Hyperprolactinemia is defined as a condition of high prolactin levels in the blood. Many factors are attributed to the development of hyperprolactinemia. Bromocriptine or cabergoline are the first line of drugs for the treatment. Refractory cases require a surgery or radiation therapy in case hyperprolactinemia is caused by macroprolactinoma. This article discusses possible causes, diagnosis, treatment and management of hyperprolactinemia.

Definition

Hyperprolactinemia, as the name suggests, is the hypersecretion of prolactin, leading to high prolactin levels in the blood. Prolactin is the hormone secreted by the anterior pituitary. The lactotroph cells of the pituitary gland secrete prolactin into the systemic circulation. Dopamine inhibits the prolactin secretion whereas the thyrotropin-releasing hormone (TRH) and estrogen stimulate the secretion of prolactin.

Increased levels of prolactin also inhibit the gonadotrophin releasing hormone (GnRH) from the hypothalamus which results in a decrease in the levels of the
leutinizing hormone (LH) and the follicle stimulating hormone (FSH).

This, in turn, decreases estrogen levels leading to cessation of ovulation and menstruation. This is the reason why affected women do not have their menstruation during the lactation period.

The prolactin hormone is responsible for the production of breast milk. The primary function of prolactin is to stimulate and maintain lactation in the postpartum period. It promotes the growth and development of the mammary glands during pregnancy and prepares the breasts for producing milk. It also causes a decrease in the sexual drive and the reproductive function.

The secretion of prolactin is episodic and the levels vary with age and during the menstrual cycle. The levels increase post sleep and post meals. Physiologically, exercise, pregnancy and stress also cause an increased secretion of prolactin.

**Pathophysiology of Hyperprolactinemia**

Prolactin is secreted from the anterior pituitary under direct influence of several hormones that stimulate its secretion—thyrotropin releasing hormone, vasoactive intestinal peptide—and dopamine antagonists. Similarly, dopamine tonically inhibits the secretion of prolactin via D2 receptors located on the lactotrophs. Normal values of prolactin range from 0-20 ng/ml, depending on the laboratory reference value and other factors that influence the secretion of the hormone.

Upon release into the circulation, the hormone exerts its effects by stimulating breast epithelial cells thus inducing and maintaining milk production. Estrogen promotes the proliferation of pituitary lactotrophs thus favoring the process. However, it actually inhibits lactation and so there is increase in breast mass with inhibited lactation during pregnancy when estrogen levels are high. In the postpartum period, when there is a rapid decline of estrogen, lactation commences as prolactin is no longer opposed. This situation is known as puerperal hyperprolactinemia.

Non-puerperal hyperprolactinemia results from pituitary lactotroph adenomas or any pathology along the hypothalamic-pituitary dopaminergic pathways that produce prolactin.

**Causes of Hyperprolactinemia**

Because of the diverse etiologies, it may be caused by varied underlying reasons. The causes of hyperprolactinemia can be divided into the following subcategories.

**Physiological causes**

The most common physiological cause of increased serum prolactin levels is pregnancy. A normal pituitary gland grows in size during pregnancy due to estrogen-induced hypertrophy and hyperplasia of the lactotrophs. This eventually leads to a progressive increase of prolactin production and its hypersecretion during pregnancy.

The placenta produces estrogen which in turn stimulates mitosis of the lactotrophs, leading to an increase in serum prolactin to peak levels at the end of pregnancy. The levels decline at a rapid rate after delivery but remain at a slightly increased level in lactating women for many months.
In infants, prolactin levels are increased by around 10 times following delivery because of the stimulatory effect of maternal estrogen. The neonatal levels then gradually decrease to normal by about three months of age. **Other physiological causes include:**

- Lactation
- Coitus
- Nipple stimulation
- Exercise
- Stress
- Sleep
- Pseudocyesis
- Neonatal period

### Systemic disorders

Hyperprolactinemia can also occur because of primary hypothyroidism due to high thyrotropin-releasing hormone (TRH) levels. This, in turn, stimulates the prolactin release and reduces the prolactin metabolic clearance.

**Other systemic causes are:**

- Severe liver dysfunction/cirrhosis
- End-stage renal disease/chronic renal failure
- Polycystic ovary syndrome
- Chest injury (e.g., trauma, burns) or lesions (e.g., herpes zoster)
- Epilepsy/seizures
- Cranial radiation
- Adrenal insufficiency

### Pharmacological causes

The most important class of drugs that cause a rise in serum prolactin levels are dopamine receptor blockers such as neuroleptics (e.g., haloperidol, sulpiride, chlorpromazine, risperidone, etc.) and anti-emetic drugs (e.g., metoclopramide, domperidone).

The classes of drugs* that produce similar effects are:

- Anti-depressants/anti-psychotics/anti-convulsants
- Anti-histamines
- Anti-hypertensives
- Opioid compounds/cocaine
- Catecholamine depletors
- Protease inhibitors
- Cholinergic agonist
- Estrogen

* High yield for USMLE

### Pituitary causes

Pituitary adenomas (prolactinomas) are the most common cause of pathological hyperprolactinemia. Around 40% of acromegaly patients suffer from hyperprolactinemia due to hyper co-secretion of growth hormone and prolactin. Other
pituitary causes are:
- Cushing’s disease
- Empty sella syndrome
- Lymphocytic hypophysitis

Hypothalamic causes

Prolactin hypersecretion following impaired hypothalamic/tuberoinfundibular dopamine secretion may be caused by the following:
- Tumors such as craniopharyngioma, meningioma, dysgerminoma, etc.
- Suprasellar surgery
- Rathke’s cyst
- Sarcoidosis

Diagnosis of Hyperprolactinemia

For women, the range varies from 0 to 20 μg/L, and for men from 0 to 15 μg/L.

**Serum prolactin level:** A serum prolactin level higher than the upper limit of the normal level range confirms the diagnosis, provided there is no venipuncture stress. Thus, serum prolactin level more than 20 μg/L (20 ng/mL) is diagnostic of hyperprolactinemia.

Depending upon the history and thorough examination, once the diagnosis is confirmed, **further investigations are required to determine the underlying etiology**. Examples of such investigations are:
- Pregnancy test
- Thyroid function test
- Kidney function test
- Liver function test
- Imaging studies such as pituitary imaging, MRI
- Pituitary function test

During the diagnostic work-up of hyperprolactinemia, patients with pregnancy (High yield for USMLE), lactation, hypothyroidism and medications should be considered first.

Clinical Presentation of Hyperprolactinemia

The **condition may be asymptomatic**. In men and premenopausal women, hyperprolactinemia presents with typical symptoms such as:
- Hypogonadism
- Infertility-like symptoms
- Menstrual abnormalities such as amenorrhea or oligomenorrhea (in women)
- Galactorrhea (less often, but more common in women)
- Decrease in sexual function (poor libido)
- Headache
- Visual defects
- Secondary bone loss

**Other signs include:**
Erectile dysfunction (in men)
Gynaecomastia (in men)
Hirsutism (in women)

Differential Diagnosis of Hyperprolactinemia

Differential diagnosis includes:
- Pituitary adenomas
- Prolactinoma
- Acute kidney injury

For more information on differential diagnosis of hyperprolactinemia refer to the article on prolactinomas.

Management of Hyperprolactinemia

All patients with hyperprolactinemia do not necessarily need treatment. Asymptomatic patients with microprolactinomas and no interest in fertility can be observed and monitored in a routine manner through serial prolactin level measurements and annual imaging scans.

Patients indicated for treatment are:
- Patients with macroprolactinomas or growing macroprolactinomas (as suggested by serial imaging follow-ups).
- Patients with complaints of hypogonadism or fertility.
- Patients with complaints of galactorrhea or gynaecomastia.

Treatment of Hyperprolactinemia

Goals
- To control the tumor or reduce the size of the tumor in case of macroprolactinomas.
- To restore fertility and eugonadism.
- To relieve the patient from galactorrhea or gynaecomastia.
- To relieve the patient from symptoms caused due to tumor mass effect.

Lines of treatment
- Medication therapy is generally the first choice of treatment.
- For patients who do not respond to medicines, or are intolerant to medicines, surgery is the second line of treatment.
- When medicines or surgical procedures do not bring desired results, radiotherapy is considered as the third line of treatment.

Medication therapy

Dopamine agonists such as bromocriptine or cabergoline are the first line of drugs used in medication therapy for hyperprolactinemia. (High yield for USMLE.)

The therapy usually continues for 1–2 years (depending on the tumor size or symptoms). Once prolactin levels return to the normal range, medication is withdrawn. Approximately one sixth of patients maintain normal prolactin levels post withdrawal of
medication therapy.

For more on bromocriptine and cabergoline, refer to the article on prolactinomas.

Another dopamine agonist, pergolide, was previously used for the treatment of hyperprolactinemia. Pergolide was withdrawn from the US market on March 29, 2007 due to heart valve damage leading to cardiac valve regurgitation.

Surgical therapy

With the advent of surgical microscopes, transsphenoidal pituitary surgery is the preferred surgical treatment choice. Endonasal endoscopic surgery has become available more recently which seems to reduce the hospitalization time. These recent developments have made the selective removal of the pituitary adenoma possible with low complication and mortality rates.

Besides normalizing prolactin levels, the surgical therapy aims at eliminating or diminishing the mass effect of macroadenomas, often relieving the patient of neurological and visual manifestations. For the tumors with extrasellar location expanding out of the midline, the transcranial surgical approach is followed.

Radiation therapy

In patients where tumor control cannot be done by medication or surgical therapy, radiation therapy is used (rare). Radiotherapy can be given in one of the following ways:

- Conventional external beam radiation therapy.
- Stereotactic radiation therapy (photon beam, gamma knife and linear accelerator [LINAC], or proton beam).

Hormonal therapy

In patients with microprolactinoma, if the dopamine agonists are not tolerated or are contraindicated for any reason, hormonal replacement is a valid alternative to relieve the patient of symptoms related to hypogonadism. It is considered in patients who are not interested in fertility and want to get rid of symptoms such as menstrual abnormalities, sexual dysfunction, etc.

It is achieved with testosterone in men and oral contraceptives in premenopausal women. There may be a slight increase in prolactin levels in these patients. It is important to be careful and use low doses of estradiol (≤ 30 μg/day), and closely monitor prolactin levels and tumor growth in such patients.

Review Questions

1. A 32-year-old woman visits her gynecologist complaining of a period of frequent white discharge from her nipples. Past medical history reveals that she has been amenorrheic for the last four months. Her neural examination, including visual acuity, is fine. Laboratory investigation results are yet to come. Which of the following results do you expect in such a patient?

   A. Increased prolactin and increased FSH
   B. Decreased prolactin and decreased FSH
   C. Increased prolactin and decreased FSH
   D. Decreased prolactin and increased FSH
2. A 40-year-old man presents to his internist with complaints of nipple discharge for the past one month. He has a history of schizophrenia and takes medication for the same. On further questioning, he also mentions decreased sexual function. Which of the following drugs can be the most likely cause of his present symptoms?

A. Risperidone  
B. Bromocriptine  
C. Cabergoline  
D. Haloperidol

3. Which of the following clinical manifestations is not associated with hyperprolactinemia?

A. Amenorrhea  
B. Infertility  
C. Increased libido  
D. Visual defects

References

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https://www.niddk.nih.gov/health-information/endocrine-diseases/prolactinoma
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Correct answers: 1C; 2A & D; 3C

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