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Original Article

Seizures in Pediatric Patients With Primary Brain Tumors

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ABSTRACT

Background: Seizures are one of the most common symptoms of pediatric brain tumors. The purpose of this study was to define seizures related to primary central nervous system tumors and to identify risk factors predictive of seizure occurrence and recurrence.
Methods: We reviewed the records of children treated from January 1, 2004, to January 1, 2018 and collected data including age, gender, tumor location, histology, extent of initial resection, seizure characteristics, treatment modalities, recurrence, and seizure control. A binomial logistic regression was performed to determine the risk factors of seizure occurrence.
Results: During the observation period, 348 children were diagnosed with a primary brain tumor. The median age at diagnosis was 7.8 years, and the median follow-up interval was 3.9 years. There were 196 boys (56.3%). In our cohort, a total of 70 children (20.1%) experienced seizures. Most of them (64.3%) had cortical tumors. All patients with dysembryoplastic neuroepithelial tumors and 81.8% of patients with glioneuronal tumors presented seizures. Risk factors associated with an increased risk for seizures included cortical location, tumor recurrence, and age at diagnosis. Thirty-nine (86.7%) patients with seizures at diagnosis were seizure free at last follow-up (Engel 1). Significantly more patients (69.6%) with a gross total resection were withdrawn from their antiepileptic drugs when compared with those with subtotal resection (27.3%, $P = 0.007$).
Conclusions: Our study is the largest cohort in children with tumor-related seizures and brings new insight in terms of seizure risk according to tumor types and evolution following treatment.

Introduction

Brain tumors are the second most common malignancies among pediatric patients, just after acute lymphocytic leukemia, and the most frequent solid tumors.[1] Seizures are a presenting symptom in 10% to 15% of children with primary brain tumors.[2-6] Moreover, patients with brain tumors can have seizures secondary to surgery, radiation, metabolic abnormalities, tumor progression, or hydrocephalus or in end-stage illness.[7,8]

Seizures are closely linked to tumor histology and location. Typically, slow-growing tumors involving the cortex, including dysembryoplastic neuroepithelial tumors (DNETs), gangliogliomas, and oligodendrogliomas, have the highest risk of seizures.[9] These tumor types can be associated with focal cortical dysplasia.[10] Besides cortical dysplasia, the pathogenesis of tumor-related seizures is yet to be understood. Multiple factors are probably involved, but the most important mechanisms appear to be loss in the homeostasis of extracellular ions and amino acid neurotransmitters.[11]

There is limited literature on seizures related to pediatric brain tumors. We studied children with primary brain tumors at our institution over the course of 14 years to evaluate the characteristics of tumor-related seizures.

Methods

This project was approved by the ethics committee, and informed consent was waived because of the retrospective nature

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TABLE 1.
Demographics of Children With Brain Tumors

Variable	Number of Patients (%)		
	Total n = 348	Seizures n = 70 (20.1)	No Seizures n = 278 (79.9)
Age at diagnosis			
Median age (years)	7.8 (0.0-19.9)	10.2 (0.2-17.7)*	7.7 (0.0-19.9)
Follow-up			
Median duration (years)	3.9 (0.5-13.0)	4.2 (0.5-13.0)	3.9 (0.5-12.9)
Gender			
Female	152 (43.7)	28 (40)	124 (44.6)
Male	196 (56.3)	42 (60)	154 (55.4)
Seizure cause			
Presenting symptom	45 (64.2)		
Progressive tumor	10 (14.3)		
Postoperative complications	12 (17.1)		
Metabolic abnormalities	2 (2.9)		
Secondary to radiation	1 (1.4)		
Tumor location			
Cortical	65 (18.7)	45 (69.2)*	20 (30.8)
Frontal	33 (50.8)	21 (63.6)	12 (36.4)
Temporal	31 (47.7)	21 (67.7)	10 (32.3)
Parietal	19 (29.2)	12 (63.2)	7 (36.8)
Occipital	6 (9.2)	3 (50)	3 (50)
Midline	101 (29)	16 (15.8)	85 (84.2)
Infratentorial	165 (47.4)	8 (4.8)*	157 (95.2)
Other	17 (4.9)	1 (5.9)	16 (94.1)
Initial surgical resection			
Complete	161 (46.3)	29 (18)	132 (82)
Subtotal	121 (34.8)	32 (26.4)	89 (73.6)
Biopsy	22 (6.3)	3 (13.6)	19 (86.4)
No surgery	44 (12.6)	6 (13.6)	38 (86.4)
Tumor histology			
DNET	8 (2.3)	8 (100)*	-
Glioneuronal tumor	11 (3.2)	9 (81.8)*	2 (18.2)
Anaplastic astrocytoma	4 (1.1)	3 (75)	1 (25)
Pilomyxoid astrocytoma	3 (0.9)	2 (66.7)	1 (33.3)
Diffuse astrocytoma	3 (0.9)	2 (66.7)	1 (33.3)
Neurocytoma	3 (0.9)	2 (66.7)	1 (33.3)
Nongerminomatous germ cell tumor	4 (1.1)	2 (50)	2 (50)
Meningioma	7 (2)	3 (42.9)	4 (57.1)
Ganglioglioma	11 (3.2)	4 (36.4)	7 (63.6)
Choroid plexus tumor	6 (1.7)	2 (33.3)	4 (66.7)
Glioblastoma	16 (4.6)	5 (31.3)	11 (68.8)
Primitive neuroectodermal tumor	9 (2.6)	2 (22.2)	7 (77.8)
Craniopharyngioma	16 (4.6)	3 (18.8)	13 (81.3)
Pilocytic astrocytoma	84 (24.1)	11 (13.1)	73 (86.9)
Pineoblastoma	10 (2.9)	1 (10)	9 (90)
Ependymoma	26 (7.5)	2 (7.7)	24 (92.3)
Optic pathway glioma	13 (3.7)	1 (7.7)	12 (92.3)
Germinoma	15 (4.3)	1 (6.7)	14 (93.3)
Diffuse intrinsic pontine glioma	24 (6.9)	1 (4.2)	23 (95.8)
Medulloblastoma	47 (13.5)	1 (2.1)†	46(97.9)
Germinoma	3 (0.9)	-	3 (100)
Schwannoma	4 (1.1)	-	4 (100)
Other	21 (6)	5 (23.8)	16 (76.2)
Tumor recurrence or progression	57 (16.4)	34 (59.6)	23 (40.4)

Abbreviation:
DNET = Dysembryoplastic neuroepithelial tumor
The "Other" subtype included atypical teratoid rhabdoid tumors, chordomas, ependymosarcomas, gliomatosis cerebri, hemangioblastomas, diffuse leptomeningeal glioneuronal tumors, oligodendrogliomas, pituitary adenomas, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytomas.
Statistically significant *$P < 0.001$; †$P = 0.001$.

of this study. We reviewed the charts of children consecutively treated from January 1, 2004, to January 1, 2018. Patients were retrieved through our local brain tumor database. Patients younger than 21 years were included if they received a diagnosis of central nervous system tumor. Patients were excluded if the follow-up was less than six months after tumor diagnosis to better evaluate seizure incidence and outcome.

Age at diagnosis, gender, tumor location, pathology, extent of initial resection, treatment modalities, and recurrence were collected. For patients who had experienced seizures, electroencephalography (EEG) findings, seizure types, duration and frequency, and response to antiepileptic drugs (AEDs) were extracted.

Tumor location was defined according to cerebral magnetic resonance imaging and was grouped into four categories: cortical, midline, infratentorial, and other. The "other" designation included tumor involving skull base, cranial nerves, and spinal tumors. For cortical lesions, tumor location was divided according to cerebral lobe involvement: frontal, parietal, temporal, and occipital. One tumor could be classified in more than one lobe depending on its extension.

Tumor histology was defined according to the 2007 World Health Organization Classification of Tumors of the Central Nervous System when possible.[12] The pilocytic astrocytoma classification included cortical or infratentorial tumors. Optic pathway gliomas

TABLE 2.
Seizure Characteristics

Variable	Number of Patients (%)
	Total n = 70 (%)
Seizure type	
Focal aware	8 (11.4)
Focal impaired awareness	30 (42.9)
Focal to bilateral tonic-clonic	32 (45.7)
Seizure onset	
Not specified	11 (15.7)
Motor onset	22 (31.4)
Clonic	18 (81.8)
Tonic	7 (31.8)
Myoclonic	1 (4.5)
Atonic	1 (4.5)
Automatisms	2 (9)
Nonmotor onset	27 (38.6)
Sensory	9 (33.3)
Behaviour arrest	10 (37.0)
Autonomic	6 (22.2)
Cognitive	6 (22.2)
Emotional	1 (4.5)
Motor and non-motor onset	10 (14.2)
Seizure frequency	
Daily	18 (25.7)
Weekly	12 (17.1)
Monthly	12 (17.1)
Less than once a month	28 (40)

were grouped separately. This group included both sporadic tumors and those associated with neurofibromatosis type 1. Tumors were grouped as "other" when there were less than three patients with this tumor type over the observation period.

Seizures were characterized according to the International League Against Epilepsy 2017 classification.[13] Seizure outcomes were evaluated using Engel classification, dichotomized as class I (seizure free) and classes II to IV (not seizure free). Patients were considered to have refractory epilepsy if no seizure control was achieved after two AED trials.

Descriptive analysis was performed to characterize the study population. Mann-Whitney U test, chi-square, or Fisher's exact test were used to compare groups, as appropriate. A binomial logistic regression was performed to ascertain the effects of gender, age at diagnosis, length of follow-up, cortical location, glial-neuroglial histology, subtotal resection (STR), and recurrence of the brain tumor on the likelihood that patients have seizures. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure. Bonferroni correction was applied using all 10 terms in the model, resulting in statistical significance being accepted when $P < 0.005$. Based on this assessment, all continuous independent variables were found to be linearly related to the logit of the dependent variable. For all statistical tests significance level was set to $P < 0.05$. Statistical analyses were performed using statistical software SPSS, version 24 (IBM Corporation, Armonk, New York).

Results

Patient characteristics

A total of 348 patients with primary brain tumors were included in our study (Table 1). The median age at diagnosis was 7.8 years (range: 0.1 to 19.9 years old) and the median follow-up was 3.9 years (mean follow-up = 4.5 years, range: 0.5 to 12.5 years). There were 196 boys (56.3%) and 152 girls (43.7%). The most frequent histologic tumor subtypes were low-grade gliomas, medulloblastomas, and ependymomas.

Seizures in patients with brain tumors

Seventy patients (20.1%) presented with at least one seizure. The seizure was directly related to the tumor in 55 patients (78.6%) or treatment complications for 15 patients (21.4%) (Table 1). All patients with seizures had at least one EEG during their follow-up.

Seizures were a presenting symptom in 45 patients (64.3%), whereas 10 patients had seizures at tumor progression or recurrence (14.3%). Twelve patients had seizures due to postoperative complications (17.1%), two had seizures due to metabolic abnormalities (2.9%), and one had seizures secondary to radiation (1.4%).

The seizure incidence was 69.2% in cortical tumors, 15.8% for midline tumors, and 4.8% for infratentorial tumors. Of the eight children with infratentorial tumors who had seizures, only one patient had seizures at diagnosis. The other seven children had seizures at tumor relapse or progression or in the perioperative setting. One patient with medulloblastoma had metastasis at time of progression when seizures occurred.

Patients were more prone to experience seizures if they had a glioneuronal tumor (nine versus two, $P < 0.001$) or DNETs (eight versus zero, $P < 0.001$), whereas patients with medulloblastomas (one versus 46, $P = 0.001$) were less likely to present seizures. Other tumors types had low seizure incidence: optic pathway gliomas (one of 13, 7.7%), diffuse intrinsic pontine gliomas (one of 24, 4.2%), germinomas (one of 15, 6.7%), pinealoblatomas (one of 10, 10.0%) and schwannomas (zero of four). Pilocytic astrocytoma had an overall low incidence of seizure (11 of 84, 13.1%) but 72.7% of patients with cortical pilocytic astrocytoma experienced seizures.

Seizure characteristics are detailed in Table 2. Thirty patients had focal seizures with impaired awareness (42.9%), whereas 32 had focal to bilateral tonic-clonic seizures (45.7%) and eight had seizures with focal awareness (11.4%). Ten patients (14.3%) had a history of status epilepticus related to brain tumor. Seven patients (10%) presented status epilepticus at diagnosis, whereas three (4.3%) had status epilepticus at tumor relapse.

No specific EEG pattern was associated with a tumor subgroup or outcome.

Risk factors predictive of seizure occurrence and recurrence

The potential risk factors of seizure occurrence at any time included age at diagnosis, length of follow-up, glial-neuroglial tumor histology, cortical tumor location, STR at time of initial surgery, and tumor recurrence (Table 3A).

With univariate analysis, age at diagnosis, glial-neuroglial histology, cortical location, and tumor recurrence appeared to be candidate risk factors (Table 3A). Multivariate analysis (Table 3B) revealed the odds of having a seizure adjusted with sex and length of follow-up, increased by a factor of 72.3 (95% confidence interval [CI], 21.6 to 241.9) for patients with cortical tumors. Furthermore, tumor recurrence increased the risk of experiencing seizure by a factor of 9.2 (95% CI, 3.3 to 25.2), whereas glial-neuroglial histology was not predictive of seizure occurrence through the multivariate analysis. The age at diagnosis was also a risk factor for seizure (adjusted odds ratio, 1.3; 95% CI, 1.2 to 1.5), and older patients were more likely to have seizures. The logistic regression model was statistically significant, $\chi^2(4) = 177.542$, $P < 0.001$. The model explained 67.3% (Nagelkerke R^2) of the variance in seizure occurrence and correctly classified 91.8% cases. The area under the receiver operating characteristic curve was 0.945 (95% CI, 0.912 to 0.977).

TABLE 3.
Risk Factors Predictive of Seizure Occurrence (A and B) and Recurrence (C)

A. Univariate Analysis, HR, 95% CI, and *P* Values for Predictors of Seizure Occurrence

Risk Factor	*P* Value	HR	95% CI for HR	
			Lower	Upper
Age at diagnosis (years)	<0.001	1.258	1.173	1.350
Sex	0.24	0.712	0.403	1.257
Length of follow-up (months)	0.30	1.004	0.997	1.011
Cortical location	<0.001	26.738	13.073	54.686
Neuroglial histology	0.03	1.854	1.054	3.261
Tumor recurrence or progression	<0.001	11.879	6.127	23.031
Subtotal resection	0.28	0.722	0.402	1.296

B. Multivariate Analysis Adjusted OR, 95% CI, and *P* Values for Predictors of Seizure Occurrence

Risk Factor	*P* Value	Adjusted OR	95% CI for OR	
			Lower	Upper
Age at diagnosis (years)	<0.001	1.323	1.184	1.478
Sex	0.17	0.522	0.205	1.329
Length of follow-up (months)	0.63	1.003	0.991	1.015
Cortical location	<0.001	72.286	21.600	241.917
Neuroglial histology	0.81	0.886	0.334	2.350
Tumor recurrence/progression	<0.001	9.178	3.341	25.210

C. Univariate Analysis, HR, 95% CI, and *P* Values for Predictors of Seizure Recurrence

Risk Factor	*P* Value	HR	95% CI for HR	
			Lower	Upper
Age at diagnosis (years)	0.45	0.395	0.035	4.482
Sex	0.29	0.918	0.785	1.074
Length of follow-up (months)	0.79	0.863	0.301	2.477
Cortical location	0.22	2.431	0.58	10.181
Neuroglial histology	0.12	11.780	0.507	273.528
Tumor recurrence/progression	0.038	9.667	1.128	82.826
Subtotal resection	0.51	0.604	0.136	2.675

Abbreviations:
CI = Confidence interval
HR = Hazard ratio
OR = Odds ratio

Regarding risk factors predictive of seizure recurrence (Table 3C), tumor relapse or progression were considered as potential risk factors with univariate analysis ($P = 0.04$). Owing to the small sample size of patients, no potential risk factors appeared to be predictive of seizure recurrence with multivariate analysis.

AEDs and seizure control

Of 45 patients with seizures at diagnosis, 39 (86.7%) were seizure free at their last follow-up (Engel 1) (Table 4). AEDs could be withdrawn in 48.9% of patients (22 of 45), whereas the other patients were on one or two AEDs. Six patients had refractory seizures despite several AEDs. Of those, one patient with an ependymosarcoma received a total of eight AEDs. The patient underwent three STRs for the tumor located in the parietotemporal region, and the tumor residue could not be entirely removed because of its proximity to the Wernicke area. Another patient with a glioneuronal tumor received 11 AEDs. The patient underwent two STRs and still has an epileptogenic tumor residue in the temporal region.

Almost all patients who benefit from a gross total resection (GTR) were seizure free (22 of 23, 95.7%) when compared with patients with an STR (17 of 22, 77.3%). This difference was not statistically significant however ($P = 0.10$). AEDs were discontinued in more patients with a GTR (16 of 23, 69.6%) when compared with patients with an STR (six of 22, 27.3%, $P = 0.007$). Median duration on AEDs was 8.5 months (range four to 89 months) for patients with GTR compared with 22.4 months for patients with STR (range 9.5 to 57.6 months, $P = 0.38$).

Discussion

Our study is the largest cohort in children with tumor-related seizures and brings new insight in terms of seizure risk factors and outcome. In terms of demographics and tumor frequency, our study population is comparable to other series of pediatric patients with primary brain tumors.[3,6,14-16] Seizures were a presenting symptom in 12.9% of our cohort, which is similar to smaller pediatric studies but lower when compared with adult series.[2-6,17] This fact can be partly explained by the fact that posterior fossa tumors are relatively rare in adults and cortical involvement with glioblastoma multiforme, diffuse astrocytoma, and oligodendroglioma are more frequent.[18] Depending on inclusion criteria, seizures are observed in 60% to 85% of adult patients with diffuse astrocytomas and 50% to 60% of high-grade gliomas.[17,19]

In our study, 45.7% of children presented with focal to bilateral tonic-clonic seizures, which is slightly more common than a previous series where it ranged from 24% to 35%.[2,6,14] However, similar percentages are observed in other structural etiologies such as stroke, where one-third of patients experience secondarily generalized seizures.[20] Moreover, higher frequencies can be seen in posttraumatic epilepsy, where seizures are usually secondarily generalized with or without apparent focal onset in 60% to 80% of patients.[21,22]

In our study, individual risk factors for seizures included age, cortical location, and tumor recurrence. Glial-neuroglial histology was not a seizure's predictor through the multivariate analysis, which suggests that tumor location is probably more important

TABLE 4.
Treatment Modalities and Seizure Control After Surgery for Patients Presenting With Seizures at Diagnosis

	Number of Patients (%)
	Total n = 45 (%)
Seizure free at last follow-up	
Total	39 (86.7)
On monotherapy	13 (33.3)
On biotherapy	4 (10.3)
No AED	22 (56.4)
Refractory seizures at last follow-up	6 (13.3)

Abbreviation:
AED = Antiepileptic drug

than tumor histology in the pathogenesis of seizures. A larger cohort with enriched patients with DNETs, cortical pilocytic astrocytomas, and other glioneuronal tumors might reveal a difference between each tumor subtype, but this could not be carried out in our study due to sample size.

We report that 64.3% of patients experienced seizures before diagnosis, which is higher than the number recently reported by Ullrich et al. (53.5%).[6] In their study, patients were included if they were followed for more than two years, which could explain why they observed a higher percentage of late-onset seizures often associated with tumor progression.

With detailed data on 45 patients with seizures before surgery, this study adds valuable information on the outcome of these patients. Most patients (86.7%) were seizure free at last follow-up (Engel I) and were no longer on AEDs (56.4%). Ullrich et al. reported that only 39.4% were seizure free.[6] This difference is also probably related to population selection. They, however, observed that 91.5% were well controlled. Our results are similar to those of a smaller study in children with glioneuronal tumors, where the authors reported that 86.6% of patients were seizure free.[23] In a subsequent study, they showed that 98.2% of patients were seizure free if they were medically controlled before surgery compared with 88% with refractory medical epilepsy.[24] In an adult series, 80% patients with preoperative seizures became seizure free.[14] Based on our observations and available data in the literature, refractory epilepsy in children with brain tumors is not common and most patients can expect to have no or few seizures after surgery.

GTR seems to be associated with a better outcome in terms of seizure control, but our observations did not reach statistical significance, most likely due to the small sample size. Kim et al. observed in their series of pediatric patients with brain tumors that seizure outcome was more favorable (Engel's classes I and II) in patients with GTR compared with STR (100% versus 67%). The investigators did not observe significant difference in seizure outcome between patients who underwent lesionectomy and those who had an epilepsy surgery.[25] In general, seizure control in patients with brain tumor appears to be better than in patients with focal dysplasia, of whom between 50% and 80% are seizure free depending on the focal dysplasia subtype and location.[24,26,27]

No study has demonstrated superiority of an AED in terms of seizure control for patients with brain tumors. In general, we favored monotherapy, new-generation AEDs with no significant enzymatic induction, and no myelosuppression. Levetiracetam, lacosamide, lamotrigine, and clobazam are usually good options. The optimal duration of AED treatment before a withdrawal can be considered after surgery is unknown. We observed a significant difference in the percentage of patients off AEDs between those who underwent GTR and those who underwent STR. This difference could be explained by the fact that providers were more reluctant to stop AEDs in patients with STR. In accordance with this observation, the median treatment duration appears to be longer in patients with STR.

We acknowledge that our study has some limitations related to its retrospective nature. We used the 2007 World Health Organization Classification of Tumors of the Central Nervous System because most diagnoses were made before the new classification and some immunochemistry and genetic profiling were not available 10 years ago. Patients with tuberous sclerosis and subependymal giant cell astrocytomas might have been underrepresented in our cohort of patients because they are rarely treated surgically and are not currently integrated to our neuro-oncology database. In our study, we did not assess if hydrocephalus was associated with a higher likelihood of seizure. Owing to its variable severity and low incidence of associated seizures, this possible factor was not included in our analysis. Moreover, patients with seizures occurring in end-stage illness could not be captured adequately because most patients were at home or hospice and these events were often not recorded in medical charts.

Conclusion

Our study described seizure characteristics, onset, and outcome in children with primary brain tumors. More than two-thirds of patients with cortical tumors had seizures. Most pediatric patients with brain tumor can expect to be seizure free after surgery and withdrawn from their AEDs.

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