Epilepsy surgery in tuberous sclerosis: a review

LINTON T. EVANS, M.D.,1 RICHARD MORSE, M.D.,2,3 AND DAVID W. ROBERTS, M.D.1,2

1Section of Neurosurgery, 2Department of Neurology, and 3Department of Pediatrics, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire

Seizures are the initial manifestation of tuberous sclerosis complex (TSC) in 90% of individuals. The prevalence of epilepsy in TSC is 80%–90% with a large proportion refractory to antiepileptic drugs. A review of the literature of epilepsy surgery in TSC demonstrates impressive success rates for seizure-free outcomes. These studies describe a number of novel noninvasive methods for seizure localization including PET, SPECT, and magnetoencephalography. Additionally, there is a subset of patients with TSC with bilateral, multifocal, or generalized epileptiform discharges that would have previously been excluded from resection. New developments in neuroimaging and invasive monitoring with intracranial electrodes are useful methods in identifying an epileptogenic tuber in these individuals with refractory epilepsy. The authors offer a survey of the literature and description of these methods. Additionally they present an illustrative case of ictal SPECT and intracranial electroencephalography used in the preoperative evaluation of a 10-year-old girl with intractable seizures and TSC. This patient ultimately underwent resection of an epileptogenic region within the occipital lobe. (http://thejns.org/doi/abs/10.3171/2012.1.FOCUS11330)

KEY WORDS • tuberous sclerosis • seizure • epilepsy • localization • outcome

Tuberous sclerosis complex is an autosomal dominant disorder with variable effects on the CNS, as well as other tissues and organs. The pathognomic cerebral lesions are cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. Development of these lesions occurs when spontaneous or inherited mutations in the TSC1 or TSC2 loci, encoding the protein products hamartin and tuberin, lead to aberrant neuronal differentiation, proliferation, and organization.12 Seizures are the initial manifestation of the disorder in 90% of individuals and the prevalence of epilepsy in TSC is reported to be 80%–90%.26 Seizure onset is typically within the first 12 months of life. As many as one-third of these individuals will present with infantile spasms, although a number of different seizure types are frequently observed. In a study of 361 patients with TSC, epileptiform abnormalities were appreciated in 78%. Within this set of individuals, focal spike and wave discharges were observed in 35%, multifocal discharges in 25%, generalized spike and wave in 8%, and hysparrhythmia in 22%.34 The pathogenesis and molecular underpinnings of epilepsy in tuberous sclerosis are not well defined. Abnormal expression of glutamate and γ-aminobutyric acid receptors in dysplastic neurons and giant cells of cortical tubers has been described,35 as well as impaired glutamate transport in astrocytes in a mouse model of TSC.36 Interestingly, not all tubers are associated with electroencephalographic abnormalities. Imaging studies frequently reveal tubers for which there is no epileptiform correlate. Conversely, other studies have demonstrated localized epileptiform activity without a corresponding structural lesion. Using intracranial electrocorticography in 3 patients, Major et al.23 found that the epileptiform discharges emanated from the surrounding cortex rather than the tuber itself. The number, size, location, and morphology of cortical tubers have been found to influence seizure severity and degree of cognitive impairment.11,13,20,30

Unfortunately, seizures associated with tuberous sclerosis are often resistant to treatment with antiepileptic medications. The rate of epilepsy refractory to medical therapy in TSC is 50%–80%,2,10 typically developing by the age of 2. Other studies have demonstrated a positive correlation between the frequency and duration of seizures and the degree of mental retardation.39 Effective treatments to eliminate or reduce the number of seizures are essential to improving functional outcomes. Since the

Abbreviations used in this paper: AMT = α-11-C-methyl-L-tryptophan; EEG = electroencephalography; MEG = magnetoencephalography; TSC = tuberous sclerosis complex.
first published patient series of epilepsy surgery in TSC at the Montreal Neurological Institute in 1966. Surgery has proven to be an important treatment option for intractable seizures. From a systematic review of the literature, the rates of seizure-free outcome or reduction > 90% in individuals with refractory epilepsy were 57% and 18%, respectively. The range of seizure-free outcomes reported in the reviewed literature is 22%–67%. Findings associated with improvement following surgery include a single cortical tuber, focal EEG abnormalities, and focal seizures. Tonic seizures, moderate to severe mental retardation, and older age at the time of resection have been associated with seizure recurrence following epilepsy surgery. There does not appear to be a difference in outcome following resection of temporal compared with extratemporal tubers. Aside from the success of epilepsy surgery in seizure control, there are long-term benefits predicted for developmental and cognitive outcomes. Since the first descriptions of epilepsy surgery in TSC, the methods to localize epileptogenic tubers and resection have become increasingly sophisticated. In this paper we survey the literature describing resection in TSC (Table 1), focusing on recent developments in preoperative evaluation and seizure localization. An illustrative case is also presented.

**TABLE 1: Methods used in the preoperative evaluation of TSC before resection**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Neuroimaging Modality</th>
<th>MEG</th>
<th>Scalp EEG</th>
<th>Intracranial EEG</th>
<th>No. Seizure Free (%)</th>
</tr>
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<tr>
<td>Aboian et al., 2011</td>
<td>6</td>
<td>MRI/SISCOM</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>3 (50)</td>
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<tr>
<td>Carlson et al., 2011</td>
<td>14</td>
<td>MRI/PET/SPECT</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>7 (50)</td>
</tr>
<tr>
<td>Kassiri et al., 2011</td>
<td>10</td>
<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Moshelev et al., 2010</td>
<td>15</td>
<td>MRI/PET/SPECT</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>12 (80)</td>
</tr>
<tr>
<td>Wu et al., 2010</td>
<td>18</td>
<td>MRI/PET</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>12 (67)</td>
</tr>
<tr>
<td>Major et al., 2009</td>
<td>3</td>
<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Sugiyama et al., 2009</td>
<td>8</td>
<td>MRI</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Chandra et al., 2006</td>
<td>11</td>
<td>PET &amp; MRI/DTI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Jansen et al., 2006</td>
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<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>2 (67)</td>
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<tr>
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<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Weiner et al., 2006</td>
<td>23</td>
<td>MRI/PET/SPECT</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>21 (84)</td>
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<tr>
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<td>8</td>
<td>MRI/PET</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Kagawa et al., 2005</td>
<td>17</td>
<td>MRI/AMT-PET</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>12 (70)</td>
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<td>Lachhwani et al., 2005</td>
<td>17</td>
<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>11 (65)</td>
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<td>Karenfort et al., 2002</td>
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<td>no</td>
<td>yes</td>
<td>yes</td>
<td>3 (38)</td>
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<td>Romanelli et al., 2002</td>
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<td>no</td>
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<td>Ohta et al., 2001</td>
<td>1</td>
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<td>no</td>
<td>yes</td>
<td>no</td>
<td>0</td>
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<tr>
<td>Asano et al., 2000</td>
<td>7</td>
<td>MRI/PET (AMT/FDG)</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>5 (71)</td>
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<tr>
<td>Koh et al., 2000</td>
<td>11</td>
<td>MRI/SPECT</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>9 (82)</td>
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<td>Guerreiro et al., 1998</td>
<td>12</td>
<td>CT/MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Avellino et al., 1997</td>
<td>11</td>
<td>CT/MRI</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Baumgartner et al., 1997</td>
<td>4</td>
<td>MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Bebin et al., 1993</td>
<td>9</td>
<td>CT/MRI</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>6 (67)</td>
</tr>
<tr>
<td>Bye et al., 1989</td>
<td>1</td>
<td>CT</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>0</td>
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<tr>
<td>Perot et al., 1966</td>
<td>7</td>
<td>CT</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>3 (43)</td>
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</tbody>
</table>

* The length of time until follow-up varied in each study. Abbreviation: SISCOM = subtraction ictal SPECT coregistered to MRI.
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ity, although the resected tissue had histological features consistent with a tuber.

In these initial studies resection of a dominant epileptogenic focus resulted in elimination or reduction of seizures. The series presented above, however, were limited largely to patients with focal ictal epileptiform discharges or a single radiographic lesion. Localization and surgical planning in this cohort presents several unique obstacles in epilepsy surgery. Affected individuals will frequently have several seizure semiologies. Furthermore, epileptogenic tubers are often multifocal, involve both hemispheres, and reside adjacent to or within eloquent cortex. Resection of a dominant seizure focus potentially allows for a secondary focus to emerge, leading to seizure recurrence. Recognizing these potential limitations to seizure localization and resection, investigators have reported a number of novel techniques in neuroimaging and neurophysiology. The armamentarium for preoperative evaluation now includes diffusion-weighted and diffusion-tensor MRI, functional MRI, SPECT, FDG and AMT-PET, MEG, and high-resolution EEG.

**Novel Methods for Preoperative Evaluation in TSC**

Identification of cortical tubers on MRI with T2-weighted and FLAIR sequences is well described. Unfortunately, this does not allow for differentiation between epileptogenic and nonepileptogenic lesions. A recent report demonstrated that epileptogenic tubers showed a significant increase in the apparent diffusion coefficient relative to nonepileptogenic tubers and normal cortex. In a series of 15 patients, Chandra et al. demonstrated that epileptogenic tubers had increased diffusion-tensor imaging–apparent diffusion coefficients in subtuber white matter relative to nonepileptogenic tubers. More impressively, the authors found that the largest volume of hypometabolism on FDG-PET/MRI–coregistered images corresponded to epileptogenic tubers. The tuber volume measured by MRI was not statistically significant between epileptogenic and nonepileptogenic tubers. Tumors that were associated with epileptiform discharges on scalp EEG were associated with an increased volume of hypometabolism on FDG-PET. However, the ability to identify epileptogenic tubers was increased with the FDG-PET/MRI–coregistered images correlating with the epileptogenic tuber removed at the time of surgery in 88% of patients. Similarly in a report by Wu and colleagues, a subset of patients who were not initially considered surgical candidates were able to undergo focal resection following localization with FDG-PET/MRI coregistration.

In addition to FDG-PET, other studies have examined the use of AMT-PET in localization of epileptogenic tubers. The compound AMT is a tracer of serotonin synthesis, and its use in studies of epilepsy is based on the observation of increased serotonin concentration in resected epileptogenic cortex. Epileptogenic tubers have been found to have increased AMT uptake compared with surrounding cortex and nonepileptogenic tubers. In an analysis of 17 patients selected for resection, AMT-PET studies were included in the preoperative evaluation, and 77% of the cortical tubers with increased AMT uptake were within the EEG-defined region. Of those patients with a single tuber that exhibited AMT uptake, the tuber was always within the electroencephalographic region of interest. For those with multiple areas of increased tracer uptake, the lesion with the greatest uptake correlated with the epileptogenic tuber. In 1 patient, increased AMT uptake was observed in the cortical tissue adjacent to a tuber. This tissue was found to have cortical dysplasia and balloon cells on histological analysis.

An advantage of PET relative to other functional neuroimaging techniques is that it is performed in the interictal state; obtaining an ictal SPECT scan is often labor intensive and difficult. However, a number of studies have established a role for ictal SPECT in the localization of epileptogenic regions in patients with tuberous sclerosis complex. Koh et al. found areas of hyperperfusion on ictal SPECT in 10 of 18 patients that corresponded to the region of seizure onset defined by scalp EEG. Another group used subtraction ictal SPECT coregistered to MRI in the evaluation of 6 patients with TSC. This technique is believed to improve the interpretation and accuracy of ictal SPECT. Intensity differences between the interictal and ictal SPECT greater than 2 standard deviations are coregistered with the MRI. Five of the 6 patients had multiple tubers on MRI and the ictal scalp EEG was localizing in 3 patients, laterализing in 1, and generalized in 2. Five of the patients had a dominant region of hyperperfusion on subtraction ictal SPECT coregistered to MRI that was used in defining the area of resection. The 2 patients who underwent complete resection of the hyperperfused region were seizure free postoperatively. The use of MEG has been described in the evaluation of patients with TSC. It has been proposed that source localization may be more accurate with MEG than EEG. In a recent report, detection of a single seizure focus was greater with MEG than high resolution EEG in the same cohort. Additionally, the epileptogenic foci were closer to the presumed epileptogenic tubers with MEG when these results were superimposed on MRls. In a study of noninvasive testing using magnetic source imaging and FDG-PET, resection that included the magnetic source imaging dipole clusters was associated with seizure-free outcomes. In 75% of patients, MEG confirmed the localization from scalp EEG. In 10 patients with hemispheric or generalized ictal EEG onset, magnetic source imaging was localizing in 8 patients. As in other areas of epilepsy research and surgery, MEG is developing an increased role in seizure localization.

**Invasive Intracranial Monitoring**

A number of patients with TSC and intractable seizures have nonlocalizable or nonlateralizing ictal and interictal EEG findings. For these individuals, MRI studies frequently reveal numerous and bilateral cortical tubers. Additional noninvasive testing such as PET, SPECT, and MEG may offer inconsistent results with no clear epileptogenic focus. Traditionally, these patients were not considered surgical candidates. Recent studies have ad-
dressed this patient population, analyzing effective methods of epileptogenic localization. In 1 recent study, 20 patients with nonlocalizable epilepsy underwent implantation of bilateral subdural strip and depth electrodes. The results of the intracranial monitoring identified epileptogenic regions amenable to resection in 15 of 20 patients; 5 had nonlateralizable epilepsy despite intracranial monitoring. Fourteen of the patients with epileptogenic foci underwent resection, with 50% of the patients becoming seizure free.

An added benefit to the use of intracranial electrodes for monitoring is the ability to perform cortical mapping when an epileptogenic region is in proximity to eloquent cortex. In addition to monitoring with intracranial electrodes, this group has advocated multistage, 2- or 3-step resections. In select patients, intracranial electrodes are once again inserted at the time of initial resection. This method may reveal residual or secondary epileptogenic foci useful in directing additional and aggressive resections.

**Illustrative Case**

This female patient with tuberous sclerosis developed seizures at 3 years of age. The predominant seizure semiology was defined by an aura of dizziness or visual blurring, followed by tonic eye and head deviation to the right, with or without secondary generalization. Other features of her seizures included variable paresthesias of the right and left hand, drop seizures, and absence seizures. The patient described visual phenomenon of geometrical shapes and flashing lights. Her seizures were initially controlled with valproic acid. After approximately 18 months of monotherapy, her seizures recurred and were intractable to multiple antiepileptic drugs including oxcarbazepine, carbamazepine, levetiracetam, ethosuximide, vigabatrin, gabapentin, and rapamycin. The patient presented to our institution at 10 years of age for formal surgical evaluation.

Interictal scalp EEG demonstrated multifocal discharges emanating from both temporal lobes (right greater than left) and bicepolar regions. The polyspike and spike wave discharges were more frequent within the right hemisphere, with generalized polyspikes occurring during sleep. An ictal recording revealed onset of activity that came from the bilateral frontal and vertex regions.

Neuroimaging studies included MRI and SPECT. Numerous tubers and subependymal nodules were visualized on MRI (Fig. 1). There were no perfusion abnormalities on SPECT in the interictal state. The ictal study demonstrated an intense increase in perfusion to portions of the posterior right parietal, temporal, and occipital lobe (Fig. 2). From neuropsychiatric testing at the age of 6, her full scale IQ was 89, verbal comprehension index was 89 (low average), and perceptual reasoning was 90 (average range).

Considering that these initial studies were nonlocalizing, and the scalp EEG nonlateralizing, the patient underwent monitoring using bilateral intracranial electrodes. Subdural strip electrodes were positioned over the left temporal, left frontal, and right temporal convexity. Additionally, a 4 × 8 contact grid was inserted over the right parietooccipital region with interhemispheric coverage. Several ictal recordings were obtained during the period of monitoring with localization to the right occipital region (Fig. 3). Cortical mapping was performed with stimulation of this region replicating the visual phenomenon that she had described previously.

After sufficient data collection, the patient underwent a partial resection of the right occipital lobe. Review of the pathology demonstrated that the tissue from this region was a cortical tuber. Postoperatively the patient was neurologically intact. Four months following surgery the patient remains seizure free. This case demonstrates the utility of using multiple modalities in the preoperative evaluation of patients with tuberous sclerosis. The bilateral multifocal and generalized discharges on scalp EEG and ictal SPECT did not localize a resectable epileptogenic focus. In this patient, the use of intracranial electrodes was an essential component in identifying a seizure focus and tailoring the resection.

**Discussion**

Seizures are a predominant manifestation of TSC and frequently prove refractory to medical therapy. The detrimental effects of frequent and uncontrolled seizures on childhood development and cognition have been well described in individuals with TSC. An increasing number of studies have demonstrated that resection of epileptogenic regions offers a significant benefit in seizure reduction or elimination. A number of features unique to TSC complicate epilepsy surgery including bilateral multifocal or generalized epileptiform abnormalities, often extratemporal location, and the potential for secondary epileptogenic foci to appear following resection of a dominant lesion. A number of novel noninvasive methods have been used in the preoperative evaluation as discussed in this review. Successful surgical outcomes have been observed with all of the methods described as noted by the outcomes reported in Table 1. Each has limitations and none is able to differentiate epileptogenic and non-epileptogenic tubers in all patients. What is clear from review of the literature is that more than 1 method should be used in each patient to confirm and better define an
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area for resection. Although noninvasive techniques such as MRI, PET, SPECT, or MEG may be sufficient to direct resection in some patients, invasive monitoring with intracranial electrodes is invaluable in expanding the number of surgical candidates. Epilepsy surgery is a fascinating and exciting treatment for intractable seizures in tuberous sclerosis based on the potential benefits to patients, the diagnostic dilemmas it poses, and the need for further developments.

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: Roberts. Acquisition of data: Morse. Drafting the article: Evans. Critically revising the article: Roberts. Administrative/technical/material support: Roberts.

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L. T. Evans, R. Morse, and D. W. Roberts

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Address correspondence to: Linton T. Evans, M.D., Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, New Hampshire 03756. email: linton.evans@hitchcock.org.