Expanding the role of surgery in intractable extratemporal pediatric epilepsy

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The aim of epilepsy surgery in children is not only to control seizures but also to curtail future adverse neurological sequelae and improve quality of life. If presurgical evaluation demonstrates discordant or multifocal disease, intracranial surgery may be denied as a viable treatment option. When surgical therapy is offered not just as curative but also as palliative therapy, many children not considered optimal surgical candidates may benefit. From a consecutive series of 57 cases involving children who underwent intracranial epilepsy surgery at Rainbow Babies and Children’s Hospital during 2001-2005, the authors present in detail 3 cases involving children who benefited significantly from such an aggressive approach. Marked improvement occurred not only in seizure control, but also in developmental and social functioning. (DOI: 10.3171/FOC/2008/259/E15)

KEY WORDS • intractable epilepsy • extratemporal epilepsy • epilepsy surgery • multifocal seizures • long-term outcome

Outcome in epilepsy surgery is measured and reported in terms of seizure freedom or Engel class.9 Many centers with large number of patients have published their experience in case series. These series have shown similar trends: discrete lesions such as stroke and vascular malformations produce the best outcomes.4 Location of the lesion also influences outcome, with temporal lesionectomy giving better results. While these findings are more robustly reported in adults, pediatric case series document similar results. In pediatrics the outcome measure of seizure freedom may not be the appropriate gold standard for epilepsy surgery.20 If the sole consideration is seizure freedom, it can markedly limit the number of children with intractable epilepsy who are offered surgery as an option. Moreover, while seizure freedom is important, preventing cognitive and developmental decline or stagnation may be an equally valid if not a more practical and important measure of surgical success, especially since children with refractory epilepsy are at considerable risk for cognitive impairment and consequent poor school performance and behavior problems.2,3,7,8,11,24,27 With surgical success being measured not only by seizure freedom but also by developmental outcome, the pool of patients who may potentially benefit from this treatment modality greatly increases. The size of the patient pool further increases if epilepsy surgery becomes part of a multimodal treatment regimen in which attempts at preventing developmental stagnation and controlling seizures are made by multiple available avenues including medical therapy, invasive surgery, and VNS. Since the inception of our epilepsy surgery program in 2001, we have adopted such a multimodality philosophy. The more than satisfactory results in our patient cohort validate our approach. In the present paper we summarize our results and present 3 cases in detail to illustrate our integrative approach for children with intractable epilepsy not typically thought to be optimal candidates for surgical therapy.

Methods

Children who underwent extratemporal or multilobar surgical resections at Rainbow Babies and Children’s Hospital from 2001 to 2005 were identified from the surgical database. Those with discordant presurgical data or evidence of multifocal disease on EEG studies or neuroimaging were further selected. From this subset, 3 cases involving prototypical patients are presented. Institutional review board permission and written informed consent from parents were obtained prior to chart review.

Results

A total of 57 consecutive patients underwent cranial procedures to evaluate and/or treat medically refractory epilepsy in the study period, including 48 children who had chronic implantation of subdural and depth electrodes (Fig. 1). The 9 children who did not have invasive monitoring
underwent various procedures: temporal and/or extratemporal resections with electrocorticography; corpus callosotomy; or hemispherectomy. Eight (17%) of the children who had invasive monitoring did not undergo resection of the seizure focus, and 6 (75%) of these 8 underwent implantation of a VNS unit. The 8 children in this group had bilateral independent foci from multiple etiologies, including developmental delay (4 children), prematurity (1), severe head trauma (1), MCA stroke from sickle cell disease (1), and unknown (1). Their mean age at surgery, duration of seizures prior to surgery, associated comorbidities, and congruence of the presurgical data did not differ from those of the children who underwent resection. In 7 of these 8 children, the presence of bilateral foci was considered preoperatively. Three of the 8 children had initial subdural strips placed via bur holes, with one of the 3 proceeding to grid placement prior to confirmation of bilateral foci without a predominant focus. Five children underwent initial grid placement with a contralateral bur hole for subdural strips.

In the group of 40 children who had invasive monitoring followed by resection, the mean age was 9.3 ± 4.4 years (range 14 months–18 yrs), and 65% (26 of 40) were boys. The etiology of epilepsy was attributed to a specific pathogenesis in all but 6 patients (Table 1). Three patients were lost to follow-up (a 5-year-old with developmental delay and a tumor, and a 16-year-old whose development was within the normal range). The mean and median duration of follow-up for the remaining 37 children was 59 months (range 33–87 months). Outcomes were classified in a manner similar to that used in the recent case series reported by Jayakar et al.: Class I being characterized by freedom from seizures and Classes II, III, and IV being characterized by a reduction in seizure frequency of > 90%, > 50%, and < 50%, respectively. At the most recent follow-up examination, 65% of the patients had an outcome ranging from excellent to good with 41% (15 of 37) being seizure-free, and another 24% (9) having experienced a > 90% reduction in seizures. Six (16%) had a > 50% reduction in seizures, and 7 had < 50% reduction. Classification by Engel criteria showed similar, but slightly less favorable outcomes: Class I (seizure-free), 15 (41%); Class II (< 3 seizures/year), 6 (16%); Class III (> 80% reduction), 8 (22%); and Class IV (< 80% reduction), 8 (22%). All descriptions of outcomes below are based on the criteria of Jayakar and colleagues.

The majority (24 [60%] of 40) of the children had extratemporal resections (24/40), while 20% (8 of 40) had a temporal lobectomy, and 20% had extratemporal resection in addition to a temporal lobectomy. Three (38%) of the 8 children who initially underwent temporal lobectomy after invasive monitoring had recurrent seizures and had repeat invasive monitoring with additional extratemporal resections. Similarly, 4 (17%) of the 24 children who had initial extratemporal resection had recurrent seizures and underwent repeat invasive monitoring and additional extratemporal resections. Of those children who underwent repeated evaluations and additional resections, 57% (4 of 7) achieved excellent seizure control (Class I). Even though a Class III outcome may be considered a failure, 3 of 6 children who had a > 50% but < 90% reduction in seizure frequency achieved dramatic improvements in cognition and behavior. They went from experiencing daily incapacitating seizures that precluded schooling to being able to participate in standard special educational programs. Seven (19%) of the 37 children for whom follow-up data are available did not experience sustained meaningful improvement in seizure control (Class IV); 3 of these children had initial control but developed recurrent seizures after at least 6 months. Four of the 7 underwent additional invasive monitoring followed by resection. There were no statistically significant differences between the group of children

### TABLE 1

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
<th>Class IV</th>
</tr>
</thead>
<tbody>
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<td>5 (45)</td>
<td>2 (18)</td>
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<td>2 (20)</td>
<td>2 (20)</td>
<td>3 (30)</td>
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<tr>
<td>unknown</td>
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<td>3 (60)</td>
<td>1 (20)</td>
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<td>3 (75)</td>
<td>1 (25)</td>
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<td>total</td>
<td>37</td>
<td>15 (41)</td>
<td>9 (24)</td>
<td>6 (16)</td>
</tr>
</tbody>
</table>

* Values represent number of patients (%). Outcomes classified by the criteria used by Jayakar et al.: Class I, seizure freedom; Class II, > 90% reduction in seizure frequency; Class III, > 50% reduction; Class IV, < 50% reduction. Three patients were lost to follow-up. The mean and median follow-up for the 37 children was 59 months. Developmental delay is defined as delayed cognitive development beginning in infancy.
who had Class IV outcomes and those who had better outcomes in duration of epilepsy, etiology, comorbidities, or congruence of the presurgical data. For example, 3 of the 7 in the former group were less than 3 years old and had unilateral focal cortical dysplasia apparent on MR images with congruent presurgical data from video-EEG monitoring and PET. All 3 developed unremitting contralateral seizure foci. In hindsight, we are currently unable to correctly identify those children with poor outcomes preoperatively. If the threshold for offering surgery is raised too high, it may compromise offering surgery to the group of children who experienced significant improvement.

Thirty percent of the patients (11 of 37) underwent insertion of a VNS unit before or after intracranial resection to achieve optimal seizure control. Three (20%) of 15 children had seizure freedom, and 2 (22%) of 9 with Class II outcomes underwent implantation of a VNS unit in addition to resection and showed improved seizure control. Two (33%) of 6 children with Class III, and 5 (71%) of 7 children with Class IV outcomes underwent implantation of a VNS unit after intracranial resection. While one of the children with Class III outcomes experienced additional control, none of those with Class IV outcomes had a meaningful reduction in seizure frequency with VNS. The limited number of children in each category precludes drawing broad conclusions from our results.

Complications included no deaths or hematomas. Two children required early removal of the electrodes due to cerebral edema; informative localization was still completed for both. One patient had a permanent worsening of his baseline hemiparesis after resection of a motor strip focus. Six children developed infections (12.5% of patients, 4% of intracranial epilepsy procedures); none required craniectomy. The incidence of infections decreased dramatically after institution of a frequent hand-washing policy for patients in the monitoring unit. One patient developed hydrocephalus and required insertion of a lumbo-peritoneal shunt.

All children had neuropsychological assessments preoperatively. Age-appropriate full-scale IQ scores were provided in 28 patients (70%), while the remaining 12 patients had limited cognitive skills precluding full-scale IQ quantification. The mean full-scale IQ was 70.6 ± 16.2 and the median was 73. Nine children (23%) had a borderline IQ of 70–85, and only 6 (15%) had a full-scale IQ > 85. Including the 9 children over age 3 years whose IQs could not be measured and the 13 with a measured IQ < 70, 61% of the children (22 of 36) were in the retarded range. The mean full-score IQs for children with Class I or II outcomes combined, and those with Class III outcomes were similar (Classes I and II, 73.3 ± 15.5; Class III, 67 ± 18.4; t-test, p = 0.2). The mean full-scale IQ for children with Class IV outcomes (53.3 ± 2.9) was significantly lower than the mean for those with Class I or II (p < 0.001). While this analysis suggests that patients with a lower IQ do not obtain as much seizure control with surgery, 60% of the children with Class I and 33% of those with Class II outcomes had a preoperative IQ < 70.

Similarly, other etiologies considered less favorable for a good surgical outcome include meningencephalitis, multifocal perinatal injuries or other multifocal insults, and severe behavioral problems including autistic disorders. The 4 patients with an infectious etiology all had either Class I or II outcomes. Of the 12 children with epilepsy related to a prenatal or perinatal injury, 67% had a Class I or II outcome. Even though almost half of the 37 patients for whom follow-up data were available (16 of 37) had severe behavioral problems and/or autistic features, 12 (75%) of these 16 had a Class I or II outcome. Three cases are presented below to further illustrate these points.

**Illustrative Cases**

**Case 1**

This 16-year-old boy experienced his first seizure at 11 months of age in association with herpes encephalitis. Until that illness he had been a healthy infant. He was seizure free until the age of 3 years when he began having up to 3 seizures a day. Multiple seizure types occurred. These included episodes with eye deviation to the left and bilateral asymmetrical tonic posturing with the right arm extended above shoulder level. Other events were characterized by eye deviation to the left with head deviation to the right. Generalized tonic seizures with whole-body stiffening also occurred in clusters. There were marked outbursts with agitation and aggressive behaviors, especially before and after seizures. School performance was poor despite a special curriculum and a one-on-one aide. Examination was remarkable for right hemiparesis and cognitive delay.

Scalp EEG studies showed poor ictal localization with generalized attenuation and paroxysmal fast frequencies or generalized spike-and-wave discharges maximal in the anterior head regions. Magnetic resonance imaging showed left hemiatrophy with volume loss and encephalomalacia, maximal in the left temporal lobe (Fig. 2). There was decreased FDG uptake in the left temporal and parietal regions. On invasive EEG monitoring, all seizures were localized to the left frontotemporal region. The patient underwent a left frontotemporal resection at 10 years of age. Postoperatively, no seizures have occurred and he continues to follow a regimen of treatment with one seizure medication. There is marked improvement in aggressive outbursts. Despite diffuse cognitive dysfunction, several fundamental cognitive abilities have improved after surgery, including verbal fluency, visual-motor skills, and visual/nonverbal memory. The patient is currently enrolled in vocational training.

**Case 2**

This 14-year-old boy was born after a full-term gestation. When he was 7 months old he underwent imaging studies that showed signs of an in utero stroke. Hemiparesis and cognitive and social delays became apparent by 2 years of age. Seizures began at 6 years of age and were characterized by a cry and sudden fall. They increased in frequency to 4 times a day without an adequate response to multiple antiseizure medications. He had an extended hospitalization for Stevens-Johnson reaction related to an anticonvulsant. Video-EEG evaluation showed multiple seizures with widespread spike-and-wave discharges that were poorly localized. Magnetic resonance imaging revealed encephalomalacia in the left MCA distribution, including the frontal, temporal, and parietal lobes (Fig. 3). The PET scan, however, not only showed decreased metabolism in the expected hemisphere, but also decreased FDG...
uptake in the right parietal and mesial temporal regions. Since there were discordant data, strips were placed in a starburst pattern over both hemispheres with bur holes to help lateralize seizure onset. More than 90% of seizures were recorded from the left parietal region with involvement of the right parietal area within 400 ms, but 5% of seizures arose independently from the right parietal area with no left parietal involvement. After invasive monitoring with a left grid, the patient underwent a left parietal resection at 9 years of age.

Postoperatively, seizures occurred during the first 3 months, gradually decreasing in frequency. No seizures have occurred now for 5 years and the patient is no longer being treated with any antiseizure medication. Before surgical treatment, the patient functioned at a 3- to 6-year equivalent age level (5–6 years behind expected age). Postsurgically, he is functioning 4–5 years behind expected age in school and is on the honor roll.

Case 3

This 12-year-old right-handed girl began having seizures at 3 months of age, but her condition was not formally diagnosed until 2 years of age. Typical seizures were characterized by slumping forward and a blank stare, with occasional secondary generalization, occurring in flurries multiple
times a day. Along with seizures, she developed an epileptic encephalopathy characterized by autistic behavior with minimal vocalization (typically screeching) and no words. Birth history was unremarkable with a full-term gestation and uncomplicated pregnancy, labor, and delivery. She underwent a Chiari malformation Type I decompression procedure at 2 years of age but had no other surgical history. Electroencephalograms showed multifocal interictal discharges, and seizures persisted despite treatment with multiple antiseizure medications. Behavioral outbursts with violent agitation became a daily occurrence. Video-EEG studies were poorly tolerated. After much consideration, VNS was determined to be the best treatment option, and a VNS unit was implanted when the patient was 5 years old. With the VNS, there was mild benefit in both seizures and behavioral outbursts. However, 1 year later after the unit was implanted, the patient twisted and broke the electrode which then required surgical replacement. Four years later, the generator itself was replaced because of limited battery reserve. The patient habitually manipulated the incision site and within weeks the surgical site became infected, necessitating device removal. Subsequently both seizures and behavior continued to deteriorate such that her parents no longer felt that she could remain in the home.

Subsequent video-EEG monitoring showed seizures from both hemispheres although 80% were of left frontotemporal onset. Neuroimaging showed no localized lesions. Preoperatively the parents were counseled that seizure freedom was unlikely. The patient underwent a left frontotemporal resection at 10 years of age. Now, over 3 years later, seizures are markedly reduced, occurring in brief flurries of up to 6–8 seizures a day over 1 week every 3 weeks. She has had marked improvement in her behavior and some acceleration of language skill acquisition has occurred. The patient is now signing more than 30 words and attending a special school.

**Discussion**

Multifocal epilepsy may be easily apparent with a patient manifesting multiple seizure semioologies and phenotypes. Certain etiologies, especially diffuse processes such as meningoencephalitis and birth injury, dictate a propensity for multifocal epilepsy. Multifocal disease may also be suspected because of associated comorbidities such as developmental disabilities, and autistic behavior as in Case 3. Treatment of multifocal epilepsy remains a challenge, especially in pediatrics where refractory epilepsy is often associated with developmental and behavioral handicaps. In our epilepsy program, we have adopted an integrative approach using both epilepsy surgery and VNS to achieve favorable outcomes in this refractory population, with the goal of reducing the seizure burden and improving quality of life.

Meningoencephalitis, as in Case 1, typically gives rise to multiple potentially epileptogenic sites with the capability of maturing at different rates. This process may be influenced by multiple factors including the location of these sites, antiseizure drug effects further mediated by genetic and environmental factors, and time from initial injury. Alternatively, the primary epileptogenic site may influence this process both directly and indirectly via transsynaptic connections leading to secondary epileptogenesis. Given their propensity for multifocal lesions, patients with epilepsy secondary to a CNS infection are often not considered for epilepsy surgery. In one case series, however, almost 50% of patients with epilepsy secondary to CNS infection had unilateral mesial temporal sclerosis, felt to be amenable to epilepsy surgery. Conversely, Holmes et al. describe a worse outcome in this patient population given the prevalence of bilateral cortical injury.

The favorable results of a multilobar resection in Case 1, which involved a patient with a history of encephalitis and multifocal lesions (manifested by neuroimaging and clinically by cognitive delay with behavioral problems), implies 3 possibilities. First, the primary epileptogenic zone may have included a large region of the frontal and temporal lobes from the onset, or perhaps 2 epileptogenic sites coalesced into a synchronous seizure generator over time. A third possibility is that the initial seizure generator in either lobe recruited relatively healthier surrounding brain tissue, expanding its margins and its effect to the other lobe. The seizure-free outcome along with marked improvement in behavior after surgery implies that surgery is capable of arresting any of these potential mechanisms, again underscoring the different rate of maturation of multiple or secondary epileptogenic sites despite multifocal disease.

All 4 of the children with a history of meningoencephalitis in this case series achieved > 90% seizure control, and one of these children had multilobar involvement similar to the patient in case 1.

Patients with perinatal insults can also experience good results with an aggressive approach. In Case 2, presurgical evaluation showed not only poorly lateralized seizures but also contralateral hypometabolism on PET. Two independent epileptogenic regions were delineated during invasive monitoring in both hemispheres. Typically, this would imply poor surgical results. In fact, the seizures continued for 2–3 months after surgery, with gradually decreasing frequency, and subsequently resolved completely. This history illustrates the probable development of secondary epileptogenesis, probably at the “intermediate” to “independent” stage, where the secondary focus is capable of independently generating seizures. During this stage, removal of the primary lesion does not result in immediate resolution of seizures, but rather the secondary region generates fewer and fewer seizures until complete seizure freedom is attained, usually over months. The time to reach complete resolution is directly related to time of exposure of the secondary epileptogenic region to the primary seizure focus.

This case also illustrates that postsurgical seizures in the setting of more than one epileptogenic focus do not necessarily imply a poor prognosis. Occurrence of seizures within the first 7 days after surgery or acute postoperative seizures has conflicting prognostic significance in the literature. Other authors have coined the term “habitual seizures” to define postoperative seizures that have the same semiology as before surgery. Habitual seizures may occur with inadequate resection of the epileptogenic zone or from nearby maturing foci that produce similar ictal symptoms. The “running down” or disappearance of habitual seizures within 2–10 years after surgery has been seen in 14% of patients in some case series. This phenomenon is felt to be a natural progression of epilepsy after
resection of much of the epileptogenic zone. As our case illustrates, however, cessation of habitual seizures may also represent the exhaustion of secondary epileptogenic sites in the contralateral hemisphere.

Children with severe cognitive delay and behavioral abnormalities, including autism and aggression, are not routinely considered optimal surgical candidates. In Case 3, the severe behavioral issues in conjunction with multifocal interictal abnormalities led to the initial choice of VNS. After the removal of the VNS unit from the infected surgical site 5 years after implantation, seizure frequency and behavior worsened. Video-EEG monitoring was performed again and showed that in fact the majority of seizures lateralized to one hemisphere. It is possible that with age the epileptogenic sites coalesced or that the initial multifocal epileptogenic sites became less active, such that the remaining seizure generators developed a more lateralized hierarchy in epileptogenicity. The patient’s postsurgical course, with significant improvement in behavior and learning as well as improvement in her family’s quality of life, leads us to believe that patients who have previously been denied surgery may benefit from a reevaluation.

In children with intractable epilepsy who also have severe behavioral issues and mental retardation, surgery may not be the preferred option. Neurological abnormalities are common accompaniments in refractory epilepsy in children and are considered poor prognostic factors. Yet, the prevalence rate of epilepsy is 10–32% in children with mild to moderate mental retardation, and increases to 50% in children with severe retardation. A low IQ assumed to be indicative of bilateral or diffuse brain injury implies poor surgical outcomes. Several pediatric case series have, however, shown reasonable surgical outcomes in a subset of this population. Freitag and Tuxhorn describe a series of 50 children, 70% of whom had IQs < 70. Surgical outcomes were more favorable in children with relatively better cognition, but almost 50% of children with severe retardation (6 of 13) and 68% of those with mild to moderate retardation (15 of 22) still achieved seizure freedom. A population-based study from Sweden showed similar results. A seizure-freedom rate of 37% (20 of 54 patients) occurred in patients with IQs of 50–69. In the more severely retarded group with IQs < 50, 22% (4 of 18 patients) still achieved seizure freedom. This again indicates that low IQ, although in general a poor prognostic factor for epilepsy surgery outcome, may in fact be associated with a good outcome in some patients, as seen in Case 3. In our series, 57% of children with Class I, and 33% of children with Class II outcomes had an IQ < 70. Even though children with limited cognition overall may have poor results compared to children with normal cognition, our results as well as those reported in prior publications emphasize the need for individualized consideration for epilepsy surgery. Many children in this cohort can experience significant improvement in seizure control and quality of life.

If bilateral epileptogenic regions are present, or epilepsy surgery does not produce satisfactory outcomes, VNS is typically considered the next line of treatment. Alsaadi et al. studied the results of VNS in patients with bilateral temporal disease or those in whom temporal lobectomy failed. Greater than 50% seizure reduction was maintained for at least 1 year in 60% of patients. On the other hand, Koutroumanidis et al. found no benefit associated with VNS in patients who did not have good response to epilepsy surgery. This may in part be due to a small number of patients and an inadequate follow-up period. The anti-epileptogenic effect of VNS may not be seen for up to 1–2 years. Overall, patients with severe developmental deficits have a higher incidence of refractory mixed seizures than the general population with epilepsy, but the available treatment options remain the same. Although epilepsy surgery may not provide seizure freedom in this delayed population subset, it can significantly reduce seizure burden and improve the quality of life. The relatively lower morbidity of VNS unit implantation in comparison to invasive surgery in this challenging population may result in choosing VNS as the best option. As illustrated by Case 3, however, this choice may deny significant improvement in quality of life and seizure control that might result from epilepsy surgery.

In the 3 cases presented in this paper, findings on MR imaging or localized lesions were not a guiding feature as has been previously emphasized. Functional neuroimaging did lead us to further investigate the discordant EEG and PET data in Case 2. Although invasive monitoring was performed in all patients, resections were not performed with the sole aim of rendering patients seizure-free, but rather with the goal of reducing seizure burden and improving the patient’s and the family’s quality of life. In spite of these expectations, 2 of 3 patients are unexpectedly seizure free, underscoring the need for individual patient data examination and consideration for epilepsy surgery.

Conclusions

Traditionally, epilepsy surgery has been recommended in adults with well-demarcated lesions such as those of mesial temporal sclerosis, which yields the highest seizure freedom rates. Epilepsy surgery in children with temporal lobe lesions has shown similar success. The refractory epilepsy cohort differs markedly in children and adults. Poorly controlled seizures often emerge in childhood with diffuse or multifocal lesions and comorbidities, especially in the extratemporal regions. Because of their multifocal nature, such seizures have not traditionally been treated with epilepsy surgery when the predominant focus has been seizure freedom.

We have presented the clinical course and treatment of 3 patients who would not routinely have been considered optimal surgery candidates. Epilepsy surgery in these patients served as both curative and palliative therapy. The surgical outcomes in these patients suggest reconsideration of the quest for an ideal surgical candidate. Many patients not thought to be good candidates because of the underlying etiology or associated behavioral issues may in fact benefit from epilepsy surgery and deserve another look. Epilepsy surgery’s optimal utilization in pediatrics may be as part of an arsenal of treatment modalities which in combination or succession bring the best possible outcomes, not only in terms of seizure control but also in terms of cognition, socialization, and development. In pediatrics, epilepsy surgery remains controversial and in general is a less well-accepted treatment modality than medical treatment with antiseizure medications. The reluctance to treat pediatric patients surgically may represent an overly pro-
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tective attitude that prevents or at least hinders attainment of the best possible outcomes in our patients.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


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