Hyperprolactinaemia

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Clin Med 2008;8:216–9

Hyperprolactinaemia is the most common pituitary hormonal abnormality, characterised by excess circulating levels of the polypeptide hormone prolactin. Its clinical significance is related to its effect on gonadal and mammary function, causing anovulatory infertility, sexual dysfunction and galactorrhoea.

Understanding the basic physiology of prolactin secretion is of utmost importance to establish the aetiology of hyperprolactinaemia. When indicated, dopamine agonist treatment is the most effective therapy to control prolactin level, ameliorate hyperprolactinaemic symptoms and shrink the size of a prolactin secreting tumour.

Pathophysiology

The secretion of prolactin from the anterior pituitary is under the inhibitory control of dopamine produced by the hypothalamus and transported via the portal circulation in the pituitary stalk (infundibulum). This is the main mechanism for regulating the circulating level of prolactin, but other hormones such as oestrogens, thyrotrophin-releasing hormone, oxytocin and vasopressin are also known to stimulate its release. Any disease process that either interferes with the dopaminergic inhibitory pathway or causes autonomous production of prolactin within the pituitary therefore results in raised prolactin levels (Table 1).

Clinical evaluation (Table 2)

A meticulous clinical assessment is mandatory to identify the aetiology of hyperprolactinaemia and evaluate its consequences.

A review of medical and psychiatric history is important, with particular emphasis on the use of antidopaminergic drugs. Features of hypothyroidism and polycystic ovarian syndrome should be looked for as both conditions are associated with modestly raised prolactin levels.

Symptoms of headache and visual disturbance are useful clues for the presence of a larger pituitary tumour; hence a relevant history and visual field testing are necessary. Frequent clinical consequences of hyperprolactinaemia are:

- menstrual disturbance in the form of oligomenorrhoea or amenorrhoea
- anovulatory infertility
- sexual problems manifesting as low libido (erectile dysfunction in men)
- galactorrhoea (gynaecomastia in men may reflect hypogonadism).

Investigations

A careful clinical evaluation should dictate the need for and the extent of further investigation.

Biochemical evaluation

A basic biochemical profile to assess renal, liver and thyroid function must be part of the initial work-up, particularly with modest hyperprolactinaemia. Serum prolactin level should be checked on at least two separate occasions as mild elevations could be caused by a variety of stresses such as exercise, sexual intercourse, meals and venepuncture.[1]

The degree of elevation of prolactin level could provide a rough guide as to the aetiology of hyperprolactinaemia. Non-tumoral causes of hyperprolactinaemia rarely give rise to prolactin levels over 2,000 mu/l. Microprolactinomas and stalk disconnection by a non-prolactin secreting tumour may cause prolactin levels up to 5,000 mu/l. A serum prolactin level above 10,000 mu/l is strongly suggestive of a diagnosis of a macroprolactinoma, although the size of the tumour does not necessarily correlate with the prolactin level.[1–4]

Radiological imaging

When clinical and biochemical evidence indicates hyperprolactinaemia secondary to hypothalamo-pituitary pathology, radiological imaging with magnetic resonance imaging (MRI) or computed tomography, and also formal visual field assessment should be undertaken. MRI is the preferred mode of imaging as it provides better resolution and good delineation of adjacent anatomical structures – bearing in mind that microadenomas (<1 cm) are a frequent occurrence in the normal

Table 1. Causes of hyperprolactinaemia.

Physiological	Pregnancy Lactation Sexual intercourse Stress Exercise
Iatrogenic	Antipsychotics: phenothiazine, haloperidol, risperidone Antidepressants: tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors Antidopaminergics: antiemetics (metoclopramide, domperidone) Antihypertensives: methyldopa, verapamil Others: oestrogens, opiates, cimetidine
Pathological	Prolactinoma Stalk disconnection: non-functioning pituitary adenomas, sarcoidosis, tuberculosis, histiocytosis, lymphocytic hypophysitis Idiopathic (non-tumoral) hyperprolactinaemia
Miscellaneous	Primary hypothyroidism Polycystic ovary syndrome Chest wall lesions (eg herpes zoster, burns) Hepatic and renal failure

population (10–20%).[5,6] The absence of any demonstrable lesion on MRI could imply either a very small microadenoma (<2 mm) or a non-tumour related cause of hyperprolactinaemia.

Hyperprolactinaemia and macroprolactin

When a raised prolactin level is detected in an asymptomatic patient or the level of prolactin is thought to be out of proportion to the clinical features, the presence of macroprolactin should be suspected. Macroprolactin is a hormonally inert large molecular weight prolactin-immunoglobulin G complex which is detected by most prolactin assays. Polyethylene glycol precipitation of complexes allows accurate estimation of monomeric prolactin levels in this situation, a technique now widely employed in many laboratories. However, macroprolactin can also coexist with truly raised prolactin level and its presence should not be a distraction from making a diagnosis of hyperprolactinaemia when clinical evaluation is suggestive.[7]

Treatment

Not all patients with hyperprolactinaemia need active treatment. This is particularly true for patients with asymptomatic mild elevations of prolactin with normal ovulatory function. Such patients can safely be monitored at regular intervals with measurement of prolactin levels unless there are progressively increasing increments of prolactin or evolving symptoms.[8]

Cases of drug-induced hyperprolactinaemia could be ameliorated by withdrawing or changing the offending agent where this is practical. This may not always be feasible, for example with antipsychotic medications, in which case sex steroid replacement may be considered if the patient is significantly hypogonadal.

Dopamine agonists for hyperprolactinaemia

The most effective treatment modality for hyperprolactinaemia is one of the dopamine agonists, of which bromocriptine, cabergoline and quinagolide are the three drugs currently in use in the UK. They differ in their efficacy, affinity and selectivity for D2 receptors as well as side effect profile.

Bromocriptine, the oldest member of the group, is still used widely. It is usually prescribed at a low starting dose which can gradually be increased to a (usual) maximum of 2.5 mg twice or three times daily. This improves tolerability of its side effects, which include nausea, dizziness, postural hypotension and low mood. Cabergoline has a better side effect profile and is superior to the other two in terms of efficacy and selectivity for D2 receptors.[9,10] It is also favoured for its longer half-life which allows a once or twice weekly dosing regimen.

The main objectives of dopamine agonist treatment in non-tumoral hyperprolactinaemia and microprolactinomas are restoration of ovulation and fertility. For macroprolactinomas, reduction of tumour volume is one of the primary targets. Dopamine agonists achieve this remarkably well, the effect can begin within days of starting treatment and they provide rates of visual recovery comparable to surgical resection of the tumour.[11]

Surgery and radio therapy for prolactinomas

Surgical resection of a prolactinoma is a second-line modality after dopamine agonist therapy. Its indication is limited to:

- patients who are either intolerant of or fail treatment with dopamine agonists
- prolactinomas presenting with acute enlargement, infarction or haemorrhage ('apoplexy')
- the very rare malignant prolactinomas.

The surgical cure rate for microprolactinomas is operator-dependent (around 75%) with a lower figure for macroprolactinomas.[12] Radiotherapy is usually restricted to those cases that are resistant to dopamine agonists and not cured by surgery as well as rare cases of malignant prolactinomas.

Special circumstances

Pregnancy and hyperprolactinaemia

The anovulatory hyperprolactinaemic woman who is being treated with dopamine agonists should be warned about the possibility of becoming pregnant and advised on contraception if pregnancy is not desired. Pregnancy

Table 2. Evaluation of the hyperprolactinaemic patient.

History	Oligomenorrhoea/amenorrhoea Galactorrhoea (gynaecomastia in men) Reduced libido (erectile dysfunction in men) Infertility Headache/visual disturbance Medical/psychiatric history Drugs causing raised prolactin
Physical examination check for:	Galactorrhoea/gynaecomastia Features of hypogonadism/hypopituitarism Visual field assessment
Investigations:	
• Biochemical	Liver and renal function Pregnancy test Thyroid function Prolactin Macroprolactin (where appropriate) Full pituitary hormonal profile (large tumours)
• Visual field assessment	
• Imaging	MRI scan (gadolinium enhanced) *or* contrast-enhanced CT

CT = computed tomography; MRI = magnetic resonance imaging.

raises particular issues in the management of hyperprolactinaemia including:

- the risk of increase in the size of a prolactinoma
- the unreliability of prolactin level measurements for monitoring disease activity, and
- the use of dopamine agonist drugs in pregnancy.[13]

Both bromocriptine and cabergoline have been safely used in pregnancy with no excess risk of congenital malformations or any other adverse outcomes.[14,15]

Microprolactinoma. The risk of significant growth of a microprolactinoma during pregnancy is minimal (<2%). Women with a microprolactinoma who have become pregnant during the course of treatment with a dopamine agonist could safely be taken off their medication and monitored clinically, with a warning to report symptoms of persistent headache or visual impairment.

Macroprolactinoma. A macroprolactinoma carries a significant risk of tumour expansion during pregnancy (20–30%). In this situation, patients can either be maintained on dopamine agonist therapy during the course of pregnancy, accepting that lactation will be suppressed, or their treatment can be withdrawn, with close clinical monitoring and the option to use non-contrast MRI of the pituitary if signs of tumour growth are detected.

Patients with a sizeable macroprolactinoma are advised to postpone pregnancy until shrinkage of the tumour is achieved with dopamine agonist treatment. Pre-pregnancy surgical debulking can also be considered as an option to prevent any significant growth during pregnancy.

Antipsychotic-induced hyperprolactinaemia

All conventional antipsychotic drugs cause a variable degree of hyperprolactinaemia through their blocking effect on D2 receptors of lactotroph cells in the pituitary. 'Atypical' antipsychotic drugs such as clozapine, quetiapine and olanzapine have minimal, often transient effects on prolactin secretion compared with conventional antipsychotics.[16] Therefore, patients who develop symptomatic hyperprolactinaemia on conventional antipsychotic drugs should be considered for switching to one of the atypical antipsychotic drugs, where this is possible without aggravating their psychotic symptoms. Dopamine agonist drugs should be used in patients with presumed antipsychotic-induced hyperprolactinaemia only rarely due to their potential to worsen the psychotic illness.[17]

Key Points

Asymptomatic cases of modest hyperprolactinaemia can safely be monitored without the need for active treatment

Dopamine agonist therapy is usually the treatment of choice for both non-tumoral and tumour-related hyperprolactinaemia

Antipsychotic and antidepressant medications are common causes of hyperprolactinaemia; when feasible, this can often be corrected by withdrawing the offending medication or switching to a drug with minimal antidopaminergic effect

Macroprolactinomas have a 20–30% risk of growth during pregnancy; hence close clinical monitoring is necessary during gestation, with regular visual field screening and pituitary imaging when indicated

Withdrawal of dopamine agonist treatment could be considered in patients where satisfactory control of hyperprolactinaemia and tumour size is achieved after 2–3 years of treatment

KEY WORDS: dopamine agonist, hyperprolactinaemia, pituitary, prolactin, prolactinoma

Remission of hyperprolactinaemia

Prolactinomas usually have an indolent natural course even when untreated. Patients treated with dopamine agonists can achieve a variable rate of remission upon discontinuation of treatment. In a prospective study of cabergoline treated hyperprolactinaemic patients over a follow-up of 2–5 years, the rates of remission were 76%, 67% and 57% for non-tumour hyperprolactinaemia, microprolactinomas and macroprolactinomas, respectively.[18]

Nadir prolactin levels and residual tumour size can be used as predictors of the likelihood of remission after withdrawal of dopamine agonist therapy.[19] It is therefore reasonable to consider withdrawing dopamine agonist treatment once satisfactory and stable control of prolactin level and reduction of tumour volume have been achieved over a period of time.

Dopamine agonists and cardiac valvulopathy

The use of ergot-derived dopamine agonists pergolide and cabergoline for treatment of Parkinson's disease (PD) has been associated with cardiac valve fibrosis.[20,21] Cabergoline is used at a higher dose for treating PD than for hyperprolactinaemia; the reported association with valvulopathy may be related to cumulative doses unlikely to be attained by most pituitary patients. However, caution is still needed and it is not yet known whether cabergoline used in smaller doses for treating hyperprolactinaemia (0.5–1 mg/week) carries a similar risk over long durations of treatment.

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