Electrocorticographic evidence of perituberal cortex epileptogenicity in tuberous sclerosis complex

Clinical article

TRACY S. MA, B.A.,1 ROBERT E. ELLIOTT, M.D.,1 VÉRONIQUE RUPPE, PH.D.,2 ORRIN DEVINSKY, M.D.,2 RUBEN KUZNIECKY, M.D.,2 HOWARD L. WEINER, M.D.,3 AND CHAD CARLSON, M.D.2

Departments of 1Neurosurgery and 3Neurosurgery and Pediatrics, Division of Pediatric Neurosurgery; and 2Comprehensive Epilepsy Center, Department of Neurology, New York University School of Medicine, New York, New York

Object. Tuberous sclerosis complex (TSC) is a multisystem autosomal dominant disorder resulting in hamartomas of several organs. Cortical tubers are the most prominent brain lesions in TSC. Treatment-resistant epilepsy often develops early in life in patients with TSC and is associated with severe intellectual and behavioral impairments. Seizures may remit following epilepsy surgery in selected cases, yet it remains unclear whether the tuber or the perituberal cortex is the source of seizure onset. In this study, the authors reviewed the onset of seizures in patients in whom depth electrodes had been placed within or adjacent to cortical tubers.

Methods. After obtaining institutional review board approval, the authors retrospectively reviewed data from 12 pediatric patients with multifocal TSC and treatment-resistant epilepsy who had undergone invasive intracranial electroencephalographic monitoring. Tubers were identified on postimplantation MRI, and all depth electrodes were located. Depth electrode contacts were classified visually as either tuber/perituberal cortex or nontuber/nonperituberal cortex. Board-certified clinical neurophysiologists reviewed the seizures to identify all electrodes involved in the ictal onset.

Results. Among 309 recorded seizures, 104 unique ictal onset patterns were identified. Of the 11 patients with electrodes recording in a tuber, 9 had seizure onsets involving the tuber. Similarly, of the 9 patients with perituberal recording electrodes, 7 had perituberal ictal onsets. Overall, there was no difference in the percentage of contacts involved in seizure onset between the tuber and perituberal cortex. In a subset of 7 patients in whom at least 1 depth electrode contact was within the tuber and 1 was in the perituberal cortex, there was no difference between the percentage of tuber and perituberal onsets.

Conclusions. Findings demonstrated heterogeneity in the ictal onset patterns as well as involvement of the tuber and perituberal cortex within and between patients. Although the data are limited by the restricted region(s) sampled with intracranial electrodes, they do suggest that cortical hyperexcitability in TSC may derive from the tuber or surrounding cortex.

KEY WORDS • tuberous sclerosis complex • epilepsy • epileptogenesis • neurosurgery • pediatric • cortical tuber

Tuberous sclerosis complex is an autosomal dominant genetic disease caused by inactivating mutations in the TSC1/TSC2 genes. It affects approximately 50,000 Americans. Hamartomas and other lesions affect multiple organ systems, including the brain, retina, heart, kidneys, and skin.12,26 Seizures usually begin very early in life during a critical window of brain development. Early-onset and treatment-resistant epilepsy probably contribute to or cause severe cognitive impairment in TSC. Cortical tubers are classic neuropathological lesions and are associated with an increased risk of developmental impairment and epilepsy.20,34,50 Seventy to 90% of children with TSC have treatment-resistant epilepsy within the 1st year of life.46

This article contains some figures that are displayed in color online but in black-and-white in the print edition.
Electrocorticographic evidence of epileptogenicity in TSC

Resection of a single, dominant epileptogenic tuber has resulted in marked improvement in the seizure profile. Early seizure control with medical or surgical intervention can positively impact cognitive development and social adjustment in TSC. However, seizure onsets in TSC are often multifocal or generalized, limiting the candidates for potential surgery. Ictal onset may arise from tubers. Intraoperative electrocorticography demonstrates epileptiform discharge activity in cortical tubers. However, the perituberal cortex, necortical tissue surrounding the tuber, may possess epileptogenic properties as well. Some cortical tubers are electrographically silent, with seizures arising from normal cortex surrounding the tuber. Thus, it remains unclear whether tubers, the perituberal cortex, or a combination of the two generate the initial ictal onset. To investigate this question, we reviewed electrographic ictal onsets in patients with TSC who had undergone EEG depth electrode studies.

Methods

The Study and Its Participants

The New York University School of Medicine institutional review board approved this study, and informed consent was waived since data were only retrospectively analyzed. Selection criteria for inclusion in the study were a history of TSC, treatment-resistant epilepsy, availability of digital EEG and MRI data, cortical tuber presence on MRI, and depth electrode placement within the tuber or perituberal cortex. Clinical charts for eligible patients were reviewed for demographic information, age at seizure onset, age at surgery, duration of epilepsy (age at diagnosis to age at surgery), postoperative seizure frequency, and number of postoperative antiepileptic drugs. The New York University School of Medicine institutional review board approved this study, and informed consent was waived since data were only retrospectively analyzed. Selection criteria for inclusion in the study were a history of TSC, treatment-resistant epilepsy, availability of digital EEG and MRI data, cortical tuber presence on MRI, and depth electrode placement within the tuber or perituberal cortex. Clinical charts for eligible patients were reviewed for demographic information, age at seizure onset, age at surgery, duration of epilepsy (age at diagnosis to age at surgery), postoperative seizure frequency, and number of postoperative antiepileptic drugs. The New York University School of Medicine institutional review board approved this study, and informed consent was waived since data were only retrospectively analyzed. Selection criteria for inclusion in the study were a history of TSC, treatment-resistant epilepsy, availability of digital EEG and MRI data, cortical tuber presence on MRI, and depth electrode placement within the tuber or perituberal cortex. Clinical charts for eligible patients were reviewed for demographic information, age at seizure onset, age at surgery, duration of epilepsy (age at diagnosis to age at surgery), postoperative seizure frequency, and number of postoperative antiepileptic drugs.

All patients underwent surgery for implantation of the electrodes, postimplantation neuroimaging, and review of the intracranial EEG studies per standard clinical protocols. In the present analysis, the neuroimaging studies were independently reviewed to assess the location of all electrodes relative to tubers. Similarly, all intracranial EEG data from the initial clinical review were independently evaluated to determine the ictal onsets zones.

Evaluation of Depth Electrode Location and Analysis of Ictal Onset in EEG

Depth electrodes were placed using a frameless stereotactic system based on recommendations of the multidisciplinary conference held prior to surgery. This decision was made on the basis of preoperative neuroimaging and EEG data. Electrodes, depth electrodes as well as subdural ones, were placed purely for clinical purposes to aid in localizing the ictal onset zone. Location and extent of resection were guided by data gathered from implanted recording electrodes and the anatomical locations of those electrodes. Independent review of postimplantation MRI studies revealed the cortical tubers and all depth electrode locations. Magnetic resonance imaging was performed in all patients prior to surgery. Typically occurring at the gray-white matter junction of the cortex, tubers were defined as regions of hyperintense signal on T2-weighted and hypointense signal on T1-weighted MRI. Postoperative images were obtained on the day following implantation to determine the location of each subdural and intraparenchymal electrode and its individual contacts, specifically their proximity to imaging-defined tubers. The T2-weighted images were obtained using either a 3- or 5-mm slice thickness. The T1-weighted images were obtained using a protocol of 1-mm slices with sagittal and coronal views. Two clinicians (either a neurosurgeon or an epileptologist) independently viewed the images and were blinded to the EEG findings.

Electrodes at the margin of a tuber or separate from an imaging-defined tuber were deemed “perituberal” (Fig. 1). Electrodes were considered “tuberal” if the contact was entirely within a tuber, as defined on postoperative MRI (Fig. 2). The relationships of individual contacts on each electrode to the brain and tubers were assessed. Contact locations were defined as perituberal (at or near the margin of a tuber) or tuberal (entirely within the volume of a tuber).

Subdural strip and grid electrodes and depth electrodes were in place overlying the cortex as well as neighboring tubers; ictal onset was localized using recordings from these electrodes. Board-certified clinical neurophysiologists reviewed all seizures and identified electrodes involved in each ictal onset. All seizures were recorded using a Nicolet BMSI 6000 system (Nicolet Instrument, Inc.). Up to 128 channels on EEG were recorded with a 400-Hz sampling rate. Schematic drawings from both the neurosurgeon and the epileptologist were visually reviewed and correlated to the MR images obtained after electrodes had been implanted to confirm electrode locations (Fig. 3). Coregistration of both the grid-positioning description in surgery and the MR images confirmed that electrically active contacts were either within the tuber or in adjacent cortex.

Statistical Analysis

All patients were segregated into 2 groups based on depth electrode placement: 1) tuber involved in seizure onset, or 2) perituberal cortex involved in seizure onset. All reported p values used the Student t-test with 2-tailed tests of significance and an α set at 0.05.

Results

Patient Demographic and Clinical Information

We studied 12 children with multifocal TSC and treatment-resistant epilepsy who had undergone surgery performed by a single pediatric neurosurgeon (H.L.W.) using invasive intracranial EEG monitoring between 2004 and 2010 at New York University’s Comprehensive Epilepsy Center. Some patients have been included in other reports on other aspects of TSC. The patients, 6 girls and 6 boys, ranging in age from 1 year 11 months to 15 years 5 months at the time of surgery (mean age 6.5 years), underwent tuber and seizure focus resection (Table 1). Age at seizure onset ranged from 4 days to
3 years (mean age 6.1 months). The duration of epilepsy from age at disease onset to age at surgery ranged from 1 year 8 months to 15 years 2 months (mean age 6.3 years). Postoperatively, 8 patients were seizure free, and 4 patients were not (1–2 daily seizures).

Seizure Onset Heterogeneity

Three hundred nine seizures were reviewed, and 104 unique ictal onset patterns (seizure types) were identified in the 12 patients (Table 2). The number of depth electrode channels involved in seizure onset was recorded for those patients with electrodes within the tuber and within the perituberal cortex. We estimated the percentage of depth electrode contacts involved in seizure onset from the number of depth electrode contacts that had the potential to be involved. The number of potential contacts that could be involved in ictal Onsets was calculated by identifying the number of contacts in either the tuber or perituberal regions and multiplying it by the number of seizures recorded in that patient. The number of contacts not recording in each seizure was noted, and this value was subtracted from the theoretical total to give the number of potential contacts that could have been involved in the ictal onset. There was no difference in the percentage of contacts involved in seizure onset between the tuber and perituberal cortex (p = 0.79). Among the 12 patients, 7 had at least 1 depth electrode contact within the tuber and 1 in the perituberal cortex; there was no difference between the percentage of tuber and perituberal Onsets within an individual patient (p = 0.45).

Discussion

Our study examining 104 ictal onset patterns in 12 patients with TSC revealed that both tubers and perituberal cortex can be involved separately or together in seizure onsets. To distinguish the epileptogenicity between a tuber and perituberal cortex requires precise placement.

![Figure 1](image1.png)

**Fig. 1.** Axial T2- (A) and T1-weighted (B) MR images showing perituberal depth electrodes (thin arrows) just anterior to a large, right temporal tuber (thick arrows). Axial T2-weighted MR image (C) demonstrating an 8-contact depth electrode with perituberal contacts in the right temporal and occipital lobes. The more lateral depths are clearly anterior to the temporal tuber (black arrow). Multplanar T1-weighted imaging was used to confirm that the most distal contact near the occipital tuber (white arrow) was located at the margin and not within the tuber.

![Figure 2](image2.png)

**Fig. 2.** Axial T2-weighted MR image (A) showing the most distal right temporal contact within the tuber (white arrow) and the second contact at the margin (perituberal, black arrow). Axial T2-weighted MR image (B) demonstrating the most distal left frontal contact within the tuber (black arrow) and the second contact at the margin (perituberal, white arrow). Sagittal T1-weighted MR image (C) showing the most distal contact (thin arrow) just deep to the tuber margin (perituberal) and the more proximal contacts entirely within this large parietal tuber (thick arrow).
Electrocorticographic evidence of epileptogenicity in TSC

of electrodes. Depth electrodes allow evaluation of deep cortical areas that are not readily recordable by scalp EEG monitoring. Stereotactic positioning effectively focuses depth electrode insertion into the region(s) of interest. Depth electrodes along with subdural grids and strips were placed during the initial implantation (Stage I) in the patients in this study. For some patients, after initial monitoring and resection, additional electrodes were implanted for a second stage of monitoring (Stage II) leading to a third surgical stage. Four patients had depth electrodes in both their first and second stages of monitoring. Placement of depth electrodes within tubers and perituberal cortex was confirmed radiologically for all 12 patients.

The loss of TSC1 or TSC2 leads to overactivation of the mammalian target of rapamycin complex 1 (mTORC1), a critical kinase that controls many cellular functions such as protein translation, proliferation, and cell size. In the brain, the mTORC1 pathway regulates processes required for neuronal function, such as dendrite and axon formation, synaptogenesis, and synaptic plasticity. Although no tubers are found in mouse models of TSC, many features of the disease are replicated, such as astrogliosis, dysplastic neurons, lamination defects, hypomyelination, and spontaneous seizures. Furthermore, in both tubers and mouse models of TSC, altered expression of neurotransmitter receptor subunits leads to neuronal hyperexcitability. In animal models, inhibition of mTORC1 by the administration of rapamycin leads to an improvement in epilepsy and cognition. Upregulation of mTORC1 is observed in tubers; however, mTORC1 activation, heterotopic neurons, and focal dyslamination are also present outside of radiographically defined tubers and are widespread in the brain. We hypothesize that hyperactivation of mTORC1 throughout the brain contributes to seizures, epilepsy, and neurocognitive dysfunction in patients with TSC. Further studies are needed to understand the anatomical and physiological substrate responsible for the neurological symptoms in TSC.

In the context of TSC, a variety of clinical studies using EEG, MRI, magnetoencephalography, PET, and/or SPECT have implicated the cortical tuber as the site of epileptogenesis. However, whether seizures begin within the tuber or the adjacent perituberal cortex remains a subject of debate. While there is a high rate of seizure freedom following single tuber resections, some patients continue to have seizures after surgery. Some surgeries may succeed because resection often involves a certain degree of excision of the surrounding cortex. Additionally, seizure freedom has been reported following the resection of normal-appearing, tuber-free cortex in patients with TSC and treatment-resistant epilepsy, which further highlights the notion of ictogenesis beyond the cortical tuber. The nature of the networks that create and propagate seizures in patients with epilepsy (TSC or otherwise) is still poorly understood. This study has several limitations. The sample size is limited, as not all patients undergoing intracranial EEG also undergo depth electrode implantation; the use of these electrodes is determined by the clinical team prior to implantation. As this was a retrospective review, uniform placement of depth electrodes between patients in both tuber and perituberal regions was impossible. These 2 factors lead to a relatively limited sample of unique patients.

**TABLE 1: Summary of characteristics in 12 patients with TSC**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age at Onset (mos)</th>
<th>Age at Op (mos)</th>
<th>Duration of Epilepsy (mos)</th>
<th>Postop Sz</th>
<th>Postop Frequency</th>
<th>Postop AED No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>3</td>
<td>23</td>
<td>20</td>
<td>Sz free</td>
<td>NA</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>6</td>
<td>51</td>
<td>45</td>
<td>Sz free</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>5.5</td>
<td>75</td>
<td>69.5</td>
<td>Sz free</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>3.5</td>
<td>108</td>
<td>104.5</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>108.25</td>
<td>104.75</td>
<td>2 daily</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>1</td>
<td>48</td>
<td>47</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>2</td>
<td>84</td>
<td>82</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>84.25</td>
<td>82.25</td>
<td>1–2 daily</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>2</td>
<td>23</td>
<td>21</td>
<td>1 daily</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>4</td>
<td>63</td>
<td>59</td>
<td>Sz free</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>6</td>
<td>145.5</td>
<td>139.5</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>145.75</td>
<td>139.75</td>
<td>Sz free</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>4</td>
<td>38</td>
<td>34</td>
<td>1–2 daily</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>4†</td>
<td>25.5</td>
<td>25.4</td>
<td>Sz free</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>36</td>
<td>185</td>
<td>182</td>
<td>Sz free</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

* AED = antiepilepsy drug; NA = not applicable; Sz = seizure.
† Defined as the period from the age at seizure onset to the age at surgery.
‡ Number of reported seizures following tuber resection.
§ Number of reported antiepilepsy drugs the patient took to control seizures after the operation.
¶ Expressed in days.
and depth electrode channels. To minimize the effects of selection bias, we consecutively identified all patients with data that met the inclusion criteria. Third, intracranial EEG was limited to the electrodes that were implanted. Other tubers or perituberal regions that were not studied may contribute to seizure onset. However, seizure-free outcomes in 8 patients (67%) in this study suggest accurate identification and removal of the epileptogenic zone. The limited sampling of the brain using the depth electrodes raises the possibility and likelihood that our findings only partly represent the degree of complexity and heterogeneity of epilepsy in TSC. Fourth, as formal genetic testing is often not performed in routine clinical care, we could not relate tuber and perituberal cortex relationships with TSC mutations. Finally, the T2-weighted MR images had slice thicknesses of 5 mm, which may limit resolution and analyses of electrode positioning relative to the tuber. Thin-cut slices with 3D reconstructive imaging would improve this but were not routinely obtained clinically at the time of the diagnostic procedures.

Data in the present study concur with emerging evidence of brain tissue surrounding the tuber as a site of ictogenesis in TSC. Epileptogenesis in the perituberal cortex has been supported in several previous studies. Chandra et al. used FDG-PET and MRI apparent diffusion coefficients to reveal epileptogenic potential in the perituberal cortex of patients with TSC. Similarly, with \( \alpha-[\text{I}C]methyl-l-\text{tryptophan (AMT)} - \text{PET} \), Juhász et al. identified cortical tissues adjacent to tubers as sites of interest in TSC epileptogenesis. Of note, Major et al. provided evidence of epileptogenic perituberal cortex in the context of electrophysiologically silent tubers by using intraoperative depth electrodes. However, in the current study we found activity in the perituberal cortex in the setting of an electrophysiologically active tuber. Further, our findings demonstrate that the site of ictogenesis may lie outside the tuber. This finding has direct implications for the surgical approaches in TSC. Our results suggest that wider resections of the dominant tuber may more effectively remove the TSC ictal onset zone.

**Conclusions**

Significant heterogeneity in ictal onset patterns and tuber and/or perituberal cortex involvement exist both within and between patients. Our findings suggest that cortical hyperexcitability in TSC may derive from the tuber or surrounding cortex. Further, prospective studies to systematically examine the role of both the tuber and surrounding cortex are needed to advance our understanding of epileptogenesis and ictogenesis in TSC.

**Disclosure**

The authors gratefully acknowledge the financial support of the Irene & Eric Simon Brain Research Foundation.

Author contributions to the study and manuscript prepa-
Electrocorticographic evidence of epileptogenicity in TSC

References


33. Ohtsuka Y, Ohmori I, Oka E: Long-term follow-up of child-

Manuscript submitted February 9, 2012. Accepted August 14, 2012. Please include this information when citing this paper: published online September 21, 2012; DOI: 10.3171/2012.8.PEDS1285. Address correspondence to: Howard L. Weiner, M.D., 317 East 34th Street, Suite 1002, New York, New York 10016, email: howard.weiner@nyumc.org.