MINI REVIEW

Galactorrhea

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Abstract

An inappropriate secretion of a milk-like substance from breasts is called galactorrhea. The commonest cause is over-secretion of the hormone Prolactin. Causes and management of prolactinemia are discussed in this paper. A protocol to investigate these cases has been given. The advent of dopamine agonists, which inhibit secretion of prolactin, has made the management of these cases simple and safe. All patients of hyperprolactinemia may have associated tumors in the pituitary (prolactinomas). If these are less than 3 cm in size, as seen on neuroimaging, medical management may be enough. Tumors exceeding 3 cm in size may need a surgical resection because they may produce compressive effects. Hypothyroidism must be excluded and, if present, treated appropriately.

Keywords: Bromocriptine, Cabergoline, Dopamine agonists, Galactorrhea, Prolactin, Prolactinoma.

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Introduction

Galactorrhea is defined as an inappropriate secretion of a milk-like substance from the nipples of either women or men and may be unilateral or bilateral. It may be watery, milky, or bloody. If bloody, one has to investigate the case for neoplasms such as duct papilloma or carcinoma. Conversely, the absence of blood does not rule out an underlying tumor.

The Talmud (a religious text of Judaism termed by Christians as Hebrew bible) describes a man who nursed his baby after the untimely demise of his wife. This may be the first recorded case of male galactorrhea.

Breast milk is normally secreted from the mother's breast after the delivery of a child, which is essential to feed the baby. It may persist for about six months after cessation of breastfeeding. It was in the 1930s that a hormone was detected by Riddle[1,2] and his associates in animals, which stimulated the secretion of breast milk in animals. It was also associated with milk crop gland development in birds. As it could stimulate lactation, the hormone was named as prolactin.

Later it was found that it is secreted by lactotroph cells of the anterior pituitary, which comprise about 15–25% of cells of the anterior pituitary. Therefore, it is also called a leuteotropic hormone (LTH). Prolactin (PRL) acts by binding to the PRL receptors located on the extracellular surface of the target tissue. On the evolutionary scale, prolactin is an ancient hormone serving multiple roles in mediating the care of progeny (sometimes called the "parenting" hormone).

Isolation of PRL in humans remained elusive till 1970[3] because bioassays that were then used could not differentiate PRL from the growth hormone (GH), which also had lactogenic properties. Development of radioimmunoassay (RIA) in 1970 made it possible to identify prolactin distinctly from GH, leading to an undeniable discovery of these two as separate hormones.

Extra-pituitary PRL[4]

PRL has also been detected in the extra-pituitary tissues (ePRL),[4] which include thymus, lymph glands, skin, mammary glands, ovaries, and prostate among others. Regulation of ePRL is different from that of the regular PRL.

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Physiology

Prolactin (PRL) is a polypeptide[5] composed of 199 amino acids and secreted by lactotroph cells of the anterior pituitary. In circulation, it is found in three sizes:

- Monomeric little PRL—23 kD—most bioactive
- Dimeric PRL—Big PRL—48–56 kD
- Polymeric form Big PRL >100 kD.

The human PRL gene is located on chromosome 6 and apparently arose from a single common ancestral gene giving rise to the relatively homologous PRL, GH, and placental-lactogen-related proteins. Hypothalamic regulation of the pituitary occurs through neuropeptidases such as GnRH and TRF. But PRL is regulated by neuroendocrine neurons via a neurotransmitter dopamine. The neuropeptidases have a stimulatory role, while dopamine inhibits the secretion of PRL. If the anterior pituitary is separated from the hypothalamus, the secretion of PRL increases, whereas the secretion of other pituitary hormones decreases. The secretory phase of the menstrual cycle is due to the release of progesterone from the corpus luteum. PRL acts to maintain the corpus luteum.

During conception, PRL helps in sustaining the pregnancy by the maintenance of corpus lutea function, leading to progesterone secretion. High levels of PRL during pregnancy inhibit gonadotropin-releasing hormone (GnRH) from the hypothalamus, thereby decreasing the secretion of FSH and LH and thus protecting a lactating mother from a premature pregnancy.

Functions of PRL

Reproductive Functions

- Maintenance of corpora lutea function
- Progesterone secretion
- Stimulation of lactation through its actions on the mammary gland. PRL along with insulin and corticoids stimulate the development of the mammary gland during pregnancy so as to prepare it for lactation at parturition.
- Regulation of maternal behavior,[6] relieving anxiety, and facilitating breastfeeding

Other Functions

- Hepatic function—bile transport and metabolism
- Pancreatic function—it has been shown in experimental animals that elevated PRL leads to expansion of beta cells and shifts in insulin and glucose.
- Immune-related functions—it has been observed that multiple sclerosis patients show remission during pregnancy. Role of prolactin in autoimmunity awaits further research.
- Clevenger and Reynolds[7] have reported a possible role of PRL in the human breast and liver cancer. They reported PRL and expression of PRL receptors in human breast cancer.

PRL in mouse cell line has been shown to inhibit the tumor suppressor activity of BRCA1.[8]

It also stimulates the proliferation of lymphocytes and reduces macrophage activity.

Causes of Galactorrhea

- *Idiopathic Galactorrhea with regular menses:* This is the commonest cause seen after parturition, which persists despite the resumption of menses. Normal prolactin levels may permit milk production as the treatment of these cases with dopamine agonists alleviates galactorrhea. It does not represent a pathologic entity.
- *Chiari-Frommel Syndrome*:[9] It is postpartum galactorrhea, amenorrhea, and utero-ovarian atrophy in non-nursing patients.
- *Hyperprolactinemia*: This is the commonest cause of Galactorrhea

Causes of Hyperprolactinemia

The fasting serum PRL level in an adult woman in reproductive age is 5–20 ng/mL.

Physiological

- Coitus, exercise, sleep, stress
- Pregnancy
- Lactation, suckling response
- Depression

Pregnancy

PRL increases throughout pregnancy. The levels are variable (35–600 ng/mL). The cause of raised PRL is increasing levels of serum estradiol during pregnancy.

Lactation and suckling

During gestation, there is lactotroph hyperplasia due to estrogen. Breastfeeding causes nipple stimulation, which releases milk probably via the neural pathway.

Table 1 shows other causes of hyperprolactinemia.

Hypothyroidism

Primary hypothyroidism predisposes to raised PRL levels. It is probably due to hypersensitivity of lactotrophs to raised levels of TRF. PRL levels in hypothyroidism rise by up to 60 ng/mL.

Drugs

Various mechanisms are described by which drugs raise PRL levels. Cessation or modification of drug therapy normalizes the PRL levels within 3–4 days.

Prolactinomas

Tumors arising from lactotroph cells are common pituitary tumors. They arise from the monoclonal expansion of a single cell, which probably has undergone a somatic mutation. In most of the lactotroph adenomas, the pituitary tumor transforming gene is over-expressed. Prolactinomas are the commonest cause of hyperprolactinemia. About 10% of tumors are composed of both lactotroph and somatotroph cells and, therefore, secrete both PRL and GH. Clinical manifestations depend on the hormone profile and patients can have acromegalic features.

Microprolactinomas—less than 1cm in diameter
Macroprolactinomas—more than 1 cm in diameter
Adenoma less than 1 cm is associated with serum PRL below 200 ng/mL
Adenomas between 1 cm and 2 cm, PRL is between 200 and 1000 ng/mL
Adenomas more than 2 cm, PRL is more than 1000 ng/mL

Clinical Features

Due to Hormonal Dysfunction

In Premenopausal women: Hypogonadism, scanty menses, secondary amenorrhea, anovulatory cycles, infertility, decreased libido, dryness of vagina, painful sex, hot flushes, and galactorrhea

In Men: Hypogonadotropic hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia, and galactorrhea

Due to the Effects of Compression

Headache, restriction of the field of vision, visual impairment, invasion of the cavernous sinus, and/or sphenoidal sinus with corresponding neurological effects.

Investigations

- Urine pregnancy test
- Serum free T3, free T4, and TSH
- Serum prolactin
- Serum growth hormone
- Serum insulin-like growth factor 1
- Serum cortisol
- Serum testosterone in males
- Perimetry and brain MRI for the size of the prolactinoma and its extension in patients presenting with compressive features

Table 1: Causes of hyperprolactinemia

Drugs	*Systemic disorder*	*Hypothalamic dysfunction*	*Pituitary*
Estrogen, OC	Chr. renal failure	Damage to stalk	Prolactinoma
Neuroleptics	Hypothyroidism	Granuloma	Acromegaly
Antipsychotics	Cirrhosis	Infiltrations	
Dopamine receptor blockers	Polycystic ovarian disease	Trauma/surgery stalk resection	Macroadenoma
Dopamine synth. inhibitors	Cranial radiation	Craniopharyngioma	Plurihumoral adenomas
Opiates	Epilepsy, chest wall trauma	Rathake's cyst	

Management[10,11]

With the advent of dopamine agonists, management of galactorrhea with hyperprolactinemia has become a lot simpler. Dopamine and its agonists inhibit prolactin synthesis and its secretion. Bromocriptine was the first dopamine agonist introduced; subsequently, another drug cabergoline (which is more effective and better tolerated than bromocriptine) was introduced. After cabergoline was available, it became the drug of choice. Treatment with cabergoline is started at 0.25 mg once or twice a week. Usually within 2–3 weeks, PRL levels are normalized. It is continued in the same dose for about 2 years. Serum PRL levels are monitored at regular intervals. If PRL levels did not normalize within 2–3 weeks, the dose is increased gradually up to a maximum dose of 1.5 mg twice or thrice weekly. Once PRL level gets normalized, the same dose is continued for 2 years. Not only does cabergoline normalize PRL levels but it also reduces the size of both micro and macro-prolactinomas without surgery. Before cabergoline was available, bromocriptine was used. It is less effective and has more side effects than cabergoline. Bromocriptine was given at a dose of 1.25–2.5 mg orally once or twice a day.

Patients with hypothyroidism should be examined for galactorrhea and their prolactin levels must be measured. In my own study,[12] I found 30% of hypothyroid patients had hyperprolactinemia and 18% of them had PRL levels between 24 and 60 ng/mL. They responded to thyroxine replacement alone. The rise in PRL levels up to 60 ng/mL can be due to hypersensitivity of lactotrophs to raised levels of TRF. Remaining 12% of cases had PRL levels between 61 and 300 ng/mL. Of these, 8 patients were found to have prolactinomas on neuro-imaging. These patients needed treatment with both thyroxine replacement and cabergoline.

Surgical removal or debulking of prolactinomas is indicated if their size is more than 3 cm. It is done through the trans-sphenoidal route. Another indication of surgery is in women who want to conceive because conception will increase the size of the tumor.

Conclusion

Most of the cases of galactorrhea are idiopathic; however, each case should be subjected to an estimation of serum TSH and PRL levels. Cases with gynecomastia without any apparent cause should also have PRL levels measured. If PRL level exceeds 60 ng/mL, neuroimaging should be carried out to evaluate the possibility of a prolactinoma. All cases of prolactinomas can be managed with the dopamine agonist cabergoline, which is a safe drug with acceptable side effects. Patients with evidence of compressive symptoms due to giant prolactinomas will need to undergo surgery. If prolactinoma is associated with hypothyroidism, thyroxine replacement must be given.

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