Neurosurgical treatment of pediatric low-grade midbrain tumors: a single consecutive institutional series of 15 patients

Clinical article

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Object. The authors delineate the long-term results of surgical treatment for pediatric low-grade midbrain glioma.

Methods. A series of 15 consecutive patients (age range 0–15 years) who underwent primary tumor resection for a low-grade midbrain glioma during the years 1989–2010 were included in this retrospective study on surgical morbidity, mortality rate, academic achievement, and/or work participation. Gross motor function and activities of daily living were scored according to the Barthel Index.

Results. Of the 15 patients, 10 were in their 1st decade (age 0–9 years) and 5 were in their 2nd decade of life (age 10–15 years) at the time of surgery. The male/female ratio was 0.50 (5:10). No patients were lost to follow-up. One patient died in the postoperative period (32 days posttreatment). Another 2 patients died during follow-up. One patient succumbed to acute bleeding in the resection cavity 8 months after surgery, and the other died of shunt failure 21 years after initial treatment. Twelve patients are alive at the time of this writing, with follow-up periods from 3 to 24 years (median 8 years).

Among the 12 survivors, the Barthel Index scores were normal (100) in 11 patients and 80 in 1 patient. A total of 25 tumor resections were performed. In 1 patient, further resection was performed 5 days after initial resection due to MRI-confirmed residual tumor. Another 5 patients underwent repeat tumor resection after MRI-confirmed progressive tumor disease and clinical deterioration ranging from 3 months to 4 years after the initial operation. Three of these 5 patients also underwent a third resection, and 1 of the 3 underwent a fourth operation. Six children received adjuvant therapy: local radiotherapy in 2 patients, chemotherapy in 3 patients, and both in 1 patient. Twelve (80%) of the 15 patients needed treatment for persistent hydrocephalus.

Conclusions. Selected cases of low-grade midbrain gliomas may clearly benefit from resection with favorable results, even for prolonged periods. Three patients in the present series died, one of whom had a prolonged survival period of 21 years. Among the 12 survivors, stable long-term results appeared obtainable in at least 9. One patient died of acute hemorrhage 8 months after initial resection; otherwise, rapid tumor progression and death were not observed. Forty percent of the patients received adjuvant treatment, with local radiotherapy, chemotherapy, or both.

Key Words • low-grade midbrain glioma • long-term results • pediatric neurosurgery • oncology

Intrinsic brainstem tumors may be a challenge to the pediatric neurosurgeon. While many of these lesions are typical diffuse pontine gliomas not amenable to surgical treatment, midbrain tumors can be better delineated with or without contrast enhancement, and surgical treatment must be considered. We have recently reported good clinical results after performing resection in 100 consecutive patients with cerebellar low-grade astrocytomas. The present report summarizes our experience with the treatment of 15 consecutive patients with low-grade midbrain gliomas that were resected from 1989 to 2010 after the introduction of MRI at our institution in 1987.

Methods

We retrospectively analyzed a nonselected cohort consisting of 15 patients aged 18 years or younger who underwent primary resection of a low-grade midbrain glioma during the years 1989–2010 in the Department of Neurosurgery at The National Hospital (now known as the Oslo University Hospital) in Norway.

Abbreviation used in this paper: NF1 = neurofibromatosis Type 1.
Pediatric low-grade midbrain gliomas: long-term results

The cases were collected from surgical protocols of the relevant time period and the histological evaluation demonstrated low-grade gliomas. This series included all cases of pediatric low-grade midbrain gliomas surgically treated in this time period. The tumor was intraxial (intrinsc) within the midbrain (mesencephalon) and had a diencephalic extension in 5 patients.

The case record data included sex, age at the time of primary tumor resection, and information on repeat operations and management of hydrocephalus (Fig. 1, Table 1). Scholastic outcome was simplified into normal versus special schooling categories, and employment attendance into categories of open, sheltered, or no work. Neurofibromatosis Type 1 (NF1) was diagnosed in 2 patients (Cases 5 and 8, Table 1).

This series comprises our operative experience in treating low-grade midbrain gliomas after the introduction of MRI at our institution in 1987. The tumor was visualized on preoperative MRI, and repeat MRI scans were acquired in the follow-up program. The aim of the surgical procedure was gross-total resection or at least a substantial reduction of the tumor volume. The degree of resection was evaluated by examining immediate postoperative MRI scans, most often obtained during the same anesthetic procedure.

Neurosurgical Treatment

The primary tumor resection was performed to obtain histological verification but also with the intention to achieve tumor control with surgery alone. The radicality of the resection varied considerably according to the tumor localization, contrast enhancement, and degree of tumor definition within the midbrain complex (i.e., how well the tumor was amenable to resection). The radicality was documented on immediate postoperative MRI scans. In 1 patient, postoperative MRI showing more residual tumor than expected led to a second resection 5 days later. MRI confirmed an approximately 50% tumor reduction in volume after the second resection, and the tumor later exhibited a remarkable response to chemotherapy.

Five other patients had a second resection due to tumor progression, with the procedures being conducted 3 months to 4 years after the initial operation. Three of these 5 patients also underwent additional resections: 3 resections in 2 patients and 4 resections in 1 patient. Details of the surgical approach, repeat resection(s) if applicable, use of adjuvant therapy (chemotherapy or radiotherapy), treatment for hydrocephalus (ventriculostomy or ventriculoperitoneal shunt), duration of follow-up, and Barthel Index scores for the living patients are listed in Table 1.

Adjuvant Therapy

Six of the 15 patients received adjuvant therapy. Three patients were given chemotherapy alone after partial tumor resection, with a remarkable response seen in 1 patient (Patient 6). One patient received both chemotherapy and local radiotherapy (Patient 1). Two other patients underwent Gamma Knife radiosurgery later on (Patient 8, 6 months after surgery; Patient 5, between the third and fourth tumor resection, 5 years after the initial tumor resection).

Assessment of Functional Status

The Barthel Index is a well-established and validated scale using 10 variables to measure performance in basic activities of daily living primarily related to personal care and mobility. Scores range from 0 to 100, with a higher score denoting greater independence. The purpose was to assess functional status and to illustrate eventual differences among subgroups within our cohort.

Results

The ages of the patients at the time of primary surgery are shown in Table 1. Ten patients were in their 1st decade and 5 were in their 2nd decade. The median age was 6 years. The male/female ratio was 0.5 (5:10).

The histological examination revealed a pilocytic astrocytoma (WHO Grade I) in 12 patients. In 2 others, the astrocytoma was fibrillary (WHO Grade II); in the last patient, the grade was uncertain.

There was 1 postoperative death. A 13-year-old boy...
died 32 days after undergoing resection of a large tumor in the tectal plate.

In this series of mesencephalic tumors with diencephalic extension in 5 of 15 patients, persistent hydrocephalus required ventriculocisternostomy or shunt insertion in 80% (12/15). Apart from 1 postoperative death described above, 12 of the remaining 14 patients are alive at the time of this writing, with follow-up durations ranging from 3 to 23 years. Two other patients also died. One patient died of acute shunt failure 21 years after initial treatment at the age of 2 years. The other patient underwent acute operative treatment after a hemorrhage in a large mesencephalic tumor at the age of 15 years. This patient recovered quite well but died 8 months later after suffering a fatal hemorrhage in the same area.

Life-threatening, repeated hemorrhage from a mesencephalic pilocytic astrocytoma was also observed in another patient in the series. In 1990, at the age of 2 years, this boy became acutely ill, and a hematoma was observed at the top of the brainstem. The MRI findings (Fig. 2A) were misinterpreted to indicate a mesencephalic arteriovenous malformation, not approved for surgical treatment. Two years later, he once again exhibited acute brainstem symptoms after repeat bleeding. After treatment with external ventricular drainage, repeat MRI disclosed a contrast-enhancing mesencephalic tumor (Fig. 2B) that was resected and proved to be a pilocytic astrocytoma. After 2 years in relatively good clinical condition, he deteriorated slowly in the ensuing year, with MRI-confirmed tumor recurrence. After a second resection, he was followed for another 18 years. Although clearly ataxic, he is a full-time employee, his Barthel Index score reflects a normal status at the age of 25 years, and his MR images reflect a satisfactory status (Fig. 2C).

### Motor Function and Activities of Daily Living

Although many of the 12 survivors have some focal neurological deficits from the brainstem, gross motor function and management of the activities of daily living are good. In terms of the Barthel Index, the scores are 100 in 11 patients and 80 in 1 patient.

### School, Education, and Work

Seven of the 12 survivors are younger than 20 years (range 9–18 years) and they all follow regular school programs.

Five patients are aged 21–28 years. Three are students, 1 works regularly, and 1 is outside the labor market.

### Discussion

While cerebellar low-grade tumors are known to be a distinct pediatric tumor with excellent results after resection, pediatric brainstem tumors have been found to have a dismal prognosis. Diffuse endopontine tumors are not amenable to resection. For these lesions, many pediatric neurosurgeons seem to dispute the value of histological verification due to the risk of complications and inconsistent WHO grading in different parts of the tumor. In recent years, several authors have advocated taking biopsy specimens because histological entities other than glioma may be encountered. In contrast to the well-known pontine gliomas of childhood, some of the tumors in the midbrain are localized. Selected cases with focal midbrain tumors are therefore candidates for resection, often with rewarding results.

The tumor may be clearly delineated within the

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**TABLE 1: Clinical characteristics of 15 patients with low-grade midbrain tumors***

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age† (yrs), Sex</th>
<th>Surgical Approach</th>
<th>Yr</th>
<th>Repeat Resection</th>
<th>Adjuvant Therapy</th>
<th>Hydrocephalus</th>
<th>Follow-Up (yrs)</th>
<th>Status‡</th>
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<tr>
<td>1</td>
<td>2, F</td>
<td>supratentorial, transcallosal</td>
<td>1989</td>
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<td>chemo &amp; LR</td>
<td>yes</td>
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<td>2</td>
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<td>infratentorial, supracerebellar</td>
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<td>no</td>
<td>yes</td>
<td>24</td>
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<td>no</td>
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<td>100</td>
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<td>chemo</td>
<td>yes</td>
<td>12</td>
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<td>no</td>
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<td>1</td>
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* chemo = chemotherapy; GKRS = Gamma Knife radiosurgery; LR = local radiotherapy.
† Age at the time of primary surgery.
‡ Status is represented as the Barthel Index score for living patients.
Pediatric low-grade midbrain gliomas: long-term results

Brainstem and may have a marked contrast enhancement. It is well known that such contrast enhancement is not a criterion for high-grade tumors in the pediatric age group, as most of them have proved to be low-grade gliomas. This subgroup of children with well-defined midbrain tumors are candidates for neurosurgical resection, although radicality is often not achieved due to the risk of severe persistent morbidity.

In 1968, Pool reported on 3 patients who had prolonged good survival ranging from 10 to 22 years after resection and radiotherapy. Because these tumors are relatively uncommon compared with the low-grade tumors localized to the cerebellar complex, long-term follow-up results after resection in relatively large consecutive series are scarce.

The present report summarizes our surgical experience in 15 consecutive pediatric cases of low-grade midbrain tumors treated over a 22-year period. Sixty-six of our 100 consecutive low-grade cerebellar astrocytomas reported on previously were operated on after the introduction of MRI—that is, within the same time period as the present series of midbrain tumors. This implies that

Fig. 2. Magnetic resonance imaging studies obtained in a 2-year-old boy presenting with hemorrhage at the top of the brainstem. A: The images were misinterpreted as representing bleeding from an AVM. B: Preoperative images (upper panels and lower left) acquired in January 1993 showing a contrast-enhancing mesencephalic tumor; image obtained after tumor resection (lower right). C: Images taken 20 years after primary resection and 17 years after the second resection. No chemotherapy or radiotherapy were needed.
there have been about 4 to 5 low-grade cerebellar tumors for each case of low-grade midbrain tumors among those operated on in the study period.

In this series, the surgical mortality rate was 6.7% (1/15). Another 2 patients died in the follow-up period. One patient died of repeat mesencephalic bleeding 8 months after resection, and the other patient of shunt failure 21 years after primary resection. Eighty percent of the patients are alive. To date, no patient has died of tumor progression, but the median follow-up period is limited to 8 years. Nevertheless, in 5 patients the observed overall survival rates range from 16 to 23 years, in addition to the patient who died of shunt failure after surviving 21 years after initial treatment.

Five patients underwent a second resection due to MRI-confirmed tumor progression, with or without clinical deterioration. In 3 of these patients, further tumor progression occurred, leading to a third resection (Table 1). One of these patients, a 6-year-old girl diagnosed with NF1, underwent a total of 4 tumor resections within a period of 8 years. Her clinical situation has thereafter been uneventful for another 8 years.

The majority of our patients appear to have at least a relatively good long-term prognosis. One of the 14 patients who survived the primary acute resection after tumor bleeding recovered very well but died after sustaining a repeat hemorrhage 8 months later. Repeat tumor bleeding was also observed in the case presented in Fig. 2.

Eighty percent of the 15 patients with midbrain tumors required treatment for persistent hydrocephalus, and 1 of these actually died of acute shunt failure 21 years after primary treatment.

Among the 12 patients still alive, the clinical status in terms of the Barthel Index is 100 in 11 patients and 80 in 1 patient.

Previous clinical patterns were essential in selection of children with dismal prognosis (e.g., patients with rapidly increasing multiple cranial deficits who would not benefit from surgery).²

Although clinical presentation is still of importance, improvement in modern imaging has been of great value. Since the introduction of MRI, improved delineation of the preoperative tumor extension within the brainstem has increased the diagnostic accuracy. Likewise, postoperative MRI reveals the radicality of resection and distinguishes between residual and recurrent tumors as well as tumor progression.

Some patients with NF1 have low-grade brainstem tumors, but the majority have indolent lesions for which resection is not indicated.¹³ In this series, there were 2 patients with NF1 who had clearly growing and expanding lesions and worsening clinical symptoms over time that necessitated resection.

Epstein and Mc Cleary,⁴ Epstein and Wisoff,⁵ and others⁶,⁷ have described the feasibility of resection for certain subgroups of pediatric brainstem tumors soon after the introduction of MRI. Because of the relatively low incidence of such tumors and the variability between cases, larger series and long-term results are uncommon.

In our series, no patients were lost to follow-up. The variability with respect to disease progression, as well as the need for adjuvant therapy, is obvious. Because many of these patients live for many years, brainstem radiotherapy should not be undertaken until further resection seems inappropriate. The role of chemotherapy is difficult to assess from this relatively small series, but individual positive responses have been observed.

Conclusions

Low-grade brainstem gliomas that are well circumscribed within the midbrain should be considered for neurosurgical resection. Although gross-total resection was not achieved in the majority of patients, tumor progression based on repeat MRI findings seemed to be slow or nonexistent. Therefore, clinical progression after long-term follow-up was rare. However, long-term survival with good clinical results appears to be obtainable in many of these patients. In our opinion, brainstem radiotherapy should be deferred until there is clinical progression for which a repeat resection is not advisable. In our group of patients operated on for midbrain tumors, 80% needed treatment for persistent hydrocephalus. Two of the 15 children with midbrain tumors experienced repeated life-threatening hemorrhage from their pilocytic astrocytoma. In 1 of them, the second hemorrhage was fatal.

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: Lundar, BJ Due-Tønnessen, Egge, Brandal. Acquisition of data: Scheie, Stensvold. Analysis and interpretation of data: Lundar, BJ Due-Tønnessen, Scheie, Brandal, Stensvold, P Due-Tønnessen. Drafting the article: Lundar. Critically revising the article: Brandal, P Due-Tønnessen. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lundar.

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