Massive prolactinoma with galactorrhoea in a prepubertal boy

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Summary: An 8 year old prepubertal boy presented with raised intracranial pressure, left proptosis and was noted to have galactorrhoea. Cranial computerized tomography revealed a large pituitary tumour infiltrating the cavernous sinus and left orbit. The serum prolactin was 180,600 mU/l (normal value < 360 mU/l). Prolactinomas are rare in children and galactorrhoea has not previously been reported in a prepubertal child. The management of massive prolactinomas is difficult, but the child presented has made an impressive response to a combination of treatment with surgery, dopamine agonist therapy and radiotherapy.

Introduction

Prolactin secreting pituitary adenomas are rare in childhood. Although hyperprolactinaemia is a recognized cause of delayed1 or arrested2,3 puberty, its presence in the completely prepubertal child has only rarely been reported.4 No children are included in two large series of patients with prolactinomas.5 6 Equally rare is the presence of galactorrhoea in the male before completion of puberty7 8 which has never previously been reported in a prepubertal child who has not been given sex steroids. We report a prepubertal boy with a large infiltrating prolactinoma associated with galactorrhoea, which has responded to a combination of neurosurgery, radiotherapy and dopamine agonist therapy.

Case report

An 8 year old boy presented in South Africa with an acute onset of headaches, blurring of vision and vomiting, following a 4-year history of intermittent headaches. Clinical examination revealed left-sided proptosis and papilloedema. A lateral skull X-ray showed an enlarged pituitary fossa, and cranial computerized tomography (CT) showed a large pituitary tumour. His serum prolactin was 180,600 mU/l (normal-less than 360 mU/l). At craniotomy, via a left frontotemporal approach, a massive locally-infiltrating pituitary tumour was found and partially excised. Phenytoin 100 mg per day and bromocriptine 7.5 mg per day were commenced postoperatively. Three months later, the family moved back to the United Kingdom. Shortly thereafter, his headaches worsened, and following an acute episode of vomiting and a grand mal convulsion, he was admitted to St Bartholomew’s Hospital for further assessment. On examination, his height was 117.2 cm (–2.8 standard deviation scores), weight 19.9 kg, and general condition poor. Left proptosis and an oculomotor palsy were noted, and bilateral, milky galactorrhoea, although not spontaneous, was easily expressed. He was prepubertal with testes of 2 ml volume bilaterally. His visual fields and acuity were full to confrontation and on Goldmann perimetry, although visual evoked responses suggested compression of the left optic nerve.

Bone age as assessed by the Tanner-Whitehouse 2 method was 6.6 years at a chronological age of 8.9 years. Skull X-ray showed gross expansion of the left side of the pituitary fossa. High resolution CT scanning (GE9800) with sagittal and coronal reconstructions revealed a grossly expanded pituitary fossa, filled with contrast enhancing tumour. There was marked extension of tumour laterally, posterolaterally, and superiorly into the hypothalamus.

At presentation plasma prolactin levels were elevated, ranging from 207,000–294,500 mU/l (Figure 1). Thyroid function and cortisol reserve were normal, but GH reserve was grossly subnormal. Serum testosterone was < 2.5 nmol/l and oestradiol < 50 pmol/l (normal prepubertal levels).

The dose of bromocriptine was increased over a 6-week period to 40 mg daily, but this was poorly tolerated due to nausea and his poor general condition. High resolution CT performed before and after two months on the higher dose of bromocriptine showed no change in the tumour size. Therefore a
second left frontal craniotomy was performed and bromocriptine therapy stopped on the day of surgery. The main mass of the soft tumour was removed by suction; extension under and medial to the left optic nerve was noted. This was noted to be a chromophobe adenoma positively immunostaining for prolactin. Postoperatively, radiotherapy with 4,500 cGy midplane dose, in 26 fractions, by three fields over 43 days, was given. Dexamethasone was given during radiotherapy and was slowly tailed off over a period of 6 months. Dopamine agonist therapy was recommenced during radiotherapy using mesulergine, an ergoline related to bromocriptine. This was well tolerated in a dose of 10 mg daily, and following its withdrawal from clinical use, was replaced by bromocriptine 40 mg daily, without side effects. The plasma prolactin had started to fall (Figure 1) during the course of radiotherapy coinciding with the start of mesulergine treatment, and had fallen from 414,000 to 16,570 mU/l at one year and 1817 mU/l at two years after radiotherapy while on 10 mg bromocriptine.

By 11 months following his second operation, hypothyroidism was biochemically evident, and replacement therapy with thyroxine 0.1 mg daily was commenced. The growth hormone response to glucagon stimulation was again poor, with a peak level of 2.3 mU/l. A growth hormone releasing factor test using the 1-29 NH₂ analogue (GRF 100 μg i.v.) showed normal release of growth hormone, up to 25.0 mU/l at 75 minutes. Biosynthetic growth hormone was commenced two years post-operatively and has resulted in an increasing height velocity from 2.9 to 10.4 cm/year.

Two years after radiotherapy, the patient is still pre-pubertal and remains well, mentally alert and attending a normal school full time. Galactorrhoea is still present on expression. A recent high resolution CT scan shows reduction in the size of tumour although a significant tumour mass remains.

Discussion

The prepubertal body described here, with a massive prolactin-secreting pituitary macroadenoma, is unusual by virtue of the large size of his tumour at presentation, the presence of galactorrhoea, and the impressive response to a combination of therapeutic regimens. Large infiltrating prolactinomas are uncommon in adults, but exceptionally so in childhood. The finding of an elevated prolactin does not always indicate a prolactinoma as the cause, but a greatly elevated level as in this patient is usually associated with a tumour that immunostains for prolactin.

Galactorrhoea occurs in 30–80% of women with prolactinomas, is less common in men, and has not previously been reported in the prepubertal male. It has been suggested that development of lactation requires not only high serum prolactin levels but also sex steroid primed breast tissue, but this was not the case in the child presented here.

Morphological examination of the tumour from the patient described demonstrated few neuro-secretory granules. The sparsity of prolactin-containing granules in association with a high serum prolactin level may reflect cell activity secreting but not storing prolactin.
Prolactin. An alternative explanation is that the bromocriptine treatment preceding surgery altered the cell morphology; previous reports have shown either an increase or decrease in prolactin immunostaining in tumours of patients pre-treated with bromocriptine in association with a reduction in cell cytoplasm which is thought to be associated with tumour shrinkage.12,13

The good growth hormone response to growth hormone releasing hormone seen in this child who had growth hormone deficiency, as defined by a glucagon test, suggests a hypothalamic defect either in the synthesis or delivery of growth hormone releasing hormone. This may have been related to the tumour bulk or surgery interrupting delivery of growth hormone releasing hormone. Alternatively, radiotherapy may have had an inhibitory role as many children who have received radiotherapy for non-pituitary tumours develop a hypothalamic defect in growth hormone release.14,15

Massive pituitary tumours present a special problem in management. They may exert local pressure effects leading to permanent neurological deficit and therefore require urgent treatment. Surgery, though usually effective in relieving local pressure, rarely leads to a cure and hypopituitarism frequently occurs.16 Radiotherapy, although effective in the long-term control of large tumours, may cause initial swelling and it is therefore dangerous to irradiate a patient in whom the tumour has a suprasellar extension. Dopamine agonist therapy with bromocriptine is now well established as the first line treatment for patients with a tumour associated with hyperprolactinaemia.17,18,19 Tumour shrinkage with bromocriptine is often dramatic in patients with greatly elevated prolactin levels, but is rarely seen in those with prolactin levels less than 1,000 mU/l.20 If sufficient tumour shrinkage occurs on dopamine agonist therapy, radiotherapy may be given without resort to surgery and long-term control of the tumour is usually achieved.21,22 After radiotherapy deficiency of GH usually occurs within 2 years and requires treatment with growth hormone in the young, while deficiencies of other pituitary hormone occur less frequently and at a later time.

The initial lack of response of our patient to bromocriptine was probably due to his inability to take the full dose as he was vomiting as a result of the tumour mass. For our patient, the close timing of the various forms of therapy makes interpretation of the contribution of each difficult. Nevertheless, it is of note that tumour shrinkage has occurred with suppression of prolactin secretion in response to a combination of post-operative radiotherapy and dopamine agonist therapy. The accompanying clinical improvement has been dramatic, although in view of the very high persisting prolactin levels, the ultimate prognosis remains guarded.

In summary, we present the first case of a prepubertal child with hyperprolactinaemia-induced galactorrhoea. The combination of surgical removal, radiotherapy and dopamine agonist therapy has led to control of this massive prolactinoma with a relatively low morbidity.

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References


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