Management of Hyperprolactinaemia

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Prolactin is solely secreted by the lactotroph cells of the pituitary gland. Hyperprolactinaemia therefore either results from hyper-secretion of lactotroph cells or decreased clearance. The regulation of secretion of prolactin differs from other pituitary hormones in that it is mainly suppressive in nature by the dopamine pathway. Hyperprolactinaemia per se can cause hypogonadotropic hypogonadism and is closely related to the reproductive axis. However, the management of hyperprolactinaemia relies heavily on the underlying causes and extends beyond its biochemical correction.

The upper normal range of prolactin is usually around 500 mIU/l. Stress and nipple stimulation are known to increase prolactin production. However, stress usually leads to a mild increase of prolactin level only, and rarely exceeds 2 fold of upper normal range. The magnitude of increase by nipple stimulation relies heavily on pre-existing lactotroph hyperplasia. Prolactin level increases during pregnancy and peaks at delivery. However, it falls rapidly after delivery and normalises usually in around 6 week’s even if the mother breastfeeds. Apart from these physiological processes, hypothalamic and pituitary diseases, and drugs interfering with the dopamine pathway are the most important causes of hyperprolactinaemia. It is obvious that prolactinomas will cause an increase in prolactin. However, it is important to realise that other pituitary adenomas, pituitary and hypothalamic diseases cause increases in prolactin as well due to disruption of dopamine inhibition. Antipsychotic drugs such as haloperidol, phenothiazine and antiemetic drugs such as metoclopramide, domperidone are the two main categories of drugs which cause increases in prolactin due to dopamine receptor blockade. Verapamil and methyldopa are the two antihypertensive drugs which cause increases in prolactin. Although oestrogen in large amounts such as that occurring in pregnancy causes an increase in prolactin, contraceptive pills generally do not. Other miscellaneous causes include chronic renal failure, hypothyroidism, chest wall injury (similar to nipple stimulation), etc.

The effect of hyperprolactinaemia alone depends on the gender and age of the patients. In premenopausal women, hyperprolactinaemia causes hypogonadotropic hypogonadism through inhibition of FSH and LH secretion, the severity of which depends on the prolactin level. The clinical features can range from shortened luteal phase, to oligomenorrhoea, to amenorrhoea. Even mild hyperprolactinaemia can cause infertility even when there is no abnormality in the menstrual cycle. Overall, hyperprolactinaemia accounts for 10-20 percent of amenorrhoea and 20% of infertility. Hyperprolactinaemia also causes galactorrhoea, which is one of the common presenting features. Women with amenorrhoea due to hyperprolactinaemia have lower bone mineral density. However, it is not clear whether women with hyperprolactinaemia but without menstrual problems have lower BMD. Post-menopausal women are hypogonadal by definition and hyperprolactinaemia does not cause galactorrhoea in these women due to lack of oestrogen, though they may give a history of previous galactorrhoea. In men, hyperprolactinaemia also causes hypogonadotropic hypogonadism, which is manifested by decreased libido, impotence and infertility. Galactorrhoea is much less common compared with women. Due to less prominent clinical features of hyperprolactinaemia in post-menopausal women and men, hyperprolactinaemia due to prolactinoma, though less common in these two groups of people, is more likely to present with visual disturbances caused by the mass effect of the tumour rather than the hormonal effects.

There are two pitfalls in biochemical assessment of hyperprolactinaemia, namely the hook effect and macroprolactinaemia. The hook effect refers to the effect that when prolactin is very high, e.g. up to 100,000 mIU/l, the signal and capture antibodies are saturated and hence gives rise to a falsely low result. This can be avoided by repeating the assay with dilution. This is particularly relevant when the prolactin level is only modestly raised while MRI pituitary shows a large pituitary adenoma, and the physician needs to differentiate a true prolactinoma from raised prolactin from stalk effect. Macroprolactinaemia is the presence of “big prolactin” which has decreased clearance and hence a falsely raised level of prolactin. This can be distinguished by gel filtration or polyethylene precipitation. The prevalence of macroprolactinaemia in patients found to have hyperprolactinaemia is as high as 10%.

Prolactin should be checked when patients present with symptoms of galactorrhoea, oligomenorrhoea, amenorrhoea, infertility, impotence and known pituitary problems. The assessment should concentrate on a detailed assessment of sexual function, especially plans for pregnancy for women of reproductive age; detailed drug history, especially history of taking antiemetic and antipsychotic drugs; previous insult to the hypothalamic pituitary region such as a history of radiotherapy to the head and neck region and neurological assessment of vision. The most readily identifiable causes are a history of taking drugs...
interfering with the dopamine pathway or a history of previous radiotherapy involving the head and neck region\textsuperscript{12}. The presence of macroprolactin interfering with the assay should be excluded since further investigation is no longer necessary if it is confirmed.\textsuperscript{13} If raised prolactin is confirmed and no obvious causes can be found from history, thyroid stimulation hormone level and renal function test will be needed to exclude hypothyroidism and renal impairment causing a raised prolactin. Sex hormone assessment will be needed to assess the effect of raised prolactin on the reproductive axis. Magnetic resonance imaging of the pituitary will always be needed to look for a mass lesion in the pituitary region unless the patient is taking any drug known to increase prolactin.\textsuperscript{14} If a mass in the pituitary hypothalamic region is found, referral to an endocrinologist for further assessment and treatment will be needed. For patients with raised prolactin, no other obvious causes and normal pituitary on MRI, they are often labelled as idiopathic hyperprolactinaemia.

It is a common pitfall to label any pituitary adenoma with raised prolactin as a prolactinoma or to treat the prolactin level alone without adequate assessment. In fact, pituitary adenomas other than prolactinoma also lead to raised prolactin due to the stalk effect, interfering with the inhibitory effect of dopamine from the hypothalamus\textsuperscript{3, 14}. The differentiation relies on the fact that most prolactinomas secret prolactin proportionally, i.e. the level of prolactin is usually proportional to the size of the prolactinoma. Prolactinomas of <1cm size are usually associated with prolactin levels less than 10 fold of upper normal range, while prolactinomas of 1-2 cm size are associated with prolactin levels of around 10-50 fold of normal upper range, though there are occasional exceptions\textsuperscript{3-15}. Therefore, if a large pituitary macroadenoma(>1cm) with modestly raised prolactin is found and the hook effect has been excluded, it suggests that the tumour is not a prolactinoma. This differentiation is important because prolactinomas, even of large size, mostly respond well to pharmacological treatment; while other pituitary tumours do not. MRI assessment is mandatory since if we treat the prolactin level alone without proper assessment, there is always the chance of missing a pituitary tumour which needs surgical intervention.

The treatment of hyperprolactinaemia relies heavily on the underlying causes, natural course of the disease and the aim of treatment. Prolactinomas can be divided into microprolactinomas (<1cm) and macroprolactinomas. Studies showed that 95% of microprolactinomas do not enlarge during the first four to six year of observation\textsuperscript{16,17}. Therefore, the indication of treatment will be the relief of symptoms (galactorrhea), normalisation of menses and improvement of fertility. For women who have hyperprolactinaemia, but are not planning for pregnancy and are asymptomatic, they can just be put on observation. Those with symptomatic treatment, dopamine agonists such as bromocriptine and carbegoline are the first line treatment. More than 90% of patients respond well to treatment. However, for macroprolactinoma, there is a high chance of tumour progression; therefore treatment is almost always indicated. Again, a dopamine agonist is the first line treatment, which leads to both reduction in prolactin level, and more importantly shrinkage of the tumour.\textsuperscript{18, 20} In fact, even for macroprolactinoma patients with visual field defects, treatment with dopamine agonists leads to rapid improvement in the visual field within days, well before imaging shows a shrinkage of the tumour in the majority of patients.\textsuperscript{2,22} Transphenoidal surgery is considered when the patient does not show satisfactory response to medical treatment or tolerate medical treatment poorly. For patients with pituitary or hypothalamic diseases other than prolactinoma, the underlying causes should be treated if possible. Dopamine agonists can be used if necessary. However, it is always important to monitor such patients closely. Pituitary function also shows improvement upon biochemical normalisation, but also management of fertility, sexual function and visual problems.

In conclusion, hyperprolactinaemia needs thorough assessment and management should include not only biochemical normalisation, but also management of fertility, sexual function and visual problems.

References