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Seizures in children with low-grade tumors: outcome after tumor resection and risk factors for uncontrolled seizures

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Object. The goals of this study were to define the incidence of seizures in children with low-grade tumors, study seizure outcome after lesionectomy in these children, and identify risk factors for poor seizure outcome.

Methods. The authors performed a retrospective chart review of children who harbored low-grade brain tumors, experienced seizures, and were treated in a single institution. Statistical analyses included step-wise as well as single-variable binary logistic regression analyses.

Fifty-five children (20%) with seizures were identified in a cohort of 280 children with low-grade tumors. Of these 55 children, 35 harbored cortical cerebral tumors and 20 had noncortical lesions, including six whose tumors were in the posterior fossa. Seizures were defined as controlled if there was no seizure in the 12 months preceding the last clinic visit. All cortical tumors were treated by lesionectomy as an initial procedure. Of the 27 children with cortical tumors whose seizures began before tumor diagnosis, 23 had complete resection and 52% of these 23 experienced no further seizures after surgery. Seizures are presently controlled in 84% of the total 55 patients at a median follow-up time of 4.5 years after the first seizure (range 1–17.4 years). Only two variables, a pericavity hyperintense signal on T_2-weighted magnetic resonance (MR) images and at least 10 seizures prior to therapy for seizures, were associated with uncontrolled seizures.

Conclusions. Lesionectomy may be appropriate in children with low-grade brain tumors. A large number of seizures before therapy and a hyperintense area around the tumor cavity on postresection MR images are associated with uncontrolled seizures. Medical therapy and tumor resection will control seizures in the majority of children with low-grade tumors.

Key Words • seizure • low-grade brain tumor • lesionectomy • outcome • pediatric neurosurgery

Seizures are common in patients with brain tumors, especially in those harboring supratentorial low-grade gliomas.[2,12] There is considerable literature on seizure outcome after surgical resection;[3,6,11,13] however, most of these studies included adults with low-grade tumors who had suffered many years of medically refractory seizures. Because of incomplete myelination, developing brain may be more vulnerable to injury from a tumor or its treatment.[2] Few data are available on long-term seizure control in adult and pediatric patients with low-grade brain tumors and on these patients' risk factors for poor seizure control.

There is continuing debate over whether lesionectomy (removal of the tumor mass only) is adequate for seizure control in children presenting with seizures.[6,9] Some neurosurgeons advocate extended resection that includes the hippocampus and amygdala in patients with chronic refractory seizures and temporal lobe tumors, especially if there is hippocampal atrophy and electrophysiological evidence of a seizure focus remote from the tumor.[10] It is not clear, however, whether extended resection is required in patients whose seizures are well controlled or have not been present long enough to induce secondary epileptogenesis.[8] Our policy is the complete removal of low-grade tumors (if safely resectable) at diagnosis. We reviewed seizure outcome in children treated at our institution.

Abbreviations used in this paper: AED = antiepilepsy drug; EEG = electroencephalography; MR = magnetic resonance; T2HI = T_2 hyperintensity.

Clinical Material and Methods

After we had obtained approval from our institutional review board, we searched the hospital database and neurology clinic records for patients with both low-grade brain tumors (World Health Organization Grades I and II) and seizures. The eligibility criteria included a diagnosis of low-grade brain tumor, treatment at our institution between January 1985 and June 2004, at least one unequivocal witnessed seizure, at least 12 months of follow-up care at our institution, and the availability of medical records. Children who experienced a single seizure within 7 days postcraniotomy were excluded from the study.

Each patients' seizure control status was defined according to the number of seizures experienced during the 12-month period immediately preceding the last follow-up examination, and was classified as the following: controlled if there had been no seizure (equivalent to Engel Class I)[4]; uncontrolled if there had been one or more seizures (Engel Classes II–IV); and intractable if there had been one or more seizures each month and treatment with at least two AEDs had failed (Engel Class IV). Children with intractable seizures, a subset of the uncontrolled seizure group, were identified to study risk factors for the worst outcome. All MR images were reviewed by a single investigator (R.B.K.). Preoperative, immediately postoperative, and the most recent MR images were reviewed. Residual tumor was deemed present if part of the tumor displayed a hyperintense signal on T_2-weighted images or if contrast enhancement persisted on the postoperative image. A T2HI was defined if a new T_2-weighted bright lesion was present outside the tumor T_2 signal in the postoperative image or if it developed sometime after the first postoperative sequence. Absence of tumor or an enhancing signal on T_2-weighted images was considered a gross-total or complete resection (Fig. 1). Tumors were considered cortical if they involved the cerebral cortex and the subcortical white matter; subcortical if they involved the basal ganglia and/or medial structures and the tumor mass did not reach the cerebral cortex; and posterior fossa if the tumor involved structures inferior to the tentorium.

At our institution, intraoperative EEG is not routinely performed if the intent of surgery is to remove an expansile lesion that we suspect is a tumor. Resection is the standard treatment, during which we attempt to approach the lesion through the noneloquent cortex, limit the cortical extension, and remove the entire lesion when possible. Frame-based or frameless stereotactic techniques are frequently used to increase surgical accuracy. We make every attempt to resect the lesion while remaining on its external margin, rather than excising it from the inside out, because we believe this gives us a better chance of obtaining a true gross-total resection with minimal microscopic residual disease. Our assessment of the degree of resection always includes an MR imaging study obtained within 72 hours after surgery to minimize any postoperative artifact. A second follow-up MR imaging study is performed 3 months after surgery. Hemostatic agents such as Gelfoam or Surgicel are never left in the operative cavity.

A backward stepwise binary logistic regression analysis was performed to determine the best subset of variables to be considered jointly. To explore the effects of the remaining candidate variables, we performed single-variable analyses. All variables were determined before data collection and included the following: patient age at tumor diagnosis, sex, number of seizures experienced before starting AED therapy, presence of focal neurological deficits, tumor location (temporal compared with extratemporal), radiation treatment, chemotherapy, need for a ventriculoperitoneal shunt, T2HI, residual tumor, number of craniotomies, and presence of sharp spikes and slow waves on EEG. Regression analyses were performed for the entire cohort of 55 children and for subsets of children with cortical (35 patients) and noncortical (subcortical and posterior fossa; 20 patients) tumors, patients in whom seizures developed before the brain tumor diagnosis (35 patients), patients in whom seizures started after the tumor diagnosis (20 patients), patients with at least 24 months of follow-up review after the seizure diagnosis (46 patients), and patients with cortical tumors who experienced seizures before the tumor diagnosis (27 patients).

Results

Demographic and Clinical Features

Of the approximately 280 patients treated for low-grade tumors during the study period, 55 (20%) experienced seizures (Table 1). All 55 are currently alive and actively participate in follow up at our neurology clinic. Among the 55 children with seizures, 35 (64% of children with seizures and 12% of all patients with low-grade tumors) presented with new-onset seizures as the clinical manifestation of the tumor; 20 others first experienced seizures after the tumor had been diagnosed. Tumors involved the cerebral cortex in

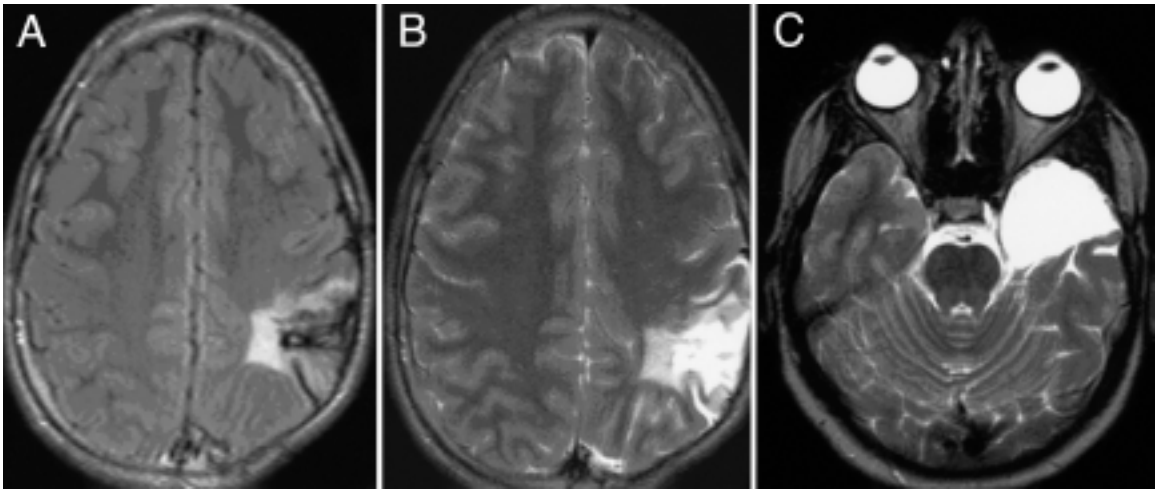

FIG. 1. Magnetic resonance images obtained in two patients. Axial fluid-attenuated inversion-recovery image (A) and a T_2-weighted image (B) showing a hyperintense signal (T2HI) around the tumor cavity in a patient with uncontrolled seizure. Absence of a hyperintense signal around the tumor cavity on T_2-weighted imaging in a patient with controlled seizures (C).

TABLE 1

*Demographic features**

Variable	Frequency (range)
no. of patients	55
male/female ratio	35:20
median age at tumor diagnosis (yrs)	9.3 (0.2–18)
median age at 1st seizure (yrs)	7.4 (0.4–23)
median follow up (yrs)†	4.5 (1–17.6)
time to tumor diagnosis (mos)‡	7.5 (0–122)
time to 1st seizure (mos)§	10.0 (0.5–126)
tumor location (no. of patients)	
cortical	35
subcortical	14
pst fossa	6

* Pst = posterior.
† Time from the first seizure to the last follow-up examination.
‡ Time from the first seizure to tumor diagnosis in 35 children.
§ Time from the craniotomy to the first seizure in 20 children.

35 patients (64%), subcortical structures in 14 patients (25%), and posterior fossa in six patients (11%); the various types and locations of the tumors are provided in Table 2. There were more boys than girls (35 compared with 20). The median age of the children at tumor diagnosis was 9.29 years (range 0.2–18 years) and the median age at first seizure was 7.4 years (range 0.4–23 years). At a median follow-up time since seizure onset of 4.5 years (range 1–17.6 years), the tumors were controlled in 46 patients (84%) and uncontrolled in nine (16% [intractable in five patients (9%)]); 22 patients (40%) were not taking any AED at the last follow-up examination (Table 3). Six patients had experienced a single seizure before tumor resection and none after surgery—all others had experienced at least two or more seizures. The median time from the first seizure to the tumor diagnosis in the 35 patients in whom seizures developed prior to tumor diagnosis was 9 months (range 0–122 months). The median time from the tumor diagnosis to the first seizure was 10 months (range 0.5–126 months) in the 20 patients in whom seizures developed after the tumor diagnosis. At least one interictal EEG recording was obtained in 44 children. Spikes or sharp waves and focal slow waves were present in 32 children (73%).

Cortical Tumors

Of the 35 children with cortical tumors, 29 (81%) underwent complete tumor resection; in 18 patients gross-total tumor resection was obtained at the initial operation, whereas in 11 patients complete tumor resection was not obtained until a subsequent surgery. None of the patients required placement of a ventricular shunt. Of the 27 children with cortical tumors who experienced seizures before tumor diagnosis, 23 (85%) underwent a complete tumor resection. Of these 23, 12 (52%) did not experience any seizure after surgery, whereas 11 (48%) experienced one or more seizures, nine (82%) of whom had suffered at least five seizures before tumor resection. Seizures are currently controlled in eight of these 11 patients. In one child, seizure control was achieved after the initial resection and AED therapy was then withdrawn. Seizures returned with tumor recurrence, however, and the lesion was treated with a second complete resection and radiation treatment. This child has intractable seizures, and treatment with multiple AEDs has failed. Another child with intractable seizures has been treated by a family physician, and his AED therapy is unchanged from that used preoperatively. The third child with uncontrolled seizures is poorly compliant with medications. In the 35 patients with cortical tumors, as of the last follow-up examination, seizures were controlled in 29 (81%) and uncontrolled in six (in four of these the seizures were intractable). Two patients with residual tumor and intractable seizures attained complete seizure control after epilepsy surgery with electrocorticography. Postcraniotomy interictal EEG was performed in 25 patients. Focal spikes and sharp waves were recognized in 15 of these children and slow waves in 10. All 35 children with cortical tumors and seizures received AED therapy initially, but AED therapy was successfully withdrawn in 18 children after complete seizure control had been attained.

TABLE 2

*Tumor types and locations**

Tumor Type	No. of Lesions			
	Total	Cortical (temporal†)	Subcortical	Pst Fossa
LGA	11	9 (4)	2	0
ganglioglioma	8	7 (4)	1	0
JPA	17	1 (1)	10	6
PXA	5	5 (2)	0	0
DNET	2	2 (1)	0	0
oligodendroglioma	11	11 (5)	0	0
CPP	1	0	1	0

* CPP = choroid plexus papilloma; DNET = dysembroplastic neuroepithelial tumor; JPA = juvenile pilocytic astrocytoma; LGA = low-grade glioma; PXA = pleomorphic xanthroastrocytoma.
† Tumor located in the temporal lobe.

TABLE 3

*Seizure control**

Variable (no. of patients)	No. of Patients (%)			
	Controlled	Uncontrolled†	Intractable	No AED‡
total no. of patients (55)	46 (84)	9 (16)	5 (9)	22 (40)
cortical tumor (35)	29 (83)	6 (17)	4 (11)	18 (51)
subcortical tumor (14)	12 (86)	2 (14)	1 (7)	2 (14)
pst fossa tumor (6)	5 (83)	1 (17)	0 (0)	2 (33)
SBD (35)	28 (80)	7 (20)	3 (9)	16 (46)
SAD (20)	18 (90)	2 (10)	2 (10)	6 (30)
follow up ≥24 mos (47)	41 (87)	6 (13)	3 (6)	21 (45)

* SAD = seizure(s) after tumor diagnosis; SBD = seizure(s) before tumor diagnosis.
† Includes partially controlled and intractable.
‡ Number of patients taking no AED as of the last follow-up examination.

Noncortical Tumors

Fourteen children harbored subcortical supratentorial tumors and began to receive AED therapy at seizure onset. In three children in whom gross-total tumor resection was achieved, seizures continued after surgery but could be controlled with medical management. Subtotal resection was achieved in five children, and six children underwent biopsy only. As of the last follow up, seizures are controlled in 12 (86%) of the 14 children, and AED therapy could be withdrawn in two. Six children with seizures had posterior

fossa tumors, and the seizures were controlled in five of them. Nine children have undergone placement of a ventriculoperitoneal shunt.

Neuroimaging Features

Preoperatively, increased Gd uptake was observed in 21 tumors: 13 of the lesions were juvenile pilocytic astrocytomas, four were pleomorphic xanthoastrocytomas, two were gangliogliomas, one was an oligodendroglioma, and one a choroid plexus papilloma. A small degree of enhancement was present after administration of Gd in seven additional tumors: four gangliogliomas, one oligodendroglioma, one fibrillary astrocytoma, and one juvenile pilocytic astrocytoma. No enhancement was present after administration of Gd in 27 tumors: 10 fibrillary astrocytomas, nine oligodendrogliomas, three juvenile pilocytic astrocytomas, two dysembryoplastic neuroepithelial tumors, two gangliogliomas, and one pleomorphic xanthoastrocytoma. A mild peritumoral edema was present around four tumors: one cortical ganglioglioma, one pleomorphic xanthoastrocytoma, and one subcortical and one cerebellar juvenile pilocytic astrocytoma—all four tumors displayed contrast enhancement. Edema around the tumor had resolved in all four cases by the 3-month follow-up examination, including a case with incomplete tumor resection. Six partially resected tumors displayed enhancement postoperatively after Gd was administered.

Risk Factor Analysis

Of the many variables studied in all 55 patients, only two—at least 10 seizures prior to AED initiation and T2HI—showed a statistically significant association with continued seizures when analyzed using the backward step-wise logistic procedure as well as single-variable analyses ($p = 0.04$ and $p = 0.01$, respectively; Table 4). The results of the joint model for T2HI and the number of seizures were very similar to the results of the single-variable analyses for these variables and, thus, the latter are discussed in a sequel. The T2HI and the number of seizures had hazard rates of 0.18 (95% confidence interval 0.04–0.78) and 0.23 (95% confidence interval 0.06–0.90), a finding suggestive that, on average, the risk for uncontrolled seizures is 77% lower when T2HI is absent and 82% lower when a higher number of pretreatment seizures is absent, keeping all other variables constant.

For noncortical tumors, all the studied variables proved not to be significant or not to be estimable in their association with uncontrolled seizures. In children with cortical tumors, the variable of at least 10 seizures prior to seizure therapy was associated with uncontrolled seizures ($p = 0.01$, hazard rate 0.10); all other studied variables were either not significantly associated with uncontrolled seizures or inestimable. In 35 patients who experienced seizures before tumor diagnosis, there was no significant association between seizure control and the duration of epilepsy prior to surgery for 1, 3, and at least 5 years ($p = 0.84$, 0.89, and 0.57, respectively); however, the variable of 10 or more seizures prior to seizure therapy was associated with uncontrolled seizures ($p = 0.02$), and the presence of T2HI showed a trend toward predicting uncontrolled seizures ($p = 0.07$). Many study variables were not estimable, while others were not significant in predicting poor seizure control in subgroups of patients in whom seizures developed after the tumor diagnosis and in patients with cortical tumors in whom seizures developed before the tumor diagnosis. Only the varriable of 10 or more seizures before AED initiation was associated with uncontrolled seizures in patients who had at least 24 months of follow up after the first seizure. Especially for the subgroup analyses, it must be noted that the low sample sizes coupled with the small number of patients with uncontrolled seizures led to very small power values to detect significance, which may in fact be present for some variables. Therefore, in the case of nonsignificant variables, we caution the reader to interpret the results as a lack of adequate evidence for an association rather than a lack of association.

Only six children (11%) experienced intractable seizures. Frequent seizures before tumor diagnosis were significantly associated with intractable epilepsy ($p = 0.04$), whereas T2HI showed a trend towar this factor ($p = 0.08$). All other studied variables, including spikes and slow waves on EEG were not significant predictors ($p > 0.1$).

Discussion

Although there are many reports of seizure outcome after resection of low-grade brain tumors, this study is unique in at least two ways. 1) Unlike studies of surgical treatment of medically refractory seizures in patients with temporal lobe tumors (mostly adults), our study provides data on the incidence of seizures in a large population of children with low-grade tumors. 2) Our study documents long-term seizure control in patients in whom the onset of seizures occurred before or after tumor diagnosis. Our data will help clinicians and surgeons to educate parents and children with low-grade tumors and seizures, especially regarding long-term seizure control.

There is an ongoing debate as to whether the initial surgery in patients with seizures should be lesionectomy or epilepsy surgery inclusive of the ictal onset zone as defined by electrocorticography.[1,3,6,9,10,12] We do not routinely perform intraoperative monitoring for frontal and parietal lobe tumors. For temporal lobe lesions, electrocorticography is only used if there is atrophy or tumor infiltration of the hippocampus–amygdala complex. In this study a few patients with subcortical tumors underwent a biopsy procedure alone; the remaining patients underwent lesionectomy as an initial procedure. Among the 23 children with complete resection of cortical tumors who experienced the first seizure prior to tumor diagnosis, 52% experienced no seizure after the tumor was resected, and improved seizure control was observed in most of the other 48%. With medical treatment, 81% of all patients with cortical tumors had controlled seizures at the last follow-up examination; only two required epilepsy surgery. The seizure control rate in this series is comparable to that reported after tumor surgeries in which intraoperative electrocorticography is used.[1,3,6,9,10,12,13] Our data are retrospective and there are a limited number of patients in the different subsets. Our findings contribute to, but do not settle, the debate of whether the initial surgical treatment should be lesionectomy or extended tumor resection with intraoperative electrocorticography. Only a randomized study with sufficient power can confirm the superiority of one procedure over the other.

TABLE 4
Risk factors for uncontrolled seizures

Variable	Proportion Affected (%)*	p Value (no. of patients)						
		Total (55)	Cortical (35)†	Noncortical (20)‡	SBD (35)	SAD (20)	FU > 2 yrs (46)	Cortical & SBD (27)
>1 craniotomy	33	0.42	0.21	NE	0.23	NE	0.80	0.11
male sex	64	0.58	0.82	0.54	0.31	NE	0.32	0.44
location								
cortical	64	0.84	NE	NE	0.69	0.76	NE	NE
temporal	33	0.47	0.34	NE	0.40	NE	0.71	0.44
age ≤3 yrs§	14	0.75	NE	0.54	1.00	NE	NE	NE
chemotherapy	16	0.64	NE	0.80	0.31	NE	NE	NE
radiotherapy	16	0.64	0.45	NE	0.31	NE	0.98	NE
residual tumor	42	0.86	0.64	0.99	0.60	0.88	0.33	0.58
VPS	13	0.87	NE	0.95	0.55	NE	NE	NE
seizure onset‖	64	0.34	0.69	0.33	NE	NE	0.37	NE
EEG spikes**	74	0.67	0.66	0.14	0.94	NE	0.84	0.67
EEG slow waves**	74	0.57	NE	0.40	0.57	NE	NE	NE
focal deficits††	26	0.81	0.97	0.80	0.25	NE	0.74	0.27
≥10 seizures‡‡	20	0.01	0.01	NE	0.02	NE	0.01	NE
hyperintensity§§	35	0.04	NE	NE	0.07	0.41	NE	NE

* Percentage of all 55 children. Abbreviations: FU = follow up; NE = not estimable; VPS = ventriculoperitoneal shunt.
† Children with tumor involving the cerebral cortex.
‡ Includes children with subcortical supratentorial tumors and those with infratentorial lesions.
§ Age at the time of tumor diagnosis.
‖ Seizure onset prior to tumor diagnosis.
** The EEG results and percentages in 44 children.
†† Focal neurological deficits.
‡‡ Number of seizures before tumor diagnosis.
§§ Hyperintensity around the tumor cavity on T_2-weighted MR images.

The effect of any residual tumor on seizure outcome is unclear: studies with and without a positive correlation have been reported.[3,5,9,13] We did not find adequate evidence to indicate that the presence of residual tumor is associated with uncontrolled seizures in this cohort. It is possible that the presence of residual tumor is important only if the tumor involves the cerebral cortex. Although 23 children (40%) had residual tumor, it involved the cortex in only nine (16%). Nevertheless, the presence of residual tumor in children with cortical tumors did not significantly correlate with seizure control. We do not want to minimize the importance of complete tumor resection in achieving good seizure control because there were seven children with medically refractory seizures in whom seizure control was attained after the initial tumor resection by lesionectomy (incomplete resection in one patient). In six other children, seizure control was attained only after a second operation to achieve a complete resection; two underwent surgery with electrocorticography and two had residual tumor.

We previously reported T2HI as a risk factor for uncontrolled seizures in a cohort of children with low- and high-grade brain tumors.[7] This association was significant in children with only low-grade tumors as well. The T2HI may represent postoperative gliosis or a recurrent tumor. Its presence also showed a trend toward correlation with uncontrolled seizures in the subgroup of patients in whom seizures occurred prior to tumor diagnosis, but its effect on seizure outcome was inestimable in subgroups of patients with cortical and subcortical tumors.

The variable of more than 10 seizures before initiation of AED therapy predicted uncontrolled seizures in all 55 children, both in those patients with cortical tumors and those with seizures prior to tumor diagnosis. All the children with noncortical tumors experienced fewer than five seizures prior to AED therapy, and this risk factor was thus not assessable in this cohort. The cause of poor seizure control in patients with at least 10 seizures prior to a definitive seizure therapy is unclear, but may represent a kindling phenomenon secondary to multiple uncontrolled seizures. This subgroup may contain candidates for up-front epilepsy surgery, but further study is required. Our policy is to resect the tumor as soon as possible if complete tumor resection can be achieved safely. Additionally, we also debulk tumors that cannot be completely resected to reduce the postoperative irradiation field.

Conclusions

This study adds to the literature supporting lesionectomy as an initial procedure for low-grade brain tumors in children presenting with seizures. However, children with multiple seizures prior to surgery may be appropriate candidates for electrocorticography-assisted initial resection. Only a large randomized study will be able to furnish answers to questions regarding when to perform epilepsy surgery in these children. Low-grade tumors in children differ biologically and behaviorally when compared with those in adults, and our data should not be applied to adult patients with tumors who have seizures. We report T2HI as a new risk factor for poor seizure outcome after resection and support previous study findings that the number of seizures experienced prior to craniotomy is a risk factor. Our results indicate that appropriate medical management will control sei-

zures in the majority of children with low-grade tumors, even in the presence of residual tumor. In addition to identifying risk factors for poor seizure control, these data will help physicians prognosticate seizure outcome after tumor resection in children with newly diagnosed low-grade brain tumor.

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