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Hyperprolactinaemia

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ABSTRACT Hyperprolactinaemia is the most common hormonal abnormality affecting the pituitary gland. The most frequently seen non-physiological causes include drug-induced hyperprolactinaemia, polycystic ovarian syndrome, and benign prolactin-secreting tumours of the anterior pituitary gland (prolactinomas). Tumours may be classified as either micro- (<1 cm in diameter), which are most common, or macroprolactinomas (>1 cm in diameter). Prolactinomas most commonly occur in women between 30 and 50 years of age and hyperprolactinaemia usually presents with galactorrhoea or symptoms of disturbed gonadal function (secondary amenorrhoea, anovulation, and infertility in women; erectile dysfunction, reduced shaving frequency in men). Macroprolactinomas may also present with local pressure effects (headache, visual fi eld loss). Dopamine agonists, such as bromocriptine and cabergoline, are the first-line treatment for both micro- and macroprolactinomas. Nowadays, surgical treatment is rarely required even for macroprolactinomas. The main aim of treatment is resolution of symptoms, and, therefore, restoration of gonadal function. For patients with microprolactinomas, dopamine agonist treatment should be withdrawn for a trial period after two to three years, as in around one-third of cases the prolactin level will return to normal. In women with microprolactinomas who become pregnant, dopamine agonists should be discontinued once pregnancy is confirmed. For women with macroprolactinomas, bromocriptine can be continued throughout the pregnancy.

KEYWORDS Hyperprolactinaemia, pituitary tumour, prolactinoma, microadenoma, dopamine agonists, macroprolactin

LIST OF ABBREVIATIONS Thyrotrophin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), polycystic ovarian syndrome (PCOS), Magnetic resonance imaging (MRI), adrenocorticotrophic hormone (ACTH)

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OVERVIEW

Introduction

Prolactin, a peptide hormone, is secreted by lactotropes, which are acidophilic cells in the anterior pituitary gland. Its secretion from the anterior pituitary is predominantly regulated by dopamine inhibitory tone. However, TRH, a hypothalamic hormone whose main role is regulation of the secretion and synthesis of TSH from the pituitary, has a modest stimulatory effect on prolactin secretion.

CAUSES

Hyperprolactinaemia is the most common hormonal abnormality affecting the pituitary gland. This is frequently due to a pituitary microprolactinoma (<1 cm in diameter), which most commonly occurs in women between 30 and 50 years of age. Macroprolactinomas (>1 cm in diameter) are more often found in men. Postmortem studies show that microprolactinomas occur in up to 10% of the population, most of who remain asymptomatic during life. Other commonly seen, non-physiological, causes of hyperprolactinaemia include drugs, primary hypothyroidism, and PCOS. Hyperprolactinaemia associated with PCOS may be seen in around 20% of patients, but the elevation of prolactin is usually modest. A full list of causes of hyperprolactinaemia is shown in Table 1.

'Idiopathic' hyperprolactinaemia

When no definite cause is found following careful evaluation, hyperprolactinaemia is often designated 'idiopathic'. In many cases it is likely this is due to a tiny microprolactinoma that is not demonstrable using current imaging techniques. On follow-up of patients with no radiological abnormalities and those with only very small microadenomas on imaging, prolactin levels return to normal in around one-third of cases. In 10–15% there is a further increase in prolactin, and in the remainder, prolactin levels remain stable.

CLINICAL FEATURES

Hyperprolactinaemia usually presents earlier in women than in men.

TABLE 1 Causes of hyperprolactinaemia.

Physiological
- Pregnancy
- Sleep
- Stress
- Sexual intercourse
- Nipple stimulation/suckling

Pituitary tumour
- Prolactinomas
- Mixed growth hormone/prolactin secreting tumour
- Non-functioning macroadenoma compressing stalk (disconnection syndrome)

Hypothalamic disease
- Mass compressing stalk (e.g. craniopharyngioma, meningioma)

Infiltration
- Sarcoidosis
- Langerhan's cell histiocytoses

Stalk section
- Head injury
- Surgery

Cranial irradiation

Drug treatment
- Dopamine receptor antagonists (metoclopramide, domperidone)
- Neuroleptics (thioridazine, haloperidol, chlorpromazine)
- Antidepressants (tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors)
- Cardiovascular drugs (verapamil, methyldopa)
- Opiates
- Protease inhibitors (zidovudine)
- Others (e.g. H2 antagonists)

Metabolic
- Hypothyroidism (TRH increases prolactin secretion)
- Chronic renal failure (reduced prolactin clearance)
- Severe liver disease (disordered hypothalamic regulation)

Other
- Polycystic ovarian syndrome
- Chest wall lesions (Herpes zoster, burns, trauma stimulates suckling reflex)

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Women

Galactorrhoea occurs in approximately 90% of women with hyperprolactinaemia. Disturbed gonadal function occurs in 95% of women, and may present with secondary amenorrhoea, oligomenorrhoea, anovulation with infertility, or with reduced libido. There is also a long-term risk of reduced bone mineral density.

Men

Disturbance of gonadal function in men may present with loss of libido, erectile dysfunction, reduced shaving frequency, and lethargy. Presentation with reduced fertility and oligospermia, or gynaecomastia and galactorrhoea can occur, but is uncommon.

Mass effect

Macroprolactinomas may present with symptoms due to local pressure effects, including headaches and visual field loss, characteristically temporal field defects due to compression of the optic chiasm. Invasion of the cavernous sinus may lead to cranial nerve palsies, and occasionally very invasive tumours may erode bone and present with a nasal cerebrospinal fluid leak or secondary meningitis.

INVESTIGATIONS

Serum prolactin

The upper limit of normal for most assays of serum prolactin is 300–500 mU/L. During pregnancy and lactation physiological levels may reach 10,000 mU/L, or occasionally higher. In non-pregnant and non-lactating patients, levels above the normal range but <1,000 mU/L are likely to be induced by stress or drugs but occasionally may be indicative of a pituitary tumour. This may be either a microprolactinoma or a non-prolactin-secreting macroadenoma causing compression of the pituitary stalk and interrupting dopamine inhibition to the lactotrope ('disconnection hyperprolactinaemia'). Pituitary imaging may, therefore, be indicated in such cases of only modest hyperprolactinaemia when the prolactin level remains persistently elevated and no other cause is identified. More commonly 'disconnection hyperprolactinaemia' presents with a prolactin level between 1,000 and 3,000 mU/L and a serum prolactin level >3,000 mU/L is highly suggestive of a prolactinoma, assuming that drug-induced hyperprolactinaemia has been excluded. A serum prolactin concentration of >6,000 mU/L is virtually diagnostic of a macroprolactinoma. Exceptions to these rough guidelines do occur, however, and a prolactin level between 1,000 and 6,000 mU/L in the presence of a macroadenoma may either be due to disconnection or due to a macroprolactinoma. Serum prolactin levels may fall with dopamine agonist therapy in either situation, but significant tumour shrinkage usually only occurs with macroprolactinomas, so these patients should be carefully followed if treated with dopamine agonists and rescanned at 6–12 weeks. Lack of tumour shrinkage suggests a non-prolactin-secreting macroadenoma with stalk effect, and surgery is advisable.

Macroprolactin

Prolactin circulates in a variety of forms. Monomeric prolactin, with a molecular mass of 23 kDa, usually accounts for 85–95% of the prolactin present and a 50 kDa ('big' prolactin) species makes up <10%. Macroprolactin ('big big' prolactin), a prolactin–IgG complex with a molecular mass

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of 150 kDa, accounts for a small but variable percentage of total prolactin. Whereas monomeric prolactin is bioactive, macroprolactin is considered biologically inactive, although it may be detected on prolactin immunoassays. In some individuals, most of the prolactin present may be in the macroprolactin form, leading to 'pseudo-hyperprolactinaemia' because the biologically inactive prolactin–IgG complex is cleared more slowly than monomeric prolactin. It is important to differentiate between the apparently benign clinical condition of macroprolactinaemia, in which hyperprolactinaemia is entirely explained by the presence of macroprolactin, and true hyperprolactinaemia, which requires treatment. It is now possible to screen for the presence of macroprolactin using the technique of polyethylene glycol extraction. This is important, as it is the level of monomeric prolactin that indicates the presence of true hyperprolactinaemia.

Dynamic tests of prolactin secretion

These tests may be useful in distinguishing between hyperprolactinaemia from a pituitary source and non-pituitary causes. In patients with a prolactinoma, there is characteristically an absent or blunted (<threefold increment) prolactin response to the intravenous administration of either TRH or metoclopramide, and pituitary imaging is necessary.

Imaging

Magnetic resonance imaging with contrast enhancement is the imaging procedure of choice. Microadenomas usually appear as hypointense lesions within the pituitary on T1-weighted images. Stalk deviation or gland asymmetry may also suggest the presence of a microprolactinoma. Macroprolactinomas may be associated with bony erosion or cavernous sinus invasion.

TREATMENT

Aims of therapy

For microprolactinomas, the main aim of therapy is resolution of symptoms and, particularly, restoration of gonadal function. When treating macroprolactinomas, reduction in tumour size and prevention of tumour expansion is clearly also important. Although microprolactinomas may increase in size without treatment, the majority do not (>90%). Macroprolactinomas, however, will continue to expand and lead to local pressure effects. Therefore, definitive treatment of these tumours is necessary.

Drug therapy: dopamine agonists

The first dopamine agonist used for the treatment of hyperprolactinaemia was bromocriptine. This ergot alkaloid is short-acting and is usually taken orally. However, side-effects are common, particularly nausea and postural hypotension. These can be reduced by slow initiation of therapy, taking the medication before going to bed, and taking the tablets with food. Nevertheless, some patients are unable to tolerate bromocriptine in an adequate dose to correct hyperprolactinaemia. The newer dopamine agonists, quinagolide and cabergoline, are better tolerated and rarely cause significant side-effects. Cabergoline has the additional advantage of a long duration of action, only needing to be taken once or twice a week, and is increasingly the drug of choice for treating hyperprolactinaemia.

Dopamine agonist treatment leads to suppression of prolactin levels in most patients, with the additional secondary beneficial effects of normalisation of gonadal function and termination of galactorrhoea. Tumour shrinkage occurs at a variable rate and extent. Ninety per cent of macroadenomas shrink, however, and the majority do so by more than half. Occasionally, complete radiological resolution of a macroadenoma may occur, but this is more common with microadenomas. Cabergoline is more effective than bromocriptine in normalising prolactin levels. In patients with microprolactinomas treated with cabergoline, normalisation of prolactin levels occurs in 83%, compared with 59% on bromocriptine.

Surgery

The trans-sphenoidal approach is now the favoured technique for most pituitary surgery. Unfortunately, the technique may be inadequate to deal with very large tumours with extensive suprasellar extension. In these situations, craniotomy is required if adequate debulking is not possible using the trans-sphenoidal approach.

Since the introduction of dopamine agonist treatment, trans-sphenoidal surgery is routinely indicated only for patients who are resistant to or are intolerant of dopamine agonists. The cure rate for macroprolactinomas treated with surgery is poor (30%), and therefore drug treatment is first-line for tumours of all sizes. However, as intimated above, surgery is appropriate for hyperprolactinaemic patients with macroadenomas that do not shrink with dopamine agonist therapy, as a significant proportion will be non-functioning tumours. Cure rates for microprolactinomas treated by surgery are >80%, but there is a risk of both hypopituitarism and tumour recurrence (4% at five years).

Radiotherapy

Conventional external beam three-field radiotherapy is able to deliver a beam of ionising irradiation accurately to the pituitary fossa, and is an effective treatment used to reduce the likelihood of tumour regrowth, to further shrink a tumour, and to treat persistent hormone hypersecretion following surgical resection. Pituitary radiotherapy is rarely indicated for the treatment of

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microprolactinomas, but is sometimes used in the management of patients with macroprolactinomas, particularly if there is difficulty tolerating medical therapy. Pituitary radiotherapy should ideally be deferred until the tumour has been shrunk away from the chiasm by dopamine agonist therapy, because of the small risk of vascular damage and consequent visual loss. It is usually only administrable once in a lifetime.

Standard pituitary irradiation leads to slow reduction (over years) of prolactin in the majority of patients. While waiting for radiotherapy to be effective, dopamine agonist therapy is continued, but should be withdrawn on a biannual basis to assess if it is still required.

Short-term complications of radiotherapy include nausea, headache, and temporary hair loss. The most common long-term complication is hypopituitarism, and the likelihood of developing post-radiotherapy hypopituitarism is increased if there is pre-existing hormonal deficiency. The classical order of development of pituitary hormonal deficiency is growth hormone, followed by gonadotrophins, ACTH, and finally TSH, and the onset is gradual. Posterior pituitary deficiencies are very rare.

PROGNOSIS

The natural history of microprolactinomas is difficult to assess. However, as intimated above, they are a common postmortem incidental finding, and <20% show any increase in tumour size during serial imaging. It has been demonstrated that hyperprolactinaemia in approximately one-third of women will resolve and so patients receiving dopamine agonist treatment for microprolactinomas should have treatment withdrawn intermittently (every two to three years) to assess the continued requirement for it.

There are few data on dopamine agonist withdrawal in macroprolactinomas in the absence of definitive treatment (radiotherapy or surgery). In the absence of definitive management of the tumour, complete withdrawal of drug treatment is likely to be associated with significant tumour enlargement.

MANAGEMENT OF PROLACTINOMAS IN PREGNANCY

Effect of pregnancy on tumour size

Risk of significant tumour enlargement is 1·5–5·5% for microprolactinomas and <10% for patients with macroprolactinomas treated for >6 months with dopamine agonist therapy.

Effect of dopamine agonists on the fetus

Over 6,000 pregnancies have occurred in women receiving bromocriptine in early pregnancy and the incidence of complications in these pregnancies with regard to fetal outcome is similar to that of the normal population. Data are available on approximately 100 children whose mothers were treated with bromocriptine throughout pregnancy, and again the incidence of congenital abnormalities is negligible.

Cabergoline is also probably safe during early pregnancy, with no apparent increased risk of fetal loss or congenital abnormalities. However, data are only available on approximately 300 pregnancies.

Management

In patients with microprolactinomas, dopamine agonist therapy should be initiated to induce normal ovulatory cycles and fertility, then discontinued as soon as pregnancy is confirmed. No formal monitoring of the microprolactinoma is required during the pregnancy as the risk of complications is low. In addition, serum prolactin levels are difficult to interpret during pregnancy as they are normally high. Visual field testing or MRI is only indicated if the patient becomes symptomatic. In the post-partum period, the prolactin level should be rechecked after cessation of breast feeding. An MRI scan to reassess the size of the prolactinoma is only required if the serum prolactin level is significantly higher than the pre-pregnancy concentration.

In cases of macroprolactinoma, dopamine agonist therapy may be used to induce ovulation, and bromocriptine may be continued throughout the pregnancy to reduce the risk of tumour growth. This is probably the safest approach. Alternatively, the bromocriptine may be discontinued after conception but such patients must be monitored very closely during the pregnancy. If symptoms of tumour enlargement develop or if there is any change in the visual fields, MRI must be performed to assess tumour growth. Although sometimes advocated in the past, with current dopamine agonist therapy tumour debulking, radiotherapy, or surgery is now very rarely required. If significant tumour enlargement of a prolactinoma occurs during pregnancy, then bromocriptine therapy is generally the treatment of choice as surgical treatment in pregnancy is associated with significant risk of fetal loss. Magnetic resonance imaging should be performed in the post-partum period in women with macroprolactinomas, to assess whether significant tumour growth has occurred.

HIGHLIGHTS

- Microprolactinomas are a common pathological cause of hyperprolactinaemia, and most commonly occur in women between 30 and 50 years of age.
- Hyperprolactinaemia usually presents with galactorrhoea or symptoms of disturbed gonadal function.

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- Treatment is aimed at restoration of gonadal function. Dopamine agonists, such as bromocriptine and cabergoline, are the first-line treatment for micro- and macroprolactinomas. With the currently available effective drug therapy, surgical treatment is rarely required even for macroprolactinomas.
- For patients with microprolactinomas, dopamine agonist treatment should be withdrawn for a trial period after two to three years, as in approximately one-third of cases the prolactin level will return to normal.
- Dopamine agonists should be discontinued once pregnancy is confirmed in patients with microprolactinomas. For women with macroprolactinomas, bromocriptine can be continued throughout the pregnancy but, alternatively, can often be withdrawn without event.

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