

# Preoperative Clinical, EEG, and Imaging Findings Do Not Predict Seizure Outcome Following Temporal Lobectomy in Childhood

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## ABSTRACT

Although certain clinical, electroencephalographic (EEG), magnetic resonance imaging (MRI), and pathologic findings in adults with intractable temporal lobe epilepsy predict seizure outcome following temporal lobectomy, predictors of seizure outcome have not been studied systematically in pediatric temporal lobectomy series. We retrospectively analyzed preoperative clinical, EEG, and neuroimaging findings with reference to seizure outcome (seizure free or non-seizure free) in 33 children (mean age, 9.3 years) who underwent tailored temporal lobe resections for intractable temporal lobe epilepsy. Trends were apparent with (1) younger age at seizure onset, younger age at surgery, shorter duration of epilepsy, localized unilateral temporal lesions on MRI, and right-sided surgery more frequently associated with a seizure-free outcome, and (2) significant prior history, daily preoperative seizures, generalized motor seizures, mental retardation, and localized unilateral temporal epileptiform EEG activity more frequently associated with a non-seizure-free outcome. However, none of these findings, alone or in combination, correlated with postoperative seizure status at a statistically significant level. Submitting the four variables generally considered to be most predictive of favorable outcome (ie, normal intelligence, unilateral ictal and interictal EEG discharges, and focal temporal MRI lesion) to a multiple-cutoff procedure did not predict seizure freedom. Our data indicate that predictors of outcome of temporal lobectomy in adults may not apply in children, perhaps due to inherent neurobiologic differences in the etiology and expression of temporal lobe epilepsy, and should therefore not be used as sole determinants of surgical candidacy in children. (*J Child Neurol* 1996;11:445-450).

Children with chronic temporal lobe epilepsy are being referred more often for epilepsy surgery. Indications for temporal lobectomy in children include frequent or severe seizures that are not controlled pharmacologically, seizures that are clinically and electrographically localized to one temporal lobe, and congruence of electroencephalographic

(EEG), imaging, and neuropsychological studies. The efficacy and safety of temporal lobectomy for intractable temporal lobe epilepsy in childhood is well established; pediatric temporal lobectomy series report that 56% to 93% of children become seizure free or experience at least a 90% reduction of seizures after the surgery.<sup>1-7</sup>

Given the intensity of the presurgical evaluation and the risks inherent in surgery, identification of patients most likely to benefit from temporal lobe surgery might enhance candidate selection and increase success rate. Preoperative features predictive of successful seizure outcome in adults undergoing temporal lobectomy include certain clinical variables<sup>8-14</sup> and specific findings on scalp EEG,<sup>15-18</sup> magnetic resonance imaging (MRI),<sup>19-21</sup> intracarotid amobarbital testing,<sup>22,23</sup> positron emission tomography,<sup>24-27</sup> and neuropsychological testing.<sup>9,28-30</sup> Postoperative findings are also reported, but are not useful in assessing candidacy for surgery. Multivariate algorithms for predicting success after cortical resection in adults are now available.<sup>28,31,32</sup>

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Although the characteristics of children who respond favorably to temporal lobectomy are reported,<sup>33</sup> few pediatric temporal lobectomy series compare outcome in unselected children and analyze specific preoperative variables for their prognostic significance. It is widely believed that normal intelligence, localized temporal EEG abnormalities, and a discrete temporal lobe lesion predict favorable seizure outcome following surgery, but this thesis has not been tested empirically. Favorable preoperative variables reported in some pediatric temporal lobectomy series include early age at operation, short duration of epilepsy, infrequent seizures, absence of secondarily generalized seizures, normal intelligence, focal spikes on interictal scalp EEG, and discrete histopathologic lesion.<sup>1,3,5,34,35</sup> However, these studies do not permit definite conclusions because of differences in inclusion criteria and surgical techniques as well as a paucity of statistical analysis.

With the aim of identifying predictors of seizure relief following surgery in children with intractable temporal lobe epilepsy, we used univariate and multivariate statistical analyses to retrospectively study preoperative variables in a series of children who underwent tailored temporal lobectomy at our center.

## METHODS

### Inclusion Criteria

This study included 33 children aged 15 years or younger with medically resistant partial seizures of temporal lobe origin who underwent temporal lobe resection at Miami Children's Hospital between 1985 and 1993. Children at our institute are considered surgical candidates if they have evidence of seizure activity arising primarily in one temporal lobe, meet our pharmacologic criteria for medical intractability,<sup>36</sup> and are experiencing severe psychosocial or cognitive impairment related to recurrent seizures. Children who do not have an adequate support system, who are medically non-compliant, or who have progressive degenerative conditions or metabolic disorders are rejected. Absence of a lesion on imaging studies, multifocal lesions, atrophy, and nonspecific findings are not exclusion criteria.

We excluded from the analysis children who underwent combined temporal and extratemporal resection, hemispherectomy, or previous extratemporal resection. We included children who had further surgery for continued seizures, but analyzed data only for the first temporal lobe surgery. Follow-up of at least 2 years was mandatory for inclusion.

All children underwent a comprehensive preoperative evaluation that included 32-channel scalp video-EEG monitoring, MRI, and psychological testing. Intracarotid sodium amytal testing and functional neuroimaging were not performed routinely. Extraoperative subdural EEG monitoring and functional mapping were performed in children who required more precise seizure localization or mapping of language cortex. Coronal and axial MRI were performed using a 0.3 Tesla magnet ( $n = 26$ ) or a 1.5 Tesla superconducting magnet ( $n = 7$ ). Cognitive development was assessed with the Wechsler Intelligence Scale for Children (WISC-R or WISC-III) ( $n = 19$ ) or the Bayley Scales for Infant Development ( $n = 2$ ); devel-

opmental history was used for the remainder. Temporal resections were tailored according to EEG, MRI, and functional mapping data.

Surgical outcome was classified as either seizure free or non-seizure free (one or more seizures postoperatively). We elected not to employ a graded postoperative seizure classification scale or quality of life measures because we sought to identify factors predicting complete rather than relative seizure freedom. In addition, patient numbers were too small for statistical analysis using such scales.

### Variables Analyzed

Eleven preoperative clinical, neuroimaging, and EEG variables were correlated with seizure outcome. For statistical analysis, EEG and MRI data were categorized into clinically meaningful groups. The following variables were analyzed:

1. Age at seizure onset (years).
2. Age at surgery (years).
3. Duration of epilepsy (years).
4. Presence of a significant history predisposing to epilepsy (eg, head trauma, central nervous system infection, neurocutaneous syndrome).
5. Presence of daily seizures.
6. Presence of generalized motor seizures, either partial secondarily generalized or myoclonic seizures or infantile spasms.
7. Presence of mental retardation, defined as a Full Scale IQ (WISC-III or WISC-R) or mental development index (Bayley Scales) less than 80, or a history of significant developmental delay in children who were not formally tested.
8. Presence of localized unilateral temporal epileptiform activity on *interictal* EEG. Epileptiform activity was defined as spikes, sharp waves, spike-slow waves or paroxysmal rhythmic delta activity. Interictal EEG recordings with poorly localized, bilateral, extratemporal, or no abnormalities were grouped together.
9. Presence of localized unilateral temporal epileptiform activity on *ictal* EEG. Ictal EEG recordings with poorly localized, bilateral, or extratemporal ictal patterns were grouped together.
10. Presence of a unilateral temporal lobe lesion on MRI (eg, hippocampal sclerosis, temporal lobe tumor). Normal or nonspecific MRI findings and extratemporal MRI abnormalities were grouped together.
11. Side of surgery.

All variables were evaluated statistically for their relationship to surgical outcome using univariate tests. Fisher's exact test or the chi-square statistic were used for the eight categorical variables and Student's *t* statistic was used for the three continuous variables. The categorical variables were then submitted to a multiple-cut-off procedure.<sup>28</sup>

## RESULTS

### Patient Data

Thirty-three children (17 males, 16 females) were included in the study. The age at surgery was 6 months to 15 years

(mean, 9.3 years). Age at seizure onset was 1 month to 8 years (mean, 3.2 years), and duration of epilepsy was 5 months to 12 years (mean, 6.1 years). Significant history included encephalitis in two, febrile seizures in two, tuberous sclerosis in two, and bacterial meningitis in one of the patients. All children had simple partial seizures or complex partial seizures. Fifteen children had additional secondarily generalized seizures and three had myoclonic seizures or infantile spasms. Twenty-five children had daily seizures. Seventeen children were mentally retarded.

Interictal EEG revealed unilateral temporal epileptiform activity in 21 children, poorly localized or bilateral or extratemporal interictal epileptiform activity in six, and no interictal epileptiform activity in six of the patients. Ictal discharges were unilateral temporal in 28 children, poorly defined and bilateral in one, bitemporal in two, and diffuse hemispheric in two of the patients.

Nineteen children had unilateral temporal lobe lesions on MRI including mass lesions in 11, hippocampal sclerosis in five, and focal signal abnormality in three of the children. Ten children had normal or nonspecific MRI findings. Of four children with extratemporal abnormalities, there were multiple bilateral cortical tubers in one, multiple bilateral cysts with cerebral atrophy in one, right cerebral dysplasia in one, and a subependymal nodule in one. No patient showed discordant lateralization from EEG and MRI findings.

Twenty-two children underwent extraoperative subdural EEG monitoring, seven of whom underwent language mapping. Anterior temporal resection tailored to the EEG and neuroimaging data was performed in all patients; seven patients had additional posterior basal temporal corticectomy.<sup>37</sup> Seventeen children had left-sided resections and 16 had right-sided resections. Mesial temporal resection was performed with suction curettage. Hippocampal tissue was available for histopathologic analysis in 10 children. Histopathology in 23 of the patients revealed developmental abnormalities, consisting of abnormalities of cortical architecture and neuronal morphology, glial-neuronal hamartomata, or neuronal ectopia. Eight children had tumors, six had dysembryoplastic neuroepithelial tumor, and two had ganglioglioma. One child had extensive cystic encephalomalacia and one child had only mild gliosis. Six children had hippocampal sclerosis associated with their tumors and developmental lesions.

There were 15 seizure-free and 18 non-seizure-free children at follow-up of 24 to 120 months (mean, 56 months). Six of the 15 seizure-free children were no longer receiving medication. Of the 18 non-seizure-free children, eight had seizure frequency decreased by 90% or more, one had seizure frequency decreased by less than 90% but more than 50%, and nine were unchanged or had less than 50% reduction in seizure frequency. In the non-seizure-free group, seizures recurred in the immediate postoperative period or up to 3 years postoperatively. No child with immediate postoperative seizures became seizure free thereafter.

### Statistical Analysis

Seizure-free and non-seizure-free children were compared on each of the 11 preoperative variables (Table 1). For the seizure-free and non-seizure-free categories, age at surgery and duration of epilepsy were normally distributed, whereas age at onset was positively skewed. Children in the non-seizure-free group were older at onset of seizures, older at time of surgery, and had a longer duration of epilepsy; however, these differences did not reach statistical significance. For the continuous variable with the lowest *P* value (age at surgery), effect size was 0.39, with power reaching only 20% ( $\alpha = 0.05$ , two-tail). A sample size of 103 would have been required to detect this effect size with a power of 80%.

Significant history, daily preoperative seizures, generalized motor seizures, mental retardation, and well-localized unilateral temporal interictal and ictal EEG activity were less frequent in children who were seizure free. Localized unilateral temporal lesions on MRI and right-sided surgery were more frequent in children who were seizure free. However, none of these trends reached statistical significance. For the categorical variable with the lowest *P* value (generalized motor seizures), effect size was 0.27, with power at 23% ( $\alpha = 0.05$ , two-tail). A sample size of 150 would have been required to detect this effect size with a power of 80%.

Because normal interictal EEG might be considered a better prognostic indicator than extratemporal and bilateral EEG abnormalities, we reanalyzed interictal EEG findings, grouping normal interictal EEG activity with localized unilateral temporal interictal EEG activity, rather than with poorly localized, bilateral, and extratemporal EEG abnormalities. Fourteen of 27 (52%) children with localized

Table 1. Correlation Between Preoperative Variables and Seizure Outcome\*

Variable	NSF	SF	Probability
Mean age at onset in years	3.50 (2.72) <sup>†</sup>	2.73 (2.38) <sup>†</sup>	<i>P</i> = .40
Mean age at surgery in years	10.00 (4.77) <sup>†</sup>	8.42 (3.26) <sup>†</sup>	<i>P</i> = .29
Mean duration of disorder in years	6.49 (3.29) <sup>†</sup>	5.68 (3.45) <sup>†</sup>	<i>P</i> = .49
Presence of significant history	5 (71%)	2 (29%)	<i>P</i> = .41
Presence of daily seizures	15 (60%)	10 (40%)	<i>P</i> = .42
Presence of generalized motor seizures	12 (67%)	6 (33%)	<i>P</i> = .13
Presence of mental retardation	10 (59%)	7 (41%)	<i>P</i> = .61
Presence of unilateral temporal interictal activity	12 (57%)	9 (43%)	<i>P</i> = .69
Presence of unilateral temporal ictal activity	15 (54%)	13 (46%)	<i>P</i> = 1.00
Presence of a unilateral temporal lesion on MRI	9 (47%)	10 (53%)	<i>P</i> = .34
Right-sided surgery	7 (44%)	9 (56%)	<i>P</i> = .23

\*Correlations presented are for 33 children who underwent tailored temporal lobectomy.

<sup>†</sup>Values in parentheses are standard deviations.

The values in parentheses are the proportion of seizure-free or non-seizure-free patients from the total number of patients who exhibited that variable.

NSF = non-seizure free; SF = seizure free.

Table 2. Seizure Outcome Following Tailored Temporal Lobectomy in Childhood\*

Number of "Favorable" Variables	Number of Subjects	NSF	SF
0	1	1	0
1	3	1	2
2	7	6	1
3	5	3	2
4	7	3	4
5	5	3	2
6	3	1	2
7	2	0	2

\*Results grouped by number of "favorable" preoperative variables. NSF = non-seizure free; SF = seizure free.

unilateral temporal interictal EEG abnormalities or normal interictal EEG were seizure free, compared to one of six (17%) children with poorly localized, bilateral, or extratemporal abnormalities; however, this did not reach statistical significance ( $P = .19$ ).

We also analyzed seizure outcome with respect to specific lesions identified on MRI. Eight of 11 (72%) children with mass lesions on MRI were seizure free compared to seven of 22 (32%) with no mass lesion ( $P < .05$ ). One of five (20%) children with hippocampal sclerosis on MRI was seizure free compared to 14 of 28 (50%) with no hippocampal sclerosis on MRI ( $P = .35$ ).

Since none of the individual preoperative variables reached statistical significance, we submitted the eight categorical variables to a multiple-cutoff procedure<sup>28</sup> to study their combined effect. For each variable dichotomy, the proportion of seizure-free versus non-seizure-free patients was determined (Table 1). When the greater proportion correlated with seizure freedom, the variable was defined as favorable. The number of favorable variables was counted for each patient. The subjects were then ordered according to the number of favorable variables and reclassified according to seizure-free and non-seizure-free outcomes (Table 2). Ten of 17 (59%) children with more than three favorable variables became seizure free following tailored temporal lobectomy compared to five of 16 (31%) children with three or fewer favorable variables. However, this result did not reach statistical significance. Using the alternative categorization of interictal EEG did not change these results.

We also tested the hypothesis that normal intelligence and localized temporal EEG and MRI abnormalities are the

Table 3. Seizure Outcome Following Tailored Temporal Lobectomy in Childhood Grouped by Number of Favorable Prognostic Indicators\*

Number of "Favorable" Variables	Number of Subjects	NSF	SF
0	5	3	2
1	9	6	3
2	14	7	7
3	4	2	2
4	1	0	1

\*Results obtained using only mental retardation, ictal and interictal EEG, and MRI. NSF = non-seizure free; SF = seizure free.

most important predictors of favorable seizure outcome. We therefore used an additional multiple-cutoff procedure to incorporate these four variables. Ten of 19 (53%) children with at least two favorable variables became seizure free compared to five of 14 (38%) children with one or no favorable variables (Table 3). However, this result did not reach statistical significance. The alternative categorization of interictal EEG changed the proportions, but not the pattern of results or the statistical significance.

## DISCUSSION

Seizure outcome in our series of tailored temporal lobectomy compares favorably with other pediatric series.<sup>1-7</sup> Seventy percent of our patients are seizure free or had a greater than 90% reduction in seizures after surgery. Prognostic trends were apparent with younger age at seizure onset, younger age at surgery, shorter duration of epilepsy, localized unilateral temporal lesions on MRI, and right-sided surgery more frequently associated with a seizure-free outcome. In contrast, significant history, daily preoperative seizures, generalized motor seizures, mental retardation, and unilateral temporal interictal and ictal EEG activity were more frequently associated with a non-seizure-free outcome. The results for EEG findings were unexpected and surprising. Nevertheless, the relative differences in the seizure-free and non-seizure-free groups were often minimal and none of the individual variables predicted seizure outcome at a statistically significant level. Similar trends lacking statistical analysis or validation are reported in other pediatric temporal lobectomy series.<sup>1,3,5,34,35</sup> These findings contrast with adult studies, which report statistically significant predictive value for certain clinical, EEG, imaging, and pathologic findings in adults with temporal lobe epilepsy.<sup>8-30</sup>

The presence of at least four favorable variables was associated with a seizure-free outcome and the presence of three favorable indicators or fewer was more frequently associated with a non-seizure-free outcome; however, these findings did not reach statistical significance. A separate multiple-cutoff analysis, in which we utilized only the four variables generally considered to be the most important predictors of seizure outcome (ie, normal intelligence, unilateral ictal and interictal EEG discharges, and focal temporal MRI lesion), also failed to demonstrate a relationship to seizure outcome. Our findings differ from those of Spencer and colleagues<sup>31</sup> who employed a similar analysis in 105 adults and reported 1 year remission of seizures after temporal lobectomy in 90% of patients who had three favorable factors, 83% with two, 53% with one, and 33% with none. Our results also differ from those of Dodrill and colleagues<sup>28</sup> who employed the multiple-cutoff procedure in adults and found that five or more favorable variables had a higher probability of seizure freedom or significant improvement following epilepsy surgery for temporal and extratemporal epilepsy. However, in contrast to our study, which defined variables as favorable or unfavorable based on the difference in the proportion of seizure-free and non-seizure-free patients

(sometimes as low as 6%), the favorable variables employed in the aforementioned studies were each statistically significant.

The lack of statistically significant predictors of seizure outcome in our study, and in previously reported pediatric temporal lobectomy series, may be due to inherent neurobiologic differences between adults and children with temporal lobe epilepsy, ie, the variables studied may not be good predictors of seizure outcome in children with intractable temporal lobe epilepsy. The age at seizure onset, age at surgery, and duration of epilepsy, although important predictors of outcome when comparing children or adolescents to adults, may be less relevant within a limited age range. Second, although neurologic insults such as prolonged febrile seizures<sup>3,8,12,38</sup> and intracranial infection<sup>38-40</sup> are usually associated with a favorable outcome following temporal lobectomy in adult studies, they were rare in our series. Third, scalp EEG may not be a good predictor of seizure outcome in children compared to adults, given that scalp EEG is often nonlocalizing in young children with partial epilepsies, instead revealing multifocal spikes, bilaterally synchronous spike-wave activity or no abnormality in a large proportion.<sup>41-45</sup> Furthermore, the prognostic significance of bilaterally independent epileptiform abnormalities on scalp EEG in adults with temporal lobe epilepsy remains controversial.<sup>9,11,15-18,46</sup> Fourth, favorable outcome from temporal lobectomy is reported in adults with preoperative MRI diagnosis of hippocampal sclerosis,<sup>19-21</sup> but hippocampal sclerosis has only recently been recognized as an important MRI finding in children with intractable temporal lobe epilepsy.<sup>38,47</sup> Hippocampal sclerosis was identified preoperatively on MRI in only five of our children, but it is possible that hippocampal sclerosis was not detected in some patients early in the series who had lower resolution MRI scans. Coinciding with previous studies that demonstrated a favorable seizure outcome after epilepsy surgery in patients with tumors,<sup>34,48-51</sup> the presence of a mass lesion on MRI was associated with seizure-free outcome in our series.

Conversely, methodological factors may offer an explanation for the lack of statistically significant predictors of seizure outcome. Low statistical power might have contributed to the absence of any statistically significant correlation between the variables studied and postoperative seizure outcome. Although increasing the number of subjects would have increased power, we would have had to include older patients and patients with extratemporal resections, which would have compromised our goal to study young children who had undergone temporal lobectomy. The study of a larger sample of children undergoing temporal lobectomy, which might require a collaborative effort from several pediatric epilepsy centers, might yield individual variables that are prognostic of outcome to a statistically significant degree. The use of a seizure-free/non-seizure-free dichotomy to analyze postoperative seizure outcome, rather than a graded scale or a scale incorporating quality of life measures, may also have

contributed to the lack of statistically significant findings in our study. However, we elected not to utilize a graded scale or a scale incorporating quality of life measures because valid pediatric scales are not currently available, grading postoperative seizures is subject to error and influenced by medication, and our interest was to identify factors that predicted absolute seizure freedom. Furthermore, patient numbers were too small for such analysis.

Another possible explanation for the lack of statistically significant predictors of seizure outcome in our study is that our center utilizes subdural EEG and functional mapping data to perform tailored temporal resection, in contrast to a standard anterior temporal lobectomy based on noninvasive data, the strategy employed in most reported pediatric temporal lobectomy series.<sup>1-3,6-7,34</sup> The surgical strategy at our center might lead to removal of more epileptogenic cortex than in patients reported in other series, changing the seizure outcome and therefore the correlation with preoperative variables. However, we do not believe that this is a significant factor, as overall seizure outcome in our study is similar to that reported in these other studies.

In conclusion, our study failed to reveal individual preoperative variables that were predictive of seizure outcome to a statistically significant degree in children with temporal lobe epilepsy undergoing temporal lobectomy. Furthermore, our data did not support the belief that normal intelligence and unilateral temporal EEG and MRI abnormalities predict a favorable outcome. Thus, predictors of surgical outcome in adults with temporal lobe epilepsy may not apply or may not be reliable in children with temporal lobe epilepsy, perhaps due to underlying differences in the etiology and expression of temporal lobe epileptogenicity at a young age. Given the poor prognosis of intractable temporal lobe epilepsy in childhood with respect to long-term seizure control and psychosocial development, we believe that all children with medically resistant temporal lobe epilepsy are potential candidates for epilepsy surgery.

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