Pathology

Hypopituitarism — Symptoms, Diagnosis and Treatment

The pituitary gland also referred to as Hypophysis, or 'Master gland' is a pea-sized organ, that lies in a protective bony enclosure called the sella turcica (saddle/chair) at the base of our brain. Read on to learn all about the pituitary gland and its hormones, as well as Hypopituitarism.

Recap: Pituitary — Anatomy and Hormones

Definition of the Pituitary Gland

The pituitary gland, the master of all endocrine glands, is physiologically divided into two larger lobes: anterior lobe (adenohypophysis) and posterior lobe (neurohypophysis). **Pars Intermedia** is a small relatively avascular zone that lies between the anterior and posterior lobe. It is rudimentary in nature. The anterior pituitary constitutes 80% of the gland. A **hypothalamohypophyseal portal vascular** system carries positively and negatively acting factors from the hypothalamus to the anterior pituitary.
The posterior pituitary consists of modified glial cells termed **pituicytes**. Axonal terminals called a hypotalamohypophyseal tract, extending from the hypothalamus through the pituitary stalk to the posterior lobe, regulates neurohypophysis hormonal regulation. These axonal terminals of the posterior pituitary store the hormones (synthesized in the hypothalamus) and release them on appropriate stimulus.
## Hormones of Anterior Pituitary

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Pituitary Cell Type</th>
<th>Target Organ</th>
<th>Function</th>
<th>Increased Production</th>
<th>Decreased Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adreno-corticotropic hormone (ACTH)</td>
<td>Corticotroph</td>
<td>Adrenal Cortex</td>
<td>Stimulate adrenocortical hormones (cortisol, androgen, and aldosterone)</td>
<td>Cushing syndrome, Nelson syndrome</td>
<td>Addison disease</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Somatotroph</td>
<td>Liver and adipose tissue</td>
<td>Stimulate protein synthesis and overall growth of most cells and tissues</td>
<td>Acromegaly Gigantism</td>
<td>Dwarfism</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Lactotroph</td>
<td>Mammary glands</td>
<td>Secretion of milk, female breast development</td>
<td>Galactorrhea and amenorrhea (females)</td>
<td>Sexual dysfunction and infertility (males)</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>Thyrotroph</td>
<td>Thyroid gland</td>
<td>Stimulate the thyroid gland to synthesize and secrete thyroid hormone</td>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>
Luteinizing hormone

Gonadotroph

Ovaries and testes

Stimulates testosterone secretion, ovulation, the formation of corpus luteum and estrogen and progesterone synthesis in ovaries.

Precocious puberty testicular failure

Hypogonadism

Kallman syndrome

Pasaqualini syndrome

Follicle stimulating hormone

Gonadotroph

Ovaries and testis

Sperm maturation, growth of follicles in ovaries

Gonadal dysgenesis

Hypogonadism

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**Hormones of Posterior Pituitary**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Synthesis</th>
<th>Target organ</th>
<th>Function</th>
<th>Increased Production</th>
<th>Decreased production</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Diuretic Hormone (ADH)</td>
<td>Supraoptic nuclei of the hypothalamus</td>
<td>Kidney</td>
<td>Water re-absorption from kidney, vasoconstriction, increase blood pressure</td>
<td>SIADH (Syndrome of inappropriate ADH secretion)</td>
<td>Diabetes Insipidus</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Paraventricular nuclei of the hypothalamus</td>
<td>Breast, uterus</td>
<td>Stimulates milk ejection and uterine contraction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypothalamus Control of Pituitary**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Releasing factor from the hypothalamus</th>
<th>Inhibitory factor from hypothalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>GHRH (growth hormone-releasing hormone)</td>
<td>GHIH (Growth hormone inhibiting hormone)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Prolactin</td>
<td>none</td>
<td>Dopamine (PIF-Prolactin inhibiting factor)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Thyrotropin-releasing hormone</td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>Corticotropin-releasing hormone</td>
<td></td>
</tr>
</tbody>
</table>

**Embryological Origin**

Anterior pituitary, **ectodermal** in origin, develops from **Rathke’s pouch**, which is an upward invagination of oral ectoderm from the roof of the **stomodeum**; in contrast, the neurohypophysis develops from the **infundibulum**, which is a downward extension of neural ectoderm from the floor of the **diencephalon**.

**Hypopituitarism**

A clinical situation characterized by a **deficiency in the pituitary hormone production**, which results from disease of the **hypothalamus** or **pituitary** itself. Hypofunction occurs when approximately **80%** of pituitary parenchyma is lost.
Etiology of Hypopituitarism

Structural defect
- Rathke’s cleft cyst
- Meningioma
- Craniophyrangioma
- Pituitary adenoma/tumors

Inflammatory causes
- Sarcoidosis
- Wegener granulomatosis
- Hemochromatosis

Congenital
- Kallman’s syndrome (GNRH deficiency)
- Hypoplasia of pituitary

Traumatic
- Head injury
- Sellar surgery
- Radiotherapy

Infections
- Tuberculosis
- Syphilis
- Encephalitis

Vascular
- Sheehan’s syndrome (Post-Partum Pituitary necrosis)
- Carotid artery aneurysm
- Subarachnoid hemorrhage

Epidemiology of Hypopituitarism

The first study on the prevalence and incidence of hypopituitarism in adults was conducted in northwestern Spain. It showed an average annual incidence rate of hypopituitarism of 4.21 cases/100,000 with this incidence being similar for both sexes. The cause of hypopituitarism was a pituitary tumor in 61%, a non-pituitary tumor in 9% and a non-tumor cause in 30%. Around 50% of patients had 3-5 pituitary hormonal deficiencies, with LH/FSH being the most prevalent.

A higher risk of chronic hypopituitarism was found after traumatic brain injury and intrasellar aneurysms.
Pathophysiology of Hypopituitarism

Damage to the pituitary gland results in a decreased target gland hormone production. There is a sequential loss of anterior pituitary hormones secondary to mass effect, occurring initially with a deficiency of Gonadotropins (LH and FSH), followed by a loss of ACTH and TSH.

Isolated deficiencies of LH, FSH, GH, ACTH, and TSH can also be seen. If the cause of decreased hormone production is direct damage to the pituitary, an increased amount of hypothalamic releasing hormones may be seen on blood examination.

Pituitary adenomas may present insidiously with a tumor compressing the surrounding pituitary tissue, or causing impaired blood flow to the normal cells by interfering with the hypothalamus-hypophyseal portal system, resulting in hypopituitarism.

Pituitary apoplexy describes a sudden onset of neurological impairment, including visual disturbance, ophthalmoplegia (III, IV, VI cranial nerve involvement) or an excruciating headache due to bleeding into or impaired blood supply of the pituitary gland. In severe cases, it can cause cardiovascular collapse, loss of consciousness and even sudden death.

A question frequently encountered in a USMLE exam is about the effect on anterior pituitary hormones if the pituitary gland is sectioned at the level of the stalk?

The answer is if it is cut at the level of a stalk, all anterior pituitary hormones will decrease except prolactin. Why? Because prolactin is continuously controlled by an inhibiting hormone from the hypothalamus. When the stalk is cut, lactotropes are released due to the inhibition from the hypothalamus and their hormone-production increases.
Sheehan Syndrome

Sheehan Syndrome (post-partum ischemic necrosis) is a frequently asked USMLE question. The clinical scenario will point toward a pregnant female with a bad obstetric history.

During pregnancy, the anterior pituitary enlarges to almost twice its original size. This physiological expansion is not accompanied by an increase in blood supply; there is relative anoxia of pituitary tissue. A further reduction in blood supply, due to post-partum hemorrhage, may precipitate infarction of the anterior pituitary. Posterior pituitary, due to its direct blood supply, is less susceptible to ischemic injury. The patient usually presents with complaints of inability to feed the baby, fatigue, and lethargy.

Symptoms of Hypopituitarism

<table>
<thead>
<tr>
<th>Hormone Deficiency</th>
<th>Symptoms/Signs</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Hypoglycemia, anorexia, vomiting, malaise, weight loss, circulatory collapse</td>
<td>Secondary adrenal insufficiency</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Reduced bone mineral density, short stature, central obesity, decreased muscle mass and strength</td>
<td>Deficiency growth hormone</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Poor or cessation of the production of breast milk</td>
<td>Prolactin secretion dysfunction</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Fatigue, lethargy, somnolence, constipation, cold intolerance, bradycardia</td>
<td>Secondary hypothyroidism</td>
</tr>
<tr>
<td>Gonadotropins (LH, FSH)</td>
<td>Amenorrhea, infertility, breast atrophy, decreased libido; atrophic testes, erectile dysfunction, decreases the strength</td>
<td>Secondary hypogonadism</td>
</tr>
<tr>
<td>ADH</td>
<td>Polyuria, polydipsia, hypernatremia, lethargy</td>
<td>Secondary renal insufficiency</td>
</tr>
</tbody>
</table>

Symptoms, due to compression, include a headache, visual field defects, and diplopia; this point towards an intracranial pathology. Compression of optic chiasma, which is adjacent to the pituitary, can result in bitemporal homonymous hemianopia.

Diagnosis of Hypopituitarism

After the clinical findings have been established, the laboratory diagnosis may deliver further indications that may support the suspected diagnosis:

1. Basal blood and stimulation tests
   - ACTH Deficiency: basal cortisol and ACTH level, short ACTH stimulation test
   - Growth hormone deficiency: growth hormone levels stimulation and suppression tests, serum insulin-like growth factor-1, insulin tolerance test
   - TSH Deficiency: basal T3 & T4 levels, serum TSH level
   - LH/FSH deficiency: serum levels of LH, FSH, and testosterone
   - ADH deficiency: water deprivation test
2. Brain imaging

- MRI or CT scan to detect pituitary tumors or any other intracranial pathology.


3. Vision tests

- To detect any defects in the visual field due to the compression of the optic chiasma.

Differential Diagnosis of Hypopituitarism

- Hyponatremia
- Kallman syndrome (idiopathic hypogonadotropic hypogonadism (IHH))
- Polyglandular autoimmune syndrome
- Septo-optic dysplasia
- Hypothyroidism
- Pituitary macroadenomas

Therapy of Hypopituitarism

Management of acute hypopituitarism

Emergency treatment comprises the following three drastic measurements after cardiopulmonary stability:

1. **Replace deficient hormone**: hydrocortisone in a stress dose is the standard of choice to replace the glucocorticoid deficiency, followed by **IV levothyroxine** for thyroid hormone replacement.
2. Treatment of the **electrolyte and cardiovascular effects** due to missing hormones
3. **Antibiotics** should be used to treat underlying infection or sepsis.
In-patient management

- Treat the underlying cause, if any, like tumors (get neurosurgical consultation)
- Replacement of hormones is the ultimate treatment of panhypopituitarism.
  
  This is done by administering:
  
  - **Hydrocortisone** for adrenal insufficiency
  - **Thyroxtine** for thyroid hormone replacement
  - **Growth hormone** by daily injections in children (discontinued after epiphysis are fused)
  - **Testosterone and estradiol** for male and female hypogonadism
  - **Desmopressin (DDAVP)** tablets or nose spray for ADH replacement
  - **Dopamine agonist (cabergoline)** for prolactin inhibition

When fertility is desired, HCG, purified or biosynthetic gonadotropin or pulsatile GnRh is given.

Prognosis of Hypopituitarism

Mortality in patients with hypopituitarism is significantly increased. The only significant independent predictive factors for survival are an age at diagnosis and hypogonadism.

A recent study suggested that females with hypopituitarism have a high incidence of cardiovascular morbidity and an increased prevalence of cardiovascular risk factors.

Review Questions

The answers are below the references.

1. A 24-year-old female presented to your clinic with a six-week history of headache, malaise and the inability to feed her baby. She gave a history of multiple blood transfusions during her post-partum period. Which one of the following is the most likely diagnosis?

   1. Neurosarcoidosis
   2. Pituitary adenoma
   3. Meningioma
   4. Sheehan’s syndrome
   5. Craniopharyngioma

2. A 40-year-old woman was diagnosed with a pituitary adenoma measuring 4mm. In the past, she complained of recurrent episodes of headache, together with visual field defects. On examination, she had bitemporal superior quadrantanopia. Investigations revealed:

   \[
   \begin{align*}
   \text{TSH} &= 0.6 \text{ mU/L (0.34-5.5)} \\
   \text{T4} &= 10.6 \text{ pmol/L (11-22)} \\
   \text{Prolactin} &= 950 \text{mU/L (60-600)} \\
   \text{IGF-1} &= 10 \text{ nmol/L (15-118)}
   \end{align*}
   \]

   Repeated MRI showed increased size of the pituitary adenoma.

   What is the best step of management?

   1. Cabergoline
2. Levothyroxine
3. Growth hormone
4. Levothyroxine, cabergoline
5. Neurosurgical referral

3. If the pituitary gland is sectioned at the level of the stalk. All of the following hormones will decrease EXCEPT?

1. Growth hormone
2. T4
3. Prolactin
4. LH
5. FSH

References


Hypopituitarism (Panhypopituitarism) via emedicine.medscape.com

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