



Wassily Kandinsky (1866-1944). *Improvisation 26*, 1912.

Early diagnosis and treatment are necessary to ensure the best possible outcomes in children with hypopituitarism.

Hypopituitarism in Childhood

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Background: *Childhood hypopituitarism may be present at birth or may be acquired. Early diagnosis and treatment promote the best possible outcomes.*

Methods: *The anatomy, etiologies, clinical presentation, diagnostic testing strategies, and current treatments relevant to childhood hypopituitarism are reviewed.*

Results: *Children with congenital hypopituitarism may present with life-threatening hypoglycemia, abnormal serum sodium concentrations, shock, microphallus in males, and, only later, growth failure. Causes of congenital hypopituitarism include septo-optic dysplasia, other midline syndromes, and mutations of transcription factors involved in pituitary gland development. Children with acquired hypopituitarism typically present with growth failure and may have other complaints depending on the etiology and the extent of missing pituitary hormones. Acquired hypopituitarism may result from tumors (most commonly craniopharyngioma), radiation, infection, hydrocephalus, vascular anomalies, and trauma.*

Conclusions: *An MRI of the head is critical in determining the etiology. Testing for pituitary hormone deficiencies is undertaken along with appropriate hormonal replacement and, in some cases, direct treatment of the cause of the hypopituitarism. All children with hypopituitarism require coordination of medical care by a pediatric endocrinologist and, when older, transition to the care of an internist endocrinologist. Referrals to a reproductive endocrinologist may be required as fertility issues arise.*

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Introduction

Hypopituitarism refers to the absence or reduction in function of two or more hormones produced by the pituitary gland. When all pituitary hormones are affected, the term *panhypopituitarism* should be used. In childhood cases, one must consider whether the hypopituitarism has its origin before or at birth or is acquired at any time after birth. The younger the child is at the time of presentation, the more likely the etiology is to be con-

genital. However, on occasion, congenital forms may present or be diagnosed well after birth and, conversely, some children with acquired forms are discovered relatively early in life. The purpose of this review is to discuss the causes of, relevant diagnostic modalities for, and treatment of hypopituitarism in childhood.

Anatomy

The adult pituitary gland is a pea-sized midline structure located below the optic chiasm. It hangs down on a pedicle (the hypothalamic-pituitary stalk) from the inferior portion of the hypothalamus. The pituitary gland contains two anatomical components. The anterior portion, also known as the adenohypophysis, receives its signals through the portal system of blood vessels that arise in the hypothalamus and traverse the stalk. The posterior section, also known as the neurohypophysis, receives its signals through axons that arise in neural bodies within the hypothalamus and also traverse down the stalk. Embryologically, the anterior pituitary gland is derived from Rathke's pouch, an evagination of the stomodeal ectoderm. In contrast, the posterior pituitary arises in the infundibulum, a part of the diencephalon.¹

Most cases of childhood hypopituitarism, especially those that develop after birth, result from diseases of the hypothalamus and the stalk that result in a failure of the normal hypothalamic signals to reach the pituitary gland. In other words, the pituitary gland is usually fully functional but is unable to produce normal levels of its stimulating hormones because it does not receive the proper stimulation by the hypothalamic-releasing hormones or factors.² Therefore, if patients with hypopituitarism could be treated with the appropriate types and doses of hypothalamic-stimulating hormones, nor-

mal hormonal production by the pituitary gland could be restored. Thus, the term hypopituitarism, while convenient, is technically incorrect. Children with congenital hypopituitarism and adults with hypopituitarism are more likely to have primary diseases of the pituitary gland compared to children with acquired hypopituitarism, in whom hypothalamic and stalk disease is much more common.

As can be seen on a normal head magnetic resonance imaging (MRI) scan, the anterior pituitary, on T1-weighted imaging, appears dark and equal in intensity to gray matter, while the posterior pituitary gland appears white and is referred to, radiologically, as the posterior "bright spot" (Fig 1A).³ This difference may reflect a layer of fat within or around the posterior pituitary. In some cases of congenital hypopituitarism, this "bright spot" is completely absent and correlates well with the clinical presence of diabetes insipidus (DI). In other cases of congenital hypopituitarism, the "bright spot" is found ectopically in an anatomical location in the normal pathway of posterior pituitary embryologic development (either at the base of the hypothalamus or in the stalk), in which case DI is usually absent (Fig 1B). Such radiological findings are sometimes helpful in securing the congenital nature of hypopituitarism. In acquired forms of hypopituitarism in which DI develops either spontaneously or postoperatively, the "bright spot" is typically absent.

Causes of Congenital Hypopituitarism

Congenital hypopituitarism may occur as a result of birth trauma and/or asphyxia or as part of one of a number of midline anatomical defects (Table 1). It may also occur secondary to a genetic mutation involving the anatomic development of the pituitary gland. The

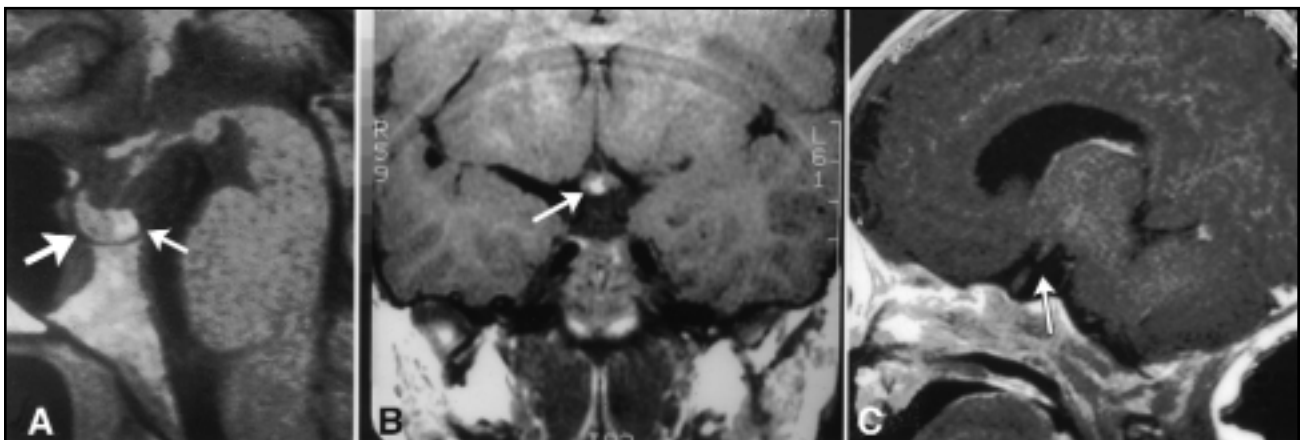


Fig 1. — (A) Normal head MRI showing a sagittal view through the pituitary gland. The large arrow indicates the anterior portion of the pituitary gland, whereas the small arrow indicates the posterior (normally whiter) portion of the pituitary gland. (B) Coronal head MRI with posterior pituitary bright spot noted ectopically at the base of the hypothalamus (arrow). (C) Sagittal MRI view of an infant pituitary gland showing a transected hypothalamic-pituitary stalk (arrow).

Table 1. — Causes of Hypopituitarism

Congenital	Acquired
Birth trauma/asphyxia	Tumors in the hypothalamic-pituitary region (eg, craniopharyngioma)
Midline defect syndromes (eg, septo-optic dysplasia)	Radiation to the head and neck region
Mutations of genes encoding pituitary transcription factors	Hydrocephalus
	Vascular abnormalities of hypothalamic-pituitary region
	Major head trauma

association of hypopituitarism with specific prenatal or birth trauma is sometimes difficult to prove. However, the pregnancy histories of the mothers of affected children have a higher than expected occurrence of complications late in gestation or around the time of birth, including placenta previa, abruptio placenta, and difficult deliveries.⁴ A congenital basis for the hypopituitarism is strongly suggested by the presence of a transected (or interrupted) hypothalamic-pituitary stalk on MRI scan⁵ (Fig 1C).

Congenital hypopituitarism may also occur as a component of one of several “midline defect syndromes.” The most common disorder in this group is known as septo-optic dysplasia, or de Morsier syndrome. This disorder includes absence of the septum pellucidum (the function of which is uncertain) in 50% of cases (hence, the designation, “septo”) and underdevelopment of the optic nerves, associated with variable degrees of reduced vision ranging from mild loss to complete blindness.⁶ Affected children may present with “wandering” or “searching” nystagmus, an irregular jerkiness of the eyeballs, representing, in a sense, a search for vision. An ophthalmologic examination may be technically difficult in affected children if the degree of nystagmus is moderate to severe but, if the examina-

tion can be successfully performed, it will show one or both optic nerve heads to have a reduced diameter. If the involvement is subtle, fundal photography may be required for direct measurement and comparison to age-matched normative data. It should be noted that most children with optic nerve hypoplasia do not actually have associated hypopituitarism; however, for any child first ascertained to have optic nerve hypoplasia, at least a one-time referral to a pediatric endocrinologist is warranted, especially if there is any associated growth delay.

Other midline associations with hypopituitarism include the presence of a fused deciduous upper central maxillary incisor (Fig 2A),⁷ cleft lip and/or palate, choanal atresia, anomalous and/or absent vascular supply to the central nervous system, and encephaloceles (either of the extrusive variety or completely internal emanating from the sphenoid sinus⁸ [Fig 2B]). If there are no associated clinical, biochemical, or radiological abnormalities, the hypopituitarism is said to have an *idiopathic* basis.

On rare occasions, congenital hypopituitarism may have a genetic basis involving one of a series of relatively recently identified pituitary transcription factors that regulate the formation of the gland and its cellular organization.⁹ One of the earliest known transcription factor genes involved in embryogenesis of the pituitary gland is *Rpx* (Rathke’s pouch homeobox, also called *HESX1*), mutations of which have been found in a few cases of septo-optic dysplasia.¹⁰ Other early transcription factor genes important in the formation of various pituitary cell populations are *LHX3*, *LHX4*, and *PROP-1* (Prophet of Pit-1). Lastly, *PIT-1* (also known as *POU1F1*) is a pituitary-specific transcription factor that is necessary for the development of somatotroph, lactotroph, and thyrotroph lineages. Inherited cases of hypopituitarism in humans have been described in conjunction with mutations of *LHX3* (associated with defi-



Fig 2. — (A) MRI depiction of a fused upper central maxillary incisor (arrow) in a child with hypopituitarism. (B) Sagittal head MRI showing a transsphenoidal encephalocele (arrows) in an adolescent with hypopituitarism. (C) Lateral view cerebral angiogram showing a suprasellar arteriovenous varix at the apex of the basilar artery (arrow). Fig 2B is reproduced with permission of Springer-Verlag GmbH & Co: Kjellin IB, Kaiserman KB, Curran JG, et al. *Pediatr Radiol*. Aplasia of right internal carotid artery and congenital hypopituitarism. 1999;29:586-588. Fig 2C is reproduced with permission from Blackwell Science Ltd: Koral K, Geffner ME, Curran JG. Trans-sphenoidal and sphenoidal encephalocele: report of two cases and review of the literature. *J Australas Radiol*. 2000;44:220-224.

ciencies of all anterior pituitary hormones except corticotropin [ACTH], along with a rigid cervical spine leading to limited head rotation), *PROP-1* (associated with deficiencies of growth hormone [GH], prolactin, thyroid-stimulating hormone [TSH], and sometimes gonadotropins and ACTH, along with limited elbow extensibility, blue sclerae, and, surprisingly, a large sella turcica in some affected individuals), and *PIT-1* (associated with deficiencies of GH, prolactin, and TSH). Due to mutations of pituitary gene transcription factors, some cases of hypopituitarism include variability in the timing of presentation of the different hormone deficiencies. For example, GH deficiency typically manifests early in life, whereas other hormone deficiencies somewhat inexplicably present later.

Unique Features of Congenital Hypopituitarism

The most important presenting feature, and perhaps most common feature, of congenital hypopituitarism is hypoglycemia.¹¹ This occurs secondary to the presence of GH deficiency with or without associated ACTH deficiency (the latter leading to cortisol deficiency). Both GH and cortisol are counterregulatory (“anti-insulin”) hormones that protect against hypoglycemia, especially during fasting. Without one or both, insulin acts in an unopposed fashion and, because of immaturity of other protective mechanisms against hypoglycemia in infants, this population is at an undue risk for low blood sugar. Thus, in infants (and sometimes in toddlers and older children) with unrecognized and/or untreated or undertreated hypopituitarism, hypoglycemia may often be recurrent and severe, potentially leading to permanent brain damage if not managed aggressively. The hypoglycemia usually resolves with replacement of GH and/or cortisol, although it may occasionally remain problematic in older children during stressful periods associated with reduced oral intake. An important caveat is that, in any term infant who develops hypoglycemia with no underlying risk factor (such as prematurity, intrauterine growth retardation, infant of a diabetic mother, etc), the diagnosis of hypopituitarism must be considered. Additionally, severe cortisol deficiency may result in presentation with hyponatremia (as cortisol is necessary for the action of anti-diuretic hormone [ADH, also known as vasopressin] to facilitate the excretion of free water by the kidneys) and/or outright shock due to its effects on blood pressure maintenance. If DI were present, shock with hypernatremia would be manifest.

Another unique feature of congenital hypopituitarism is the presence at birth of a microphallus

(small penis) in some affected males. This may result from isolated GH deficiency or from combined GH and gonadotropin deficiencies (the latter leading to testosterone deficiency in the second and third trimesters and postnatally).¹² The microphallus may enlarge solely in response to treatment with GH, suggesting that GH has a critical role in penile growth at least in fetal and early postnatal life. Thus, some pediatric endocrinologists will initiate a 6-month trial of GH therapy alone to stimulate penile enlargement. If the response were inadequate, then a short course of low-dose testosterone therapy would follow. This can be in the form of 25 mg of long-acting testosterone enanthate given as four equally spaced intramuscular injections over a 12-week period. This approach is usually successful in equalizing penile size with that of other male infants and with few or no side effects. There are, however, other pediatric endocrinologists who would administer testosterone immediately, along with GH.

Lastly, some children with congenital hypopituitarism develop a unique, noninfectious form of hepatitis. The condition is suspected if there is liver enlargement and abnormal liver function tests (predominantly indicating cholestasis) and is confirmed by the presence of characteristic giant-cell transformation of hepatocytes as seen on biopsy.¹³ The exact cause of this giant-cell hepatitis is unknown, and the condition usually remits on its own over the first few months of life without any permanent damage to the liver.

Causes of Acquired Hypopituitarism

The most concerning cause of acquired hypopituitarism is a tumor in the hypothalamic-pituitary region. The most common tumor that arises in this region in childhood is a craniopharyngioma. While craniopharyngiomas are derived from epithelial remnants of Rathke’s pouch, the same tissue that forms the anterior pituitary gland, they are not usually found exclusively within the pituitary gland, but more likely they are confined to the suprasellar region or are found in both suprasellar and intrasellar locations.¹⁴ The presenting symptoms are dependent both on the main location of the tumor and on the direction(s) that the tumor grows. For example, if the tumor grows downward, it may cause alterations in the anterior and posterior clinoid bones or in the floor of the sella turcica and/or compress the pituitary gland. If the tumor grows upward, it may compromise vision by effects on the optic nerves. While medical textbooks typically describe the most common visual change in patients with craniopharyngioma as “bitemporal hemianopsia” (loss of the outer visual fields of both eyes) due to com-

Table 2. — Hierarchy of Hypothalamic-Pituitary-Target Organ Hormones

Hypothalamus	Pituitary	Target Organ	Hormone/Function
Growth hormone-releasing hormone (GHRH)	Anterior: Growth hormone (GH)	Cartilage/liver	Insulin-like growth factor-1 (IGF-1)
Thyrotropin-releasing hormone (TRH)	Anterior: Thyroid-stimulating hormone (TSH)	Thyroid gland	T4/T3
Gonadotropin-releasing hormone (GnRH)	Anterior: Luteinizing hormone (LH) Follicle-stimulating hormone (FSH)	Ovary Testicle	Estradiol Testosterone
Corticotropin-releasing hormone (CRH)	Anterior: Corticotropin (ACTH)	Adrenal glands	Cortisol
Prolactin-inhibitory factor	Anterior: Prolactin	Breast	Milk
Hypothalamic factors	Posterior: Antidiuretic hormone (ADH)	Kidney	Urine concentration

pression of the optic chiasm, this rarely occurs so precisely. More likely is the development of “quadriopias,” which are smaller, more irregular field cuts. If the tumor grows even farther upward beyond the visual tracts, it may block the third ventricle and cause obstructive hydrocephalus, leading to headaches, vomiting, and/or blurry vision (in association with papilledema). Craniopharyngiomas are benign tumors histologically, but they are often described as “geographically malignant” based on their location and ability to wrap around vital structures (eg, optic nerves) precluding complete surgical removal. As stated previously, tumors originating in the pituitary gland are uncommon causes of acquired hypopituitarism in children. However, any surgery to remove a tumor in the hypothalamic-pituitary region may lead to hypopituitarism if it is not already present.

Another cause of acquired hypopituitarism is radiation treatment of a cancerous tumor in the head or neck region. More specifically, the radiation that is required to cure the child’s tumor may, of necessity, damage normal tissue in its path or beyond. When hypopituitarism ensues in this situation, it is usually the result of radiation-induced damage to the hypothalamus, as the pituitary gland is relatively resistant to radiation. Different hypothalamic-pituitary axes have different sensitivities to radiation. Doses as low as 18 Gy using conventional fractionation can interfere with GH dynamics; doses higher than 40 Gy can cause deficiencies of gonadotropins, TSH, and ACTH, while >50 Gy may cause hyperprolactinemia, especially among young women.

Other causes of acquired hypopituitarism in childhood include previous brain infection (encephalitis and/or meningitis), hydrocephalus (even without an underlying tumor), vascular abnormalities (such as a varix in the hypothalamic-pituitary area)¹⁵ (Fig 2C), and major head trauma usually associated with a significant loss of consciousness.¹⁶

Potential Anterior Pituitary Hormone Deficiencies

In childhood hypopituitarism, GH is the most commonly underproduced pituitary hormone, often as the result of loss of hypothalamic GH-releasing hormone (GHRH) (Table 2). The deficiency of GH primarily leads to short stature and slow height velocity. Untreated GH deficiency in children also causes disturbed body composition, with a reduction in lean body mass (ie, muscle) and an excess of fat, the latter accumulating predominantly in the cheeks of the face and in the abdomen, creating a cherubic or angel-like appearance.¹⁷

Deficiency of hypothalamic thyrotropin-releasing hormone (TRH) or pituitary TSH causes central hypothyroidism. Unlike children whose hypothyroidism is due to thyroid gland damage, those with hypopituitarism typically have somewhat higher thyroid hormone levels and thus may have few or no symptoms. In other cases, as occurs in patients with primary thyroid disease, short stature and slow height velocity, relative weight excess, constipation, dry skin, cold intolerance, and fatigue may be present.

Younger children with deficiencies of either hypothalamic gonadotropin-releasing hormone (GnRH) or the pituitary gonadotropins typically show no abnormalities since luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are normally low prior to puberty. In contrast, adolescent-aged children with deficiencies of the gonadotropins present with failure to start or progress through puberty (breast development and menstrual periods in girls and enlargement of the testicles and penis in boys). Infrequently and paradoxically, central sexual precocity can be seen in the setting of hypopituitarism.

Loss of hypothalamic corticotropin-releasing hormone (CRH) or pituitary ACTH results in an inability of the adrenal zones fasciculata and reticularis to

manufacture normal amounts of cortisol (central adrenal insufficiency). If deficient, this hormone is most likely to place a child in a life-threatening situation. While there would likely be no symptoms under normal circumstances, except maybe mild fatigue, lack of cortisol in the setting of infection, fever, surgery, trauma, etc, may cause vomiting, dehydration, shock, and even death. Biochemical correlates of cortisol deficiency include hypoglycemia and hyponatremia (with normokalemia). In this setting, mineralocorticoid function is completely normal, as aldosterone production by the zona glomerulosa of the adrenal cortex is regulated by the renin-angiotensin and not the CRH-ACTH system.

Potential Anterior Pituitary Hormone Excess

Serum levels of prolactin are usually normal or only mildly increased (if there is disruption of the hypothalamic-pituitary stalk) secondary to the loss of a normally predominant inhibitory signal from the hypothalamus. Although there are typically no symptoms in this situation, in rare cases a small amount of galactorrhea might occur.

Potential Posterior Pituitary Hormone Excess

As stated previously, a deficiency of ADH causes central or neurogenic DI. Infants and toddlers manifest DI with excessively wet diapers. If unrecognized and hence untreated, dehydration with elevated serum sodium concentrations will ensue in this age group as young children cannot report and easily satisfy heightened thirst. Older children with DI typically present with excessive day- and night-time urination, new onset of bed-wetting, and increased thirst. DI most often occurs unintentionally as a result of surgical treatment of a hypothalamic-pituitary tumor, such as a craniopharyngioma. In some cases, DI is temporary due to local postsurgical edema, but it will be permanent if surgical sacrifice close to the hypothalamus or of the stalk itself is required for complete cure of a brain tumor in the suprasellar region.¹⁸ DI may also occur in association with a diencephalic germinoma.

Diagnosis of Hypopituitarism

The final diagnosis of GH deficiency must integrate clinical, auxological (growth), and biochemical data.¹⁹ GH deficiency should be suspected if a child has reduced height velocity along with a delayed bone age, and low serum levels of the GH surrogates, insulin-

like growth factor-1 (IGF-1), and insulin-like binding protein-3 (IGFBP-3) not otherwise explained by young age and/or undernutrition. The next step is then to measure serum GH levels. Unfortunately, beyond the first month of life, measurement of GH levels in a random blood sample is without value (to secure a diagnosis of GH deficiency) because most of the body's GH is made during sleep, with several significant peaks linked to deep (stage III-IV EEG) sleep, the first cycle of which usually occurs at approximately 60 to 90 minutes after falling sleep. Random GH measurements during the day, even in tall individuals, are frequently low and thus potentially misleading.

If most or all of these criteria are met, GH testing is then recommended by any of several physiologic or pharmacologic methods. The most commonly employed physiologic stimulus is exercise, but this is often difficult to standardize. Overnight serial blood sampling every 20 to 30 minutes was common in the early 1990s but lost favor because of inconvenience, cost, and lack of reproducibility.

A more common approach is stimulation testing (also referred to as provocative testing) with medications known to activate the physiologic regulation of GH secretion, notably the α -adrenergic pathway (eg, clonidine²⁰ at the following dosages according to body weight: 50 μ g for body weight 5 to 15 kg, 75 μ g for 15.1 to 20 kg, 100 μ g for 20.1 to 25 kg, 150 μ g for 25.1 to 35 kg, 200 μ g for 35.1 to 50 kg, and 250 μ g for more than 50 kg).

Blood samples are procured 60 and 90 minutes after the clonidine is taken. Clonidine may cause sleepiness and a mild fall in blood pressure, but these effects are transient and usually resolve within 90 minutes. To mimic the other physiologic pathway of GH regulation involving the dopaminergic system, L-dopa combined with Inderal (propranolol) has been used, but L-dopa was recently taken off the market. These and all other stimulation tests must be performed in the fasting state (and, hence, early in the morning), as glucose intake suppresses GH secretion. GH provocation tests can also be performed using glucagon (0.1 mg/kg, maximum dose 1 mg)²¹ or insulin (0.05 to 0.1 units of regular insulin per kilogram, depending on the index of suspicion), the latter known as an insulin tolerance test (ITT).²² In both cases, hypoglycemia is induced. In the case of glucagon, blood sugar initially rises followed by stimulation of endogenous insulin leading to late hypoglycemia. For a hypoglycemic stimulus to be deemed adequate to stimulate GH, the plasma glucose concentration needs to fall by at least 50% from baseline. In the glucagon test, blood sampling is performed every 15 minutes for 1 hour and then every 30 minutes for the next 2 hours out

to 180 minutes. For the ITT, blood sampling is performed every 15 minutes for 1 hour and then again 30 minutes later, with bedside and laboratory glucose testing, along with GH measurements at all time points and cortisol measurements at 0, 60, and 90 minutes. To obtain these multiple blood samples, a heparin lock should be placed in a large-bore vein at the start of the study. Glucagon or hypoglycemia itself may cause nausea and vomiting. Hypoglycemia results in uncomfortable adrenergic manifestations such as sweatiness, excessive hunger, and shakiness, and may also cause neuroglycopenic manifestations such as loss of consciousness or seizures. These tests can also be used to assess cortisol production, thus eliminating the need for an additional stimulation test either on the same day or on a different day. As such, these tests are moderately dangerous and need to be performed by experienced personnel in a hospital outpatient unit with resuscitative equipment and expertise as well as with a physician in attendance throughout the test. If dangerous hypoglycemia associated with diminished mental status occurs, 2 mL/kg of 25% dextrose should be immediately administered intravenously. The test will still be valid because the hypoglycemic stimulus was delivered so all blood samples should continue to be collected.

Arginine is another GH secretagogue that requires a 45-minute intravenous infusion (5 mL/kg of 10% arginine hydrochloride).²² Arginine is an amino acid that is a non-specific stimulator of multiple hormones including insulin and glucagon, in addition to GH. There are no side effects with its use. Lastly, intravenous GHRH (at a dose of 1 µg/kg body weight) may be employed with sampling at 0, 5, 30, 45, 60, 90, and 120 minutes.²³ Its only frequent side effects are local injection site reactions.

GH deficiency is traditionally defined by all GH levels on all tests being less than 10 ng/mL as measured by traditional double-antibody radioimmunoassay. In certain clinical situations, such as known surgical transection of the hypothalamic-pituitary stalk or the administration of high-dose radiation to the hypothalamic-pituitary region, less rigorous GH testing is required.

Of note, the blood of children with untreated panhypopituitarism is mildly acidotic secondary to the absence of GH and its ability to regulate acid-base metabolism by the kidney.²⁴ Its presence is detected by finding a slightly low serum bicarbonate level that corrects completely with GH replacement.

The diagnosis of central hypothyroidism due to TSH deficiency requires low levels of free and/or total thyroxine (T_4) in serum. On occasion, the free T_4 level is at the low end of the normal range. A TSH level generally is not helpful. With pituitary failure, the TSH level

would obviously be low or not measurable. Surprisingly, if the problem arises in the hypothalamus, the TSH is usually in the normal range or occasionally even slightly elevated for uncertain reasons. In some situations, administration of synthetic TRH, the hypothalamic factor that controls pituitary TSH secretion, may be necessary. This test can help distinguish whether the deficiency lies at the level of the pituitary (in which case the TSH level is very low and fails to increase) or at the hypothalamus (in which case the TSH level rises excessively and stays elevated for a longer period of time than occurs normally).²⁵

The diagnosis of LH and FSH deficiencies in childhood can be the most problematic of all the pituitary hormones as throughout most of the first 10 years of life the serum concentrations of children are naturally low. Because LH and FSH levels are slightly higher in the first 6 months of life and then increase significantly after 10 years of age, random testing at these ages may indicate low levels.²⁶ Such testing is most informative when, in the teenager, there is also a failure to show clinical pubertal changes by age 13 years in girls (lack of breast development, sexual hair, and menses) and by age 14 years in boys (lack of testicular enlargement, penile growth, and sexual hair). In females, radiological confirmation of lack of pubertal initiation by pelvic ultrasound may be helpful if the ovaries and uterus are prepubertal in size.

As stated previously, cortisol deficiency is the most important parameter to consider in view of its role in regulating vital functions during stressful situations. Using random blood testing for this diagnosis requires an understanding of both the age-related changes (lower levels in younger than in older children) and "diurnal" changes (by time of day) in cortisol levels.²⁷ More specifically, in older children and adults, the highest cortisol levels are found at 8:00 AM. Thus, a low 8:00 AM serum cortisol level (less than 3 µg/dL in children between the ages of 1 and 16 years) would suggest deficiency. An indirect clue to the presence of cortisol deficiency is an increased percentage of eosinophils on a peripheral blood smear. As mentioned previously, more rigorous testing can be accomplished as part of the glucagon or insulin hypoglycemia GH tests or after administration of metyrapone, CRH, or low-dose synthetic ACTH, drugs that stimulate the adrenal glands to produce more cortisol if they can. The use of ACTH provocation may occasionally give a misleading picture of adequate adrenal reserve as sufficient cortisol may be produced in response to exogenous ACTH stimulation but is not produced under daily living conditions.

Prolactin excess is present if there is an elevated prolactin concentration in a random blood sample.

ADH deficiency or central DI is suspected if urination and thirst are excessive, and it is strongly suggested by the presence of increased levels of serum sodium along with dilute urine. If the diagnosis remains unclear, a water deprivation test can firmly prove or disprove this diagnosis.²⁸ This test involves fasting by the child (no food or liquids) for up to 8 hours and observing the child's urine output. A normal child will reduce urine output to avoid dehydration since there is no fluid intake. Under the same circumstances, a child with DI will continue to urinate and, if not monitored carefully, could become dehydrated and develop an elevated serum sodium concentration. Specific mathematical criteria that are derived from blood and urine test results during the water deprivation test are used to make the diagnosis of DI. This test should always be done under close medical supervision in either an experienced outpatient procedure unit or an inpatient setting.

Once the diagnosis of hypopituitarism has been made by appropriate hormonal testing, a head MRI

scan (with gadolinium contrast) must be performed to look for a possible organic or structural basis. Nonserious abnormalities that can be associated with hypopituitarism include a small pituitary gland (for age) with filling of the sella with cerebrospinal fluid (empty sella) (Fig 3A) and an ectopic posterior pituitary gland. A midline syndrome is suggested by the absence of the septum pellucidum and/or the corpus callosum. The most critical reason for obtaining the MRI scan is to detect a brain tumor in the hypothalamic-pituitary area, the most common of which is a craniopharyngioma. Radiological evidence of craniopharyngiomas can be seen on a lateral skull-ray in 89% of cases, which makes this an important screening test when this diagnosis is suspected in a child²⁹ (Fig 3B). Findings include erosion of the normal sellar architecture and/or the presence of suprasellar calcification. On MRI scans, the tumor usually contains a mixture of solid and cystic components (Fig 3C) and may contain a ring of calcification around a cystic component (the latter best seen on a computed tomographic scan) (Fig 3D). Other abnormalities that can be seen on the MRI scan include a transected stalk, small optic nerves, hydrocephalus, and vascular abnormalities.

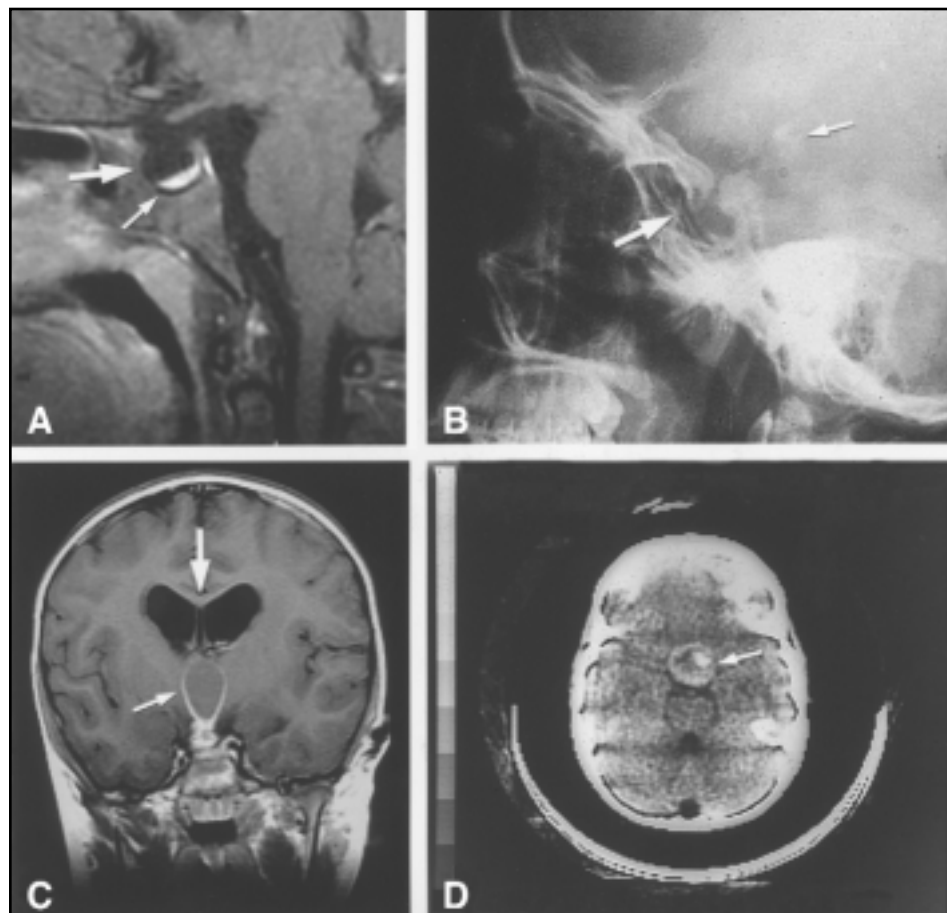


Fig 3. — (A) Sagittal head MRI showing compressed pituitary contents (small arrow) with filling of sella turcica by cerebrospinal fluid (empty sella) (large arrow). (B) Lateral skull radiograph showing erosion of sella turcica (large arrow) and suprasellar calcification (small arrow) caused by a craniopharyngioma. (C) Coronal head MRI showing a craniopharyngioma in the suprasellar region containing a large cyst (small arrow) within a contrast-enhanced thin shell, along with mild hydrocephalus (large arrow). (D) Head CT scan showing contrast-enhanced ring of calcification around a craniopharyngioma and internal calcification (arrow).

Treatment of Hypopituitarism

If an underlying cause is discovered on the MRI of the head, such as a tumor and/or hydrocephalus, appropriate neurosurgical intervention is required. For example, removal or debulking of a tumor and shunting for hydrocephalus, respectively, would be undertaken. Additionally, radiation therapy may be required to treat certain types of tumors. Chemotherapy is used less often to treat brain tumors. In most cases, these treatments, while potentially life-saving, do not reverse the hypopituitarism. The diagnosis of specific hormonal deficiencies present prior to any neurosurgical procedure has limited impor-

tance as all deficiencies will persist and all intact axes will likely be sacrificed during the surgical procedure. Since these patients uniformly receive high-dose glucocorticoid (dexamethasone) treatment to reduce any swelling around the tumor before and during the surgery, this serves to prevent possible adrenal insufficiency that, if present and not managed aggressively, could lead to great morbidity and even death. If DI is present preoperatively, it should be readily apparent on clinical and biochemical grounds and easily managed by a capable anesthesiologist. If GH, thyroid hormone, and/or gonadotropin deficiencies are present preoperatively and not recognized and treated, there would be no significant effect on the immediate postoperative recovery.

To treat GH deficiency in a child with remaining growth potential, replacement with GH is usually undertaken. GHRH, the hypothalamic stimulator of GH, is also approved by the US Food and Drug Administration (FDA) for this purpose, but it is effective only if the pituitary gland is fully functional. Unfortunately, optimal dosing and frequency of administration of GHRH remain unknown. Thus, GH itself is preferentially administered. It is typically given subcutaneously either with a 31-gauge needle and syringe, pen system with a 31-gauge needle, or "needleless" injector system. The usual dose range is between 0.18 and 0.3 mg per kilogram of body weight per week divided into 6 or 7 daily doses administered generally in the evening to simulate the fact that most of the GH manufactured by the body is at night during sleep (nyctohemeral rhythm).³⁰ A long-acting, once- or twice-monthly formulation of GH administered subcutaneously with a special 22-gauge needle has recently been approved by the FDA. If the hypopituitarism is caused by a brain tumor or its treatment, commencement of GH treatment is usually delayed for 1 year until the clinical status of the tumor is clearly defined. This practice is based on logic because there are no scientific data showing that GH causes tumor growth or recurrence. Other GH formulations delivered intranasally or by inhalation are under development. When the growth potential of a child with hypopituitarism has been fully or nearly fully attained, a transition to adult GH dosing should be considered (approximately one sixth to one third the pediatric dose). While the need for GH retesting is recommended for children with isolated GH deficiency before commencing adult dosing (as approximately 50% will have normal GH responses on retesting³¹), this should not be required when there are multiple hormone deficiencies.

One unusual circumstance, which usually arises following surgery for a craniopharyngioma, occurs when the child begins to gain excess weight and grow nor-

mally to excessively in height with documented GH deficiency and without institution of GH treatment. The cause of this paradox, dubbed "the growth without GH syndrome,"³² is unknown, but the condition can be debilitating secondary to large weight accumulation. There is no proven treatment for this situation, although research trials with appetite depressants, anti-neurosis/anti-anxiety drugs, and analogs of somatostatin that inhibit GH, insulin, and other hormones are in progress.³³

Oral levothyroxine (brand name or generic) is the specific treatment for central hypothyroidism, as TRH and thyrotropin (TSH), while available as drugs for dynamic testing of thyroid function, are not FDA-approved for treatment purposes. The dose of levothyroxine for treatment of central hypothyroidism in children is approximately 50 $\mu\text{g}/\text{m}^2$ per day (or approximately half that used to treat primary hypothyroidism). The adequacy of the dose can be readily determined by measuring the serum level of free T_4 . TSH levels should not be monitored as the patients are TSH-deficient.

For documented deficiencies of LH and FSH, a more practical approach than replacing the gonadotropins is replacing the corresponding sex steroid(s), ie, estrogen (orally or by patch) and progesterone (orally) in girls and testosterone in boys (by long-acting monthly injection in the early adolescent period or by injection, daily skin patch, or daily skin gel in the late adolescent period). Some pediatric endocrinologists will also prescribe a low dose of testosterone to adolescent girls without which they may not have any pubic or axillary hair development, although this is not currently the general standard of care. These approaches will provide appropriate adolescent physical development and protect against osteoporosis but, as such, will not restore fertility. When affected subjects reach the age when they are imminently ready to have children, their hormone replacement regimens need to be altered based on the location of the damage. More specifically, if the hypothalamus is damaged and the pituitary gland is proven to be intact, treatment with the hypothalamic hormone GnRH by pump will stimulate the subject's pituitary gland to produce LH and FSH and, thus, induce egg or sperm development. If pituitary function is damaged, coordinated treatment with synthetic LH (as human chorionogonadotropin [hCG]) and FSH (either as human menopausal gonadotropin [hMG] or recombinant FSH) needs to be initiated. In either case, the treatment program is complex and requires the supervision of an experienced endocrinologist with expertise in reproductive disorders.

The most practical approach to restoration of normal adrenal function is replacement of cortisol (also

known as hydrocortisone), since CRH and ACTH are approved only for testing of the adrenal axis. In children, oral hydrocortisone is usually given 2 or 3 times daily at a dose of 10 to 15 mg/m² per day. This dose is equal to approximately 1.5 to 2 times the body's normal daily production rate of cortisol but provides appropriate replacement as only 50% to 90% of an oral dose is absorbed. Many of the commonly used replacement regimens use a higher dose in the morning than at other times of the day in an attempt to simulate the normal diurnal variation in cortisol production, in which the adrenal glands make more cortisol earlier than later in the day. Recently, liquid suspensions of cortisol were removed from the market so that only tablet formulations remain, with the lowest pill dose containing 5 mg. To provide a liquid glucocorticoid formulation as required by infants and toddlers, prednisone suspension (5 mg/5 mL) can be used, remembering that prednisone is 4 times the milligram-for-milligram potency of cortisol. Thus, a 10-mg dose of cortisol is equal to a 2.5-mg dose of prednisone. Another glucocorticoid formulation that can be used (and is available in both tablets and liquid) is dexamethasone that is 25 to 100 times more potent than cortisol. Because of the wide range of potency equivalence between dexamethasone and hydrocortisone, use of this formulation is sometimes problematic as it is easy to unintentionally overdose. As stated previously, there is no need to prescribe replacement of mineralocorticoid as, with central adrenal insufficiency, the kidney still responds normally in terms of sodium and potassium balance that is regulated by the renin-angiotensin system. With significant illness, stress, and/or injury, the glucocorticoid dose must be doubled or tripled for 1 or more days depending on the length and severity of the illness, stress, and/or injury. If there is significant vomiting, a child with adrenal insufficiency should be taken to the physician or to the emergency room. As a precaution, all children should have injectable hydrocortisone at home (in the form of 100- or 250-mg Solu-Cortef Act-o-Vials). Lastly, older children (who are not with their parents all the time) and adolescents must wear Medic-Alert identification indicating the presence of hypopituitarism and adrenal insufficiency.

For the treatment of central DI, replacement of ADH may be accomplished with a number of formulations. During surgery and other critical situations, ADH should be administered as a continuous intravenous infusion. In most day-to-day situations, desmopressin acetate is the preferred replacement therapy. This formulation has been structurally modified to prolong its duration of action and to eliminate any tendency of the drug to cause hypertension. Desmopressin acetate was originally developed for intranasal administration using a "rhinal tube" (allowing provision of doses as low as 2.5 µg that might be required in a

young child). In infants, desmopressin acetate use requires even more attention to fluid intake and formulation. Subcutaneous administration may be the optimal method of delivery in this age group. More recently, the nasal preparation became available as a fixed-dose, metered pulse spray (similar to asthma medication), with each pulse providing a 10-µg dose. Most recently, an oral formulation of desmopressin acetate has become available as 0.1- or 0.2-mg tablets. In prescribing oral desmopressin acetate, it is important to remember that, since most of the drug is inactivated in the stomach, a 20-fold higher oral dose (compared to the nasal dose) must be prescribed.³⁴

Conclusions

Hypopituitarism in childhood may have either a congenital or an acquired basis. A head MRI scan is critical in attempting to determine the specific cause in either case. Identified hormone abnormalities require treatment with appropriate hormonal replacement therapies, including GH, usually for life. All children with hypopituitarism require supervision of medical care by a pediatric endocrinologist and, when older, appropriate transition to an internist endocrinologist or to a reproductive endocrinologist.

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