DILEMMAS IN THE MANAGEMENT OF PROLACTIN EXCESS

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These cases from the Department for Endocrine and Metabolic Diseases at the Western General Hospital, Edinburgh, are presented with the kind permission and support of Professor C.R.W. Edwards and Dr. P.L. Padfield.
"If a woman who is neither pregnant, nor has given birth, produces milk, then her periods will have stopped."

- Hippocrates, circa 420 B.C. Aphorisms, Book Five, 39.

It is perhaps remarkable that we have only recently known of the existence of prolactin in man, despite the fact that Hippocrates commented on the relationship between milk secretion and gonadal function. The advent of readily available radioimmunoassay for prolactin has resulted in the increasing recognition of patients with prolactin excess. Hyperprolactinaemia is now a common clinical problem, and may be found in as many as 30% of women who present with amenorrhoea. Despite its common occurrence, many aspects of the investigation and management of hyperprolactinaemia remain controversial.

In women, hyperprolactinaemia usually presents clinically with amenorrhoea, oligomenorrhoea, or infertility. Galactorrhoea, and symptoms of oestrogen deficiency, may also be prominent. In men, hyperprolactinaemia is associated with loss of libido and impotence. Patients whose hyperprolactinaemia is due to large pituitary adenomas may present with local effects of expansion of the tumour, such as headache, visual disturbance due to pressure on the optic chiasma, or hypopituitarism. Less commonly, large tumours may cause hydrocephalus by occlusion of the foramen of Monro, hemiplegia or epilepsy, or may erode into the sphenoid sinus, producing CSF rhinorrhoea. Pituitary apoplexy, due to haemorrhage or infarction in a pituitary tumour, may present with headache, impairment of vision or consciousness, and meningism.

Hyperprolactinaemia may be caused by drugs, most notably dopamine receptor antagonists such as phenothiazines and metoclopramide, dopamine depleting agents such as methyldopa and reserpine, and oestrogen preparations. Primary hypothyroidism, chronic renal failure, and polycystic ovarian syndrome may also be associated with elevated levels of prolactin. After drugs are excluded, however, pituitary or
hypothalamic disease is the most frequent cause of prolactin excess. It may result from secretion of prolactin by pituitary tumours, whether primary prolactin-secreting tumours (prolactinomas) or other pituitary tumours which contain some prolactin secreting cells, as in some cases of acromegaly. Any pituitary adenoma, or other lesion in the hypothalamus, such as craniopharyngioma, may disturb the dopamine-mediated hypothalamic inhibition of prolactin secretion, and so cause hyperprolactinaemia.

At least 40% of the large pituitary adenomas which were previously described as non-functioning, have been shown to secrete prolactin. At the other end of the scale there are patients in whom there is great difficulty in distinguishing between functional hyperprolactinaemia, and small prolactinomas. Sophisticated imaging techniques, such as computerised tomography (CT) and nuclear magnetic resonance (NMR) are able to demonstrate small adenomas in some of these patients, although at the limit of resolution, low-density artefacts present a major problem in the interpretation of CT scans. As NMR scanning becomes more widely available it is possible that more patients with "functional" hyperprolactinaemia will be shown to have small adenomas.

There are three potentially effective forms of treatment for prolactinomas: surgery, radiotherapy, and medical treatment with dopamine agonists such as bromocriptine, pergolide, or lysuride. Surgery can be performed by the trans-sphenoidal, trans-ethmoidal, or intracranial approaches. The trans-sphenoidal operation, as used sixty years ago by Cushing, has now been repopularised and is widely used. The intracranial approach is still used by some neurosurgeons to deal with adenomas with suprasellar extension, but these tumours can often be decompressed satisfactorily by the trans-sphenoidal route. However, the rate of long term cure of microprolactinomas by trans-sphenoidal surgery alone remains disappointing, and the results of surgery for macroprolactinomas are worse.

Radiotherapy is a well established means of treating pituitary tumours. It is
not immediately effective in controlling hormone secretion, although it reliably prevents further tumour growth. Only recently has there been published data regarding its effectiveness in the treatment of microprolactinomas. There is an appreciable incidence of hypopituitarism, often developing several years after radiotherapy, and this risk cannot be ignored, especially in young people. The best treatment for a patient with a prolactinoma, whether large or small, therefore remains controversial. In addition, as the natural history of functional hyperprolactinaemia and microprolactinoma remains imperfectly understood, it is not yet clear whether definitive treatment is necessary in a patient who no longer desires fertility and is asymptomatic.

Four cases are presented which illustrate these problems in the management of prolactinoma. These patients were seen during an eight month period at the Metabolic Unit, Western General Hospital.
Case 1

A thirty-seven year old woman presented with a history of severe headaches since the birth of her second child, seven years previously. Two years previously she had complained of tiredness, hot flushes, and dizziness. She was discovered to be hypothyroid, with a low plasma thyroxine and free thyroxine index. Plasma thyroid stimulating hormone (TSH) was undetectable at that time, indicating hypothyroidism secondary to pituitary or hypothalamic disease, but this was not investigated further. She was commenced on thyroxine (50 micrograms daily) with some improvement in her general condition. She continued to have severe bifrontal and occipital headaches, and three months later her periods stopped. There had been no previous history of menstrual irregularity.

She was referred to Edinburgh because of persistence of severe headaches. Clinical examination was normal apart from bilateral galactorrhoea. Plain skull radiographs were normal, but a high definition CT scan of the pituitary fossa demonstrated a low density lesion within the fossa, with upward distension of the diaphragma sellae, consistent with a partially cystic adenoma.

Basal prolactin was elevated at 3,725 mU/l (reference range 60 - 380 mU/l). Standard combined pituitary function testing was performed, with intravenous injection of 0.1 units of soluble insulin per kilogram body weight, 0.2 mg of thyrotrophin releasing hormone (TRH), and 50 micrograms of gonadotrophin releasing hormone (GnRH). No change occurred in growth hormone (GH) or TSH levels and gonadotrophin responses were subnormal. Prolactin rose from 2,644 mU/l to 3,888 mU/l.

On the basis of these results, a diagnosis of prolactinoma with secondary panhypopituitarism was made, and she was commenced on treatment with hydrocortisone. Bromocriptine was started, building up gradually to a dose of 7.5 mg daily.

On bromocriptine, serum prolactin fell to undetectable levels.

Two months later, she was readmitted for review. There had been a dramatic improvement in her headaches, which were occurring much less frequently. Her appetite had improved, and she had regained weight, but her periods had not
returned. Prolactin levels remained undetectable on bromocriptine. Visual fields were mapped and found to be completely normal. A second CT scan was of technically poor quality. Positive contrast cisternography was performed, and although the diaphragma sellae appeared to bulge slightly upward, there was no substantial filling defect within the basal cisterns to indicate the presence of suprasellar tumour. Contrast did not enter the fossa, excluding the development of an empty sella syndrome.

This woman had therefore experienced an excellent symptomatic response to bromocriptine. The initial CT scan, and the failure of the lesion to shrink significantly with bromocriptine treatment, suggested that the tumour had a large cystic component. It was felt for this reason that trans-sphenoidal surgery might not be successful at removing all of the tumour tissue. The alternatives were therefore to continue bromocriptine treatment indefinitely, or to advise treatment with radiotherapy, with continuation of bromocriptine until prolactin levels were suppressed. It was decided to continue bromocriptine, and undertake elective radiotherapy.
A thirty year old woman had presented with infertility three years earlier. She had undergone a normal menarche at the age of fifteen, but thereafter her periods had been irregular. The only abnormality detected was an elevated prolactin at 1,670 mU/l. She was commenced on treatment with bromocriptine, and became pregnant within a few weeks, with no intervening menstrual period. Her bromocriptine was withdrawn, and the pregnancy continued satisfactorily, although she suffered from severe headaches. She had a normal delivery, and gave birth to a healthy daughter.

Following her pregnancy she used an intrauterine device for contraception, and normal menstruation did not return. She noticed galactorrhoea on nipple stimulation. The intrauterine device was subsequently removed, and she again failed to conceive, and was referred to the endocrine clinic for that reason. Galactorrhoea was confirmed clinically, and her optic fundi and visual fields were normal. Basal prolactin was 1,469 mU/l. Combined anterior pituitary function testing was completely normal. Prolactin rose only from 917 mU/l to 1305 mU/l. Normal individuals show an elevation of prolactin by at least 100% in response to TRH, and a subnormal response in a patient with an elevated basal level is thought to indicate a prolactinoma, rather than functional hyperprolactinaemia. This hypothesis is examined further in the discussion below.

A high definition CT scan of the pituitary fossa demonstrated a normal sized pituitary gland, with a convex upper margin on the left side. A small area of low density was seen within the gland, measuring about 3.6 mm in diameter. These appearances were considered to be compatible with a microadenoma.

Treatment with bromocriptine resulted in prolactin falling to undetectable levels, and pregnancy followed within two months. Her past history of headaches during pregnancy was suggestive of expansion of the pituitary tumour, and bromocriptine was therefore continued throughout the present pregnancy.

Headaches recurred at 4-5 months, but had disappeared by 7 months. Close monitoring of her visual fields has revealed no abnormality, and prolactin levels remain suppressed. At the time of writing her pregnancy continues satisfactorily.
Case 3

A thirty-five year old man, who had been deaf and dumb since birth, presented with sudden onset of severe headache and drowsiness. Subarachnoid haemorrhage was excluded by lumbar puncture, but subsequently he developed a left sided oculomotor nerve palsy. A tentative diagnosis of posterior communicating artery aneurysm was made, and he was transferred to the Department of Surgical Neurology for further investigation. Cerebral angiography showed no vascular abnormalities, but marked enlargement of the pituitary fossa was discovered. A high definition CT scan demonstrated an enhancing pituitary tumour, eroding the walls of the fossa, and extending into the suprasellar region in the midline. Positive contrast cisternography confirmed that there was suprasellar extension.

His symptoms thereafter improved spontaneously, and the third nerve palsy recovered over the course of a few days. He was able to give a history of predominantly left sided headaches for about eight years. There were no symptoms of hypothyroidism or diabetes insipidus. Although his sexual function was apparently normal, he appeared clinically hypogonadal. His body hair was sparse, there was no gynaecomastia or galactorrhoea, and his testes were normal in volume, though rather soft in consistency. Optic fundi and visual fields were normal. Basal plasma cortisol was low at 131 nmol/l, rising subnormally to 499 nmol/l after intramuscular Synacthen. Plasma thyroxine was 56 nmol/l, with a low free thyroxine index at 33. An initial prolactin assay indicated a marked elevation, in excess of 4,000 mU/l. He was therefore commenced on hydrocortisone and thyroxine, with a provisional diagnosis of pituitary apoplexy due to partial infarction or haemorrhage in a large prolactinoma, with secondary hypopituitarism.

He remained well, and elective investigation was carried out some weeks later. Visual fields and acuity had remained normal. Basal serum prolactin was in excess of 33,000 mU/l. Serum testosterone was low at 6.3 nmol/l. Combined pituitary function testing revealed normal adrenocorticotropic hormone (ACTH) reserve, as cortisol rose from 403 nmol/l to 670 nmol/l, but deficiency of GH and GnRH.

The elevated prolactin level confirmed that the adenoma was still active,
and the patient was commenced on treatment with bromocriptine, slowly increasing to 15 mg daily. Hydrocortisone and thyroxine were withdrawn. He remained well, and further investigation was undertaken two months later. Visual fields and acuity remained normal. Plasma thyroxine was 62 nmol/l, with a free thyroxine index just below the normal range at 56. Basal cortisol remained adequate at 359 nmol/l. A further high definition CT scan of the pituitary fossa showed a considerable reduction in the mass of the tumour. There was no longer any suprasellar extension on the left side, and the upper surface of the tumour now had a concave appearance. The prolactin level was much lower, but still considerably above normal at 7,000 mU/l. Bromocriptine treatment was therefore continued, and the dosage increased gradually to 22.5 mg daily. In order to provide long term suppression of the prolactinoma, a three week course of 4 MeV pituitary radiotherapy was arranged. This was carried out with minimal side effects, and the patient remains well. In view of his persisting low testosterone levels, (although surprisingly he continued to claim that his sexual function was normal) he was commenced on monthly injections of testosterone depot.
Case 4

A fifty-nine year old man presented with deteriorating vision, affecting especially the left eye, for about nine months, with more rapid deterioration over the three weeks before presentation. He could perceive no more than finer movements with the left eye, and the acuity of the right eye was 6/36. Clinical assessment of his visual fields indicated complete loss of peripheral vision in the left eye. The optic fundi were normal.

He had noticed a decrease in body hair over a period of some years, and had been impotent for four years. On examination he had pale skin, scanty pubic hair, and almost no axillary hair. His testes were normal in volume, but soft in consistency.

A plain skull radiograph showed considerable enlargement of the pituitary fossa. Combined CT scanning and positive contrast cisternography demonstrated a large pituitary adenoma with marked suprasellar extension, and a small cystic component was noted within the lesion.

Basal plasma cortisol was undetectable on two occasions, indicating ACTH deficiency, and he was commenced on hydrocortisone, and all further invasive investigations were performed under steroid cover. Thyroxine was also low at 39 nmol/l, and thyroxine replacement was commenced.

Assessment of visual fields by Goldmann perimetry showed a small central field, to white light only, on the left. On the right, there was a normal field to white light, but with red light, a temporal hemianopia was revealed.

Early neurosurgical intervention was planned to preserve his remaining vision, and hopefully to restore some of the loss. However, a preliminary report on the prolactin assay indicated that it was very high, and a trial of bromocriptine treatment was undertaken, with prompt recourse to surgery available in the event of further visual impairment. He was started on bromocriptine, initially in a dose of 2.5 mg at night, increasing to 15 mg daily over the next four days. Visual fields were mapped daily, and revealed a dramatic improvement in both eyes. By/
By the fourth day of treatment, the visual field to white light in the left eye had expanded considerably, and a small field to red light was detectable in the superior temporal quadrant. Expansion of the fields continued daily, with a concomitant improvement in acuity, and on the tenth day, the only remaining defect in the left eye was a central scotoma and inferior temporal quadrant anopia detectable with red light only. The visual field of the right eye became completely normal to both white and red light. After one month of treatment with bromocriptine, the visual field of the left eye was also completely normal, with an acuity of 6/18.

The improvement in his vision obviated the urgent need for surgery. Treatment with bromocriptine, hydrocortisone, and thyroxine was continued. The initial serum prolactin was found to be grossly elevated at 57,100 mU/l. His serum testosterone was low at 3.9 nmol/l, and he was therefore given monthly injections of testosterone depot. His serum prolactin fell to 5,950 mU/l after two weeks of treatment with bromocriptine, and was 2010 mU/l after one month.

He was thereafter followed closely, with monthly assessment of visual fields and measurement of prolactin. His visual fields remained full, but after three months his serum prolactin had risen to 4,500 mU/l, and bromocriptine was therefore increased from 15 mg to 20 mg daily. Positive contrast cisternography was repeated, and showed no evidence of suprasellar extension. He remained well, and serum prolactin fell to 1,563 mU/l.

Nine months after his initial presentation, he received a fifteen day course of 4 MeV pituitary radiotherapy to achieve long-term suppression of the tumour. Thereafter his bromocriptine was reduced to 7.5 mg daily, with a resultant rise in serum prolactin levels to 2,610 mU/l. Visual fields remained normal. A CT scan showed a large tumour still present within the eroded fossa, but with no suprasellar extension. A small low density area was again noted within the tumour.

Bromocriptine was subsequently withdrawn completely, with prolactin levels rising again, and becoming stable at around 7,000 mU/l. Hydrocortisone, thyroxine,
1. At presentation
Marked suprasellar extension (Arrowed)

2. After treatment with bromocriptine
No extension into basal cisterns now evident.

CASE 4: POSITIVE CONTRAST CISTERNOMGRAPHY
and testosterone replacement therapy were continued as before, and he remained well. A CT scan, ten months after his course of radiotherapy, showed the pituitary tumour to be unchanged in size, extending up to the level of the posterior clinoids. However, there were multiple low density areas within the tumour, indicating that it had become cystic to a far greater extent.

The patient remains well, with normal visual fields, and the most recent serum prolactin level was 7,600 mU/l.
Discussion.

The four cases presented demonstrate the diverse ways in which prolactinomas present, and also how dramatically successful treatment of these lesions can be. However, they also highlight some of the unresolved dilemmas in the management of patients with hyperprolactinaemia.

The first case represents an unusual presentation of a prolactinoma in a woman of 37, with a long history of severe headache before the features of hypopituitarism developed. Treatment with bromocriptine was successful in abolishing her symptoms, but she now has hypopituitarism, and requires treatment with hydrocortisone and thyroxine. It is possible that gonadotrophin function will return following suppression of prolactin levels, but oestrogen replacement therapy would require caution, as oestrogen treatment is known to stimulate prolactin secretion, and oestrogens have been implicated in the genesis and growth of prolactinomas. As bromocriptine has produced an excellent symptomatic response in this patient, it might be suggested that it should be continued indefinitely. However, the long term use of bromocriptine has not yet been studied adequately, and possible failure of compliance would remain a lifelong hazard. In a patient who has already developed panhypopituitarism, this need no longer be considered as a potential complication of trans-sphenoidal surgery or radiotherapy. Both are now very safe procedures, but the long term hazards must be considered, especially in young patients. Late complications of pituitary radiotherapy, affecting the brain or optic tracts, are uncommon with modern techniques. Trans-sphenoidal surgery was considered as an effective means of decompressing the gland in this case, but as the lesion was partially cystic, it was felt that it would be impossible to ensure complete removal of the adenomatous tissue. Megavoltage radiotherapy results in rapid control of tumour growth, but its effects on hormone secretion take longer. It was therefore decided to treat this patient by radiotherapy, with continuation of bromocriptine until it becomes effective.
The second case demonstrates the successful restoration of fertility in a woman with hyperprolactinaemia, and the difficulties in subsequent management. Amenorrhoea due to hyperprolactinaemia is readily treated by bromocriptine, which reduces serum prolactin to normal levels, and results in ovulatory cycles in most patients. Bergh and Millius followed 120 women with amenorrhoea due to hyperprolactinaemia. 90 of these patients had radiological evidence of pituitary adenoma. Ovulatory cycles were established in 94%, and of 54 women who presented with infertility, 46 became pregnant.

Rapid expansion of pituitary prolactinomas during pregnancy is a recognised hazard, and probably reflects a response to elevated oestrogen levels. In patients with microadenomas, or no radiological evidence of adenoma, the incidence of tumour expansion sufficient to result in local pressure effects has been shown to be less than 5%. In patients with macroprolactinomas, however, pregnancy presents a considerable risk of complications due to expansion of the pituitary adenoma. 35% of 61 women developed serious complications during pregnancy. However, in those patients who have had ovulation induced by bromocriptine, complications appear to be much less frequent, and bromocriptine can be safely reintroduced to treat those which do occur. Turkalj et al. undertook surveillance of the use of bromocriptine in pregnancy, and reviewed 1,410 pregnancies during which bromocriptine had been given, and demonstrated no increased risk to the foetus.

The second case also demonstrates problems in the diagnosis of microprolactinomas. The patient's basal prolactin level was 1,876 mU/l. Prolactin levels in excess of 2,000 mU/l are usually due to adenoma, but functional hyperprolactinaemia can be associated with prolactin levels up to 4,000 mU/l, and conversely, adenomas may be found with prolactin levels less than 1,000 mU/l. Hypersecretion of prolactin due to hypothalamic lesions, or pituitary adenomas with suprasellar extension, which is due to disturbance of the dopamine-mediated hypothalamic inhibition of prolactin secretion, usually results in prolactin levels in the range 600-2,000 mU/l. In normal subjects, exogenous TRH and metoclopramide both cause an increase
in prolactin levels. Intravenous TRH results in a 500% increase of prolactin above basal, and oral metoclopramide produces a mean increase of 1,750%. It has been suggested that increments of less than 100% above basal indicate the presence of a microprolactinoma, rather than functional hyperprolactinaemia. However, the evidence in favour of this hypothesis is based on surgical exploration of those patients who fail to respond to these agents, and naturally, histological data cannot be obtained in all patients tested. As the natural history of small prolactinomas is not fully understood, it cannot be inferred that small prolactinomas are not present in those patients who do not fulfil the test criteria, do not undergo surgical exploration, and have no further progression of the disorder.

CT scanning does not resolve the problem of diagnosis as simply as might be expected. Areas of low density within the sella may be seen as an artefact in CT images, due to the surrounding high density of the bones of the base of the skull. In addition, pituitary microadenomas are found at post-mortem in as many as 32% of patients with no history of endocrine disturbance, although it is likely that such abnormalities are much less common in a younger population. In a study of CT scans of the pituitary fossa in normal individuals, 20% showed discrete low density areas.

The second case also raises the question of whether treatment of hyperprolactinaemia is indicated when fertility is no longer desired. It seems that most microprolactinomas do not progress to become macroprolactinomas. March et al. followed 43 patients with untreated hyperprolactinaemia for between 3 and 20 years. Only two patients showed radiological evidence of progression. Equally, it is not known whether excess prolactin is, in itself, harmful. This issue is of importance in the management of cases 3 and 4, where large prolactinomas responded well to initial treatment with bromocriptine, and subsequently radiotherapy was used. In these patients there was no evidence of further local expansion of the tumour, yet prolactin levels remained elevated. Women in whom ovulatory cycles are suppressed by hyperprolactinaemia will be oestrogen deficient, and are likely to be at risk of severe osteoporosis. Such women have been shown
to have reduced bone density\textsuperscript{18}.

None of the patients discussed underwent pituitary surgery. Trans-sphenoidal surgery may be used as the initial treatment for microprolactinomas, and Teasdale\textsuperscript{5} has followed 40 women who presented with infertility, and have been treated with surgery alone. 65\% were fertile following the operation, and only four patients developed new endocrine deficiency. Trans-sphenoidal surgery is also suitable for the treatment of large prolactinomas, after the use of bromocriptine to shrink the tumour down into the fossa. However, the most recent report from Hardy's group\textsuperscript{19} indicates a surprisingly high recurrence rate of hyperprolactinaemia following trans-sphenoidal surgery for microprolactinomas. Over a six year period, 40\% of the patients followed after successful microadenectomies showed a recurrence of prolactin excess. Whether this is due to a failure to remove the whole adenoma, or to a hypothalamic or other abnormality resulting in a tendency to generate new prolactinomas, is not known.

**Conclusion.**

These four cases of prolactinoma illustrate the different ways in which this condition can present. In each case, investigation and treatment have been successful, and yet the best therapeutic approach remains controversial. Prolactin excess is a common condition, and the techniques available for its investigation and treatment have undergone major advances. It is the fundamental biology of prolactin excess which remains poorly understood. More sophisticated investigative techniques, such as NMR imaging, and increasing information about the natural history of prolactinomas, with careful long term follow-up of patients such as these, will hopefully provide answers to the questions raised in this discussion.

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