Investigation of hyperprolactinaemia

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Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.

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The primary action of prolactin is to assist in the development and maturation of the breast and stimulate lactation. Prolactin is secreted by lactrotroph cells in the anterior pituitary gland and is mainly under inhibitory control by dopamine, which is produced by the hypothalamus. Thyrotrophin-releasing hormone (TRH), oestrogen and vasoactive intestinal peptide stimulate secretion of prolactin.

Hyperprolactinaemia is the most common endocrine disorder of the hypothalamic–pituitary axis and the prevalence has been reported to range from 0.4 to 5% in adults.[1] The rate of hyperprolactinaemia is estimated at 9% in women with amenorrhoea, 25% in women with galactorrhoea, 16 to 30% in women with infertility and up to 70% in women with both amenorrhoea and galactorrhoea.[1] Infertility may be consequent to luteal phase abnormalities or hypogonadotrophic hypogonadism. Hypogonadism also leads to a reduction in bone mineral density, and hyperprolactinaemia has been associated with an increased risk of fracture.

In men, hyperprolactinaemia typically presents with symptoms related to low serum testosterone levels, such as reduced libido, impotence, fatigue or decreased muscle strength. Gynaecomastia, or rarely galactorrhoea, may also occur. Given the more subtle clinical features of hyperprolactinaemia in men and also in postmenopausal women, patients may also present with mass effect symptoms such as headache or visual loss.[2]

The following three cases illustrate how to investigate high prolactin levels in a man with muscle weakness and decreased libido, a woman with schizophrenia and a young woman with oligomenorrhoea and acne.

Case 1

A 41-year-old man presents with a 6- to 12-month history of muscle weakness, fatigue and decreased libido. He has also noticed some central weight gain and has been having frontal headaches. There are no visual symptoms. He is otherwise well and takes no medications. Initial investigations reveal a testosterone level of 5 nmol/L (reference range [RR], 10.0–32.0 nmol/L), luteinising hormone (LH) level of 1 IU/L (RR, 1.7–8.6 IU/L), follicle-stimulating hormone (FSH) level of 2 IU/L (RR, 1.5–13.0 IU/L) and prolactin level of 24,516 mIU/L (RR: 50–350 mIU/L).

What is the mechanism by which prolactin lowers levels of testosterone (or oestradiol in women)?

Elevated prolactin levels (particularly levels greater than twice the upper limit of normal) have a direct inhibitory effect on release of gonadotrophin-releasing hormone (GnRH) from the hypothalamus. Lack of pulsatile GnRH release inhibits LH and FSH secretion from the pituitary, with consequent reductions in testosterone (or oestradiol) and impairment of gonadal steroidogenesis.

Can there be any other cause of hyperprolactinaemia apart from a prolactinoma in this case?

No (with few exceptions). There are many causes of hyperprolactinaemia (see Boxes 1 and 2). As a general rule, prolactin levels more than five times the upper limit of normal are due to a prolactinoma. Prolactin concentrations of more than 2000 mIU/L are rarely due to stalk effect.

1. Causes of hyperprolactinaemia

Physiological causes
- Pregnancy, lactation
- Coitus, nipple stimulation
- Sleep
- Stress (acute), exercise

Pathological causes
- Prolactinoma
- Hypothalamic–pituitary disease or stalk damage ('stalk effect')
  - compressive nonfunctioning pituitary macroadenoma
  - sella surgery
  - Rathke's cyst
  - suprasellar tumors: craniopharyngioma, germinoma, hypothalamic metastases, meningioma
  - granulomas
  - infiltrations
  - irradiation
  - lymphocytic hypophysitis
  - trauma
- Prolactin cosecretion
  - acromegaly
  - Cushing's disease (rare)
- Hypothyroidism
- Chest wall injury
- Chronic renal failure

Pharmacological causes (see Box 2)

Other causes
- Idiopathic hyperprolactinaemia
- Macroprolactinaemia

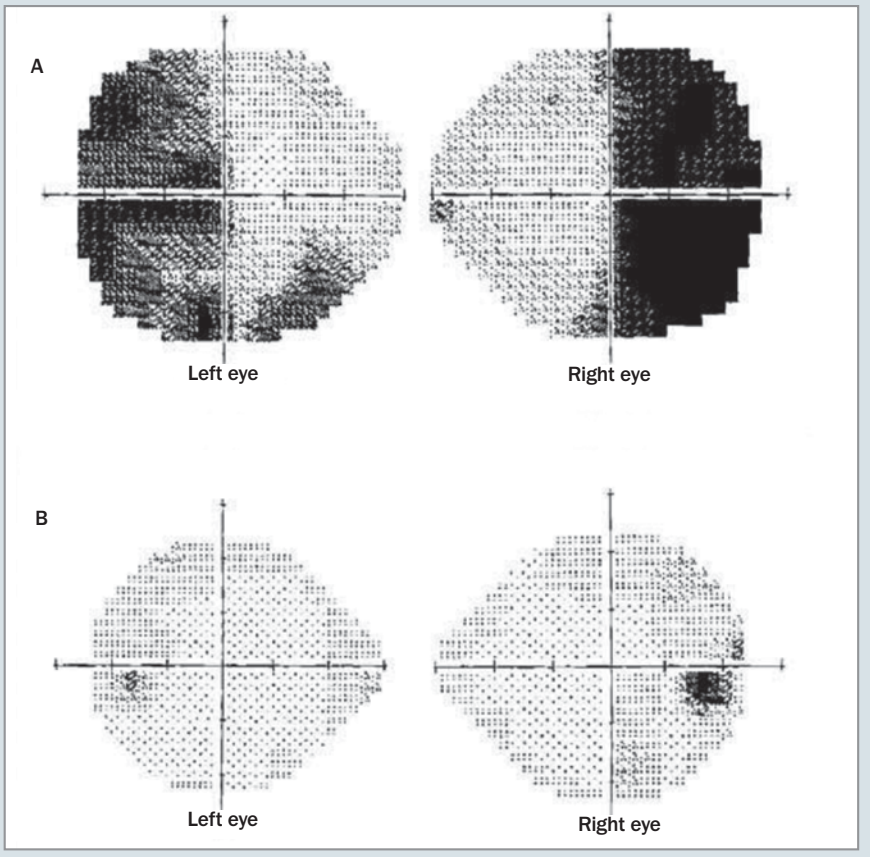


Figure 1. Visual field testing showing the loss of visual fields in a patient with a macroprolactinoma with chiasmal compression (black areas) before initiation of dopamine agonist therapy (panel A) and normalisation (white areas) after two months of treatment (panel B).

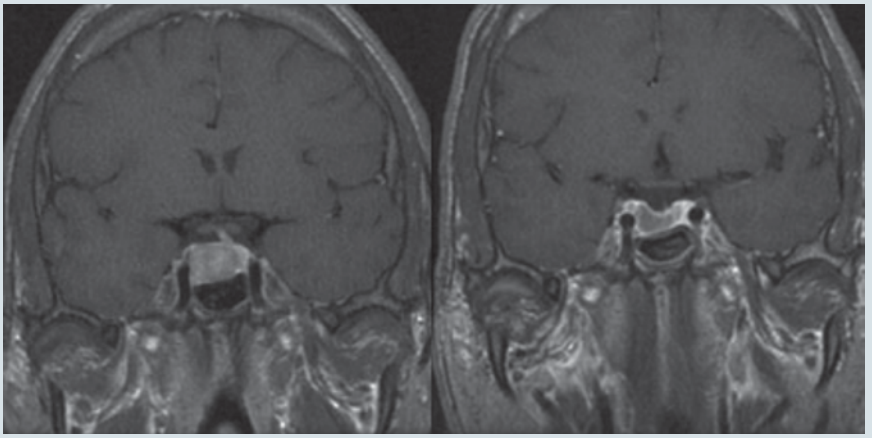
What is the mechanism that may explain a modest elevation of prolactin levels in a patient with a macroadenoma?

For prolactinomas, serum prolactin levels generally parallel tumour size. Macroprolactinomas (>10 mm in diameter) are typically associated with prolactin levels greater than 5000 mIU/L. In a patient with a macroadenoma but only mild hyperprolactinaemia (e.g. prolactin level of 900 mIU/L) this would most likely be due to another subtype of pituitary tumour with associated stalk compression.[3,4] Another explanation (rarely encountered these days as the prolactin assays have improved) is the so-called 'hook effect'. This occurs when a very high serum prolactin level saturates both the capture and signal antibodies used in immunoradiometric and chemiluminescent prolactin assays, preventing the binding of the two in a 'sandwich'. The result is an apparent prolactin concentration that is only modestly elevated. This artefact can be eliminated by using a 1:100 serial dilution of the serum samples.

What investigations should be carried out next for this patient?

In any patient with a pituitary macroadenoma, the potential for mass symptoms as well as hyposecretion of pituitary hormones need to be considered. Rarely, mixed hypersecreting tumours, mostly growth hormone and prolactin, may be encountered. All patients with hyperprolactinaemia should have a full pituitary profile performed, which includes a 9 am serum cortisol, thyroid-stimulating hormone (TSH), free T4 (more important than TSH measurements in pituitary disease), LH, FSH, testosterone (oestradiol in women), and insulin-like growth factor-1 (IGF-1) measurements. A dedicated pituitary MRI should be performed to look for a hypothalamic–pituitary lesion. In addition, if a macroadenoma is found, patients should undergo formal visual field assessment preferably by an ophthalmologist to determine whether optic chiasmal compression is present (which can be found even in patients not reporting visual disturbance; see Figure 1). Bone mineral density (BMD) should be assessed in all patients with hypogonadotrophic hypogonadism.[5]

Outcome: This man was found to have a 15 mm pituitary macroadenoma on MRI (Figures 2a and b), which did not contact the optic chiasm and thus caused no visual field loss. The remainder of the pituitary profile was normal and BMD showed mild osteopenia (T-score -1.5 in the spine). He was treated with 0.5 mg cabergoline weekly and his prolactin level fell to 2468 mIU/L when tested a month later. The cabergoline dose was then increased to 0.5 mg twice weekly, leading to normalisation of prolactin and



Figures 2a and b. MRI scans of a pituitary macroprolactinoma (a, left) before treatment and (b, right) after treatment with dopamine agonist therapy showing regression of the tumour.

testosterone levels at his three-month follow up, a reduction in tumour size by 50% on repeat MRI at six months and improvement in BMD at one year after diagnosis.

Case 2

A 32-year-old woman with a history of schizophrenia presents with 12 months of amenorrhoea and galactorrhoea. Her medications include risperidone and quetiapine. Her prolactin level is elevated at 2100 mIU/L (RR, 85–500 mIU/L), LH level 2 IU/L (RR, basal 2.0–12 IU/L; mid cycle 8.0–90 IU/L), FSH level 3.5 IU/L (RR, basal 1.5–10 IU/L; mid cycle, 7.0–22 IU/L) and oestradiol level less than 50 pmol/L (RR, follicular phase <320; preovulatory phase 150–2000; luteal phase 125–1300 pmol/L).

What is the most likely cause of the hyperprolactinaemia in this case?

The most likely cause is drug-induced hyperprolactinaemia (see Box 2), which is common and occurs by various mechanisms including alteration of the hypothalamic–dopamine system and/or antagonism of the pituitary dopamine receptors. The most commonly encountered drug class causing hyperprolactinaemia is antipsychotic medications. The frequency and extent of antipsychotic-induced hyperprolactinaemia varies considerably between different drugs within the class. Overall in patients with schizophrenia treated with antipsychotics, more than 65% of women of reproductive age and 40 to 70% of men will have hyperprolactinaemia. The atypical antipsychotic agents differ in their ability to cause hyperprolactinaemia due to differences in their D2 receptor binding activity and duration, presence of partial agonist activity, and ability to cross the blood–brain barrier.

Of the atypical antipsychotics, risperidone and amisulpride are associated with the highest rates of hyperprolactinaemia (70 to 100%); quetiapine is associated with rates of 0 to 29% and olanzapine with 6 to 40%, whereas clozapine infrequently elevates prolactin levels (5% of patients) due to weak affinity with D2 receptors. On the other hand, aripiprazole has a high D2 receptor affinity but rarely causes hyperprolactinaemia (5% of patients) possibly because it is a partial agonist at the D2 receptor.[6,7]

Should an MRI be performed in this setting?

The degree of hyperprolactinaemia may vary in patients receiving antipsychotic medications. In one UK study of 178 patients, 33.1% patients receiving antipsychotics had elevated prolactin levels, in whom 53% had prolactin levels below 1000 mIU/L.[6,8] However, in 19% of patients, all of whom were women, the prolactin level was above 2000 mIU/L. Most clinicians would arrange a pituitary MRI in a patient with a prolactin level more than five times the upper limit of normal.

Hyperprolactinaemia usually normalises after three to four days of cessation of the offending medication but in a patient with an unstable psychiatric state, cessation of an effective agent might not be feasible. A treating psychiatrist should always be consulted before a decision is made on withdrawal of an antipsychotic medication. A normal historical prolactin level without use of antipsychotics is reassuring and in these cases, a mildly elevated prolactin concentration in the absence of any symptoms of mass effect requires only close monitoring and obviates a need for an MRI if prolactin levels remain stable.

If a previously normal prolactin level has not been noted and the potentially offending medication must be continued, the patient should undergo a pituitary MRI. Furthermore, a full pituitary profile should be performed in these patients. If there are concerns about more widespread pituitary dysfunction or any mass effect symptoms, then an MRI is also warranted.

Outcome: In this case, careful discussion with the treating psychiatrist led to cessation of risperidone and commencement of aripiprazole with resolution of hyperprolactinaemia and return of menses.

2. Causes of drug-induced hyperprolactinaemia

Antipsychotics
- Typical: phenothiazines
- Atypical: risperidone, quetiapine, olanzapine

Prokinetic agents
- Metoclopramide, domperidone

Opioids
- Opiates, methadone, morphine, apomorphine, heroin

Anticonvulsants
- Phenytoin

Antihypertensive drugs
- Verapamil (nondihydropyridine calcium channel blocker), alpha-methyldopa, labetalol

Antidepressants
- Tricyclic antidepressants: amitriptyline, clomipramine
- Monoamine oxidase inhibitors
- Selective serotonin reuptake inhibitors: fluoxetine, citalopram, paroxetine

Others
- Oestrogens, testosterone (via aromatisation to oestrogen), anaesthetics, cimetidine, ranitidine, cocaine, marijuana, alcohol, sibutramine

Case 3

A 25-year-old woman presents with oligomenorrhoea and acne. She has a body mass index of 26 kg/m² and is otherwise well. Investigations reveal a prolactin level of 960 mIU/L (RR, 85–500 mIU/L), LH level of 12 IU/L (RR, basal: 2.0–12 IU/L; mid cycle 8.0–90 IU/L), FSH level of 3 IU/L (RR, basal 1.5–10 IU/L; mid cycle 7.0–22 IU/L), oestradiol level of 260 pmol/L (RR, follicular phase <320, preovulatory phase 150–2000, luteal phase 125–1300 pmol/L) and free androgen index 4% (RR, 0.3–4%).

What other investigations should be performed to determine the cause of hyperprolactinaemia?

The most common form of prolactin in serum (85%) is 23.5 kD in size. Macroprolactin is a term used to describe aggregates of prolactin and antibodies that range in size from about 150 to 170 kD. These complexes are less bioactive, and macroprolactinaemia should be suspected when typical symptoms of hyperprolactinaemia are absent. Many commercial assays do not detect macroprolactin and it is measured along with the common prolactin, giving an overall higher estimate of prolactin levels in an individual. An inexpensive way to detect the presence of macroprolactin in the serum is to pretreat the serum with polyethylene glycol to precipitate macroprolactin before the immunoassay for prolactin.[9]

However, macroprolactinaemia may also occur in patients with conventional symptoms of hyperprolactinaemia. These symptoms are either secondary to excess levels of monomeric prolactin (in addition to macroprolactin) or due to macroprolactin produced by a pituitary adenoma, with biological activity of macroprolactin comparable with that of monomeric prolactin. It should be regarded as a pathological biochemical variant of hyperprolactinaemia and a full work up should be carried out in symptomatic patients to identify an exact cause.

Up to 40% of patients with overt primary hypothyroidism and up to 22% of those with subclinical hypothyroidism could have mild elevation of prolactin levels. In most cases the values return to normal when the hypothyroidism is corrected. It is thought that hyperprolactinaemia in people with hypothyroidism results from increased hypothalamic synthesis of TRH.

People with Cushing's syndrome can present in a similar way to those with polycystic ovary syndrome (PCOS) and this should be screened for using a 24-hour urine free cortisol collection and/or overnight dexamethasone suppression test. Be aware that oestrogen, such as that used in the oral contraceptive pill, raises total serum cortisol levels by increasing cortisol-binding globulin and thus measurement of serum cortisol levels is not the preferred screen for Cushing's syndrome. Insulin-like growth factor-1 level should also be measured because acromegaly may also present as PCOS.

In the presence of healthy oestradiol levels and normal anterior pituitary function, it remains possible that isolated mild hyperprolactinaemia could be the result of a tiny microadenoma. In such cases, it would be reasonable to simply monitor the prolactin level, with a significant rise in prolactin level or development of mass effect symptoms then prompting further investigation with a pituitary MRI.

A detailed history, with particular attention to concurrent medications, and physical examination are important and should be the first steps in the evaluation of all patients with hyperprolactinaemia. Look for evidence of chest wall trauma and also consider stress and nipple stimulation as potential causes for a mild prolactin elevation. In these circumstances, avoidance of any stimuli should result in a normal prolactin level when checked three months later.

In a substantial number of patients whose serum prolactin concentration is under 2000 mIU/L, no cause is found (termed idiopathic hyperprolactinaemia). It may be secondary to a tiny microprolactinoma that is too small to be detected on imaging or due to hypothalamic-regulatory dysfunction. In one-third of such patients, elevated prolactin levels eventually resolve, and in one-half prolactin levels will remain stable.

Is PCOS associated with hyperprolactinaemia?

In clinical practice, it is not unusual to find hyperprolactinaemia (30%) associated with PCOS. The exact mechanism is not known but it may be due to elevated oestrogen levels, abnormal LH pulsatility or reduction in dopaminergic tone. In addition, pathological hyperprolactinaemia can mask underlying PCOS through gonadotrophic inhibition. In general, just as for patients suspected of having drug-induced hyperprolactinaemia, it should not be automatically presumed that PCOS is the cause of hyperprolactinaemia and these patients warrant a full pituitary profile, screening for macroprolactin, and pituitary imaging if there is evidence of other pituitary dysfunction or mass effect symptoms.

Outcome: This young woman was diagnosed with PCOS after excluding hypothyroidism, congenital adrenal hyperplasia and Cushing's syndrome. With diet and exercise she lost 7 kg in bodyweight with return of regular menses, reversal of clinical and biochemical hyperandrogenism and normalisation of prolactin levels.[1] **ET**

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COMPETING INTERESTS: None.