Hypopituitarism

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Endocrinology  Volume 4, Part 3  1
INTRODUCTION

Hypopituitarism refers to the decreased secretion of one or more anterior pituitary hormones. The clinical presentation depends on how rapidly the anterior lobe is affected, the specific cells involved, and the severity of the functional impairment.

In the classic case of anterior pituitary hormone loss, gonadotropins are affected first, followed by growth hormone (GH), thyroid-stimulating hormone (TSH; thyrotropin), and finally adrenocorticotropic hormone (ACTH; corticotropin). Hypopituitarism may develop acutely, such as pituitary apoplexy following hemorrhage into a preexisting pituitary adenoma. In contrast, radiation therapy exerts its effects slowly, and the hormone deficiency may not manifest clinically for months to years.

In assessing the clinical presentation of a patient with hypopituitarism, one should consider the loss of each anterior pituitary hormone individually. With some exceptions, the loss of production of an anterior pituitary hormone results in clinical manifestations similar to those arising from failure of the target gland the pituitary hormone controls. The most common presenting symptom of hypopituitarism in men and premenopausal women is hypogonadism, secondary to gonadotropin deficiency or hyperprolactinemia.1 The failure to lactate following parturition may indicate a lack of prolactin secretion, the only known clinical manifestation of prolactin deficiency. ACTH deficiency causes clinical manifestations of cortisol deficiency and adrenal insufficiency. TSH deficiency results in symptoms of thyroxine deficiency and hypothyroidism. GH deficiency presents as short stature in children; adverse consequences in adults may include an increase in fat mass and a diminution of lean muscle mass, a decrease in bone mineral density, and a diminished sense of well-being.

If hypopituitarism is the result of a pituitary or sellar mass, there may be central symptoms related to the mass as well as its direction of extension. Symptoms include headache, visual loss secondary to superior extension and involvement of the optic chiasm, cranial nerve involvement and ophthalmoplegia secondary to lateral extension into the cavernous sinus, and epistaxis or rhinorrhea secondary to inferior extension.

A variety of conditions may affect the pituitary gland or hypothalamus to cause hypopituitarism (Table 1). More than 50% of cases are caused by benign pituitary macroadenomas or their treatment.2 Hypothalamic lesions also may produce hypopituitarism. The hyposecretion of pituitary hormones typically has no diagnostic value in differentiating between hypothalamic and pituitary causes of hypopituitarism. The exception is the development of spontaneous diabetes insipidus, suggesting a hypothalamic disease. Because vasopressin-producing neurons terminate in the median eminence, pituitary lesions alone will not cause diabetes insipidus.3 In contrast, the hypersecretion of a specific pituitary hormone identifies the lesion causing hypopituitarism as a pituitary adenoma, as well as the type of adenoma. It should be noted, however, that a prolactin level between 20 and 200 ng/dL may result from a lactotroph adenoma or another mass causing a stalk effect, interrupting dopamine’s inhibitory role in prolactin secretion.3

This manual provides an overview of the clinical and endocrine approach to partial pituitary failure and panhypopituitarism. The clinical work-up of potential hormone deficiencies using both static and dynamic endocrine testing are discussed, and key points regarding appropriate hormone replacement therapies are addressed.

DIAGNOSIS OF HYPOPITUITARISM

CASE PRESENTATION

Initial Presentation

A 39-year-old woman is referred by her primary care physician to an endocrine clinic for further evaluation of a 4-month history of worsening frontal headaches and a suspected pituitary tumor.

History

The patient was well until the onset of the headaches, which were initially relieved by acetaminophen
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and nonsteroidal antiinflammatory agents. After 2 months of successful conservative medical management, the patient began to complain of increasing intensity of the headaches and minimal relief from the medications. A computed tomography (CT) scan of the head revealed a homogeneously enhancing, slightly enlarged pituitary gland (13 mm). This finding prompted referral for endocrine evaluation.

In the endocrine clinic, the patient complains of a 3- to 6-month history of hot flashes, insomnia, fatigue, anorexia, and diffuse body aches. She also reports a 7.5-kg loss of body weight during the same time period. On further questioning, the patient admits to cold intolerance but denies heat intolerance as well as any change in bowel habits, tremulousness, palpitations, chest pain, loss of axillary or pubic hair, or change in her hair, skin, or nails. She has no history of polydipsia, polyuria, or nocturia; galactorrhea; change in facial appearance; increased shoe, glove, or ring size; centripetal weight gain; striae; or easy bruising. The patient had two successful pregnancies, the first when she was 27 and the second 2 years later. She lactated and breast-fed without difficulty. Although typically regular, her menstrual cycles have been irregular for the past 3 to 6 months; her last menstrual period was 1 month ago. She has no family history of endocrine or pituitary disorders.

Physical Examination

On physical examination the patient appears fatigued but otherwise well. Her blood pressure is 130/86 mm Hg, pulse is 82 bpm, and respiratory rate is 12 breaths/min. She is not orthostatic and appears well hydrated. Skin examination is unremarkable, physical stigmata of Cushing’s disease or acromegaly are absent, and no galactorrhea is noted with breast compression. No defect is detected in her visual fields. There is a delay in the relaxation phase of the Achilles deep tendon reflexes.

Laboratory Studies

Routine laboratory studies (ie, electrolytes, blood urea nitrogen, creatinine, complete blood count with differential, urinalysis) completed recently by the patient’s primary care physician were all within the normal range.

- What is the endocrine differential diagnosis for this patient?

This patient’s recent history of headaches combined with hot flashes and menstrual cycle disturbance suggests the possibility of estrogen withdrawal. Estrogen withdrawal itself has been shown to be the basis of vasomotor lability that accounts for hot flashes.1 Classically, the gonadotropins are the first hormones to be lost in primary disease of the pituitary gland, as is suspected in this case.5

The patient’s fatigue, cold intolerance, and general aches may indicate primary or secondary hypothyroidism. These same symptoms, accompanied by weight loss, also suggest the possibility of adrenal insufficiency in a patient with a suspected pituitary disease. There is no reason to believe that the patient previously had insufficient prolactin secretion, given her ability to lactate. Her history does not suggest diabetes insipidus. These historical points, in conjunction with an abnormal pituitary gland visualized on CT, warrant an endocrine evaluation. It is prudent to perform endocrine testing before proceeding to magnetic resonance imaging (MRI) due to the prevalence of incidentally discovered pituitary adenomas.

- How are specific anterior pituitary hormone deficiencies diagnosed?

Table 1. Causes of Partial Pituitary Failure and Panhypopituitarism

<table>
<thead>
<tr>
<th>Pituitary Disease</th>
<th>Panhypopituitarism</th>
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<tr>
<td>Pituitary adenomas</td>
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<td>Other benign tumors (craniopharyngiomas, meningiomas)</td>
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<td>Cysts</td>
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<td>Malignant tumors (rare)</td>
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<td>Metastatic disease (rare)</td>
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<tr>
<td>Pituitary surgery or radiation</td>
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<tr>
<td>Infiltrative disease (hemochromatosis, lymphocytic hypophysitis)</td>
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<td>Infarction (Sheehan syndrome)</td>
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<td>Infection, abscess</td>
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<td>Pituitary apoplexy</td>
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<td>Empty sella syndrome</td>
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<tr>
<td>Genetic disease</td>
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</tbody>
</table>

Hypothalamic disease

| Mass lesions                      |                   |
| Benign or malignant tumors        |                   |
| Metastatic disease (most commonly from lung or breast) | |
| Radiation therapy for central nervous system and nasopharyngeal malignancies | |
| Infiltrative disease (sarcomiosis, Langerhans cell histiocytosis) | |
| Trauma (skull base fracture)      |                   |
| Infection                         |                   |
Testing for hypopituitaryism should be done on the grounds of a clinical suspicion that one or more anterior pituitary hormones may be insufficient. This suspicion may arise from the clinical presentation or from the knowledge of a sellar or suprasellar lesion that may involve the pituitary gland or hypothalamus. Under baseline conditions, some patients with hypopituitarism may be asymptomatic; therefore, the knowledge of a pituitary lesion without symptoms is a sufficient reason to test the pituitary axis. The exception may be a pituitary incidentaloma that is less than 10 mm. In this case, the most cost-effective approach is to obtain a serum prolactin level. If this is normal and the patient has no other symptoms of pituitary dysfunction, other significant hormone abnormalities are not likely to exist. Such a lesion should not be ignored, however, and repeat MRI after 6 to 12 months is generally recommended to assess for further growth.

The diagnosis of hypopituitarism depends on the demonstration of a subnormal secretion of one or more pituitary hormones via static and dynamic tests of pituitary function. The status of one pituitary hormone does not predict the status of another, and each hormone must be tested directly.

**GONADOTROPIN DEFICIENCY**

Gonadotropin deficiency often presents earlier in women than in men and is most common in women of childbearing age. The hypogonadism, or ovarian hypofunction, results in hypo-estrogenemia and a variety of clinical symptoms (ie, amenorrhea or oligomenorrhea, fatigue, vaginal dryness, hot flashes). Menopause and/or primary ovarian failure is documented by the presence of low estrogen levels and elevated gonadotropin levels. Secondary hypogonadism is associated with low estrogen levels and inappropriately normal gonadotropin levels. After several years, breast tissue and bone mineral density may decline, and the patient may present with fine facial wrinkles.

In men, testicular hypofunction and resultant decreased testosterone secretion typically cause a decreased libido and fatigue within months. Years of testosterone deficiency will result in losses to muscle mass and bone mineral density.

The approach to diagnosing gonadotropin deficiency in a patient with hypopituitarism varies with the gender of the patient. The best test of gonadotroph deficiency in a premenopausal woman is the menstrual history. In a woman with known pituitary or hypothalamic disease and normal menses, no tests of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) secretion are necessary, as a normal menstrual history is a more sensitive indicator of intact pituitary-gonadal function than any available biochemical test. In a woman with oligomenorrhea or amenorrhea, LH and FSH levels should be measured to distinguish ovarian disease from pituitary or hypothalamic disease.

LH and FSH are secreted in a pulsatile manner so that a single measurement may be in the normal range in a woman with oligomenorrhea; however, normal values are inappropriate in women with amenorrhea and in postmenopausal women. Estradiol levels may be low or normal in women with gonadotropin deficiency and provide little information beyond the menstrual history. Men with gonadal failure may have normal or low serum LH or low FSH levels, but normal values are inappropriate if the serum testosterone is decreased, suggesting pituitary or hypothalamic disease.

Although widely used, the serum LH response to a single bolus of gonadotropin-releasing hormone (GnRH) does not help distinguish secondary hypogonadism due to pituitary disease from that resulting from hypothalamic disease. Patients with hypogonadism due to pituitary disease and those with hypothalamic disease may have a normal or subnormal LH response to GnRH stimulation.

**THYROTROPIN DEFICIENCY**

The clinical presentation of TSH deficiency is that of hypothyroidism, and the degree of clinical signs and symptoms typically parallels the degree of thyroxine deficiency. Some patients, however, may present with an insidious course despite marked TSH deficiency. Some of the more common nonspecific signs and symptoms include fatigue, lethargy, cold intolerance, constipation, dry skin, facial puffiness, bradycardia, a delayed relaxation phase of the deep tendon reflexes, and anemia.

The adequacy of TSH secretion is assessed by the simple measurement of serum free thyroxine (FT$_4$) concentration. If the serum FT$_4$ is normal, the TSH secretion is normal; if the serum FT$_4$ is low, TSH secretion is low. In patients with secondary or tertiary hypothyroidism due to pituitary or hypothalamic disease, respectively, the TSH alone is not helpful in making the diagnosis of hypothyroidism, because the TSH is usually in the normal range.

Patients with secondary hypothyroidism usually have a normal or low TSH concentration. Either is inappropriate for the low serum FT$_4$ concentration. On occasion, such a patient may have an elevated TSH because the hypothalamic or pituitary disease has caused secretion of TSH that has diminished biologic activity yet retains immunologic activity. Failure of the serum TSH concentration to increase following administration of thyrotropin-releasing hormone (TRH) confirms the
diagnosis of secondary hypothyroidism, but this finding usually is not necessary to make the diagnosis.

**CORTICOTROPIN DEFICIENCY**

ACTH deficiency, leading to secondary adrenal insufficiency, presents with signs and symptoms of cortisol deficiency. In its most severe form, secondary adrenal insufficiency may lead to death secondary to vascular collapse, as cortisol is necessary for the maintenance of peripheral vascular tone. Mild chronic deficiency presents in a more insidious manner, with symptoms including fatigue, anorexia, weight loss, decreased libido, lassitude, hypoglycemia, and eosinophilia.

Primary and secondary adrenal insufficiency are clinically distinct in two ways. First, secondary adrenal insufficiency is characterized by normal renin-angiotensin-aldosterone responses and normal mineralocorticoid secretion. ACTH deficiency with resultant secondary adrenal insufficiency does not cause salt wasting, volume contraction, or hyperkalemia. Hypovolemia is unusual and is less severe in secondary than in primary adrenal insufficiency. Second, ACTH deficiency does not result in hyperpigmentation, which is characteristic of primary adrenal insufficiency. Both forms of adrenal insufficiency may result in hyponatremia due to the inappropriate secretion of antidiuretic hormone (ADH; vasopressin). The hyponatremia results from the impairment of renal free water excretion and subsequent water retention. Cortisol deficiency is responsible for the syndrome of inappropriate ADH secretion (SIADH); corticosteroid replacement therapy results in a correction in renal concentrating abilities.

Ninety percent of patients with impaired ACTH secretion have a decreased response to cosyntropin (synthetic ACTH 1-24) stimulation. The standard test is performed by the intravenous or intramuscular administration of a high dose (250 mcg) of cosyntropin. The adrenal response is evaluated by measuring cortisol levels 30 and 60 minutes following injection. If corticotroph and adrenal secretion are normal, the serum cortisol concentration should rise to an absolute level of 18 mcg/dL or higher.

A subnormal cortisol response to synthetic ACTH confirms the diagnosis of adrenal insufficiency but does distinguish between primary and secondary insufficiency. A low-dose test, using 1 mcg of cosyntropin, may be more sensitive than the high-dose test. The results of low-dose testing have been shown to correlate highly with those of insulin-tolerance testing in the evaluation of a possible ACTH deficiency. The low-dose test may detect partial adrenal insufficiency that may be missed by the high-dose test, which uses a supraphysiologic stimulus.

A normal cortisol response to synthetic ACTH excludes primary adrenal insufficiency but does not exclude secondary adrenal insufficiency of recent onset. Recent pituitary lesions do not allow sufficient time for adrenal atrophy to occur, and the adrenal glands may respond to ACTH stimulation. Therefore, a pituitary lesion of recent onset with resultant undersecretion of corticotropin may be missed by relying on the cosyntropin stimulation test. In a similar manner, the cosyntropin stimulation test may miss chronic partial pituitary ACTH deficiency. For these reasons, patients with a pituitary lesion and a normal response to synthetic ACTH require a dynamic test of corticotroph reserve. In patients with severe corticotropin deficiency for more than a few weeks, the serum cortisol response to synthetic ACTH will be decreased or absent as a result of adrenal atrophy.

There are several tests of ACTH reserve, including the metyrapone test and the insulin-induced hypoglycemia test. The results of the metyrapone test correlate well with the serum cortisol response to surgical stress. Metyrapone blocks the activity of 11-hydroxylase, the enzyme that catalyzes conversion of 11-deoxycortisol to cortisol. Therefore, metyrapone administration results in an increase in ACTH secretion and 11-deoxycortisol, with a concomitant reduction in cortisol secretion. Interpretation of the metyrapone test requires adequate inhibition of cortisol secretion. Inadequate inhibition may result from noncompliance, malabsorption, or rapid metabolism of metyrapone, which may result from medications such as phenytoin therapy.

Insulin-induced hypoglycemia is a sufficient stress to stimulate ACTH and therefore cortisol secretion. The insulin-induced hypoglycemia test involves measuring serum glucose, cortisol, and GH concentrations before, at baseline, and at 15, 30, 60, 90, and 120 minutes after an insulin injection (0.1 unit per kg body weight). The serum glucose should decrease to less than 50% of the baseline value or less than 40 mg/dL (2.2 mmol/L) for adequate hypothalamic-pituitary stimulation. The serum cortisol should increase to 20 mcg/dL or higher, and the serum GH should increase to 10 ng/mL or higher. Because of the risks associated with hypoglycemia, this test must be performed under the direct supervision of a physician. Contraindications include a history of a seizure disorder, coronary artery disease with a history of angina, altered mental status, or generalized debility.

**GROWTH HORMONE DEFICIENCY**

There is increased interest in testing GH secretion and reserve in patients with hypothalamic or pituitary
Hypopituitarism
disease, given the recent approval of GH therapy for
treatment of abnormal body composition and dyslipi-
demia in adults with GH deficiency. The diagnosis of
GH deficiency in adults is likely if the patient has docu-
mented panhypopituitarism. In patients with organic
pituitary disease, GH secretion is more likely to be affect-
ected than are TSH and ACTH secretion. In patients with
organic pituitary disease and no other pituitary hor-
mone deficits, the likelihood of GH deficiency is 45%.
The likelihood is nearly 100% in patients with multiple
hormone deficits. Furthermore, multiple deficiencies
of other pituitary hormones, including TSH, ACTH,
and gonadotropins, correlate highly with an inadequate
GH response to direct stimulation.

A single GH measurement is not useful in making a
diagnosis of GH deficiency, as GH is secreted in a pul-
satile manner and the serum concentration is normally
low during most of the day. Measurement of serum
insulin-like growth factor 1 (IGF-1; somatomedin C),
which is dependent on GH secretion, may indicate a
deficiency of somatotroph function, if the patient is not
malnourished, chronically ill, or elderly (all conditions
that decrease the production of IGF-1). However,
serum IGF-1 measurements do not distinguish reliably
between normal and subnormal GH secretion in adults.
In two series of more than 200 adults with proven GH
deficiency, 34% to 51% had a serum IGF-1 within the
normal range.

Provocative tests to diagnose GH deficiency include
insulin-induced hypoglycemia, arginine infusion, and
a single dose of levodopa. A subnormal serum GH
response is considered to be a peak value less than
5 ng/mL. Each of the provocative tests should be
completed in the morning after an overnight fast. A
single test of GH reserve may be subnormal in a nor-
mal person. It is important to note that obesity blunts
the GH response to all of the provocative tests.

PROLACTIN DEFICIENCY

The only known clinical manifestation of prolactin
deficiency is the inability to lactate postpartum, a po-
tential clue to a previously subclinical pituitary ab-
normality. The serum prolactin level is rarely low and
may be increased in patients with hypothalamic-
pituitary disease of almost any cause. Prolactin mea-
surement may provide useful information for identify-
ing the cause of hypopituitarism as well as the potential
cause of hypogonadism. However, testing for prolactin
deficiency is unnecessary. Dynamic testing of lactotroph
reserve with TRH is not useful, because it does not dif-
ferrate between the various causes of hyperpro-
lactinemia.

ENDOCRINE EVALUATION OF CASE PATIENT

Laboratory evaluation of the patient’s pituitary and
target gland function reveals the following findings:

- Prolactin, 18 ng/mL (normal, less than
20 ng/mL)
- Estradiol, 95 pg/mL (normal, 30 to
400 pg/mL [adult premenopausal]; less than
20 pg/mL [postmenopausal])
- FSH, 4.3 mIU/mL (normal, 0.6 to
13.3 mIU/mL [adult premenopausal]; 31 to
134 mIU/mL [postmenopausal])
- LH, 3.8 mIU/mL (normal, 0.5 to
12.8 mIU/mL [adult premenopausal];
13.8 to 72 mIU/mL [cycle peak]; 15 to
64 mIU/mL [postmenopausal])
- TSH, 0.6 mcU/mL (normal, 0.3 to
3.8 mcU/mL)
- FT4, 0.6 ng/dL (normal, 0.8 to 1.8 ng/dL)
- Cortisol, random, 1.2 mcg/dL (normal, 5 to
25 mcg/dL [8 AM]); after administration of
250 mcg cosyntropin: at 30 min, 3.2 mcg/dL;
at 60 min, 3.6 mcg/dL
- ACTH, 18 pg/mL (normal, 9 to 52 pg/mL
[8 AM])
- GH, 0.9 ng/mL (normal, 0 to 5.6 ng/mL)
- IGF-1, 182 ng/mL (normal, 90 to 360 ng/mL)

- How should these endocrine test results be inter-
preted?

With normal estradiol and gonadotropin levels, this
patient has no laboratory evidence for the diagnosis of
hypogonadism, suggesting that her symptoms may be
caused by other hormone deficiencies. The patient’s
fatigue, cold intolerance, and general aches may reflect
her hypothyroidism. The FT4 is low, consistent with
hypothyroidism. The TSH is inappropriately normal,
suggesting a pituitary or hypothalamic cause for the
hypothyroidism.

The patient’s low random cortisol value suggests
adrenal insufficiency, which also may have caused her
fatigue, aches, and anorexia. The preservation of axil-
dary and pubic hair suggests that the adrenal insufficien-
cy is not long-standing, as adrenal androgens are neces-
sary for the maintenance of axillary and pubic hair in
women. In the absence of steroid therapy, an unde-
tectable or subnormal morning cortisol concentration
suggests adrenal insufficiency. A serum cortisol of
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3 mcg/dL or less (normal, 5 to 25 mcg/dL), confirmed on a second occasion, is strong evidence of adrenal insufficiency. In a patient with a disease known to result in hypopituitarism, this is usually secondary adrenal insufficiency. If the 8 AM cortisol level is equal to or greater than 18 mcg/dL, basal ACTH secretion is sufficient, and adrenal insufficiency is excluded. Serum cortisol values between 3 mcg/dL and 18 mcg/dL are intermediate, an indication of the necessity to test pituitary reserve. This patient’s subnormal response to the cosynotropin stimulation test indicates adrenal insufficiency. The normal ACTH in this patient is inappropriate for her low level of circulating cortisol and establishes the diagnosis of secondary adrenal insufficiency.

Does this patient require further testing?

Given this patient’s endocrine findings and the pituitary abnormality suggested on her earlier CT scan, she should undergo MRI of the brain and pituitary gland to identify the specific nature of the abnormality. MRI is the single best method of visualizing sellar masses, and no other imaging modality usually is necessary. Normal pituitary tissue—and most sellar masses—emit a signal that is similar to or slightly greater in intensity than that of central nervous system (CNS) tissue. Normal pituitary tissue takes up gadolinium to a greater degree than CNS tissue, resulting in a higher intensity signal than is emitted from the surrounding CNS tissue.

FURTHER EVALUATION OF CASE PATIENT

The patient’s clinical and biochemical evidence for secondary hypothyroidism and adrenal insufficiency and her lack of evidence for other hormone abnormalities lead the endocrinologist to conclude that she has partial hypopituitarism secondary to a mass lesion in the sella turcica. MRI studies of the brain are ordered to evaluate the sellar region.

Brain Imaging

MRI of the brain demonstrates a smooth mass (14 mm × 22 mm × 13 mm) that fills the sella turcica and extends superiorly, with a mass effect on the central portion of the optic chiasm. The infundibulum is buckled and slightly displaced upward and to the right, without significant thickening or abnormal enhancement. The sphenoid sinus, cavernous sinus, and carotid arteries all appear normal. The mass is isointense with gray matter on T-1 and T-2 weighted images before administration of gadolinium, and it displays homogeneous enhancement after gadolinium administration. The appearance suggests the possibility of a pituitary adenoma.

Visual Field Testing

The involvement of the optic chiasm on this patient’s MRI prompts visual field testing, which reveals a subtle bilateral defect of the superior temporal visual field that is more prominent on right side. No other abnormalities are noted. These findings are consistent with a mass effect at the level of the optic chiasm.

What is the differential diagnosis of this patient’s MRI findings?

DIFFERENTIAL DIAGNOSIS OF A SELLA MASS

The differential diagnosis of a sellar mass is summarized in Table 2.

Pituitary Adenomas

Benign adenomas of the anterior pituitary are classified based on size (ie, microadenomas if less than 10 mm; macroadenomas if greater than 10 mm) and function. Any anterior pituitary cell type may give rise to an adenoma and result in increased secretion of the hormone or hormones produced by that cell type and/or decreased secretion of other hormones due to compression of the other cell types. However, impaired vision caused by suprasellar extension of the adenoma, with subsequent compression of the optic chiasm (Figure 1), is the most common reason for a person with a pituitary adenoma to seek medical attention. Some patients may be unaware of changes in their vision, or the onset of the deficit may be so gradual that a patient may not seek ophthalmologic consultation for months or even years. The most frequent complaints of patients with chiasmal compression from pituitary tumors are progressive loss of central acuity and dimming of the visual field, especially in the temporal portion, resulting in peripheral field deficits. Diplopia may rarely result from involvement of the third, fourth, or sixth cranial nerves in the cavernous sinus, resulting in a disturbance of ocular motility.

Other Benign or Malignant Tumors

Craniopharyngiomas are solid or mixed solid-cystic benign tumors that arise from the remnants of Rathke’s pouch along a line from the nasopharynx to the diencephalon. Most are intrasellar or suprasellar. Craniopharyngiomas usually occur in childhood and adolescence, with the most common presentation being growth retardation; pituitary hormone deficiencies, including diabetes insipidus, also are common. Meningiomas are benign tumors that also may occur in or near the sella. Malignancies that may arise within the parasellar region include germ cell tumors, sarcomas, and choromas. Germ cell tumors metastasize readily but are
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Chordomas are aggressive tumors that often arise in the clivus and present classically with headaches, visual impairment, and anterior pituitary deficiencies. Pituitary carcinomas are rare and are characterized by rapid growth, invasiveness, and extrapituitary involvement.31 Metastasis to the sellar region also may occur. Metastases to the pituitary gland are most often associated with breast cancer in women and lung cancer in men, but other tumors also metastasize to the pituitary gland.33 Granulomatous hypophysitis may be an isolated lesion or a component of systemic sarcoidosis or other inflammatory disorders (eg, Takayasu’s arteritis). Rathke’s cleft, arachnoid, and dermoid cysts also may produce sellar enlargement. An arteriovenous fistula in the cavernous sinus may cause modest enlargement of the pituitary gland, which returns to normal after the fistula is blocked. Finally, there are a few recognized forms of physiologic pituitary enlargement, including lactotroph hyperplasia in the peripartum period and thyrotroph hyperplasia due to long-standing and profound primary hypothyroidism.34

How should this patient be managed?

A biopsy of this patient’s pituitary lesion is necessary to make a final diagnosis. Given her adrenal insufficiency, she should receive stress doses of corticosteroids prior to proceeding to the operating room, to protect her from the stress of general anesthesia and a surgical procedure. Following the surgical procedure the patient should be treated with replacement doses of corticosteroids and thyroid hormone. It is important to emphasize that thyroxine replacement should not commence until adrenal function and ACTH reserve have been tested and treated if necessary. Treatment of hypothyroidism alone, in a patient with coexisting hypothyroidism and hypoadrenalism, may increase the severity of cortisol deficiency by increasing the metabolic rate and accelerating the metabolism of the little cortisol that may still be produced.5

Management of a patient with a pituitary adenoma is beyond the scope of this manual. An earlier manual in this volume (see Volume 4 Part 1, Acromegaly and Hyperprolactinemia) provides further details regarding the management of a pituitary adenoma, including surgical approaches and alternatives to surgery (ie, radiotherapy, gamma knife therapy).

BIOPSY AND DIAGNOSIS OF CASE PATIENT

The patient is treated with stress doses of corticosteroids. Transsphenoidal surgical exploration of the pituitary gland demonstrates an enlarged, tough, fibrous, and yellowish gland. No separate mass is seen. The lower portion of the gland is removed to decompress the optic chiasm, and residual tissue is left in place with the hope of maximizing functional pituitary recovery.
Frozen-section biopsy yields a diagnosis of lymphocytic hypophysitis.

- What are the distinguishing clinical features of lymphocytic hypophysitis?

**LYMPHOCYTIC HYPOPHYSITIS**

Lymphocytic hypophysitis is an uncommon pituitary disorder that is considered an autoimmune disease. It occurs predominantly in women and usually manifests during the late pregnancy or postpartum period. The disease has rarely been encountered in men and postmenopausal women. The pathophysiology is that of lymphocytic infiltration of the pituitary gland, potentially leading to panhypopituitarism.

Clinically and radiologically, lymphocytic hypophysitis may mimic the presentation of a nonfunctioning pituitary adenoma, although hyperprolactinemia may occur. Brain MRI cannot always differentiate lymphocytic hypophysitis from pituitary adenoma; however, some features may favor lymphocytic hypophysitis, including dural enhancement and extrapituitary involvement within the subarachnoid space. Some patients have evidence of other associated autoimmune disorders (thyroiditis, adrenalitis), and antipituitary antibodies have been found in some cases.

The pattern of pituitary hormone deficits is somewhat unique in lymphocytic hypophysitis, and the loss of pituitary function is often out of proportion to the degree of pituitary enlargement. Gonadotroph and somatotroph function are more likely to be preserved than corticotroph or thyrotrroph function, unlike the findings of hypopituitarism due to a sizable pituitary adenoma. An isolated hormone deficiency, particularly of corticotropin, can occur. Diabetes insipidus is not characteristic, as the posterior pituitary and the pituitary stalk typically are spared. Definitive diagnosis requires a biopsy demonstrating diffuse infiltration with lymphocytes, plasma cells, and a few eosinophils.

The natural history of lymphocytic hypophysitis is uncertain, and the value of therapy over observation is debatable. The response to steroid therapy has been inconsistent, and surgical removal may not be necessary as pituitary size and function may return to normal in any case. Surgical treatment is necessary for decompression of lesions involving the optic chiasm or other parasellar structures; whether surgery is indicated in the absence of visual field defects remains unclear. Given the anecdotal evidence for regression and a return of pituitary function, conservative medical management of lymphocytic hypophysitis may be appropriate in some cases.
bioactive cortisol. Although small deviations from the optimal replacement dose usually are not detected, an excessive dose can lead to symptoms of Cushing’s disease and bone loss, while an inadequate dose may result in the persistence or recurrence of the symptoms of cortisol deficiency. Thus, patients are treated with the lowest dose that does not result in clinical symptoms (fatigue, orthostasis, weight loss) or biochemical abnormalities consistent with underreplacement. The best guides to adequate replacement include a sense of well-being, a good appetite, and normal electrolyte levels. The appearance of signs of Cushing’s disease (hypertension, weight gain, facial fullness) indicate overreplacement.

Patient education is vital in the treatment of chronic adrenal insufficiency, as the major risk is the lack of normal serum cortisol in response to stress (surgery, febrile illness, trauma, emotional or psychological stressors). The usual recommendation is for patients to double their replacement dose in such situations and to notify their physician. Patients also should be encouraged to wear a medical alert bracelet indicating a diagnosis of adrenal insufficiency and to have prefilled dexamethasone syringes readily available in the event of an emergency (major injury, inability to tolerate oral medications, acute adrenal insufficiency and loss of consciousness).

The usual daily dose of hydrocortisone varies according to a patient’s weight, with 30 mg/day sufficient for a 70-kg patient. Typically, two-thirds of the dose is given upon awakening, and one-third is given in the late afternoon. This traditional twice-daily replacement regimen of hydrocortisone may not be as optimal as a once-daily regimen using a long-acting glucocorticoid. The oral administration of hydrocortisone does not mimic the normal daily rhythm of cortisol secretion. Within 30 minutes of ingestion, the serum cortisol concentration rises rapidly, and levels quickly exceed the binding capacity of corticosteroid-binding globulin and reach much higher concentrations than normal. The kidneys rapidly filter the free or unbound cortisol, resulting in a rapid decline in serum total cortisol concentrations, after which the decline slows (plasma half-life of 80 minutes). The net effect is a transient marked elevation in the serum cortisol concentrations followed by low levels until the next dose. Furthermore, by the time a patient takes the morning dose of hydrocortisone, the normal endogenous cortisol levels would be peaking or would have already peaked. A transient morning adrenal insufficiency may account for early morning symptoms of fatigue, nausea, and headache.

For these reasons, some authors recommend that patients with adrenal insufficiency be treated with a longer-acting synthetic glucocorticoid, such as prednisone or dexamethasone. The longer duration of action provides a smoother physiologic profile, avoiding the marked changes in the serum glucocorticoid concentrations that occur with the shorter-acting formulations. The usual oral replacement doses for dexamethasone and prednisone are 0.5 mg and 5 mg, respectively. Again, the goal of therapy is to provide the lowest dose that relieves the symptoms of glucocorticoid deficiency, while avoiding the symptoms or signs of Cushing’s disease, which indicate excessive glucocorticoid replacement.

Unlike the treatment of primary adrenal insufficiency, mineralocorticoid replacement is rarely necessary in hypopituitarism. The major regulators of aldosterone secretion are angiotensin II and potassium, not ACTH. Therefore, aldosterone secretion is usually maintained in the patient with hypopituitarism.

**TREATMENT OF THYROTROPIN DEFICIENCY**

The thyroxine deficiency that results from TSH deficiency is treated with levothyroxine. Treatment can be given once daily, as there is little if any variation in the normal endogenous secretion of thyroxine. The thyroid hormone dose should be adjusted according to the clinical response, with the goal of therapy being the normalization of the FT4 concentration, usually to the middle or upper limits of normal. The serum TSH cannot be used as a guide to the adequacy of levothyroxine therapy in patients with secondary and tertiary hypothyroidism.

**TREATMENT OF GONADOTROPIN DEFICIENCY**

Treatment of LH and FSH deficiency depends on the gender of the patient and whether or not fertility is desired. In men who are not interested in fertility, testosterone replacement is sufficient. The choices are similar to those for replacement in primary hypogonadism. Serum testosterone levels must be used to monitor the adequacy of treatment. Men with secondary hypogonadism who wish to become fertile may be treated with gonadotropins (if they have pituitary disease) or with gonadotropins or GnRH (if they have hypothalamic disease).

Women with hypogonadism who are not interested in fertility can be managed with estrogen-progestin replacement therapy. Measurements of LH and FSH cannot be used to monitor the adequacy of treatment. Women with secondary hypogonadism who wish to become fertile can be treated with gonadotropins or GnRH.

**TREATMENT OF GROWTH HORMONE DEFICIENCY**

Patients with GH deficiency that is acquired in adulthood must meet at least two criteria for therapy:
Endocrinology

Hypopituitarism

a poor GH response to two standard stimuli, and hypopituitarism due to pituitary or hypothalamic disease. There is substantial evidence that GH treatment in these patients increases muscle mass and decreases fat mass; less convincing evidence exists regarding improvement in bone mineral density. The evidence for improved sense of well-being, increased muscle strength, and improved lipid profiles are conflicting.

Recombinant human GH is administered by subcutaneous injection once daily, usually in the evening. The optimal dose for adults with hypopituitarism has not been determined. Most patients over the age of 60 will have IGF-1 levels in the reference range with a dose of 5 mcg/kg body weight; a few patients will require only half this dose. A 1998 consensus conference recommended a starting dose of 0.3 to 0.5 mg/day (approximately 2 to 5 mcg/kg body weight). Monitoring should be done by measuring serum IGF-1; after 2 months of therapy, the IGF-1 level should be in the normal range. If not, the daily dose should be increased in stepwise increments every 2 months until the level is normal. If side effects occur or if the IGF-1 level exceeds the normal range, the dose should be decreased.

The most common side effects of adult GH therapy are peripheral edema, arthralgias, carpal tunnel syndrome, paresthesias, and worsened glucose tolerance. Less common side effects include benign intracranial hypertension and macular edema and proliferative retinopathy in the absence of diabetes mellitus. Side effects are more common in older and heavier patients and in those who are overtreated, as judged by a high serum IGF-1 concentration during therapy.

CASE RESOLUTION

Following surgery and discharge from the hospital, the patient is initially treated with a 2-week course of high-dose steroids. Her visual field deficits and headaches resolve and she is subsequently placed on a twice-daily hydrocortisone regimen (20 mg in the morning and 10 mg in the afternoon). Thyroid replacement also is initiated at this time, beginning with a dose of 100 mcg of levothyroxine and titrating upward, with the goal of achieving thyroid hormone levels in the middle to upper limits of normal.

After 3 months of replacement therapy the patient is feeling well and her clinical symptoms have resolved. A follow-up cosyntropin stimulation test demonstrates persistent hypoadrenalism. Thus, the patient is continued on daily thyroid hormone and corticosteroid therapy.

REFERENCES

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