Revista de Endocrinología y Nutrición

Volumen *Volume* **13** **Suplemento** *Supplement* **1** **Julio-Septiembre** *July-September* **2005**

Artículo:

Hypopituitarism

Revista de Endocrinología y Nutrición Vol. 13, No. 3. Supl.1
Julio-Septiembre 2005
pp S47-S51

Hipófisis

Hypopituitarism

Mark E. Molitch*

* Division of Endocrinology, Metabolism and Molecular Medicine. Northwestern University Feinberg School of Medicine.

Hypopituitarism indicates the diminished production of one or more anterior pituitary hormones. Although the recognition of complete or panhypopituitarism is usually straightforward, the detection of partial or selective hormone deficiencies is more challenging. Pituitary hormone deficiencies can be caused by loss of hypothalamic stimulation (tertiary hormone deficiency) or by direct loss of pituitary function (secondary hormone deficiency). The distinction between hypothalamic and pituitary causes of hypopituitarism is important for establishing the correct diagnosis and but less so when applying and interpreting the relevant diagnostic endocrine tests. With improved procedures for testing the hypothalamic-pituitary axis, it is apparent that hypothalamic causes of hypopituitarism are more common than previously appreciated. When hypopituitarism is accompanied by diabetes insipidus or hyperprolactinemia, one should particularly consider hypothalamic causes of pituitary dysfunction.

CAUSES OF HYPOPITUITARISM

A variety of congenital and acquired causes of hypopituitarism have been described *(Table I)*. Sporadic and familial forms of panhypopituitarism occur, but the underlying genetic or developmental defects have not been elucidated. Congenital combined deficiencies of GH, PRL, and TSH are caused by mutations in the gene encoding Pit-1, a pituitary-specific transcription factor that is involved in the development of somatotroph, lactotroph, and thyrotroph cell lineages. Different types of Pit-1 mutations are inherited in an autosomal dominant or recessive pattern. When gonadotrophs are also deficient, mutations may be present in the genes for transcription factors that are active earlier in the development of the pituitary lineages, such as *Lhx3* and *Prop-1*.

Gene mutations have been found at several steps leading to pituitary hormone secretion, including those for the hypophysiotropic releasing factor receptors for GnRH, GHRH, and TRH; those for the pituitary hormone structures for GH, ACTH, and the a subunits of FSH, TSH, and LH; and those for the target organ receptors for GH, ACTH, TSH, and LH. Best studied are mutations of the GH gene, which include large deletions and point mutations; some of these can be inherited in an autosomal dominant manner, apparently because the mutant hormone impairs GH biosynthesis and normal function of the somatotroph cell. Mutations of the other types described earlier generally cause autosomal recessive forms of selective hormone deficiencies.

The most common embryopathic disorders to affect the hypothalamus are the midline cleft syndromes, which cause varying degrees of defects of midline structures, especially the optic and olfactory tracts, the septum pellucidum, the corpus callosum, the anterior commissure, the hypothalamus, and the pituitary. The clinical features of patients with midline cleft defects varies in severity from cyclopia to cleft lip and from isolated hypothalamic hormone defects to panhypopituitarism. The combination of absent septum pellucidum associated with optic nerve hypoplasia is referred to as *septo-optic dysplasia* and is associated with abnormalities of hypothalamic and other diencephalic structures. Some patients with septo-optic dysplasia and hypothalamic hypopituitarism have sexual precocity, presumably caused by a lack of inhibitory influences from other parts of the hypothalamus and intact GnRH-producing structures. Children with very mild midline cleft defects consisting of just cleft lip, cleft palate, or both have been found to have a markedly increased risk of having GH and other pituitary hormone deficiencies. Recent MRI studies of patients with "idiopathic" GH deficiency show absence of the infundibulum in nearly 50%.

Table 1. Causes of hypopituitarism.

Genetic defects
Hypophysiotropic hormone gene defects
Hypophysiotropic hormone receptor gene defects
GHRH receptor defect
GnRH receptor defect
TRH receptor defect
Pituitary hormone gene defects
Gonadotropins: LH β- and FHS β-subunit gene defects
Growth hormone: defects in GH gene
Thyrotropin: defects in TSH β-subunit
Multiple hormone (GH, PRL, TSH) defects: due to mutation in Pit-1 gene and Propl gene
Pituitary hormone receptor genetic defects
Growth hormone receptor defects: GH insensitivity syndrome (Laron-type dwarfisin)
ACTH receptor defects: congenital insensitivity to ACTH
LH receptor defects
FSH receptor defects
TSH receptor defects
Congenital embryopathic defects
Anencephaly
Midline cleft defects: septo-optic dysplasia, basal encephalocele, cleft lip and palate
Pituitary aplasia
Kallmann's syndrome (GnRH defect with anosmia)
Acquired defects
Tumors: pituitary adenomas, craniopharyngiomas, dysgerminomas, meningiomas, gliomas, metastatic tumors, hamartomas, Rathke's cleft cysts
Irradiation
Trauma: surgery, external blunt trauma
Empty sella syndrome
Vascular
Pituitary apoplexy
Sheehan's syndrome
Internal carotid aneurysm
Vasculitis
Inflammatory/infiltrative diseases
Sarcoidosis
Langerhans' cell histiocytosis (histiocytosis X, eosinophilic granuloma)
Tuberculosis, syphilis
Meningitis
Lymphocytic hypophysitis, infundibulohypophysitis
Metabolic
Hemochromatosis
Amyloidosis
Critical illness
Malnutrition
Anorexia nervosa
Psychosocial deprivation
Idiopathic

Mutations responsible for these developmental defects are the subject of active investigation. One possible mutation that has been found is in the *Hesx1* gene (also called *Rpx*, for Rathke's pouch homeobox), which is a member of the paired-like class of homeobox genes expressed in the thickened layer of oral ectoderm that gives rise to Rathke's pouch. Many other transcription factors have been described that are expressed sequentially during embryogenesis in Rathke's pouch that are important in the ultimate development of the normal pituitary cell lineages. Mutations have been found in many of these transcription factors genes, including *Pit-1* and *Prop-1* (discussed above); *Lhx3* and *Lhx4* which give similar clinical findings to *Prop-1* mutations but have additional cervical spine and skull base abnormalities; and *Sox3*, which gives rise to isolated GH deficiency and variable mental retardation and facial abnormalities . Combined pituitary hormone deficiency has an incidence of about 1 in 8,000 births and about 10% have an affected relative; it appears that more than half of these cases are due to *Pit-1* or *Prop-1* deficiencies.

Neoplastic lesions, particularly pituitary adenomas, are the most common cause of acquired hypopituitarism. Pituitary adenomas cause hypopituitarism in several different ways. In some cases, there is direct destruction or compression of the normal pituitary. Compression of the pituitary stalk can impair blood supply to the pituitary as well as decrease input from hypothalamic hormones. Hemorrhage into tumors can lead to pituitary infarction. When tested carefully, most patients with macroadenomas have partial deficiencies of one or more pituitary hormones, most often involving GH and gonadotropins. A mild degree of hyperprolactinemia is characteristic of disorders that cause stalk compression, and hyperprolactinemia further impairs gonadotropin secretion. A variety of other neoplasms that occur near the sella, such as craniopharyngiomas, can also cause hypopituitarism.

Radiation causes hypopituitarism primarily because of its effects on hypothalamic function, although high-dose radiation (e.g., proton beam) can also cause direct pituitary damage. The sellar region is subjected to radiation in the treatment of pituitary adenomas, craniopharyngiomas, optic gliomas, meningiomas, dysgerminomas, and neoplasms of the oropharynx. Importantly, the effects of radiation can be delayed as much as several years, and patients at high risk should be evaluated at about yearly intervals for radiation-induced hypopituitarism. Although GH and gonadotropin deficiencies develop first in most patients, ACTH or TSH deficiencies occasionally occur first, emphasizing the need to evaluate each of the major axes.

Empty sella syndrome can occur as a primary or as an acquired condition. It is caused by defects in the diaphragma sellae that allow herniation of the arachnoid membrane

into the hypophyseal fossa. In long-standing cases, sellar enlargement occurs, probably because of persistent transmission of intracranial pressure. With appropriate imaging studies, the pituitary gland can be seen as a flattened rim of tissue along the floor of the sella. Primary empty sella occurs most commonly in women and may be associated with features of benign intracranial hypertension. Pituitary function in patients with primary empty sella syndrome is usually normal, although 15% have mild hyperprolactinemia, probably because of stretching of the pituitary stalk. Acquired forms may occur as a result of surgery, radiation, or pituitary infarction (usually of an adenoma).

Pituitary apoplexy is usually caused by hemorrhage into a tumor with associated infarction. In the absence of a tumor, predispositions to apoplexy include trauma, pregnancy, anticoagulation, sickle cell anemia, and diabetes mellitus. Pituitary infarction in the peripartum period is referred to as Sheehan's syndrome and is usually associated with significant obstetric hemorrhage and hypovolemia. Although Sheehan's syndrome may manifest acutely with vascular collapse, it more commonly has a subacute manifestation consisting of postpartum inability to lactate, amenorrhea, and symptoms of adrenal insufficiency. Sheehan's syndrome is now infrequent, owing to improvements in obstetric care.

Infiltrative diseases such as sarcoidosis, histiocytosis, and tuberculosis usually cause hypopituitarism by infiltrating the hypothalamus and stalk rather than the pituitary. In lymphocytic hypophysitis, there is massive infiltration of the pituitary by lymphocytes and plasma cells

Table II. Test of pituitary insufficiency.

Hormone	Test	Interpretation
Growth hormone (GH)	*Insulin tolerance test:* Regular insulin (0.5-0.15 U/kg) is given IV and blood is drawn at -30, 0, 30, 45, 60, and 90 min for measurement of glucose and GH	If hypoglycemia occurs (glucose < 40 mg/dL), GH should increase to > 5 µg/L.*
	Arginine-GHRH test: GHRH 1µg/kg IV bolus followed by 30 min finsuion of L-arginine (30g)	Normal response is GH > 4.1 µg/L
Adrenocorticotropic Hormone (ACTH)	Insulin tolerance test: Regular insulin (0.5-0.15 U/kg) is given IV and blood is drawn at -30, 0, 30, 45, 60, and 90 min for measurement of glucose and cortisol.	If hypoglycemia occurs (glucose < 40 mg/dL), cortisol should increase by > 7 µg/dL or to >20 µg/dL.
	Metyrapone test: Metyrapone (30 mg/kg-max. 2 g) at midnight with measurements of plasma 11-deoxycortisol and cortisol at 8 AM. ACTH can also be measured. A 3-day test is also available. Basal cortisol should be > 5-6 µg/dL before test.	A normal response is 11-deoxycortisol > 7.5 µg/dL or ACTH > 75 pg/mL. Plasma cortisol should fall below 4 µg/dL to ensure an adequate response.
	*ACTH stimulation test: ACTH 1-24 (Cosyntrop*in), 0.25 mg IM or IV. Cortisol is measured at 0, 30, and 60 min.	A normal response is cortisol > 18 µg/dL. In suspected hypothalamic-pituitary deficiency, a low dose (1 µg) test may be more sensitive.
Thyroid-stimulating hormone (TSH)	*Basal thyroid function tests:* free T_4, free T_3, TSH.	Low free thyroid hormone levels in the setting of TSH levels that are not appropriately increased.
Luteinizing hormone (LH), follicle-stimulating hormone (FSH)	*Basal levels of LH, FSH, testosterone, estrogen*	Basal LH and FSH should be increased in postmenopausal women. Low testosterone levels in conjunction with low or low-normal LH and FSH are consistent with gonadotropin deficiency.
	*GnRH test: GnRH (1*00 µg) IV with measurements of serum LH and FSH at 0, 30, and 60 min.	In most normal persons, LH should increase by 10 IU/L and FSH by 2 IU/L. Normal responses are variable, and repeated stimulation may be required.

with destruction of the parenchyma; it is believed to have an autoimmune basis. The lesion that develops is usually large, and patients present with either symptoms or signs of hypopituitarism or those of a mass lesion (i.e., visual field defects and/or headaches). Some patients may have mild hyperprolactinemia and diabetes insipidus. There seems to be a particular predilection for damage to the corticotroph cells, resulting in ACTH/adrenal insufficiency. Almost all cases have been reported in women, and most present during or after pregnancy. Because of the presentation as a mass lesion during pregnancy, such lesions may be confused with prolactinomas, but the mild PRL elevation points to a nonsecretory lesion rather than a prolactinoma. MRI cannot reliably differentiate pituitary adenoma from hypophysitis, although hypophysitis usually manifests with a diffuse enlargement of the pituitary that enhances, rather than as a focal lesion. Diagnosis is usually made by biopsy, but the lesion may be suspected clinically if it manifests during or just after pregnancy. Careful pituitary function testing is mandatory, because many of the patients in the reported cases went undiagnosed and died of adrenocortical insufficiency. Although the prognosis is not clear, a number of cases have resolved spontaneously. An entity with similar histologic findings involving the stalk and posterior pituitary, referred to as *infundibuloneurohypophysitis*, can cause diabetes insipidus. The causes and interrelationships between these entities remain unknown.

The pituitary may undergo damage because of iron deposition in patients with hemochromatosis and amyloid fibrils in patients with systemic amyloidosis. Functional, reversible hypopituitarism of varying degrees occurs in patients with severe systemic illness, severe psychosocial and emotional deprivation, and severe weight loss - particularly in those with anorexia nervosa.

DIAGNOSIS AND TREATMENT

The diagnosis of hypopituitarism rests on the stimulation tests that are summarized in *Table II*. Children diagnosed with GH deficiency during childhood should be retested as adults when considering continuation of GH therapy, unless the GH deficiency was documented to be due to a proven genetic defect or structural lesions

Table III. Hormone replacement in hypopituitarism.

Pituitary axis	Hormonal replacements
Growth hormone (GH)	In children, GH (0.25 mg/kg) SC daily. In adults, GH (0.3-1.2 mg) SC daily. Titrate dose to achieve IGF-1 levels in upper part of normal range. Women receiving oral estrogens require higher doses
Prolactin	None
Adrenocorticotropic hormone-cortisol	Prednisone (2.5 mg PO qAM; 2.5 mg PO qPM) or hydrocortisone (10-20 mg PO qAM; 5-10 mg PO qPM). Dose adjusted on clinical basis. Stress dosing: 50 – 75 mg hydrocortisone IV q8h
Thyroid-stimulating hormone-thyroid	L-Thyroxine (0.075-0.15 mg) PO qd
Gonadotropins-gonads	Pulsatile GnRH (via pump) can be used for GnRH-deficient subjects, or FSH and LH (or hCG) can be used to induce ovulation in women. hCG alone, or FSH and LH, can be used to induce spermatogenesis in men. In men, testosterone enanthate (100-300 mg) IM q1-3 weeks or testosterone cyclopentylpropionate (100-300 mg) IM q1-3 weeks. Testosterone transdermal patches can also be used (5 mg qd). Testosterone gel (1%) 1-2 packets (5-10 g) daily. In women, conjugated estrogens (0.625-1.25 mg) or mestranol (35 mg) PO days 1-25 each month cycled with medroxyprogesterone acetate (5-10 mg) PO days 15-25 each month. Low-dose contraceptive pills may also be used. Estrogen-containing transdermal patches are also available.
Posterior pituitary	Desmopressin, 0.5-0.2 mL (5-20 µg) intranasally once or twice daily, or tablets (0.1-0.4 mg every 8-12 hr) or 0.5 mL (2 µg) SC.

* Replacement therapy is dictated by the types of hormone deficiencies and by the clinical circumstances. In each case, the recommended preparations and doses are representative but need to be adjusted for individual patients. Other hormonal preparations are also available. FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone.

causing multiple hormone deficiencies. A recent study evaluated the relative performance of the GHRH-arginine test, the ITT, arginine alone, clonidine, levodopa, and the combination of arginine plus levodopa in the diagnosis of adult GH deficiency. The overall performance of the GHRH-arginine test, with 95% sensitivity and 91% specificity at a GH cutoff of 4.1 µg/L at the central laboratory used, compared well to the ITT, which had an optimal GH cutoff of 5.1 µg/L (96% sensitivity and 92% specificity). However, if a patient has deficiencies in three or more other axes, they have a greater than 95% chance of being GH deficient. Measurement of IGF-I alone is not sufficient to make a diagnosis of GH deficiency, as many patients with defective GH responses have IFG-I level in the low-normal range.

Therapy for hypopituitarism depends on the nature and severity of the hormone deficiencies as well as on the desired clinical endpoints. The goal is to replace hormones in a physiologic manner, with efforts to avoid the consequences of overreplacement. In patients with acquired forms of hypopituitarism (e.g., pituitary tumors, radiation treatment), it is not uncommon to encounter a mixture of partial hormone deficiencies. It is generally prudent to provide hormone replacement if partial deficiency is suspected, because patients may experience symptoms over a number of years before an unequivocal diagnosis of hormone deficiency is made. Examples of hormonal replacement paradigms are provided in *Table III*. Adjustment of hormone doses is done primarily based on clinical findings; it should be remembered that the TSH level is not helpful for adjusting thyroxine doses in patients with central hypothyroidism. Even when conventional hormone replacement (adrenal, thyroid, gonadal) is carried out appropriately, there is an approximately twofold excess risk of death reported in patients with hypopituitarism.

Although untreated GH deficiency has been hypothesized to be the cause of this excess risk, this has not been proven. The benefits of GH therapy are less clear than those for the other pituitary hormones and include improvements in body composition, bone and quality of life; although there are few adverse effects, treatment involves daily injections. GH in adults is generally started at a dose of 0.2 – 0.3 mg daily and adjusted upwards gradually with the goal of achieving an IGF-1 level in the upper part of the normal range. Women receiving oral estrogens usually require substantially higher doses of GH than men. It should be emphasized that for GH treatment, long-term clinical outcomes studies on hard endponts such as fractures, clinical heart disease, cancer, and mortality are still lacking at present.

SUGGESTED READING

1. Agha A, Rogers B, Sherlock M et al. Anterior pituitary dysfunction in survivors of traumatic brain injury. *J Clin Endocrinol Metab* 2004; 89: 4929-4936.
2. Aimaretti G, Ambrosio MR, Di Somma C et al. Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. *Clin Endocrinol (Oxf)* 2004; 61(3): 320-326.
3. Arafah BM. Reversible hypopituitarism in patients with large non-functioning pituitary adenomas. *J Clin Endocrinol Metab* 1986; 62: 1173-1179.
4. Arafah BM. Medical management of hypopituitarism in patients with pituitary adenomas. *Pituitary* 2002; 5: 109-117.
5. Bates AS, Van't Hoff W, Jones PJ, Clayton RN. The effect of hypopituitarism on life expectancy. *J Clin Endocrinol Metab* 1996; 81: 1169-1172.
6. Biller BMK, Samuels MH, Zagar A et al. Sensitivity and specificity of six tests for the diagnosis of adult growth hormone deficiency. *J Clin Endocrinol Metab* 2002; 87: 2067-2079.
7. Cohen LE, Radovick S. Molecular basis of combined pituitary hormone deficiencies. *Endocr Rev* 2002; 3: 431-442.
8. Feigl GC, Bonelli CM, Berghold A, Mokry M. Effects of gamma knife radiosurgery of pituitary adenomas on pituitary function. *J Neurosurg* 2002; 97(5 suppl): 415S-421S.
9. Gama R, Smith MJ, Wright J, Marks V. Hypopituitarism in primary haemochromatosis: recovery after iron depletion. *Postgrad Med J* 1995; 71: 297-298
10. Hartman ML, Crowe BJ, Biller BMK, Ho KY, Clemmons DR, Chipman JJ. Which patients do not require a growth hormone (GH) stimulation test for the diagnosis of adult GH deficiency? *J Clin Endocrinol Metab* 2002; 87: 477-485.
11. Kaltsas GA, Powles TB, Evanson J et al. Hypothalamo-pituitary abnormalities in adult patients with Langerhans cell histiocytosis: clinical, endocrinological, and radiological features, and response to treatment. *J Clin Endocrinol Metab* 2000: 85; 1370-1376.
12. Lamberts SWJ, deHerder WW, van der Lely AJ. Pituitary insufficiency. *Lancet* 1998; 352: 127-134.
13. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Applegate G, Sutton ML. Hypopituitarism following external radiotherapy for pituitary tumours in adults. *Q J Med* 1989; 70(262): 145-160.
14. Rosen T, Bengtsson BA. Premature mortality due to cardiovascular disease in hypopituitarism. *Lancet* 1990; 336: 285-288.
15. Tomlinson JW, Holden N, Hills RK et al. The West Midlands Prospective Hypopituitary Study Group. Association between premature mortality and hypopituitarism. *Lancet* 2001; 357: 425-431.
16. Vance ML. Hypopituitarism. *N Engl J Med* 1994; 330: 1651-1662.
17. Webb SM, Rigla M, Wägner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. *J Clin Endocrinol Metab* 1999; 84: 3696-3700.
18. Zargar AH, Masoodi SR, Laway BA et al. Clinical spectrum of Sheehan's syndrome. *Ann Saudi Med* 1996; 16: 338-341.