Review Article

Adult hypopituitarism: Are we missing or is it clinical lethargy?

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ABSTRACT

Hypopituitarism, a disease of varied etiologies, is a serious endocrine illness that requires early recognition and prompt treatment to avoid its severe deleterious effects. In adults it is often missed due to non-specific symptoms of growth hormone deficiency and hypogonadism or mild deficiencies of other pituitary hormones. In some it may present with acute onset of symptoms suggestive of acute adrenal (corticotropin) insufficiency or symptoms due to mass lesion in/or around pituitary. High index of suspicion is required to seek hypopituitarism in patients with non-specific symptoms such as fatigue and malaise. Treatment of isolated hormone deficiency, partial or panhypopituitarism, has gratifying results although they require lifelong treatment and follow-up.

Key words: Adrenal insufficiency, growth hormone deficiency, hypogonadism, hypopituitarism, hypothyroidism

Introduction

Hypopituitarism is the partial or complete insufficiency of anterior pituitary hormone secretion and may result from pituitary or hypothalamic disease. The earlier reported incidence of (12–42 new cases per million per year) and prevalence of (300–455 per million) are probably underestimated.[1] In a population-based study of hypopituitarism in 1998, the prevalence of hypopituitarism was 46 cases per 100,000 individuals and the incidence was 4 cases per 100,000 per year.[2] With Indian population of 1.2 billion (Census-2011), this will calculate to about 350,000–555,000 cases of hypopituitarism. Dr Kochupillai estimated total prevalence of pituitary disorder to 4 million in the year 2000.[3] Various studies, commonly from India, have shown that the neuroendocrine disturbances in anterior pituitary hormone secretion are common following postpartum pituitary necrosis,[4] radiation damage,[5,6] traumatic brain injuries (TBI),[7,8] cerebrovascular accidents,[9] snake bite,[10] tuberculosis,[11] granulomatous or autoimmune hypophysitis,[12-14] sarcoidosis[15] empty sella,[16] and pituitary abscess.[17] These cases are often missed than those due to pituitary tumors or postpituitary surgery. Unlike diseases that involve the pituitary directly, any of these conditions can also diminish the secretion of vasopressin, resulting in diabetes insipidus.

Clinical manifestations depend on the extent of hormone deficiency and may be non-specific and thus the diagnosis is often missed. The progressive loss of pituitary hormone secretion is usually a slow process, which can occur over a period of months or years. Hypopituitarism does occasionally start suddenly with rapid onset of symptoms. Generally, growth hormone (GH) is lost first, and then luteinizing hormone (LH) deficiency follows. The loss of follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropin (ACTH) hormones and prolactin typically follow much later.[18]

Hypopituitarism is defined as deficiency of one or more hormones of the pituitary gland which can result from diseases of the pituitary gland or from diseases of the hypothalamus causing diminished secretion of hypothalamic

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releasing hormones, thereby reducing secretion of the corresponding pituitary hormones.[18] However, when one hormone is deficient, it is usually called isolated deficiency, e.g.. isolated GH deficiency or isolated ACTH deficiency. Deficiency of a single pituitary hormone occurs less commonly than deficiency of more than one hormone. The deficiency of all anterior pituitary hormones is termed panhypopituitarism, and less than all is often termed partial hypopituitarism.[19,20] The hypothalamus regulates pituitary secretion by the production of releasing hormones and posterior pituitary hormones, and hence its dysfunction can also lead to hypopituitarism.

Causes

Hypopituitarism and panhypopituitarism can be congenital or acquired. Congenital hypopituitarism is usually present in children,[21] hence will not be discussed in detail. However, some patient, when grown in adulthood, may come under care of physician. Any disease that affects the pituitary gland can result in diminished secretion of one or more pituitary hormones. These diseases include mass lesions, surgery to excise mass lesions, and many other disorders. Also any disease involving the hypothalamus can affect secretion of one or more of the hypothalamic hormones that influence secretion of corresponding pituitary hormones. The most common causes include intracranial tumors (including pituitary and hypothalamic tumors), excision of these tumors, and irradiation to head region.[5,22] Pituitary autoimmunity is also thought to play a role in causing hypopituitarism following postpartum hemorrhage.[23] Common causes of hypopituitarism due to either pituitary or hypothalamic diseases are enumerated in Table 1.

Various studies have shown that cases of hypopituitarism have been on the rise likely due newer insight in causes like postradiotherapy radiation damage,[5,6] TBI[7,8] and postcerebrovascular accidents.[9] With low radiation doses (<30 Gy), GH deficiency usually occurs in isolation in about 30% of patients, while with radiation doses of 30–50 Gy, the incidence of GH deficiency can reach 50–100% and long-term gonadotropin, TSH, and ACTH deficiencies occur in 20–30%, 3–9%, and 3–6% of patients, respectively. With higher dose cranial irradiation (>60 Gy) or following conventional irradiation for pituitary tumors (30–50 Gy), multiple hormonal deficiencies occur in 30–60% after 10 years of follow-up.[5,6] Some degree of hypopituitarism is found in 35–40% of TBI patients.[7,8] A rule of ¾ can be applied clinically for hypopituitarism after TBI—¾ cases are male <40 years of age, ¾ cases occurs after road traffic accidents, and ¾ cases manifests within 1 year.[8] Hypopituitarism has been observed in 19% of patients with ischemic stroke and 47% of patients with subarachnoid hemorrhage, presenting as an isolated deficiency in most cases.[9] Major risk factors for developing hypopituitarism after ischemic stroke include certain clinical (preexisting diabetes mellitus, medical complications during hospitalization) and radiological (Alberta Stroke Programme Early CT Score ≤ 7) parameters.[24]

Table 1: Causes of adult hypopituitarism

Congenital hypoptuitarism
Hypoplasia of pituitary
Associated with septo-optic dysplasia, holoprosencephaly, Choromosome 22 deletion syndrome, Rapaport syndrome
Single gene defect leading to multiple or isolated hormone deficiency
Late onset PIT-1 mutations, PIT-1 circulating antibodies
Acquired hypopituitarism
Tumor secretary OR non-secretary pituitary adenomas
Other tumors such as meningioma, craniopharyngioma, optic nerve glioma, metastasis
Surgery
Radiation
Trauma
Inflammation - autoimmune hypophysitis
Infiltration–sarcoidosis, tuberculosis, Wegner's granulomatosis
Infections–tuberculous meningitis
Vascular–Sheehan's syndrome, subarachnoid hemorrhage, pituitary apoplexy
Snake bite, cerebrovascular disease
Hemochomatosis or hemosiderosis
Empty sella syndrome
Other diseases (as this list is not exhaustive)

Clinical Evaluation

The clinical manifestations of hypopituitarism depend on the type and degree of hormone deficiency and the rapidity of its onset.[7] Thus, a patient may present with acute adrenal (corticotropin) insufficiency or profound hypothyroidism, with symptoms indicating a pituitary mass lesion, or the most often than not with nonspecific symptoms of fatigue and malaise. As a general rule, the secretion of gonadotropins and GH is more likely to be affected than ACTH and TSH although exceptions can occur.

Symptoms attributed to GH deficiency in adults include lack of vigor, decreased tolerance of exercise, and decreased social functioning. However, patients never complain or are unaware of these symptoms. Fine facial wrinkles may result from a deficiency of GH and from hypogonadism. GH deficiency also leads to diminished muscle mass, increased fat mass, increased serum low-density lipoprotein cholesterol, and decreased bone mineral density.[25] The degree of symptoms and abnormal physical findings of secondary hypothyroidism usually parallels the degree of thyroxine deficiency, but some patients with marked TSH deficiency may have few or no symptoms.[26] Secondary adrenal insufficiency also causes non-specific symptoms

such as fatigue, weakness, anorexia, weight loss, nausea, vomiting, abdominal pain, and altered mental activity. Men with hypogonadism have decreased libido and erectile dysfunction ranging from decreased tumescence to complete impotence. The physical examination is usually normal if hypogonadism is of recent onset. Diminished facial and body hair, and fine facial wrinkles are characteristic of long-standing hypogonadism. Women of reproductive age with hypogonadism have alterations in menstrual function ranging from regular but anovulatory cycles to oligomenorrhea or amenorrhea. Women with long-standing ACTH and gonadotropin deficiency often have loss of axillary and pubic hair.[26] The only known presentation of prolactin deficiency is the inability to lactate after delivery.

Symptoms of visual defects or compressive symptoms due to involvement of surrounding structures such as hypothalamus, cavernous sinus, temporal lobe, frontal lobe, and brainstem almost always suggest mass lesion in sellar region. These patients require magnetic resonance imaging pituitary. If mass lesion is detected, these patients require team approach with neurosurgeon and radiotherapist.

Pituitary apoplexy is the abrupt destruction of pituitary tissue resulting from infarction or hemorrhage into the pituitary, usually into an undiagnosed tumor. Other predisposing factors are diabetes mellitus, radiation therapy, anticoagulant therapy or bleeding disorders (snake bite), and postpartum hemorrhage (Sheehan's syndrome). The clinical features of pituitary apoplexy include the sudden onset of severe headache, vomiting, visual loss, cranial-nerve palsy (cranial nerves III, IV, or VI), hypotension, shock, and a variably depressed sensorium.[27]

Hormonal Evaluation

Hormonal evaluation will depend on the availability of laboratory facilities, particularly in India. However, facilities to perform hormone levels are available at all level with establishment of collection centers of various laboratories.

First step will be to send thyroid profile, basal cortisol, and prolactin level. If report shows low total T3, low total T4 with low or low normal TSH, it confirms secondary hypothyroidism. Basal cortisol <3 μg/dl suggests adrenal insufficiency secondary to ACTH deficiency, and both together confirms hypopituitarism. Increased prolactin level in presence of hypopituitarism should increase suspicion of mass lesion or pituitary stalk lesion common with infiltrative diseases.

Second step is required if above values are within normal limits and clinical suspicion is high. Sample should be sent for free T3, free T4, post -ACTH cortisol, LH, FSH, and testosterone levels. ACTH stimulation test ideally should be done with intravenous ACTH (inj synecthen 250 μg). This test can be done at any time of the day and irrespective of meal intake. However, there is problem with availability of inj synecthen in India. Hence, this test can be done with Inj Prolongatum (ACTH) which is easily available as vial of 10 ml in strength of 60 IU/ml. Each IU is equivalent to 25 μg of ACTH. With insulin syringe 10 IU can be injected intramuscularly (upto 7 marking in 40 IU insulin syringe).[28] Low FT3, low FT4, and post-ACTH cortisol <18 μg/dl confirm hypopituitarism. Low or normal LH and FSH in postmenopausal women and with amenorrhea in premenopausal women indicate secondary hypogonadism. Serum testosterone level <3 ng/ml with normal or low LH and FSH in male suggests secondary hypogonadism.

At specialized centers, GH and cortisol level can be assessed with insulin hypoglycemia test. All hormones can also be tested with injection of various releasing factors; however, in India these releasing hormones are neither easily available nor many centers perform it. Hence, these tests are not discussed here.

Imaging

After the clinical and biochemical diagnosis of hypopituitarism has been made, an imaging study should be performed to determine whether a mass is present. The most informative image is an magnetic resonance imaging scan with intravenous gadolinium. Recent advances in pituitary imaging have been discussed in recently reviewed article in this journal.[29]

Hormonal Replacement Therapy

Treatment of patients with hypopituitarism is the sum of the treatments of each of the individual pituitary hormonal deficiencies detected. Replacement of the hormones that are deficient is required lifelong. This should be emphasized since patients often resist long-term therapy because of publicity about the adverse effects of medications. The treatments of deficient hormones are in many ways the same as the treatments of primary deficiencies of the respective target glands, but differ in some other ways.

L-thyroxine (100–150 μg) can be given once daily empty stomach in morning, because there is little, if any, variation in its secretion. The goal of therapy should be a normal serum T4 value. The factors that influence dosing are similar to those of primary hypothyroidism, but treatment of secondary hypothyroidism differs in two ways. First, T4 should not be administered until adrenal function,

including ACTH reserve has been evaluated and either found to be normal or treated. In a patient with coexisting hypothyroidism and hypoadrenalism, treatment of the hypothyroidism alone may increase the clearance of the little cortisol that is produced, thereby increasing the severity of the cortisol deficiency. Second, measurement of serum TSH cannot be used as a guide to the adequacy of L-thyroxine replacement therapy. The treatment goal should be a serum T4 concentration in the middle of the normal range, T3 level mid-normal range.

Adrenal insufficiency should be treated with hydrocortisone (10 mg on awakening, 5 mg at noon and 5 mg in the evening) or prednisone (5 mg on awakening and 2.5 mg in the early evening) to simulate the normal circadian rhythm of cortisol secretion. Because there is no test to assess the adequacy of the replacement, the optimal replacement glucocorticoid and the optimal doses are not known. While monitoring the patient, watch for blood pressure, glucose intolerance, and cushingoid feature and if present, require reduction in the dose. Once the proper replacement regimen has been determined, the doses usually do not need to be changed except for an increase in the glucocorticoid dose (which is generally doubled) during intercurrent illness. Unlike the situation in primary adrenal insufficiency, mineralocorticoid replacement is rarely necessary in these patients.

Lower doses of dehydroepiandrosterone (DHEA) may be effective in women with ACTH deficiency (secondary adrenal insufficiency). In a study of 38 women with hypopituitarism, administration of DHEA (20–30 mg/day for 6 months) resulted in increases in serum androgens, axillary and pubic hair, and energy, but no increase in sexual interest or activity.[30] In a second trial of DHEA in men and women with panhypopituitarism (ACTH and gonadotropin deficiency), modest and minor improvements were seen in psychological well-being in the women and men, respectively.[31]

Treatment of LH and FSH deficiency depends upon gender and whether or not fertility is desired. Premenopausal women should be treated with estrogen and progesterone, given in a cyclic pattern that reproduces the normal process of endometrial growth and sloughing; an oral contraceptive may also be used. Women with secondary hypogonadism who wish to become fertile are candidates for either gonadotropin therapy or pulsatile GnRH.[32]

Testosterone replacement is sufficient in men who have hypogonadism and who are not interested in fertility. Transdermal testosterone is recommended to most hypogonadal men, especially a gel, because it usually produces normal serum testosterone concentrations, and most patients find it the most convenient. Some men, however, prefer injections of testosterone enanthate because of the freedom from daily application. For some patients, cost may be an issue. In general, the newest preparations, the gels, cost the most; patches, somewhat less; and injectable esters, the least. Men who begin using a transdermal preparation need to be seen 2–3 months after the initiation of therapy to measure the serum testosterone concentration and evaluate the possibility of undesirable effects. Men who use the body patch or a 5 g dose of the gel (containing 50 mg of testosterone), but whose serum testosterone concentration is not high enough, can try wearing two patches or applying 7.5 or 10 g of the gel (containing 75 or 100 mg of testosterone, respectively). The initial regimen of testosterone enanthate should be 200 mg every 2 weeks. The patient should be seen approximately 2–3 months later and if he is bothered by fluctuations in energy, mood, or libido, the regimen can be changed to 100 mg once a week or transdermal testosterone can be offered again. If fertility is in question, men can be treated with gonadotropins or gonadotropin-releasing hormone therapy.[33]

Treatment of GH deficiency in adults has been a matter of debate for long. GH therapy has been shown to offer benefits in body composition, exercise capacity, skeletal integrity, and quality of life measures, and it is most likely to benefit those patients who have more severe GHD. Thus, patients with clinical manifestations and unequivocal evidence of GH deficiency due to organic disease of childhood-onset or adult-onset may warrant GH replacement. Recombinant human GH is administered by subcutaneous injection once a day, usually in the evening. The initial goal is to start with a lower than maintenance dose and to gradually increase the dose, to minimize side effects. The starting dose should be 2–5 μg/kg body weight once daily toward the lower end of the range. If the serum IGF-1 concentration has not increased to within the normal range after 2 months, the daily dose should be increased in stepwise increments at 2-month intervals until it is normal. A dose of greater than 10–12 μg/kg is not likely to be needed. If side effects occur or the serum IGF-1 concentration increases to above normal at any dose, the dose should be decreased. The eventual goal is to find the GH dose that maintains the serum IGF-1 concentration within the middle of the age-adjusted normal range. GH dosing regimens usually need to be individualized. The risks of GH treatment are low. The most common side effects of GH treatment in adults with hypopituitarism are peripheral edema, arthralgias, carpal tunnel syndrome, paresthesias, and worsening of glucose tolerance. The final decision to treat adults with GHD requires thoughtful

clinical judgment with a careful evaluation of the benefits and risks specific to the individual.

Recommendations mentioned in this article are consistent with the Endocrine Society Clinical Practice Guidelines.[34]

Conclusions

Diagnosis of hypopituitarism requires active clinical suspicion on subtle symptoms the patient presents, with clinical background of probability. These patients are often visiting various specialists before diagnosis is made. It is treatable, and a patient with this condition should be able to perform normal activities as long as the appropriate hormonal therapy is used consistently and properly. Even after the proper regimen has been established, a patient with hypopituitarism requires lifelong medical follow-up.

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