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Hyperprolactinaemia in Men: A Review of Clinical Presentation, Diagnosis and Treatment

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SUMMARY

Hyperprolactinaemia is one of the commonest non-diabetes endocrine disorder seen by Endocrinologists. Prolactin is a polypeptide hormone secreted by the anterior pituitary gland. Its main physiological role is in milk production. Hyperprolactinaemia is more common among females and there is paucity of literature on hyperprolactinaemia among men.

The causes of hyperprolactinaemia include physiological causes (such as sleep), drugs, sellar masses, including prolactinoma, other endocrine disorders such as hypothyroidism. The clinical presentation in males results from the disruption of the hypothalamus-pituitary-testicular axis and mass effect. It is an important and often overlooked cause of hypogonadism in males. Men usually present with macroprolactinomas with accompanying symptoms of mass effect such as visual impairment.

Diagnosis of hyperprolactinaemia is made from relevant symptoms and signs and confirmed by immunoassay of the serum prolactin. Other relevant investigations need to be done to identify the potential causes of the disorder. Magnetic resonance imaging is the radiological investigation of choice to visualize the pituitary.

Treatment of hyperprolactinaemia in males is dependent on aetiology and symptomatology. Some medications may need to be stopped or changed. Pharmacotherapy with dopamine agonists is the first line treatment of prolactinomas. Symptomatic cases of prolactinomas with drug resistance or drug intolerance are referred for surgery or radiotherapy.

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Background

Hyperprolactinaemia is an endocrine disorder characterized by excess amount of serum prolactin. Prolactin is a polypeptide hormone made up of 128 amino acids [1]. Its name is derived from its ability to stimulate lactation. It is a single chain of amino acids with a molecular weight of 23KDa [2]. The hypothalamus secretes a hormone called dopamine which acts to regulate prolactin production through negative feedback. The gene encoding prolactin is found on chromosome 6. The documented physiological roles of prolactin is synthesis of milk in the third trimester and sustenance of milk production in the postpartum period [1]. Prolactin has structural homology with other hormones such as growth hormone and human placenta lactogen [2].

The amount of prolactin secreted physiologically varies between the genders. In males, it is about 10-20µg/L and in non-pregnant and non-lactating females, it is about 15-25 µg/L. The amount secreted is also increased in physiological conditions such as sleep, pregnancy and lactation [2]. Prolactin is produced in some specialized cells within the anterior pituitary called lactotrophs or mammotrophs [3]. Its secretion is stimulated by the hypothalamus-secreted tripeptide thyrotropin secreting hormone and inhibited by dopamine, gamma aminobutyric acid (GABA), somatostatin, thyroid hormones and glucocorticoids [4]. Documented non-lactation effects of prolactin include immune regulation, fluid and electrolyte regulation and tissue growth [2].

Hyperprolactinaemia is the most common hypersecretion disorder of the pituitary gland and it is 4 times commoner in women compared to men [5]. There is paucity of information about the occurrence of hyperprolactinaemia in men compared with women. It is commonest among young people (20-40) years, in both males and females although men tend to present slightly later compared to women [5]. The clinical presentation is also gender-specific. The commonest presentations among women are menstrual disorders and galactorrhoea while fertility disorder and mass effects are the commonest presentations among men. The diagnosis of hyperprolactinaemia is confirmed by assaying the patient's serum for prolactin. The mainstay of treatment is pharmacotherapy using dopamine agonists such as bromocriptine and cabergoline.

Clinical presentation of hyperprolactinaemia in men

He clinical presentation of hyperprolactinaemia in men may be subacute (lasting for weeks) chronic (lasting for months or years)

[2]. In the subacute phase, men tend to present with reduced libido and erectile dysfunction.[5] In order for males to be fertile, the physiological roles of the hypothalamic-pituitary-testicular axis need to be intact. The intact functioning of the axis is needed for spermatogenesis, maturation of sperm, maintenance of masculine characteristics and behaviours. Hyperprolactinaemia disrupts the pulsatile physiology this axis leading to infertility and reduced libido [6]. Also, hypogonadism that results from hyperprolactinaemia may result in loss `of body muscle mass, osteopenia or even osteoporosis and loss of male facial hair [7]. Hyperprolactinaemia in males is associated with arrest of spermatogenesis leading to reduced motility of spermatozoa, impaired quality, reduced ejaculate volume and oligozoospermia [8]. There is significant alterations in the morphology and volume of the testes, resembling pre-pubertal testes.

Pituitary tumours, called prolactinomas, are a common cause of hyperprolactinaemia in males [8]. Other causes include drugs (such as antipsychotics such as risperidone, tricyclic antidepressants, opioids and metoclopramide), hypothyroidisms, other sellar and parasellar tumours, chronic kidney disease, chronic liver disease and chest wall injuries and other conditions such as varicella zoster [8].

Prolactinomas are divided into two on the basis of size; microprolactimoas are less than 1cm while macroprolactinomas are greater than 1cm in size [9]. Prolactinomas greater than 4cm are called giant prolactinomas. Women usually present with microprolactinomas whereas men present more with macroprolactinomas [9]. The disturbance of menstruation and the presence of unsightly galactorrhoea tend to make women present early, hence as microplactinomas. The large and locally invasive nature of the prolactinomas in men makes them present more with mass effects and especially visual damage. The mass effect symptoms include headache due to stretch of the diaphragm sellae, loss of vision due to compression of the optic chiasm, double vision due to compression of the cranial nerves in the carotid sinus and sometimes cerebrospinal fluid (CSF) rhinorrhoea due to the invasion of the floor of the sella turcica [9].

Diagnosis of hyperprolactinaemia in men

A good history should be taken and a detailed physical examination, including examination of the testes, neurological examination, visual field and visual acuity should be performed. The serum prolactin is then assayed. A single fasting sample taken without excessive venipuncture stress is enough to diagnose hyperprolactinaemia once it is above the reference range which varies with the laboratory and assay methodology [1]. Automated immunoassay methodology is often employed by most laboratories to assay for prolactin. There are two scenarios that deserve being mentioned here. The first is the 'hook effect' which occurs when a very high serum prolactin level (>5000 μg/L) saturates both the capture and signal antibodies used in measurement assays preventing the binding of the two in a sandwich giving a falsely normal serum prolactin level [10]. A 1/100 dilution of the sample can circumvent this potential laboratory error. The second scenario is the presence of non-bioactive polymeric prolactin isoform called macroprolactin. It interferes with the prolactin immunoassays giving falsely elevated serum prolactin level [11]. Addition of polyethylene glycol can provide an accurate measurement of the normal prolactin isoform.

A mild elevation in serum prolactin could be due to stressors such as exercise or venipuncture or due to medications [12]. These need to be considered in this situation. Other relevant biochemical investigations, depending on the clinical scenario, include follicle stimulating hormone (FSH), leutinizing hormone (LH), testosterone, thyroid function test, kidney function test as well as liver function test [12]. Pituitary neuroimaging, preferably medical resonance imaging (MRI) is very crucial for a male with hyperprolactinaemia. Ophthalmology consultation is also important in patients with sellar/parasellar masses.

Treatment of hyperprolactinaemia in men

Treatment is given according to the aetiology and symptomatology of the hyperprolactinaemia. Identified stressors are removed while the serum prolactin assay is repeated. In cases of drug-induced hyperprolactinaemia, the offending drugs may be discontinued after consulting the appropriate specialists, for example, a consultation with the psychiatrist may be sought before discussing neuroleptics. Alternative medications that do not cause hyperprolactinaemia may be considered. Hypothyroidism should be treated appropriately and this is all that is required in cases of hypothyroidism-induced hyperprolactnaemia. Chronic kidney disease or chronic liver disease should be treated appropriately.

Non-prolactinoma masses and infiltrative diseases involving the hypothalamus and/or pituitary gland may require surgical intervention. So, neurosurgical consultation may be sought. Macroprolactinaemia has no clinical significance and does not require any medical or surgical intervention [1].

The first line treatment of prolactinoma is pharmacotherapy through the use of dopamine agonists [12]. This may require urgent commencement in macroadenomas, especially when visual impairment is involved. Dopamine agonists shrink the tumor, lower serum prolactin levels and reduce the symptoms and signs of hypogonadism. The preferred dopamine agonist is cabergoline because it has demonstrated higher efficacy at reducing prolactinoma size and lowering serum prolactin levels [12]. Other dopamine agonists that can be used include bromocriptine, pergolide and quinagolide. Serum prolactin levels are measured regularly and the tolerability of the drug is also assessed. MRI is done after 6 months for macroploctinomas to determine the degree of tumor shrinkage. Dopamine agonists dose adjustments are considered depending on the monitored prolactin levels. [12] Men with hyperprolactinaemia who are not responding to dopamine agonist or cannot tolerate the medications should be considered for surgery with or without radiotherapy.

Conclusion

Hyperprolactinaemia is a common disorder seen by Endocrinologists. It is more reported among women than men. It has physiological and pathological causes. Hypogonadism is the commonest clinical presentation of hyperprolactinaemia among men. Diagnosis is made from history, physical examination and relevant biochemical and radiological investigations. Treatment is according to the cause. Dopamine agonists are the mainstay of treatment of prolactinomas. Drug-resistant prolactinomas and other sellar masses may benefit from neurosurgical intervention.

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