Atypical pediatric ganglioglioma is common and associated with a less favorable clinical course

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Objectives Ganglioglioma (GG) is commonly recognized as a low-grade tumor located in the temporal lobe, often presenting with seizures. Most are amenable to complete resection and are associated with excellent oncological outcome. The authors encountered several GGs in various locations, which seem to have a less favorable clinical course than GGs in the temporal lobe.

Methods The authors performed a single-center retrospective review of all children with a histological diagnosis of GG who were treated at Children’s Hospital Colorado between 1997 and 2013. Each tumor was categorized by 2 pediatric neuroradiologists as typical or atypical based on preoperative MRI appearance. Typical lesions were cortically based, within a single cerebral lobe, well-circumscribed, and solid or mixed solid/cystic. The treatment and clinical course of each patient was analyzed.

Results Thirty-seven children were identified, with a median age at presentation of 8.2 years and median follow-up of 38.0 months. Eighteen tumors (48.6%) were typical and 19 (51.4%) were atypical. All typical lesions presented with seizures, whereas no atypical lesions did so. Sixteen (88.9%) typical lesions were located in the temporal lobe. In the atypical group, tumor location was variable, including 11 (57.9%) in the brainstem. Death during follow-up was statistically more common in the atypical group (31.6% vs 0%, p = 0.02). Gross-total resection (GTR) was achieved for 15 of 16 typical tumors (93.8%), compared with 3 atypical tumors (15.8%, p < 0.0001). Presentation with seizure or non-brainstem location were each associated with survival (p = 0.02 and 0.004, respectively). The presence of mutation in BRAF exon 15 did not differ between the 2 groups.

Conclusions Pediatric GG with typical imaging features is associated with excellent rates of GTR and overall survival. Atypical GG is commonly encountered, less amenable to GTR, and associated with a worse outcome. This may relate to anatomical or biological characteristics and merits further investigation.

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Key Words ganglioglioma; atypical ganglioglioma; pediatric brain tumor; brain tumor; oncology

Ganglioglioma (GG) of the central nervous system is a rare tumor composed of both neoplastic glial and ganglion cells. Nearly 80% of GGs occur in patients younger than 30 years old and they comprise 1%–7% of pediatric brain tumors. GG classically arises in the temporal lobe, and patients present with medically refractory seizures. The typical imaging appearance of GG is a cortically based, solid or cystic, partially enhancing mass that may contain calcifications. Histologically, GG is usually benign, and the prognosis following complete resection is favorable. While features such as anaplasia and necrosis are uncommon, they are associated with the need for adjuvant therapy.

In contrast to typical GGs, atypical lesions may present with alternative clinicoradiographic features. By imaging, some GGs have ill-defined borders with patchy paint brush enhancement, suggesting a more infiltrative nature. In addition, progression occurs in up to 15% of supratento-
rial GGs that are not amenable to complete resection.\textsuperscript{22} As such, adjuvant treatment following subtotal resection is often recommended and may include radiation\textsuperscript{1,22,24,26} and/or chemotherapy.\textsuperscript{25}

We observed that a substantial portion of our patients with GG presented with atypical clinical and imaging features. We hypothesize that these patients have a more complex clinical course than those who present with more typical features.

Methods

After obtaining institutional review board approval, we conducted a single-center retrospective review of all patients with a histological diagnosis of ganglioglioma following surgical treatment at Children’s Hospital Colorado between 1997 and 2013. Patients were included if they were younger than 21 years of age at the time of diagnosis. With the exception of a single patient, cases without preoperative imaging available for review were excluded. This patient was included for some portions of the analysis because the lesion was documented to be in the cerebellar hemisphere, which qualified it as atypical.

Preoperative MRI for each patient was reviewed independently by 2 pediatric neuroradiologists (N.V.S. and L.Z.F.). A tumor was categorized as typical by imaging if it was cortically based, confined to a single cerebral lobe, well-circumscribed, and solid or mixed solid/cystic. Tumors lacking these characteristics were categorized as atypical. Discrepancies regarding imaging characteristics were resolved through review with the senior author. When available, additional imaging studies, including head CT, spine MRI, and postoperative MRI were reviewed after the assignment of each tumor to a radiographic group.

Clinical data were gathered from the electronic medical record independent of the radiology review process. These included patient demographics, presenting symptoms, treatment, and clinical course (including overall survival, event-free survival, and site of progression/reurrence). \textit{BRAF} \textit{V600E} mutational status of the tumor tissue was assessed as previously described\textsuperscript{19} and recorded when available. Based on the combination of the operative report and postoperative imaging study, extent of resection was categorized as gross-total resection (GTR), subtotal resection (STR), or biopsy. Using SAS version 9.3, data were analyzed using the chi-square test, Fisher’s exact test, and Wilcoxon rank-sum tests, where appropriate; \( p < 0.05 \) was considered statistically significant.

Results

Radiographic Features

Thirty-seven patients met the inclusion criteria. Based on imaging features, 18 tumors (48.6\%) were categorized as typical (Fig. 1) and 19 (51.4\%) were described as atypical (Fig. 2, Table 1). Among the typical tumors, 16 (88.9\%) were located within the temporal lobe, with 2 lesions (11.1\%) in the frontal lobe. In the atypical group, no tumor was located within the temporal lobe. Supratentorial atypical tumors were located in the frontal or parietal lobes (\( n = 3 \)), deep gray matter (\( n = 2 \)), and suprasellar region (\( n = 1 \)). The remaining 13 atypical tumors were infratentorial or in the cervical spinal cord (Table 1).

While, by definition, all 18 typical tumors were considered to be well circumscribed, 9 of 18 atypical tumors (50.0\%) also met this criterion. Twelve typical tumors (66.7\%) were mixed solid/cystic, and 6 were solid. In the atypical group, 5 of 18 tumors (27.8\%) were mixed solid/cystic, and the remaining 13 (72.2\%) were solid.

Among typical tumors, 6 (33.3\%) demonstrated homogeneous enhancement and 5 (27.8\%) showed heterogeneous enhancement. The remaining 5 typical tumors (27.8\%) did not demonstrate enhancement; however, contrast was not administered in 2 of these imaging studies. In the atypical group, 4 of 18 tumors (22.2\%) demonstrated homogeneous enhancement, 12 of 18 (66.7\%) heterogeneous enhancement, and 2 of 18 (11.1\%) did not enhance. One patient in the atypical group who harbored a cerebellar GG had only postoperative imaging available for review, and 1 patient with a typical temporal lobe GG had only preoperative brain CT.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Preoperative MR images demonstrating a typical-appearing GG. A: Axial T1-weighted image without contrast demonstrating a well-circumscribed cortically based solid/cystic lesion within the left temporal lobe. B: Axial T2-weighted image demonstrating the same well-circumscribed cortically based lesion within the left temporal lobe. C and D: Postcontrast T1-weighted sagittal (C) and coronal (D) images demonstrating contrast enhancement of the same lesion.}
\end{figure}
Radiographically atypical ganglioglioma

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Patient and Presenting Characteristics

The median age at diagnosis for all patients was 8.2 years (Table 2). The typical group included 10 males (55.6%) and had a median age of 8.9 years (range 1–19 years). The atypical group included 8 males (42.1%) and had a median age of 6.6 years (range 5 days–19 years). All 18 patients in the typical group presented with seizure. In the atypical group, no patient presented with seizure. Symptoms at presentation in the atypical group included long tract signs (n = 7), headache/vomiting (n = 7), lower cranial nerve deficits (n = 5), cerebellar symptoms (n = 2), sensory complaints (n = 2), developmental delay (n = 1), and no symptoms (n = 1).

Surgical Treatment

The surgical approach for each patient was based on the principle of safe maximal resection while minimizing the risk of neurological compromise. Electrophysiological monitoring was used for all cases of brainstem or spinal cord tumors that were not limited to stereotactic biopsy (8/12). Seven of the 11 patients with brainstem GG underwent STR, rather than diagnostic biopsy only. Each of these lesions was exophytic and causing substantial mass effect. As such, we pursued a strategy of maximal safe resection. One patient in the typical group elected not to undergo resection. GTR was therefore achieved in 16 of 17 (94.1%) cases in the typical group and STR in 1 of 19 (5.3%) in the atypical group. Therefore, patients in the atypical group were significantly less likely to receive GTR (p < 0.0001, Table 3). STR was completed in 1 of 17 (5.9%) in the typical group and STR or biopsy in 16 of 19 (84.2%) in the atypical group. Four of the brainstem lesions and 1 thalamic lesion in patients with atypical tumors underwent stereotactic biopsy (5 of 19; 26.3%). In both typical and atypical tumors located exclusively within a cerebral or cerebellar hemisphere, GTR was achieved in 18 of 19 (94.7%).

Histopathological Examination

All tumors underwent histopathological examination and immunohistochemical staining for GFAP and neurofilament protein. Specimens showed a mixture of mature ganglion-type neurons and astrocytic glial component on H&E staining, and immunohistochemical tests revealed proliferative activity of the glial cells. All typical lesions were WHO Grade I. In the atypical group, 1 lesion was a WHO Grade III anaplastic GG and 2 of 19 (10.5%) demonstrated characteristics of additional neoplastic lesions. In one case, a parietal GG gave rise to an atypical teratoid/rhabdoid tumor (AT/RT), as previously described.15 In the

![Fig. 2. Preoperative MR images demonstrating an atypical-appearing GG. A: Sagittal T1-weighted image demonstrating a well-circumscribed intraaxial hypointense solid pontine lesion with small cystic components. B: Axial T2-weighted image of the same lesion. C: Sagittal T2-weighted FLAIR image demonstrating the same lesion. D: Postcontrast T1-weighted coronal image demonstrating partial contrast enhancement of the same lesion with asymmetrical extension into the right cerebellar peduncle.](image-url)

<p>| TABLE 1. Imaging characteristics of tumors assessed (n = 37) |
|--------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Typical Group</th>
<th>Atypical Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>16 (88.9)</td>
<td>0</td>
</tr>
<tr>
<td>Frontal or parietal</td>
<td>2 (11.1)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Deep GM</td>
<td>0</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Suprasellar</td>
<td>0</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Infratentorial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Cervical cord</td>
<td>0</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>16 (88.9)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>2 (11.1)</td>
<td>17 (89.5)</td>
</tr>
<tr>
<td>Characteristics*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-circumscribed</td>
<td>18</td>
<td>9/18 (50.0)</td>
</tr>
<tr>
<td>Cortically based</td>
<td>18</td>
<td>2/18 (11.1)</td>
</tr>
<tr>
<td>w/in a single cerebral lobe</td>
<td>18</td>
<td>2/18 (11.1)</td>
</tr>
<tr>
<td>Expansile/infiltrative</td>
<td>0</td>
<td>10/18 (55.6)</td>
</tr>
<tr>
<td>Mixed cystic &amp; solid</td>
<td>12 (66.7)</td>
<td>5/18 (27.8)</td>
</tr>
<tr>
<td>Solid</td>
<td>6 (33.3)</td>
<td>13/18 (72.2)</td>
</tr>
<tr>
<td>Adjacent edema</td>
<td>6 (33.3)</td>
<td>10/18 (55.6)</td>
</tr>
<tr>
<td>Ventriculomegaly</td>
<td>0</td>
<td>7/18 (38.9)</td>
</tr>
<tr>
<td>Enhancement†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonenhancing</td>
<td>5 (31.3)</td>
<td>2/18 (11.1)</td>
</tr>
<tr>
<td>Homogeneously enhancing</td>
<td>6 (37.5)</td>
<td>4/18 (22.2)</td>
</tr>
<tr>
<td>Heterogeneously enhancing</td>
<td>5 (31.3)</td>
<td>12/18 (66.7)</td>
</tr>
</tbody>
</table>

GM = gray matter.
* One patient did not have preoperative MR images available.
† Two patients with typical GG did not have postcontrast imaging.

GTR (p < 0.0001, Table 3). STR was completed in 1 of 17 (5.9%) in the typical group and STR or biopsy in 16 of 19 (84.2%) in the atypical group. Four of the brainstem lesions and 1 thalamic lesion in patients with atypical tumors underwent stereotactic biopsy (5 of 19; 26.3%). In both typical and atypical tumors located exclusively within a cerebral or cerebellar hemisphere, GTR was achieved in 18 of 19 (94.7%).
other case, a GG was diagnosed in concert with pilomyxoid astrocytoma. This diagnosis was confirmed with electron microscopy and on repeat tumor resection.

BRAF V600E mutational status was available for 26 specimens (68.4%; 7 in the typical group and all 19 in the atypical group). Among typical tumors, 4 of 7 (57.1%) expressed the BRAF V600E mutation, while 6 of 19 (31.6%) atypical tumors expressed the V600E mutation and 2 (10.5%) expressed other BRAF exon 15 mutations. In 2 cases, both wild-type tumors from the atypical group, examination of a second specimen was undertaken following tumor recurrence. In both cases, the second specimen demonstrated wild-type expression. Tumors were not evaluated for the presence of the KIAA1549-BRAF mutation.

**Adjuvant Therapy**

Patients who had imaging evidence of residual tumor, tumor recurrence, or progression were considered for further surgery with or without adjuvant chemotherapy and/or radiation therapy, as deemed appropriate by the multidisciplinary neurooncology team. No patient with a typical tumor required a second operation, adjuvant chemotherapy, or radiation therapy. In the atypical group, 2 of 19 patients (10.5%) underwent a second surgery, both of whom had initial STR. Chemotherapy was required in 13 of 19 (68.4%), and 8 of these patients also received radiation therapy. Among these 8 patients, 1 underwent proton beam therapy and 7 received photon-based fractionated radiation (54 Gy in 30 fractions). Tumors that expressed the BRAF V600E mutation were considered for treatment with the BRAF antagonist Vemurafenib (Zelboraf, Genentech Inc.).

**Follow-Up**

The overall median follow-up was 38 months (range 0.5–155 months) from diagnosis. In the typical group, the median follow-up was 56.5 months (range 0.5–155 months; Table 2). In the atypical group, the median follow-up was 25.0 months (range 1–151 months). Local recurrence was identified in 1 patient (5.5%) in the typical group and 7 (36.8%) in the atypical group. Metastatic disease occurred in 0 patients in the typical group and 2 (10.5%) in the atypical group. One patient whose initial surgery achieved GTR was noted to have a very slowly growing local recurrence that has not required intervention. No other patient whose initial surgery achieved GTR presented with recurrence or metastatic disease. There were no deaths in the

<table>
<thead>
<tr>
<th>TABLE 2. Clinical characteristics of patients at presentation and follow-up (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Median age (yrs)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Primary presentation</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
<tr>
<td>Headache/evidence of elevated intracranial pressure</td>
</tr>
<tr>
<td>Focal neurological deficits</td>
</tr>
<tr>
<td>Developmental delay</td>
</tr>
<tr>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Extent of resection*</td>
</tr>
<tr>
<td>GTR or complete laser ablation</td>
</tr>
<tr>
<td>STR</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
<tr>
<td>Adjuvant therapy†</td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Outcomes†</td>
</tr>
<tr>
<td>Mean follow-up (mos)</td>
</tr>
<tr>
<td>Median follow-up (mos)</td>
</tr>
<tr>
<td>Metastasis</td>
</tr>
<tr>
<td>Local recurrence</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

* One patient with incomplete surgical data was excluded.
† Two patients with less than 1 month of follow-up were excluded.

**TABLE 3. Association between GTR and presenting clinical or imaging characteristics**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>GTR (n = 18)</th>
<th>No GTR (n = 17)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>15</td>
<td>1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Atypical</td>
<td>3</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>15</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nonseizure</td>
<td>3</td>
<td>16</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any cerebral</td>
<td>17</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Noncerebral</td>
<td>1</td>
<td>15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporal</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nontemporal</td>
<td>5</td>
<td>16</td>
<td>0.0001</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Nonbrainstem</td>
<td>18</td>
<td>7</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**TABLE 4. Association between death during follow-up and presenting clinical or imaging characteristics**

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Alive (n = 29)</th>
<th>Dead (n = 6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical</td>
<td>16</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Atypical</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nonseizure</td>
<td>13</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>Any cerebral</td>
<td>18</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Noncerebral</td>
<td>11</td>
<td>5</td>
<td>0.07</td>
</tr>
<tr>
<td>Temporal</td>
<td>14</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nontemporal</td>
<td>15</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>Brainstem</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Nonbrainstem</td>
<td>24</td>
<td>1</td>
<td>0.004</td>
</tr>
<tr>
<td>GTR</td>
<td>16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Non-GTR</td>
<td>12</td>
<td>5</td>
<td>0.18</td>
</tr>
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</table>
typical group, and there were 6 (31.6%) deaths in the atypical group \((p = 0.02; \text{Table 4})\), occurring between 1 and 39 months from diagnosis. The patient who died at 1 month from diagnosis had a parietal tumor that was demonstrated to be a GG that subsequently developed additional mutations, leading to a mixed GG/AT/RT phenotype.\(^15\) While the behavior of the AT/RT component of the lesion almost certainly drove the patient’s clinical course, the origins of the tumor as a GG led to its inclusion in this analysis.

Patients who presented with seizures \((n = 18; 48.6\%)\), which coincided with being in the radiographically typical group, were significantly more likely to have a GTR \((p < 0.0001)\) and significantly less likely to die during the follow-up period \((p = 0.02)\) when compared with children with all other primary sign/symptoms at presentation \((\text{Tables 3 and 4})\). Children who presented with a GG in a cerebral lobe \((n = 19; 54.3\%)\) were significantly more likely to have a GTR than those with tumors in all other locations \((p < 0.0001)\). While these patients were also more likely to be alive at the last follow-up, the difference was not statistically significant \((p = 0.07)\). This was also true for patients who presented with a tumor in the temporal lobe versus any other location \((p = 0.0001 \text{ for GTR}; p = 0.06 \text{ for death during the follow-up period})\). Children who presented with a GG of the brainstem \((n = 11; 29.7\%)\) were significantly less likely to have a GTR \((p = 0.0001)\) and significantly more likely to die during the follow-up period \((p = 0.004)\) when compared with children with tumors in all other locations. Patients who had a GTR \((n = 17)\) did not have a significant survival benefit when compared with patients who had an STR or biopsy \((p = 0.18)\). The sample size did not provide adequate power to perform multivariate regression analysis for treatment or death.

**Discussion**

Ganglioglioma is most commonly understood to be a rare tumor that presents with a medically refractory seizure disorder and intraaxial temporal lobe location.\(^6\) This single-center experience supports the notion that a substantial portion of pediatric GGs demonstrate an atypical imaging appearance and clinical presentation. These tumors are associated with a less favorable clinical course. Among 37 tumors in our series, 18 (48.6%) presented with imaging characteristics that are commonly associated with typical GG. These lesions were well-circumscribed, cortically based masses within a single cerebral lobe, and with a solid or solid/cystic appearance.\(^21,27\) Masses without these characteristics \((n = 19; 51.4\%)\) were categorized as atypical. After defining the groups based on these radiographic parameters, we analyzed the clinical presentation, management, and outcomes of the patients in each group. This demonstrated a significantly lower likelihood of both GTR \((p < 0.0001)\) and survival \((p = 0.02)\) for children who presented with atypical-appearing GGs.

**Radiographic Features**

The 2 populations in this study were defined by differences in the imaging characteristics of their lesions. The criteria we selected to represent a typical lesion were based on a combination of clinical experience and existing literature.\(^{13,14,17,18,21,27}\) We limited typical lesions to those that were cortically based, well demarcated, within a single cerebral lobe, and with solid or mixed solid/cystic character. Any lesion not meeting these criteria was considered atypical. While the temporal lobe is, without question, the most common location for GGs, multiple authors\(^{13,14,21,27}\) have reported that 10%–15% of these lesions arise within other cerebral lobes. Therefore, location outside the temporal lobe alone did not characterize a tumor as atypical. However, with a larger sample size, it may be possible to determine if temporal lobe location alone is associated with better overall survival and rates of GTR than other anatomical sites.

Many authors describe the cortex as the most common location for supratentorial GGs. Im and colleagues\(^{13}\) described a pattern of poor cortical demarcation in 44% of their cases and sharp demarcation in 32%. In our experience, GGs of the cerebral hemispheres are usually well-demarcated lesions, which led to our decision to specify this characteristic for typical lesions. We chose not to use the presence of tumor-associated calcifications as a criterion for typicality because this study relied primarily on MRI, with the resultant challenges regarding the identification of calcifications with this modality. Although somewhat subjective, the decisions to use only MRI features and to specify that typical lesions be well-demarcated were supported by existing literature and our clinical experience.

**Clinical Presentation**

The primary presenting symptom of patients with typical GGs was medically refractory seizures in all 18 cases. Surprisingly, in the atypical group, no patient presented with seizures. Therefore, seizures were the primary presenting symptom in 18 of 37 cases (48.6%). This is slightly lower than the rate of seizures in comparable sized series, which range from 68% to 92%.\(^{7,8,12,13,25}\) While many of these series include adult patients, and ours is limited to the pediatric population, the difference in seizure prevalence is more likely explained by a higher proportion of atypical lesions in our population than in prior reports. For example, Haydon and colleagues\(^{12}\) reported seizures at presentation in 37 of 53 patients (70%), from a series in which 42 of 53 tumors (89%) were located within the cerebral cortex. El Khashab and colleagues\(^{8}\) limited their series to patients with low-grade GG, with 68% of their patients harboring tumors in the cerebral cortex and 68% presenting with seizure. Zentner and colleagues\(^{22}\) reported on 47 of 51 patients (92%) who presented with seizures, but only 2 cases (4%) in the series were infratentorial. Im and colleagues\(^{13}\) presented a series in which 82% of cases were supratentorial, versus 67.6% (25/37) in our series. In a series with tumor demographics more similar to ours, Lou and colleagues\(^{21}\) reported that 72% were supratentorial tumors, with seizures at presentation in 48% of cases (16/33).

While seizures were common in the typical group, children with atypical GG presented with a broader range of symptoms, corresponding to the anatomical sites of their lesions. In this group, focal neurological deficit was a presenting symptom in 10 patients (52.6%; Table 2). This is similar to previous reports regarding brainstem/infratentorial...
torial GGs.\textsuperscript{9,18,21,29} Previously reported series of brainstem GG reported evidence of elevated intracranial pressure, cranial nerve deficits, and/or cerebellar signs in every patient.\textsuperscript{2,29} Six of the 9 patients (66.7\%) with infratentorial tumors reported on by Lou and colleagues\textsuperscript{21} presented with headache and vomiting. Gleckman and Smith\textsuperscript{8} reported on a 3-year-old girl who died following sudden respiratory failure due to an undiagnosed infiltrative medullary GG. Among the 6 supratentorial atypical lesions in our series, 2 presented with hemiparesis, 2 with headache, 1 with leg weakness, and 1 was asymptomatic. These data support the notion that atypical GGs lead to clinically relevant differences in presentation and behavior, when compared with typical GGs.

**Surgical Treatment**

Multiple reports,\textsuperscript{7,8,12,13} including this one, demonstrate that GTR, when safely achievable, is expected to be curative and should be the operative goal when GG is suspected. Among our patients in the typical group, GTR or complete laser ablation (n = 1) was achieved in 16 of 17 cases (94.1\%). At a median of 56.5 months of follow-up, none of these patients has required additional therapy and 1 (5.9\%) has demonstrated very slow growth of potential recurrent tumor over the course of 6 years. While GTR alone was not associated with a significant survival advantage (p = 0.18; Table 4), patients with typical-appearing tumors did have a significant survival advantage over the atypical group, which had a lower rate of GTR (15.8\%). Consistent with this finding, Haydon and colleagues\textsuperscript{12} recently reported that greater volumetric extent of resection was the most important variable associated with prolonged recurrence-free survival. This was also consistent with the reports of Compton and colleagues\textsuperscript{2} and Im and colleagues,\textsuperscript{13} who reported no patients with recurrent tumor after GTR. While univariate analysis indicated improved progression-free survival following GTR in their series, multivariate analysis of the experience of El Khashab and colleagues from Dallas\textsuperscript{8} demonstrated that presentation with seizures was the only variable significantly associated with the absence of tumor recurrence. Our data also indicate that presentation with seizure is associated with a greater likelihood of GTR and survival. Unfortunately, our sample size did not allow us to complete a multivariate analysis, which might provide greater insight into the relationship between seizure presentation, GTR, and survival.

Multiple reports demonstrate that tumor location has the greatest impact on the likelihood of GTR.\textsuperscript{2,7,12,29} Atypical GGs, such as those in the brainstem or deep supratentorial structures, are less likely to be completely removed operatively. These data are germane to our hypothesis, that is, that tumors with atypical imaging features differ in presentation and behavior from typical GGs. While we observed only nonsignificant evidence of a survival advantage following GTR, there were no recurrences in this group. However, GTR was not achieved in the majority of atypical tumors. It is unclear whether this was due to the anatomical locations of the lesions, more infiltrative behavior resulting from biological differences, or other factors.

**BRAF Mutation and Relevance**

The clinical relevance of the BRAF V600E mutation in GG has been demonstrated.\textsuperscript{16,25} Among GGs of the posterior fossa and spinal cord, Gupta and colleagues\textsuperscript{10} found that 43\% harbored the BRAF V600E mutation. This is similar to the rate of BRAF exon 15 mutations we observed in atypical tumors (8/19; 42.1\%), although these data were only available in 68\% of our cases. Of these 8, 5 arose in the brainstem, 2 were thalamic, and 1 was a parietal GG from which an AT/RT arose. While recent work from our institution showed differential gene expression between brainstem and supratentorial GG,\textsuperscript{8} the presence of the BRAF V600E mutation did not vary between GGs of the infra- and supratentorial spaces.\textsuperscript{19} Our findings, that the BRAF V600E mutation was not more common in atypical tumors, supports the latter report. This finding is expected, however, given the overlap among specimens from the same institution. Our finding does support the idea, however, that the more aggressive clinical course of atypical tumors may not be attributable to the presence of the BRAF V600E mutation. This may limit the utility of antitumor agents targeting this mutation. It is unclear whether the more aggressive clinical course of atypical tumors results from other genetic or epigenetic mechanisms, or from the surgical constraints related to tumor location. Further investigations of the biology of atypical GG will be required to shed light on this issue.

**Follow-Up and Adjuvant Therapy**

The protocols for adjuvant therapy and patient follow-up were consistent with previously published reports.\textsuperscript{7,8,11–13,18,22,27} Specifically GTR was the operative goal for all patients. Adjuvant therapy was reserved for patients whose tumors were not amenable to a substantial operative debulking or tumors that progressed and were not deemed candidates for near- or gross-total resection. Given the high rate of GTR in the group of patients with typical tumors (15/16; 93.8\%), it is not surprising that each of the 13 patients who required adjuvant chemotherapy as a component of initial therapy was from the atypical group. Among these 13 patients, 8 also received radiation therapy. One additional patient, also from the atypical group, received radiation therapy without chemotherapy. The greater need for adjuvant therapy in the atypical group (68.4\% vs 0\% in the typical group) again supports the belief that atypical-appearing tumors merit a different clinical approach than typical-appearing GGs.

**Limitations**

As an analysis of retrospective data from a single center, this study has several limitations. As with any conclusions derived from a single center, our findings may not be generalizable. In addition, our definition of a typical lesion required judgment regarding whether a lesion was cortically based and well circumscribed. While 2 independent pediatric neuroradiologists agreed upon the characteristics of each case, the subjective nature of these assessments could impact the reproducibility of the data. Lastly, the relatively small sample size limited our ability to evaluate some relationships in a robust manner, as demonstrated by...
a number of findings that approached, but failed to dem-
strate, statistical significance.

Conclusions

We categorized typical pediatric GGs as well-circum-
scribed, cortically based lesions within a single cerebral
lobe. These tumors present almost exclusively with sei-
zures, and oncological cure can be expected following
GTR. Alternatively, GGs without these imaging charac-
teristics portend a much more serious prognosis. These tu-
mors were common in our series (> 50%), presented with
a variety of focal neurological findings other than seizures,
and were much less likely to be amenable to complete op-
erative removal. While the rates of BRAF V600E mutation
do not appear to differ between typical and atypical
GGs, both biological and anatomical characteristics may
contribute to the less favorable prognosis of children with
atypical lesions. It should be noted, however, that the gen-
eralizability of our findings may be limited by the relative-
ly small sample size (n = 37) and the retrospective nature of
the investigation.

Pediatric GG with typical radiological features is asso-
ciated with excellent rates of GTR and overall survival.
GG without these characteristics may be associated with
greater challenges regarding surgical resection and out-
come. This may relate to anatomical or biological charac-
teristics and merits further investigation.

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Disclosure
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Conception and design: Hankinson, Patibandla, Torok, Liu, Handler, Stence, Fenton. Acquisition of data: Hankinson, Patibandla, Dorris, Fenton. Analysis and interpretation of data: Hankinson, Patibandla, Dorris, Torok, Liu, Stence, Fenton. Drafting the article: Hankinson, Patibandla, Torok, Handler, Stence, Fenton. 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: Hankinson. Statistical analysis: Torok. Study supervision: Hankinson.

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