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391 Hypopituitarism

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Hypopituitarism Deficient production of anterior pituitary hormones leads to features of hypopituitarism. Impaired production of one or more of the anterior pituitary trophic hormones can result from inherited disorders; more commonly, adult hypopituitarism is acquired and reflects the com pressive mass effects of tumors or the consequences of local pituitary or hypothalamic traumatic, autoimmune, inflammatory, or vascular damage. These processes also may impair synthesis or secretion of hypothalamic hormones, with resultant pituitary failure (Table 391-1). PART 12 Endocrinology and Metabolism ■ ■DEVELOPMENTAL CAUSES OF HYPOPITUITARISM Pituitary dysplasia may result in aplastic, hypoplastic, or ectopic pituitary gland development. Because pituitary development follows midline cell migration from the nasopharyngeal Rathke's pouch, mid line craniofacial disorders may be associated with pituitary dysplasia. Acquired pituitary failure in the newborn also can be caused by birth trauma, including cranial hemorrhage, asphyxia, and breech delivery. A large number (>50) of transcription factors and growth factors are critical for the development of the hypothalamus and pituitary gland and the function of differentiated anterior pituitary cell lineages. Muta tions have been described in the HESX1, SOX2, SOX3, LHX3, LHX4, OTX, GLI2, PAX6, BMP4, ARNT2, FGF8, FGFR1, SHH, PROKR2, GPR161, IGSF1, PITX2, and CHD7 genes, among others. Heterozygous loss-of-function or autosomal recessive mutations disrupt hypothalamic and pituitary development at different developmental stages, causing a wide array of phenotypes ranging from severe syndromic midline and other defects to combined pituitary hormone defects or isolated hor mone deficiencies. Depending on the gene involved, the pituitary may be hypoplastic, hyperplastic, or ectopic. Midline defects include variable combinations of abnormal development of the eyes, corpus collosum, vertebrae, and genital systems. Pituitary dysfunction ranges from iso lated hormone deficiency to combined pituitary hormone deficiency (CPHD) and arginine vasopressin deficiency (AVP-D). In addition to these syndromic developmental disorders, some mutations affect specific pituitary cell lineages. For example, Pit-1 mutations cause combined growth hormone (GH), prolactin (PRL), and thyroid-stimulating hormone (TSH) deficiencies. These patients usually present with growth failure and varying degrees of hypothy roidism. The pituitary may appear hypoplastic on magnetic resonance imaging (MRI). Prop-1 is expressed early in pituitary development and appears to be required for Pit-1 function. Familial and sporadic PROP1 mutations result in combined GH, PRL, TSH, and gonado tropin deficiency. Over 80% of these patients have growth retarda tion; by adulthood, all are deficient in TSH and gonadotropins, and a small minority later develop adrenocorticotropic hormone (ACTH) deficiency. Because of gonadotropin deficiency, these individuals do not enter puberty spontaneously. In some cases, the pituitary gland appears enlarged on MRI. TPIT mutations result in ACTH deficiency associated with hypocortisolism. Mutations in NR5A1 (also known as steroidogenic factor 1 [SF1]) impair development of gonadotropes, as well as adrenal/gonadal development. ■ ■HYPOTHALAMIC ENDOCRINE DYSFUNCTION Hypothalamic disorders can affect temperature regulation, appetite, sleep-wake cycles, autonomic systems, behavior, and memory, as well as multiple endocrine systems. Selected examples of hypothalamic disorders that affect the endocrine system are described below. Kallmann Syndrome Kallmann syndrome results from defective hypothalamic gonadotropin-releasing hormone (GnRH) synthesis and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia (Chap. 403). Classically, the syndrome may also be associated with color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism, and neurologic abnormalities

TABLE 391-1 Etiology of Hypopituitarisma Development/structural Midline cerebral defect syndromes Pituitary dysplasia/aplasia Primary empty sella Congenital hypothalamic disorders (septo-optic dysplasia, Prader-Willi syndrome, Bardet-Biedl syndrome, Kallmann syndrome) Congenital central nervous system mass, encephalocele Genetic Combined pituitary hormone deficiencies Isolated primary hormone deficiencies Traumatic Surgical resection Radiotherapy damage Head injuries Neoplastic Pituitary adenoma Parasellar mass (germinoma, ependymoma, glioma) Rathke’s cyst Craniopharyngioma Hypothalamic hamartoma, gangliocytoma Pituitary metastases (breast, lung, colon carcinoma) Lymphoma and leukemia Meningioma Infiltrative/inflammatory Lymphocytic hypophysitis Hemochromatosis Sarcoidosis Histiocytosis X Granulomatous hypophysitis Transcription factor antibodies Immunotherapy Vascular Pituitary apoplexy Pregnancy-related (infarction with diabetes; postpartum necrosis) Subarachnoid hemorrhage Sickle cell disease Arteritis Snake bite venom Infections Fungal (histoplasmosis) Parasitic (toxoplasmosis) Tuberculosis Pneumocystis jirovecii Drug-induced CTLA-4 inhibitors PD-1/PD-L1 inhibitors aTrophic hormone failure associated with pituitary compression or destruction usually occurs sequentially: growth hormone > follicle-stimulating hormone > luteinizing hormone > thyroid-stimulating hormone > adrenocorticotropic hormone. During childhood, growth retardation is often the presenting feature, and in adults, hypogonadism is the earliest symptom. Abbreviations: CTLA-4, cytotoxic T lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1. such as mirror movements. The initial genetic cause was the X-linked KAL gene, mutations of which impair embryonic migration of GnRH neurons from the hypothalamic olfactory placode to the hypothalamus. Since then, more than a dozen additional genetic abnormalities, in addition to KAL mutations, have been found to cause isolated GnRH deficiency. Autosomal recessive (i.e., GPR54, KISS1) and dominant (i.e., FGFR1) modes of transmission have been described, and there is a growing list of genes associated with GnRH deficiency (including GNRH1, PROK2, PROKR2, CHD7, PCSK1, FGF8, NELF, WDR11, TAC3, TACR3, and SEMA3E). Some patients have oligogenic

mutations in which mutations in a combination of different genes lead to the phenotype. Associated clinical features, in addition to GnRH deficiency, vary depending on the genetic cause. GnRH deficiency prevents progression through puberty. Males present with delayed puberty and pronounced hypogonadal features, including micro penis, probably the result of low testosterone levels during infancy. Females present with primary amenorrhea and failure of secondary sexual development. Kallmann syndrome and other causes of congenital GnRH deficiency are characterized by low luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels and low concentrations of sex steroids (testosterone or estradiol). In sporadic cases of isolated gonadotropin deficiency, the diagnosis is often one of exclusion after other known causes of hypothalamic-pituitary dysfunction have been eliminated. Repetitive GnRH administration restores normal pituitary gonadotropin responses, pointing to a hypothalamic defect in these patients. Long-term treatment of males with human chorionic gonadotropin (hCG) or testosterone restores pubertal development and secondary sex characteristics; women can be treated with cyclic estrogen and progestin. Fertility may be restored by the administration of gonado tropins or by using a portable infusion pump to deliver subcutaneous, pulsatile GnRH. Bardet-Biedl Syndrome This very rare genetically heterogeneous disorder is characterized by intellectual disability, renal abnormalities, obesity, and hexadactyly, brachydactyly, or syndactyly. Central AVP-D may or may not be associated. GnRH deficiency occurs in 75% of males and half of affected females. Retinal degeneration begins in early childhood, and most patients are blind by age 30. Numerous subtypes of Bardet-Biedl syndrome have been identified, with genetic linkage to at least nine different loci. Several of the loci encode genes involved in basal body cilia function, and this may account for the diverse clinical manifestations. Leptin and Leptin Receptor Mutations Deficiencies of leptin or its receptor cause a broad spectrum of hypothalamic abnormalities, including hyperphagia, obesity, and central hypogonadism (Chap. 413). Decreased GnRH production in these patients results in attenuated pituitary FSH and LH synthesis and release. Prader-Willi Syndrome This is a contiguous gene syndrome that results from deletion of the paternal copies of the imprinted SNRPN gene, the NECDIN gene, and possibly other genes on chromosome 15q. Prader-Willi syndrome is associated with hypogonadotropic hypogo nadism, hyperphagia-obesity, chronic muscle hypotonia, intellectual disability, and adult-onset diabetes mellitus. Multiple somatic defects also involve the skull, eyes, ears, hands, and feet. Diminished hypo thalamic oxytocin- and AVP-producing nuclei have been reported. Deficient GnRH synthesis is suggested by the observation that chronic GnRH treatment restores pituitary LH and FSH release. ■ ■ACQUIRED HYPOPITUITARISM Hypopituitarism may be caused by accidental or neurosurgical trauma; vascular events such as apoplexy; pituitary or hypothalamic neoplasms, craniopharyngioma, lymphoma, or metastatic tumors; inflammatory disease such as lymphocytic hypophysitis; autoimmune hypophysitis associated with checkpoint inhibitor cancer immunotherapy; infiltra tive disorders such as sarcoidosis, hemochromatosis (Chap. 426), and tuberculosis; or irradiation. Patients with brain injury, including from contact sports trauma, motor vehicle accidents, explosive causes, subarachnoid hemorrhage, and irradiation, can experience transient or long-term hypopituita rism. These traumatic and vascular conditions likely account for about 5% of hypopituitarism, reflecting the growing prevalence and recogni tion of these disorders. Long-term periodic endocrine follow-up is indicated because hypothalamic or pituitary dysfunction will develop in 25–40% of these patients. Hypothalamic Infiltration Disorders Sarcoidosis, histiocy tosis X, amyloidosis, and hemochromatosis frequently involve both

hypothalamic and pituitary neuronal and neurochemical tracts. Con sequently, AVP-D is a common presentation, reported in half of patients with these disorders. Growth retardation is seen if attenuated GH secretion occurs before puberty. Hypogonadotropic hypogonad ism and hyperprolactinemia are also common.

Inflammatory Lesions Pituitary damage and subsequent secre tory dysfunction can be seen with chronic site infections such as tuber culosis, with opportunistic fungal infections associated with AIDS, and in tertiary syphilis. Other inflammatory processes, such as granulomas and sarcoidosis, should be considered in the differential diagnosis of imaging studies suggestive of a pituitary adenoma. These lesions may cause extensive hypothalamic and pituitary damage, leading to hor mone deficiencies. Hypopituitarism CHAPTER 391 Cranial Irradiation Cranial irradiation may result in long-term hypothalamic and pituitary dysfunction, especially in children and adolescents, as they are more susceptible to damage after whole-brain or head and neck therapeutic irradiation. The development of sub sequent hormonal abnormalities correlates strongly with irradiation dosage and the time interval after completion of radiotherapy. Up to two-thirds of patients ultimately develop hormone insufficiency after a median dose of 50 Gy (5000 rad) directed at the skull base. The devel opment of hypopituitarism occurs over 5–15 years and usually reflects hypothalamic damage rather than primary destruction of pituitary cells. Although the pattern of hormone loss is variable, GH deficiency is most common, followed by gonadotropin, TSH, and ACTH defi ciency. When deficiency of one or more hormones is documented, the possibility of diminished reserve of other hormones is likely. Accord ingly, anterior pituitary function should be continually evaluated over the long term in previously irradiated patients, and replacement therapy instituted when appropriate (see below). Lymphocytic Hypophysitis This occurs most often in post partum women; it usually presents with hyperprolactinemia and MRI evidence of a prominent pituitary mass that often resembles an adenoma, with mildly elevated PRL levels. Pituitary failure caused by diffuse lymphocytic infiltration may be transient or permanent but requires immediate evaluation and treatment. Rarely, isolated pituitary hormone deficiencies have been described, suggesting a selective auto immune process targeted to specific cell types. Most patients manifest symptoms of progressive mass effects with headache and visual distur bance. The erythrocyte sedimentation rate often is elevated. Because it may be indistinguishable from a pituitary adenoma on MRI, hypophy sitis should be considered in a postpartum woman with a newly diagnosed pituitary mass before an unnecessary surgical intervention is undertaken. The inflammatory process often resolves after several months of glucocorticoid treatment, and pituitary function may be restored, depending on the extent of damage. Immunotherapy and Hypophysitis Pituitary cells express cyto toxic T lymphocyte antigen-4 (CTLA-4), and up to 20% of patients receiving cancer immunotherapy with CTLA-4 inhibitors (e.g., ipi limumab) may develop hypophysitis with heterogeneously associ ated thyroid, adrenal, islet, and gonadal failure. Hypophysitis is also reported with PD-1/PD-L1 inhibitors (e.g., pembrolizumab and nivolumab) and may show delayed presentation. HLA type DQ0602 is associated with checkpoint inhibitor–associated hypophysitis in 39% of such patients. Pituitary hormone replacement, with or without high-dose glucocorticoids, may be safely tolerated with continued immunotherapy. Pituitary Apoplexy Acute intrapituitary hemorrhagic vascular events can cause substantial damage to the pituitary and surround ing sellar structures. Pituitary apoplexy may occur spontaneously in a preexisting pituitary adenoma; postpartum (Sheehan's syndrome); or in association with diabetes, hypertension, sickle cell anemia, or acute shock. The hyperplastic enlargement of the pituitary, which occurs normally during pregnancy, increases the risk for hemorrhage and infarction. Apoplexy is an endocrine emergency that may result in severe hypoglycemia, hypotension and shock, central nervous system

(CNS) hemorrhage, and death. Acute symptoms may include severe headache with signs of meningeal irritation, bilateral visual changes, ophthalmoplegia, and, in severe cases, cardiovascular collapse and loss of consciousness. Pituitary computed tomography (CT) or MRI may reveal signs of intratumoral or sellar hemorrhage, with pituitary stalk deviation and compression of pituitary tissue.

Patients with no evident visual loss or impaired consciousness can be observed and managed conservatively with high-dose glucocorti coids. Those with significant or progressive visual loss, cranial nerve palsy, or loss of consciousness require urgent surgical decompression. Visual recovery after sellar surgery is inversely correlated with the length of time after the acute event. Therefore, severe ophthalmoplegia or visual deficits are indications for early surgery. Hypopituitarism is common after apoplexy. PART 12 Endocrinology and Metabolism Empty Sella A partial or apparently totally empty sella is often an incidental MRI finding and may sometimes be associated with intracranial hypertension. These patients usually have normal pitu itary function, implying that the surrounding rim of pituitary tissue is fully functional. Hypopituitarism, however, may develop insidiously. Pituitary adenomas also may undergo clinically silent infarction and involution with development of a partial or totally empty sella by cerebrospinal fluid (CSF) filling the dural herniation. Rarely, small but functional pituitary adenomas may arise within the rim of normal pituitary tissue, and they are not always visible on MRI. ■ ■PRESENTATION AND DIAGNOSIS The clinical manifestations of hypopituitarism depend on which hormones are lost and the extent of the hormone deficiency (see below). GH deficiency causes growth disorders in children and leads to abnormal body composition in adults. Gonadotropin deficiency causes menstrual disorders and infertility in women and decreased sexual function, infertility, and loss of secondary sexual characteris tics in men. TSH and ACTH deficiencies usually develop later in the course of pituitary failure. TSH deficiency causes growth retardation in children and features of hypothyroidism in children and adults. Secondary adrenal insufficiency caused by ACTH deficiency leads to hypocortisolism with relative preservation of mineralocorticoid production. PRL deficiency causes failure of lactation. When lesions involve the posterior pituitary, polyuria and polydipsia reflect loss of AVP secretion. In patients with long-standing pituitary damage, epi demiologic studies document an increased mortality rate, primarily from increased cardiovascular and cerebrovascular disease. Previous head or neck irradiation is also a determinant of increased mortality rates in patients with hypopituitarism, especially from cerebrovascular disease. ■ ■LABORATORY INVESTIGATION Biochemical diagnosis of pituitary insufficiency is made by demon strating low levels of respective pituitary trophic hormones in the setting of low levels of target organ hormones. For example, low free thyroxine in the setting of a low or inappropriately normal TSH level suggests secondary hypothyroidism. Similarly, a low testosterone level without elevation of gonadotropins suggests hypogonadotropic hypogonadism. Provocative tests may be required to assess pituitary reserve (Table 391-2). GH responses to insulin-induced hypogly cemia, arginine, glucagon, l-dopa, growth hormone–releasing hor mone (GHRH), or growth hormone–releasing orally active ghrelin receptor agonist macimorelin can be used to assess GH reserve. Corticotropin-releasing hormone (CRH) administration induces ACTH release, and administration of synthetic ACTH (cosyntropin) evokes adrenal cortisol release as an indirect indicator of pituitary ACTH reserve (Chap. 398). ACTH reserve is most reliably assessed by measuring ACTH and cortisol levels during insulin-induced hypoglycemia. However, this test should be performed cautiously in patients with suspected adrenal insufficiency because of enhanced susceptibility to hypoglycemia and hypotension. Administering insu lin to induce hypoglycemia is contraindicated in patients with active coronary artery disease or known seizure disorders.

TREATMENT Hypopituitarism Hormone replacement therapy, including glucocorticoids, thyroid hormone, sex steroids, GH, and AVP, is usually safe and free of complications. Treatment regimens that mimic physiologic hor mone production allow for maintenance of satisfactory clinical homeostasis. Effective dosage schedules are outlined in Table 391-3. Patients in need of glucocorticoid replacement require especially careful dose adjustments during stressful events such as acute ill ness, dental procedures, trauma, and hospitalization. ■ ■DISORDERS OF GROWTH

AND DEVELOPMENT Skeletal Maturation and Somatic Growth The growth plate is dependent on a variety of hormonal stimuli, including GH, insulinlike growth factor (IGF)-1, sex steroids, thyroid hormones, paracrine and circulating growth factors (e.g., fibroblast growth factor family), and cytokines. The growth-promoting process also requires caloric energy, amino acids, vitamins, and trace metals and consumes ~10% of normal energy production. Malnutrition impairs chondrocyte activity, increases GH resistance, and leads to reduced circulating IGF-1 and IGF binding protein (IGFBP)-3 levels. Linear bone growth rates are very high in infancy and are pituitary dependent. Mean growth velocity is ~6 cm/year in later childhood and usually is maintained within a given range on a standardized percen tile chart. Peak growth rates occur during midpuberty when bone age is 12 (girls) or 13 (boys). Secondary sexual development is associated with elevated sex steroids that cause progressive epiphyseal growth plate closure. Bone age is delayed in patients with all forms of true GH deficiency or GH receptor defects that result in attenuated GH action. Short stature may occur as a result of constitutive intrinsic growth defects or because of acquired extrinsic factors that impair growth. In general, delayed bone age in a child with short stature is suggestive of a hormonal or systemic disorder, whereas normal bone age in a short child is more likely to be caused by a genetic cartilage dysplasia or growth plate disorder (Chap. 425). GH Deficiency in Children Isolated GH deficiency is character ized by short stature, micropenis, increased fat, high-pitched voice, and a propensity to hypoglycemia due to relatively unopposed insulin action. Familial modes of inheritance are seen in at least one-third of these individuals and may be autosomal dominant, recessive, or X-linked. About 10% of children with GH deficiency have mutations in the GH-N gene, including gene deletions and a wide range of point mutations. Mutations in transcription factors Pit-1 and Prop-1, which control somatotrope development (see above), result in GH deficiency in combination with other pituitary hormone deficiencies, which may become manifest only in adulthood. The diagnosis of idiopathic GH deficiency should be made only after known molecular defects have been rigorously excluded. GHRH RECEPTOR MUTATIONS Recessive mutations of the GHRH receptor gene in subjects with severe proportionate dwarfism are asso ciated with low basal GH levels that cannot be stimulated by exogenous GHRH, GH-releasing peptide, or insulin-induced hypoglycemia, as well as anterior pituitary hypoplasia. The syndrome exemplifies the importance of the GHRH receptor for determining somatotrope pro liferation and hormonal responsiveness. GH INSENSITIVITY This is caused by defects of GH receptor structure or signaling. Homozygous or heterozygous mutations of the GH recep tor are associated with partial or complete GH insensitivity and growth failure (Laron syndrome). The diagnosis is based on normal or high GH levels, with decreased circulating GH-binding protein (GHBP), and low IGF-1 levels. Very rarely, defective IGF-1, IGF-1 receptor, or IGF-1 signaling defects are also encountered. STAT5B mutations result in both immunodeficiency as well as abrogated GH signaling, leading to short stature with normal or elevated GH levels and low IGF-1 levels. Circulat ing GH receptor antibodies may rarely cause peripheral GH insensitivity.

TABLE 391-2 Tests of Pituitary Sufficiency HORMONE TEST BLOOD SAMPLES INTERPRETATION GH Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV) –30, 0, 30, 60, 120 min for glucose and GH GHRH/L-arginine test: GHRH 1 µg/kg IV and arginine 30 g IV over 30 min 0, 15, 30, 45, 60, 120 min for GH Normal GH response is BMI dependent: 11 µg/L if BMI

<25 kg/m2, 8 µg/L if BMI 25-20, and 4 µg/L if BMI ≥30 Not available in the United States Ghrelin receptor agonist test: 0.5 mg/kg PO 0, 30, 45, 60, 90 min for GH Normal response is GH >2.8 µg/L Glucagon test: 1 mg IM (1.5 mg if body weight >90 kg) 0, 30, 60, 90, 120, 150, 180, 210, 240 for

GH l-Dopa test: 500 mg PO 0, 30, 60, 120 min for GH Normal response is GH >3 μg/L PRL TRH test: 200–500 μg IV 0, 20, and 60 min for TSH and PRL Normal PRL is >2 μg/L and increase >200% of baseline ACTH Insulin tolerance test: Regular insulin (0.05–0.15 U/kg IV) –30, 0, 30, 60, 90 min for glucose and cortisol CRH test: 1 μg/kg CRH IV at 8 a.m. 0, 15, 30, 60, 90, 120 min for ACTH and cortisol Metyrapone test: Metyrapone (30 mg/kg) at midnight Plasma 11-deoxycortisol and cortisol at 8 a.m.; ACTH can also be measured Standard ACTH stimulation test: ACTH 1-24 (cosyntropin), 0.25 mg IM or IV 0, 30, 60 min for cortisol and aldosterone Low-dose ACTH test: ACTH 1-24 (cosyntropin), 1 μg IV 0, 30, 60 min for cortisol Cortisol should be >21 μg/dL 3-day ACTH stimulation test consists of 0.25 mg ACTH 1-24 given IV over 8 h each day Cortisol >21 μg/dL TSH Basal thyroid function tests: T4, T3, TSH Basal measurements Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased indicate pituitary insufficiency TRH test: 200–500 μg IV 0, 20, 60 min for TSH and PRLa TSH should increase by >5 mU/L unless thyroid hormone levels are increased LH, FSH LH, FSH, testosterone, estrogen Basal measurements Basal LH and FSH should be increased in postmenopausal women Low testosterone levels in the setting of low LH and FSH indicate pituitary insufficiency GnRH test: GnRH (100 μg) IV 0, 30, 60 min for LH and FSH In most adults, LH should increase by 10 IU/L and FSH by 2 IU/L Normal responses are variable Multiple hormones Combined anterior pituitary test: GHRH (1 μg/kg), CRH (1 μg/kg), GnRH (100 μg), TRH (200 μg) are given IV –30, 0, 15, 30, 60, 90, 120 min for GH, ACTH, cortisol, LH, FSH, and TSH aEvoked PRL response indicates lactotrope integrity. Abbreviations: T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin-releasing hormone. For other abbreviations, see text. NUTRITIONAL SHORT STATURE Caloric deprivation and malnutri tion, uncontrolled diabetes, and chronic renal failure represent sec ondary causes of abrogated GH receptor function. These conditions also stimulate production of proinflammatory cytokines, which act to exacerbate the block of GH-mediated signal transduction. Children with these conditions typically exhibit features of acquired short stature with normal or elevated GH and low IGF-1 levels. PSYCHOSOCIAL SHORT STATURE Emotional and social deprivation lead to growth retardation accompanied by delayed speech, discordant hyperphagia, and an attenuated response to administered GH. A nur turing environment restores growth rates. ■ ■PRESENTATION AND DIAGNOSIS Short stature is commonly encountered in clinical practice, and the decision to evaluate these children requires clinical judgment in asso ciation with auxologic data and family history. Short stature should be evaluated comprehensively if a patient’s height is >3 standard deviations below the mean for age or if the growth rate has decelerated. Skeletal maturation is best evaluated by measuring a radiologic bone

Glucose <40 mg/dL; GH should be >3 μg/L Normal response is GH >3.0 μg/L if BMI <25 kg/m2 or if BMI 25-30 and low pretest probability, and GH >1.0 μg/L if BMI 25-30 and high pretest probability or if BMI >30 Hypopituitarism CHAPTER 391 Glucose <40 mg/dL Cortisol should increase by >7 μg/dL or to >20 μg/dL Basal ACTH increases 2- to 4-fold and peaks at

20–100 pg/mL Cortisol levels >20–25 μg/dL Plasma cortisol should be <4 g/dL to assure an adequate response Normal response is 11-deoxycortisol >7.5 μg/dL or

ACTH >75 pg/mL Normal response is cortisol >21 μg/dL and aldosterone response >4 ng/dL above baseline Combined or individual releasing hormone responses must be elevated in the context of basal target gland hormone values and may not be uniformly diagnostic (see text) age, which is based mainly on the degree of wrist bone growth plate fusion. Final height can be predicted using standardized scales (BayleyPinneau or Tanner-Whitehouse) or estimated by adding 6.5 cm (boys) or subtracting 6.5 cm (girls) from the midparental height. ■ ■LABORATORY INVESTIGATION Because GH secretion is pulsatile, GH deficiency is best assessed by examining the response to provocative stimuli, including exercise, insulin-induced hypoglycemia, and other pharmacologic tests that normally increase GH to >7 μg/L in children. Random GH measure ments do not distinguish children with normal GH levels from those with true GH deficiency. Adequate adrenal and thyroid hormone replacement should be assured before testing. Age-matched IGF-1 levels are not sufficiently sensitive or specific to make the diagno sis but can be useful to confirm GH deficiency. Pituitary MRI may reveal pituitary mass lesions or structural defects. Molecular analyses for known mutations should be undertaken when the cause of short stature remains cryptic or when additional clinical features suggest a genetic cause.

TABLE 391-3 Hormone Replacement Therapy for Adult Hypopituitarisma HORMONE DEFICIT HORMONE REPLACEMENT ACTH Hydrocortisone (10–20 mg/d in divided doses) Cortisone acetate (15–25 mg/d in divided doses) Prednisone (5 mg a.m.) TSH l-Thyroxine (0.075–0.15 mg daily) FSH/LH Males Testosterone gel (5–10 g/d) Testosterone skin patch (5 mg/d) PART 12 Endocrinology and Metabolism Testosterone enanthate (200 mg IM every 2 weeks) Females Conjugated estrogen (0.65–1.25 mg qd for 25 days) Progesterone (5–10 mg qd) on days 16–25 Estradiol skin patch (0.025–0.1 mg every week), adding progesterone on days 16–25 if uterus intact For fertility: menopausal gonadotropins, human chorionic gonadotropins GH Adults: Somatotropin (0.1–1.25 mg SC qd) Children: Somatotropin (0.02–0.05 mg/kg per day) AVP Intranasal desmopressin (5–20 g twice daily) Oral 300–600 μg qd aAll doses shown should be individualized for specific patients and should be reassessed during stress, surgery, or pregnancy. Male and female fertility requirements should be managed as discussed in Chaps. 403 and 404. Note: For abbreviations, see text. TREATMENT Disorders of Growth and Development Replacement therapy with recombinant GH (0.02–0.05 mg/kg per day SC) restores growth velocity in GH-deficient children to ~10 cm/year. If pituitary insufficiency is documented, other associ ated hormone deficits should be corrected, especially adrenal ste roids. In selected situations, GH treatment may be combined with strategies to delay puberty (e.g., GnRH agonist) or reduce sex ste roids (e.g., aromatase inhibitors) as a means to mitigate sex steroid effect on epiphyseal closure. GH treatment is also moderately effec tive for accelerating growth rates in children with Turner syndrome and chronic renal failure. Treating psychosocial or constitutional (idiopathic) short stature with GH is not uniformly recommended as these children may only experience modest additive growth, which should be weighed against GH cost and side effect profiles. In patients with GH insensitivity and growth retardation due to mutations of the GH receptor, treatment with IGF-1 bypasses the dysfunctional GH receptor. ADULT GH DEFICIENCY Adult GH deficiency (AGHD) usually is caused by acquired hypotha lamic or pituitary somatotrope damage. Acquired pituitary hormone deficiency follows a typical pattern in which loss of adequate GH reserve foreshadows subsequent hormone deficits. The sequential order of hormone loss is usually GH → FSH/LH → TSH → ACTH. Patients previously diagnosed with childhood-onset GH deficiency should be retested as adults to affirm the diagnosis. ■ ■PRESENTATION AND DIAGNOSIS The clinical features of AGHD include changes in body composi tion, lipid metabolism, and quality of life as well as cardiovascular dysfunction (Table 391-4). Body composition changes are common and include reduced lean body mass, increased fat mass with selective deposition of intraabdominal visceral fat, and increased waist-to-hip ratio. Hyperlipidemia, left ventricular dysfunction, hypertension, and increased plasma fibrinogen levels also may be present. Bone mineral content is reduced, with resultant increased fracture rates. Patients

TABLE 391-4 Features of Adult Growth Hormone Deficiency Clinical Impaired quality of life Decreased energy and drive Poor concentration Low self-esteem Social isolation Body composition changes Increased body fat mass Central fat deposition Increased waist-to-hip ratio Decreased lean body mass Reduced exercise capacity Reduced maximum O2 uptake Impaired cardiac function Reduced muscle mass Cardiovascular risk factors Impaired cardiac structure and function Abnormal lipid profile Decreased fibrinolytic activity Atherosclerosis Omental obesity Imaging Pituitary: mass or structural damage Bone: reduced bone mineral density Abdomen: excess omental adiposity Laboratory Evoked GH <3 ng/mL IGF-1 and IGFBP-3 low or normal Increased LDL cholesterol Concomitant gonadotropin, TSH, and/or ACTH reserve deficits may be present Abbreviation: LDL, low-density lipoprotein. For other abbreviations, see text. may experience social isolation, depression, and difficulty maintain ing gainful employment. Adult hypopituitarism is associated with a threefold increase in cardiovascular mortality rates in comparison to age- and sex-matched controls, and this may be due to GH deficiency, as patients in these studies were replaced with other deficient pituitary hormones. ■ ■LABORATORY INVESTIGATION AGHD is rare, and in light of the nonspecific nature of associated clinical symptoms, patients appropriate for testing should be selected carefully on the basis of well-defined criteria. With few exceptions, testing should be restricted to patients with the following predisposing factors: (1) pituitary surgery, (2) pituitary or hypothalamic tumor or granulomas, (3) history of cranial irradiation, (4) radiologic evidence of a pituitary lesion, and (5) childhood requirement for GH replace ment therapy. The transition of a GH-deficient adolescent to adult hood requires retesting to document subsequent AGHD. Up to 20% of patients previously treated for childhood-onset GH deficiency are found to be GH sufficient on repeat testing as adults. A significant proportion (~25%) of truly GH-deficient adults have low-normal IGF-1 levels. Thus, as in the evaluation of GH deficiency in children, valid age-matched IGF-1 measurements provide a use ful index of therapeutic responses but are not sufficiently precise for diagnostic purposes. The most validated test to distinguish pituitarysufficient patients from those with AGHD is insulin-induced (0.05– 0.1 U/kg) hypoglycemia. After glucose reduction to ~40 mg/dL, most individuals experience neuroglycopenic symptoms (Chap. 418), and peak GH release occurs at 60 min and remains elevated for up to 2 h. About 90% of healthy adults exhibit GH responses >5 μg/L; AGHD is defined by a peak GH response to hypoglycemia of <3 μg/L. Although insulininduced hypoglycemia is safe when performed under appropriate

History of pituitary pathology Clinical features present Evoked GH <3 μg/L Exclude contraindications Treat with GH 0.1–0.3 mg/d Check IGF-1 after 1 mo Titrate GH dose up to 1.25 mg/d 6 mo No response Response Discontinue Rx Monitor IGF-1 Levels FIGURE 391-1 Management of adult growth hormone (GH) deficiency. IGF, insulinlike growth factor; Rx, treatment. supervision, it is contraindicated in patients with diabetes, ischemic heart disease, cerebrovascular disease, or epilepsy and in elderly patients. Alternative stimulatory tests include intravenous arginine (30 g), GHRH (1 μg/kg), oral ghrelin receptor agonist (0.5 mg/kg), and glucagon (1 mg). Combinations of these tests may evoke GH secretion in subjects who are not responsive to a single test. TREATMENT Adult GH Deficiency Once the diagnosis of AGHD is unequivocally established, replace ment of GH may be indicated. Contraindications to therapy include the presence of an active neoplasm, intracranial hypertension, and uncontrolled diabetes and retinopathy. The starting adult dose of 0.1–0.2 mg/d should be titrated (up to a maximum of 1.25 mg/d) to maintain IGF-1 levels in the mid-normal range for age- and sexmatched controls (Fig. 391-1). Women require higher doses than men, and elderly patients require less GH. Long-term GH maintenance sustains normal IGF-1 levels and is associated with persistent body composition changes (e.g., enhanced lean body mass and lower body fat). High-density lipoprotein cholesterol increases, but total cholesterol and insulin levels may not change significantly. Lumbar spine bone mineral density increases, but this response is gradual (>1 year). Many patients note significant improvement in quality of life when evaluated by standardized questionnaires. The effect of GH replacement on mortality rates in GH-deficient patients is currently the subject of long-term prospective investigation. Recently approved long-acting GH preparations for patients with AGHD require weekly injections. Ideally, dosing should be titrated to achieve normal but not supra-normal IGF-1 levels. Early reports indicate that side effects appear similar to subcutaneous formulations. About 30% of patients exhibit reversible dose-related fluid retention, joint pain, and carpal tunnel syndrome, and up to 40% exhibit myalgias and paresthesia. Patients receiving insulin require careful monitoring for dosing adjustments, as GH is a potent counterregulatory hormone for insulin action. Patients with type 2 diabetes mellitus may initially develop further insulin resistance. However, glycemic control usually improves with the sustained loss of abdominal fat associated with long-term GH replacement. Headache, increased intracranial pressure, hypertension, and tinnitus occur rarely. Pituitary tumor regrowth and progression of skin lesions or other tumors have not been encountered in long-term surveillance programs with appropriate replacement doses.

ACTH DEFICIENCY

■ ■PRESENTATION AND DIAGNOSIS Secondary adrenal insufficiency occurs as a result of pituitary ACTH deficiency. It is characterized by fatigue, weakness, anorexia, nausea, vomiting, and, occasionally, hypoglycemia. In contrast to primary adrenal failure, hypocortisolism associated with pituitary failure usually is not accompanied by hyperpigmentation or mineralocorticoid deficiency. ACTH deficiency is commonly due to glucocorticoid withdrawal after treatment-associated suppression of the hypothalamic-pituitaryadrenal (HPA) axis. Isolated ACTH deficiency may occur after surgical resection of an ACTH-secreting pituitary adenoma that has suppressed the HPA axis; this phenomenon is in fact suggestive of a surgical cure. The mass effects of other pituitary adenomas or sellar lesions may lead to ACTH deficiency, usually in combination with other pituitary hormone deficiencies. Partial ACTH deficiency may be unmasked in the presence of an acute medical or surgical illness, when clinically significant hypocortisolism reflects diminished ACTH reserve. Rarely, TPIT or POMC mutations result in primary ACTH deficiency. Hypopituitarism CHAPTER 391 ■ ■LABORATORY DIAGNOSIS Inappropriately low ACTH levels in the setting of low cortisol levels are characteristic of diminished ACTH reserve. Low basal serum cortisol levels are associated with blunted cortisol responses to ACTH stimulation and impaired cortisol response to insulin-induced hypoglycemia or testing with metyrapone or CRH. For a description of provocative ACTH tests, see Chap. 398. TREATMENT ACTH Deficiency Glucocorticoid replacement therapy improves most features of ACTH deficiency. The total daily dose of hydrocortisone replacement preferably should not exceed 20 mg daily, divided into two or three doses. Prednisone (5 mg each morning) is longer acting and has fewer mineralocorticoid effects than hydrocortisone. Some authorities advocate lower maintenance doses in an effort to avoid cushingoid side effects. Doses should be increased severalfold during periods of acute illness or stress. Patients should wear medical alert bracelets and/or carry identification cards with information about their glucocorticoid requirements. GONADOTROPIN DEFICIENCY Hypogonadism is the most common presenting feature of adult hypo pituitarism even when other pituitary hormones are also deficient. It is often a harbinger of hypothalamic or pituitary lesions that impair GnRH production or delivery through the pituitary stalk. As noted below, hypogonadotropic hypogonadism is a common presenting fea ture of hyperprolactinemia. A variety of inherited and acquired disorders are associated with isolated hypogonadotropic hypogonadism (Chap. 403). Hypothalamic defects associated with GnRH deficiency include Kallmann syndrome and mutations in more than a dozen genes that regulate GnRH neu ron migration, development, and function (see above). Mutations in GPR54, DAX1, NR5A1, kisspeptin, the GnRH receptor, and the LHβ or FSHβ subunit genes also cause pituitary gonadotropin deficiency. Acquired forms of GnRH deficiency leading to hypogonadotropism are seen in association with anorexia nervosa, stress, starvation, and extreme exercise but also may be idiopathic. Hypogonadotropic hypo gonadism in these disorders is reversed by removal of the stressful stimulus or by caloric replenishment. ■ ■PRESENTATION AND DIAGNOSIS In premenopausal women, hypogonadotropic hypogonadism presents as diminished ovarian function leading to oligomenorrhea or amenor rhea, infertility, decreased vaginal secretions, decreased libido, and breast atrophy. In hypogonadal adult men, secondary testicular failure

Revision #1
Created 2026-01-06 16:35:10 UTC by Omar Ayman
Updated 2026-01-06 16:35:10 UTC by Omar Ayman