HYPERPROLACTINAEMIA

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PROLACTIN

The common association of galactorrhoea with amenorrhoea or oligomenorrhoea has been recognised for centuries, but it was not until biological assays in the 50's and 60's showed that this was a pituitary hormone under tonic inhibition from the hypothalamus that further study was possible. Prolactin was distinguished from growth hormone in 1971 and sequenced in 1977. It circulates as a monomer although dimeric, polymeric and glycosylated forms exist. Its gene is on chromosome 6. Prolactin is related to the growth hormone family, all found on chromosome 17.

Prolactin's main action is on the mammary gland, where in the presence of other hormones, it can initiate and maintain lactation in men and women. During pregnancy the high circulating levels of oestrogen and progesterone inhibit lactation, and of course the concentrations of these hormones fall dramatically after delivery with obvious results. In the hypothalamus, physiological or pathological hyperprolactinaemia inhibits the pulsatile release of Leutinising Hormone Releasing Hormone (LHRH) causing inhibition of gonadal function. These two functions account for the clinical syndrome of amenorrhoea/galactorrhoea. There are prolactin receptors in many other tissues, whose function is largely unknown.

The dominant control mechanism for prolactin is tonic inhibition by dopamine from the hypothalamus. However, there is a close relationship with the thyroid axis as thyrotrophin releasing hormone (TRH) also stimulates prolactin. Furthermore, hypothyroid patients may have hyperprolactinaemia and even galactorrhoea which resolves with thyroxine treatment (see below).

CAUSES OF HYPERPROLACTINAEMIA

Prolactin is a stress hormone and will therefore rise in response to pain, and to psychological and other stresses. Thus, the first thing to do when mild hyperprolactinaemia is found is to repeat the test in relaxed surroundings. A number of other conditions should also be quickly excluded, including pregnancy and primary hypothyroidism. After drugs have been excluded, most of the other causes relate to altered dopaminergic control of the pituitary and pituitary disease. An abbreviated list of causes of hyperprolactinaemia is given in Table 1.

PROBLEMS RELATED TO HYPERPROLACTINAEMIA

Once pregnancy, drugs and hypothyroidism have been excluded, a few women will have the hyperprolactinaemic

Physiological

Pregnancy

Lactation, nipple stimulation

Sleep

Exercise

Stress

Drugs

Dopamine blockers (neuroleptics, metoclopramide, domperidone, sulpiride)

Methyldopa, carbidopa, benserazide

Tricyclic antidepressants

Reserpine

Opiates

Verapamil

Some herbal remedies

Oestrogens, TRH, VIP

Other diseases

Primary hypothyroidism

Chronic renal failure

Cirrhosis

Polycystic ovarian syndrome (PCOS)

Hypothalamic Disease

eg: tumours, infiltrations (sarcoidosis, TB, etc), AV malformations, irradiation

Pituitary stalk transection /compression

Pituitary disease

Micro- and macro-prolactinoma

Other hormone-secreting adenomas, co-secreting prolactin

Macro-adenomas and other pituitary lesions preventing dopamine delivery to lactotrophes. Some (eg craniopharyngiomas) may occur at hypothalamic or stalk level.

Table 1 - Causes of hyperprolactinaemia (common conditions in **bold**)

variant of polycystic ovarian syndrome (PCOS) and most of the rest will have prolactinomas. Most prolactinomas will be micro-lesions occurring in women. A much smaller number will have macro-prolactinomas or other pituitary macro-lesions interfering with dopamine delivery. For prolactinomas, the usual problems to deal with are galactorrhoea, hypogonadism resulting in infertility and hypogonadism potentially leading to osteoporosis. Loss of libido may occur (often complained of by the partner), and in men impotence may be a problem. Macro-prolactinomas are commoner in men. Here the size of the pituitary lesion is of prime importance and consideration should be given to visual field loss, ophthalmoplegia and other hormone deficiencies. It is also important to distinguish a macroprolactinoma from a non-functioning tumour with secondary hyperprolactinaemia because the first will probably shrink with medical therapy whilst the second will not.

DIAGNOSIS

We therefore have to differentiate between macro-prolactinomas, other pituitary or parapituitary mass lesions,

microprolactinomas and non-pituitary disease. We also need to define clearly which patients can safely have pituitary imaging omitted to save on this scarce resource.

Once drugs have been excluded, screening tests guided by the clinical picture should be undertaken (Table 2). LH and FSH assays are useful in postmenopausal women to exclude pituitary failure (low), whilst in a young woman a high LH:FSH ratio might suggest the hyperprolactinaemic variant of PCOS. The prolactin level should be repeated in a relaxed environment. We have previously found many cases of hyperprolactinaemia return to normal during the course of investigation (13% in a consecutive series of 100 cases from Aberdeen)⁽¹⁾.

Initial tests

Repeat prolactin value
Pregnancy test (young women)
TSH (with free T₄ and T₃ when not markedly elevated)
Renal function
Liver function
LH and FSH in women
Testosterone/17 β -oestradiol

Further tests (not always required)

Domperidone testing
CT (or preferably MRI) pituitary scanning
Endocrine assessment of other pituitary function
Visual field testing

Table 2 – Tests in the investigation of hyperprolactinaemia

Basal prolactin concentration is of considerable diagnostic value for pituitary **macrolesions**. When the basal prolactin concentration is >5000mU/l, the lesion is highly likely to be a macroprolactinoma and if >6000mU/l certainty is virtually assured. In the range 2500–6000mU/l there is approximately a 50% chance of the lesion not being a prolactinoma, whilst very few macro-prolactinomas will have a prolactin <2000mU/l^(2,3), although occasionally this will happen⁽¹⁾. Conversely macrolesions that are not prolactinomas will usually have low grade hyper-prolactinaemia (<2000mU/l). Therefore the basal prolactin value cannot be used to avoid pituitary imaging⁽⁴⁾. Most microprolactinomas have basal prolactin values between 1000 and 5000 mU/l, although some will be lower.

Dynamic function tests are being reassessed. The most commonly used test is the TRH test, but this has not proved to be sufficiently discriminatory. I currently use the *domperidone test*^(3,4). Domperidone is a potent D₂ antagonist which does not cross the blood/brain barrier. It therefore acts directly on the median eminence and pituitary gland without the risk of dystonic reactions occasionally seen with metoclopramide. Originally it was thought that, by measuring concurrently the prolactin and TSH (which is also under dopamine inhibition) response to domperidone, physiological hyperprolactinaemia could be separated from microprolactinomas which in turn could be distinguished from “disconnection” hyperprolactinaemia. Theoretically, a normal response is represented by a large rise in prolactin with little TSH response; a microprolactinoma has autonomous prolactin production with a blunted response but shows an exaggerated TSH response because of chronic dopamine exposure; and “disconnection” hyperprolactinaemia shows a blunted response of both prolactin and TSH because dopamine cannot reach the appropriate pituitary cells. The test was validated with histological proof of final diagnosis.

Unfortunately results are rarely as clear cut as the theory. The domperidone test is unable to distinguish different forms of macrolesion in the pituitary. In particular it does not help to distinguish between macroprolactinomas and other tumours with a basal prolactin range of 2000–5000 mU/l. Furthermore, occasional patients with macro-lesions have an exaggerated TSH response to domperidone so that the typical microprolactinoma response pattern described above cannot avoid pituitary imaging⁽¹⁾. However, a normal **prolactin** response to domperidone does not need scanning on the basis of our results, which would have reduced the number of MRI scans requested by 24% in this series. This proposal⁽¹⁾ modifies that of Stewart et al⁽⁴⁾, who suggested that all women with persistent hyperprolactinaemia >1000mU/l would need scanning. The test is also useful in patients with a normal or near normal MRI scan. In this situation, a microprolactinoma response pattern to domperidone (exaggerated TSH with blunted prolactin) assists management.

Assessment of adrenal and thyroid axis reserve and visual field testing should be considered with any macro-lesion.

TREATMENT

Between eighty-five and ninety percent of macroprolactinomas will shrink significantly with dopamine agonist therapy⁽⁷⁾. Some, however, do not. Most of the shrinkage occurs in the first few weeks or months, but occasionally slow responders are found that may take six months or more to reduce in size. The important thing is to determine which of these tumours are likely to shrink and which are not. It is therefore worth considering an acute response test to bromocriptine in macrolesions, especially if visual fields are threatened. The acute response test will not distinguish macroprolactinomas from non-prolactinoma macro-lesions. If there is no prolactin response to bromocriptine, the lesion will be a non-shrinking macroprolactinoma. This result would enable a rapid decision to move to surgical treatment. Unfortunately many non-shrinking prolactinomas still reduce prolactin secretion on bromocriptine. In other cases, a trial of therapy with monitoring of visual fields and repeat scanning may be more appropriate. If no response is obtained, surgery with radiotherapy should be considered. Occasionally complications can occur with medical therapy: for example, when a macroprolactinoma has invaded the nasal sinuses rapid shrinkage may cause CSF rhinorrhoea. Macroprolactinomas can rarely escape control and start to enlarge again even during therapy. Follow-up is always required.

Microprolactinomas rarely enlarge, even when stimulated by oestrogens. Therapy should be aimed at the clinical problem. Where galactorrhoea and/or fertility are the problem, dopamine agonist therapy should be given. It is essential to warn the woman that fertility may return very quickly, often preceding menstruation so that contraceptive measures should be used where appropriate. If treatment is aimed at preventing osteoporosis rather than fertility or galactorrhoea, oestrogen replacement therapy until the woman is within the postmenopausal age group with careful follow-up for pituitary expansion is an alternative approach. There is continuing debate as to whether hyperprolactinaemia itself can cause osteoporosis. In men, only a small proportion of patients fully regain adequate testosterone levels, so that testosterone replacement therapy should be considered.

The most widely used dopamine agonist is bromocriptine, although this is often poorly tolerated. It should be gradually introduced with food at night. Multiple daily doses are required, which means that compliance may be a problem. The much longer-acting drug cabergoline is better tolerated, only needs to be taken once or twice a week and may be more effective⁽⁸⁾. The drug, however, has not been in use for long enough for us to be confident of its safety in pregnancy, whereas bromocriptine is known to be safe. I am not currently aware of any problems with cabergoline in this respect and experience is rapidly accumulating.

When a prolactinoma fails to respond to one of these ergopeptine drugs, it may be worth trying an ergoline compound, such as pergolide or quinagolide, instead.

PATIENT SUPPORT GROUP AND INFORMATION

Recently a patient support group called Pit Pat has been formed by the Pituitary Foundation for patients with pituitary disorders. Leaflets on the pituitary gland, prolactinoma, Cushing's, acromegaly, diabetes insipidus and pituitary replacement therapy are available. All the leaflets have been written by specialists in the field with the patient in mind. They can be obtained by writing to

The Pituitary Foundation
17/18 The Courtyard
Woodlands
Almondsbury
BRISTOL
BS12 4NQ
Tel: 01454 201612
Fax: 01454 616071

Please state your name and address, whether you are a patient, friend or relative, GP, specialist, nurse or other role, and which leaflet you are particularly interested in. The Pituitary Foundation is a registered charity, entirely funded by voluntary donations and sponsorship. They state on their literature "Contributions are welcome, but are not a condition of membership".

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