

Hypopituitarism: Emergencies

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CLINICAL RECOGNITION

Hypopituitarism usually has an insidious presentation over weeks to months and often remains clinically silent until a particular stressful event such as a concurrent infection or trauma at which time marked symptoms are evident. The reason for a protracted course until deficiency is clinically evident is due to the slow depletion of pituitary hormones. The end endocrine organs also have other, albeit less effective, ways of dealing with lack of pituitary input (for example non-ACTH stimulation of cortisol from the adrenal or constitutive activation of the TSH receptor at a low the thyroid). The presentation level in of hypopituitarism is different from the catastrophic clinical situation such as a hemorrhagic infarct into the pituitary that results in acute pituitary insufficiency and cardiovascular collapse. The latter is referred to as

pituitary apoplexy and is discussed in another chapter. The more common presentation is in a patient who slowly develops fatigue and rather nonspecific symptoms.

Each cell in the pituitary is responsible for one or more pituitary hormones and hyposecretion of the hormone can result in a variety of symptoms as summarized in Table 1. Although the symptoms are rarely pathognomonic for hypopituitarism or a particular hormone insufficiency, collectively the presence of symptoms such as body fatigue and failure to thrive with or without cardiovascular compromise in the right clinical scenario, should alert the physician to a pituitary etiology.

| Table 1. Signs of Symptoms of Hypopituitarism in Adults | | | | |
|---|-----------------------|--------------------------|--|--|
| Cell Type, Pituitary Hormone | Affected Hormone | Symptoms/Signs | | |
| Corticotrophs, ACTH | Cortisol | Hypoglycemia | | |
| | | Hyponatremia | | |
| | | Hypotension -> Shock | | |
| Thyrotrophs, TSH | T4, T3 | Confusion -> Coma | | |
| | | Hypothermia | | |
| | | Bradycardia | | |
| | | Hyponatremia | | |
| | | Lethargy | | |
| | | Edema | | |
| Gonadotrophs, LH/FSH | Testosterone/Estrogen | Deceased muscle mass | | |
| | | Deceased libido | | |
| | | Deceased muscle strength | | |
| | | Hair loss | | |
| | | Amenorrhea | | |
| | | Infertility | | |
| Somatotrophs, GH | GH/IGF-1 | Decreased muscle mass | | |
| | | Lethargy | | |
| Lactotrophs, Prolactin | | Failure of lactation | | |

Often times, patients with panhypopituitarism can present with slight elevation, as opposed to deficiency, in prolactin levels causing amenorrhea and/or galactorrhea. This is because damage to the pituitary stalk (usually from mass effect) can cause interruption of the continuous dopaminergic inhibition of the lactotrophs resulting in elevated prolactin levels (usually less than 200 ng/mL). It is important to be able to differentiate this entity from a prolactinoma, which usually presents with levels above 200ng/mL.

Hypopituitarism can also manifest with deficiency of vasopressin (AVP) if there is damage to the posterior pituitary. This will cause the clinical syndrome known as diabetes insipidus, which classically manifests with polyuria, polydipsia, hypernatremia, and low urine osmolarity.

Often it will be difficult for the physician at the bedside to determine whether the suspected hormone deficiency is in fact due to a pituitary insufficiency or primary failure of one of the major endocrine glands such as the adrenal, thyroid, or gonads. While some clues may come from the history, the suggestion that one or more endocrine glands are dysfunctional should alert the physician to a pituitary etiology. The presenting signs and symptoms are similar in both children and adults although the presentation in children is usually much more dramatic. The signs are more often associated with cardiovascular instability, failure to gain weight or grow depending on the degree of pituitary hormone deficiency and can be present at birth or later.

PATHOPHYSIOLOGY

The etiologies of hypopituitarism are either congenital or acquired. While congenital hypopituitarism is usually associated with early onset hemodynamic instability, growth disturbances and failure to thrive the symptoms may not manifest until puberty when a surge in pituitary hormones is required for normal physiology, and puberty is halted. Although isolated pituitary hormone deficiencies are found (usually due to genetic defects in specific pituitary cell transcription factors), when two pituitary cell lines are impaired it is generally an indication that all five cell lines are malfunctioning. There is however, a predictive order of loss of hormonal function, with a tendency to preserve the most crucial hormones for survival. (Usually manifesting first with loss of somatotrophs and gonadotrophs and last with loss of corticotroph function). The acquired causes of hypopituitarism are listed in <u>Table 2</u>. One should also consider the possibility of hypothalamic disease as a cause of pituitary insufficiency.

| Table 2. Causes of Hypopituitarism | | |
|--|--|--|
| Congenital | | |
| Gland Malformation | | |
| Transcription Factor Defects | | |
| Acquired | | |
| Destruction due to tumors (e.g. Craniopharyngioma, non-secreting pituitary adenomas, hamartomas) | | |
| Infection (e.g. Tuberculosis) | | |
| Destruction due to inflammation (e.g. Sarcoid, Hemochromatosis) | | |
| Postsurgical | | |
| Post-radiation | | |
| Hemorrhage | | |
| Abrupt Hormone Therapy Withdrawal | | |
| | | |

DIAGNOSIS AND DIFFERENTIAL

Diagnostic Tests

ACTH

There is a general lack of enthusiasm in measurement of static hormones for the diagnosis of hypopituitarism This is in part due to the variable nature of hormone secretion in normal physiological states. Cortisol is released from the adrenal gland in a pulsatile fashion under the direction of ACTH. Furthermore, ACTH secretion is responsive to the hypothalamic factor, corticotropin releasing hormone (CRH), which is also released in an episodic manner. Therefore, depending on the instance that blood is sampled; there can be significant variation in the absolute values of ACTH and cortisol. The hypothalamic factor, CRH is not readily measured in the blood and the normal reference values have not been established in the literature.

It is important to keep in mind that measurement of total cortisol in serum is also influenced by the presence of cortisol binding globulin (CBG) which can be affected by clinical scenarios like liver failure, sepsis, and high estrogen states, such as pregnancy and use of oral contraceptives.

Provocative tests are more useful in the assessment of the hypothalamic-pituitary-adrenal axis than are static and unstimulated values of hormones. The screening test of choice to rule out adrenal insufficiency (both primary and secondary) is the 8:00 serum cortisol level (ruled out if >20 μ g/dL but can vary depending on the assay). The ACTH stimulation test can be used for confirmation (<u>Table 3</u>) for summary of tests). This test however, might not be able to diagnose acute secondary adrenal insufficiency in which case, it might be necessary to perform the insulin tolerance or metyrapone stimulation test.

TSH

Unlike cortisol levels, static thyroid hormone levels can provide valuable diagnostic information. While there is also pulsatile fluctuation in serum concentrations of TSH, the excursions are much less than with cortisol due to the longer half-life of T4 (7 days versus minutes for cortisol).

It is important to point out however, that the clinician should never rely on the measurement of an isolated TSH level (without free T4 measurement) when suspecting secondary hypothyroidism, as this entity can often present itself with an inappropriately normal TSH level in the presence of a low T4.

GONADOTROPINS

Similar. to the thyroid, gonadal hormones (testosterone and estrogen) are readily measured in the blood and are more stable and less disturbed by pulsatile secretion. Baseline AM measurement of the gonadal hormone LH and FSH can be useful to distinguish primary (gonadal) versus secondary (pituitary) disease. It is worth mentioning that although unlikely to cause changes in clinical management, a low FSH level in a postmenopausal woman can be a very sensitive test to screen for hypopituitarism when clinically suspected.

| Table 3. Tests Used in the Diagnosis of Hypopituitarism | | | |
|--|--------------------------------------|--|--|
| Test for Hormonal Deficiency | Expected Result if Deficient | | |
| ACTH | | | |
| 8:00 AM Cortisol | <20 µg/dl | | |
| Insulin Tolerance (0.1U/Kg) | Cortisol <20µg/dl | | |
| ACTH Stimulation (250 µg) | Cortisol <20 µg/dl* | | |
| Metyrapone stimulation test | ACTH <75pg/mL | | |
| TSH | | | |
| T4/T3/TSH | Dec./Dec./Dec or not elevated | | |
| Gonadotropins | | | |
| Testosterone or Estradiol | Lower than reference range | | |
| LH/FSH | Normal or lower than reference range | | |
| Growth Hormone | | | |
| IGF-1 | Lower than reference range | | |
| Insulin Tolerance (0.1U/Kg) | Growth Hormone <5.1 ng/ml | | |
| Glucagon Stimulation (1mg) | <3 ng/ml | | |
| *May not be abnormal in acute hypopituitarism as adrenal response to ACTH may remain intact. | | | |
| | | | |

Note- hormone levels that are considered abnormal will vary depending upon the assay used

Imaging Studies

Imaging studies, namely a dedicated MRI of the pituitary, are important in determining the presence of a structural lesion, however the presence (or absence)

of a tumor or mass does not always correlate with pituitary function.

TREATMENT

The objective of treatment of hypopituitarism is to replace deficient hormones. It is usually not practical to directly replace the pituitary hormone, but rather treatment is with the end-organ hormone (e.g. thyroid hormone is used for TSH deficiency rather than TSH and corticosteroids for ACTH deficiency rather than ACTH).

In general, it is recommended to begin by replacing the hormones with more critical metabolic functions first. Glucocorticoids should be instituted first to avoid an adrenal crisis, followed by thyroid replacement therapy and after this if appropriate, gonadal and growth hormone replacement.

Titration of glucocorticoid replacement is quite challenging, as one cannot rely on cortisol or ACTH

levels to assess for under or over replacement. The corticosteroid replacement dose is usually estimated based on body mass weight and delivered at different doses throughout the day trying to mimic as much as possible its physiologic circadian rhythm. The recommended doses in <u>table 4</u> are guidelines only and need to be titrated by the bedside physician based on the specific clinical situation. It is extremely important to emphasize to other clinicians and patients with adrenal insufficiency, that during acute sickness and high stress situations, higher doses of glucocorticoid replacement are needed.

Thyroid replacement therapy is somewhat easier to titrate, as free T4 levels can be quite useful. The clinician however, should avoid the mistake of following TSH levels, as they will not be useful in secondary hypothyroidism.

| Table 4. Treatment of Hypopituitarism | | | | |
|---------------------------------------|---------------------|---------------------------------|--|--|
| Pituitary Hormone/ Treatment | Acute | Chronic Deficiency | | |
| ACTH | | | | |
| Hydrocortisone | 50-100 mg IV Q8H | | | |
| Hydrocortisone | | 15 mg q AM, 5 mg q3PM | | |
| TSH | | | | |
| Levothyroxine | 1.6 ug/kg daily | 1.6 ug/kg daily | | |
| LH/FSH | | | | |
| Testosterone (men) | | Transdermal-5 gm qD | | |
| | | IM – Test. Cypionate 200 mg q 2 | | |
| | | weeks | | |
| Estrogen (women) | | Varies | | |
| Growth Hormone | | | | |
| Growth Hormone | No acute indication | 0.05 mg/kg/d | | |

For details of hormone therapy see the appropriate Endotext chapters

FOLLOW-UP

After the diagnosis is made and acute treatment is started (<u>Table 4</u>, Acute) a decision needs to be made whether continued chronic therapy with hormone replacement is needed. A month after discharge from the hospital and recovery from the acute event, if necessary, patients are retested to determine if the endocrine defect persists. This will depend on the etiology as removal of tumor or reversal of an infiltrative process sometimes allows recovery of function. Repeat testing will confirm whether the

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GUIDELINES

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