

## Clinical Presentation and Diagnosis: Growth Hormone Deficiency in Adults

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In the United States, growth hormone deficiency (GHD) affects 50 000 adults, with 6000 new cases yearly.<sup>1</sup> Patients with GHD have decreased or absent growth hormone (GH) production as a result of hypothalamic or pituitary disorders resulting in underactive pituitary gland function (ie, hypopituitarism). GHD is distinct from somatopause, a term that describes the gradual decline in GH production through normal adulthood. Adults with hypopituitarism routinely receive replacement cortisol, thyroid hormone, and gonadal hormone replacement therapy. Until the past decade, GH replacement therapy had been primarily reserved for pediatric use. GHD in adults, however, represents a serious clinical disorder, which is distinct from pediatric GHD and can be treated with recombinant human GH replacement therapy.

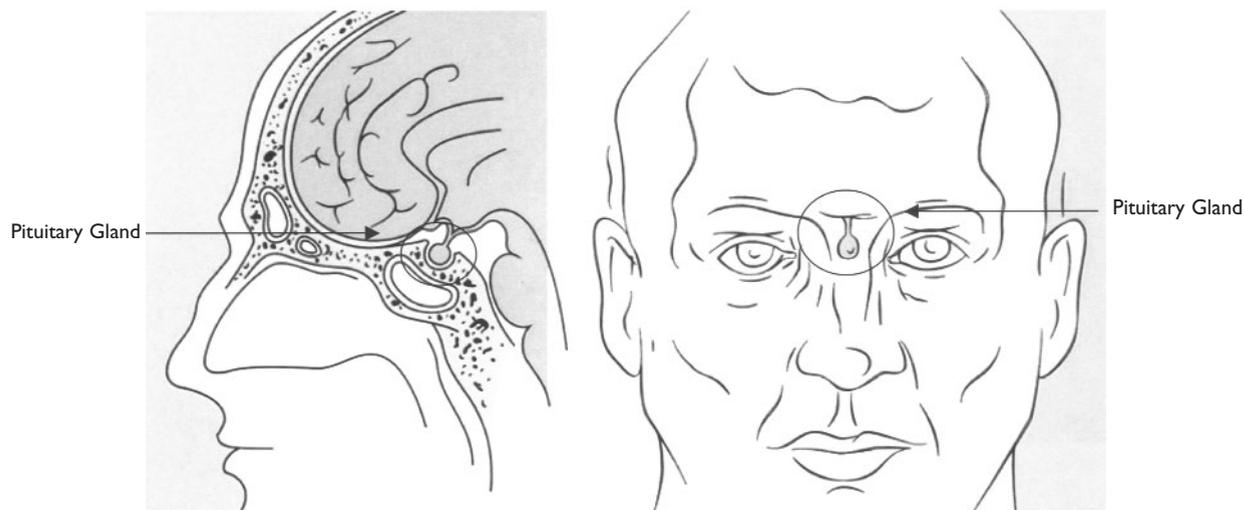
GH is produced in the pituitary gland, which is located at the base of the brain behind the sphenoid sinus in a small bony cavity called the sella turcica (Figure 1). The pituitary gland secretes hormones from 2 distinct lobes, each derived from different embryonic tissue (Figure 2). These hormones affect numerous body systems.

The posterior lobe of the pituitary gland, an extension of the hypothalamus, secretes 2 hormones: arginine vasopressin (also called antidiuretic hormone), which stimulates the kidney to reduce urine output, and oxytocin, which causes uterine contractions. The anterior lobe secretes 6 hormones: luteinizing hormone, which stimulates the secretion of sex steroids from the gonads; follicle-stimulating hormone, which stimulates ovulation and sperm production; prolactin (PRL), which targets the

mammary glands to stimulate milk production; adrenocorticotropic hormone, which targets the adrenal cortex to cause glucocorticosteroid production; thyrotropin influences the production of thyroid hormones; thyroid stimulating hormone (TSH) targets the thyroid; and, finally, GH (also called somatotropin), which targets many tissues to promote growth and control protein, lipid, and carbohydrate metabolism. Of all the anterior pituitary hormones, only GH and PRL act independently and not through a target endocrine gland. The effects of an excess or deficiency in hormone production are listed in Table 1. The typical managed care organization formulary includes drug therapies for all of the hormone deficiency states, and for several of the hormone excess states.

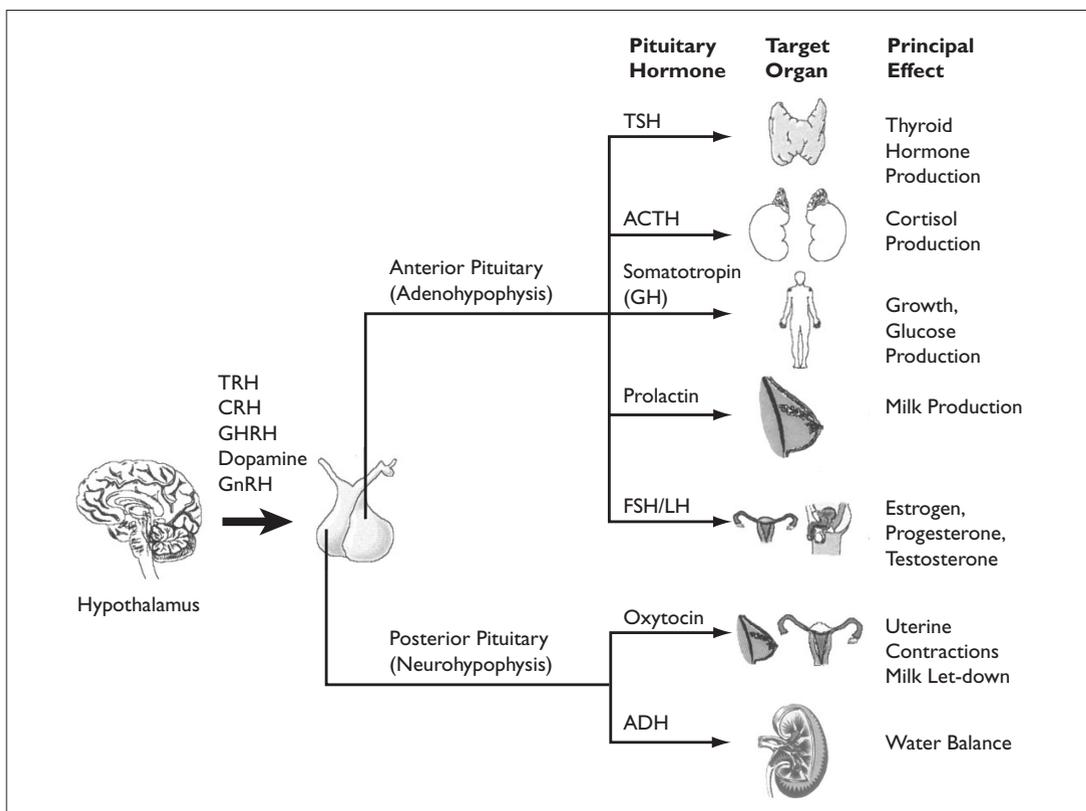
The pituitary is the master gland, but it is also controlled by hormones originating in the hypothalamus, an area of the brain just above the pituitary. Anatomically linked to the pituitary through a funnel-shaped structure called the infundibulum, the hypothalamus controls pituitary function by secretion of releasing and inhibiting factors. GH release is stimulated by GH-releasing hormone (GHRH) and inhibited by somatostatin. During a 24-hour period, pulses of GHRH and somatostatin stimulate or inhibit the pituitary to release GH in discrete bursts, with a distinct diurnal phase resulting in most of the 24-hour GH secretion during sleep. Most healthy individuals, therefore, have little measurable GH secreted during much of the daylight hours. Measurement of a single blood sample for GH is therefore not helpful in making the diagnosis of GH excess or deficiency. When GH deficiency is considered, stimulation testing (sometimes

**Figure 1.** Pituitary Gland



Source: *Acromegaly* by AG Harris, 2001.

**Figure 2.** Hypothalamic-pituitary Hormone Relationships



TRH indicates thyrotropin-releasing hormone; CRH, corticotropin-releasing hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin-releasing hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; ADH, antidiuretic hormone. Adapted from *Acromegaly* by AG Harris, 2001.

**Table 1.** Pituitary Dysfunction

Hormone Excess	Hormone Deficiency
<ul style="list-style-type: none"> <li>■ Hyperprolactinoma</li> <li>■ Acromegaly</li> <li>■ Cushing's disease</li> <li>■ Hyperthyroidism</li> <li>■ Syndrome of Inappropriate Antidiuretic Hormone (SIADH)</li> </ul>	<ul style="list-style-type: none"> <li>■ Absence of postpartum lactation</li> <li>■ Hypogonadism (GnRH or LH/FSH)</li> <li>■ GHRH or GH deficiency (GH/IGF-1)</li> <li>■ Hypoadrenalism (cortisol) (CRH or ACTH)</li> <li>■ Hypothyroidism (thyroxine) (TRH or TSH)</li> <li>■ Diabetes insipidus (AVP)</li> </ul>

GnRH indicates gonadotropin-releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GHRH, growth hormone releasing hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; AVP, arginine vasopressin.

termed “provocative testing” or “dynamic hormone testing”) is usually performed. When GH enters the circulatory system it attaches to GH receptors in virtually all body tissue to produce and stimulate local insulin-like growth factor 1 (IGF-1) production. At the tissue level, many of the effects of GH are mediated by IGF-1. In addition, regulation of GH production by the pituitary is controlled by negative feedback from IGF-1.

The level of GH production normally varies among individuals and groups of individuals. For example, premenopausal women produce more GH, and, as people age, production of GH gradually declines. Further, the extent of excessive visceral fat is negatively correlated with GH production, whereas exercise appears to be positively correlated.<sup>2</sup> There are many different etiolo-

**Table 2.** Etiology of Adult GHD

<ul style="list-style-type: none"> <li>■ Pituitary disease                             <ul style="list-style-type: none"> <li>• Tumors, sellar masses/cysts</li> <li>• Post irradiation</li> <li>• Post surgery</li> <li>• Apoplexy</li> </ul> </li> <li>■ Hypothalamic disease</li> <li>■ Craniopharyngioma</li> <li>■ Head trauma</li> <li>■ Childhood-onset</li> </ul>
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GHD indicates growth hormone deficiency.

gies for GHD in adults. **Table 2** describes the causes of pituitary or hypothalamic damage that results in a decrease in GH secretion. The majority of patients with pituitary hormone abnormalities present initially with a pituitary tumor or other sellar lesions. Pituitary tumors may secrete an excess of 1 pituitary hormone or be clinically nonfunctioning, producing clinical problems by mass effect, such as headaches or visual field abnormalities accused by compression of the optic chiasm. Pituitary hormone deficiencies may be secondary to compression of the normal gland by a cyst or tumor, or from treatment of the tumor, which may include surgery and radiation. Hypopituitarism may also result from other causes, such as head trauma, infiltrative hypothalamic disorders, or infection. In addition, for some children with GHD, the disorder persists in adulthood.

In adults, GHD can produce metabolic disturbances that may compromise the patient’s health and quality of life and increase cardiovascular (CV) risk. The most salient features of GHD in adults include decreased lean body mass, increased visceral fat and subcutaneous fat, decreased bone mass, and hyperlipidemia.<sup>2</sup> GHD has been linked to a higher risk of bone fractures, an increase in carotid artery intimal thickness, and elevations in certain markers of CV risk, among them C-reactive protein and homocysteine. It has been shown that the degree of elevation in lipid level<sup>3</sup> and the severity of bone mineral loss correlate with the severity of GHD.<sup>4</sup>

Epidemiologic studies have clearly shown that adults with hypopituitarism, including GHD, display an increased risk for CV and cerebrovascular disease and premature mortality (**Figure 3**).<sup>5,6</sup>

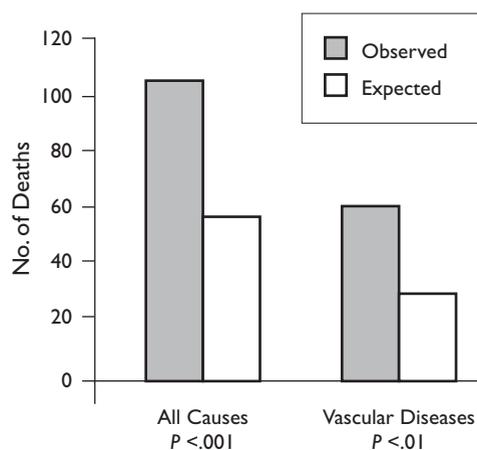
In the transitional patient, GHD can induce deleterious metabolic events similar to those in adults. A 2-year, placebo-controlled trial examined 64 young adults (mean age, 23 years) who had pediatric GHD, current GH levels of less than 5 µg/L, and were not taking GH for an average of 5.6 years.<sup>7</sup> At baseline, 22% of these patients demonstrated evidence of below average bone mineral density, 59% were overweight or obese, and 45% had total cholesterol levels of more than 200 mg/dL.

For the clinician, diagnosing GHD can be a daunting process. Because GH is secreted in a diurnal pulsatile manner and has a short half-life of only 19 minutes, it is frequently undetectable in blood samples without provocative testing. Numerous pharmacologic agents can be used to assess GH production and secretion by the pituitary in adults (Table 3). These include insulin, arginine, levodopa (L-dopa), arginine plus L-dopa, arginine plus GHRH, and the glucagon test. None display perfect sensitivity and specificity; however, the insulin tolerance test (ITT) and arginine-GHRH are excellent tests. A cut point of  $<5 \mu\text{g/L}$  has been suggested to optimize sensitivity of detection of GHD without sacrificing too much specificity.<sup>2</sup> The choice of diagnostic test by the endocrinologist depends on many factors and relates to the clinical setting.

The ITT is considered the gold standard for determining GHD.<sup>2</sup> Insulin-induced hypoglycemia provokes the pituitary to secrete GH. Once basal glucose levels are lowered, GH levels are assessed at 30, 45, and 60 minutes after insulin administration. However, with ITT, the plasma glucose level suggested as an optimal GH stimulus,  $<40 \text{ mg/dL}$ , is a level well below normal (70-120 mg/dL) and may produce symptoms and signs of hypoglycemia and some serious side effects such as seizures. The ITT requires stable and adequate hormonal replacement for other hormone deficiencies and the presence of obesity may result in false positives. The ITT is also contraindicated in patients older than 55 years of age and in patients with an abnormal electrocardiogram, a history of ischemic heart disease, or seizure disorder. Because the ITT is technically demanding, the physician's personal experience with this test is critical to its success as a diagnostic tool.<sup>8,9</sup>

Alternative GH provocation tests include the use of GH stimulatory substances, such as arginine, a somatostatin antagonist, with or without GHRH, and L-dopa, alone or in combination with arginine. The combination of arginine plus GHRH is considered an excellent alternative to ITT for most patients.<sup>8,10</sup> ITT produces a global central nervous system challenge based on acute glucose deprivation; in contrast, the argi-

**Figure 3.** Hypopituitarism and Mortality



Source: Rosen T, et al. *Lancet*. 1990;336:285-288.

nine-GHRH test is a more direct challenge to the pituitary and does not involve a comprehensive neurologic response. Because of these differences and the fact that performing an ITT is a higher risk procedure and requires more personnel, the arginine-GHRH test is likely the overall test of choice in clinical practice. In a study that included 157 patients with GHD, a GH response of  $9 \mu\text{g/L}$  or less with an arginine-GHRH test was diagnostic for severe GHD and correlated with lipid abnormalities.<sup>5</sup> Another study has suggested a cutoff of  $4.1 \mu\text{g/L}$  for confirming the diagnosis of GHD.<sup>8</sup> It is important to note that the arginine-GHRH test may be falsely normal in patients with hypothalamic disease, such as caused by radiation or infiltrative disorders. Compared with ITT and arginine-GHRH, arginine alone and L-dopa alone or in combination with arginine, as well as clonidine alone, are less specific for making the diagnosis of GHD unless very low cut points are used.<sup>8</sup> Clonidine also results in very poor diagnostic performance. Hypotension is a concern when performing the clonidine and L-dopa test. The glucagon stimulation test is lengthy, requiring multiple blood samples, and is less sensitive than ITT.

The dynamic test using L-dopa is of academic interest because it is not available for clinical use and it poorly diagnoses adult

**Table 3.** Provocative Dynamic Tests of Growth Hormone Secretion

Test	Administration	Timing of Samples (min)	Advantages	Disadvantages
Insulin tolerance test (ITT)	0.05-0.15 unit/kg IV; glucose concentrations must fall to <2.2 mmol/L (40 mg/dL)	0, 15, 30, 60, 75, 90, 120; alternatively at 0, 30, 45, 60, 90	Most established test; tests pituitary-adrenal axis in addition to GH secretion.	Use extra caution in patients aged >60 years. Contraindicated in patients with electrocardiographic findings, history of ischemic heart disease, cerebrovascular disease, history of seizure disorder (eg, traumatic brain injury); other disadvantages include hypoglycemia; patient discomfort; results dependent on sex, weight, and other hormones.
Arginine + GHRH	Arginine: 0.5 g/kg IV over 30 min (max 30 g); GHRH: 1 µg/kg IV given at 0 time, before arginine	0, 15, 30, 45, 60 (up to 90); alternatively at 0, 30, 60, 90, 120	Safer than ITT with equal diagnostic accuracy except in some patients with hypothalamic disease/radiation. Applicable to broader patient population.	Less established diagnostic value compared with ITT; arginine contraindicated in liver or renal disease; GHRH may cause facial flushing or metallic taste. May be falsely normal in patients with a hypothalamic source of GH deficiency.
Arginine	0.5 g/kg IV over 30 min (max 30 g)	0, 15, 30, 45, 60; alternatively at 0, 30, 60, 90, 120	Safer than ITT. Applicable to broader patient population.	Less established diagnostic value compared with ITT; less discriminatory than ITT; arginine contraindicated in liver or renal disease.
Glucagon	1 mg IM	0, 30, 60, 90, 120, 150, 180; alternatively at 9, 60, 120, 180, 240	Tests pituitary-adrenal axis in addition to GH secretion.	Less effective stimulation of GH; less discriminatory than ITT; may cause nausea and vomiting.
Levodopa (L-dopa)	500 mg (>35 kg) PO	0, 60, 90; alternatively at 0, 30, 60, 90, 120	Safer than ITT.	Contraindicated in elderly, SBP <100 mm Hg; less effective stimulation of GH; less discriminatory than ITT; may cause hypotension, nausea, and vomiting.
Clonidine	0.2 µg/kg IV over 10 min	0, 30, 60, 90, 120		Causes a fall in blood pressure and may cause drowsiness; the patient should remain recumbent throughout the procedure; much less discriminatory than ITT.

IV indicates intravenously; GH, growth hormone; GHRH, growth hormone releasing hormone; IM, intramuscularly; PO, orally; SBP, systolic blood pressure.

Source: Adapted from Monson JP, Cook DM. *Growth Hormone Deficiency in Adults: A Pocket Guide to Clinical Management*. 2003.

GHD. We should, therefore, consider this stimulation test as a very crude screening test for GHD. The stimulation test using clonidine has evidence that it is extremely poor in discriminating for GHD in adults.<sup>11</sup>

IGF-1 levels are a valuable biochemical marker of GH secretion. Low IGF-1 levels in

the setting of hypothalamic-pituitary disease suggest GHD. Low IGF-1 may also result from causes other than GHD, such as malnutrition, diabetes, hypothyroidism, or liver disease. However, IGF-1 levels are a poor diagnostic test for adult GHD if in the normal range.<sup>9</sup> A normal IGF-1 level does not exclude GHD,

**Table 4.** American Association of Clinical Endocrinologists (AACE), Growth Hormone Research Society (GRS), and British Endocrine Society (BES) Guidelines for Growth Hormone Deficiency Diagnosis in Adults

	AACE	GRS	BES
Patient population	History of pituitary disease, CO-GHD, or history of radiation	Same	Patients with GHD determined by an ITT or glucagon test with adequate supplementation of other deficient hormones and clinical features of GHD
Number of tests	One stimulation test	One or 2 tests with isolated GHD	One stimulation test
Test of choice	ITT	Same	Same

CO-GHD indicates child-onset growth hormone deficiency; GHD, growth hormone deficiency; ITT, insulin tolerance test. Source: Monson JP, Cook DM. *Growth Hormone Deficiency in Adults: A Pocket Guide to Clinical Management*. 2003.

and, nonetheless, once GHD is documented, IGF-1 levels are useful in following treatment and evaluating GH dose adjustments.

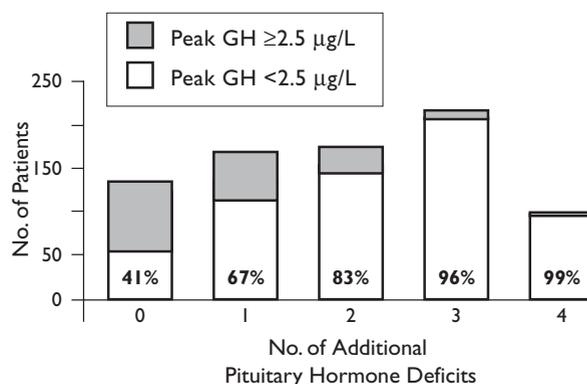
The American Association of Endocrinologists, the Growth Hormone Research Society, and the British Endocrine Society have proposed guidelines for the diagnosis of adult GHD. These guidelines (Table 4) all recommend the ITT as the test of choice but vary somewhat based on variations in practice among members of these societies.

Difficulty in conducting GH stimulation testing is often a barrier to diagnosing GHD. Conducting either an ITT or arginine-GHRH stimulation test with approximately 6 blood samples during a 2-hour period requires added, expensive personnel costs, especially for those in solo practice. The majority of clinicians in contact with patients who have GHD do not have residents, fellows, or dedicated nurses to perform these intensive testing protocols. In addition, the special equipment needed for these tests, such as infusion pumps, intravenous solutions, and exam rooms, may not be readily available. Therefore, some patients who are at risk for GHD do not get treated because they do not undergo diagnostic testing. A recent pilot study provided a regional endocrine testing facility for practicing endocrinologists based on the premise that patients belong to the referring endocrinologist, all data goes back to the patient through the referring physician, and no patient recruitment occurs with the testing. This pilot has been successful in

helping endocrinologists gain access to high-quality testing facilities.<sup>12</sup>

When GHD is highly probable, such as in patients with a history of pituitary disease, the presence of 3 or 4 other pituitary hormone deficiencies, and low IGF-1 levels, stimulation testing may not be necessary. Indeed, the probability of GHD in adults ranges from 91% to 100% in the presence of 3 to 4 other pituitary hormone deficiencies (Figure 4).<sup>11</sup>

**Figure 4.** GHD Risk Based on Other Pituitary Hormone Deficiencies



GHD indicates growth hormone deficiency; GH, growth hormone. Source: Reference 11.

Note: The number of patients within each subgroup of number of pituitary hormone deficiencies divided by whether the peak GH concentration was  $< 2.5$   $\mu\text{g/L}$  or  $\geq 2.5$   $\mu\text{g/L}$  on standard GH stimulation test. The figure shows the percentage of patients within each subgroup with a peak GH level  $< 2.5$   $\mu\text{g/L}$ .

Because GHD in adults is a deficiency associated with known morbidity, higher CV mortality, and there is an approved replacement medication available, it is important that diagnosis and treatment be offered to appropriate patients. The possibility of GHD should be considered in patients with other pituitary hormone deficiencies and those who have had surgery in the sellar area. In addition, patients with pituitary-hypothalamic radiation exposure, including brain irradiation, childhood-onset GHD, or head trauma are prime candidates for testing as well. It is controversial whether testing for GHD is appropriate in patients with systemic symptoms or signs consistent with GHD (ie, low energy, unexplained metabolic syndrome, or display inexplicably low bone density in the absence of other causes). Although more than 90% of adults with GHD have some form of pituitary-hypothalamic disease, the remaining 10% are idiopathic with normal pituitary magnetic resonance imaging findings. Once identified, GH treatment should be weighed against alternative options, such as treatment with statins and bisphosphonates.<sup>12</sup> Further research will determine the importance of evaluating this population. Currently, it is important to identify and treat patients with pituitary-hypothalamic disease and a high likelihood of definite GHD.

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