Bromocriptine-induced cerebrospinal fluid rhinorrhea following successful treatment of invasive prolactinoma

Abstract

The authors present a case of a 36-year-old man who developed spontaneous cerebrospinal fluid (CSF) rhinorrhea after two years of bromocriptine therapy for an invasive prolactin secreting pituitary adenoma. The patient had never undergone any surgery or radiotherapy in the region of the tumour. The CSF fistula was best demonstrated by means of computed tomography cisternography. Magnetic resonance imaging and subsequent surgery confirmed the presence of an empty sella with complete regression of the tumour. A review of the pertinent literature revealed seven similar cases. The clinical and radiological features of patients at risk of developing this rare complication are described, and the treatment options discussed. (p40-45)

Keywords: Invasive prolactinoma, bromocriptine, cerebrospinal fluid rhinorrhea and transsphenoidal surgery.

Introduction

Cerebrospinal fluid (CSF) rhinorrhea is a well-known complication of the surgical treatment of pituitary adenoma, being encountered in 1-3.1% of the operated cases. In contrast, spontaneous CSF rhinorrhea after bromocriptine therapy is rare and so far only 7 such cases have been reported in the pertinent literature.

In this report, the authors describe a new case of CSF rhinorrhea that developed in the course of bromocriptine therapy for an invasive prolactin secreting pituitary adenoma. The aim is to draw attention to this rare complication and outline the clinical and radiological characteristics of patients who are at risk of developing this rare complication.

Case Report

This 36-year-old man had been complaining of frontal headache for five years and decreased libido for two years. Moreover, he noticed some blurring of vision with drooping of the left eyelid one month prior to presentation to hospital. There was no history of galactorrhea, but the patient suffered from a bout of meningococcal meningitis 14 years earlier.
Neurological examination showed bilateral upper quadrant anopsia and partial left third nerve palsy. Systemic examination was unremarkable, apart from bilateral gynaecomastia.

A random serum prolactin level was 11,350 ng/ml (normal: 35-380), whereas basal levels of other hormones were within normal limits.

Computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed a large intrasellar and suprasellar tumour that invaded both cavernous sinuses. There was complete destruction of the sellar floor, dorsum sella and the upper clivus, and the tumour filled the sphenoid air sinus and broke through its floor into the epipharynx (Fig. 1).

As the patient was reluctant to undergo surgical resection of the tumour, he was started on bromocriptine at a dose of 15 mg/day that was later increased to 30 mg/day. Within seven days there was a dramatic improvement in his visual field and eyelid drooping. The serum prolactin level normalised within two weeks of treatment and serial MRI showed progressive regression of the tumour.

While still on bromocriptine therapy, the patient noticed two years later dripping of a clear watery fluid from his left nostril especially during physical straining and coughing, associated with bifrontal headache. His serum prolactin level was 53.3 ng/ml. MRI revealed a large empty sella with no definite evidence of a tumour residue (Fig. 2). CT cisternography using Omnipaque® showed a totally destroyed sella and dye in the sphenoid air sinus (Fig. 3).

**Operation**
The patient was operated via transnasal, transsphenoidal microsurgical approach. The floor of the sphenoid sinus was eroded on the left side and the sinus was empty and devoid of septum. With the exception of thin marginal bone flakes, the floor of the sella was completely missing. The dura propria of the sella was also defective. The pituitary fossa was occupied by cystic structures
and thin, grayish, fibro-gelatinous membranes, but no tumour tissue could be seen. The pituitary gland was identified as a small yellow mass on the right side of the fossa. The pituitary fossa and sphenoid sinus were packed respectively with fat and muscle pieces obtained from the right thigh. The margins of the muscle plug were finally sealed up by using a tissue glue (Tisseel®). An external lumbar CSF drain was inserted immediately postoperatively to eliminate the risk of early CSF leakage that may interfere with good healing of the reconstruction. The postoperative course was uneventful and CSF rhinorrhea ceased completely. The lumbar drain could be removed 5 days later and bromocriptine therapy was discontinued gradually. At last follow-up examination one year after surgery, the patient was neurologically intact and free of recurrence of either tumour or CSF rhinorrhea. His basal hormone levels, including prolactin, were within normal limits.

Discussion

Invasive prolactinoma has always posed a therapeutic challenge to neurosurgeons, endocrinologists and radiotherapists. With tumour extensions into complex neighbouring anatomical structures, such as the cavernous sinus and skull base, a cure of these lesions by surgery alone could be expected in only an exceptional case of localised invasion, which can be exposed and resected radically. Consequently, a combination of different therapeutic modalities is necessary for the treatment of the vast majority of these lesions. In recent years, bromocriptine has emerged as the treatment of first choice for most prolactin secreting pituitary adenomas, including large and invasive lesions. It has been shown that 80% of macroadenomas shrink under the influence of this dopamine agonist, often associated with a significant decline in serum prolactin level and improvement of pre-existing visual disturbances. Although adverse reactions during bromocriptine therapy are not uncommon, they are usually transient and limited to dizziness and gastrointestinal discomfort. The manifestation of CSF rhinorrhea during the treatment with bromocriptine, as in our case, is in contrast rare, and has so far been described in 20 other patients in the literature. However, 13 out of these 20 patients had at some stage, before or during bromocriptine therapy, undergone transnasal/transsphenoidal surgery or craniotomy, sometimes combined with postoperative radiotherapy. Truly spontaneous CSF rhinorrhea during bromocriptine therapy had probably occurred in only 8 cases, including this case (Table 1). The onset of CSF rhinorrhea was early (within the first 6 weeks of treatment) in one half, but late (between 9-24 months of treatment) in the other half of patients. All 8 patients shared the common feature of harbouring a large invasive prolactinoma that had widely eroded the sellar floor and often extended into the sphenoid sinus.

Although CSF rhinorrhea may be directly caused by tumours invading the skull base, the causative role of bromocriptine in the development of CSF rhinorrhea in patients with invasive prolactinomas is highly probable. Most of these patients had a

Figure 3 - CT cisternography showing a destroyed sella and dye leaked to the sphenoid air sinus
Table 1 - A summary of reported cases of spontaneous CSF rhinorrhea during bromocriptine therapy for invasive macroprolactinoma

<table>
<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Year</th>
<th>Age</th>
<th>Sex</th>
<th>Duration of symptoms</th>
<th>Prolactin level (ng/ml)</th>
<th>Bromocriptine dose (mg/day)</th>
<th>Interval to onset of rhinorrhea</th>
<th>Meningitis</th>
<th>Repair of CSF rhinorrhea</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Afshar &amp; Thomas (4)</td>
<td>1982</td>
<td>28</td>
<td>F</td>
<td>12y</td>
<td>185</td>
<td>5 po</td>
<td>1 w</td>
<td>N</td>
<td>TSP¹</td>
<td>Fibronectrotic tissue, no residual tumour</td>
</tr>
<tr>
<td>2</td>
<td>Wilson, et al. (5)</td>
<td>1983</td>
<td>32</td>
<td>F</td>
<td>8y</td>
<td>200</td>
<td>7.5 po</td>
<td>5 w</td>
<td>N</td>
<td>TCR²</td>
<td>Partial excision of tumour, rhinorrhea recurred after 2 weeks. Transsphenoidal repair.</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10y</td>
<td>454</td>
<td>7.5 po</td>
<td>6 w</td>
<td>N</td>
<td>TSR</td>
<td>Rhinorrhea recurred after 6 weeks. Transcranial repair + removal of residual tumour. Postoperative radiotherapy.</td>
</tr>
<tr>
<td>4</td>
<td>Kok, et al. (6)</td>
<td>1985</td>
<td>47</td>
<td>M</td>
<td>4y</td>
<td>13500</td>
<td>15 po</td>
<td>9 m</td>
<td>N</td>
<td>TSP</td>
<td>Rhinorrhea ceased when bromocriptine was discontinued and recurred when resumed. Necrotic tissue removed.</td>
</tr>
<tr>
<td>5</td>
<td>Bronstein, et al. (7)</td>
<td>1989</td>
<td>52</td>
<td>F</td>
<td>20y</td>
<td>1110</td>
<td>5 po</td>
<td>16 m</td>
<td>N</td>
<td>TSP</td>
<td>Small amount fibrotic tumour removed</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3y</td>
<td>1700</td>
<td>10 po</td>
<td>17 m</td>
<td>Y</td>
<td>TSP</td>
<td>Residual tumour</td>
</tr>
<tr>
<td>7</td>
<td>Barlas, et al (8)</td>
<td>1994</td>
<td>46</td>
<td>F</td>
<td>16y</td>
<td>310</td>
<td>5 po</td>
<td>15 d</td>
<td>Y</td>
<td>TSP</td>
<td>Rhinorrhea ceased when bromocriptine was discontinued and recurred when resumed.</td>
</tr>
<tr>
<td>8</td>
<td>Elgamal, et al.</td>
<td>2001</td>
<td>36</td>
<td>M</td>
<td>2y</td>
<td>11350</td>
<td>15 po</td>
<td>2 y</td>
<td>N</td>
<td>TSP</td>
<td>Fibroglutinous tissue, no residual tumour</td>
</tr>
</tbody>
</table>
long-standing medical history of a pituitary tumour and yet they developed CSF rhinorrhea only after bromocriptine therapy was started. In addition, in some of these patients a transient cessation of the CSF leakage could be observed when bromocriptine therapy was interrupted. The rhinorrhea is most likely a consequence of bromocriptine-induced tumour shrinkage. Clayton, et al. demonstrated that dramatic (up to 40%) volume reduction of large invasive prolactinomas could occur within 8 days of bromocriptine therapy. As the tumour shrinks, direct communication between the CSF space and the nasopharyngeal airway may develop as a result of downward extension of the subarachnoid space into the dilated and eroded sella and unplugging of the defect in the roof of the sphenoid sinus.

Spontaneous bromocriptine-induced CSF rhinorrhea carries a fairly high risk of ascending meningitis. Two out of the eight patients discussed here developed this serious complication. Therefore, it is mandatory that patients on bromocriptine therapy for macroprolactinoma be well informed about these potential hazards and closely supervised during the treatment.

The question regarding the best treatment for bromocriptine-induced CSF fistula is more difficult to answer. A good control of the CSF leak may be achieved with simple procedures, such as an external lumboperitoneal shunt. On the other hand, recurrent fistula may develop after transsphenoidal or transcranial repair. Patients with residual tumour at the time of repair seem to be at a higher risk of recurrence of the fistula especially if bromocriptine is continued postoperatively, probably as a result of further shrinkage of the residual tumour. This hypothesis would also explain cases in which CSF rhinorrhea developed not as an immediate complication of transsphenoidal or transcranial resection of prolactinoma but later during postoperative bromocriptine therapy. We, therefore, emphasise the importance of good clearance of the area of the fistula of all tumour tissue prior to packing of the defect. The intraoperative use of tissue glue together with the external lumbar drainage in the early postoperative days, as in our case, are further measures to minimise the risk of recurrence.

**Conclusion**

Spontaneous bromocriptine-induced CSF rhinorrhea is very rare and may be expected in patients with invasive macroprolactinomas. Its onset can be early within the first few weeks or late after several months of treatment. Presumably, it is caused by unplugging of an eroded area in the skull base as a result of tumour shrinkage under the influence of bromocriptine. Patients with macroprolactinoma must be forewarned of this risk and supervised closely. Transsphenoidal surgery with postoperative external lumbar CSF drainage offers an effective method of treatment for this complication.

**References**

BROMOCRIPTINE-INDUCED CSF RHINORRHEA • Elgamal, et al


