Brainstem gangliogliomas: a retrospective series

Clinical article

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Object. The authors retrospectively analyzed data on brainstem gangliogliomas treated in their department and reviewed the pertinent literature to foster understanding of the preoperative characteristics, management, and clinical outcomes of this disease.

Methods. In 2006, the authors established a database of treated lesions of the posterior fossa. The epidemiology findings, clinical presentations, radiological investigations, pathological diagnoses, management, and prognosis for brainstem gangliogliomas were retrospectively analyzed.

Results. Between 2006 and 2012, 7 patients suffering from brainstem ganglioglioma were treated at the West China Hospital of Sichuan University. The mean age of the patients, mean duration of symptoms prior to diagnosis, and mean duration of follow-up were 28.6 years, 19.4 months, and 38.1 months, respectively. The main presentations were progressive cranial nerve deficits and cerebellar signs. Subtotal resection was achieved in 2 patients, and partial resection in 5. All tumors were pathologically diagnosed as WHO Grade I or II ganglioglioma. Radiotherapy and adjuvant chemotherapy were not administered. After 21–69 months of follow-up, patient symptoms were resolved or stable without aggravation, and MRI showed that the size of residual lesions was unchanged without progression or recurrence.

Conclusions. The diagnosis of brainstem ganglioglioma is of great importance given its favorable prognosis. The authors recommend the maximal safe resection followed by close observation without adjuvant therapy as the optimal treatment for this disease.

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KEY WORDS • brainstem • ganglioglioma • diagnosis • microsurgery • prognosis • oncology

GANGLIOGLIOMAS (WHO Grade I–II) are rare tumors of the CNS composed of both neuronal (ganglion cells) and glial elements.13 They are known to have benign histological and biological features with a favorable prognosis.5 Most occur in the temporal lobe; however, these tumors can be found anywhere throughout the CNS.10 The brainstem is an unusual location for gangliogliomas, and thus to our knowledge, only a limited number of cases have been reported.1–3,7,12,17,19 In this report, we summarized our experience in the surgical treatment of 7 brainstem gangliogliomas in the past 6 years and reviewed the relevant literature to promote understanding of the epidemiological findings, presentations, and management of this disease.

Abbreviation used in this paper: GFAP = glial fibrillary acidic protein.

Methods

In 2006 we established a database of posterior fossa lesions. For the present study we searched the database for patients with brainstem gangliogliomas and retrospectively analyzed the records of those treated in the Department of Neurosurgery of our hospital between April 2006 and March 2012. All patients had a pathologically diagnosed WHO Grade I–II ganglioglioma. Intraoperatively, tumors were seen arising from the brainstem. We excluded from analysis those patients in whom either anaplastic ganglioglioma had been diagnosed or malignant transformation had occurred. Data on patient age, sex, symptoms, neurological signs at admission, and duration of clinical history prior to diagnosis were obtained. Data
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on radiological (tumor location, hydrocephalus, associated cysts, and enhancement pattern) and histopathological studies, treatment strategies (surgical approach and extent of resection), and follow-up were also noted.

Results

Patient Sample

Seven patients suffering from brainstem gangliogliomas were treated via microsurgical removal in our department between April 2006 and March 2012. The clinical data are summarized in Table 1. The patients included 4 males and 3 females, with a mean age of 28.6 years. The patients underwent routine admission examinations including a clinical history, neurological examination, and laboratory test. The symptoms and signs consisted of typical cranial nerve deficits in 5 patients and cerebellar signs in 4. The involved cranial nerves included V–VII and IX–XII, and long tract signs were absent. Although the mean duration of symptoms prior to diagnosis was 19.4 months, the patients in Cases 5 and 6 had short histories lasting 1 and 3 months, respectively, while the others had a relatively longer history of 10–60 months. Moreover, signs of increased intracranial pressure were not observed.

Radiological Investigation

Magnetic resonance imaging studies, including T1-weighted, T2-weighted, and Gd-enhanced T1-weighted sequences, were performed in all patients. The MRI characteristics are shown in Table 2. Locations of the tumors were centered on the lower part of the brainstem, including the medulla, lower pons, and cerebellar peduncles. None of the tumors involved the midbrain. Lesions were hyperintense on T2-weighted images and isointense to slightly hypointense on T1-weighted images. Tumor enhancement and an associated cyst were observed in Cases 1 and 2. The tumor in Case 1 was a cystic solid lesion, and the mural nodule was remarkably enhanced. The tumor in Case 2 was a giant lesion with an atypical border and enhanced heterogeneously. Enhancement was not observed in the other 5 cases (Fig. 1). Moreover, hydrocephalus and peritumoral edema were absent in all 7 cases.

Surgical Management

The treatment strategy for brainstem tumor was tailored to the individual. In all patients resection was performed via posterior fossa craniectomy. All patients underwent surgery via the suboccipital midline approach or suboccipital retrosigmoid approach based on the location of the tumor. The aim of surgery was to remove the cystic and exophytic portions of tumor. Diffused portions of the tumors that infiltrated the brainstem and cerebellar peduncles were not resected. Electrophysiological stimulation of the tumor bed and floor of the fourth ventricle was repeated to confirm preservation of brainstem nuclei. Postoperative radiotherapy and chemotherapy were not given.

Two patients underwent subtotal resection, and the other 5 underwent partial resection. Given the hard texture of the lesion and the involvement of important structures (brainstem and cerebellar peduncles), it was not possible to define a clear boundary between brainstem and tumor; thus, total resection was achieved in none of the cases. Intraoperatively, the tumors were grayish. The main goal of surgery was to remove the cystic and exophytic part of the tumor (Fig. 2).

None of the patients was suffering from severe hydrocephalus requiring surgical intervention before tumor removal, and there were no surgery-related deaths.

Histological Analysis

All of the histological specimens revealed a mixture of mature ganglion-type neurons and astrocytoma on H & E staining, confirming ganglioglioma. The immunohistochemical tests, including those for GFAP and neurofilaments, revealed the proliferative activity of the glial cells, and the results were positive. Tumors in Cases 1 and 3 were pathologically diagnosed as WHO Grade II gangliogliomas (Fig. 3), and the others were classified as WHO Grade I gangliogliomas.

Follow-Up and Prognosis

Follow-up was performed at 3 months, 9 months, and then once a year after the operation. During the follow-up period, all patients underwent clinical assessments including neurological examination and cranial MRI. Changes in neurological dysfunction (improved or aggravated) and in the size of residual tumor (increased or stable) were noted.

The mean follow-up was 38.1 months (range 21–69 months). Within 24 hours after surgery, the neurological

<p>| TABLE 1: Summary of clinical characteristics in 7 patients with brainstem gangliogliomas |
|---|---|---|---|</p>
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Duration of Symptoms Prior to Diagnosis (mos)</th>
<th>Symptoms &amp; Signs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39, M</td>
<td>12</td>
<td>diplopia, strabismus, facial numbness, dizziness</td>
</tr>
<tr>
<td>2</td>
<td>17, F</td>
<td>60</td>
<td>trigeminal neuralgia, facial numbness, ataxia</td>
</tr>
<tr>
<td>3</td>
<td>28, F</td>
<td>14</td>
<td>none, ataxia</td>
</tr>
<tr>
<td>4</td>
<td>52, M</td>
<td>36</td>
<td>none, ataxia</td>
</tr>
<tr>
<td>5</td>
<td>6, F</td>
<td>1</td>
<td>gaze palsy, ataxia</td>
</tr>
<tr>
<td>6</td>
<td>9, M</td>
<td>3</td>
<td>dysphagia, ataxia</td>
</tr>
<tr>
<td>7</td>
<td>49, M</td>
<td>10</td>
<td>limited neck mobility, ataxia</td>
</tr>
</tbody>
</table>

* There were no cases of increased intracranial pressure.
functional status improved in 3 patients (Cases 1, 2, and 6), remained similar to the preoperative state in 3 patients (Cases 3, 4, and 7), and deteriorated in 1 patient (Case 5). There were no surgery-related deaths. During the follow-up period, neurological dysfunctions in 6 patients (Cases 1–4, 6, and 7) resolved gradually and in 1 patient (Case 5) were stable without aggravation. Magnetic resonance imaging showed that the sizes of residual tumors were unchanged, and no tumor recurrence was observed in the follow-up period. Therefore, radiotherapy and chemotherapy were not given.

Discussion

Gangliogliomas, first described by Perkins in 1926, are rare tumors of the CNS composed of both neuronal (ganglion cells) and glial elements. These tumors are known to have a benign histological and biological nature with a favorable prognosis; however, rare cases of anaplastic gangliogliomas and malignant transformation have been reported occasionally. According to subsequent reports, gangliogliomas account for about 0.4% of all CNS tumors, and nearly 80% of them occur in the first 3 decades of life. The natural history of this disease can be as long as several years, which suggests that differentiation of the tumor cells is good and that growth is slow. Gangliogliomas are prevalent in the supratentorial compartment and occur mostly in the temporal lobe; however, these tumors can occur within any part of the neuraxis. Gangliogliomas are prevalent in the supratentorial compartment and occur mostly in the temporal lobe; however, these tumors can occur within any part of the neuraxis.

In the present study, we described 7 patients with pathologically diagnosed ganglioglioma at our hospital in the past 6 years. The cases we reported included 4 males and 3 females with a mean age of 28.6 years, and the symptoms of the patients included typical cranial nerve deficits and cerebellar signs, whose mean duration prior to diagnosis was 19.4 months. Instead of the seizures typically caused by gangliogliomas located in the temporal lobe, often there are no early symptoms of brainstem gangliogliomas, and even its mild discomfort could easily be ignored. Hence, the typical age of patients presenting with brainstem gangliogliomas would be older and the duration of symptoms prior to diagnosis would be longer.

Radiological investigations of gangliogliomas are variable without special features as compared with other tumors in the same location, especially when they occur in the brainstem. According to the limited cases reported, the MRI appearance of brainstem gangliogliomas is nonspecific. They can appear to be well-demarcated solid masses or appear as cystic with a mural nodule. Frequently, gangliogliomas are hyperintense on T2-weighted images.

**TABLE 2: Summary of radiological, treatment, and follow-up factors**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor Location</th>
<th>Radiological Study*</th>
<th>Resection Type</th>
<th>Follow-Up (mos)</th>
<th>Karnofsky Performance Scale Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>medulla, pons, peduncle</td>
<td>yes homogeneous</td>
<td>subtotal</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>peduncle</td>
<td>yes heterogeneous</td>
<td>subtotal</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>medulla, peduncle</td>
<td>no none</td>
<td>partial</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>medulla, pons, peduncle</td>
<td>no none</td>
<td>partial</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>medulla, pons</td>
<td>no none</td>
<td>partial</td>
<td>33</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>medulla</td>
<td>no none</td>
<td>partial</td>
<td>21</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>medulla</td>
<td>no none</td>
<td>partial</td>
<td>21</td>
<td>90</td>
</tr>
</tbody>
</table>

* There were no instances of hydrocephalus.

**Fig. 1.** Magnetic resonance images showing different patterns of enhancement of brainstem gangliogliomas. The tumor in Case 1 (A) enhanced homogeneously with an associated cyst after administration of Gd. The tumor in Case 2 (B) enhanced heterogeneously. The tumors in Cases 4 (C) and 7 (D) did not enhance after administration of Gd.
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and isointense to slightly hypointense on T1-weighted images. In many cases, the lesion can be enhanced, ranging from moderate to remarkable. Peritumoral edema and hydrocephalus are unusual. If edema is observed, the tumor could be anaplastic. Moreover, calcification occurs frequently in brainstem gangliogliomas. Among our cases, only 2 were associated with a cyst, whereas the rest were diffusive lesions. The patterns of enhancement were variable: the lesion in Case 1 was homogeneously enhanced, while in Case 2 it was heterogeneously enhanced; the others had no enhancement. Peritumoral edema, obstructive hydrocephalus, and calcification were not observed in any of our cases. Thus, the nonspecific clinical and radiological presentations made the tentative diagnosis of brainstem gangliogliomas difficult. But because of the disease’s favorable prognosis, the diagnosis of brainstem ganglioglioma is of great importance. According to our experience, the differential diagnosis should include pilocytic astrocytoma (Case 1), diffuse astrocytoma (Cases 3–7), and medulloblastoma (Case 2). Advanced MRI techniques, such as diffusion tensor imaging, dynamic susceptibility-weighted contrast-enhanced perfusion imaging, and proton magnetic spectroscopy, have been proven to be useful in differentiating medulloblastomas from gangliogliomas.

Gross-total resection is recommended as the optimal treatment for intracranial gangliogliomas. The completeness of resection is the main factor affecting prognosis and recurrence. The 10-year rate of survival for patients with supratentorial gangliogliomas can be as high as 85%. However, total resection of brainstem gangliogliomas is still unavailable because of the important structures involved and the hard texture of the lesion. Nevertheless, partial resections of brainstem gangliogliomas also carry a favorable long-term outcome, with 5-year survival potentially as high as 78%. Hence, the main goal of surgery is to remove the exophytic and relatively superficial part of the tumor to confirm the diagnosis and improve symptoms.

The role of radiotherapy and chemotherapy is dubious. It has been reported that gangliogliomas are not sensitive to radiotherapy, and deleterious side effects would influence development of the CNS in children. Moreover, some studies have even demonstrated that radiation might predispose a ganglioglioma to malignant degenera-
tion. However, Rades and colleagues have shown another view recently: radiotherapy improved local control of intracranial gangliogliomas that had been subtotally resected. But these authors did not focus on the role of radiotherapy in brainstem gangliogliomas, probably because of the low morbidity. On the other hand, chemotherapy is reported to have minor benefits in controlling tumor progression, and fatal complications such as severe hematological aplasia have been reported. Therefore, we suggest reserving radiotherapy and chemotherapy only for patients with tumor progression and recurrence.

In the current study, subtotal and partial resections were achieved through posterior fossa craniectomy. With the help of intraoperative neurophysiological monitoring and brainstem mapping techniques, important structures of the brainstem were successfully protected, especially for tumors with a hard texture and obex involvement. Postoperatively, no further treatments were administered after 21–69 months of follow-up, MR images showed the sizes of residual tumors were unchanged, and the patients’ symptoms were stable or resolved gradually without aggravation. Therefore, we recommend the maximal safe surgery followed by close observation without adjuvant treatment. If a tumor recurrence is observed in the follow-up period, a second surgery or radiotherapy should be considered individually.

Since there are few large series of brainstem gangliogliomas, the optimal treatment for this disease is still unclear. Our data from 7 patients are insufficient to draw a conclusion, and more studies are necessary to establish an appropriate strategy.

Conclusions

Brainstem gangliogliomas are rare but their diagnosis is of great importance because of their favorable prognosis. We recommend the maximal safe surgery followed by close observation without adjuvant therapy as the optimal treatment for this disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Hui. Acquisition of data: Liu. Analysis and interpretation of data: Wang. Drafting the article: Zhang, Liu. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hui. Study supervision: Hui, Ju.

References
