Seizures as the Clinical Presenting Symptom in Children with Brain Tumors

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Abstract
This study summarizes our clinical and surgical experience with pediatric brain tumors that were initially presented with seizures. The records of 367 consecutive children, treated for brain tumors between the years 1996 and 2007, were retrospectively analyzed, focusing on the clinical manifestations, diagnostic gap, and postoperative seizure follow-up that lasted at least 2 years. Seizures, mainly focal, were the clinical manifestation of brain tumor in 57 of 367 children. Normal neurologic examination and electroencephalography (EEG) were in 77.8% and 37.5%, respectively. Diagnostic gap correlated with low-grade and temporal lobe tumors. Postoperative follow-up revealed freedom of seizure in 77.6%. Favorable seizure outcome correlated with low preoperative seizures frequency, preoperative response to antiepileptic drugs, and hemispheric tumor location. We conclude that response to antiepileptic drugs, generalized seizures, normal EEG, and normal neurologic examination should not exclude tumor etiology. Moreover, broader indications for imaging should be employed while evaluating a child with a seizure.

Keywords
brain tumor, epilepsy, diagnostic gap, postoperative seizures

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Pediatric brain tumors account for 16.6% to 21.7% of all childhood malignancies.¹,² These are the most common solid tumors and the leading cause of cancer-related morbidity and mortality in this age group.³ Since the 1980s, an increase in the incidence of pediatric brain tumors has been reported, and whether this tendency represents an etiologic phenomenon or is a result of the improvement and greater availability of diagnostic tools is still under debate.⁴

Although seizure is a common presenting symptom of pediatric brain tumors, the latter is only a rare cause of epilepsy in childhood. Seizure is the most common neurologic disorder in childhood⁵ and is responsible for about 150,000 American children and adolescents who apply for medical care annually.⁶ However, brain tumors have been estimated to be the cause for seizures in only 0.2% to 0.3% of cases.⁷ A recent study suggests that glutamate secretion from gliomas may induce seizures.⁸ Yet the exact relationship between brain tumors and seizures is poorly understood.

In the search for suggestive characteristics of neoplastic etiology, we aim to describe a cohort of children with brain tumors who presented with seizures, focusing on the clinical manifestations, diagnostic gap, and postoperative seizure outcome.

Patients and Methods
Medical records of consecutive children aged 0 to 19 years whose symptoms were diagnosed as brain tumor and were treated by the senior author (SC) at the Dana Children’s Hospital in Tel Aviv from 1996 to 2007 were retrospectively analyzed. The medical records of the group that presented with seizures at the time of diagnosis were reviewed, including ambulatory and hospital records, neurologic consultations, neurosurgery files, pathologic records, neurologic follow-up in the Pediatric Neurology unit, and electroencephalographic (EEG) recordings. When necessary, an additional phone survey was conducted. Only records of patients with postoperative follow-up of at least 2 years were included in the study. We recorded information on demographic data: age, sex, family history; clinical data: patient history, neurologic findings, EEG findings, imaging findings; tumor characteristics: pathology, grading, location; seizure characteristics: type, duration, frequency, response to antiepileptic drugs, and an Engel score. Diagnostic gap was defined as the time between the onset of the first presenting symptom until radiologic diagnosis, and it was classified according to a symptom interval of 3 subgroups: less

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than 3 months, between 3 months and 1 year, and more than 1 year. The Institutional Ethics Review Committee approved the study.

Statistical Analysis
Data were summarized using the FileMaker Pro 7 database. Statistical analysis was performed using the SPSS software package, version 19.0 (SPSS Inc, Chicago, Illinois). Descriptive statistics were used to describe the general features of the study population. Chi-square was used to compare the "seizures only" group and "seizures with associated manifestation" for tumor characteristics (eg, hemispheric location, tumor grading) and seizure characteristics (eg, seizure type, seizure frequency). Student t test was used for comparison of these 2 groups for age and diagnostic gap. Pearson correlation coefficient was used for examining the correlation between the diagnostic gap and tumor grading and hemispheric location. Correlation of postoperative seizure outcome (Engel score) with preoperative seizure frequency, preoperative antiepileptic drug response, and tumor location (hemispheric vs midline) were performed using the Spearman correlation coefficient. Statistical significance was defined as P < .05.

Results
Patient Characteristics
Seizure as the clinical manifestation of brain tumor was present in 57 of 367 children with brain tumor (15.5%). Three children were lost to follow-up; thus the study group comprised 54 children. There were 27 boys and 27 girls. The mean age at symptom onset was 7.1 years (range, 1 month to 19 years). Two of the children had tuberous sclerosis, one had ulcerative colitis, and another one had acute myeloid leukemia that presented 9 years before the brain tumor.

Tumor Characteristics
Almost all tumors (n = 51/54) were supratentorial (94.4%). The tumor was located in the cerebral hemisphere in 90.7%, and at midline in 9.3%. Most tumors (51.9%) were found in the temporal lobe and 31.5% in the frontal lobe. Tumor type was mainly (74.1%) gliomas, including 12 gangliogliomas, 12 pilocytic astrocytomas, and 10 astrocytomas. The most common nonglial tumors were dysplastic neuroepithelial tumors in 7 patients (14.8%). Tumor grading was mainly low-grade (88.9%), whereas only 11.1% were high-grade tumors (WHO grade III, IV).

Clinical Manifestations
In 48 children, seizures were the first symptom. Six had other symptoms prior to seizures: 2 had headaches, 2 experienced recurrent vomiting, and 2 displayed behavioral changes. Neurologic examination at diagnosis was normal in 42 children (77.8%). Abnormal findings among the remaining 6 children were visual field disturbances (5), cerebellar signs (2), focal motor deficits (2), torticollis (1), strabismus (1), and hypotonia (1) (Figure 1).

Seizures were the only clinical manifestation in 24 children (who had no other symptoms and normal neurologic examinations). The most common accompanying symptoms were a new onset of educational or behavioral difficulties (n = 9), headache (n = 8), and vomiting (n = 7). Other signs and symptoms at diagnosis were visual difficulties (n = 3), limb weakness (n = 2), torticollis (n = 1), urinary incontinence (n = 1), and febrile disease (n = 1).

Seizure Characteristics
Seizure duration before diagnosis ranged from a few days to 141 months, with a median of 5.5 months. Seizures occurred on a daily basis (53.7%), weekly (24.1%), or less than once a week (22.3%). Seizure type was mostly partial (85.2%) including simple partial seizures (18.5%), complex partial seizures (42.6%), and partial with secondary generalization (24.1%). Eight children had generalized seizures, of which 7 had tonic-clonic seizures and 1 had myoclonic seizures. Forty-nine of 54 were treated with antiepileptic drugs prior to the diagnosis, of which 32.6% had complete responses, 40.8% had partial responses, and the remaining 26.6% had no response.

EEG Findings
EEG examination was abnormal in 30 cases (62.5%). The positive findings were focal epileptiform patterns in 23 cases, 3 with focal slowing, 3 with generalized slowing, and 1 with generalized epileptiform activity. Location of epileptic activity was “focal in tumor area” in 18 cases, “focal but not in tumor area” in 8, and 4 cases displayed generalized activity. Six children did not have an EEG examination at diagnosis. EEG was normal in the remaining 18 cases (37.5%).

Diagnostic Gap
The time between initial symptom onset and tumor diagnosis ranged between a few days to 141 months. Median symptom interval was 6 months. Delayed diagnosis of more than 3 years was found in 11 cases, and more than 5 years in 5 cases. A prolonged diagnostic gap was found in correlation with low-grade tumors (P < .05), as all cases with a delay in diagnosis of more than 1 year (n = 18) were caused by low-grade tumors, whereas
reduction with surgery were originally nonresponsive to antiepileptic drugs (Table 3). Hemispheric tumor location as compared to midline tumors also correlated with a better seizure outcome ($r = 0.344$, $P < .05$).

**Discussion**

In this study, we describe the characteristics of children with brain tumors who presented with seizure. This is one of the largest series reported,9–11 providing a detailed description of nosology in relation to tumor features.

Seizures were the clinical manifestation of pediatric brain tumor in 15.5% of cases. This finding is in agreement with other studies, as was shown in a meta-analysis indicating that seizures account for about 13% of pediatric brain tumor presentation.14

Tumors that had seizure manifestations were, as expected, almost all supratentorial, mostly gliomas, with a relatively high frequency of gangliogliomas, frequently temporal lobe located, and low-grade as described by previous studies.14–16

We found that in most cases (30/54), the tumor presented with additional manifestations besides seizures. Coexistence of classical symptoms of brain tumors such as behavioral changes, headaches, vomiting, or abnormal neurologic findings should be explored.17 Nevertheless, it should be emphasized that in a significant number (44%) of cases, seizures were the only clinical evidence of a brain tumor. The fact that the neurologic examination is usually normal is well established in the literature.9–11,18 Blume et al suggested the high possibility of existence of tumors in the setting of chronic uncontrolled partial seizures that accompany a normal neurologic examination, as well as preserved intelligence.12 This distinguishes seizures from any other clinical manifestation of brain tumor, in which all other presenting symptoms tend to be associated with abnormal neurologic examinations.17

As expected, partial seizures were found in the majority (85.2%) of seizure type caused by brain tumor, and among them the most common were complex-partial seizures. Appearance of partial seizures should raise a suspicion of neoplastic etiology and requires neuroimaging clearance.19 Other indications for imaging are a prolonged postictal period, malignancy history, cognitive or other neurologic dysfunction, and age younger than 2 years.20,21 Nevertheless, the 7 cases that were manifested with generalized seizure in our cohort, emphasize

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**Table 1. Diagnostic Gap and Tumor Grading.**

<table>
<thead>
<tr>
<th>Diagnostic Gap</th>
<th>Low Grade</th>
<th>High Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>14</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>3-12 months</td>
<td>16</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>18</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>6</td>
<td>54</td>
</tr>
</tbody>
</table>

* Pearson correlation, $P < .05$.

**Table 2. Seizure Outcome (Engel Score) and Preoperative Frequency of Seizures.**

<table>
<thead>
<tr>
<th>Engel Score</th>
<th>Rare Seizures</th>
<th>Weekly Basis</th>
<th>Daily Basis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>12</td>
<td>8</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>11</td>
<td>26</td>
<td>49</td>
</tr>
</tbody>
</table>

* Spearman correlation, $r = 0.312$, $P < .05$, $n = 49$ (5 deceased).

**Table 3. Seizure Outcome (Engel Score) and Preoperative Antiepileptic Drugs Response.**

<table>
<thead>
<tr>
<th>Engel Score</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>No Response</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15</td>
<td>14</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
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<td>2</td>
<td>2</td>
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<tr>
<td>III</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>3</td>
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<tr>
<td>IV</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>18</td>
<td>13</td>
<td>46</td>
</tr>
</tbody>
</table>

* Spearman correlation $r = 0.481$, $P < .01$, $n = 46$ (5 deceased, 3 did not receive preoperative antiepileptic drugs).
the fact that a neoplasm cannot be ruled out in this setting. Generalized seizures as a clinical manifestation of pediatric brain tumors have been described in several case series, accounting for up to 46.7% of the cases, especially in infants and toddlers.\textsuperscript{22}

Most children in our series responded to preoperative antiepileptic drugs, either by complete or partial response (32.6% and 40.8%, respectively). This is in agreement with other studies that found that most children with brain tumor will respond well to the antiepileptic medications.\textsuperscript{23,24}

EEG is an important tool in seizure evaluation, indicating abnormal findings in 62.5% of cases. Typical findings like epileptiform activity or slowing\textsuperscript{25} are expected to be focal in the tumor area, but focal findings not in the tumor area and generalized disorder were also found, as well as 18 cases (37.5%) with normal EEG. This supports the conclusion of Williams et al that neither generalized abnormality nor a normal EEG excludes the diagnosis of tumor. Repeated studies may be more sensitive whenever clinical manifestations do not match investigation results.\textsuperscript{10}

The mean diagnostic gap in our group (19.5 months) was considerably affected by a few exceptional cases, making the median results (5.5 months) more reliable in describing the general group population. However, this number is still higher than the usual delay in the diagnosis of pediatric brain tumors.\textsuperscript{18,26} but it corresponds with the statement that the diagnostic gap of pediatric brain tumors is prolonged significantly in seizures, compared to other presenting symptoms.\textsuperscript{17,27}

Though the prognostic effect of a shortened diagnostic delay is still questionable in pediatric brain tumors,\textsuperscript{28} the improvement in the quality of life of the child and family following seizure reduction is beyond any doubt.\textsuperscript{29}

The finding that low-grade tumors are associated with prolonged delay is already known.\textsuperscript{18,26} Possible explanation suggests that the grading reflects the tumor "behavior," and thus low-grade tumors may have an indolent appearance, which leads to a prolonged delay in diagnosis.\textsuperscript{30} In addition, we found that tumor location in the temporal lobe was correlated with prolonged delay in diagnosis, as compared to location in the frontal lobe. Prolonged delay in diagnosis of temporal lobe tumors has also been described previously,\textsuperscript{31} though the given explanation that false-negative computed tomographic scans were 2-fold in frequency in temporal than in other lobes can only partially explain this phenomenon in the magnetic resonance imaging (MRI) era.\textsuperscript{13}

Surprisingly, the subgroup of children presented with seizures only (no accompanying symptoms and normal neurologic examinations) and had a shorter delay (4.6 months) in diagnosis, compared to children with additional manifestations. We could have presumed that the existence of further signs and symptoms would raise suspicion and shorten the delay. On the other hand, the shortened delay may be the cause of the single manifestation, and further manifestation would have appeared with a delayed diagnosis.\textsuperscript{18,32}

One of the main arguments for the significance of an earlier diagnosis of a pediatric brain tumor is the great improvement in the postoperative seizure burden. For 87.8% of the children who at least reported a worthwhile improvement (Engel I-III) in seizure outcome, including 77.6% who were seizure free, it strengthens the importance of shortening the delay.

The correlation between preoperative seizure control and favorable seizure outcome has recently been described.\textsuperscript{33} The correlation between tumor location (cerebral hemisphere or midline) to seizure outcome probably reflects the tumor resectability and the relationship between gross-total resection or subtotal resection to seizure outcome, which is well established.\textsuperscript{34} Other predictors that have been described in the literature as correlating with favorable seizure prognosis were seizure duration of less than 1 year\textsuperscript{35} and temporal lobe tumor location.\textsuperscript{34} Cortical dysplasia existence was found to be a negative predictor.\textsuperscript{35} The innovation in our study is the association between preoperative seizure frequency to postoperative seizure outcome. All children with a seizure frequency of less than once a week (n = 12) were later seizure free.

In conclusion, the fact that tumors presented with seizure are still being overlooked and the delay in their diagnosis is considerably higher suggests that wider indications for imaging should be employed while evaluating a child with a seizure. Response to antiepileptic drugs, generalized seizures, and normal EEG should not exclude tumor etiology. Seizure outcome correlates with hemispheric tumor location, seizure frequency, and preoperative response to antiepileptic drugs.

**Author Contributions**

AFV and NN are both first authors who contributed equally to this work. AFV planned the research with NN and CS; instructed NN in his work and closely followed the research development; processed and analyzed the data with NN; and reviewed and corrected the written work. NN planned the research with AFV and CS; read the literature and prepared the introduction; collected all the data and processed and analyzed it statistically with AFV; wrote the research manuscript draft and corrected it according to AFV’s and CS’s instructions; designed the tables and figure; and wrote the final manuscript. UK was in charge of the electroencephalography (EEG) section; designed the EEG evaluation form; and helped interpret unclear EEG results. CS, the senior author and surgeon of the children, proposed the research and planned it with AFV and NN; instructed NN in his work and followed the research development; and later on reviewed and corrected the written work.

**Declaration of Conflicting Interests**

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**Ethical Approval**

The Institutional Ethics Review Committee approved the study.
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