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Surgery for extratemporal nonlesional epilepsy in children: a meta-analysis

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Abstract
Purpose Previous small studies have demonstrated that seizure outcomes following surgery for extratemporal lobe epilepsy (ETLE) in children are worse than those for temporal lobe epilepsy. We have conducted a meta-analysis of the available literature to better understand ETLE surgical outcomes in children.
Methods We searched PubMed (1990–2009) for appropriate studies using the following terms: ETLE, ETLE surgery, ETLE surgery outcome, frontal lobe epilepsy, occipital lobe epilepsy, and parietal lobe epilepsy. Our collected data included patient age at seizure onset and surgery, the cerebral lobe involved with epileptogenesis, MRI findings, predominant seizure semiology, intracranial monitoring use (electrode implantation), epileptic region histopathology, and postoperative seizure outcome. Statistical analysis was performed to determine associations among these variables and postoperative outcome.
Results Ninety-five patients from 17 studies satisfied the inclusion criteria. Pathological findings (p=0.039) and seizure type (p=0.025) were significantly associated with outcome: A larger proportion of patients with cortical dysplasia and complex partial seizures experienced better outcomes. Age at surgery (p=0.073) and the cerebral resection site (p=0.059) were marginally associated with seizure outcome.
Conclusions This study confirms previous reports: Surgical outcomes for ETLE epilepsy are significantly worse than those for temporal lobe epilepsy. The reasons for this difference may include the diffuse nature of the pathology involved in ETLE, difficulty in localizing the seizure focus in young children, and involvement of "eloquent" non-resectable cortex in epileptogenesis. Because of the reporting variability among different epilepsy centers, more uniform protocols are necessary for fair evaluation and comparison of outcomes among the different centers.

Keywords ETLE · ETLE surgery · ETLE surgery outcome · Epilepsy

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Introduction

Epilepsy in children is commonly the result of a congenital malformation of the cerebral cortex. Epilepsy in adults, in contrast, is usually due to neoplasm, injury, or other type of acquired cortical abnormality. Extratemporal lobe epilepsy (ETLE) is more commonly seen in children [1–3], consistent with the congenital nature of the extratemporal epileptic foci. Siegel et al. [4] have suggested that this is due to the progression of cortical maturation, which begins in the central part of the brain, so any congenital deformities become apparent in the extratemporal areas

first. Epileptic foci in adults, on the other hand, are typically acquired and located in the temporal lobe [5]. In general, patients with ETLE, both children and adults, have worse postoperative outcomes than the patients with temporal lobe epilepsy (TLE) because the frontal, parietal, and occipital lobes contain areas for speech, sensorimotor processing, visual processing, and other "higher functions" that can become involved in epileptogenesis. Since these important cortical regions must be spared, completely removing a focus in ETLE is often impossible [6]. In contrast, surgical resection in the temporal lobe may be completed with more favorable outcomes [7]. This analysis considers the postoperative seizure outcomes of children with ETLE without lesions.

ETLE can be difficult to treat, in part, because localizing the epileptogenic focus to a specific resectable cerebral region is difficult. Certain seizure foci may be difficult (if not impossible) to localize by surface electroencephalograph (EEG) recording. In 1998, Westmoreland [8] demonstrated that certain frontal lobe foci show no evidence of EEG change. Furthermore, the seizures that begin outside the temporal lobe can quickly propagate to other parts of the brain, further complicating seizure focus localization [6]. It may be possible to estimate the location of seizure focus by careful observation of the semiology and progression of the seizure [9, 10]; however, the exact localization of seizure focus may be difficult in young children due to their inability to tolerate intracranial monitoring studies through implanting intracranial electrodes.

Each previously reported study related to ETLE surgery in children describes a small number of patients and their surgical outcomes. The authors, therefore, have conducted a meta-analysis of the available literature regarding ETLE surgery in children to gain a better understanding of these outcomes. The primary concern in this study is to determine which of the preoperative variables under consideration is strongly associated with postoperative seizure outcome in children.

Patients and methods

We collected data from previously reported studies in English literature conducted on the surgical outcome of ETLE in children (aged 17 years or younger). PubMed searches were used to identify relevant papers with the following search terms: ETLE, ETLE surgery, ETLE surgery outcome, frontal lobe epilepsy, occipital lobe epilepsy, and parietal lobe epilepsy. The bibliographies of these papers were then searched individually to find additional relevant studies. Some of the discovered studies included clinical outcome on both adults and children; the data related to children were extracted individually in these studies.

All accessible studies published after 1990 were reviewed. The year 1990 was chosen because most studies published after that year included magnetic resonance imaging (MRI) findings, essential for this analysis. To be included in this study, all patients had at least 1 year follow-up. Some of the studies did not define seizure outcome in terms of the Engel system; in each of these cases, the given definition of each outcome class was translated into the Engel system for use in this analysis. Studies that included only a summary of demographic information without mentioning the outcome related to the individual patient were excluded, so that individual variables could be considered for each patient.

Children with nonlesional epilepsy, including cortical dysplasia with an extratemporal focus, were included. Multilobar foci that included the temporal lobe were included, but purely temporal lobe foci were excluded. "Lesion" was defined not by MRI findings but on the basis of histopathological results. Patients with tumors, vascular lesions, multiple sclerosis, and heterotopias were excluded. We included the patients with the following histopathological diagnosis: cortical dysplasia, gliosis, inflammation, polymicrogyria/ulegyria, neuronal loss, and "normal." A large subset of pediatric patients in these studies underwent hemispherectomy; this population was not considered to be a part of the nonlesional ETLE population and was excluded from our analysis. This procedure circumvents the classical dilemma related to exact seizure focus localization and ETLE surgery: to remove the epileptogenic focus while sparing as much of the surrounding eloquent cortex as possible. All the other types of surgical procedures, such as lobectomy, topectomy, focal resection, and multiple subpial transection, were considered.

Data for these patients were extracted from 15 [11–25] case series and two [26, 27] case reports. All studies were retrospective. They often included both pediatric and adult patients. In those studies that included all age groups, the information regarding pediatric patients was extracted and included in our analysis. Specific types of data collected were the following: age of seizure/surgery, duration of epilepsy, outcome class (as defined by the Engel classification system) [28], histopathological findings, predominant seizure semiology (classified as simple partial, complex partial, generalized, or infantile spasms), location of focus (lobe of brain), surgery type/location, lateralization, MRI findings, and whether or not the patient underwent intracranial monitoring through electrode implantation.

The relationships between the preoperative variables and seizure outcomes were analyzed using R (version 2.4.1, Vienna, Austria). Each variable was compared to outcome individually to determine if there was a significant association between the variable and outcome (specifically,

seizure freedom). Continuous variables (age of onset/surgery and duration of epilepsy) were summarized using mean and standard deviation and were compared across groups using ANOVA. Categorical variables were summarized using frequency and percentage and were compared using Fisher's exact test (Table 1).

Results

Overall seizure outcome

There were 95 patients who satisfied the above inclusion criteria and were included in this study. Of these patients, 32 (33.7%) had Engel class I outcome or complete seizure freedom; 14 patients (14.7%) had Engel class II outcome (<90% seizure reduction or freedom with medication), 24 (25.3%) had Engel III (>75% seizure reduction), and 25 (26.3%) had Engel IV or no worthwhile improvement. Combining the patients in classes I, II, and III, 70 (73.7%) of the patients had a worthwhile reduction in seizure frequency, while 25 (26.3%) did not benefit from surgery.

Preoperative factors related to surgical outcome

The mean age of seizure onset for the study group was 4.5± 3.6 years. This variable was not associated with seizure outcome (p=0.505). The mean duration of epilepsy was 6.4±4.2 years and similarly was not associated with postoperative outcome (p=0.292). The mean age at the time of surgery for the study group was 9.6±5.6 years. The association between age at surgery and outcome was found to be marginally significant (p=0.073). Some patients did not have data points for every variable. In these cases, only those patients with the available data for a given variable were included in the final analysis.

Seizure semiology was classified as complex partial (CPS), generalized (GS), infantile spasms (IS), and "other," which included simple partial seizures and mixed-type seizures. Sixty-five of the 95 patients had information available regarding their seizure type. A significant association was found between seizure semiology and outcome class (p=0.025). Of those patients in this group who had an Engle class I outcome (n=28), 14 (50%) experienced CPS, nine (32.1%) experienced GS, four (14.3%) had IS, and one (3.6%) had "other" types of seizures.

Histopathology data were available for every patient but one. Pathological results were divided into three categories for analysis: cortical dysplasia (CD), gliosis, and "other." The "other" category included neuronal loss, encephalitis, polymicrogyria, ulegyria, chronic inflammation, and "normal." A significant association was found between histopathology and outcome class (p=0.039). Notably, in the class I group (n=27), 18 (66.7%) of the patients had CD, nine (33.3%) had gliosis, and no patient fits into the "other" category.

To increase the number of patients in the categories analyzed, the types of surgery performed to remove the epileptic focus were divided into frontal resections (including frontal total/partial lobectomy), posterior cortical resections (parietal and occipital partial/total lobectomy), and "other" (includes central/multilobar resections and multiple subpial transection). The association between surgery type and outcome class was found to be marginally significant (p=0.059) with the patients undergoing surgery in the posterior cortical regions enjoying better outcomes. Seventy-six of the 95 patients in the study had available data regarding the type of surgery. Among these patients, 21 (27.6%) had Engel class I outcome, 12 (15.8%) had class II outcome, 20 (26.3%) had class III, and 23 (30.3%) had class IV outcome. Among those patients who had class I outcome, nine (42.9%) underwent frontal lobe surgery, nine (42.9%) underwent posterior cortical surgery, and three (14.3%) underwent "other" surgeries.

Lateralization of the seizures had no association with seizure outcome (p=0.976). One patient had a bilateral focus, and this patient was in Engel class III with respect to seizure frequency postoperatively. The rest of the patients were evenly distributed among the four classes and hemispheres (see Table 1). Abnormal MRI findings also had no significant association with seizure outcome (p=0.902). Finally, the use of intracranial monitoring had no association with seizure outcome (p=0.124), with a largely even distribution of patients among the four classes.

Discussion

The diagnosis of ETLE and its surgical treatment requires a multidisciplinary comprehensive preoperative evaluation. The history should include careful documentation of ictal behavior, which may, in some cases, help to localize the epileptogenic focus to a particular lobe or region of the brain (this may prove difficult in infants). In addition to providing valuable localizing information, seizure semiology may be a significant predictor of postoperative outcome. As shown by our data, there is a significant association between seizure type and outcome class: More patients with complex partial seizures experienced an Engel class I outcome. The young child with a developing and quite plastic cortex is very vulnerable to generalized seizures. Over the course of many years, repeated generalized seizures can be a significant detriment to normal cognitive development and involve more cortical regions in seizure generation, resulting in worse outcomes.

Table 1 The clinical details of patients included in this study by outcome class [2,4,7–10,12,21,22,24,26–29,37,40,46???]

	Outcome class								*p* value
	I		II		III		IV		
	n		*n*		*n*		*n*		
Age at onset (years)	20	5.1 (3.8)	7	5.2 (3.4)	11	4.0 (2.7)	9	3.1 (4.3)	0.505
Age at surgery (years)	32	10.7 (5.5)	14	6.3 (6.7)	24	10.5 (4.7)	25	9.0 (5.6)	0.073
Duration (years)	20	7.6 (4.3)	7	5.8 (4.4)	11	6.2 (3.7)	9	4.4 (4.0)	0.292
Seizure type	28		12		14		11		0.025
Complex partial		14 (50.0%)		3 (25.0%)		7 (50.0%)		1 (9.1%)	
Generalized		9 (32.1%)		2 (16.7%)		5 (35.7%)		6 (54.5%)	
Infantile spasms		4 (14.3%)		7 (58.3%)		2 (14.3%)		2 (18.2%)	
Other		1 (3.6%)		0 (0.0%)		0 (0.0%)		2 (18.2%)	
Pathology	27		12		20		22		0.039
Cortical dysplasia		18 (66.7%)		9 (75.0%)		8 (40.0%)		11 (50.0%)	
Gliosis		9 (33.3%)		1 (8.3%)		11 (55.0%)		8 (36.4%)	
Other		0 (0.0%)		2 (16.7%)		1 (5.0%)		3 (13.6%)	
Location	32		14		24		25		N/A
Frontal		11 (34.4%)		4 (28.6%)		9 (37.5%)		16 (64.0%)	
Central		4 (12.5%)		0 (0.0%)		1(4.2%)		0 (0.0%)	
Posterior		13 (40.6%)		9 (64.3%)		7 (29.2%)		5 (20.0%)	
Other		4 (12.5%)		1 (7.1%)		7 (29.2%)		4 (16.0%)	
Surgery type	21		12		20		23		0.059
Frontal		9 (42.9%)		3 (25.0%)		10 (50.0%)		11 (47.8%)	
Post. cortex resection		9 (42.9%)		9 (75.0%)		5 (25.0%)		5 (21.7%)	
Other		3 (14.3%)		0 (0.0%)		5 (25.0%)		7 (30.4%)	
Lateralization	30		14		24		25		0.976
Bilateral		0 (0.0%)		0 (0.0%)		1 (4.2%)		0 (0.0%)	
Left		16 (53.3%)		7 (50.0%)		12 (50.0%)		13 (52.0%)	
Right		14 (46.7%)		7 (50.0%)		11 (45.8%)		12 (48.0%)	
MRI	28		14		15		13		0.902
Abnormal		14 (50.0%)		7 (50.0%)		6 (40.0%)		7 (53.8%)	
Intracranial monitoring	30		11		22		22		0.124
Yes		15 (50.0%)		3 (27.3%)		14 (63.6%)		15 (68.2%)	

Continuous measures summarized using mean (SD) and compared across groups using ANOVA. Categorical variables summarized using frequency (percent) and compared across groups using Fisher's exact test

N/A not tested

The next step in the diagnosis of ETLE is to perform neuroimaging, including functional imaging studies [MRI, positron emission tomography (PET), and single photon emission computed tomography (SPECT), the latter two typically performed ictally and interictally]. PET and SPECT scans may show hypermetabolism or hypoperfusion at the region of the seizure focus [16, 29]. Our analysis found that the presence of a structural abnormality on MRI did not have an association with postoperative seizure outcome. This finding may be due to the nature of malformation of cortical development such as cortical dysplasia; the affected brain tissue often extends beyond the visible MRI abnormality [23].

Some patients may require intracranial EEG monitoring, which is typically used when the imaging, history, and scalp EEG do not point to a specific focus [30]. Centeno and colleagues [31] report little value in intracranial monitoring in infants and very young children since the cortex is not well-developed to allow for the precise localization of seizure focus. Since the seizure foci of the patients who undergo intracranial EEG monitoring cannot be localized by noninvasive means, these patients may or may not be destined for a worse outcome regardless of the type of monitoring used [31, 32]. The data reviewed does not ascribe any significance to the use of intracranial monitoring as a predictor of outcome.

The treatment of both temporal and extratemporal epilepsy begins with a trial of antiepileptic drug therapy. Usually multiple drugs are tried for a period of up to 2 years before the surgical option is entertained [33, 34]. Although earlier surgery may be beneficial, our data support no significant association between the duration of epilepsy and postoperative seizure outcome. One of the interesting findings in childhood epilepsy that is not observed in adult epilepsy is spontaneous remission of seizures with cortical maturation [30, 33]. As such, caution should be exercised in pursuing an aggressive course of surgical treatment for every patient with a difficult-to-localize focus. Indeed, Huttenlocher [35] warned that immediate surgical recourse may not be warranted. This particular study, however, compared the outcomes of children with regard to intelligence scores and found that children with near-normal or normal intelligence had the highest rates of spontaneous remission. It did not characterize the type of epilepsy by syndromes in each group. Such benign epilepsies include Rolandic epilepsy, Panayiotopoulos syndrome, and idiopathic childhood occipital epilepsy of Gastaut, among others. These seizure disorders are often self-limiting and require no surgical intervention [36].

When the surgical option is pursued, the location of the surgery (and by extension, the location of the epileptic focus) may have some predictive value with regard to the seizure outcome after the operation. Although statistical significance was not attained, the trend in the data show that children who undergo surgery of the frontal lobe tend to have worse outcomes, whereas children who undergo surgery of the posterior cerebral cortex may fair better. This finding echoes that of Elsharkawy and colleagues [37]. In children, this association is likely observed because the frontal lobe is relatively immature compared to the posterior cortices and may be more vulnerable to repeated seizure activity and the development of multifocal seizures.

Several groups have established that ETLE surgery has a significantly worse outcome than that of TLE surgery [6, 37–41]. Whereas children with TLE have favorable outcomes (Engel I or II) at a rate of 75%, ETLE patients may experience such outcomes at a rate of 50% [30]. Our analysis shows an even lower seizure freedom rate (33.7%). ETLE outcomes may be poor primarily because of the pathology involved in the disease. The pathology is generally widespread, congenital, and often involves eloquent cortex, whereas TLE is usually associated with mainly temporal lobe involvement and is more amenable to aggressive resection [3, 5]. Our data demonstrate that a positive histopathological finding has a favorable association with postoperative outcome. Specifically, a majority of patients in the Engel outcome class I group harbored cortical dysplasia. Dysplastic cortex is more likely to be identified against normal cortex intraoperatively as compared to neuronal loss, polymicrogyria, and inflammation. However, the diffuse nature of the focus, a result of maturation of the cortex beginning in the central area of the brain (the area most commonly involved with dysplastic cortex) [4], often leads to subtotal resection. Other investigators have also found more favorable outcomes among patients with structural abnormalities [4, 13, 31, 42]. Elsharkawy and colleagues [40] demonstrated that, among ETLE patients, those with malformations of cortical development (MCD or no focal lesion) have a 33.3% chance of seizure-free outcome, whereas the patients with neoplasms have a 56% rate.

Improving the outcomes in ETLE surgery has proven a difficult task. Although several suggestions have been advocated, no strong evidence supports a particular approach. Some groups have claimed the duration of epilepsy as a significant predictor of seizure outcome [3, 4, 43]. The reasoning behind this argument is that, in children, the cortex can recover more readily from more aggressive resection otherwise not well-tolerated later in life. However, Fogarasi and coworkers [44] have contradicted this claim. Fogarasi's finding is supported by our data: The patients with class I outcomes had the highest mean age at surgery, this association was marginally significant ($p=0.073$). It is possible that with progressive development of the cerebral cortex, the seizures focus "matures" and is more "focal" and, therefore, amenable to focal resection.

In order to improve surgical outcomes from ETLE surgery, multiple methods and techniques have been proposed. Bauman and others have suggested resection of seizure focus in multiple stages, particularly among the patients whose seizure focus prove difficult to localize or resides close to the eloquent cortex. These authors claimed seizure freedom in 60% of patients, with 50% of the patients improving over baseline after the second procedure [13]. Shukla and colleagues [41] suggested that careful selection of the patients for surgery is the best way to improve outcomes. Others have proposed that seizure freedom should not be considered as the only endpoint for ETLE surgery [34, 45, 46]. These studies base such reasoning on the fact that ETLE surgical outcomes are already poor, so the focus of treatment should be on improving patients' quality of life by reducing seizure frequency rather than eliminating seizures. However, even these studies disclosed that patients who are seizure free have a better quality of life than the patients whose seizures persist in any form after surgery [37, 47]. Therefore, we believe that seizure freedom should remain the goal of epilepsy surgery, while diagnostic and surgical techniques should be developed and improved to increase the proportion of patients who become (and remain) seizure free.

Most importantly, there is a marked lack of uniformity among epilepsy centers regarding how patients are evaluated preoperatively and treated operatively. The methods of reporting are diverse. These deficiencies prevent fair comparison of the various treatment paradigms across different centers. Many studies do not report the data that are required to understand their treatment paradigm in an effort to work toward more desirable outcomes. Basic data such as the use of intracranial monitoring, location of the seizure focus, and age of the patient at surgery and at seizure onset were missing in some of the studies included in the present meta-analysis. The development of more uniform protocols for preoperative evaluation and reporting will allow for the collection of the data that can be used to compare outcomes from different treatment paradigms and ultimately improve outcomes in this population.

This meta-analysis is limited by its constituent studies, namely, by their small sample size. Each individual study was usually the experience of one center and often contained no more than 20 patients without a non-surgical control group. One study that did have a control group found that 21% of the patients on a medical course of treatment achieved seizure freedom [48]. This study, however, did not randomize patients to each treatment option. The patients in the study were taken from the population that was deemed unfit for surgery, and this likely resulted in the introduction of a selection bias. The inclusion of studies with adequate data in our analysis is also another source of selection bias. Several studies with relatively large number of patients had to be excluded since the clinical details related to the individual patients were not available.

Conclusions

This meta-analysis confirms the findings of previous studies that outcomes of ETLE surgery in the patients without lesions are poor. Factors significantly associated with postoperative seizure outcome in children are the seizure type (the patients experiencing CPS appear to have better outcomes) and pathological findings (patients with cortical dysplasia appear to have better outcomes than patients with other pathologies). Factors that are marginally associated with outcome include the location of surgery and age at surgery. Although not formally tested, the location of surgery appears to suggest that frontal lobe foci are associated with worse outcomes. Older children may experience better outcomes, probably due to the greater difficulty in localizing the epileptic region in very young children. In order to improve surgical outcomes, it may be necessary to resect epileptic tissue in multiple stages, as well as to carefully select patients to undergo surgery. Although there is no solid evidence in support of a particular method to improve outcomes, further studies should be performed to develop new techniques to increase the rate of seizure freedom in this population. The goal of surgery should remain to provide the patient with seizure freedom.

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