Regular Review

Prolactinomas

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The discovery of prolactin as a human hormone in 1970 transformed our understanding of pituitary tumours. Using radioimmunoassay, early workers were able to show that the serum prolactin activity was raised in many patients with pituitary tumours: some 60-70% of tumours previously considered to be functionless were found to be associated with hyperprolactinaemia.¹

Prolactin is under predominantly inhibitory control by the hypothalamus, dopamine being released from nerve terminals in the median eminence into the portal capillary blood of the pituitary stalk under basal conditions and tonically inhibiting the lactotrophs secreting prolactin. This in turn implies that any lesion interfering with or disrupting the pituitary stalk or portal vasculature will modify this inhibition, and may give rise to hyperprolactinaemia. Similarly, drugs that interfere with dopaminergic function, such as many major tranquilisers and metoclopramide, which are dopamine receptor blocking drugs, or reserpine and methyl dopa, which deplete the brain of dopamine, may also cause hyperprolactinaemia—as may hypothyroidism and renal failure.²

The term "prolactinoma" is used to describe a pituitary tumour that secretes prolactin; this may be identified by direct immunostaining of such tumours with specific anti-prolactin antiserum.³ With most prolactinomas the main clinical problems due to the tumour are secondary to the raised serum prolactin activity, which usually causes menstrual disturbances (amenorrhoea, oligomenorrhoea, or cycles with a deficient luteal phase) and sometimes galactorrhoea (in 30-80% of cases, depending on the enthusiasm with which it is sought). About one fifth of women with amenorrhoea have hyperprolactinaemia and the same proportions are found in the other types of menstrual disorder.² Prolactinomas are less common in men, in whom the hyperprolactinaemia causes decreased libido as well as impotence.

Prolactinomas in women are not rare, but almost all are less than 1 cm diameter and are referred to as microadenomas. Asymmetry or small "blisters" of the pituitary fossa may frequently be seen in good quality plain skull radiographs in such patients, though such minor changes of the fossa are not always pathological.⁴ More recently, high resolution computed tomography with high doses of intravenous contrast and detailed reconstructions of the pituitary and hypothalamus in sagittal and coronal planes have shown small tumours in most patients with hyperprolactinaemia and normal skull radiographs.⁵ Again, it has been suggested that some of the apparent abnormalities within the pituitary seen on such scans are not necessarily pathological and may represent small cysts, areas of necrosis, or artefacts.^{6,7} Nevertheless, persistently high serum prolactin activity in a patient with an

abnormal high resolution computed tomogram is strongly suggestive of a prolactinoma. No dynamic test of prolactin secretion (with thyroid releasing hormone, metoclopramide, domperidone, nomifensine) has been shown to provide more information than can be obtained from several random prolactin samples, since patients with prolactinomas do not invariably show the characteristic absence of a prolactin response in the tests. Furthermore, the results do not affect management. Most patients with average basal prolactin activities of over 2000 mU/l prove to have pituitary tumours with cells that stain immunologically for prolactin; but lower values are not uncommon with such tumours, while raised activities may sometimes be seen, even up to values of over 2000 mU/l, when the pituitary tumour is functionless (R Ross *et al*, abstract 1863, seventh international congress of endocrinology, Quebec City, 1984). These tumours, which may be called "pseudoprolactinomas" after the suggestion by R Randall, of the Mayo Clinic, apparently cause hyperprolactinaemia because the presence of the tumour mass obstructs the capillary vessels in the pituitary stalk and so blocks the delivery of hypothalamic dopamine; as a result the normal pituitary lactotrophs then secrete excess prolactin. Non-pituitary tumours such as craniopharyngiomas, germinomas, or meningiomas may also distort the pituitary stalk or median eminence and thus present as pseudoprolactinomas.⁸

Are prolactinomas becoming more common? Serum levels of prolactin have been measurable routinely only for the past decade, and most prolactinomas are so small that they do not cause either local problems (headache, field defects) or hypopituitarism. Several eponymous syndromes described in the past such as the Chiari-Frommel, Forbes-Albright, Argonz del Castillo syndromes were merely different manifestations of prolactinomas. Possibly the incidence of prolactinomas may have been increased by the use of oral contraceptives containing oestrogen as oestrogens cause hypertrophy of the lactotrophs during pregnancy⁹ and may stimulate the size and secretion of some prolactinomas.¹⁰ Microadenomas are frequently found at routine necropsy³; most must be subclinical and presumably without clinical significance unless stimulated to grow, perhaps by oestrogen. Yet, though high doses of oestrogen undoubtedly have a stimulant effect, there is little evidence that the low dose used in contemporary oral contraceptives can produce tumours¹¹; a recent survey of 230 healthy women attending a family planning clinic showed that the distribution profile of serum prolactin activities was identical in those using oral contraceptives and in non-users.¹² Nevertheless, oestrogens should never be given to a woman with undiagnosed menstrual

irregularity unless she has been shown to have a normal serum prolactin activity; but, on the other hand, if hyperprolactinaemia is controlled with bromocriptine a combination oral contraceptive may be prescribed so long as the serum prolactin activity is monitored.¹³

Treatment

Most prolactinomas retain their dopamine receptors, and the serum prolactin activity may be lowered to within the normal range in almost every case with a dopamine receptor agonist. The prototype drug is the semisynthetic ergot derivative bromocriptine; its side effects may almost always be avoided if it is given in the middle of meals in slowly rising doses to a usual maintenance dose of 2.5 mg twice or three times daily. Newer ergot derivatives differ in being more potent; lisuride is shorter acting than bromocriptine,¹⁴ and pergolide¹⁵ and possibly mesulergine¹⁶ are longer acting. The use of pergolide and mesulergine allows treatment once daily; the side effects appear similar, since they are more a function of innate dopamine agonist action and the rate of increase of dosage than of any specific preparation. Occasionally, a patient intolerant of one drug may be more tolerant of another so that a choice of agents is useful¹⁶—and these newer agents should be substantially cheaper to market than the expensive bromocriptine.

Restoration to normal of the serum prolactin activity by treatment with any dopamine receptor agonist rapidly restores normal gonadal function in either sex. Menstruation becomes regular and ovulatory in most patients, and galactorrhoea is inhibited, independently of the length of the history of amenorrhoea. Fertility is restored rapidly, and conception is usually achieved if it is wanted. Normally we would advise the patient to establish regular menstruation over some three months while using mechanical contraception before attempting conception and to use a sensitive pregnancy test to establish conception a few days after the first missed period. Bromocriptine should then be stopped. Conceptions thus achieved seem to have normal rates of multiple birth, miscarriage, and fetal malformation.¹⁷ Usually treatment with bromocriptine need not be continued once conception has been established, and it is not our practice to do so routinely, but in some other units continuation of bromocriptine throughout pregnancy seems also to be free of complications.

For most patients with small prolactinomas (microadenomas) the first line treatment is a dopamine agonist alone. There is a theoretical risk that such tumours may enlarge during pregnancy under stimulation by oestrogens but the risk has probably been overestimated and is less than 5%. Cautious physicians, however, would probably wish to monitor such patients during pregnancy for symptoms (headache) and signs (visual field defects) of expansion of the tumour. Transsphenoidal surgery should be offered to those patients persistently intolerant of or insensitive to treatment with dopamine agonists. Such surgical ablation of small tumours is variably successful in lowering prolactin activities to normal, however; the best results show only 80-85% success rates.¹⁸ Furthermore, the recurrence rate is as high as 50% by five years in those patients whose prolactin activity returns to normal in the immediate post-operative period.¹⁹

More problematic is the management of the smaller group of women with prolactinomas over 1 cm diameter, referred to as macroadenomas, or with smaller tumours with a high

secretory capacity or aggressive history. While the risk of complications from the tumour during pregnancy may not be as high as the 25% once suggested,^{20, 21} they undoubtedly occur sufficiently often to influence management. One approach has been to offer these patients prophylactic transsphenoidal surgery. Unfortunately, these operations are even less successful than in small tumours and only infrequently does the serum prolactin activity return to normal. The success rate is especially low in patients with serum prolactin activities above 2000 mU/l.^{18, 19} Even if normal activities are achieved by surgery initially, hyperprolactinaemia seems to recur within five years in most patients with macroadenomas.¹⁹ Some authorities advise no ablative treatment before conception and would treat any complications from the tumour that arise during pregnancy with bromocriptine to shrink the mass of the lesion.²² An alternative stratagem is to treat these more aggressive tumours with prophylactic radiotherapy, most often by external beam megavoltage radiotherapy using a linear accelerator. In a recent survey of the latter technique, no complications occurred from the tumour in pregnancy and later the serum prolactin activity progressively fell in 26 of the 27 patients when off all treatment.²³ The reduction in prolactin activity in response to radiotherapy is, however, slow so that interim treatment is needed with a dopamine agonist. In this series, the incidence of hypopituitarism was low, and serum prolactin activities were returned to normal in about one third of these patients when they were assessed one to 11 years (mean four years) after treatment. In combination with medical treatment, radiotherapy gave an apparent ovulation rate of 97% and a successful conception rate of 86%. For the megavoltage to be safe, however, it is essential to use low dose fractions (less than 180 cGy (rads)/day), multiple fields, a maximum dose of 4500 cGy from a linear accelerator, and the head must be immobilised by an individually made skin tight plastic cassette fully enclosing the head.

Although the clinical course of prolactinomas is not well documented, in the absence of treatment most tumours seem to remain static, some progress, and a few apparently disappear, often after pregnancy.^{1, 24} Large tumours often recur even if operated on unless radiotherapy is given.²⁵ The evidence is now unequivocal that bromocriptine and related drugs can actually shrink most prolactinomas concomitant with the fall in serum prolactin activity.²⁶⁻²⁸ The lactotrophs lose their hormone packed cytoplasm and appear quiescent.²⁹ This effect may occur remarkably quickly, leading to a disappearance of visual field defects in patients whose tumours have large suprasellar extensions, improvement often starting within a few days. Most studies, however, have shown a rise in the serum prolactin and re-expansion of the tumour mass once bromocriptine has been stopped.^{30, 31} Radiotherapy given once the tumour has shrunk back into the fossa prevents this re-expansion.

Truly functionless tumours rarely appear to shrink with bromocriptine.³² Nevertheless, it may be reasonable to attempt to shrink any large pituitary tumour associated with hyperprolactinaemia by treatment with a dopamine agonist, while carefully monitoring the patient's condition, particularly if she has a suprasellar extension or a field defect. Considerable shrinkage is seen in at least two thirds of prolactinomas, and if compression of the optic chiasma resolves external radiotherapy should be given as definitive treatment to prevent tumour "escape."³³ If the tumour fails to shrink adequately within three months our policy is then to refer the patient for surgery—transsphenoidal if possible for patients with small or moderate extrasellar extensions, while large

extensions require transfrontal decompression. Postoperative radiotherapy is then necessary to reduce the probability of recurrence.²⁵

In patients with smaller prolactinomas one view has been that the benign clinical course of the condition dictates that bromocriptine should be used only for severe symptoms—for example, amenorrhoea or infertility. Yet hyperprolactinaemia is almost always associated with some dyspareunia or impaired libido and there is a risk of the development of osteoporosis^{34,35}; so there are few patients in whom treatment is not indicated. Perhaps the exception are women who menstruate at least every other month and are without symptoms.

More men than women with prolactinomas present with local problems due to the mass of tumour and such tumours are usually large. Changes in libido and potency due to hyperprolactinaemia respond to bromocriptine unless there is associated deficiency of gonadotrophin, in which case additional replacement treatment with androgens is necessary. One suggestion has been that the rarity of small prolactinomas in men is due to the infrequent referral of men

complaining of erectile failure for endocrine screening, though there are few data to support this contention.³⁶

What of the future? Many more dopamine agonists seem likely to be developed, and the side effects of the newer agents may possibly be dissociated from their ability to suppress prolactin. Other drugs which theoretically should aid in prolactin suppression, such as γ -aminobutyric acid receptor agonists or oestrogen antagonists, have not given particularly promising results. There is now good evidence, however, that part of the hypogonadism secondary to hyperprolactinaemia is mediated by increased hypothalamic opiate tone, which inhibits the normal pulsatile secretion of gonadotrophins,³⁷⁻³⁹ and in the future patients intolerant of dopamine receptor agonists may possibly be treated with opiate antagonists active by mouth.

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