Outcome following surgery for temporal lobe epilepsy with hippocampal involvement in preadolescent children: emphasis on mesial temporal sclerosis

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Object. The authors conducted a multiinstitutional, retrospective analysis to better define outcome and prognostic indicators for temporal lobe epilepsy surgery for suspected mesial temporal sclerosis (MTS) in young children.

Methods. Data were collected for all children undergoing temporal resections at four epilepsy centers over approximately 10 years. Children with a histopathological diagnosis of neoplasm were excluded.

Forty-nine patients (28 boys and 21 girls) were included in the study. Their mean age at surgery was 9.1 years (range 1.25–13.9 years). The mean age at seizure onset was 3.2 years (range birth–10 years). Histopathological examination demonstrated MTS in 26 cases, gliosis in nine, dysplasia in five, glissos with dysplasia in four, and nonspecific or normal findings in five. Forty-one anterior temporal lobectomies (nine tailored) and eight selective amygdalohippocampectomies were performed (28 left side, 21 right side). Twenty-nine children (59.2%) underwent invasive monitoring. Operative complications included extraaxial hematomas (two cases), cerebrospinal fluid leaks (two cases), and hydrocephaus (one case), each in children undergoing invasive monitoring. The mean duration of follow up was 26.4 months (range 5–74 months) overall and 23.9 months (range 6–74 months) for the Engel Class I subgroup. Outcomes at the most recent follow-up examination were categorized as Engel Class I–II in 31 (63.3%) of 49 children overall, 20 (76.9%) of 26 children with confirmed MTS, four (36.4%) of 11 children with gliosis, and four (57.1%) of seven children with dysplasia. All patients who underwent selective amygdalohippocampectomies had confirmed MTS and Engel Class I outcomes. Patients with more than one seizure type (p = 0.048) or moderate to severe developmental delay (p = 0.03) had significantly worse outcomes (Engel Class III or IV). Age at seizure onset, age at surgery, and duration of seizure disorder were not significantly related to outcome. There was a trend for bilateral or extratemporal findings on electroencephalography (EEG) (p = 0.157), high preoperative seizure frequency (p = 0.097), and magnetic resonance (MR) imaging findings inconsistent with MTS (p = 0.142) to be associated with worse outcome, although it did not reach statistical significance. In only 12 (46.1%) of the 26 patients with confirmed MTS was the condition prospectively diagnosed on preoperative MR imaging.

Conclusions. Younger children with temporal lobe epilepsy have satisfying surgical outcomes, particularly when MTS is present. Magnetic resonance imaging may not be as sensitive in detecting MTS in children as in older patients. Negative predictors identified include multiple seizure types and preoperative developmental delay. Multifocal or bilateral EEG findings, high preoperative seizure frequency, and MR imaging findings inconsistent with MTS also independently suggested worse outcome.

Key Words • epilepsy surgery • mesial temporal sclerosis • temporal lobe • pediatric neurosurgery

In adults, temporal lobe resection for medically refractory complex partial seizures has been shown to consistently produce initial satisfactory outcomes in up to 82% of patients,4,6,15 with the results of longer-term follow up suggesting that seizures recur in up to 50% of adults.9 Results in children have not been as consistent,1,3,7,11,16 perhaps due to the frequency of dual pathological conditions, such as the coexistence of MTS and abnormalities such as cortical dysplasia, neoplasia, or neuronal tumors in the temporal lobe.8,14 Although surgical outcomes for children with TLE remain reassuringly high,1,10,12,16,17 they may be less pre-

Abbreviations used in this paper: EEG = electroencephalography; FDG = [18F]fluorodeoxyglucose; MR = magnetic resonance; MTS = mesial temporal sclerosis; PET = positron emission tomography; TLE = temporal lobe epilepsy.
dictable due to the more heterogeneous nature of pediatric TLE.

In addition to the lack of reliable prognostic data available for families with children with TLE to consider, the choice of resection procedure remains controversial. Although some authors have reported excellent outcomes for selective amygdalohippocampectomy in children, others have identified better outcomes using standardized anterior temporal resections including more neocortical removal.

To date, there has been no published report of a multi-institutional series of surgical cases in which the authors have specifically analyzed data pertaining to a large cohort of preadolescent children with hippocampal sclerosis and TLE. Our intention in this study was to collectively analyze cases involving young patients who had undergone temporal lobe surgery for epilepsy to better understand surgical outcomes and prognostic indicators in the subset of children undergoing either temporal lobectomy or selective resections for hippocampal sclerosis. Children with neoplastic temporal lobe lesions such as astrocytomas or neuronal–glial tumors were excluded from the study. Of course, the definitive diagnosis of MTS is ultimately based on histopathological findings, information not available when the physician is faced with the need to make decisions about surgical treatment. In this paper we focus on the cohort of preadolescent children with suspected mesial temporal lobe epilepsy.

Clinical Material and Methods

Data Acquisition

Patient data was obtained by reviewing the medical records of all children younger than 14 years of age who underwent mesial temporal lobe resections at one of four specific epilepsy centers during the period from September 1993 to August 2004. The four centers were located at St. Louis Children’s Hospital, St. Louis, Missouri; Children’s Hospital and Regional Medical Center, Seattle, Washington; Rainbow Babies and Children’s Hospital, Cleveland, Ohio; and Royal Liverpool Children’s NHS Trust and Walton Centre for Neurology and Neurosurgery, Liverpool, United Kingdom. All children with neoplastic temporal lobe lesions were excluded from the study. Information collected included patient demographics, clinical history, preoperative studies, seizure type and frequency, procedures performed, surgical and neurological complications, histopathological findings, and Engel classification at the most recent follow up (range 5–74 months after surgery). Data collection was performed in a retrospective fashion after approval from the institutional review board of each institution was obtained.

Data Evaluation

Continuous data (patient age at surgery, age at seizure onset, duration of seizure disorder, and seizure frequency) were compared using the nonparametric Mann–Whitney rank sum test. Ordinal data (EEG and MR imaging findings, histopathological diagnosis, and seizure types) were analyzed using the Pearson chi-square test. To maximize statistical power, we combined the data into two groups—an Engel Class I–II group and an Engel Class III–IV group. Therefore data from the single patient with Engel Class II outcome was combined with the Engel Class I group for statistical analysis. The Yates correction for continuity was used to adjust the Pearson chi-square test when the number of patients in a given group was too low to maintain power greater than 0.8. Statistical analyses were performed using SigmaStat 3.0 and SPSS 13.0 for Windows (SPSS, Inc.).

Results

Demographic Data

Forty-nine children (28 boys and 21 girls) who underwent surgery at four different institutions were included in the current study. Their age at surgery ranged from 1.25 to 13.9 years (mean 9.1 years). Thirty-seven were right-handed, five were left-handed, and handedness was indeterminate in seven. Developmental delay, as documented in the medical record, was present in 15 children (30.6%), whereas 13 (26.5%) were described as having “low-normal” or “borderline” intelligence, and 20 (40.8%) were reported to have normal intelligence. Of this latter group, two children exhibited intellectual regression following seizure onset. In one case data on intellectual development were not available. The mean duration of follow up was 26.4 months (range 5–74 months) overall and 23.9 months (range 6–74 months) for the Engel Class I subgroup.

Seizure Characteristics and Historical Risk Factors

Among the 49 children included in the study, the median age at seizure onset was 2 years (mean 3.2 years). The median duration of time from seizure onset to the date of surgery was 5.1 years (range 0.8–13.1 years). Seizure frequency was highly variable (range 1–1500 per month, median 15 seizures per month). The majority of children (47 [95.9%] of 49) experienced complex partial seizures, but there was variability in seizure type within this population. Ten (21.3%) of the children with complex partial seizures also intermittently demonstrated secondary generalization, and six (12.8%) exhibited other seizure types (simple partial in three children, absence in two, and myoclonic in one). One child experienced simple partial seizures with secondary generalization, and one child suffered infantile spasms exclusively.

In 23 (46.9%) of the 49 cases, there was no significant medical history or clearly identified risk factor for seizures. Five children (10.2%) previously had one or more febrile seizures, and four children (8.2%) had suffered significant closed head injuries. Four (8.2%) had imaging-confirmed perinatal infarcts or intraventricular hemorrhage. Three children (6.1%) had been treated for encephalitis, and two (4.1%) had central nervous system abnormalities of unknown origin (microcephaly in one child and cortical dysplasia/atrophy in the other). A family history of seizures was identified in two children (4.1%). Other relevant historical findings in individual patients included neurofibromatosis Type 1, an intracerebral arteriovenous malformation, diabetes mellitus Type 1 with a significant hypoglycemic event, hypothyroidism, autism (in an adopted child with no other known medical history), and a history of neonatal sepsis.

Preoperative Evaluation

The preoperative evaluations varied somewhat from institution to institution. For example, PET scans were obtained in most (20 of 27) of the children treated at St. Louis.
Children’s Hospital, whereas the other institutions did not use PET routinely. However, all 49 children in the study underwent preoperative MR imaging and EEG. Forty-five of the children underwent inpatient video EEG monitoring. In 15 children, Wada testing was performed, and three children underwent functional MR imaging to assess the location of language functions. Neuropsychological testing was performed in 38 children.

**Effect of Cognitive Development on Postoperative Seizure Control**

Due to the extensive neurological and often neuropsychological evaluations that were performed prior to surgery, cognitive development was assessed and recorded in a detailed manner in all but one child. In sum, 28 children were classified as “borderline” or developmentally delayed, and 20 were found to have normal intelligence. There was a statistically significant difference in how these children fared following surgery (p = 0.03)—outcomes were classified as Engel Class I–II in 80.0% of the children with normal intelligence but in only 50.0% of developmentally delayed children (Table 1).

**Lack of Relationship Between Surgical Outcome and Patient Age or Duration of Seizure Disorder**

To evaluate the effect of patient age at surgery on outcome following surgery, we divided the cohort according to postoperative Engel class. There were 31 children in the Engel Class I–II group (median age 11.3 years) and 18 in the Engel Class III–IV group (median age 9.5 years). No statistically significant difference with respect to age at surgery was detected between these groups (p = 0.24, Mann–Whitney rank sum test). When age at seizure onset was considered with respect to outcome (Engel Class I–II: 31 children, median age at seizure onset 2.0 years; Engel Class III–IV: 18 children, median age at seizure onset 2.5 years), again no statistically significant difference was found (p = 0.85). Similarly, overall duration of seizure disorder was not found to differ significantly between outcome groups (Engel Class I–II: range 0.8–13.1 years, median 5.3 years; Engel Class III–IV: range 1.8–11.8 years, median 5.05 years; p = 0.50).

**Correlation Between Higher Preoperative Seizure Frequency and Poorer Postoperative Seizure Control**

The frequency of seizures varied greatly among the patients in the study population, ranging from 1 to 1500 seizures per month. It should be recognized that estimates of seizure frequency, as reported by family members, may be inaccurate—particularly at higher rates. Nevertheless, we analyzed seizure frequency with respect to postoperative Engel class. Median values for preoperative seizure frequency in the postoperative Engel Class I–II and Engel Class III–IV groups were 13.5 and 45.0 seizures per month, respectively. Statistical evaluation of these groups revealed no statistically significant difference (p = 0.097, Mann–Whitney rank sum test), although there seemed to be a non-significant trend for worse outcome with higher preoperative seizure frequencies (Table 1).

**Correlation Between Presence of Multiple Seizure Types and Postoperative Seizure Control**

Complex partial seizures were far and away the most common seizure type in the study population and were exhibited by 47 of the 49 children. However, 16 of these children with complex partial seizures also exhibited other seizure types, such as absence, myoclonic, simple partial, or secondarily generalized. Only two children did not have complex partial seizures; one of these two had infantile spasms only, whereas the other had simple partial seizures with secondary generalization. To identify factors that might predict a favorable postoperative outcome, we separated the cases into two groups: cases in which the children exhibited only one seizure type and those in which the children suffered multiple types of seizures. Twenty-four patients with only one seizure type achieved Engel Class I–II outcomes, and nine had Engel Class III–IV outcomes. Of those with more than one type of seizure, seven had Engel Class I–II outcomes and nine had Engel Class III–IV outcomes. Comparison of these groups demonstrated that children with only one type of seizure were statistically more likely to have an Engel Class I–II outcome (p = 0.048; Table 1). If the child who only exhibited infantile spasms is eliminated from the analysis, the difference is further supported (p = 0.03).

**Lack of Relationship Between Imaging Findings and Postoperative Seizure Control**

Findings on MR imaging consistent with MTS, as determined by an attending neuroradiologist, were confirmed in 19 children. Outcomes were classified as Engel Class I–II in 14 of these children and as Engel Class III–IV in five. In 12
Interictal PET Studies and Postoperative Seizure Outcome

Lack of Relationship Between Lateralizing Findings on PET and Postoperative Seizure Control

Preoperative EEG (routine interictal or video EEG) was performed in all cases; in one case, however, the findings were unavailable at the time of data collection. Thus, EEG data were reviewed for a total of 48 patients. Of these, 31 had EEG data that showed temporal spikes (interictal EEG) and/or spike-and-wave discharges (ictal EEG) ipsilateral to the side later resected. In eight children EEG showed abnormalities in the ipsilateral hemisphere but in extratemporal areas. Bilateral abnormalities (bitemporal or multifocal) were observed in eight children. To evaluate the relationship between preoperative EEG findings and postoperative outcome, we compared the Engel class at the most recent follow up in those children with ipsilateral temporal EEG findings with that of those with bilateral EEG abnormalities, and no significant relationship was found (p = 0.157, Pearson chi-square test)—although, again, bilateral EEG findings were associated with a trend toward worse outcome (Table 1).

Lack of Relationship Between Lateralizing Findings on Interictal PET Studies and Postoperative Seizure Outcome

Twenty of 27 children treated at St. Louis Children’s Hospital underwent FDG PET as part of the preoperative evaluation. Intertictal PET revealed hypometabolism in the ultimately resected temporal lobe—that is, it provided useful lateralizing information—in 18 patients: 12 had Engel Class I outcomes (67%), and six (33%) had Engel Class III–IV outcomes. One patient in whom PET revealed bilateral, symmetrical temporal hypometabolism subsequently underwent bilateral strip electrode placement, which demonstrated a predominance of seizures originating from the right side of the brain—this patient had an Engel Class III outcome after a right temporal lobectomy. Another patient in whom PET demonstrated contralateral temporal hypometabolism had an Engel Class I outcome after a right temporal lobectomy. The remaining four patients had Engel Class III–IV outcomes. One patient each, in whom PET demonstrated contralateral temporal hypometabolism and contralateral temporal hypermetabolism, had Engel Class III–IV outcomes. In ten children, MR imaging demonstrated various other conditions, including agenesis of the corpus callosum in one child, hamartoma in two, cortical dysplasia in three, optic glioma in one, hemispheric atrophy in two, and encephalomalacia in one. Statistical evaluation revealed that neither the imaging diagnosis of MTS nor hippocampal asymmetry offered reliably predictive information regarding postoperative Engel class (p = 0.142, Pearson chi-square test), although there was a trend toward worse outcome in cases in which the MR imaging findings were inconsistent with MTS (Table 1).

Correlation Between Histological Evidence of MTS and Better Seizure Control

Analysis of resection specimens revealed MTS in 26 of 49 cases. In the remaining 23 cases (described as “non-MTS” in Table 1), histopathological examination revealed gliosis in 13 specimens (with cortical dysplasia in four), dystrophic cortex alone in five specimens, lymphocytic infiltrate in one case, prior hemorrhage in one case, and non-specific findings in three specimens. Surgical outcome in the cases of histologically confirmed MTS was Engel Class I–II in 20 cases and Engel Class III–IV in six. Surgical outcome in the other 23 cases was Engel Class I–II in 11 cases and Engel Class III–IV in 12. Children with MTS were significantly more likely to have an Engel Class I–II outcome than those who did not have MTS (p = 0.035; Table 1).

Surgical Complications and Morbidity

Operative complications included extraaxial hematomas in two children, cerebrospinal fluid leaks in two, and hydrocephalus in one—each of these occurred among the 29 children who underwent invasive monitoring. Transient neurological complications, which also occurred only in children who had undergone invasive monitoring, included mild hemiparesis in two children and dysphasia in one. Arterial superior contralateral quadrantoparaplegia was detected in one patient who underwent standard temporal lobectomy with amygdalolimbicampectomy, anterior temporal lobectomy with amygdalolimbicampectomy, or tailored resection) was not performed.

Discussion

Interpretation of our results must be tempered with an understanding of the inherent difficulties in gathering retrospective data from multiple institutions over a time span of 12 years. Interpretations of MR imaging, histopathological, and electrophysiological studies gathered from retrospec-
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tive chart reviews are vulnerable to potentially significant variability between and even within institutions. The presurgical workups at the various institutions were similar, although there were some differences (for instance, most children treated at St. Louis Children’s Hospital underwent presurgical PET evaluation whereas none treated in the United Kingdom did).

Negative predictors of seizure freedom, not surprisingly, included developmental delay and multiple seizure types, suggesting a more diffuse process than a single temporal lobe focus in the cases in which those factors were present. Nevertheless, good outcomes (Engel Class I or II) were observed in a significant percentage of the children with these risk factors (50 and 44%, respectively, of those with developmental delay or multiple seizure types). In some cases, members of families of children with poor outcomes (Engel Class III) reported significant decreases in seizure frequency with attendant improvements in quality of life and decreases in anticonvulsant medication requirements, and these cases may perhaps be unnecessarily categorized as surgical failures.

We were unable to identify any other statistically significant prognostic variables predictive of seizure outcome given the statistical power of our sample size. Although the presence of extratemporal or bilateral EEG findings (p = 0.157), high seizure frequency (p = 0.097), or MR imaging findings inconsistent with MTS (p = 0.142) did not significantly predict worse outcome with respect to postoperative seizure control, there did seem to be a clinically meaningful trend for these factors. Given the relative rarity of MTS in preadolescent children, we pooled data from four different epilepsy centers to better identify outcome predictors. It is reasonable to expect that the non–statistically significant factors identified (seizure frequency and extratemporal EEG and MR imaging findings) may be clinically meaningful predictors, but in this study we did not achieve the statistical power necessary to confirm their significance. Children with histologically confirmed MTS had better outcomes than those with gliosis or dysplasia (Engel Class I–II: 76.9% compared with 36.4 and 57% for gliosis and dysplasia, respectively; p = 0.035), but MR imaging was not highly sensitive or specific for detecting hippocampal sclerosis, at least based on clinical neuroradiological reports. Failure to correlate preoperative MR imaging findings with the histopathological diagnosis of MTS in nine of 26 cases may have been due to differences in imaging techniques and sequences used at different institutions over a 12-year period. Furthermore, some patients underwent preoperative MR imaging at sites outside our epilepsy centers, making further analysis difficult. The use of MR imaging units that have higher field strengths and provide improved resolution of medial temporal structures as well as the use of standardized epilepsy imaging protocols may result in improvements in the presurgical detection of MTS. The inability to prospectively identify pathological MTS on preoperative MR imaging in a preadolescent cohort is a significant issue given the importance of such findings for decision making in adult epilepsy. The generally good outcome observed in this patient cohort, however, suggests that the lack of imaging–confirmed MTS should not be an impediment to surgery.

The Montreal group recently reported on a large series of 109 pediatric patients undergoing temporal lobe surgery for intractable TLE. Their series included a large number of adolescent patients as well as patients with neoplasms and vascular malformations, making direct comparison difficult. Nevertheless, they identified preoperative multifocal or bilateral EEG findings as a significant risk factor for unfavorable outcomes. One would reasonably expect this correlation, as our data also suggest.

In a recently published, single-institution retrospective survey of 390 consecutive brain MR imaging studies performed in children referred for any disorder, the rate of identifying MTS was 3% (12% in the subgroup of pediatric patients with epilepsy referred for MR imaging) and all MTS cases were found in children with seizures. 12 Terra-Bustamante et al. 16 recently published a report of 35 patients (age range 1–18 years) who underwent surgery for intractable TLE, in which they suggested that the youngest patients could be considered as a special subgroup of patients with TLE, with distinct ictal semiology and different etiological, electrophysiological, and outcome profiles. Their study included adolescent patients, and they determined that in patients younger than 6 years of age MTS was quite rare and dysplastic lesions predominated (six of seven cases). Postoperative seizure outcome was assessed as Engel Class I or II in four (57.1%) of the seven children who were 5 years of age or younger. We identified a somewhat higher rate of MTS in the younger children in our study: our rate of MTS in patients who were younger than 6 years old at the time of surgery was 45.5% (five of 11 patients), but we observed similar seizure outcomes (Engel Class I–II: six [54.5%] of 11). We did not identify a statistically significant relationship between younger age and seizure outcome, validating an aggressive approach in any case of intractable TLE, regardless of age at seizure onset or time of surgery.

Our study does little to answer the question regarding the role of selective mesial resection as opposed to more extensive resections involving temporal neocortex. Our findings indicate that children with concordant MR imaging, EEG, and PET findings are candidates for selective amygdalohippocampectomy or more extensive procedures. Although all children in this study who underwent selective amygdalohippocampectomy had Engel Class I outcomes, their mean age was relatively high for this study population (11.25 years), and the results of noninvasive studies were highly concordant in each of these cases. These children would certainly have had similar seizure control rates with more extensive resection. Five of 49 patients had operative complications, and transient neurological deficits were seen in four patients, all of whom underwent invasive recording. The surgical placement of electrodes for ictal localization prior to resection may have contributed to an increased surgical complication rate. Identification of presurgical predictors of postoperative seizure freedom in younger patients with TLE may reduce the need for invasive EEG in some patients.

Conclusions

Although less common in younger children than adults, TLE associated with MTS can be surgically treated with similarly satisfying outcomes in preadolescent patients. Selective amygdalohippocampectomy may provide excellent results in selected preadolescent children with concordant preoperative studies. Children with histologically confirmed MTS had the best postoperative seizure control rates in our
study; it should be noted, however, that clinical MR imaging may not be as sensitive in detecting MTS in this population as in older patients.

We identified two prognostic indicators associated with poor outcome: developmental delay and multiple seizure types. Multifocal or bilateral EEG findings and high preoperative seizure frequency may also be related to less favorable outcomes, although the association in our series was not statistically significant. Families of children with these negative risk factors may be counseled regarding the likelihood of less optimal surgical outcome, but surgery may still be a reasonable option for these children, offering the possibility of meaningful seizure control despite the risk factors.

Acknowledgment

We are grateful to Dr. Ed Trevathan of Washington University and St. Louis Children’s Hospital Department of Neurology for his direction in the initial preparation and revision of this manuscript.

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Manuscript submitted June 1, 2006. Accepted November 20, 2006. Address reprint requests to: Matthew D. Smyth, M.D., One Children’s Place, Suite 4520, Department of Neurosurgery, St. Louis, Missouri 63110-1077. email: smythm@nsurg.wustl.edu.