Diagnosis and Differential Diagnosis

Three different tests are performed in combination to assess for endogenous hypercortisolism. A 24-hour urine collection may show an elevated cortisol level, but this test is not reliable in patients with renal dysfunction. A second test, the 1-mg dexamethasone suppression test, measures an 8 AM fasting cortisol level after a dose of 1 mg dexamethasone given at 11 PM the night before. Cortisol suppression to less than 1.8 µg/dL is considered a normal response. Another diagnostic test is the late-night salivary cortisol measurement, using saliva collected at 11 PM on two consecutive nights. The test relies on a normal sleep cycle. Individuals who are using inhaled or topical steroids are not good candidates because of a high rate of false-positive results. A single positive finding is not sufficient to make this diagnosis and must be repeated and confirmed by doing additional tests. Because of the potential of cyclic ACTH overproduction by these tumors, repeat testing is recommended for individuals with high clinical suspicion but negative initial testing.

Pathologic hypercortisolism should be differentiated from physiologic activation of the hypothalamic-pituitary-adrenal axis, which can be observed in conditions such as critical illness, eating disorders, alcoholism, pregnancy, severe neuropsychiatric illness, and poorly controlled diabetes. Further, pathologic hypercortisolism can be ACTH dependent or independent. Once the diagnosis of ACTH-dependent hypercortisolism is established, a pituitary MRI should be performed, because most of these patients have a corticotroph adenoma; however, 40% to 45% of ACTH-secreting pituitary tumors are not seen even with MRI scanning. In those cases, patients with ACTH-dependent Cushing's syndrome should have inferior petrosal sinus sampling (IPSS) for ACTH with CRH stimulation; this differentiates between pituitary and ectopic ACTH overproduction by demonstrating a pituitary-to-peripheral ACTH gradient.

Treatment and Prognosis

The treatment involves removal of the pituitary tumor by an experienced neurosurgeon. Options after a failed resection include reoperation, bilateral adrenalectomy, radiotherapy, or pharmacotherapy. Pharmacotherapeutic agents include ketoconazole, metyrapone, mitotane, cabergoline, pasireotide, and mifepristone. In severe cases, intravenous etomidate may be used to stabilize patients for surgery. Long-term remission after resection of a pituitary microadenoma ranges from 69% to 98%, with a recurrence rate of 3% to 19%.

GONADOTROPINS

The two gonadotropins, LH and FSH, are glycoprotein hormones that are synthesized and secreted by gonadotrophs in anterior pituitary. They are both composed of an alpha and a beta subunit, the latter of which gives each its specific biologic function. These hormones bind to the receptors in the gonads (ovaries and testes) and modulate gonadal function. Secretion is regulated both by gonadotropin-releasing hormone (GnRH) from the hypothalamus and by feedback from circulating sex steroids (estrogen and testosterone).

Gonadotropin Deficiency (Hypogonadotropic Hypogonadism)

Definition

Hypogonadotropic hypogonadism is characterized by decreased or absent secretion of LH and FSH, which causes reduced secretion of the sex steroids (estrogen and testosterone).

Clinical Presentation

Signs and symptoms depend on the time of onset and the extent of gonadotropin deficiency. If deficiency occurs during fetal life, it can cause ambiguous genitalia. If deficiency occurs after birth but before puberty, it can cause delayed or absent sexual development. Onset after puberty often causes insidious changes and may remain undiagnosed for years, especially in men. The usual presentation after puberty includes symptoms of hypogonadism as well as infertility.

Diagnosis and Differential Diagnosis

The diagnosis is made by the presence of low or inappropriately normal FSH and LH levels along with low sex steroids (estrogen or testosterone). Causes of gonadotropin deficiency can be congenital (Kallman's syndrome, Prader-Willi syndrome, septo-optic dysplasia) or acquired, as in hemochromatosis, hyperprolactinemia, sellar tumors, cranial irradiation, and inflammatory and infiltrative disorders.

Treatment

For women, replacement therapy in the form of oral or transdermal estrogen should be continued until the age of natural menopause. Progesterone addition to induce withdrawal bleeding is essential in women with an intact uterus to prevent endometrial hyperplasia. For men, testosterone replacement is available in multiple forms, including an intramuscular injection product, several gels, and a patch. Fertility treatment requires additional therapy with recombinant FSH and LH in women or human chorionic gonadotropin (hCG) and FSH in men.

Gonadotropin-Secreting Pituitary Tumors

Definition and Epidemiology

Gonadotropin-secreting pituitary tumors are usually large and typically manifest with signs and symptoms of mass effect. Patients can also have symptoms of hypogonadism and other pituitary hormone deficiencies. These tumors can secrete FSH, LH, and/or alpha subunit.

Diagnosis and Differential Diagnosis

Hormonal evaluation reveals elevated FSH, LH, and/or alpha subunit in the absence of low estrogen or testosterone. Immunoperoxidase staining on surgical specimens is also needed to establish the diagnosis, especially in the case of postmenopausal women.

Treatment

Primary treatment is transsphenoidal surgical removal. Radiation therapy may be used as an adjunct treatment because of the size and more aggressive nature of these tumors, compared with true nonsecretory pituitary tumors.