β-cell response to glucose. Homozygotes with the same variants are completely unable to secrete insulin in response to glucose and develop a form of PND. Patients with heterozygous variants have a higher threshold for insulin release but are able to secrete insulin adequately at higher blood glucose levels (typically 125 mg/dL [7 mmol/L] or higher). This results in a relatively mild form of diabetes (HbA_{1c} is usually less than 7%), with mild fasting hyperglycemia and IGT in most patients. MODY2 may be misdiagnosed as T1DM in children, gestational diabetes in pregnant women, or well-controlled T2DM in adults (see Table 629.12). An accurate diagnosis is important because most cases are not progressive, and except for gestational diabetes, may not require treatment. When needed, they can usually be treated with small doses of exogenously administered insulin. Treatment with oral agents (sulfonylureas and related drugs) can be successful and may be more acceptable to many patients.

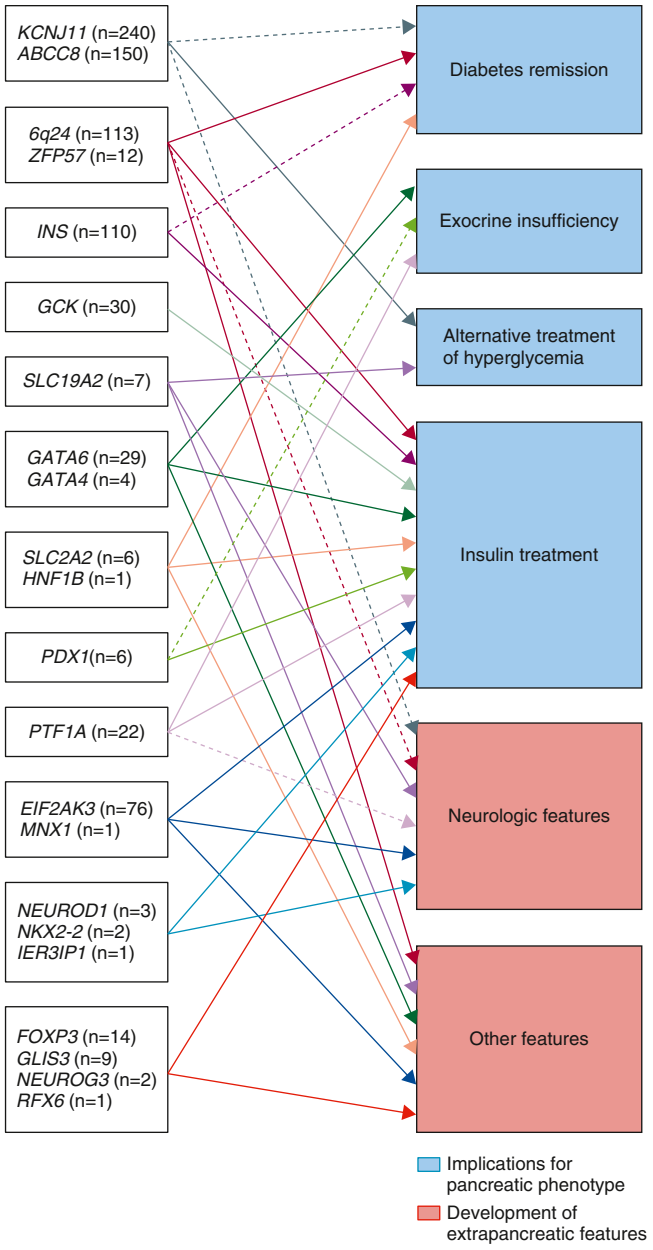


Fig. 629.12 A genetic diagnosis guides clinical management. Schematic representation of genetic causes of neonatal diabetes and the implications of this genetic diagnosis. *n* indicates the number of patients identified with pathogenic variants in each of the genes in the 1,020 neonatal diabetes patient cohort. *Solid arrows* indicate implications for most pathogenic variants in the genes. *Dashed arrows* indicate the implications for specific variants. *(From De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet. 2015;386:957–963. Fig. 3.)*

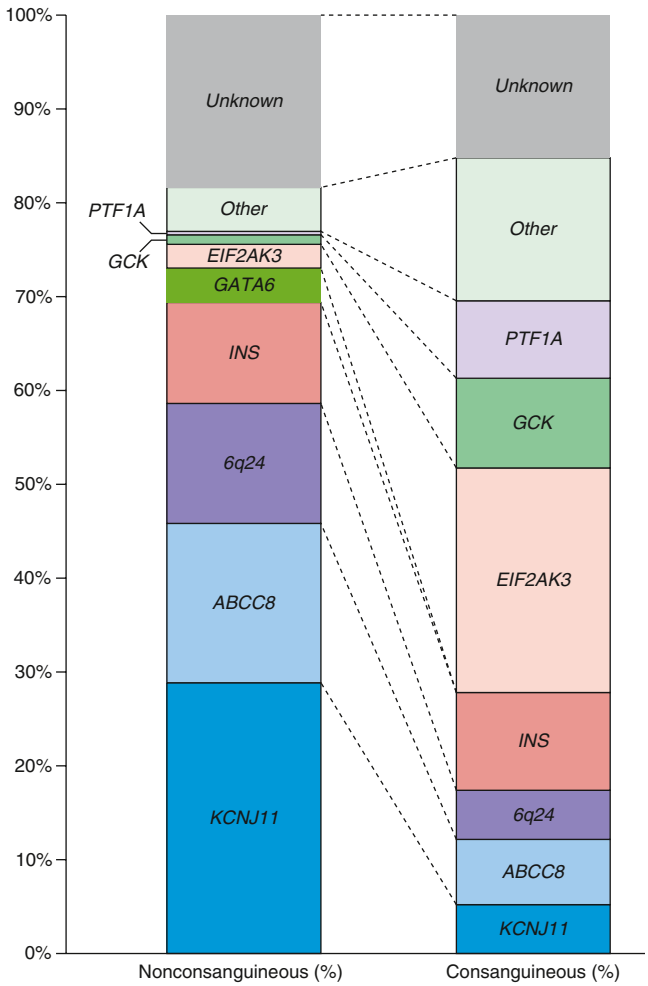


Fig. 629.13 Different genetic causes of neonatal diabetes in patients born to nonconsanguineous and consanguineous parents. Comparison of genetic causes of neonatal diabetes in nonconsanguineous (*n* = 790) and consanguineous groups (*n* = 230). Consanguinity is defined by parents being second cousins or more closely related or by the presence of 1.56% or higher total homozygosity. Genes involved in less than 2.5% of patients in both cohorts were grouped in the other category. *(From De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. Lancet. 2015;386:957–963. Fig. 2.)*

MODY3

Patients affected with pathogenic variants in the transcription factor hepatocyte nuclear factor-1α show abnormalities of carbohydrate metabolism varying from IGT to severe diabetes and often progressing from a mild to a severe form over time. They are also prone to the development of vascular complications. This is the most common MODY subtype and accounts for 30–60% of all cases of MODY. These patients are very sensitive to the action of sulfonylureas and can usually be treated with relatively low doses of these oral agents, at least in the early stages of the disease. In children, this form of MODY is sometimes misclassified as T1DM and treated with insulin. Evaluation of autoimmune markers helps to rule out T1DM; genetic testing for MODY is available and is indicated in patients with relatively mild diabetes and a family history suggestive of autosomal dominant inheritance. Accurate diagnosis can lead to avoidance of unnecessary insulin treatment and specific genetic counseling (see Fig. 629.14).

Less Common Forms of Monogenic Diabetes

Hepatocyte nuclear factor-4α (MODY1), insulin promoter factor (IPF)-1, also known as (PDX-1) (MODY4), hepatocyte nuclear factor 1β/TCF2 (MODY5), and NeuroD1 (MODY6) are all transcription factors that are involved in β-cell development and function, and mutations in these lead to various rare forms of MODY. In addition to diabetes, they can also have specific findings unrelated to hyperglycemia; for example, MODY1 is associated with low triglyceride and lipoprotein levels, and MODY5 is associated with renal cysts and renal dysfunction. In terms of treatment, MODY1 and MODY4 may respond to oral sulfonylureas, but MODY5 does not respond to oral agents and requires treatment with insulin. NeuroD1 defects are extremely rare and not much is known about their natural history.

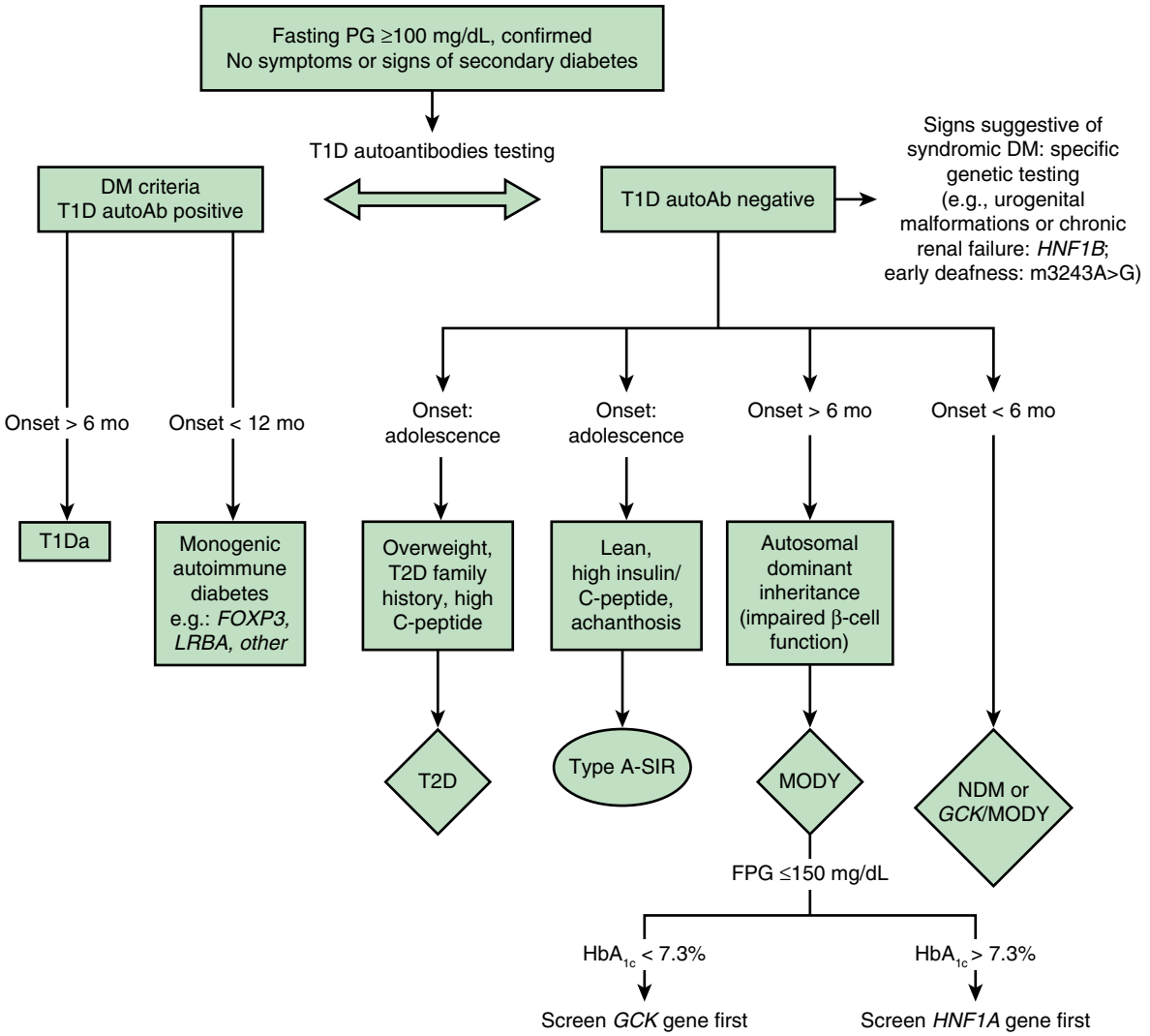


Fig. 629.14 Diagnostic algorithm of monogenic forms of diabetes. Negativity of genetic testing of two common subtypes of MODY in children and adolescents implies that further testing is mandatory if the clinical diagnosis is robust. FPG, fasting plasma glucose; MODY, maturity onset diabetes of the young; NDM, neonatal diabetes mellius; SIR, severe insulin resistance. *(From Barbetti F, D'Annunzio G. Genetic causes and treatment of neonatal diabetes and early childhood diabetes. Best Pract Res Clin Endocrinol Metab. 2018;32[4]:575-591. Fig. 1.)*

Primary or secondary defects in the glucose transporter-2, which is an insulin-independent glucose transporter, may also be associated with diabetes. Diabetes may also be a manifestation of a polymorphism in the glycogen synthase gene. This enzyme is crucially important for storage of glucose as glycogen in muscle. Patients with this defect are notable for marked insulin resistance and hypertension, as well as a strong family history of diabetes.

Another form of IDDM is **Wolfram syndrome** (Table 629.17). Wolfram syndrome 1 is characterized by diabetes insipidus, DM, optic atrophy, and deafness—thus the acronym **DIDMOAD**. Some patients with diabetes appear to have severe insulinopenia, whereas others have significant insulin secretion as judged by C-peptide. The overall prevalence is estimated at 1 in 770,000 live births. The sequence of appearance of the stigmata is as follows: non-autoimmune IDDM in the first decade, central diabetes insipidus and sensorineural deafness in ~65–75% of the patients in the second decade, renal tract anomalies in ~50% of the patients in the third decade, and neurologic complications such as cerebellar ataxia and myoclonus in half to two thirds of the patients in the fourth decade. Other features include primary gonadal atrophy in most males and a progressive neurodegenerative course with neurorespiratory death at a median age of 30 years. Some cases are caused by pathogenic variants in *WFS-1*. Wolfram syndrome 2 has early-onset optic atrophy, DM, deafness, and a shortened life span but no diabetes insipidus; the associated gene is *CISD2*. Other forms of Wolfram syndrome may be caused by variants in mitochondrial DNA. Other syndromes associated with diabetes are noted in Table 629.17.

Mitochondrial Gene Defects

Pathogenic variants in mitochondrial DNA are associated with **maternally inherited DM and deafness**. The most common mitochondrial DNA variant in these cases is the variant m.3243A>G in the transfer RNA leucine gene. This variant is identical to the variant in MELAS (myopathy, encephalopathy, lactic acidosis, and strokelike syndrome), but MELAS syndrome is not associated with diabetes; the phenotypic expression of the same defect varies. Diabetes in most of these cases presents insidiously, but approximately 20% of patients have an acute presentation resembling T1DM. The mean age of diagnosis of diabetes is 37 years, but cases have been reported as young as 11 years; not all patients have deafness. This variant has been estimated to be present in 1.5% of Japanese people with diabetes, which may be higher than the prevalence in other ethnic groups. Metformin should be avoided in these patients because of the theoretical risk of severe lactic acidosis in the presence of mitochondrial dysfunction. Some children with mitochondrial DNA mutations affecting complex I and/or complex IV may also develop diabetes.

Table 629.16 Clinical Characteristics of Maturity-Onset Diabetes of the Young (MODY) Genetic Subtypes

MODY TYPE	GENE NAME (LOCUS)	PREVALENCE (%)	OTHER FEATURES	TREATMENT
MODY 1	*HNF4A* (20ql2)	5–10	Neonatal hyperinsulinemia and hypoglycemia with associated macrosomia, low serum levels of cholesterol	Sensitive to sulfonylureas
MODY 2	*GCK* (7pl3)	30–60	Mild fasting hyperglycemia throughout life, often asymptomatic, gestational diabetes, low birthweight (with unaffected mother)	No treatment outside of pregnancy
MODY 3	*HNF1A* (12q24.2)	30–60	Glycosuria	Sensitive to sulfonylureas
MODY 4	*PDX1* (13ql2.1)	<1	Homozygote: pancreatic agenesis	Diet, OAD, or insulin
MODY 5	*HNFIB* (17q21)	5–10	Diabetes in association with renal and genitourinary abnormalities	Insulin
MODY 6	*NEUROD I* (2q31.3)	<1	Obesity and insulin resistance	OAD or insulin
MODY 7	*KLF11* (2p25)	<1	Impaired glucose tolerance to overt diabetes	OAD or insulin
MODY 8	*CEL* (9p34)	<1	Diabetes and pancreatic exocrine deficiency	OAD or insulin
MODY 9	*PAX4* (7q32)	<1	Ketosis-prone diabetes	Diet, OAD, or insulin
MODY 10	*INS* (llpl5.5)	<1	May result in neonatal diabetes, antibody-negative diabetes, and MODY	OAD or insulin
MODY 11	*BLK* (8p23)	<1	Obesity common	Diet, OAD, or insulin
MODY 12	*ABCC8* (11pl5.1)	<1	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas
MODY 13	*KCNJ11* (11p 15.13)	<1	Usually associated with neonatal diabetes, rare cause of MODY	Sensitive to sulfonylureas
MODY 14	*APPL1* (3pl4.3)	<1	Adult-onset diabetes	Diet, OAD, or insulin

ABCC8, ATP-binding cassette, subfamily C (CFTR/MRP), member 8; APPL1, adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1; BLK, B-lymphocyte kinase; CEL, carboxyl ester lipase enzyme; GCK, glucokinase; HNF1A, hepatocyte nuclear factor-lα; HNF1B, hepatocyte nuclear factor-lβ; INS, preproinsulin; KCNJ11, potassium channel, inwardly rectifying subfamily J, member 11; KLF11, Kruppel-like factor 11; NEUROD 1, neurogenic differentiation factor 1; OAD, oral antidiabetic; PAX4, paired box gene 4; PDX1, pancreas/duodenum homeobox protein 1.
Modified from Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep. 2018;18:58. Table 1.

Abnormalities of the Insulin Gene

Diabetes of variable degrees may also result from pathogenic variants in the insulin gene that impair the effectiveness of insulin at the receptor level. Insulin gene defects are exceedingly rare and may be associated with relatively mild diabetes or even normal glucose tolerance. Diabetes may also develop in patients with faulty processing of proinsulin to insulin (an autosomal dominant defect). These defects are notable for the high concentration of insulin as measured by radioimmunoassay, whereas MODY and glucose transporter-2 defects are characterized by relative or absolute deficiency of insulin secretion for the prevailing glucose concentrations.

GENETIC DEFECTS OF INSULIN ACTION

Various genetic variants in the insulin receptor can impair the action of insulin at the insulin receptor or impair postreceptor signaling, leading to insulin resistance. The mildest form of the syndrome with variants in the insulin receptor was previously known as **type A insulin resistance**. This condition is associated with hirsutism, hyperandrogenism, and cystic ovaries in females, without obesity. Acanthosis nigricans may be present, and life expectancy is not significantly impaired. More severe forms of insulin resistance are seen in two variants in the insulin receptor gene that cause the pediatric syndromes of **Donohue syndrome** (formerly called *leprechaunism*) and **Rabson-Mendenhall syndrome**.

Donohue Syndrome

This is a syndrome characterized by intrauterine growth restriction, fasting hypoglycemia, and postprandial hyperglycemia in association with profound resistance to insulin; severe hyperinsulinemia is seen during an OGTT. Various defects of the insulin receptor have been described, thereby attesting to the important role of insulin and its receptor in fetal growth and possibly in morphogenesis. Many of these patients die in the first year of life. Potential treatments include high-dose insulin, metformin, and continuous IGF-1 via insulin pump.

Rabson-Mendenhall Syndrome

This entity is defined by clinical manifestations that appear to be intermediate between those of acanthosis nigricans with insulin resistance type A and Donohue syndrome. The features include extreme insulin resistance, acanthosis nigricans, abnormalities of the teeth and nails, and pineal hyperplasia. It is not clear whether this syndrome is entirely distinct from Donohue syndrome; however, by comparison, patients with Rabson-Mendenhall tend to live significantly longer. Therapies with modest benefit have included IGF-1 and leptin.

Lipoatrophic Diabetes

Various forms of lipodystrophy are associated with insulin resistance and diabetes (Table 629.18). **Familial partial lipoatrophy**, or **lipodystrophy**, is associated with pathogenic variants in *LMNA*, encoding nuclear envelope proteins lamin A and C. **Severe congenital generalized lipoatrophy** is associated with variants in the seipin and *AGPAT2* genes, but the mechanism by which these variants lead to insulin resistance and diabetes is not known.

Stiff-Person Syndrome

This is an extremely rare autoimmune CNS disorder that is characterized by progressive stiffness and painful spasms of the axial muscles

Table 629.17 Syndromic Forms of Diabetes that May Present in Childhood or Early Childhood

SYNDROME	GENE (LOCUS)	INHERITANCE	TYPE OF DIABETES	CLINICAL FEATURES
Diabetes and deafness	Mitochondria tRNA	Maternal	Insulin deficient	Adult-onset diabetes, sensorineural deafness
Wolfram syndrome 1	*WFS1*(4p16)	AR/AD	Insulin deficient	Childhood-onset diabetes, optic atrophy, deafness, diabetes insipidus
Wolfram syndrome 2	*CISD2*(4q24)	AR	Insulin deficient	Childhood-onset, diabetes, optic atrophy, deafness, and defective platelet aggregation
Thiamine-responsive megaloblastic anemia syndrome	*SLC19A2*(1q23)	AR	Vitamin dependent	Childhood-onset diabetes, megaloblastic or sideroblastic anemia, sensorineural deafness
Mitchell-Riley syndrome	*RFX6*(6q22)	AR	Insulin deficient	Rare cases with childhood-onset, pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia
Alström syndrome	*ALMS1*(2p13)	AR	Insulin resistant	Childhood to early adulthood, pigmentary retinopathy, deafness, obesity, dilated cardiomyopathy
Bardet-Biedl syndrome	*BBS1–BBS21*	AR/DR	Insulin resistant	Childhood to early adulthood, developmental delay, pigmentary retinopathy, polydactyly, obesity, hypogonadism
Insulin resistance syndrome type A	*INSR*(19p13)	AD/AR	Insulin resistant	Childhood to early adulthood, obesity, diabetes, and acanthosis nigricans

ALMS1, Alström syndrome 1; AD, autosomal dominant; AR, autosomal recessive; BBS, Bardet-Biedl; CISD2, CDGSH iron sulfur domain 2; DR, digenic recessive; INSR, insulin receptor; RFX6, regulatory factor X6; SLC19A2, solute carrier family 19 member 2; tRNA, transfer RNA; WFS1, wolframin.
Modified from Sanyoura M, Philipson LH, Naylor R. Monogenic diabetes in children and adolescents: recognition and treatment options. Curr Diab Rep. 18:58, 2018. Table 2.

Table 629.18 Clinical and Biochemical Features of Inherited Lipodystrophies

	CONGENITAL GENERALIZED LIPODYSTROPHY		FAMILIAL PARTIAL LIPODYSTROPHY	
SUBTYPE	***BSCL1***	***BSCL2***	***FPLD2***	***FPLD3***
DEFECTIVE GENE	***AGPAT2***	***BSCL2***	***LMNA***	***PPARG***
Clinical onset	Soon after birth	Soon after birth	Puberty	Usually puberty, but may present in younger children
Fat distribution	Generalized absence	Generalized absence	Loss of limb and gluteal fat; typically excess facial and nuchal fat; trunk fat often lost	Loss of limb and gluteal fat; preserved facial and trunk fat
Cutaneous features	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women	Acanthosis nigricans and skin tags; hirsutism common in women
Musculoskeletal	Acromegaloid features common	Acromegaloid features common	Frequent muscle hypertrophy; some have overlap features of muscular dystrophy	Muscle hypertrophy
Nonalcoholic fatty liver disease	Severe	Severe	Yes	Yes
Dyslipidemia	Severe; associated with pancreatitis	Severe; associated with pancreatitis	Yes, may be severe	Yes, may be severe
Insulin resistance	Severe; early onset	Severe; early onset	Severe	Severe; early onset in some
Diabetes onset	<20 yr	<20 yr	Variable; generally later in men than women	Variable; generally later in men than women
Hypertension	Common	Common	Common	Very common
Other		Mild mental retardation possible		

From Semple RK, Savage DB, Halsall DJ, O'Rahilly S. Syndromes of severe insulin resistance and/or lipodystrophy. In Weiss RE, Refetoff S, eds. *Genetic Diagnosis of Endocrine Disorders*. Philadelphia: Elsevier; 2010: Table 4.2.

and very high titers of glutamic acid decarboxylase antibodies. About one third of patients also develop T1DM.

Systemic Lupus Erythematosus

In rare cases, patients with systemic lupus erythematosus may develop autoantibodies to the insulin receptor, leading to insulin resistance and diabetes.

CYSTIC FIBROSIS–RELATED DIABETES

See Chapter 454.

As patients with cystic fibrosis (CF) live longer, an increasing number are being diagnosed with **cystic fibrosis–related diabetes (CFRD)**; up to 20% of children and 50% of adults are affected with CFRD. There is an association with pancreatic insufficiency, and there may be a higher risk in patients with class I and class II CF transmembrane conductance regulator variants. Cross-sectional studies indicate that the prevalence of IGT may be significantly higher than this, and up to 65% of children with CF have diminished first-phase insulin secretion, even when they have normal glucose tolerance. In Denmark, oral glucose tolerance screening of the entire CF population demonstrated no diabetes in patients younger than 10 years, diabetes in 12% of patients age 10-19 years, and diabetes in 48% of adults age 20 years and older.

Patients with CFRD have features of both T1DM and T2DM. In the pancreas, exocrine tissue is replaced by fibrosis and fat; many of the pancreatic islets are destroyed. The remaining islets demonstrate diminished numbers of β-, α-, and pancreatic polypeptide-secreting cells. Secretion of the islet hormones insulin, glucagon, and pancreatic polypeptide is impaired in patients with CF in response to a variety of secretagogues. This pancreatic damage leads to slowly progressive insulin deficiency, of which the earliest manifestation is an impaired first-phase insulin response. When patients age, this response becomes progressively delayed and less robust than normal. At the same time, these patients develop insulin resistance because of chronic inflammation and the intermittent use of corticosteroids. Insulin deficiency and insulin resistance lead to a gradual onset of IGT that eventually evolves into diabetes. In some cases, diabetes may wax and wane with disease exacerbations and the use of corticosteroids. The clinical presentation is similar to that of T2DM in that the onset of the disease is insidious and the occurrence of ketoacidosis is rare. Islet antibody titers are negative. Microvascular complications do develop but may do so at a slower rate than in typical T1DM or T2DM. Macrovascular complications do not appear to be of concern in CFRD. Several factors unique to CF influence the onset and the course of diabetes: (1) frequent infections are associated with waxing and waning of insulin resistance; (2) energy needs are increased because of infection and pulmonary disease; (3) malabsorption is common, despite enzyme supplementation; (4) nutrient absorption is altered by abnormal intestinal transit time; (5) liver disease is frequently present; (6) anorexia and nausea are common; (7) there is a wide variation in daily food intake based on the patient's acute health status; and (8) both insulin and glucagon secretion are impaired (in contrast to autoimmune diabetes, in which only insulin secretion is affected).

IGT and CFRD are associated with poor weight gain, and there is evidence that treatment with insulin improves weight gain and slows the rate of pulmonary deterioration. Because of these observations, guidelines recommend that routine diabetes screening of all children with CF begin at age 10 years. Despite debate over the ideal screening modality, the recommendation is the 2-hour OGTT, although growing evidence suggests a role for mid-OGTT hyperglycemia at the 1-hour mark as a clinically relevant finding. When hyperglycemia develops, the accompanying metabolic derangements are usually mild, and relatively low doses of insulin usually suffice for adequate management. Basal insulin may be started initially, but basal-bolus therapy similar to that used in T1DM will eventually be needed. Dietary restrictions are minimal, as increased energy needs are present and weight gain is usually desired. Ketoacidosis is uncommon but may occur with progressive deterioration of islet cell function. IGT is not necessarily an indication for treatment, but patients who have poor growth and inadequate weight gain may benefit from the addition of basal insulin even if they do not meet the criteria for a diagnosis of diabetes.

Friedreich Ataxia

Friedreich ataxia (FRDA) is a multisystem neurodegenerative disorder resulting from alterations in *FXN*. Approximately 20% of patients with FRDA will develop diabetes. Individuals with early-onset diabetes during childhood display a phenotype similar to T1DM characterized by insufficient pancreatic insulin secretion, hyperglycemia, and ketosis. Insulin therapy is typically required from diagnosis. By contrast, adults with FRDA who develop diabetes have a phenotype more similar to T2DM, where insulin resistance appears to play a role in the pathogenesis.

DRUGS

High-dose oral or parenteral steroid therapy usually results in significant insulin resistance leading to glucose intolerance and overt diabetes. The immunosuppressive agents cyclosporine and tacrolimus are toxic to β cells, causing IDDM in a significant proportion of patients treated with these agents. Their toxicity to pancreatic β cells was one of the factors that limited their usefulness in arresting ongoing autoimmune destruction of β cells. Streptozotocin and the rodenticide Vacor are also toxic to β cells, causing diabetes.

There are no consensus guidelines regarding treatment of *steroid-induced hyperglycemia* in children. Many patients on high-dose steroids have elevated blood glucose during the day and evening but become normoglycemic late at night and early in the morning. In general, significant hyperglycemia in an inpatient setting is treated with short-acting insulin on an as-needed basis. Basal insulin may be added when fasting hyperglycemia is significant. Outpatient treatment can be more difficult, but when treatment is needed, protocols similar to the basal-bolus regimens used in T1DM are used.

Immune checkpoint inhibitors used to treat malignancies by blocking inhibitory immune receptors have been associated with the rare development of DM and other autoimmune diseases. DM may develop after one to two cycles of therapy and present with DKA. Some are GAD antibody positive; all require insulin therapy.

GENETIC SYNDROMES ASSOCIATED WITH DIABETES MELLITUS

A number of rare genetic syndromes associated with IDDM or carbohydrate intolerance have been described (see Tables 629.1 and 629.17). These syndromes represent a broad spectrum of diseases, ranging from premature cellular aging, as in **Werner** and **Cockayne** syndromes (see Chapter 109), to excessive obesity associated with hyperinsulinism, resistance to insulin action, and carbohydrate intolerance, as in **Prader-Willi syndrome** (see Chapters 97 and 98). Some of these syndromes are characterized by primary disturbances in the insulin receptor or in antibodies to the insulin receptor without any impairment in insulin secretion. Although rare, these syndromes provide unique models to understand the multiple causes of disturbed carbohydrate metabolism from defective insulin secretion or from defective insulin action at the cell receptor or postreceptor level.

AUTOIMMUNE DISEASES ASSOCIATED WITH T1DM

IPEX Syndrome

IPEX (immunodysregulation, polyendocrinopathy, and enteropathy, X-linked) is a genetic syndrome leading to autoimmune disease. In most patients with IPEX, pathogenic variants in *FOXP3,* a specific marker of natural and adaptive regulatory T cells, leads to severe immune dysregulation and rampant autoimmunity. Autoimmune diabetes develops in >90% of cases, usually within the first year of life, and is accompanied by enteropathy, failure to thrive, and other autoimmune disorders.

Autoimmune Polyendocrine Syndromes

Autoimmune polyendocrine syndrome type 1 (APS-1, also known as *APCED*) is a syndrome of multiple endocrinopathy related to pathogenic variants in *AIRE*. It typically first manifests in infancy with

recurrent mucocutaneous candidiasis, followed variably by hypocalcemia (autoimmune hypoparathyroidism), adrenal insufficiency (Addison disease), T1DM, hypothyroidism (Hashimoto disease), celiac disease, and other autoimmune conditions. It is clear that any patient with an autoimmune disease is at increased risk for the development of T1DM (and any patient with T1DM is at increased risk of other autoimmune diseases) and should be counseled regarding the signs and symptoms of new-onset diabetes. See Table 629.11 for recommendations regarding screening tests to look for other autoimmune diseases in patients with T1DM.

Chronic lymphocytic thyroiditis (Hashimoto thyroiditis) is frequently associated with T1DM in children (see Chapter 604). About 20% of patients with insulin-dependent diabetes have thyroid antibodies in their serum; the prevalence is 2-20 times greater than in control populations. Only a small proportion of these patients acquire clinical hypothyroidism; the interval between diagnosis of diabetes and thyroid disease averages about 5 years.

Celiac disease, which is caused by hypersensitivity to dietary gluten, is another autoimmune disorder that occurs with significant frequency in children with T1DM (see Chapter 384). It is estimated that approximately 7–15% of children with T1DM develop celiac disease within the first 6 years of diagnosis, and the incidence of celiac disease is significantly higher in children younger than 4 years of age and in females. Young children with T1DM and celiac disease can present with gastrointestinal symptoms (abdominal cramping, diarrhea, constipation, gastroesophageal reflux), growth failure as a consequence of suboptimal weight gain, unexplained hypoglycemic reactions because of nutrient malabsorption, and less commonly hypocalcemia caused by severe vitamin D malabsorption; in some cases the disease can be asymptomatic.

When diabetes and thyroid disease coexist, the possibility of autoimmune adrenal insufficiency should be considered. It may be heralded by decreasing insulin requirements, increasing pigmentation of the skin and buccal mucosa, salt craving, weakness, asthenia and postural hypotension, or even frank adrenal crisis. This syndrome is unusual in the first decade of life, but it may become apparent in the second decade or later.

Circulating antibodies to gastric parietal cells and to intrinsic factor are 2-3 times more common in patients with T1DM than in control subjects. The presence of antibodies to gastric parietal cells is correlated with atrophic gastritis, and antibodies to intrinsic factor are associated with malabsorption of vitamin B_{12}. However, megaloblastic anemia is rare in children with T1DM.

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