Cerebrospinal fluid rhinorrhoea during treatment of pituitary tumours with bromocriptine

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Abstract. Bromocriptine is widely used in the treatment of hyperprolactinaemia. It has also been shown to be effective in reducing the size of large pituitary tumours, particularly those secreting prolactin. We describe CSF rhinorrhoea in two such patients during treatment with bromocriptine and believe that this complication developed as a result of contraction of the tumour exposing a defect in the sella floor. The possibility of this complication, especially in patients with downward extension of tumour, should be noted.

Cerebrospinal fluid (CSF) rhinorrhoea is a rare but well documented complication of pituitary tumours (Cole & Keene 1980). It has also been described during bromocriptine treatment of patients after incomplete resection of prolactinomas (Aronoff et al. 1979; Baskin & Wilson 1982) and after radiotherapy (Landolt 1982). We report two cases, one with a prolactinoma and the other with a mixed growth hormone and prolactin secreting tumour, where this complication occurred during bromocriptine treatment prior to surgery. In the second case CSF leakage recurred during bromocriptine treatment after surgery.

Case Reports

Case 1
A 32 year old woman presented with increasing headache. She had had secondary amenorrhoea for 8 years until 3 months prior to presentation when she had two menstrual periods following treatment for migraine with an ergot derivative. She gave no history of galactorrhoea and clinical examination was normal. Visual fields were full. Skull X-ray showed marked enlargement of the pituitary fossa with erosion of the anterior and posterior clinoids. An axial plane computerized tomographic scan revealed supra- and parasellar extension of the tumour with ballooning into the sphenoid sinus (Fig. 1). Serum prolactin was greater than 200 µg/l (exact level not known; normal less than 20 µg/l). Gonadotrophin and thyrotrophin responses to pituitary stimulation tests were normal.

Treatment was commenced with bromocriptine and the dose increased to 7.5 mg/day. Three weeks later she complained of a stuffy sensation in her nose. Serum prolactin at that time was 376 µg/l. After a further 2 weeks she developed rhinorrhoea and the lightly blood stained fluid dripping from her nose contained glucose consistent with it being CSF. Surgery was performed by the transfrontal route and the bulk of the tumour removed. It was noted to have burrowed under the left internal carotid artery. A musculo-fascial graft was placed in the tumour bed to repair a defect in the fossa floor. Histology confirmed a chromophobe adenoma with no evidence of unusually active growth.

Post-operatively the patient became panhypopituitary but serum prolactin remained elevated at 709 µg/l. CSF leakage recurred 2 weeks after surgery. She was not on bromocriptine at that time. Further surgery by the transphenoidal route was performed and a 1 cm defect found in the antero-inferior part of the sella floor. The exposed dura appeared penetrated by tumour at the most anterior part of the bony defect in the fossa floor. Residual tumour was found in the fossa and removed. The floor was then repaired with a fascial graft. She had been restarted on bromocriptine (7.5 mg/day) prior to her second operation and the serum prolactin level had fallen to 240 µg/l. Postoperatively the serum prolactin remained elevated at 301 µg/l and bromocriptine was restarted in a dose of 7.5 mg/day. She did not develop
any further nasal stuffiness and CSF leakage did not recur. Her headaches were completely relieved but her amenorrhoea continued due to hypopituitarism. Serum prolactin measured 2 months later was 289 µg/l. She died from unrelated causes 6 months after surgery but no post-mortem findings relating to the pituitary are available.

**Case 2**

A 50 year old man presented with arthritis in his hips and knees. He was noted to be mildly acromegalic in appearance and did admit that his hands had increased in size. He had also been impotent for 10 years. There was nothing else of note on examination apart from a small

**Fig. 1.**
Axial plane computerised tomographic scan of Case 1 following iv contrast medium. Suprasellar extension of a large pituitary tumour is shown.

**Fig. 2.**
Latera skull X-ray of Case 2 showing destruction of the pituitary fossa floor and anterior wall with attenuation of the dorsum sella.
goitre. Visual fields were full. Fasting growth hormone was 40.3 mU/l (normal less than 20 mU/l) and did not suppress with glucose. Basal serum prolactin was 454 µg/l. The remainder of pituitary function was normal. Skull X-ray showed enlargement of the pituitary fossa with destruction of the anterior wall and floor (Fig. 2). An axial plane computerized tomographic scan revealed a large pituitary tumour with extension downwards, anteriorly and laterally.

Bromocriptine therapy was commenced (7.5 mg/day). Four weeks later he developed nasal stuffiness and after a further 2 weeks noted clear fluid dripping from his nose when he bent forward. This contained 5 mmol/l glucose consistent with it being CSF. At that time the basal serum growth hormone level had fallen to 20.4 mU/l and the prolactin level to 266 µg/l.

Transsphenoidal surgery revealed a shallow sphenoid sinus. The sella floor was bulging into the sinus and was composed of dura with a few flecks of expanded bone attached to it. Anteriorly the dura was penetrated by tumour. This was confirmed histologically. The tumour was removed and the sella floor repaired with a fascial graft. Histologically it was a chromophobe adenoma, again with no evidence of unusually active growth.

Post-operatively the patient made a good recovery. Basal growth hormone level was reduced to 20.7 mU/l but did not suppress with glucose. Serum prolactin remained elevated at 368 µg/l but otherwise pituitary function was normal. Bromocriptine was restarted (7.5 mg/day) to control the hyperprolactinaemia. Three weeks later the complained of nasal stuffiness and had developed overt CSF rhinorrhoea after 6 weeks. Serum prolactin had fallen to 289 µg/l. Transfrontal surgery was performed and confirmed the presence of residual tumour and a defect in the sella floor. This was repaired with a fascial graft. Post-operatively the patient was panhypopituitary but still had an elevated prolactin level. He was treated with radiotherapy and given no further bromocriptine.

Discussion

Bromocriptine is a synthetic ergot alkaloid which acts as a dopamine agonist. It was initially used to treat patients with hyperprolactinaemia (Lutterbeck et al. 1971; Besser et al. 1972) but more recently has also been shown to be effective in reducing the size of large pituitary tumours, particularly those secreting prolactin (McGregor et al. 1979; Wass et al. 1982). Regression of the tumour usually takes place during long-term treatment but in some cases a few weeks of bromocriptine treatment has been sufficient (Thorner et al. 1980). We believe that the development of CSF rhinorrhoea in the two patients described here was a result of contraction of the tumour by bromocriptine exposing a defect in the sella floor. This is supported by the findings at surgery and the fact that the hormone levels in the second patient fell substantially during the first 6 weeks of treatment. The initial hormone levels in the first patient were not accurately known and therefore a fall could not be confirmed.

CSF leakage recurred in both these patients after the first operation. In the first case it recurred within days and was unrelated to the use of bromocriptine. In the second case bromocriptine had been restarted and may have resulted in contraction of residual tumour and exposure of the surgical defect in the sella floor. That was the suggested reason for CSF leakage in the three cases where it was described following incomplete resection of prolactinomas (Aronoff et al. 1979; Baskin & Wilson 1982). Rapid tumour shrinkage caused by irradiation combined with bromocriptine therapy was also considered to be a factor in the development of CSF rhinorrhoea in three patients reported by Landolt (1982), two of whom had prior surgery and the third had very extensive tumour invasion of the clivus and air sinuses.

The surgical treatment of CSF rhinorrhoea in the presence of invasive pituitary tumours is difficult as it is unlikely that all tumour tissue can be removed (Guiot 1978). Previous investigators (Cole & Keene 1980) have preferred the transsphenoidal technique which offers the advantage of direct access to tumour in the floor of the sella and may provide a firm bed of graft tissue if a subsequent procedure to occlude the fistula by the transfrontal route is necessary as in our second case. The transfrontal approach was chosen initially in our first case because the defect in the floor of the sella was relatively small and it was believed that muscle packing in the pituitary fossa would be well supported by the remaining bone in the general concavity of the anterior and inferior aspects of floor of the sella. The transsphenoidal approach would have involved removal of some of that supporting bone. After the intrasellar graft was fixed, a supplementary transsphenoidal graft completed closure of the fistula. Therefore, while an initial transsphenoidal approach is the method of choice in many cases, there is a place for supplementing one approach with the other.

One of the known side effects of bromocriptine is nasal congestion but this did not recur in the first patient after surgery and therefore the initial nasal
stiffness was probably due to early CSF leakage. Histologically neither of these tumours showed evidence of usually active growth. However, both behaved in a locally invasive manner and both had eroded the sella floor prior to treatment. We are unaware of other published case reports of CSF leakage during bromocriptine treatment of large pituitary tumours in the absence or surgical intervention or radiotherapy. We draw attention to this possible complication especially in patients with downward extension of tumour.

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References


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