

## Approach to Hypopituitarism

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### ABSTRACT

Hypopituitarism is a serious endocrine disorder that requires early recognition and prompt treatment to avoid its severe deleterious effects. In adults manytimes it can present with non-specific symptoms and hence high index of suspicion is necessary for early diagnosis. Panhypopituitarism refers to the loss of secretion of at least three pituitary hormones. Replacement of the deficient hormones is the cornerstone of therapy. It also requires life-long followup by endocrinologist. In this article, causes, clinical features, and the management of hypopituitarism including endocrine replacement therapy is discussed

**Keywords :** hypopituitarism, growth hormone deficiency, pituitary hormone replacement therapy, endocrine replacement therapy

### Introduction :

Hypopituitarism was first described by Simmonds in 1914. It refers to decreased secretion of pituitary hormones resulting from disease of either pituitary or hypothalamus. Clinical manifestations depend on

cause, severity and rate of development of hormone deficiency. Optimally replacing deficient hormones can be challenging. In these patients in addition to morbidity caused by hormonal deficiencies increased mortality due to cardiovascular and cerebrovascular diseases is seen<sup>1</sup>.

### Causes :

#### Major causes of hypopituitarism

<b>Hypothalamic diseases</b>
Mass lesions – Benign (craniopharyngiomas) and malignant tumors (metastatic from lung, breast, etc)
Radiation – For CNS and nasopharyngeal malignancies
Infiltrative lesions – Sarcoidosis, Langerhans cell histiocytosis
Infections – Tuberculous meningitis
Other – Traumatic brain injury, stroke
<b>Pituitary diseases</b>
Mass lesions – Pituitary adenomas, other benign tumors, cysts
Pituitary surgery
Pituitary radiation
Infiltrative lesions – Hypophysitis, hemochromatosis
Infection/abscess
Infarction – Sheehan syndrome
Apoplexy
Genetic mutations
Empty sella

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A special mention has to be made of hypophysitis which is autoimmune involvement of pituitary gland. Lymphocytic and granulomatous hypophysitis<sup>2</sup> are the most common forms, but new variants have recently been reported due to cancer

therapy with monoclonal antibodies against cytotoxic T-lymphocyte antigen-4 (CTLA-4)<sup>3</sup>, IgG4 related hypophysitis<sup>4</sup>, Ribavarin related hypophysitis<sup>5</sup>. It has wide spectrum of presentation and needs high index of suspicion for diagnosis.

### **Clinical Features :**

The presentation of hypopituitarism can be nonspecific and needs high index of suspicion especially in nontumorous etiologies like hypophysitis or Sheehan's syndrome<sup>6</sup>.

Situations where hypopituitarism should be suspected

1. Tumors in hypothalamus pituitary region
2. Empty sella syndrome
3. past history of pituitary surgery
4. past history of CNS irradiation
5. past history of excessive postpartum bleeding
6. CNS granulomatous / inflammatory / infiltrative diseases
7. Gradual onset, unexplained, progressive asthenia, loss of appetite, hypotension, hyponatremia especially if MRI shows ESS or enlarged pituitary as in Lymphocytic hypophysitis.

### **General Principles :**

**The clinical manifestations of hormonal deficiencies depend on**

- 1. Rapidity**
- 2. Severity**
- 3. Single vs. multiple hormones involved**
- 4. Hypothalamic involvement**

In situations like pituitary apoplexy which is of rapid onset, clinical picture may be profound hypotension due to ACTH deficiency. Timely suspicion and diagnosis of ACTH deficiency and treatment in the form of corticosteroids can be life saving.

In partial, nonacute deficiencies, presentation is very subtle with nonspecific symptoms and may be missed for long time. But when severe deficiency of ACTH is present it can lead to significant loss of appetite, weight and profound weakness. Of course

multiple hormone deficiencies complicate the picture more. Infertility may be the issue leading to investigations for pituitary disorder.

If hypopituitarism is due to hypothalamic disorder then DI usually accompanies hypopituitarism.

**Sequence of hormonal involvement is often characteristic.** Hypopituitarism arising from tumor or irradiation typically involves GH and gonadotropins first followed by ACTH and TSH. As opposed to that lymphocytic hypophysitis (LYH) which cause ACTH and TSH deficiency first and gonadotropins are preserved till end.

### **CLINICAL FEATURES OF INDIVIDUAL HORMONE DEFICIENCY<sup>7</sup> -**

#### **1. ACTH DEFICIENCY :**

ACTH deficiency is potentially life threatening component of hypopituitarism. If develops rapidly as in apoplexy it results in profound hypotension and can be fatal if untreated.

As opposed to that chronic slow onset deficiency can present as progressive fatigue, weight loss, loss of appetite and profound weakness. Radiotherapy which is given postoperatively for pituitary tumors takes long time for its action and hormonal deficiencies start manifesting almost a year after therapy is over. If patients are not aware of these delayed effects and are not periodically screened for deficiencies, these can be missed. This happens frequently if treating doctor is not aware of past surgery and postop radiotherapy. Hence delayed sequel of radiotherapy must be kept in mind and patients should be informed accordingly.

Examination reveals skin pallor as opposed to hyper pigmentation as seen in primary adrenal failure. Hyponatremia is less common than primary adrenal deficiency as aldosterone axis is preserved. Sometimes loss of appetite and weight loss can be so severe that they are searched for occult malignancy. Replacing deficient hormone gives dramatic and rewarding results.

#### **2. TSH :**

TSH deficiency occurs late. Symptoms are like primary hypothyroidism e.g. cold intolerance,

fatigue, constipation. However they are milder than primary as some TSH is always preserved.

### 3. GONADOTROPIN DEFICIENCY :

The features of gonadotropin deficiency depend on whether it occurs before or after puberty.

#### *In male*

The **prepubertal** onset leads to lack of testicular and penile growth with eunuchoid proportions (arm span exceeding height by 5 cm).

The **postpubertal** onset can cause reduction of testicular size, loss of body hairs and wrinkled skin of ageing in youth. Oligo \Azoospermia may lead to infertility.

#### *In females*

The **prepubertal** onset leads to subnormal development of breast and amenorrhea.

The **post pubertal** onset in adults causes amenorrhea, oligomenorrhea, infertility, breast atrophy, vaginal dryness, dyspareunia. Pubic and axillary hairs are spared unless ACTH deficiency also occurs.

### 4. ADH :

Polydipsia, polyuria with nocturnal are classic symptoms of ADH deficiency causing Diabetes insipidus (DI). If cortisol deficiency is present it masks the features of DI and become manifest only after cortisol is replaced.

In postsurgical cases triphasic response in the form of temporary DI, SIADH and again permanent DI is seen.

### 5. PROLACTIN :

Failure of lactation is the symptom of prolactin deficiency if it happens in postpartum period.

### 6. GROWTH HORMONE :

**In children** it can cause short stature.

**In adults** it causes increased body fat with loss of muscle mass and strength. Impaired psychological wellbeing with depression, anxiety and increased social isolation. They are obese with increased abdominal obesity and reduced exercise performance. Postsurgical radiotherapy also predisposes them for increased morbidity from cerebrovascular diseases.

### LOCAL MANIFESTATIONS :

The tumour may cause visual field defects, cranial nerve palsy and can be a clue towards central etiology. Acute severe headache is usually present only in pituitary apoplexy cases. Otherwise headache is not a manifestation of pituitary adenoma.

### DIAGNOSIS

Diagnostic evaluation can be divided into radiological imaging and endocrine evaluation.

#### 1. IMAGING :

MRI offers higher resolution so is preferred modality for pituitary imaging.

#### 2. ENDOCRINE EVALUATION :

##### **BASAL**

At basal level cortisol, electrolytes, T3, T4, TSH, PRL IGF-1, LH, FSH, Testosterone in males and estradiol in females.

**DYNAMIC TEST** is usually required for diagnosis of ACTH and ADH, GH deficiency

### ACTH DEFICIENCY TESTING

#### **Basal :**

Low basal cortisol with inappropriately normal or low ACTH is s\o ACTH deficiency. If suspected in a sick patient after collecting sample for ACTH and cortisol, cortisol replacement should be started immediately as ACTH deficiency can be life threatening. Dynamic testing can be performed at later date<sup>8</sup>.

A basal morning cortisol more than 18 mcg\dl indicates normal HPA axis and basal morning cortisol less than 3 mcg\dl **suggests cortisol deficiency and dynamic testing is not required.** Patients with levels between 3-18micro\dl need dynamic testing.

#### **Dynamic testing :**

ITT (insulin tolerance test): ITT is considered as gold standard. Following injection of 0.1 unit /kg of insulin when adequate hypoglycemia (< than 40 mg\dl) is achieved cortisol is collected. If it is more than 18 mcg\dl or rises by more than 7 mcg\dl it is considered adequate. ITT is unpleasant for patients

and carries a risk of precipitation of seizure episode or loss of consciousness.

**SYNACTHEN / SHORT ACTH TEST :** It is associated with less morbidity so used as surrogate test for diagnosis of ACTH deficiency. Although it is a test to see adrenal reserve it gives valuable information in ACTH deficiency except in acute ACTH deficiency as adrenal cortex takes time to atrophy. One hour post IM injection of 250 IU Synacthen cortisol sample is collected. There are usually no side effects. Interpretation is done same as described in ITT.

### TSH

It is characterized by low T4 with low or inappropriately normal TSH. T3 concentration is typically normal in mild deficiency as peripheral conversion of T4 to T3 is upregulated.

### GONADOTROPINS

In **postmenopausal females** absence of typical elevation of gonadotropins is indicative of deficiency.

In **premenopausal females** amenorrhea with low estradiol and low FSH, LH is sufficient for diagnosis.

In **males** low testosterone with low FSH, LH is suggestive of hypogonadism.

### ANTIDIURETIC HORMONE

Deficiency of ADH can be diagnosed if polyuria (250 ml/hour) occurs due to excretion of hypotonic urine (specific gravity <1.005 or urine osmolality < 200 mOsm/kg H<sub>2</sub>O). It can happen transiently in 30 % of postoperative pituitary surgery cases.

### GROWTH HORMONE DEFICIENCY

For diagnosis of GH deficiency basal GH has no value.

The post clonidine stimulation GH less than 7 ng/dl is suggestive of partial GHD and less than 10 is suggestive of GHD.

### MANAGEMENT

Management can be separated into treatment of

1. Underlying etiology for hypopituitarism

2. Hormone replacement therapy

**Underlying disease process** will need surgery if tumor is cause.

### Hormone replacement therapy-

#### 1. ACTH-

The aim of glucocorticoid therapy is to mimic physiological hormone concentration, ensure adequacy of hormone even in acute illness or stress and avoiding over replacement. It is a walk on tight rope.

Different forms of glucocorticoids are available for treatment with merits and demerits of each one. Hydrocortisone, prednisolone, dexamethasone are available. Hydrocortisone 15-20 mg in 2-3 divided doses is given. In Indian setting if hydrocortisone availability is problem prednisolone 5 mg at 8 am and 2.5 mg at 4 pm can be given. In acute crisis if patient is not tolerating orally then self injection of dexamethasone can be taught till they reach hospital.

In special situations like Cushing's syndrome due to pituitary adenoma, post adenoma removal they develop transient ACTH deficiency and need to be supplemented with glucocorticoids for 3-4 weeks. This looks like a paradox as we are giving steroid in treatment of Cushing's but it is essential till adrenals recover from chronic suppression. Later as morning cortisol recovers steroids can be gradually withdrawn.

#### Need for mineralocorticoid coverage

Unlike primary adrenal insufficiency, mineralocorticoid replacement is rarely necessary in hypopituitarism as Angiotensin II and potassium, not ACTH, are the major regulators of aldosterone secretion.

The essential component of glucocorticoid replacement is educating the patient about life long need of therapy and also need to double or triple the dose during minor or major illness. Wearing a medic alert is advisable. Attaching details of a sick day schedule for glucocorticoid replacement in a case file of patient helps local physician to manage acute crisis till he reaches endocrinologist.

## 2. TSH deficiency

It is treated with thyroxin T<sub>4</sub>, starting with 1.6 mcg/kg/day. Lower doses may be used in elderly or patients with IHD. **ACTH deficiency must be identified and treated first before giving thyroxin in order to avoid adrenal crisis.** Aim is to keep T<sub>4</sub> in higher side of normal. As is done in primary hypothyroidism TSH measurement is not helpful in titrating the dose.

## 3. GONADOTROPIN DEFICIENCY

Treatment of gonadotropins deficiency depends upon gender and whether or not fertility is desired.

**Men** - Testosterone replacement is indicated in men who have secondary hypogonadism and in whom fertility is not the goal of therapy. Men with secondary hypogonadism who wish to become fertile can be treated with gonadotropins or gonadotropin-releasing hormone (GnRH).

**Women** - Women with hypogonadism due to pituitary disease, who are not interested in fertility, should be treated with estrogen-progestin replacement therapy. The goal of treatment is **not** the same as in postmenopausal women, in whom the goal is to relieve hot flashes. Instead, the goal is similar to that of replacement of thyroxin (T<sub>4</sub>) and cortisol i.e. to replace the missing hormones as physiologically as possible. Cyclical conjugated equine estrogen 0.625 mg orally day 1-25 with medroxyprogesteron acetate 10 mg orally day 16-25 is optimum for females with intact uterus.

Females desirous of fertility should be treated with HCG as source of LH and HMG as source of FSH. Various ovulation induction protocols are practiced and hence patient needs expert guidance to choose a protocol which will be cost-effective for her optimum fertility success.

## 4. GROWTH HORMONE DEFICIENCY

Growth hormone replacement is very rewarding in GHD children. In children it can be given as SC injection at night in the dose of 0.03 mg/kg body weight. In patients of hypopituitarism with multiple hormonal deficiencies before giving GH therapy making patients euthyroid and replacing

cortisol with lowest possible but safe dose is essential. Even during GH therapy, TSH deficiency can be unmasked especially in first 3 months hence TFT should be monitored at 3 months and then annually. If growth is normal till adolescent age then puberty can be stimulated by giving gonadal steroids at 11-12 years in girl and 12-13 years in boys.

In adults with GHD decision to start therapy (0.3 mg/day SC) should always be discussed with patient. Replacing GH improves their metabolic parameters like adverse lipids, bone and muscle mass.

## 5. ADH:

Intranasal desmopressin via nasal tube starting with 5 mcg twice daily helps in normalizing urine output<sup>9</sup>. Subsequent doses need monitoring and it is always better to under replace ADH to avoid hyponatremia due to fluid retention. Oral DDAVP in the dose of 300- 600 mcg daily can be given in chronic DI.

## SUMMARY:

Although pituitary is a tiny gland it harbours extremely important centrally situated control of endocrine milieu of body. If acute involvement like apoplexy goes undiagnosed it can be fatal due to ACTH deficiency. Otherwise chronic slow onset development of deficiencies can take long time till they are diagnosed. Once diagnosed it is essential to screen for multiple hormonal deficiencies with proper stimulation tests as basal value has no significance in few hormones like GH. Replacing deficient hormone in optimum dose is walk on tight rope as they are to be given lifelong. They should be replaced in a manner as close to nature as possible. This requires proper dosing and timing to match circadian rhythm. Overall hypopituitarism management can test the skills of endocrinologist to suspect, diagnose and optimally replace deficient pituitary hormones but is satisfying and rewarding.

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