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Diagnosis and Treatment of Hypopituitarism

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Hypopituitarism is a chronic endocrine illness that caused by varied etiologies. Clinical manifestations of hypopituitarism are variable, often insidious in onset and dependent on the degree and severity of hormone deficiency. However, it is associated with increased mortality and morbidity. Therefore, early diagnosis and prompt treatment is necessary. Hypopituitarism can be easily diagnosed by measuring basal pituitary and target hormone levels except growth hormone (GH) and adrenocorticotropic hormone (ACTH) deficiency. Dynamic stimulation tests are indicated in equivocal basal hormone levels and GH/ACTH deficiency. Knowledge of the use and limitations of these stimulation tests is mandatory for proper interpretation. It is necessary for physicians to inform their patients that they may require lifetime treatment. Hormone replacement therapy should be individualized according to the specific needs of each patient, taking into account possible interactions. Long-term endocrinological follow-up of hypopituitary patients is important to monitor hormonal replacement regimes and avoid under- or overtreatment.

Keywords: Hypopituitarism; Adrenocorticotropic hormone deficiency; Thyrotropin deficiency; Gonadotropin deficiency; Growth hormone deficiency; Anti-diuretic hormone deficiency

INTRODUCTION

Hypopituitarism is defined as the total or partial loss of anterior and posterior pituitary gland function that is caused by pituitary or hypothalamic disorders [1]. The incidence rate (12 to 42 new patients per million per year) and the prevalence rate (300 to 455 patients per million) seems to underestimate the actual incidence of this disorder given that as many as 30% to 70% of patients with brain injury exhibit symptoms of diminished hormone secretion from their pituitary gland [2]. Additionally, factors such as the cause of hypopituitarism, age of onset, and the speed and degree of loss of hormone secretion may affect the clinical manifestations of hypopituitarism. For example, although a partial hormone deficiency that progresses slowly may go undetected for years, the sudden and complete loss of hormone secretion results in an emergency situation that requires immediate medical attention [2]. The treatment of hypopituitarism typically involves a replacement of the deficient hormone but care must be taken because several studies have reported an increased incidence of cardiovascular disorders and number of deaths among these patients [3]. Additionally, a significant proportion of patients who have been treated for a hormone deficiency suffer from more or less vague discomforts and a reduced quality of life [4]. The present review will describe the general aspects of hypopituitarism focusing on the limitations of the stimulation test and hormone replacement treatment.

CAUSES OF HYPOPITUITARISM

A variety of diseases may cause hypopituitarism and, accord-

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Table 1. Causes of Hypopituitarism

Primary hypopituitarism
- Neoplasms leading to pituitary destruction
Intrasellar tumors (adenomas, craniopharyngiomas)
Parasellar tumors (meningiomas, optic nerve gliomas)
Metastatic tumors (breast, lung, melanoma, renal cell carcinoma)
- Ischemic necrosis of the pituitary
Postpartum (Sheehan's syndrome)
Diabetes mellitus
Other systemic disorders (sickle cell disease and traits, temporal arteritis, eclampsia, atherosclerotic disease, hemorrhagic fever with renal syndrome)
- Pituitary apoplexy (nearly always secondary to a pituitary tumor)
- Cavernous sinus thrombosis
- Aneurysms of intracranial internal carotid artery
- Infectious disease (tuberculous meningitis, fungal disease, malaria, HIV)
- Infiltrative disease (hemochromatosis, secondary amyloidosis)
- Immunological or inflammatory (lymphocytic or granulomatous hypophysitis, sarcoidosis)
- Primary empty sella syndrome
- Iatrogenic
Nasopharyngeal, pituitary, or brain irradiation
Surgical destruction
- Genetic (PIT-1, GH, β-LH, GHRH-R mutations or deletions)
- "Idiopathic" (GH, ACTH, TSH, others): frequently monohormonal
Secondary hypopituitarism: pituitary stalk, hypothalamus or other central nervous system diseases
Tumors (craniopharyngioma, germ cell tumor, metastasis, lymphoma, leukemia)
Infiltrative (hemochromatosis, lipid storage disease)
Traumatic brain injury
Hormone-induced (glucocorticoids, gonadal steroids)
Iatrogenic (surgical, irradiation)
Infectious (HIV, tuberculosis)
Nutritional (starvation, obesity)
Anorexia nervosa
Severe systemic illness (interleukin mediated)
Psychoneuroendocrine (psychosocial dwarfism, stress-associated amenorrhea)
Genetic (vasopressin-neurophysin gene, KAL1 gene)

Adapted from Prabhakar et al. [5].
HIV, human immunodeficiency virus; PIT-1, POU domain, class 1, transcription factor 1; GH, growth hormone; β-LH, luteinizing hormone-β; GHRH-R, growth-hormone-releasing hormone receptor; ACTH, adrenocorticotropic hormone; TSH, thyroid stimulating hormone; KAL1, Kallmann syndrome 1.

ingly, this disorder can be divided into two types depending on its cause [1]. Primary hypopituitarism is caused by disorders of the pituitary gland itself and may be due to the loss, damage, or dysfunction of pituitary hormone-secreting cells. On the other hand, secondary hypopituitarism is the result of diseases of the hypothalamus or pituitary stalk interrupting the nerve or vascular connections to the pituitary gland, thereby reducing the secretion of the pituitary hormones (Table 1). Reductions in hormone secretion in the posterior pituitary gland may largely be due to failures in hormone synthesis or secretion from the hypothalamus while decreased hormone secretion in the anterior pituitary gland may be due to deficiencies in the activity of one or more of the neurohormones secreted from the hypothalamus [1].

Primary hypopituitarism

The most common causes of primary hypopituitarism are pituitary adenoma and complications from surgery or radiation therapy for the treatment of pituitary adenoma [5]. In these situations, the diameter of the pituitary adenoma is 1 cm or larger and, the onset of hypopituitarism is usually slow unless the patient suffers from a pituitary apoplexy whose symptoms occur within several hours or a few days [5]. Several putative mechanisms of hormone deficiency include the application of direct pressure onto or damage to the normal tissues surrounding the tumor, mechanical compression of the portal veins by the pituitary stalk, raised intrasellar pressure, and focal necrosis due to the prolonged portal vein interruption [5]. Furthermore, inflammatory hypophysitis (including various types of autoimmune

hypophysitis), which has an unknown etiology and presents with symptoms that are difficult to differentiate from those associated with a tumor, is another possible cause of hypopituitarism [5]. Although this cause is rare, it is known to exhibit clinical features such as the isolated or combined lack of adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), gonadotropin, and/or growth hormone (GH) [5].

Radiation exposure for the treatment of malignant conditions in the head and neck area may also cause hypopituitarism [6]. Additionally, a variety of hormone deficiencies may occur when treating a pituitary tumor with radiotherapy and the onset of these conditions depends on the total amount of radiation, whether fractioning was done, and the time elapsed after radiation [5]. The frequency of the manifestation of a hormone deficiency is greater than 50% at 10 years after the radiation exposure. Most patients, like patients with pituitary adenomas, present with a typical course starting with GH deficiency, gonadotropin deficiency, ACTH deficiency, progressing to TSH deficiency (or TSH deficiency followed by ACTH deficiency) [7]. Additionally, although further study is warranted, it is generally accepted that the incidence of hypopituitarism is lower following gamma knife radiosurgery than after conventional radiotherapy techniques [5].

The occurrence of hypopituitarism following surgery to remove a pituitary tumor varies from 10% to 25% and may have to do with the size of the tumor, the degree of invasion, the quantity of remaining normal tissues, and the degree of technical competency of the neurosurgeon [5]. In rare cases, hypopituitarism has been observed when a cytomegalovirus infection occurs in patients with the AIDS virus [8]. Sheehan's syndrome, which is hypopituitarism caused by the postpartum hemorrhage of the pituitary gland, frequently occurred in the past but it is rarely seen today [5]. Tuberculosis meningitis and hemorrhagic fever with renal syndrome, which were occasionally observed in the past but are virtually nonexistent today [1]. In still rarer cases, solitary or complicated pituitary hormone deficiency syndromes may occur due to genetic causes and typically affect children (Table 2) [5].

Table 2. Genetic Causes of Hypopituitarism

	Genetic defect	Hormone deficiencies
Combined	PIT-1 (POU1F1)	GH, TSH, PRL
	PROP-1	GH, LH/FSH, TSH, ACTH, PRL
	HESX1 (Rpx)	GH, LH/FSH, TSH, ACTH, ADH
	LHX3/LHX4	GH, LH/FSH, TSH, PRL
	PITX2	GH, PRL
Isolated	GH	GH
	GHRH receptor	GH
	HESX1	GH
	KAL	GnRH (FSH/LH)
	GnRH receptor	FSH/LH
	DAX1/AHC	FSH/LH
	TBX19 (TPIT)	ACTH
	LH-β	LH
	TSH-β	TSH
	TRH receptor	TSH
	Vasopressin-neurophysin II	ADH

Adapted from Prabhakar et al. [5].
PIT-1, POU domain, class 1, transcription factor 1; GH, growth hormone; TSH, thyroid stimulating hormone; PRL, prolactin; PROP-1, prophet of Pit-1 gene; HESX1, homeobox expressed in ES cells 1; LH, luteinizing hormone; FSH, follicle stimulating hormone; ACTH, adrenocorticotropic hormone; ADH, anti-diuretic hormone; LHX3, LIM/homeobox protein Lhx3; LHX4, LIM/homeobox protein Lhx4; PITX2, paired-like homeodomain transcription factor 2; GHRH, growth-hormone-releasing hormone; KAL, Kallmann syndrome; GnRH, gonadotropin releasing hormone; DAX1, dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1; AHC, adrenal hypoplasia congenita; TBX19, T-box transcription factor 19; TRH, thyroid releasing hormone.

Secondary hypopituitarism

Damage to the pituitary stalk often occurs after the head and/or neck injury accompanying a fracture of the bones surrounding the sella turcica [5]. Additionally, tumors near the sella turcica may press against the stalk and damage it. The stalk is often accidentally severed during surgery on a sellar or parasellar mass [1]. Central nervous system disorders involving the hypothalamus, such as craniopharyngioma and germ cell tumor, may also cause hypopituitarism by impeding the secretion of releasing hormone from hypothalamus [1]. Depending on the anatomical location of the lesion, patients may manifest symptoms consistent with a single hormone deficiency, panhypopituitarism, or a posterior pituitary failure (diabetes insipidus) [1]. Recently, the prevalence of idiopathic hypopituitarism has increased but it is thought that these cases are likely due to a severed stalk resulting from traumatic brain injury (TBI) or hypothalamic damage [1]. Similarly, the incidence of hypopituitarism after a TBI seems to be more frequent than previously thought as the prevalence rate ranges from 30% to 70% based on the patients' charateristics and the types of diagnostic tests [2]. The most common problem associated with hypopituitarism is a GH deficiency. Following TBI, the early diagnosis of a hormone defi-

ciency has an important impact on their degree of recovery from TBI [2]. Additionally, it has been demonstrated that hormone replacement therapy improves rehabilitation outcome and the quality of life of a patient [9]. Whereas approximately half of the patients who exhibit hypopituitarism within 6 months of a TBI recover normal pituitary function within 1 year, some patients with normal hormone levels after a TBI develop new hormone deficiency after 12 months [2]. Early posttraumatic panhypopituitarism generally persists [2]. Thus, it is recommended to re-evaluate anterior pituitary function and quality of life after approximately 6 to 12 months of an injury [2]. However, it is controversial regarding the most appropriate early evaluation time after this type of injury.

It is also important to closely monitor patients after a subarachnoid hemorrhage because the symptoms of a pituitary hormone deficiency may become evident [2]. Generally, the loss of pituitary function due to secondary hypopituitarism (dysfunction in the hypothalamus or pituitary stalk) is less serious than primary hypopituitarism but diabetes insipidus is more frequent in secondary hypopituitarism [1].

Health problems such as metabolism disorders, systemic diseases, and stress can all be related to selective pituitary hormone deficiencies. The influence of stress seems to manifest via inflammatory cytokines such as interleukin 1 (IL-1) and IL-6, which have severely suppressive effects on thyroid releasing hormone (TRH) and gonadotropin releasing hormone (GnRH) levels while at the same time stimulating the secretion of corticotropin releasing hormone (CRH). This is one possible explanation for euthyroid sick syndrome or hypothalamic amenorrhea because when the original stress is eliminated, these suppressive effects are also ameliorated. In contrast, inflammatory or invasive diseases that destroy the hypothalamus may explain the infrequent recovery of neuroendocrine function in patients suffering from these disorders even after the underlying disease is treated [1].

In rare cases, genetic conditions such as Kallmann syndrome or neurohypophyseal diabetes insipidus may contribute to reduced pituitary function. Kallmann syndrome manifests from a wide array of genetic mutations, including the KAL1 gene [10]. In these patients, there is a loss of GnRH neurons in the hypothalamus which leads to GnRH deficiencies and hypogonadotropic hypogonadism (the lack of secondary sex characteristics) in conjunction with olfactory loss (anosmia or hyposmia) that is due to olfactory bulb loss or hypoplasia [10]. There is also a condition known as neurohypophyseal (familial) diabetes insipidus that is triggered by mutations of the neurophysin II part of the vasopressin-neurophysin precursor genes [11]. Due to these mutations, the precursor genes do not divide into vasopressin and neurophysin II which, in turn, causes an excessive accumulation of the precursor substance within the cells that leads to the eventual death of the hypothalamic neurons (apoptosis) in which these genes are expressed. Depending on the genetic disorders or degree of the mutation, the symptoms manifest immediately after the birth or during childhood [11].

CLINICAL FEATURES

The underlying pathology, speed of onset and the severity of hypopituitarism have a significant impact on the clinical features [5]. In particular, if hypopituitarism is caused by a space-occupying lesion (tumor), then mass effects such as headache, visual impairment, and rarely, personality changes and hypothalamic syndrome may appear [5]. The clinical expression of severe panhypopituitarism, which typically occurs immediately after hypopituitary patients discontinue hormone replacement or following the pituitary apoplexy or hypophysectomy, may be evident within several hours (diabetes insipidus) or a few days (adrenal insufficiency) [4]. However, most patients exhibit a slow and progressive loss of pituitary function with a relatively mild and vague or nonspecific clinical symptoms. In fact, in many cases, these patients are not diagnosed with hypopituitarism for a prolonged time [3].

GH-secreting cells (somatotrophs) are particularly vulnerable to pressure, which is why GH deficiency occurs first and most frequently among all pituitary hormones, followed by deficiencies of gonadotropin (luteinizing hormone [LH] and follicle stimulating hormone [FSH]), TSH and ACTH (or ACTH and TSH), and prolactin [12]. The most common hormones that show selective deficiencies are GH and gonadotropins. Children tend to suffer from GH deficiency while adults often complain of symptoms from gonadotropin deficiency [3]. The clinical symptoms stemming from a lack of ACTH, TSH, and/or gonadotropins vary somewhat but are similar to those associated with target gland hormone deficiency; the major symptoms are listed in Table 3 [4].

If ACTH deficiency is partial, then the patient may experience a relatively normal and event-free life, but patients with severe ACTH deficiency suffer from a variety of vague and nonspecific complaints [13]. ACTH deficiency (secondary adrenal insufficiency) is different from a primary adrenal insufficiency (Addison's disease) in that the true onset of an Addisonian crisis (adrenal crisis) is very rare because aldosterone se-

Table 3. Clinical Symptoms and Signs of Hypopituitarism

Corticotroph deficiency Acute: fatigue, weakness, dizziness, nausea, vomiting, hypotension, hypoglycemia Chronic: tiredness, pallor, anorexia, weight loss, hypoglycemia
Thyrotropin deficiency Tiredness, cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, slow mental processes
Gonadotropin deficiency Men: loss of libido, impaired sexual function, decreased muscle and bone mass, erythropoiesis and hair growth Women: amenorrhea, oligomenorrhea, infertility, loss of libido, dyspareunia (short term), osteoporosis, premature atherosclerosis (long term)
Growth hormone deficiency Adults: decreased muscle mass and strength, increased visceral fat mass, fatigue, premature atherosclerosis, decreased quality of life
Prolactin deficiency Inability to breast feed
Anti-diuretic hormone deficiency Polyuria, polydipsia, nocturia

Adapted from van Aken et al. [4], with permission from Springer.

cretion is partially independent of the pituitary gland [13]. Although it is possible that aldosterone secretion may be diminished in the case of hypopituitarism due to ACTH deficiency, the residual secretion of aldosterone, which is controlled by the renin/angiotensin system, is sufficient for the maintenance of normal plasma volume and blood pressure except acute stress [13]. No hyperpigmentation has been observed in other cases of ACTH deficiencies [13]. Because ACTH stimulates the secretion of adrenal androgen, the lack of adrenal androgen due to ACTH deficiency may contribute to the loss of sexual desire in females and it may become the primary cause for the loss of pubic and axillary hair [13]. In contrast, the loss of adrenal androgen is not as important for males due to the abundant testosterone that is secreted from the testicles [13].

TSH deficiency produces symptoms that are similar to those associated with primary hypothyroidism except that its clinical symptoms are not as severe [14]. Although the underlying mechanism has yet to be ascertained, the cases of family with isolated TSH deficiency have been reported [15].

In both males and females, complete FSH/LH deficiency is tantamount to the loss of the target organs function (gonads) but the clinical expression varies depending on whether it occurs prior to or after puberty [6]. Partial FSH/LH deficiency due to hypothalamic lesions may often be associated with the loss of sexual desire, oligomenorrhea, and anovulation, In most cases, both LH and FSH are diminished at the same time, but cases in which just one of these hormones is deficient have been reported [6].

GH deficiency results in growth disorders; the degree of decreased GH secretion and the extent of the growth delay may be severe when they are associated with organic illnesses of the pituitary gland [16]. On the other hand, when there is no organic illness (idiopathic GH deficiency), the deficiency in GH secretion and the accompanying growth delay vary widely such that the height of the affected children may be the same as shorter unaffected children of the same age [16]. In the case of idiopathic severe GH deficiency, they presented fasting hypoglycemia, and it is of the utmost importance to perform a detailed assessment of the family history and to conduct complementary hormone measurements. On the other hand, a GH deficiency in adults is difficult to clinically diagnose because it is usually nonspecific. The typical symptoms include fatigue, general weakness, reduced vitality and physical strength, and diminished mental agility. Additionally, moderate obesity with evident visceral deposition may occur and hyperlipidemia, reduced levels of high density lipoprotein cholesterol, osteopenia, and reduced myocardial contractility are typically observed [16]. The increase in cardiovascular risks may be related to an increased frequency of metabolic syndrome and a higher incidence of death among these patients [16].

Prolactin deficiency cause only one clinical symptom, which is the inability to produce milk after childbirth [6]. A lack of prolactin is more closely associated with difficulty synthesizing milk than with producing milk and is not clinically important in countries where artificial lactation is readily available [6]. However, because prolactin is regulated by dopamine, which acts as a neuroendocrine inhibitor in the hypothalamus, hyperprolactinemia accompanied by other pituitary hormone deficien-

cies is more frequent and problematic and may result in hypogonadism [6].

Of the two posterior pituitary hormones, oxytocin and vasopressin (anti-diuretic hormone [ADH] or arginine vasopressin [ADH]), only vasopressin deficiency leads to the clinical presentation. The major symptoms include polydipsia, polyuria, and nocturia. The onset of the disorder may be acute or chronic depending on the underlying diseases [6]. Because patients with partial diabetes insipidus may not show severe symptoms, this disorder may not be immediately diagnosed. Moreover, the symptoms associated with diabetes insipidus may improve when accompanied by an anterior pituitary hormone deficiency, in particular ACTH deficiency or severe TSH deficiency. This may be because there is an enhanced secretion of ADH due to a cortisol deficiency or because ADH functionality of the renal tubule is strengthened [6]. Accordingly, the symptoms of diabetes insipidus reappear after cortisol or thyroxine replacement.

DIAGNOSIS

The diagnosis of hypopituitarism is made by measuring basal hormone levels in the morning fasting status or performing stimulation tests if necessary. Six anterior pituitary hormones (GH, prolactin, LH, FSH, TSH, and ACTH) as well as target hormones can be measured via sensitive and reliable immunoassay techniques. Other pituitary hormones except GH and ACTH deficiency can be diagnosed with basal hormone measurement. Hence, combined pituitary function tests (i.e., the cocktail test) is rarely used [17].

Measurement of basal hormone levels is sufficient for the differentiation of hypopituitarism from primary target organ hormone deficiency. For example, the lack of an increase in pituitary hormone levels in conjunction with reduced target organ hormone levels is typically observed in case of a hypothalamic or pituitary gland disease [4]. Conversely there is an increase in pituitary hormone levels when there is target organ hormone deficiency. Thus, the differentiation of a target organ deficiency from a hypothalamic or pituitary gland disease is relatively simple but a stimulation test may also be necessary to determine the origin of the disease, albeit rarely. The expected values and responses of the pituitary gland and target organ hormones under basal and stimulated states are provided in Table 4. In several cases, it is necessary to distinguish between a pituitary disease (primary hypopituitarism) and a hypothalamic disease (secondary hypopituitarism), but this is not easily accomplished. In these situations, it is helpful to diagnose hypothalamic diseases based on the expression of clinical manifestations, such as diabetes insipidus or hypopituitarism accompanying hyperprolactinemia, neuro-ophthalmological symptom, such as visual impairments, neuropsychiatric symptoms [5]. For purposes of differentiation, a stimulation test using hypothalamus releasing hormones can be performed. However, sellar magnetic resonance imaging (MRI) can distinguish pituitary diseases from hypothalamic diseases, and treatment is not different. Thus, differentiation pituitary diseases from hypothalamic diseases may not be necessary.

ACTH deficiency

Pituitary ACTH deficiency is difficult to diagnose using basal ACTH or cortisol measurements. Because cortisol levels are normally at their peak in the morning due to diurnal rhythm, it is advisable to measure these concentrations at approximately 8:00 AM to 9:00 AM [4]. If the cortisol level is very low (<3 to 4 μg/dL) or very high (>15 to 16 μg/dL) then a stimulation test is not needed. Because this value is not absolute, a stimulation test is only necessary when a definite diagnosis is required and, in this case, ACTH deficiency can be diagnosed by measuring ACTH and/or cortisol levels via the administration of metyrapone, ACTH, or CRH, or with an insulin-induced hypoglyce-

Table 4. Diagnostic Evaluation of Hypopituitarism

	Basal		Stimulatory		
	Pituitary hormone	Target gland hormone	Pituitary hormone Target gland hormone	Hypothalamic hormone	
				Pituitary hormone	Target gland hormone
Normal	N	N	N	N	N
Target gland disease	↑	↓↓	↓↓	↑↑	↓↓
Pituitary disease	↓↓	↓	N-↑	↓↓	↓↓
Hypothalamic disease	N-↓	↓	N-↑	N-↑	N-↑

N, normal concentration; ↑, increase; ↑↑, further increase; ↓, decrease; ↓↓, further decrease.

mia test (insulin tolerance test) [4]. The insulin tolerance test has long been considered to be the gold standard test for this diagnosis but it may cause severe hypoglycemia [4]. However, it can be safely administered under the close supervision of a physician to effectively determine the level of GH secretion as well as the presence of an ACTH deficiency. In a clinical context, the rapid ACTH stimulation test, which measures cortisol levels after the administration of ACTH, is preferred if the risk of hypoglycemia is evident in a patient (normal level, >18 to 20 μg/dL) [4]. An insulin tolerance test is conducted when it is necessary to determine GH levels.

It is widely accepted that maximum serum cortisol levels can be observed after the administration of doses of ACTH much lower than the usual dose of 250 μg that is given in the rapid ACTH test [18]. This implies that the sensitivity of the test can be improved by reducing the amount of ACTH that is administered. Indeed, several studies have reported that the low-dose 1 μg ACTH stimulation test is more sensitive than the usual 250 μg ACTH dose that is generally used in the rapid ACTH test for diagnosing adrenal gland hypofunction (central or secondary adrenal insufficiency) due to ACTH deficiency [18]. However, the low-dose ACTH stimulation test has not yet replaced the standard 250 μg stimulation test in clinical contexts because other studies have reported that the low-dose diagnostic test is not as precise as the conventional high-dose test and that there are technical problems associated with diluting a 250 μg solution into a 1 μg solution [19]. A recent study conducted by the present author indicated that the low-dose 1 μg ACTH stimulation test is not superior to the standard high-dose 250 μg test [20]; as a result, this author continues to utilize the conventional high-dose ACTH stimulation test. Furthermore, the findings of this study demonstrated that the normal range of the cortisol response during the ACTH stimulation test exceeded 18 μg/dL for patients with hypopituitarism and 20 μg/dL for all others. This is likely because other pituitary hormone deficiencies typically accompany ACTH deficiencies, which would make the cortisol response of these patients lower than that of healthy individuals [20].

TSH deficiency

It is possible to diagnose a TSH deficiency using only a thyroid function test. Despite the presence of reduced free thyroid hormones, TSH concentrations that are at or below the normal range (with often a slight increase in its concentration) imply that there is a problem in the pituitary gland or the hypothalamus [4]. TSH deficiency can be easily distinguished from primary hypothyroidism in cases where the TSH level increases inordinately [5]. Although the TRH stimulation test is not administered clinically [21], it is possible to easily distinguish pituitary lesions from hypothalamic lesions because hypothalamic diseases result in an increased but delayed TSH response [21].

Gonadotropin deficiency

In many cases, it is possible to diagnose gonadotropin deficiency using a basal hormone test and an evaluation of clinical symptoms. This is particularly true for postmenopausal females because it is always possible to diagnose this population based on the lack of an increase in gonadotropin concentrations [2,4]. For males, this diagnosis can be made based on normal or reduced serum LH and FSH concentrations despite reduced serum testosterone levels [4]. For females, it is possible to make this diagnose based on reduced levels of estradiol and normal or reduced levels of LH and FSH in conjunction with oligomenorrhea or amenorrhea. Moreover, it is also necessary to distinguish gonadotropin deficiencies that are due to hyperprolactinemia, which frequently occurs in male and female hypopituitary patients [4], and to determine whether reduced serum testosterone levels in males are due to decreased levels of sex-hormone binding globulin. In a clinical context, the GnRH stimulation test is often performed to diagnose gonadotropin deficiency and may be helpful for identifying problems in the pituitary gland and hypothalamus [10]. However, it takes several days of stimulation for the gonadotrophs that were not stimulated by GnRH due to a hypothalamic disease to detect the gonadotropin secretion response. This makes it difficult to determine the primary cause of a gonadotropin deficiency with only a single GnRH injection.

GH deficiency

When diagnosing GH deficiency in adult patients, the basal GH concentration is not considered to be valuable but measures of insulin-like growth factor 1 (IGF-1) may be of some use, although they are not sufficient themselves [4]. Thus, a stimulation test is necessary for a definitive diagnosis. Additionally, the use of previous test results and other data is warranted, including past medical records detailing GH deficiencies, organic pituitary gland diseases, and other pituitary hormone deficiencies during childhood (during which it is sufficient to use a single stimulation test) [4,5]. Although controversy remains regarding which GH stimulation test is the most appropriate for the purpose, the most widely used and reliable measure is the insulin tolerance test in which GH levels lower

than 3 μg/L are considered to indicate a severe deficiency, GH levels between 3.0 and 4.9 μg/L indicate a partial deficiency, and GH levels higher than 5.0 μg/L are considered normal [4]. For patients in whom hypoglycemia is contraindicated, it is possible to administer a variety of stimulation tests and, in this case, the diagnostic criteria of GH deficiency according to the type of stimulation tests and standard GH assay [4].

ADH deficiency

The diagnosis of posterior pituitary hormone deficiency can be easily made through a review of clinical symptoms/signs and a water deprivation test [5]. Additionally, the recently available plasma ADH concentration measurement technique can distinguish central diabetes insipidus from nephrogenic diabetes insipidus although it cannot differentiate central diabetes insipidus from compulsive water drinking or psychogenic polydipsia [5]. Given the limited availability of reliable laboratories that are capable of testing blood ADH levels and the longer time that it takes to perform and analyze these levels compared to the performance of the water deprivation test, the blood ADH test is conducted only when absolutely necessary [5].

Re-evaluation of pituitary gland function

It is advisable to re-evaluate pituitary gland functionality 2 to 3 months after an operation because, although most hypopituitarism symptoms are irreversible, a patient may recover some of level of function [4]. When a pituitary hormone deficiency occurs following a TBI, it is also necessary to re-evaluate function after some time has elapsed. In addition, of the patients with prolactinoma that are treated with a dopamine agonist, two-thirds recover pituitary gland function [22], which indicates that sporadic re-evaluations of pituitary gland function can prevent unnecessary replacement therapy. Similarly, children who exhibit an idiopathic single GH deficiency or severe GH deficiencies due to radiotherapy require re-evaluation of their GH function when they reach maturity [4].

TREATMENT

The pre- and postoperative incidence rates of hypopituitarism are similar because some hormone function can be recovered following the removal of a pituitary tumor [5] whereas deficiencies in other pituitary hormones may develop after surgery. Except in cases such as transient diabetes insipidus after surgery or hypopituitarism after TBI, most hypopituitarism symptoms are irreversible [4]. This is why it is necessary for physicians to inform their patients that they may require lifetime treatment unless there are special circumstances, such as the discontinuation of estrogen replacement after menopause [3]. Accordingly, the primary goals of treatment should be centered around the recuperation of the physiological health of the patient in terms of growth, reproduction, metabolism, and body composition [2,4,5].

Although replacement with hypothalamic or pituitary hormones are physiologic (at least theoretically), we administrate target organ hormone due to the high cost and inconvenience of repeated injections. Exception is GH or ADH replacement and the recovery of reproductive abilities [3]. In clinical situations, prolactin and oxytocin deficiency are generally not treated [4]. Although the basic principles underlying the replacement of deficient hormones remain very clear and simple, it is not possible to replace hormones to physiological levels using current treatment technologies and there are limitations to monitor the treatment response [3,4]. There is no doubt that hypopituitarism is associated with an increased incidence of cardiovascular death but the mechanisms linking these disorders remain unclear [3]. However, possible contributing factors include GH deficiencies that are left untreated, replacement of other target hormones in non-physiological ways, and the specific underlying disease. For example, if hypopituitarism develops in a patient with acromegaly, Cushing's disease, or craniopharyngioma then the underlying disease may increase the mortality [3]. Similarly, the method of tumor treatment will matter because surgery, pharmacotherapy, or i.e., radiotherapy may increase the incidence of death [3]. Given that there is a variety of causes underlying hypopituitarism as well as varying degrees of hormone deficiencies and types of deficient hormones, it is important to individualize hormone replacement therapy to the specific needs of a particular patient.

ACTH deficiency

ACTH deficiency can be treated with either hydrocortisone or prednisolone, which is a synthetic corticosteroid drug [3]. In patients with hypopituitarism whose aldosterone levels are approximately normal, there is no need to replace mineralocorticoids [3]. However, in most cases of hypopituitarism, ACTH deficiency is only partial which makes it difficult to determine whether the patient needs lifetime therapy or treatment only under conditions of stress [3]. If blood cortisol levels exceed 10 μg/dL during a stimulation test in conjunction with the absence of specific deficiency symptoms, then there is likely to be a partial deficiency and, thus, it would be advisable for the physi-

cian to either monitor the patient but not administer medicine or to observe the progress of the patient after administration of 10 mg of hydrocortisone or 2.5 mg of prednisolone [3]. If there is little difference in clinical response before and after the administration, the treatment can be discontinued. If clinical improvement is seen in patients after the administration, it must be decided whether the treatment can proceed using the same dose or if it should be slightly increased to 12.5 to 15.0 mg of hydrocortisone or to 3.75 mg of prednisolone. The choice of hydrocortisone or prednisolone is at the physician's preference but the use of hydrocortisone, which is more physiologic glucocorticoid, is recommended because prednisolone has been associated with more side effects following long-term use despite the longer and stronger efficacy [3].

The dose of the drug may be steadily increased but it is advisable that administration of hydrocortisone be performed only once or twice a day with daily dose of 10 to 15 mg. Although the most commonly used treatment regimens include two times per day, some doctors advocate the use of three administration. It may also be possible to treat patients with a partial deficiency using 5 to 10 mg of hydrocortisone once a day [3]. When using prednisolone, it is desirable to take 2.5 to 3.75 mg once a day on an empty stomach [3]; the present author prefers to use once a day prednisolone with administration of 2.5 and 3.75 mg on alternate days. In terms of the appropriate dosage, there are no biochemical markers to aid in the determination of proper glucocorticoid levels and, as a result, it is recommended that the minimum dose needed to improve patients' symptoms [3]. When using hydrocortisone, the measurement of cortisol concentrations in the blood or urine does not aid in determining proper dosage. The recommended doses for hydrocortisone (20 mg a day) and prednisolone (5 mg) are clearly excessive for the average Korean patient. Although there is a new slow-acting formulation of hydrocortisone and a special hydrocortisone drug has been designed to take into account the diurnal differences that parallel normal cortisol secretion [3]. It is too early to tell if these drugs are appropriate for clinical purposes.

Under stressful conditions, a patient must be treated with the same methods as those used to treat patients with primary adrenal insufficiency; i.e., increase the dose by 2- to 3-fold for mild stress and administer an intravenous (IV) injection of hydrocortisone (150 to 200 mg) a day for severe stress. Moreover, it is necessary to increase glucocorticoid doses by 1.5- to 2-fold when used in tandem with liver enzyme inducers such as phenytoin, barbiturate, rifampin, and carbamazepine, and to reduce the glucocorticoid dose when liver enzyme inhibitors such as ketoconazole, itoconazole, cyclosporine, and tacrolimus are being used [3]. If the liver or renal function of a patient is not at an ideal level, the dose should not be adjusted [3].

For pregnant women, it is advisable to prescribe hydrocortisone rather than prednisolone because the latter can pass through the placental barrier [4]. During the first trimester of pregnancy, there is no need to increase the dose of glucocorticoid but an increase of approximately 50% (2.5 to 10.0 mg) is needed during the third trimester due to increased levels of corticosteroid binding globulin [4]. At the time of delivery, a large amount of hydrocortisone needs to be injected intravenously [4]. In contrast to pregnant females, females that are receiving estrogen therapy do not require an adjustment in glucocorticoid doses [4]. Although several studies have indicated that replacement with dehydroepiandrosterone (DHEA), which is the adrenal androgen that is typically deficient in women, improves sexual desire [23], it is not yet recognized as a standard replacement treatment. In these situations, the patient must be trained regarding the onset of acute adrenal insufficiency (adrenal crisis), which requires an increase in dose, and must always carry a hydrocortisone injection as well as a card indicating his/her status as an adrenal insufficient patient. Additionally, the patient should learn how to self-inject hydrocortisone.

TSH deficiency

TSH deficiency is treated with L-thyroxine (T4) [4]. Because the biological activities of currently available drugs are quite similar to T4, there is no need to change doses when shifting from one drug to another [4]. It is advisable to initiate drug treatment with 25 to 50 μg per day and then steadily increase the dose to 75 to 125 μg per day (0.6 μg/kg×body weight/day) and to administer the drug on an empty stomach [4]. Since the TSH concentration has dropped below normal levels, it is more appropriate to evaluate the treatment response using clinical symptoms and measures of plasma free T4 concentrations [3,4]. These levels should be measured prior to administration and then maintained within the mid-range of normal concentrations.

Triiodothyronine should not be used to treat hypopituitarism except under special circumstances. In patients with clear indications of adrenal insufficiency, glucocorticoids should be administered prior to or in conjunction with T4 to prevent adrenal crisis [3]. When used in combination with liver enzyme inducers such as phenytoin, barbiturate, rifampin, and carbamazepine, the dose of T4 should be increased by 30% to 50%, especially when treating females in early pregnancy and patients

receiving estrogen [3,4]. On the other hand, the T4 dose should be reduced by approximately 20% when it is given to patients receiving testosterone or to those who are elderly [3,4]. Additionally, although there is no need to adjust the dose when a patient exhibits reduced liver or renal function, it must be increased in the case of nephrotic syndrome [3,4].

Gonadotropin deficiency

For patients with hypogonadotropic hypogonadism, it is important to consider both gonad steroid replacement treatment and fertility. Androgen replacement for men can be accomplished using testosterone; for example, the treatment preferred by the present author includes intramuscular injections of testosterone enanthate or cypionate (200 mg per injection) every 3 to 4 weeks and oral pills of testosterone undecanoate (80 to 120 mg twice a day) with or immediately after a meal. Korean patients require smaller doses of testosterone than Western patients but have few problems taking the medication orally. In addition to shots and tablets, a transdermal gel can be applied to the skin of the patient, a patch can be applied on the patient's testicles or other sites, and pellets can be implanted in a muscle once every 6 months [3,4]. Although these drugs are expensive, the biological activity of testosterone is excellent. Recently, a novel testosterone undecanoate injection that is administered intramuscularly once every 3 months was introduced and shown to effectively maintain appropriate concentrations of testosterone in the blood [4]. However, the drug chosen for treatment depends on the patient based on factors such as efficacy, side effects, convenience, and cost.

The primary goal of gonadotropin treatment in males is to completely recover characteristics such as beard growth, physical strength, sexual desire, and sexual functionality. For patients who have yet to undergo puberty, the initial dose must be small and then it can be gradually increased depending upon the clinical response and presence of side effects until a maximum dose is reached. In addition to the clinical response, measures of serum testosterone concentrations are helpful for determining the appropriate dose when intramuscular delivery methods are used and it is advisable to maintain blood testosterone concentrations at 400 to 700 μg/dL in the middle of an injection procedure [2]. For elderly patients or patients with obstructive sleep apnea syndrome, it is desirable to adjust the testosterone dose downward. Side effects of testosterone were erythrocytosis, acne, prostate hyperplasia, prostate cancer, and/or reduced spermatogenesis [4]. In the initial stages of testosterone treatment, it is important to perform hematocrit and reduce the dose if the result is over 50% and discontinue treatment if the result is over 55%. For patients over 40 years of age, a prostate cancer test is also necessary and a digital rectal exam and blood prostate-specific antigen (PSA) test should be conducted 3 to 6 months after treatment and once per year thereafter. If the results of the PSA test are over 3 ng/mL immediately after treatment, show an increase of 1.4 ng/mL at 1 year after treatment, or exhibit a PSA growth rate of more than 0.4 ng/mL per year for more than 2 years and there are unusual findings from the digital rectal exam or prostate ultrasonic test, the patient must visit a urologist [24].

When a male patient wishes to father a child, various infertility treatments can be used depending on the type of disease. In the case of hypothalamic hypogonadotropic hypogonadism, sporadic GnRH treatment using an infusion pump (2 μg via subcutaneous injection every 2 hours) will restore masculinity and improve sperm count. However, this technique is used only infrequently due to the inconvenience of continuously carrying a bulky infusion pump. Similar to the case of hypopituitary hypogonadotropic hypogonadism, treatment with gonadotropin is used in this situation [2]. Like gonadotropin, human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG; which is a drug extracted from the urine of menopausal women, generic name: menotropin) are available commercially as are recombinant LH (rLH) and FSH (rFSH) [2]. Gonadotropin typically needs to be injected intramuscularly 2 to 3 times per week, although subcutaneous injection is also available, and its use requires regular sperm analysis to determine the efficacy of the treatment [2]. Approximately 60% of males whose sperm counts have recovered to normal levels exhibit a restoration of their reproductive abilities [2]. If a patient suffers from hypogonadotropic hypogonadism prior to puberty, his testicles will be smaller than normal and the possibility of maintaining full reproductive abilities is very low, even following treatment [2]. Thus, prepubescent patients are advised to undergo gonadotropin treatment even though it is considerably more expensive and inconvenient than other methods.

For females with hypopituitarism, the administration of ethinyl estradiol (2 to 4 mg a day), which is a conjugated estrogen (0.625 to 1.25 mg a day) combined with progesterone, or the use of oral contraceptives can fully restore regular menstruation prior to menopause [2]. However, if the patient did not fully physically develop during puberty, then it is necessary to increase the estrogen dose during the initial stages of treatment and administer daily administration without drug holiday. For females with an intact uterus, administration of medroxypro-

gesterone (10 mg), which is a type of progesterone, 12 to 14 days per month in conjunction with estrogen treatment is recommended [2]. Transdermal estrogen patches may also be used as a complementary measure and, although it is an expensive regimen, it is efficacious for maintaining biological activity. Treatment must be continued at least until menopause to prevent osteoporosis and to maintain the antiatherosclerotic lipoprotein effects and, after menopause, the dose of estrogen should be progressively reduced until treatment is discontinued. Moreover, the patient should take annual mammography and breast ultrasound and gynecologic exam if unexpected vaginal bleeding or the patient wants to get pregnant [2].

Similar to males, the restoration of reproductive ability may be accomplished via the administration of hCG and hMG (or rLH and rFSH) as these hormone therapies are known to improve the possibilities of ovulation and conception. Due to recent advancements in dosage determination and supervising techniques, the incidence rates of ovarian hyperstimulation and multiple pregnancies have substantially declined, although these risks are still present. With respect to the possibility of these risks, the pulsatile injection of GnRH rather than gonadotropin treatment is considered to be much safer in hypothalamic hypogonadism. Additionally, the GnRH-based treatment is more effective and has fewer side effects but, in real clinical situations, the gonadotropin treatment is preferred due to the inconvenience of carrying the injection pump and other disadvantages [2].

For patients with hyperprolactinemia, which in most cases represents only a slight increase unless it is prolactinoma, the administration of a small amount of a dopamine agonist (bromocriptine or cabergoline) will return prolactin levels to normal [4]. If prolactinoma is present, then treatment with an adequate dose of a dopamine agonist is conducted for an extended period so that the prolactin levels can be reduced to within a normal range. If gonadotropin deficiency continues despite treatment, then the appropriate (male/female) hormone replacement treatment can be initiated.

GH deficiency

In the past, GH replacement treatment is generally only utilized in children with growth disorder due to GH deficiency. However, the recent development of recombinant human GH has made it possible to use GH to treat adults with hypopituitarism or reduced GH secretion (e.g., due to obesity, old age, burn injury, and catabolic disease) [5]. This treatment technique was used in Europe earlier than in the United States and showed positive results including the post-treatment normalization of body composition (reduced body fat and increased muscle mass), improvements in muscular strength and physical vitality, increased bone density, reduced cardiovascular risks (particularly improved dyslipidemia), enhanced cardiac function, and improved mental health [5]. The recommended initial dose of GH is 0.5 units a day but the dose steadily increases after a few weeks. According to the experience of the present author, the maintenance dosage for Korean patients is 1 to 2 units per day with smaller amounts for older people. The best way to gauge the dosage over an extended period of time is to determine the optimal amount (lowest dose) at which the body composition of the patient can be maintained at a normal level. During short treatment periods, it is advisable to maintain IGF-1 levels within the mid-ranges according to the gender and age of the patient [5].

Males respond to GH treatment better than females, which implies that females will require a greater number of doses than males. This is likely because the efficacy of GH in the liver is interfered with by orally-administered estrogen which, in turn, inhibits the production of IGF-1. In contrast, testosterone tends to enhance IGF-1 levels [4]. The administration of GH also seems to influence the metabolism rates of hydrocortisone and T4 such that the doses of these drugs need to be adjusted upward [2]. If cortisone, which is not used in Korea, is utilized instead of hydrocortisone, then problems may occur but there will not be a need to adjust the dose of hydrocortisone, at least in the experience of the present author. GH treatment is never recommended for patients with malignant tumors, increased intracranial pressure, or proliferative diabetic retinopathy or for pregnant females [5]. A majority of the short-term side effects associated with GH treatment stem from overdoses or retained fluids due to normal GH mechanisms while side effects such as arthralgia, dilated cardiomyopathy, and diabetes mellitus have been reported with the long-term use of GH [5]. However, most of these side effects disappear once the dose is reduced. The effects of GH emerge after a few months of treatment and patients with more severe deficiencies exhibit the most improvement. In terms of body composition, a full recovery of muscular strength and physical ability may take several years [4].

After 20 years of using GH treatment for hypopituitarism patients, there is still no evidence demonstrating that this regimen may increase the incidence of cancer or cause the recurrence of a tumor [5]. Nonetheless, patients undergoing GH treatment warrant careful observation to identify the development of additional risk factors. Additionally, future studies are required to determine whether GH treatment may reverse the

high mortality (or shortening of life expectancy) due to cardiovascular events. Because GH requires daily subcutaneous injections and its efficacy is not evident over extended periods of time, patients tend to discontinue treatment or receive the treatment only infrequently. Recently, a once-a-week self-administered subcutaneous injection of GH was developed and is currently undergoing clinical study. Once this treatment modality is made available in Korea, it is expected that the compliance rate for GH treatment will improve substantially.

ADH deficiency

Diabetes insipidus that results from ADH deficiency can be easily treated with a novel synthetic analogue of vasopressin known as desmopressin (1-desamino-8-D-arginine vasopressin [DDAVP]) which specifically interacts with ADH V2 receptors in the kidney [3]. DDAVP can be administered orally at doses of 0.1 to 0.2 mg 2 to 3 times a day, nasally at doses of 10 μg/0.1 mL 2 to 3 times per day, or intravenously at 1 to 2 μg twice a day. Beginning with oral doses at 0.05 mg one a day (before bedtime) or 0.05 mg twice a day, it is possible to gradually increase the dose or adjust the intervals between doses depending on the amount of urine. As a result, it is necessary to perform regular tests to assess electrolyte levels, particularly serum sodium levels. This drug is considered to be safe even during pregnancy but the dose should be increased during the second trimester based on the amount of urine and the degree of thirst [3]. When it is not feasible to orally administer DDAVP, for example, following surgery, it is necessary to utilize IV techniques when there is a rapid increase in urine volume by closely monitoring the amount of urine and serum sodium levels in the urine [3]. In the postoperative period, it is better to administer the drug when necessary rather than regular administration. It is advisable to regularly resume oral drug if the patient can take the drug orally. If there is an abrupt decrease in the amount of urine in conditions such as dehydration due to diarrhea, vomiting, or severe perspiration, DDAVP can be administered as needed. Drugs such as glucocorticoids, T4, alcohol, lithium, and demeclocycline decrease DDAVP efficacy. On the other hand, drugs like chlorpropamide, carbamazepine, and nonsteroidal anti-inflammatory medications can enhance DDAVP actions. In this case, the patient may suffer from either hypernatremia or hyponatremia and, thus, close supervision is warranted. If diabetes insipidus is accompanied by hypopituitarism, particularly in conjunction with an adrenal insufficiency or severe T4 deficiency, symptoms such as polyuria, polydipsia, and nocturia improve due to increased ADH secretion and action. As a result, this may lead medical staff to believe that the patient's symptoms are improving but once the patient complements his/her deficient hormone levels, the symptoms associated with diabetes insipidus will return. However, diabetes insipidus may improve over time especially if it is due to only a partial deficiency. Currently, it is better to discontinue drug administration intermittently and resume the treatment regimen only if urine volume increases [3].

CONCLUSIONS

Hypopituitarism can be easily diagnosed using basal hormone tests except GH and ACTH deficiency, which require the stimulation tests. These conditions are irreversible for most hormone-deficient patients and, except for older females who are experiencing menopause, patients will need to undergo lifetime hormone replacement treatment. Orally-administered target organ hormones are utilized, except for GH and ADH. When administering glucocorticoid, it is desirable to prescribe hydrocortisone at doses of 10 mg (one a day, in the morning) or 12.5 to 15.0 mg (10.0 to 2.5 mg or 5.0 mg twice a day) depending on the clinical response. Under stressful conditions, the dose needs to be increased and, in the case of a TSH deficiency, T4 can be administered according to the clinical response and measurement of free T4 concentrations (usually 75 to 125 μg one a day).

When gonadotrophin deficiency occurs in a male patient, it is important to administer testosterone orally or intramuscularly and to adjust the dose by closely monitoring the clinical response of the patient and his testosterone concentrations. For female patients, estrogen and progesterone should be alternately administered and gonadotrophin should be prescribed when the patient wishes to conceive. In the case of GH-deficient children, the administration of GH is a must. It can also be given to adults because its efficacy has been proven in this population, as long as there are no adverse side effects. When diabetes insipidus is present, it is more appropriate to administer DDAVP orally or nasally while determining its dose based on the amount of urine and the results of electrolyte levels. DHEA treatment for females is not yet recommended but further studies are called for in this area.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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