Failed epilepsy surgery for mesial temporal lobe sclerosis: a review of the pathophysiology

Fernando L. Vale, M.D.,1 Glen Pollock, D.V.M., M.D.,1 and Selim R. Benbadis, M.D.2

Departments of 1Neurosurgery and 2Neurology, University of South Florida, Tampa, Florida

Object. The object of the current study was to review the electrophysiology and pathological substrate of failed temporal lobe surgery in patients with mesial temporal sclerosis.

Methods. A systematic review of the literature was performed for the years 1999–2010 to assess the cause of failure and to identify potential reoperation candidates.

Results. Repeat electroencephalographic evaluation documenting ipsilateral temporal lobe onset was the most frequent cause for recurrent epileptogenesis, followed by contralateral temporal lobe seizures. Less frequently, surgical failures demonstrated an electroencephalogram that was compatible with extratemporal localization. The generation of occult or new epileptogenic zones as well as residual epileptogenic tissue could explain these findings.

Conclusions. The outcome of temporal lobe surgery for epilepsy is challenged by a somewhat consistent failure rate. Reoperation results in improved seizure control in properly selected patients. A detailed knowledge of the pathophysiology is beneficial for the reevaluation of these patients.


Key Words • temporal lobe epilepsy • temporal lobectomy • surgical failure • mesial temporal sclerosis

Temporary lobe surgery is an effective treatment for medically resistant mesial TLE. Mesial TLE is characterized by complex partial seizures with typical semiology manifested as epigastric and/or olfactory auras, complex automatisms, loss of awareness, and rarely, generalized convulsive episodes.48 Epilepsy that is refractory to medical treatment is common, especially if hippocampal sclerosis is present.26

The efficacy of temporal lobe surgery to treat refractory epilepsy has been demonstrated in a prospective randomized trial.33 The “ideal” surgical candidate has mesial TLE with unilateral ictal EEG findings and ipsilateral MRI findings suggestive of MTS. Abnormal signal on FLAIR and T2-weighted imaging, decreased volume, and loss of anatomical configuration of the hippocampal formation are considered the hallmarks of radiographic MTS. The presence of radiographic MTS is considered a predictive factor for favorable seizure outcome after surgical intervention.2,10,22,29 Temporal lobe resection has reported success rates ranging from 70% to 90%,8,24,44,45 Certainly, the existence of preoperative bilateral MTS or extrahippocampal pathology is associated with a greater likelihood of seizure recurrence, and as a result, this group of patients will not achieve the same degree of seizure control as patients with unilateral disease.

McIntosh et al.32 performed a systematic review of results for temporal lobe surgery for epilepsy. The authors reported that the proportion of patients with documented seizure-free outcome varied widely between 33% and 93% (median 70%). They identified multiple issues when gathering the data, such as differences in definition of outcome, different types of pathology included, and length of follow-up that accounted for the discrepancy in outcome.

Although surgery is considered to be a safe and effective treatment in patients with TLE, the results of this procedure for patients with unilateral MTS are challenged by a somewhat consistent failure rate. The reasons for failure are not well known and there are no data available on the clinical predictors of failed surgery.3,31 Previous studies have demonstrated that late recurrence after initial seizure freedom is not a rare event, but risk factors specific to the event remain elusive. Therefore, the purpose of this study is to discuss the electrophysiology and pathological substrate behind failed temporal lobe resection in patients with unilateral radiographic MTS. This patient population is considered the “ideal” candidate for

Abbreviations used in this paper: EEG = electroencephalography; MTS = mesial temporal sclerosis; TLE = temporal lobe epilepsy.
temporal lobe resection and represents a more homogenous group of patients who are most likely to benefit from surgery and thus represent the best group within which to analyze surgical failures.

Methods

A comprehensive literature review using PubMed was performed. The following search terms were used in multiple combinations: “epilepsy surgery,” “temporal lobe,” “temporal lobe seizures,” “failure,” and “outcome.” We also searched the bibliographies of review articles, original articles, and book chapters in an attempt to add relevant articles. Literature searches were restricted to English-language full-length articles published between January 1999 and December 2010.

To be considered for this review, patients must have presented with: 1) mesial TLE as characterized by complex partial seizures with the typical clinical semiology of mesial origin (epigastric or psychic aura); 2) video-EEG findings compatible with unilateral ictal temporal lobe onset; 3) high-resolution brain MRI (1.5 T or higher) suggestive of unilateral MTS; 4) a surgical procedure involving either an anterior temporal lobectomy or selective amygdalohippocampectomy; 5) surgical outcome based on Engel classification; 6) at least 1 year of follow-up; and 7) be ≥ 15 years of age at the time of surgery. Because of variation in study design, surgical technique, and outcome reporting, it is difficult to establish the exact proportion of patients who fail to achieve seizure control with surgery. Outcome was defined according to a modified Engel classification: 1) Class I, seizure free with or without residual auras; Class II, rare disabling seizures (> 90% seizure reduction); Class III, < 90% seizure reduction; and Class IV, no worthwhile improvement. Surgical failures were defined as Engel Class III–IV, which included patients with frequent seizures and unsatisfactory outcome. We independently assessed study eligibility and extracted data, resolving disagreements through discussion. The literature search resulted in 651 references, 79 of which were potentially eligible and were selected for full text review. Sixty-five articles were excluded for the following reasons: < 12 months follow-up (3/65, 4.6%), mixed pathology (29/65, 44.6%), absence of hippocampal atrophy on MRI (20/65, 30.8%), pediatric patients < 15 years of age included in series (2/65, 3.1%), outcome not determined by Engel classification (2/65, 3.1%), review article (1/65, 1.5%), no analysis of failures (5/65, 4.6%), and study with < 20 patients (3/65, 4.6%). Eight articles were useful for discussion in regards to outcomes and 5 articles were included for analysis of surgical failures.

Results

Five publications5,17,38,41,43 had enough documentation to assess the causes of failures for this unique population of surgical patients. Only 2 studies27,38 provided enough information to document incidence of surgical failure in addition to the origin of the problem. Eight studies27,38,41,43,49,96,13,23 were helpful in documenting the failure rate of temporal lobe surgery in this population (Table 1). Major surgical failures tended to occur early in the follow-up period, usually less than 1 year. Furthermore, the frequency of seizures was significantly lower in patients with late recurrence than in those with an early recurrence of seizures.5,38 Despite differences in follow-up periods in those studies, the long-term seizure-free rate following resective temporal lobe surgery appears to be similar to that reported in short-term controlled studies.49

There were a total of 686 patients identified who met the outcome inclusion criteria. All patients underwent similar mesial temporal lobe resection, but underwent a variable amount of cortical resection based on the descriptions of the surgical technique. However, the surgical approach has not been found to be predictive of outcome.9,16,46 The incidence of failure was 8.9% (61/686; Table 1). Hardy et al.16 and Hennessy et al.17 did not use the Engel classification but documented a failure rate (similar to Engel Class III/IV) of 7.6% and 12%, respectively. Surgical failures (Engel Class III/IV) tended to occur within 1 year. In addition, complete discontinuation of antiepileptic drugs after 2 years has not been associated with an increased rate of recurrence.10 Fifty-five patients were identified with known electroencephalographic cause for persistent seizures (Table 2). The most common documented reason for failure was persistent unilateral temporal lobe epileptic foci (65%) followed by contralateral seizure onset (29%), and the least frequent cause for recurrent seizures was extratemporal localization (5%).

Discussion

Patients with mesial TLE in the setting of radiographic findings suggestive of unilateral MTS are the ideal candidates for surgical intervention. Medical treatment failures are common, whereas surgery results in seizure control rates of up to 70%–90%.26,54 Nevertheless, some patients do not have a significant improvement of their condition with surgery, even with complete resection of the suspected epileptogenic zone. Clinical factors such as seizure frequency, duration of epilepsy, sex, age of onset, and laterality of seizure focus have not been shown to

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Class I (%)</th>
<th>Class II (%)</th>
<th>Class III/IV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowe et al., 2004</td>
<td>48</td>
<td>40</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Dupont et al., 2006</td>
<td>110</td>
<td>78</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Bonilha et al., 2007</td>
<td>43</td>
<td>33</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Georgakoulas et al., 2008</td>
<td>50</td>
<td>37</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Karasu et al., 2008</td>
<td>56</td>
<td>43</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Ozkara et al., 2008</td>
<td>165</td>
<td>129</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Tezer et al., 2008</td>
<td>109</td>
<td>90</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Ramos et al., 2009</td>
<td>105</td>
<td>91</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>total (%)</td>
<td>686</td>
<td>541 (78.9)</td>
<td>84 (12.2)</td>
<td>61 (8.9)</td>
</tr>
</tbody>
</table>

* Engel Class III/IV considered a treatment failure.
Failed epilepsy surgery for mesial temporal lobe sclerosis

TABLE 2: Postoperative EEG findings in failed temporal lobe surgery*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Patients w/ MTS</th>
<th>Surgical Failures (%)</th>
<th>Ipsilat Temporal Seizure Type (%)</th>
<th>Contralat Temporal Seizure Type (%)</th>
<th>Extratemporal Seizure Type (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hennessy et al., 2000</td>
<td>165</td>
<td>20 (12)</td>
<td>12 (60)</td>
<td>6 (30)†</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Schwartz &amp; Spencer, 2001</td>
<td>NR</td>
<td>5</td>
<td>4 (80)</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td>González-Martínez et al., 2007</td>
<td>NR</td>
<td>10</td>
<td>5 (50)</td>
<td>4 (40)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Salanova et al., 2005</td>
<td>NR</td>
<td>12</td>
<td>10 (83)</td>
<td>2 (17)†</td>
<td>0</td>
</tr>
<tr>
<td>Ramos et al., 2009</td>
<td>105</td>
<td>8 (8)</td>
<td>5 (62.5)</td>
<td>3 (37.5)</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>55</td>
<td>36 (65)</td>
<td>16 (29)</td>
<td>3 (5)</td>
<td></td>
</tr>
</tbody>
</table>

* Contralat = Contralateral; Ipsilat = Ipsilateral; NR = not reported.
† One patient with bitemporal onset.

be risk factors for postoperative seizure recurrence.7,25,38 Other authors have identified frequent secondarily generalized seizures,16,20 history of encephalitis,41 and head trauma,50 as poor predictive factors for good outcome. These findings suggest the presence of a more extensive seizure focus or multifocal epilepsy than what is observed in the typical patient with mesial TLE. In reality, the vast majority of studies have failed to identify factors that are predictive of outcome.1,14,16,25,33,38,51

Unfortunately, predictive clinical risk factors have remained elusive. Nevertheless, these patients should not be considered absolute failures of surgical management, instead they should be restudied to determine why surgery failed and to decide if further surgical intervention is indicated. A detailed knowledge of the pathophysiology is required to define potential treatment options.

Reasons for Failure of Temporal Lobe Resection

In general, there are 3 main reasons why epilepsy surgery, regardless of pathology, can fail: incomplete resection of the epileptogenic focus, inaccurate localization and/or mapping of the epileptogenic focus, and the generation of a new epileptogenic focus and/or the emergence of an occult epileptogenic area. To better understand the reasons for failure, attention should be placed on the pathological substrate of this group, which includes residual epileptogenic structures, generation or reactivation of a new epileptogenic focus in the form of contralateral MTS, dual pathology, or possibly, surgical scar. These pathological entities can result in the recurrence of seizures in the temporal or extratemporal cortex. The clinical semiology and electrophysiology of recurrent seizures can then present as ipsilateral temporal, contralateral temporal, or extratemporal seizures.

Ipsilateral Temporal Lobe Seizures. Ipsilateral temporal lobe seizures remain the most common cause of failed surgery (Table 2). Ipsilateral recurrent seizures tend to have both the electrodagnostic (ictal and interictal epileptiform discharges) and clinical features of temporal lobe epilepsy. Three pathological conditions could potentially explain surgical failures in this situation: residual mesial structures, dual pathology, and surgical scar.

Residual Mesial Structures. Wyler et al.55 in a prospective, randomized clinical trial established the superior outcome of temporal lobe surgery associated with aggressive hippocampectomy. Removal of the mesial structures (hippocampus/parahippocampus gyrus) to the level of the superior colliculi allows for better seizure control in patients with TLE. In addition, no increased neuropsychological morbidity was found with more extensive resection of the mesial structures. Since 1995, standardization of the mesial temporal resection has been well established. Hennessy et al.17 reported 5 of 20 patients and Ramos et al.38 documented 1 of 8 patients with residual mesial structures and recurrent seizures. They acknowledged that incomplete resection of mesial structures is a potential cause of failure and reoperation might be beneficial in selected patients.

Occult or New Epileptogenic Area. Patients who have adequate resection of the mesial structures and continue to have ipsilateral temporal seizures remain a clinical challenge. Frequently, imaging studies do not reveal any anatomical abnormalities, making it difficult to identify the new epileptogenic zone and therefore plan further treatment. If we come to believe that MTS is the consequence of a more diffuse insult to the brain, it is possible that once the hippocampus is removed other areas of the brain, with a higher seizure threshold and not detected by our current neurophysiology and neuroimaging studies, it can become epileptogenic. Assuming their preoperative imaging was otherwise normal, these patients likely harbor radiographic occult dual pathology. The role of invasive EEG recordings with strips, grids, or depth electrodes in this group is not clear but may be beneficial during the reevaluation phase if further surgery is contemplated.

Dual pathology can take the form of cortical dysplasias, neuronal heterotopias, or migrational disorders and has been the main cause of surgical failures in recent series.27,28,43 The presence of dual pathology in patients with MTS has been well described in the literature. Some authors have found a 15%–30% incidence of this type of dual pathology in their series of patients with TLE.27,41 In this situation both the dysplastic temporal neocortex and the sclerotic hippocampus can be epileptogenic. It appears that the contribution of the hippocampus to seizure generation corresponds to the degree of hippocampal pathology, whereas even mild forms of cortical dysplasia can be epileptogenic.15 This finding has major prognostic implications for patients who undergo selective (limited)
temporal lobe surgery as MRI may not detect mild neuronal and cortical abnormalities that have epileptogenic potential. Li et al. reported a series of patients in whom removal of both the sclerotic mesial structures and extra-hippocampal lesions resulted in a 73% seizure-free rate. These are encouraging results but only apply to those patients in which the dual pathology was identified and precisely localized preoperatively.

Surgical Scar. Although the gliotic scar is widely accepted as a cause of epilepsy, there is no direct evidence that scar formation contributes to epileptogenesis. It has been proposed that the meningocerebral scar that forms following trauma to the brain plays an important role in the development of posttraumatic epilepsy. In an animal study epileptogenesis was blocked by procedures that inhibit scar formation. Hennessy et al. stated that epileptogenesis related to a surgical scar was an unlikely explanation for recurrent seizures arising adjacent to the resection. Pathological findings compatible with gliosis at the resection edge may suggest epileptogenic potential. However, surgical scar as a cause of recurrent epilepsy remains a controversial subject.

Contralateral Temporal Lobe Seizures. Limited knowledge of the pathophysiology of MTS has prevented the identification of factors that precipitate neuronal loss and gliosis of the hippocampus. The pathogenesis of mesial TLE is associated with an event that probably injures the hippocampus at some time prior to habitual seizure onset. This event likely affects both hippocampi in an asymmetrical way. Febrile seizures have been recognized as a common offender, but controversy still exists regarding the etiological relationship between MTS and epilepsy. Some investigators view hippocampal sclerosis as the primary cause of TLE, whereas others interpret the changes to be the result of chronic seizure activity. Regardless of the origin, it appears that mesial TLE is a bilateral disease with a broad range of lateralization. Autopsy series corroborate that a high proportion of patients with epilepsy suffer from bitemporal hippocampal sclerosis. Preoperative volumetric MRI studies suggest that most patients with mesial TLE have some degree of bilateral, asymmetrical hippocampal pathology. As a result, a high proportion of surgical failures demonstrate contralateral temporal epileptiform activity and in some cases, significant MRI findings to suggest MTS.

Patients with contralateral temporal epileptiform activity are well documented in their respective series of surgical failures by Gonzalez-Martinez et al., Hennessy et al., Ramos et al., Salanova et al., and Schwartz and Spencer (Table 2). The events leading to activation of this new epileptogenic area are not understood. Unfortunately, this group of patients is not eligible for further resective surgery as bilateral mesial temporal resections may result in devastating cognitive and behavioral deficits. Further therapeutic options are limited to medical therapy and possible placement of a vagus nerve stimulator.

Extratemporal Seizures. Extratemporal seizure origin is not a common cause of failure for patients with MTS (Table 2). The number of documented cases in the literature is scarce. Gonzalez-Martinez et al. reported 1 of 10 patients, and Hennessy et al. documented 2 of 20 patients with extratemporal epileptiform activity in their respective series of surgical failure. For patients with TLE these areas most likely represent dual pathology not diagnosed by the initial neurophysiological and radiographic studies. An extratemporal lesion may cause local epileptiform activity, which then spreads to the hippocampal circuitry, and produces stereotypical complex partial seizures. As a consequence, the hippocampus would then undergo neuronal loss and/or reorganization. In these patients, removal of both the lesion and the atrophic hippocampus should be considered as it provides the best chance for seizure control. To further support this probable scenario, recent evidence suggests that some TLE surgical failures could be related to unrecognized insular epilepsy.

Treatment Options

Based on current experience and available literature, reoperation might be of benefit in selected patients. Further surgical intervention can be considered for those patients with ipsilateral temporal seizures, with or without residual mesial structures, and those with extratemporal seizures if a lesion or epileptogenic cortex can be identified. Results of reoperation are difficult to predict as there are few series published in this particular group of patients. In the study by Gonzalez-Martinez et al., reoperation consisted of extending the previous resection margin in patients with MTS, which led to good outcomes in only 3 (30%) of 10 patients. However, on further analysis, 4 of these 10 patients were found to have contralateral temporal epileptic activity, explaining their poor outcomes. This finding demonstrates the importance of repeated EEG prior to planning for further resections on surgical failures. Ramos et al. documented 2 of 4 patients who initially had complete resection of the mesial structures and improved to Engel Class I/II with an extended neocortical resection along the basal and lateral cortex of the previous resection cavity. For patients with persistent ipsilateral seizure onset, extension of the cortical resection along the surgical scar appears to be beneficial approximately 50%–60% of the time. A Phase II evaluation (invasive EEG monitoring with subdural grids/strips/depth electrodes) can be considered prior to further surgical intervention if there are clinical concerns regarding ictal onset localization. Neuropathology correlation with surgically treated TLE patients demonstrates that a subgroup of patients can benefit from more extensive neocortical resection. A significant association between MTS and malformations of cortical development has been found in some patients. Furthermore, Bonilha et al. recently observed that a better surgical outcome was obtained with the removal of the entorhinal cortex in addition to the hippocampus. No pathological correlation was described with their findings, but their conclusion certainly warrants further investigation.

For those patients with contralateral temporal seizures or nonlocalizable seizure onset, a vagus nerve stimulator may be implanted as a last surgical option.
Failed epilepsy surgery for mesial temporal lobe sclerosis

are no large series reporting the use of a vagus nerve stimulator for failed surgery in MTS cases. Outcome has not improved in the few reported cases.15,38 Further understanding of the pathophysiology and mechanisms of epileptogenesis of MTS is necessary before more conclusions are drawn. Whatever the explanation is, it appears that the mechanisms of relapse are heterogeneous. These findings suggest that larger epileptogenic zones exist in these refractory patients. Accurate identification of the epileptogenic area is critical for success. Postsurgery seizure-free outcome should be the goal. Improvement in quality of life may not be observed even in cases in which seizure frequency was greatly reduced. The evolving field of magnetoencephalography and advanced neuroimaging (3-T MRI) may play an essential role in the future for diagnosis of intractable epilepsy, and hopefully allow for a higher rate of seizure-free outcome.33,52

Conclusions

Reasons for failure of temporal lobe surgery are multifactorial and clinical predictors are lacking. Ipsilateral recurrent seizures appear to be the most common finding in failed temporal lobe surgery. The generation of new or occult epileptogenic zones in the form of dual pathology or scar tissue is a possible explanation. Incomplete resection of the epileptogenic zones in the form of residual hippocampus is no longer a common cause for surgical failures. Contralateral epileptogenesis also remains a frequent finding. Repeat evaluation is recommended as reoperation results in improved seizure control in properly selected patients. Detailed knowledge of the pathophysiology is beneficial for the treatment of these patients.5

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Vale, Benbadis. Acquisition of data: Vale, Pollock. Analysis and interpretation of data: Vale, Pollock. Drafting the article: Vale, Pollock. Critically revising the article: Benbadis. Reviewed submitted version of manuscript: Vale. Approved the final version of the manuscript on behalf of all authors: Vale. Study supervision: Vale.

References

24. Kelemen A, Rásonyi G, Szucs A, Fabó D, Halász P: [Predic-
F. L. Vale, G. Pollock, and S. R. Benbadis

42. Sano K, Malamud N: Clinical significance of sclerosis of the cornu ammonis: ictal psychic phenomena. AMA Arch Neurol Psychiatry 70:40–53, 1953

Manuscript submitted November 11, 2011. Accepted December 20, 2011. Please include this information when citing this paper: DOI: 10.3171/2011.12.FOCUS11318. Address correspondence to: Fernando L. Vale, M.D., Department of Neurosurgery, 2 Tampa General Circle, USF Health, 7th floor, Tampa, Florida 33606, email: fvale@health.usf.edu.