Bromocriptine treatment of invasive giant prolactinomas involving the cavernous sinus: results of a long-term follow-up

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Object. The aim of this study was to observe long-term clinical outcomes in a group of patients treated with bromocriptine for invasive giant prolactinomas involving the cavernous sinus.

Methods. Data from 20 patients with invasive giant prolactinomas at the authors’ institutions between July 1997 and June 2004 were retrospectively reviewed. The criteria to qualify for study participation included: 1) tumor diameter greater than 4 cm, invading the cavernous sinus to an extent corresponding to Grade III or IV in the classification scheme of Knosp and colleagues; 2) serum prolactin (PRL) level greater than 200 ng/ml; and 3) clinical signs of hyperprolactinemia and mass effect. Among the 20 patients who met the criteria, six had undergone unsuccessful transcranial or transsphenoidal microsurgery prior to bromocriptine treatment and 14 patients received bromocriptine as the primary treatment. Eleven of the 20 patients underwent adjuvant radiotherapy.

After a mean follow-up period of 37.3 months, the clinical symptoms in all patients improved by different degrees. Tumor volume on magnetic resonance images was decreased by a mean of 93.3%. In 11 patients, the tumor had almost completely disappeared; in the other nine patients, residual tumor invaded the cavernous sinus. Visual symptoms improved in 13 of the patients who had presented with visual loss. Eight patients had normal PRL levels. The postoperative PRL level was more than 200 ng/ml in seven patients. During the course of drug administration, cerebrospinal fluid leakage occurred in one patient, who subsequently underwent transsphenoidal surgery. No case of apoplexy occurred during bromocriptine treatment.

Conclusions. Dopamine agonist medications are effective as a first-line therapy for invasive giant prolactinomas. Because they can significantly shrink tumor volume and control the PRL level, treatment mass vanishes in some patients after bromocriptine treatment; in other patients with localized residual tumor, stereotactic radiosurgery is a viable option so that unnecessary surgery can be avoided. The application of radiotherapy does not reliably shrink tumor volume.

Key Words • giant prolactinoma • invasiveness • bromocriptine • cavernous sinus

Prolactin-secreting adenoma, the most common type of hyperfunctioning pituitary adenoma, accounts for approximately 50 to 60% of all functional pituitary tumors. Significant advances in the last few decades have contributed to the effective management of prolactinomas, including pharmacological therapies, microsurgical and endoscopic techniques, and stereotactic radiosurgery. Giant prolactinomas with cavernous sinus invasion, a rare subcategory of prolactinomas, occurring with characteristics of hyperprolactinemia and invasive growth remain one of the greatest challenges in neurosurgery. Hyperprolactinemia commonly causes reproductive and sexual dysfunction. Because of invasive growth, giant adenomas can compress or destroy adjacent structures, resulting in neurological dysfunction such as visual loss, cavernous sinus compression, and so forth. The aim of treatment has two aspects: to normalize the hyperprolactinemic state and preserve residual pituitary function, and to eliminate mass effect and prevent tumor recurrence. Improving the quality of life through the amelioration of sexual dysfunction and reproductive difficulties is also an important factor. Treatment is a complex issue because of the involvement of the cavernous sinus as well as other parasellar and basal forebrain structures. Pharmacological therapy with a dopamine agonist remains the mainstay of treatment. We report on a group of patients with invasive giant prolactinomas involving the cavernous sinus who had undergone long-term follow-up review after bromocriptine treatment.

Clinical Material and Methods

Patient Population and Inclusion Criteria

Giant pituitary adenomas have been previously defined as those measuring 4 cm or larger in diameter. We adopted the classification system of Knosp, et al., and defined invasiveness as Grade III or IV according to this scheme. Criteria for inclusion in the present study consisted of the following: 1) tumor size larger than 4 cm in diameter with invasion of the cavernous sinus corresponding to Grade III

Abbreviations used in this paper: CSF = cerebrospinal fluid; MR = magnetic resonance; PRL = prolactin.
TABLE 1
Pretreatment disease manifestations in 20 patients with invasive giant prolactinomas

<table>
<thead>
<tr>
<th>Pretreatment Symptom</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>visual change</td>
<td>14 (70)</td>
</tr>
<tr>
<td>headache</td>
<td>10 (50)</td>
</tr>
<tr>
<td>decreased libido</td>
<td>9 (56)*</td>
</tr>
<tr>
<td>impotence</td>
<td>3 (19)*</td>
</tr>
<tr>
<td>amenorrhea</td>
<td>4 (100)†</td>
</tr>
<tr>
<td>galactorrhea</td>
<td>2 (50)†</td>
</tr>
<tr>
<td>vertigo</td>
<td>2 (10)</td>
</tr>
<tr>
<td>intracranial hypertension</td>
<td>2 (10)</td>
</tr>
<tr>
<td>nasal obstruction &amp; hemorrhage</td>
<td>1 (5)</td>
</tr>
<tr>
<td>facial numbness</td>
<td>1 (5)</td>
</tr>
<tr>
<td>episodic facial pain</td>
<td>1 (5)</td>
</tr>
<tr>
<td>axillary &amp; pubic hair loss</td>
<td>4 (20)</td>
</tr>
<tr>
<td>obesity</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

* In male patients, the incidence of decreased libido and impotence was nine of 16 and three of 16, respectively.
† In female patients, the incidence of amenorrhea and galactorrhea was four of four and two of four, respectively.

TABLE 2
Pretreatment and posttreatment visual field statuses in patients with invasive giant prolactinomas*

<table>
<thead>
<tr>
<th>Pre-Tx VF</th>
<th>Post-Tx VF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case No.</td>
<td>OD</td>
</tr>
<tr>
<td>1</td>
<td>anopsia</td>
</tr>
<tr>
<td>2</td>
<td>TH</td>
</tr>
<tr>
<td>3</td>
<td>TH</td>
</tr>
<tr>
<td>4</td>
<td>anopsia</td>
</tr>
<tr>
<td>5</td>
<td>anopsia</td>
</tr>
<tr>
<td>6</td>
<td>anopsia</td>
</tr>
<tr>
<td>7</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>T</td>
</tr>
<tr>
<td>9</td>
<td>TH</td>
</tr>
<tr>
<td>10</td>
<td>TH</td>
</tr>
<tr>
<td>11</td>
<td>T</td>
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<tr>
<td>12</td>
<td>T</td>
</tr>
<tr>
<td>13</td>
<td>TH</td>
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<td>14</td>
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<tr>
<td>19</td>
<td>N</td>
</tr>
<tr>
<td>20</td>
<td>N</td>
</tr>
</tbody>
</table>

* N = normal; OD = oculus dexter; OS = oculus sinister; T = tubular; TH = temporal hemianopia; Tx = treatment; VF = visual field.
† Most recent finding.

Treatment Methods

Six patients who had undergone unsuccessful surgery at other hospitals received bromocriptine treatment at our hospital. Four patients were treated using craniotomy (Cases 6, 7, 11, and 13), one transsphenoidal surgery (Case 20), and one transnasal surgery (Case 2). According to postoperative MR imaging and endocrinological examination data, these six patients met the diagnostic criteria for invasive giant prolactinomas, and therefore were included in our study. To determine the outcomes of bromocriptine treatment, tumor volume based on postoperative MR images was calculated in the same manner as the volume before bromocriptine treatment. The other 14 patients initially received bromocriptine treatment. Eleven patients in our study group underwent adjuvant radiotherapy. Bromocriptine was orally administered before sleep at night at an initial dose of 2.5 mg/day to reduce the occurrence of orthostatic hypotension. Within 2 to 3 weeks, the dose was gradually increased to 7.5 mg/day (that is, 2.5 mg three times/day), which was the effective treatment dose. In cases in which patients experienced adverse effects (such as gastrointestinal discomfort, dizziness, and so forth) after taking bromocriptine only half of a tablet (1.25 mg) was subsequently administered, and the dose was slowly increased; for example, 1.25 mg/day was added every week, and most patients were able to tolerate the entire dose after the gradual adaptation.

Results

Posttreatment Courses

All patients were closely followed up by the first author (Z.B.W.) between 7 and 71 months posttreatment (mean follow up of 37.3 months; Figs. 1–4). Follow-up examina-
tion took place mainly in the outpatient clinic and was supplemented by telephone interview. The 3-month, 6-month, and 1-year follow ups were conducted after bromocriptine treatment; thereafter, a follow up was undertaken every 1 to 2 years. The follow-up examination included cranial MR imaging with contrast, endocrinological laboratory tests, vision and visual field checks, and so forth. If the patient’s state of health deteriorated, he or she had the opportunity to visit the doctor immediately. Initially, three patients experienced different degrees of bromocriptine-related side effects, such as nausea, gastrointestinal discomfort, orthostatic dizziness, fatigue, nasal congestion, and so forth. A lower drug dose was administered, and the dose was subsequently increased gradually; each of the three patients was able to tolerate the entire dose following this strategy.

On Day 140 after bromocriptine administration, CSF leakage occurred in the patient in Case 3. He continued to take the drug and was simultaneously given conservative treatment, with no effect. Transsphenoidal surgery was performed to excise the greater part of the tumor and to repair the CSF leak. Two months after the administration of bromocriptine in the patient in Case 12, the tumor decreased in size by 88%. One year after taking the drug consistently, the patient’s residual tumor shrank no further and was localized in the sella, involving the left cavernous sinus. In October 2002, the patient underwent transsphenoidal surgery for tumor excision and continued to take bromocriptine postoperatively. At present, the tumor has disappeared completely and the patient’s PRL level is normal. No instance of tumor apoplexy occurred while taking bromocriptine.

**Effects of Treatment on Presenting Symptoms and Visual Fields**

In the 14 patients with visual loss—excluding the patient in Case 9 whose visual deterioration was considered to be related to radiotherapy—the visual symptoms were improved in 93% to various extents. Visual field impairment was ameliorated in all of these patients, as shown in Table 2. In the 10 patients with headaches, symptoms disappeared in eight and were ameliorated in the other two. In nine patients with sexual dysfunction and a decrease in PRL levels, sexual function improved to various degrees; in six, a hyperprolactinemia occurred while taking bromocriptine.

**Prolactin Levels**

In eight patients, PRL levels decreased to less than 25 ng/ml after bromocriptine treatment, as shown in Table 3. In seven patients, levels continued to exceed 200 ng/ml. In five patients, PRL levels were between 25 and 200 ng/ml. Normal pituitary function was preserved in all patients, without...
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evidence of panhypopituitarism. No case of diabetes insipidus was observed.

Tumor Volume Change on MR Imaging

After treatment with bromocriptine, tumor volume decreased dramatically in all patients, with a mean reduction of 93.3% (range 61–100%; Table 3). On MR images obtained in 11 patients, the tumor had almost completely disappeared; on images obtained in the other nine, residual tumor remained in the cavernous sinus areas. Among the 20 patients, tumors involved 31 lateral cavernous sinuses; during follow up, the lesion disappeared in 20 sinuses. In the course of tumor reduction, lesions in the suprasellar area commonly shrank first, followed by those in the sphenoid sinus and the intrasellar region. Tumors in the cavernous sinus area were always the last to shrink.

Discussion

Effectiveness of Bromocriptine in the Treatment of Invasive Giant Prolactinomas

Dopamine agonist medication is the first consideration in the treatment of prolactinomas. Bromocriptine can normalize the serum PRL level in more than 90% of cases and reduce tumor volume in approximately 85% of cases. Its main mechanism involves the dopamine D2 receptors on the cell membrane of PRL cells, which is selec-
tively activated; thus, the transcription and expression of the PRL gene and the metabolism of PRL cells are inhibited, leading to decreased synthesis and secretion of PRL. In addition, the involution of the endoplasmic reticulum and Golgi apparatus and the suppression of cell proliferation cause a reduction in tumor volume. With the reduction in lesion volume and the control of the PRL level, clinical symptoms are ameliorated. Headache and sexual dysfunction are improved to differing degrees. The extent and rate of the reduction in tumor volume can be astonishing; for example, during the mean follow-up period of 37 months in the present study, tumor volumes decreased by a mean of 93.3% overall and lesions almost disappeared in 11 patients, according to MR imaging studies (Figs. 1 and 3). Shrivatava and colleagues reported on 10 cases of giant prolactinomas that had been treated with bromocriptine, only five of which involved the cavernous sinus. During a mean follow-up period of 6.7 years, tumor volume decreased by a mean of 69%. Other authors have reported that in cases of giant prolactinomas, visual symptoms improve several days to several weeks after treatment with bromocriptine. Posttreatment visual improvement was not significantly different after drug administration compared with that following surgery. If, after drug administration, the tumor had obviously diminished but vision and visual fields had not improved, ocular defects were rarely improved by subsequent surgery. The blood supply to the optic nerve and chiasm can be impaired during the surgical separation of adhesions between the giant tumor and the optic nerve. Bromocriptine treatment gradually reduces tumor volume and therefore does not contribute to acute damage of the optic nerve and chiasm. In 13 (93%) of 14 patients with visual deterioration, visual symptoms improved. After taking bromocriptine, vision initially improved in the patient in Case 9; 6 months after radiotherapy, however, the patient’s vision deteriorated. Hence, visual loss was attributed to radiotherapy. Visual improvement usually occurred within several weeks after beginning bromocriptine treatment and has occurred even on the 1st day after commencing treatment.

Influence of Sex on Treatment Effects

Compared with those in women, the tumors in men are larger, PRL levels are higher, and tumors invade the cavernous sinus more often. In the present study, most patients were male, with a ratio of 4:1 (male/female). Among the four female patients, excluding the woman in Case 5, PRL levels continued to exceed 200 ng/ml after treatment, and amenorrhea did not improve. Among the 16 male patients, PRL levels decreased to within normal range in seven cases,
but exceeded 200 ng/ml in four cases. Rates of PRL level control in both sex groups were statistically analyzed, and there was no significant difference (p > 0.05). In the four female patients, tumor volume decreased by a mean of 90%, during a mean follow-up period of 30 months. In the 16 male patients, tumor volume decreased by a mean of 94% during a mean follow up of 39 months. There was no significant difference in tumor volume reduction between the sexes.

**Correlation Between PRL Level Decrease and Tumor Volume Shrinkage**

Do tumor volume and PRL level decrease at the same rate? Does the PRL level always decrease to a normal level after tumor disappearance? Data in our study showed that in 11 patients in whom tumors had either completely or almost vanished according to MR imaging, the PRL level was normalized (< 25 ng/ml) in five and was not normalized in the other six. Of the latter six patients, four had PRL levels higher than 200 ng/ml. In patients who continued to demonstrate a high PRL level, tumor disappearance on MR images did not necessarily indicate complete lesion resolution, because the tumor had invaded adjacent structures or the bone matrix and possessed a strong ability to excrete PRL (Figs. 1 and 2). These patients not only continued to take bromocriptine, but were also closely monitored, because once administration of the drug was terminated, the tumor could recur immediately.17 On the other hand, among eight patients whose PRL levels decreased to normal, the tumor remained visible on MR images obtained in three patients. In five patients whose MR imaging studies were negative for tumor and whose PRL levels were normal, it was suggested that bromocriptine therapy be withdrawn. Close monitoring for recurrent hyperprolactinemia and renewed tumor growth was established.9 Tumor volume shrinkage and controlled PRL levels were not equally sensitive to bromocriptine, and there was no positive correlation between tumor size and PRL level.25,47

**Sequence of Tumor Volume Shrinkage**

During follow up, we found an interesting phenomenon: after treatment with bromocriptine, tumors growing into the suprasellar area shrank first (for example, tumors protruding into the third ventricle or the temporal lobe). In the nine patients with residual tumors, the remnant always involved the cavernous sinus (Fig. 3). In three patients (Cases 5, 9, and 16), tumor volume was reduced within several weeks to several months after taking the drug. As drug therapy was prolonged, the tumor diminished slowly, particularly any residual tumor involving the cavernous sinus. In the patient in Case 16 (Fig. 4), tumor volume shrank by 76% 12 months after initial bromocriptine administration. In the subsequent 2 years, the tumor shrank no further, and the PRL level was not satisfactorily controlled. This condition could be considered late resistance and may have occurred for the following reasons. 1) After drug administration, tumor fibrosis becomes progressive and, to a certain extent, the tumor can shrink no further. 2) The absence, lower expression level, or a postreceptor defect of the dopamine D2 receptors on the surface of tumor cells may contribute to this condition.23 Caccavelli, et al.3 considered drug resistance to be strongly associated with the decrease in D2 receptor gene transcription, resulting in a fourfold decrease in the number of D2 receptors on the cell membrane.

**Indications for Surgery in Patients With Invasive Giant Prolactinomas**

Pituitary tumors with lateral extension into the cavernous sinus pose a formidable surgical challenge. Recently, authors have sought to modify the standard transsphenoidal approach to resect pituitary adenomas with cavernous sinus invasion.12,20,22,25,42 Note, however, that surgical outcomes were rather unsatisfactory in patients with pituitary adenomas of Grade III or IV, according to the classification of Knosp and colleagues.28 Losa, et al.,24 reported on 19 PRL-secreting pituitary adenomas with cavernous sinus invasion; the disease was cured in just one patient through early surgery. Increasingly, many investigators have chosen to perform selective tumor removal with subsequent radiosurgical treatment of residual adenoma within the cavernous sinus to avoid complications of cranial neuropathies. In treating PRL-secreting adenomas, shrinking the tumor volume and controlling the PRL level are equally important. As a result of the tumor’s intrusive growth and cavernous sinus invasion, it is usually impossible to achieve complete resection through a single operation.21,49 As mentioned earlier, bromocriptine first shrinks the part of a tumor that aggressively extends into the suprasellar space and compresses the optic nerve (as in Cases 4, 5, 8, and 17); therefore, bromocriptine treatment, as a first-line therapy for invasive giant prolactinomas, can reduce the necessity for surgery and associated risks and costs.23 The cure rate following bromocriptine treatment for invasive giant prolactinomas involving the cavernous sinus has not been previously reported. The following conditions are still indications for surgery: 1) intolerance or resistance to bromocriptine; 2) occurrence of CSF leakage while taking bromocriptine which cannot be conservatively treated; and 3) tumor apoplexy causing significant clinical symptoms, such as sudden severely decreased vision.14,41,45,47,58 In the patient in Case 12, the tumor shrunk during the 2nd month of bromocriptine therapy. After 1 year of subsequent drug therapy, residual tumor was localized in the sella turcica and the left cavernous sinus, without further reduction; transsphenoidal surgery was performed to excise the remnant. The patient has continued to take bromocriptine postoperatively, and at present, the tumor has vanished completely and the PRL level is normal.

**Timing of Radiotherapy**

Because of potential side effects, radiotherapy is presently regarded as an adjunctive therapy after surgery or drug treatment.10,19,31,36,58 In our series, 11 patients underwent radiotherapy within 2 months of starting bromocriptine to accelerate shrinkage of the tumor volume and to enhance control of the PRL level. Positive effects were achieved during a mean follow-up period of 37.5 months: tumor volume shrank by a mean of 93.5%. However, the use of radiotherapy should be carefully considered. In patients with hypopituitarism and sharply decreased vision and in young wom-
en who wish to remain fertile, radiotherapy is not a feasible choice. In the nine patients who did not undergo radiotherapy, tumor volume shrank by a mean of 93% during a mean follow up of 37 months, and there was no significant difference between the groups with or without adjuvant radiotherapy. In other words, traditional radiotherapy did not enhance tumor volume shrinkage. Given the positive effects of bromocriptine treatment on invasive giant prolactinomas and the potential side effects of traditional radiotherapy, the latter method is selected more and more cautiously. On the other hand, after bromocriptine treatment, if the tumor is localized to limited areas and continuous drug administration does not shrink the tumor, one might perform gamma knife surgery, which could control the residual tumor with cavernous sinus invasion. Some authors have proposed a technique for pituitary gland transposition, which involves transposing the normal pituitary gland away from the cavernous sinus tumor and interposing a fat graft between the gland and the tumor. This process increases the distance between the two to facilitate radiosurgical treatment of residual tumor, thereby reducing the effective biological dose to the normal pituitary gland.

Conclusions

We reported on 20 patients with invasive giant prolactinomas in the cavernous sinus who had experienced successful treatment outcomes. In summary, bromocriptine can dramatically reduce tumor volumes and control prolactinoma levels in a relatively short treatment period. During a mean follow up of 37.3 months, the tumors in 11 patients disappeared almost completely on MR images; in the nine patients, tumor volume shrank by 61 to 97%, with residual tumor involving the cavernous sinus. If a localized residual tumor does not demonstrate additional shrinkage with continuous drug therapy, gamma knife surgery may be a good option.

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References


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