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Ictal EEG remains the prominent predictor of seizure-free outcome after temporal lobectomy in epileptic patients with normal brain MRI☆

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Summary

Purpose: While an abnormal pre-operative high-resolution brain MRI portends a favorable outcome in patients undergoing resective epilepsy surgery for medically intractable localization-related epilepsy (LRE), a normal MRI is less favorable. Ascertaining desirable pre-operative predictors for successful anterior temporal lobectomy (ATL) in LRE patients with a normal brain MRI is essential to better anticipate surgical outcome.
Methods: Patients with LRE and normal temporal structures on MRI underwent ATL at two epilepsy centers in the southeastern US (FL and NC). Outcome was separated into those patients that were seizure free (SF), and those that were not seizure free (NSF), and those NSF were stratified in accordance with the Engel classification system. Those with a pre-operative history of clinical risk factors, unilateral anterior temporal interictal epileptiform discharges (IEDs), well localized scalp ictal EEG with rhythmic temporal theta at onset, localized PET/ictal SPECT, and Wada asymmetry with $>2.5/8$, were evaluated for the purpose of predicting outcome. Where appropriate, data is presented as a median (mean $\pm$ S.D.).
Results: Thirty-nine patients, median age 33 years, were followed up 2 years (3 ± 1.2) after ATL. Overall, 22/39 (56.4%) patients were identified as SF, and 17/39 (43.6%) patients were NSF. Ictal EEG with rhythmic temporal theta at onset

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was the only predictive measure of seizure-free outcome ($p = 0.001$, Fisher's exact test), and also favorably correlated with seizure reduction ($p = 0.0001$, $r^2 = 0.34$, multiple regression analysis). None of the other predictors examined added greater predictive value.
Conclusions: ATL is a favorable option for patients with LRE even when high-resolution brain MRI reveals normal temporal structures. Normal brain MRI patients with localizing pre-operative scalp ictal EEG, have better outcomes following ATL.

Introduction

Temporal lobe epilepsy remains the most common source of complex partial seizures in adults with medically intractable localization-related epilepsy (LRE).[1–3] Mesial temporal sclerosis is the most common pathology, and can be readily visualized on high-resolution brain MRI. Therefore brain MRI is critical in the pre-surgical evaluation process of patients with LRE.[4,5] However, brain MRI may be normal in up to one-third of the patients undergoing anterior temporal lobectomy (ATL) for LRE.[6–8]

Temporal lobectomy has proven to be a more favorable treatment for intractable partial-onset seizures than continued medical management.[9] An abnormal MRI is more predictive of a SF outcome for temporal lobectomy in LRE.[9–11] Single-center reports of temporal lobectomies that have been performed in patients with intractable LRE and normal pre-operative brain MRIs, have demonstrated the potential for a seizure-free outcome.[12,13]

The pre-operative evaluation for anterior temporal lobectomy begins by addressing clinical risk factors during historical review in addition to the lateralizing features associated with the ictal semiology. Pre-operative ancillary testing routinely include adjunctive studies that help localize the epileptogenic zone. In addition to a high-resolution brain MRI, the pre-surgical evaluation includes interictal EEG, ictal EEG during video-EEG monitoring, PET and ictal SPECT scanning, and WADA testing. Following ATL, most seizure recurrences that occur, do so after 6 months following surgery.[14] Therefore, at least 1 year follow-up of patients would be necessary to determine the success of the predictive parameters.

This dual center study was undertaken to further examine possible predictors of a seizure-free outcome after ATL in patients with intractable LRE and normal pre-operative high-resolution brain MRI. The benefit of temporal lobectomy in patients with LRE and normal brain MRI have been controversial.[8,13,15] Thus far, individual center data has been reported, and thus we report our dual center study assessing multiple pre-operative predictors.

Methods

In two southeastern US tertiary-care epilepsy centers, 253 post-ATL patients from Tampa, FL (2000–2007) and 27 post-ATL patients from Durham, NC (2003–2004) were evaluated retrospectively. The patients selected all had medically intractable LRE determined to reflect temporal lobe epilepsy. All patients had normal mesial temporal structures including no asymmetries of the amygdala and hippocampus by utilizing high-resolution MRI with a dedicated epilepsy protocol (see Table 1). The ultimate designation as a "normal" high-resolution brain MRI was based upon the final result obtained from the surgical decision-making, multi-disciplinary, assessment of the neuroradiogaphic findings judged to be normal not only by neuroradiology, but also by neurosurgery and epileptology services. All patients were evaluated following a minimum of 1 year after ATL.

Table 1 MRI protocol GE 1.5T LX HORIZON Version 9.1

	TR	TE	TI	Flip	Thickness	Matrix	Nex
T1 Flair sag	2000	7.5	750	90	5 skip 2	256 × 256	2
DWI ax	Routine						
GRE ax	500	20		20	5 skip 2	256 × 128	1
Flair ax	8000	120	2200	90	5 skip 2	256 × 224	1
T2 ax FSE	5000	85		90	5 skip 2	512 × 256	2
Flair cor	8000	120	2200	90	4 skip 1	256 × 224	1
T2 cor FSE	5000	85		90	4 skip 1	512 × 256	2
T2 cor IR	5500	20	200	90	4 skip 0	256 × 256	2
3D fspgr-IR preped cor	14	6	600	15	1.6 mm zipx2	256 × 192	1

Seizure outcome was classified SF versus NSF and detailed according to the classification system by Engel. Parameters evaluated included institution at which the surgery was undertaken, a clinical assessment of TLE risk factors, PET brain scan, the presence of unilateral (>90%) anterior temporal interictal epileptiform discharges, reproducible ictal EEG with rhythmic ictal temporal theta discharges at onset, and a significantly asymmetric Wada test result. Temporal interictal epileptiform discharges that were lateralized >90% to a single temporal lobe was selected to ensure a lateralized discharge that has been previously identified as a favorable pre-operative predictor of SF outcome in the surgical treatment of epilepsy.[16] Clinical assessment was focused upon sites that presented specific risks for mesial temporal lobe epilepsy and were noted if the patient had a history of childhood febrile convulsions, psychic aura, ictal fear, or the presence of complex partial seizures only without generalized tonic—clonic seizures (10*). When a PET scan was unobtainable, normal or non-localized to the site of presumed epileptogenicity, an ictal SPECT was attempted. In the event that both techniques were obtained, if an ictal SPECT was available, it was more heavily weighted than PET when a clear regional hyperperfusion was present. Patients who required intracranial electrodes for localization were examined separately.

Statistical analysis

Data were stored in Microsoft Excel (Microsoft Corp., Redmond, WA) files. Statistical analysis utilized Graphpad Instat version 3.06 (Graphpad Software Inc., San Diego, CA). Comparison of data was done using Fisher's exact test or Chi-square test for independence when Fisher's exact test was inappropriate. Where appropriate, data are presented as median, mean ± standard deviation (S.D.) and compared using Mann—Whitney test. Pre-operative predictors of outcome were correlated to the surgical outcome using linear multiple regression analysis. The multiple regression predictors included ictal EEG localization, interictal epileptiform discharge localization*, WADA test, clinical history, PET/SPECT scan localization and correlated them to the surgical outcome (seizure-freedom). The predictors that did not correlate significantly were dropped from the multiple regression analysis until only significant predictors were included.

Results

Thirty-nine patients that underwent ATL were retrospectively identified to have had normal high-resolution brain MRI pre-operatively. The patients were composed of 62% females, and 38% males, with a median age of 33 years (33.8 ± 10.9) (Table 2). Twenty-two of the 39 (56.4%) patients were identified as SF and 17/39 (43.6%) were NSF. The largest sample of patients was obtained from the 1st center comprising 82% of the SF patients and 88% of those patients that were NSF. Right temporal lobectomy represented 45.5% of the SF patients versus 35.3% of those NSF (Table 2). Intracranial electrodes were required prior to excisional surgery in 18.2% of the SF patients and in 23.5% of the NSF patients (Table 2).

Two patients were found to be class IV. One of the NSF patients had psychogenic non-epileptic seizures post-operatively, and therefore an accurate outcome classification could not be determined. One SF patient had undergone a co-incidental parietal craniotomy for a meningioma following seizure onset and was independent of her seizures. Three NSF patients had repeated temporal lobe resections.

Of the SF patients, 81.9% had a PET scan, 13.6% had an ictal SPECT scan performed and 4.5% had neither (Table 3). All of the patients that were NSF had either a PET scan (88.2%) or an ictal SPECT scan (11.8%) pre-operatively. Wada testing was performed on 90.9% of the seizure-free patients, and 88.2% of the not seizure-free patients. Only the ictal EEG was significantly different between those SF and NSF patients ($p = 0.001$, Fisher's exact test) (Table 3).

Using a step-wise linear multiple regression analysis, parameters including the institution at which

Table 2 Patient demographics

	Seizure free ($n = 22$)	Not seizure free ($n = 17$)	p-Value
Gender	45.5% M, 54.5% F	29.4% M, 70.6% F	0.34
Age (years)	36.0 (34.5 ± 10.4)	33.5 (35.1 ± 12.6)	0.89
Duration of symptoms (years)	10.0 (13.2 ± 12.3)	14.0 (16.3 ± 9.2)	0.18
Follow-up duration (years)	2.5 (2.7 ± 1.30)	2.0 (2.4 ± 1.11)	0.65
Intracranial electrodes	18.2%	23.5%	0.71
Lobectomy side	45.5% (right)	35.3% (right)	0.74

Table 3 Pre-operative predictors

		Seizure free (n = 22) (%)	Not seizure free (n = 17) (%)	p-Value
Pre-op PET/SPECT localization	Positive	68.2	76.5	0.63
	Negative	27.3	23.5	
	Not tested	4.5	0.0	
Pre-op ictal EEG localization	Positive	90.9	41.2	0.001*
	Negative	9.1	58.8	
Pre-op interictal EEG localization	Positive	72.7	64.7	0.73
	Negative	27.3	35.3	
Pre-op WADA asymmetry	Positive	40.9	29.4	0.77
	Negative	50.0	58.8	
	Not tested	9.1	11.8	
Pre-op clinical history	Positive	27.3	35.3	0.73
	Negative	72.7	64.7	
Medical institution	Institution 1	83.3	89.5	0.67
	Institution 2	16.7	10.5	

* Significantly different between seizure free and not seizure free using Fisher's exact test.

the operation was undertaken, clinical assessment of TLE risk factors, PET brain scan, the presence of unilateral (>90%) anterior temporal interictal epileptiform discharges, reproducible ictal EEG with rhythmic ictal temporal theta discharges at onset, and a significantly asymmetric Wada test were correlated against post-operative seizure outcome. Only ictal EEG localization was significantly correlated with a SF outcome ($p = 0.0005$, $r^2 = 0.29$) (Fig. 1).

Discussion

Temporal lobectomy remains a favorable therapeutic option for patients with intractable temporal epilepsy despite a normal pre-operative high-resolution brain MRI. While 3-T imaging may help redefine how "normal" is interpreted, our study used a dedicated epilepsy protocol that is currently the most widely employed technique for patients that

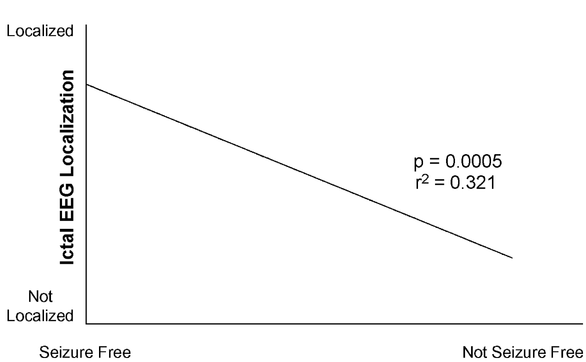

Figure 1 Pre-operative ictal EEG localization vs. patient outcome.

undergo resective epilepsy surgery (10). More than 50% of the patients were SF after temporal lobectomy and these results compare favorably with prior reports from other centers.[13,17,18]

With the exception of ictal EEGs, the pre-operative assessment in patients with a normal high-resolution brain MRI and intractable temporal epilepsy remains restricted to ictal EEG. In our study, a pre-operative localizing ictal EEG manifest as rhythmic ictal theta at seizure onset has proven to be a reliable predictor of seizure reduction following temporal lobectomy in LRE patients with a normal high-resolution brain MRI. This agrees with other single-center studies that have found the utility of ictal EEG.[17,19] Still, other studies disagree that the ictal EEG is a predictive tool when the brain MRI is normal.[20] However, when the ictal EEG is manifest as rhythmic temporal theta at onset, this has correlated with mesial temporal lobe onset and may help explain why this subset demonstrated a favorable outcome despite normal neuroimaging of the temporal lobe structures.[21]

Medial temporal lobe epilepsy is the most common form of localization-related epilepsy in adults. Anterior temporal interictal epileptiform discharges are the most consistent interictal feature on EEG and carry a heightened predisposition for the expression of complex partial seizures of temporal lobe origin.[22] One-third of patients have bilateral interictal epileptiform discharges that occur maximally in non-REM sleep.[23]

Interictal anterior temporal epileptiform discharges on scalp EEG have been used as an indicator of temporal lobe epilepsy, and may reflect the pathophysiology of the underlying substrate.[24] In our study, epileptiform discharges of >90% on interictal EEG were not found to be a reliable indicator of a SF outcome following temporal lobectomy in agreement with other outcome studies in patients with LRE and normal pre-operative brain MRI.[19,25] One smaller study from the UK evaluating the interictal EEGs of a smaller patient population concluded other predictors are necessary for favorable surgical outcome[25] though this was not found in the current study on multiple regression analysis. A second smaller study examined the outcome predictors of LRE patients with normal pre-operative MRI and drew conclusions similar to our own that ictal EEG was a favorable outcome predictor.[11] In counter distinction, they found benefit by combining localizing interictal and ictal EEG to predict outcome.[11] Our results demonstrated no added predictive value by combining ictal with localizing interictal EEGs (or other variables such as PET or Wada). These differences may be due to our larger sample size and combined results from two centers.

Both rCMR (PET) and rCBF (SPECT) are techniques of functional neuroimaging that allow visualization of rCMR and have similar sensitivities and specificities relative to seizure lateralizing capability.[26,27] PET was selected as the initial functional measure of rCBF due to its greater ease of interictal acquisition, and established reliability in sensitivity and specificity for pre-surgical evaluations in epilepsy.[26] PET (SPECT) scans have had some successes in the past in predicting the location of the epiletogenic zone, though the predictive role of a pre-operative brain PET with a normal high-resolution brain MRI has thus far received little attention.[27,28] We found no predictive value to localize the epileptogenic zone in those patients who were seizure free following ATL that had been noted to have a normal high-resolution brain MRI pre-operatively.

Childhood febrile convulsions,[29] psychic auras[30] or ictal fear,[31] and complex partial seizures without generalized tonic—clonic seizures[10] are risk factors that have been associated with TLE. While auras are a common manifestation of LRE, other auras and multiple auras were not assessed in the present study due to the more limited specificity relative to outcome. Ictal semiology is important in pre-operative localization, yet it was not included in our analysis because of the possibility of introducing a subjective misrepresentation over multiple captured seizures with varying degrees of manifestations. In our cohort, we found that the clinical risks were collectively not a predictor of outcome. Recently, a large multi-center study, which did not exclude patients with abnormal MRIs, also found no predictor value for clinical history when a history of CPS only was excluded.[10]

The Wada test is routinely used as a predictor of memory loss after temporal lobectomy.[32] One study found the Wada test limited in the ability to predict favorable outcome post-temporal lobectomy.[33] Patients were selected for intracranial electrodes as well as Wada testing following a multi-disciplinary surgical planning conference. Wada was not utilized when it was felt to be unlikely to change the consequences of a resection for an individual patient. Given prior limitation of Wada/repeat Wada, this study was not performed at both centers in every case.[34] With a normal brain MRI, our study did not support the Wada test as an independent predictor for a SF outcome for temporal lobectomy on LRE patients.

Limitations of this study include the relatively small number of patients included in the analysis. Furthermore, post-operative pathology was not helpful in confirming localization, and therefore, pathology was not additive. However, most pathological results of "non-specific gliosis" from the largest cohort would have had little bearing as a pre-operative predictor which was the focus of this study. Due to the disproportionate difference in sample sizes between the number of patients submitted from the two centers, no institutional comparative analysis could be drawn.

Conclusions

In this dual centered study we examined multiple, commonly used, pre-surgical testing parameters and found that surface-based ictal EEG was the best predictor of a SF outcome following ATL in patients with medically intractable LRE and normal pre-operative high-resolution brain MRI. With more than half of the patients demonstrating a SF outcome, anterior-medial temporal lobectomy remains a favorable therapeutic option for these patients. Furthermore, multi-centered studies comparing and contrasting results of ATL in patients with normal pre-operative brain MRI are warranted to determine reproducibility of these results from one surgical experience to another.

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