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Medically intractable temporal lobe epilepsy in patients with normal MRI: Surgical outcome in twenty-one consecutive patients[☆]

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ABSTRACT

Introduction: Abnormal MRI findings localizing to the mesial temporal lobe predict a favorable outcome in temporal lobe epilepsy surgery. The purpose of this study is to summarize the surgical outcome of patients who underwent a tailored antero-temporal lobectomy (ATL) with normal 1.5 T MRI. Specifically, factors that may be associated with favorable post-surgical seizure outcome are evaluated.
Methods: A retrospective analysis of the Rush University Medical Center surgical epilepsy database between 1992 and 2003 was performed. Patients who underwent an ATL and had a normal MRI study documented with normal volumetric measurements of hippocampal formations and the absence of any other MRI abnormality were selected for this study. Demographic information was collected on all patients. Seizure outcomes were evaluated using Engel's classification. A two-sided Fisher exact test with Bonferroni correction was performed in statistical analyses.
Results: Twenty-one (21) patients met the inclusion criteria of normal 1.5 T MRI and underwent a tailored temporal lobectomy. Mean age at time of surgery was 28 years (SD = 8.1, range 11–44) and mean duration of the seizure disorder was 13.4 years (range 2–36). Risk factors for epilepsy included head injury ($n = 4$), encephalitis ($n = 3$), febrile seizures ($n = 2$), and 12 patients had no risk factors. Pathological evaluation of resected tissue revealed no abnormal pathology in 12/21 patients (57%). After a mean 4.8 years follow-up post-surgical period, 15/21 (71%) patients were free of disabling seizures (Engel I outcome). At 8.3 years follow-up, 13/21 (62%) patients had similar results. Absence of prior epilepsy risk factors was the only statistically significant predictor of an Engel class I outcome ($p < 0.0022$).
Conclusion: Patients with medically intractable epilepsy and normal MRI appear to benefit from epilepsy surgery. Absence of prior epilepsy risk factors may be a positive prognostic factor.

1. Introduction

The advent of magnetic resonance imaging (MRI) has significantly advanced the field of epilepsy. In patients with medically intractable temporal lobe epilepsy (TLE), visualization of a lesion or evidence of mesial temporal sclerosis (MTS) has been reported to be a prognostic indicator of good surgical outcome.[1–6] When paired with concordant data from electrophysiologic and functional neuroimaging studies (PET, MRS), MRI findings that localize to the mesial temporal lobe are associated with post-surgical seizure-freedom in 70–90% of patients.[3,4,7–11] Conversely, localization is challenging when the MRI is normal, reflected in a historically less favorable surgical outcome.[12–22]

Surgical planning of medically refractory epilepsy begins with a thorough history and physical examination followed by video-electroencephalographic (EEG) monitoring studies in order to localize the epileptogenic zone, and high resolution MRI studies of the brain. When the latter are normal, functional neuroimaging studies can be used to confirm a temporal epileptogenic focus. Such is the case in 18–37% of all intractable epilepsy patients who have no abnormalities on MRI despite an identifiable focus on EEG studies.[14,17,19–21]

The purpose of this study is to investigate the post-surgical seizure outcome of patients with pharmaco-resistant TLE who had a normal 1.5 T brain MRI studies with documented normal volumetric measurements of the hippocampal formation. In addition, we attempted to identify variables associated with

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remission of non-disabling seizures (complex partial and secondarily generalized tonic-clonic seizures).

2. Materials and methods

A retrospective analysis of the Rush University Medical Center surgical epilepsy database between 1992 and 2003 was performed. The search identified 248 patients with TLE. The standard preoperative evaluation of surgical patients at our institution includes an extensive history and physical examination and has been reported in previous studies.[23] In brief, patients undergo video-EEG scalp electrodes and often sphenoidal electrodes placed under fluoroscopic guidance. High resolution MRI studies are carried out in all patients. Imaging sequences consist of sagittal and axial pre- and post contrast T1-weighted acquisitions, axial T2-weighted acquisition, coronal FLAIR and Proton Density images, coronal post-contrast T1 and T2-weighted images, and coronal spoiled GRASS acquisition images targeted to the hippocampal formations for volumetric analysis. The protocol used to measure the volume of hippocampal formation has been described in a previous publication.[24] In eight patients, subdural electrodes were placed in an initial procedure for more extensive monitoring particularly when the focus was left sided, to aid in language mapping, and in cases with non-corcordant data from other localized studies. In all patients, the epileptogenic zone was confirmed with intraoperative electrocorticography using a 40 electrode grid positioned over the temporal lateral convexity and strips covering basal temporal, orbito-frontal and basal-temporal occipital cortex.

The procedure performed was a tailored antero-temporal lobectomy (ATL). Cortical resection was performed to remove the epileptogenic zone with average extent of resection being 4.6 cm (range 1.5–7 cm) from the temporal tip. Care was taken to remain conservative in language dominant temporal lobes versus larger resections, if necessary, in non-dominant lobes and where lateral seizure foci were identified. In each case the entire amygdala was resected, although hippocampal resection varied between partial (to the choroidal point) and complete (to the tectal plate).

Inclusion criteria for the study were surgical cases demonstrating an epileptogenic zone in the temporal lobe in the absence of any abnormalities on MRI, including normal volumetric analysis and post-surgical seizure outcome data with a minimum of a two-year post-surgical period. Of the 248 patients, 21 (8%) met these criteria and were included in the series. Demographic information collected on all patients is included in Table 1, in addition to gender, side of operation, age at time of surgery, duration of seizure disorder, risk factors for epilepsy, use of functional neuroimaging (PET, SISCOM), use of video-EEG with intracranial recordings, presence of abnormal pathology in resected tissue, extent of resection, seizure focus location, and mean follow-up. Neuropsychological results were uniformly obtained preoperatively in all patients, but not uniformly postoperatively and therefore have been excluded.

Functional neuroimaging studies were carried out in 13 patients; 11 had a positron emission tomography study (PET) with 15 mCi of fluorine-18 deoxyglucose (PET) and two had a subtraction ictal SPECT co-registered to MRI (SISCOM) study using 25.1 mCi of technetium-99 m hexamehylpropylamine oxime [Tc99m-HMPAO (Ceretec)].

Pathology specimens were obtained from all included patients and evaluated for microscopic evidence of pathology by an attending neuropathologist. Patients were followed for the duration of the study for assessment of seizures outcome at the Rush University Medical Center epilepsy clinic. Seizure outcomes were classified according to Engel's four categories; class I being no seizures, class II being rare seizures, class III being limited improvement, and class IV being no improvement or worsened seizures.

Statistical analyses were carried out with a two-sided Fisher exact test to evaluate the association between Engel class I seizure outcome and each of the recorded variables. A Bonferroni correction was performed given the high number of variables included.

3. Results

Among the 21 patients, 11 (52%) underwent a right ATL and 10 (48%) a left-sided resection. Identified risk factors for epilepsy included a prior history of head injury ($n = 4$), encephalitis ($n = 3$), febrile seizures ($n = 2$), while no risk factor was identified in 12 patients. Among the 11 patients who underwent a PET study only, 8 were localizing to one temporal lobe, while none of the SISCOM studies performed in 2 patients yielded localizing data. Two post-operative patients who did not improve after resection underwent post-operative PET/SISCOM studies and both patients localized to the frontal lobe.

All patients underwent intraoperative electrocorticography. Subdural electrodes were placed in 8/21 patients in a separate procedure prior to resection. Three of these 8 patients had localizing PET studies while the remaining 5 patients had nonlocalizing or no metabolic imaging performed. Six of the 21 patients had a lateral seizure focus, while 15/21 had a mesial focus.

Pathological evaluation of resected tissue revealed no abnormal pathology in 12/21 (57%) patients. Six patients (28.5%) had hippocampal sclerosis, 2 (9.5%) had heterotopia, and 1 (5%) had evidence of dysembryoblastic neuroepithelial tumor that was found anterior to the hippocampus and did not appear on any pre-operative MRI sequence.

Table 1
Patient demographics.

Demographics	
Male	8
Female	13
Right lobectomy	11
Left lobectomy	10
Mean age at surgery (years)	28 (range 11–4)
Mean seizure duration (years)	19.1 (range 2–36)
Mean seizure freq/month	15 (range 6–20)
Head injury	4
Encephalitis	3
Febrile seizure	2
PET or SISCOM imaging	13
PET only	11 (8 localizing)
SISCOM only	2 (0 localizing)
Subdural electrodes	8
Normal pathology	12
Hippocampal sclerosis	6
Heterotopia	2
Dysembryoblastic neuroepithelial tumor	1
Extent of resection	4.6 cm (range 1.5–7 cm)
Mean follow-up	8.5 yrs (range 4–14 yrs)

Table 2
Engel class outcomes.

Engel class	Number of patients at mean follow-up (%)	
	4.8 years	8.3 years
I	15 (71%)	13 (62%)
IA	9 (43%)	9 (43%)
II	2 (10%)	4 (19%)
III	3 (14%)	4 (19%)
IV	1 (5%)	0 (0%)

Table 3
Variables predicting outcome.

Variable predicting Engel class I outcome	*p*-Value
Absence of risk factor	0.0022
Side of surgery	0.02
Extent of resection	0.08
Mean follow-up	0.18
Metabolic imaging	0.39
Seizure frequency	0.39
Mesial versus lateral seizure focus	0.63
Hippocampal resection	0.67
Age at surgery	1.0
Abnormal pathology	1.0
Subdural electrodes	1.0
Duration of epilepsy	1.0
Sex	1.0

Long-term seizure outcomes are represented in Table 2. At mean 4.8 years follow-up, 15/21 (71%) of patients had excellent seizure control (Engel class I), which was 13/21 (62%) at 8.3 years follow-up.

There was no mortality in the studied patient population. Two patients (9.5%) had transient post-operative anomia, which resolved over time.

Statistical analysis of factors affecting Engel class I outcome are shown in Table 3. Absence of prior epilepsy risk factors was the only statistically significant predictor of Engel class I outcome ($p < 0.0022$). Due to the high number of variables present, a Bonferroni correction was performed which lowered the alpha level of each variable to 0.0045. Eleven out of 12 patients (92%) without any identifiable risk factor had an Engel class I outcome, whereas 2/9 patients (22%) of patients with a risk factor had Engel class I outcomes. Table 4 describes localizing tools (imaging or recordings) in relation to outcome.

4. Discussion

Surgery on temporal lobe epilepsy with imaging evidence of pathology yields excellent results in carefully selected patients. The problem arises when the MRI study fails to reveal an anatomic lesion that corresponds to the electrophysiological data. Early studies reported post-operative seizure-free rates in patients with normal MRI studies as low as 29%.[12–22] However, with improvements in functional neuroimaging studies, seizure localization has improved with a resultant more favorable outcome in surgery. Siegel et al.[19] reported on 24 patients with focal epilepsy and normal MRI studies. Ictal as well as interictal SPECT studies were utilized in addition to the traditional scalp and/or invasive EEG monitoring. Eighty-three percent of patients had satisfactory outcome with 15 (62%) of them being seizure-free at two years or greater follow-up (Engel class I). In similar fashion, Bell et al.[13] analyzed their forty-four patients with normal 1.5 or 3 T MRI's undergoing anterior temporal lobectomy. Of note, eleven of these patients were found on re-review of the MRI's to have subtle hippocampal or amygdaloid abnormalities, and this cohort trended towards improved outcomes. Overall, sixty percent had Engel class I outcome at greater than 1 year, with 47.5% achieving class Ia status. No preoperative risk factors predicted statistically significant improved outcome in their series, although negative scalp EEG and localizing SISCOM both exhibited improved trends.

In the presented series of 21 patients, 15 (71%) were seizure-free at average 4.8 years follow-up. This number decreased to 13 (62%) patients by 8.3 years of follow-up.

According to our analysis, two of the patients with an Engel class I at 4.8 years worsened to a class II at 8.3 years (in reference to Table 4, patient #2 worsened at the 99th postoperative month and patient #6 at the 100th postoperative month), while the one Engel class IV patient at 4.8 years improved to Engel class III at 8.3 years (in reference to Table 4, patient #17 improved at the 100th postoperative month).

Absence of prior seizure risk factors appears to predict a favorable outcome based on the statistical analysis ($p < 0.0022$). The results are very plausible, as some of the risk factors identified (head injury and encephalitis) tend to injure the brain diffusely. Therefore, a unilateral resection may not improve seizure outcome in this patient population. This is an important finding and addition to the literature as it helps with the decision to consider surgery or intracranial monitoring.

We initially thought that age at the time of surgery would be a predictor of good seizure outcome, but this did not reach clinical significance in our cohort ($p = 1$). Younger age has been associated with improved seizure control in prior literature, hypothetically resulting from the younger neural tissue, per se, and not the duration of chronic seizure activity.[6,16,22]

Of interest, complete hippocampal resection to the tectal plate as compared to only partial resection (resection to the choroidal

Table 4
Localizing studies and identified seizure focus location related to seizure outcome.

Patient	PET	SPECT	Subdural electrode	Mesial versus lateral focus	Engel outcome at 8.3 years
1	None	None	None	Mesial	I
2	None	None	None	Mesial	II
3	None	None	Yes	Lateral	I
4	None	None	None	Mesial	I
5	None	None	None	Mesial	I
6	None	Non localizing	None	Mesial	II
7	Localizing	None	None	Mesial	I
8	Localizing	None	None	Lateral	I
9	Localizing	None	None	Mesial	I
10	Non localizing	None	None	Mesial	I
11	Non localizing	None	Yes	Mesial	III
12	Localizing	None	Yes	Mesial	I
13	None	None	None	Mesial	I
14	Localizing	None	None	Lateral	I
15	Localizing	None	Yes	Mesial	I
16	Localizing	None	Yes	Lateral	II
17	Localizing	None	None	Mesial	III
18	None	None	Yes	Mesial	I
19	Non localizing	None	Yes	Lateral	III
20	None	Non localizing	None	Lateral	III
21	None	None	Yes	Mesial	I

point) did not predict improved outcome ($p = 0.67$). However, partial resections tended to be performed early in the study while complete resections tended to be performed later.

It would be interesting to correlate extent and side of resection to neuropsychological outcomes, as this was not evaluated and is a limitation in our series. We are aware of previous reports suggesting neuropsychological changes following similar procedures. This is an area we are currently exploring.

We attribute our favorable seizure outcomes to several factors. Careful selection of patients with convergent confirmatory data, however, is most critical. A thorough clinical history evaluating for the presence of symptoms attributable to a temporal lobe focus is paramount to localizing seizures. In fact, specific distinctions between mesial versus lateral temporal lobe source of seizures can sometimes be predicted based on a detailed seizure history.[2,25,26] Furthermore, the presence of a discreet zone of low voltage fast activity and a prolonged conduction time has independently shown to be associated with an improved surgical outcome.[7,11,12,20,26]

Ictal SPECT and 18-fluordesoxyglucose (^{18}FDG) PET studies have been shown to accurately localize temporal lobe foci in 73% of cases.[10,27–30] This number is comparable to the predictive accuracy of subdural electrodes. The use of SISCOM is also routinely used at our institution. O'Brien et al.[31] demonstrated that SISCOM images were localizing in 45/51 (88.2%) of temporal lobe patients compared to 20/51 (39.2%) of patients whose ictal and interictal SPECT images were inspected by the traditional side-by-side method ($p < 0.001$). Bell et al.[13] demonstrated an improved trend in outcome when SISCOM was localizing in their series. Proton magnetic resonance spectroscopy (^{1}H-MRS) has also been used in normal temporal lobe epilepsy. Decreased ratios of ictal focus N-acetyl aspartate to choline have been shown in the majority of these patients.[32,33]

Invasive monitoring by placement of subdural or epidural electrodes is employed in many of our more recent normal MRI temporal lobe operations. Data from these recordings provide information to further elucidate a mesial versus lateral source of seizures. In addition, mapping of the lateral cortical areas allows for a "tailored" temporal neocorticectomy in addition to resection of the mesial structures.

Finally, it is important to note that normal 1.5 T MRI with thin cut protocol does not necessarily predict normal pathology. Nine of 21 of our patients (43%) had abnormal pathology, including hippocampal sclerosis, heterotopia, and even dysembryoblastic neuroepithelial tumors. This can directly be attributable to the 1.5 T power of the MRI. Numerous reports exist showing improved lesion recognition through the use of 3 T MRI.[34–37] The higher signal-to-noise ratio of high-field MR systems provides this increased anatomic resolution. Although it is unclear if re-review showing subtle abnormalities in eleven of their 44 patients could be attributable to 1.5 T versus 3 T MRI in the Bell et al.[13] series, they insightfully acknowledge that subtle findings may in fact be present but missed. On re-review of the MRI's in our series, subtle findings continue to be absent. However, 3 T MRI was not been applied to this cohort. Knake et al.[35] used 3 T MRI to identify focal lesion in 15 of 23 patients (65%) whose 1.5 T MRI were normal. Because of this, we now commonly use 3 T MRI in cases of normal 1.5 T MRI.

While we believe our results illustrate important findings regarding surgery in patients with normal 1.5 T MRI, a few limitations should be highlighted. This was a retrospective study describing seizure outcomes in a small cohort, primarily due to the limited number of patients fitting our criteria. Additionally, correlative neuropsychological data is not included due to our continued investigation using this outcome measure.

5. Conclusion

Patients with medically intractable epilepsy and normal 1.5 T MRI who have good ictal and interictal localization to a single temporal lobe and convergent confirmatory testing are likely to benefit from temporal lobe epilepsy surgery. Absence of epilepsy risk factors, such as head trauma, encephalitis, or febrile seizures was a statistically significant predictor of good outcome in our series.

Conflict of interest statement

No potential conflict of interest––financial, personal, or professional––exists or could be construed as existing for this manuscript.

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