

The OHSU Pituitary Unit

Pituitary Hormone Deficiency and Replacement

The pituitary gland is a small organ (about the size of a pea) which is attached to the underside of the brain. It is divided into anterior and posterior portions (each derived from different embryonic tissues) and releases many different hormones which together regulate metabolism and influence virtually every cell in the body. The pituitary's vital role in regulating many endocrine systems has earned it its name of "the master gland".

Pituitary hormone deficiency can have many causes including prior pituitary surgery, head irradiation, infiltrative disease, trauma, infection, and genetic abnormalities, but the vast majority of cases are caused by benign pituitary tumors (macroadenomas) pressing on and destroying the cells of the pituitary gland. Some tumors make excess hormone (prolactinomas, Cushing's disease, acromegaly, etc) but this section will focus on pituitary hormone deficiency and replacement.

Adrenal Insufficiency Due to ACTH Deficiency

ACTH (adrenocorticotropic hormone) is normally made by the anterior pituitary and stimulates the adrenal glands to release cortisol. Cortisol is necessary for maintaining vascular tone (blood pressure), and effects bone density, growth, kidney function, the immune system, and the brain (behavior and cognition). It also plays a role in the processing of sugar and fat.

Loss of ACTH from the pituitary causes adrenal insufficiency and can be life threatening if untreated. Adrenal insufficiency due to pituitary disease is referred to as secondary or central adrenal insufficiency since the underlying problem is not at the adrenal glands themselves. Signs and symptoms of adrenal insufficiency include stomach pain, nausea and vomiting (especially in the morning), dizziness with standing, and even loss of consciousness. The associated electrolyte abnormalities can be very dangerous as well. Adrenal insufficiency is typically diagnosed by detecting either a low early morning serum cortisol or an inadequate cortisol response (less than 18 mcg/dl) to ACTH administration (Cortrosyn stimulation test).

Treatment is aimed at replacing the adrenal hormone cortisol which is a glucocorticoid steroid. Hydrocortisone or prednisone are most commonly used and either can be taken orally. A hydrocortisone dose of 20 to 25 mg per day constitutes an adequate replacement dose in most adults. Hydrocortisone (in solution) can also be administered intravenously or intramuscularly. Most of the daily dose is typically administered in the morning (to mimic the normal physiologic pattern) and administration is often divided into two or three doses throughout the day (e.g., 15 mg at 8:00 a.m. and 10 mg at 3:00 p.m. of hydrocortisone).

Patients with adrenal insufficiency should wear a "medic alert" indicator (e.g., bracelet) to notify medical personnel of the need for increased steroid dose in the case of trauma or severe illness. These patients should also discuss with their endocrinologist a plan to temporarily increase steroid dose in the context of illness, trauma or planned surgery. Finally, in the presence of multiple pituitary hormone deficiencies, cortisol treatment should be initiated before beginning thyroid hormone replacement. This is because an underlying adrenal insufficiency may be masked by a patient's thyroid hormone deficiency and treatment with thyroid hormone alone could potentially precipitate overt adrenal crisis.

Thyroid Hormone Deficiency

TSH (thyroid stimulating hormone) is made in the anterior pituitary gland and is responsible for stimulating the release of thyroid hormone from the thyroid gland (a small butterfly shaped gland in the neck). Thyroid hormone is necessary for maintaining normal body metabolism. Systems effected by thyroid hormone include oxygen and fat metabolism and heat production. It effects the function of the heart, lungs, blood cells, bone and muscle. It also influences the nervous, digestive and endocrine systems.

Inadequate TSH production from the pituitary leads to central or secondary hypothyroidism (low thyroid hormone levels) and is associated with constipation, cold-intolerance, muscle weakness, memory loss, fatigue, dry skin, and hair loss, brittle nails and water retention (partial list). If left untreated, severe hypothyroidism can lead to coma and even death.

Thyroid hormone can be replaced orally and the initial dose is calculated based on weight. Thyroid hormone has a long half-life in the blood stream so serum thyroid hormone level is typically re-measured six weeks or more after starting or adjusting a dose. Since "central" or pituitary caused hypothyroidism is a result of inadequate TSH from the pituitary, TSH levels should not be used as a "bioassay" to determine adequacy of treatment. As a result, when treating central hypothyroidism, most endocrinologists titrate serum thyroid hormone level to the mid normal range. However, the laboratory "normal range" is really a population normal so an individual's optimal level may be closer to the high or low extreme of the "normal" range. For this reason, symptoms and physical exam may also be helpful in determining final dose.

Sex Hormone Deficiency

LH and FSH (luteinizing hormone and follicle-stimulating hormone) are both released by the anterior pituitary gland and stimulate and coordinate sex hormone production and function. In men these hormones stimulate testosterone production and sperm maturation in the testes. In women these

hormones effect estrogen and progesterone production from the ovary and influence normal ovulation and menstruation.

LH/FSH deficiencies lead to hypogonadism (low estrogen in women and low testosterone in men). Signs and symptoms are largely sex specific: Men manifest with decreased sexual interest and sexual dysfunction (impotence). They may have loss of pubic hair, testicle size, energy, muscle mass and bone density. They may also develop breast tenderness, hot flashes and night sweats. Signs of decreased gonadotropins in women include menstrual irregularities, infertility, decreased sexual interest, bone loss and hot flashes.

Testosterone can be replaced in men via bimonthly subcutaneous injections or through transdermal delivery (patch or testosterone gel preparation). Therapy is contraindicated in men with history of prostate cancer or significantly elevated hematocrit levels. Caution should be taken in treating individuals with sleep apnea, congestive heart failure, and obstructive prostate enlargement. Serum testosterone levels can be reassessed six to eight weeks after initiation of treatment, at six months, and then yearly. The goal of treatment is to normalize serum testosterone level as well as optimize clinical response.

Sex hormone replacement in women is typically accomplished via oral preparations (estrogen or estrogen/progestin combination) or transdermally (gels, creams, patches, etc). These methods of replacement are typically very efficacious at minimizing postmenopausal symptoms such as hot flashes. However, estrogen replacement has become a very controversial topic in recent months since the discontinuance of the combined estrogen plus progestin arm of the Women's Health Initiative (WHI). This part of the study was stopped due to unacceptably high adverse outcomes.

Growth Hormone (GH) Deficiency

GH production in children is responsible for normal growth and development (it results in short stature if deficient). In adults, growth hormone plays an important role in heart function and bone metabolism and effects metabolism of protein, carbohydrate, and fat. It also is important for maintaining a generalized sense of well being.

Growth hormone is typically the first hormone to be lost due to the "mass effect" of an enlarging pituitary tumor. GH is made in the anterior pituitary gland. Signs and symptoms of GH deficiency have been described as the Adult Growth Hormone Deficiency (GHD) Syndrome and include fatigue (low energy), feelings of social isolation, bone loss, and lipid abnormalities leading to increased risk of cardiovascular problems.

GH replacement is administered daily via a subcutaneous injection (injection under the skin with a very small insulin type needle). Symptoms occurring at initiation of therapy ("start-up" symptoms) include muscle or joint pain, headaches, and blurred vision. These typically resolve with time and can be minimized by starting with low doses and slowly working up to therapeutic levels. By contrast, symptoms of GH excess include musculoskeletal pain, peripheral edema, and carpal tunnel syndrome. These symptoms can be largely alleviated by lowering GH dose. Normalizing serum IGF-1 (a factor produced in the liver in response to GH stimulation) is the goal in titrating GH administration but symptoms of GH excess often play an important role in determining final GH dose.

Other Hormone Deficiencies

Prolactin is released from the anterior pituitary during and after pregnancy. Its primary functions are to stimulate postpartum milk production and to contribute to breast development in preparation for milk production during pregnancy. It is not replaced when deficient.

ADH (antidiuretic hormone, vasopressin) is released from the posterior pituitary gland and stimulates water retention in the kidneys. ADH is stimulated in response to dehydration and altered salt concentration in the blood stream. ADH deficiency leads to diabetes insipidus which is characterized by excessive urination and thirst. Diabetes insipidus (DI) is occasionally caused by the mass effect of adenomas but is more frequently associated with more invasive tumors that damage the hypothalamus. It can also be caused by pituitary surgery itself (particularly in the hands of non-expert surgeons).

ADH can typically be replaced with once or twice per day dosing with few complications. ddAVP can be administered orally in pill form or via nasal preparation (spray or rhinal tube). Undertreatment leads to the inconvenience of excessive thirst and urination. Over-treatment can lead to abnormally low (even dangerously low) sodium levels and therefore should be avoided.

Oxytocin is also released from the posterior pituitary. It induces uterine contraction during the birthing process. It also plays a role in milk ejection from the breast. It is not necessary to replace when deficient.

Useful Reading:

1) 1997 Consensus Guidelines for the Diagnosis and Treatment of Adults with Growth Hormone Deficiency: Summary Statement of the Growth Hormone Research Society Workshop on Adult Growth Hormone Deficiency. The Journal of Clinical Endocrinology and Metabolism. 83:379-381.

2) Lamberts, S. et al. (1998) Pituitary Insuficiency. The Lancet (352):127-34.

3) Freda, PU and Wardlaw, SL (1999) Clinical Review 110: Diagnosis and Treatment of Pituitary Tumors. The Journal of Clinical Endocrinology and Metaboloism. 84(11): 3859-3866.

4) Arafah, BM and Nasrallah, MP (2001). Pituitary Tumors: Pathophysiology, Clinical Manifestations and Management. Endocrine-Related Cancer. 287-305.

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