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Surgical Outcome in Tuberous Sclerosis Complex: A Multicenter Survey

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Summary: Multicenter, retrospective analysis of 70 subjects with TSC following surgery for relief of epilepsy revealed significant associations between younger age at seizure onset, present/prior history of infantile spasms, interictal focality (bilateral versus unilateral), and absence of residual postoperative predominant tuber, and poorer postoperative outcome ($p < 0.01$). Ictal multifocality, mental retardation, and discordant EEG and MRI data showed a negative trend toward outcome, but were not significant. **Key Words:** Tuberous sclerosis—Surgical—Outcome.

Epilepsy often complicates tuberous sclerosis complex (TSC). Cortical tubers are pathognomic of TSC and contribute to the pathogenesis of seizures. Depending on the seizure type, ictal EEG can display focal or generalized seizures, including infantile spasms. Focal features often reflect the predominant epileptogenic tuber topography.

Seizures in TSC are often resistant to antiepileptic drug (AED) therapy, but surgery may control seizures in selected cases. Outcome is best in patients with a single seizure type, single tuber, or one large tuber, with convergent clinical, imaging and neurophysiologic data (Romanelli et al., 2004), and no mental retardation (Jarrar et al., 2004). Current techniques allow for better localization of epileptogenic tissue, leading to improved surgical outcome (Weiner, 2004; Weiner et al., 2004).

METHODS

Patients

Data were included from the Child Neurology and Metabolic Diseases Department from the University Hospital Robert Debré; NYU Tuberous Sclerosis Center, NY, New York; Department of Neurology and Neurosurgery and Human Genetics, Montreal Neurological Institute; the Department of Neurology, Cincinnati Children's Hospital Medical Center; Division of Neurology, British Columbia's Children's Hospital; Department of Neurology, Mayo Clinic. Portions of this work have been published in prior reports (Guerreiro et al., 1998; Weiner et al., 2006).

Subjects consisted of a consecutive series of patients who underwent preoperative assessment and surgery, between 1977 and 2003 (except one patient underwent preoperative assessment in 1950). The study population comprised 70 TSC patients who underwent surgery for refractory epilepsy. Descriptive statistics for interval data are reported in Table 1, and frequency data are reported in Table 2, along with results from statistical analyses. The number of surgical stages refers to the number of operations during a single hospitalization. Single-stage surgery was a resection in one operative procedure. Two-stage surgery was an intracranial EEG study followed by resection. Three-stage surgeries consist of a two-stage surgery followed by an additional intracranial EEG monitoring with additional resection.

Surgical procedures included corpus callosotomy, lesionectomy, lobar resection or lesionectomy, and lobar

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TABLE 1. *Means and standard deviations for interval variables for total sample and by Engel Class*[a]

Characteristic	Total	Engel Class I	Engel Class II-IV	p-Value univariate
Age at seizure onset (n = 69)	13.6 (20.1)	18.3 (25.7)	8.4 (11.4)	.041*
Age at TSC diagnosis (n = 64)	34.4 (67.1)	36.7 (68.6)	32.0 (66.7)	.785
Age at surgery (n = 70)	9.9 (10.2)	9.4 (10.2)	10.4 (10.4)	.699
Number of cortical tubers (n = 53)	6.1 (5.9)	5.3 (5.4)	7.1 (6.5)	.272
Time from surgery to evaluation (n = 70)	5.2 (8.0)	4.6 (9.3)	5.7 (6.5)	.565

All ages described in months, while time from surgery to evaluation refers to number of years. Values represent mean (SD); p indicates difference between subgroups using *t*-tests.

[a]I versus II–IV.

resection. Lesionectomies were those surgeries consisting of a single or multiple tuberectomies and bilateral tuberectomies. Lobar resections could be single or multilobe and also comprised hemispherectomies.

Outcome

Surgical outcome was defined as Engel Class I-IV (Engel et al., 1993) for correlation and regression analyses. Engel Class was divided into two groups for univariate analyses: Class I (seizure freedom) versus Classes II–IV (presence of seizures).

Analyses

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v11.0.3). Pearson correlations between all variables are reported in Table 3. Interval data were also divided into groups (defined in Table 2) so that all variables could be subjected to the same analyses. Categorical data were first analyzed using the chi-square test (univariate), and variables that were found to be significant were then subjected to a linear regression analysis using Engel Class (I-IV) as the criterion variable (multivariate). A Bonferonni correction was applied during chi-square and correlation analyses due to the large number of variables (significance values set at 0.01). The association between outcome and the following variables was examined: sex; age of seizure onset; age at TSC diagnosis; presence/prior history of infantile spasms; the presence or absence of mental retardation; number of cortical tubers; ictal and interictal focality (unilateral vs. bilateral); concordance between ictal scalp EEG and ictal intracranial EEG with principal tuber location, age at surgery, number of surgical stages, extent of surgical procedure, presence of residual dominant tuber, and time from surgery to postsurgical classification.

RESULTS

Of the total sample, 37 subjects (53%) had Engel Class I outcome, 8 (11%) had Engel Class II outcome, 13 (19%) had Engel Class III outcome, and 12 (17%) had Engel Class IV outcome. The sex of the patient was not associated with outcome.

Mental retardation

None of the analyses that examined the association between mental retardation and surgical outcome were significant.

Age at TSC diagnosis

None of the analyses that examined the association between age at TSC diagnosis and surgical outcome were significant.

Cortical tubers

None of the analyses that examined the association between number of cortical tubers and surgical outcome were significant. While there was no difference in outcome based on location or laterality of the dominant tuber, the relationship between the presence of residual dominant tuber on MRI and the location of the resection approached significance ($X^2 = 5.159$; $p = 0.076$). Only those patients with frontal lobe tubers were found to have undergone a complete resection of the tuber. The ability to interpret these results is limited by the small number of patients who underwent complete resection.

Seizure variables

The result of the chi-square analysis for age of seizure onset (12 months or earlier vs. after 12 months of age) was significant. When age of onset was entered into a regression equation, it did not explain a significant amount of variance in Engel Class outcome, which was likely due to its high correlation with other predictor variables. There was a strong association between current or prior infantile spasms and poor seizure outcome. Of those patients who had experienced infantile spasms, 72% continued to have seizures after surgery. The relationship between interictal (but not ictal) focality and seizure outcome approached significance, and of those patients with unilateral focus identified on interictal EEG, 69% were seizure free after surgery. When both ictal and interictal focality were entered into a regression equation with other variables that were found to be significant through chi-square analyses, the relative contributions of each was reversed (although neither was significant). This appeared to be due to the significant correlation between interictal focality and the presence of infantile spasms (bilateral focality was associated with infantile spasms). Correlations between ictal

TABLE 2. *Characteristics of the total sample and by Engel Class*[a]

Characteristic	Total	Engel Class I	Engel Class II–IV	p-Value univariate	p-Value multivariate[b]
Sex					
Female	39	20 (51.3)	19 (48.7)	0.767	
Male	31	17 (54.8)	14 (45.2)		
Age of seizure onset					
≤12 months	53	23 (53.4)	30 (56.6)	0.008[b]	0.609
>12 months	16	13 (81.2)	3 (18.8)		
Age at TSC diagnosis					
≤12 months	44	20 (45.5)	24 (53.8)	0.147	
>12 months	20	13 (65.0)	7 (35.0)		
Infantile spasms present					
Yes	32	9 (28.1)	23 (71.9)	0.000[c]	0.004[b]
No	38	28 (73.7)	10 (26.3)		
Presence of mental retardation					
Yes	46	24 (52.2)	22 (47.8)	0.457	
No	21	13 (61.9)	8 (38.1)		
Number of cortical tubers					
≤4	29	17 (58.6)	12 (41.4)	0.745	
>4	24	13 (54.2)	11 (45.8)		
Side of dominant tuber					
Left hemisphere	24	13 (54.2)	11 (45.8)	0.977	
Right hemisphere	33	18 (54.5)	15 (45.5)		
Location of dominant tuber					
Frontal	33	19 (57.6)	14 (42.4)	0.656	
Temporal	11	7 (63.6)	4 (36.4)		
Other[c]	17	8 (47.1)	9 (52.9)		
Ictal focality					
Unilateral	44	28 (63.6)	16 (36.4)	0.036	0.076
Bilateral	13	4 (30.8)	9 (69.2)		
Interictal focality					
Unilateral	35	24 (68.6)	11 (31.4)	0.007[b]	0.418
Bilateral	31	11 (35.5)	20 (64.5)		
Correlation between tuber location and surface EEG					
Yes	53	32 (60.4)	21 (39.6)	0.154	
No	13	5 (38.5)	8 (61.5)		
Correlation between tuber location and intracranial EEG					
Yes	38	22 (57.9)	16 (42.1)		
No	5	2 (40.0)	3 (60.0)	0.449	
Age at surgery					
≤5 years	35	18 (51.4)	17 (48.6)	0.811	
>5 years	35	19 (54.3)	16 (45.7)		
Number of surgical stages					
1	39	22 (56.4)	17 (43.6)	0.158	
2	17	6 (35.3)	11 (64.7)		
3	13	9 (69.2)	4 (30.8)		
Extent of Surgery					
Corpus callosotomy	6	1 (16.7)	5 (83.3)	0.027	0.864
Lesionectomy	14	6 (42.9)	8 (57.1)		
Lobar resection	8	2 (25.0)	6 (75.0)		
Lesionectomy and lobar resection	39	26 (66.7)	13 (33.3)		
Presence of residual tuber tissue on MRI					
Yes	45	29 (64.4)	16 (35.6)	0.006[b]	0.039[b]
No	8	1 (12.5)	7 (87.5)		
Time from surgery to evaluation					
≤ 2 years	31	20 (64.5)	11 (35.5)	0.081	
>2 years	39	17 (43.6)	22 (56.4)		

[a]I versus II – IV.
[b]Values represent n (%); indicates the difference between subgroups by X^2 test (univariate) or forward stepwise regression analysis (multivariate) is significant at $p < 0.01$.
[c]This group includes patients with the dominant tuber in the parietal lobe, occipital lobe, subcortical areas, and multilobar focality (frontotemporal, frontoparietal, parietotemporal), due to the small number of patients in each of these groups. Of note, analyses using "multilobar" as its own group (n = 7) did not yield significant results.

scalp EEG/intracranial EEG and MRI localization of the predominant tuber were not significantly correlated with outcome, likely because the majority of patients going to surgery had concordant clinical findings.

Surgical variables

None of the analyses that examined age at surgery (using both interval data and categorical groupings) was associated with outcome. The number of stages of surgery was not associated with outcome. Although the analyses that examined the association between extent of surgical procedure and seizure outcome were not significant, there was a trend toward better seizure outcome in those patients that had more extensive procedures.

Postoperative variables

The relationship between seizure freedom and the presence of residual dominant tuber postoperatively was significant, although the direction of this relationship was contrary to expectations (i.e., presence of residual tuber was associated with better outcome). Of those patients who were found to have residual dominant tuber tissue postoperatively (as identified on MRI), 64% were seizure free, while 88% of patients with no residual tissue continued to have seizures postoperatively. When this variable was entered into a multiple regression equation with other significant variables, it explained a significant amount of unique variance in outcome level.

DISCUSSION

Our retrospective, multicenter study of epilepsy surgery in 70 TSC patients revealed that poor outcome with regard to seizure freedom was associated with: early age of seizure onset, history of infantile spasms, and multifocal interictal activity. Methods taken by each center to isolate the dominant epileptogenic tuber were widely variable, with some reporting CT, PET, and SPECT results. Only MRI and EEG data were consistently reported among all centers, and were considered in the analysis. The presence of residual tuber on MRI was found to be significantly associated with good seizure outcome, which is likely a coincidental finding and raises important questions about the epileptogenicity of the tuber itself versus the surrounding brain tissue. However, this finding could also indicate patients with more complete tuber resections required larger resections overall, which could reflect more severe epilepsy. There was no significant association of tuber location with surgical outcome, but tubers in frontal locations appeared to be associated with more thorough resections, suggesting an influence of surgical approach on tuber removal (however, this was not a significant finding given the small numbers of the dataset). The current study suggests that in individual TSC patients, characteristics other than focality and MRI/EEG concordance should be examined, which are variables found to be significant in other studies (Jarrar et al., 2004; Romanelli et al., 2004; Lachhwani et al., 2005). Factors representing general neurological compromise may be important, such as the age at seizure onset and the presence of infantile spasms. Early onset seizures may disrupt neural networks and contribute to development of treatment-resistant epilepsy (Weiner et al., 2006).

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