Epileptic Disord 2020; 22 (5): 633-41

Successful epilepsy surgery for tuberous sclerosis complex evaluated by stereoelectroencephalography

Choong Yi Fong [1,2], Andrew Bleasel [2], Mark AJ. Dexter [2], John A. Lawson [3], Chong H. Wong [2]

[1] Division of Paediatric Neurology, Department of Paediatrics, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[2] Department of Neurology and Neurosurgery, Westmead Hospital, Westmead, Australia
[3] Department of Paediatric Neurology, Sydney Children's Hospital, Randwick, Australia

Received January 29, 2020; Accepted July 27, 2020

ABSTRACT – Evaluating the candidacy for epilepsy surgery in patients with tuberous sclerosis can be challenging, particularly when non-invasive investigations do not show a clear epileptogenic zone. Stereoencephalography may be useful in such cases. We present a case in which the primary epileptogenic tuber was successfully identified by stereoencephalography, which resulted in seizure freedom following epilepsy surgery. [*Published with video sequences*].

Key words: tuberous sclerosis, surgery, epileptogenic zone, stereoencephalography

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem neurocutaneous disorder in which the majority of patients develop epilepsy (Chu-Shore *et al.,* 2010; Jeong and Wong, 2016; Krueger, 2013). Approximately 60% of patients with TSC and epilepsy have antiepileptic drug (AED)-resistant epilepsy (Chu-Shore *et al.,* 2010). Accurate identification of the primary epileptogenic tuber or network is essential as epilepsy surgery in patients with a well-localised seizure focus results in a good seizure outcome in 65-75% of TSC patients (Weiner *et al.,* 2006; Jansen *et al.,* 2007; Fallah *et al.,* 2013; Fallah *et al.,* 2015).

Epilepsy surgical evaluation is challenging in TSC patients with multiple bilateral tubers as non-invasive investigations, such as scalp electroencephalogram (EEG), interictal positron emission tomography (PET) and ictal single-photon computed tomography (SPECT) are likely to exhibit multiregional and often discordant findings. Invasive monitoring using a combination of either intraoperative electrocorticography (ECoG) or long-term extraoperative ECoG with subdural grids and depth electrodes is often used to try to assist in localisation of the epileptogenic focus in these patients. However, invasive monitoring using grids or strips has limitations including spatial sampling of the brain in patients with multiple bi-hemispheric tubers. Subdural electrodes may only be used to evaluate cortical surfaces.

VIDEOS ONLINE

Correspondence:
Chong Wong
Department of Neurology and Neurosurgery,
Westmead Hospital,
Darcy Road, Westmead,
NSW 2145, Australia
<chong.wong@health.nsw.gov.au>

doi:10.1684/epd.2020.1211

In these circumstances, stereoelectroencephalography (SEEG) potentially plays an important role as multiple bilateral tubers may be monitored simultaneously. SEEG has the added advantage of being able to evaluate the superficial and deep cortex. We report a case of complex refractory focal epilepsy in a patient with TSC, explored by means of SEEG, in which the patient became seizure-free after epilepsy surgery.

Clinical history

A 17-year-old, right-hand dominant male with *de novo TSC-2* gene mutation was referred to our unit for pre-epilepsy surgical evaluation. Antenatal, birth and family history were unremarkable. TSC was recognised at eight months and subsequently confirmed on genetic testing. Epilepsy onset occured at the age of four months with infantile spasms which were well controlled on vigabatrin treatment. He subsequently remained seizure-free from the age of 14 months off AED treatment.

From the age of two years, he then developed stereotyped focal seizures. Initially, the semiology was of laboured breathing and jaw clenching associated with stiffening of both arms that lasted 10-15 seconds. Over the last few years, he described an aura with sensation around his lower lip and mouth, that was non-lateralising. This was followed by stiffening of the jaw accompanied by drooling and axial tonic posturing that could progress to an asymmetric bilateral tonic posture. He was fully aware during the seizure but unable to speak. Seizures lasted 5-45 seconds and occurred once a day. He was refractory to multiple AED treatments including valproate, lamotrigine, topiramate, levetiracetam and lacosamide. He was on vigabatrin at 2,000 mg twice daily, carbamazepine at 400 mg twice daily and zonisamide at 250 mg (am) and 100 mg (pm) when referred to our unit.

Non-invasive investigation

Previous scalp video-EEG (VEEG) at the age of 11 and 12 years showed multiregional interictal epileptiform discharges over the right central, right posterior temporal, left frontal and left parietal regions. Electrographic seizures were also recorded, arising independently from the right central and left frontal region.

Repeat VEEG at 17 years old showed frequent interictal spike-wave discharges, alternating between the left and right centro-temporal region (C3-T3, C4-T4). Seven stereotyped seizures were captured, associated with a typical aura followed by axial tonicity with neck extending forward, pouting of lips with jaw clenched, evolving to the left arm held in a flexed tonic posture. Ictal EEG changes were non-localising and non-lateralising (*figure 1*).

Neuropsychological assessment showed that his intellectual capacities were within normal range with the exception of mild delay in processing speed. He had no visual-verbal dissociation. He was attending mainstream secondary school with good academic achievements and was doing well psychosocially.

High-resolution 3-Tesla brain MRI showed multiple bilateral cortical and subcortical tubers in all lobes with hyperintensity on T2-weighted and fluid-attenuated recovery (FLAIR) sequences (*figure 2*) and multiple calcified small subependymal nodules. Subependymal giant-cell astrocytoma was absent. None of the tubers were calcific or enhanced with gadolinium. Interictal brain FDG-PET showed multiple areas of focal hypometabolism coinciding with each of the tubers (*figure 2*). Over the years, three ictal HMPAO-SPECT studies had been performed. In the earliest ictal SPECT study, injection was performed three seconds after seizure onset, showing increased perfusion to bilateral central regions (the left being more hyperperfused than the right) (*figure 2*).

In addition to subependymal nodules, and subcortical and cortical tubers on MRI, other investigations also confirmed cardiac rhabdomyomas and bilateral renal angiomyolipomas. The patient had undergone regular surveillance with echocardiogram and renal ultrasound with no intervention required.

Stereoencephalographic (SEEG) evaluation

All of the pre-epilepsy surgical evaluation data were reviewed at a multidisciplinary team meeting. The hypothesis was a perisylvian epilepsy on the basis of semiology of lower lip sensory aura, with subsequent spread to the surrounding regions. A second hypothesis considered was seizure arising from the mesial frontal region, Brodmann Area (BA) 6. Electrographic seizures recorded during previous scalp VEEG also raised concerns that seizures could be arising from "silent" cortex in the frontal regions. Following detailed informed consent, a decision was made to proceed to SEEG with bilateral implantation, targeting tubers in these regions including MRI-visible bilateral frontal tubers in BA 46. Eighteen intracerebral bilateral electrodes (Dixi medical, Besancon France of 0.8 mm with 8-18 contacts, length of 2 mm, diameter of 0.8 mm) were implanted with emphasis on the right frontal dorsolateral to mesial and right opercular to insular region (*figure 3*).

Two independent populations of interictal discharges were recorded without reduction of AEDs. The first population showed continuous periodic spike-wave discharges at the right inferior precentral

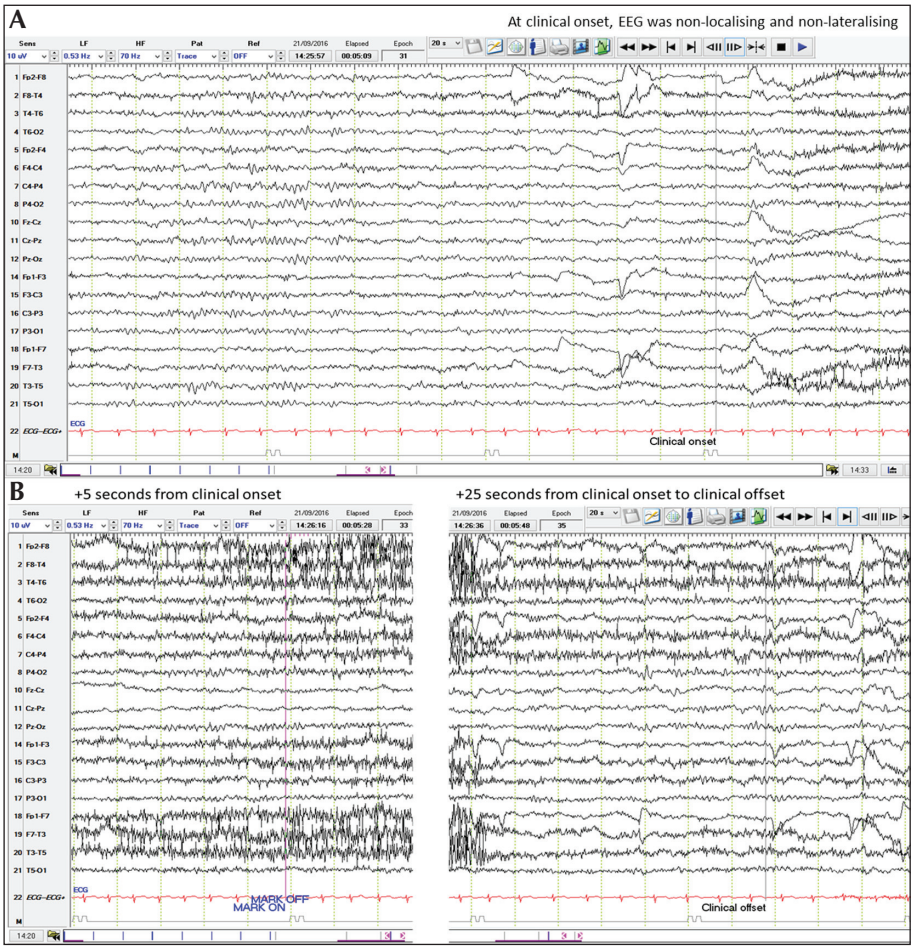

Figure 1. Ictal EEG showing non-localising and non-lateralising EEG at seizure onset (A). In the body of the seizure, EEG was marred by EMG artefacts (B).

(Y11-14; BA 4) and right inferior postcentral (S12-16; BA 1) gyrus with high-frequency oscillations (HFOs) seen in the right inferior pre and post central region, Y11-14 and S11-16 (*figures 4, 5*). A second population showed continuous periodic spike wave at the left orbitofrontal cortex (E'1-3, BA 11) and the left anterior middle frontal gyrus (E'12-14, BA 46) with discharges also showing fast activity with HFOs in E'12-14 (*figures 4, 5*). Both interictal spike populations were associated with hypometabolic tubers evident on MRI-PET imaging.

Multiple typical auras were recorded, often progressing among the stereotyped motor manifestations described before (*video sequences 1, 2*). Some seizures could progress further as a right face and neck clonic seizure (*video sequence 3*) or bilateral convulsive seizures. EEG seizure onset preceded clinical onset in all events and was marked by an abrupt change to low-voltage fast activity (LVFA) with DC shift replacing the continuous discharges seen in the right inferior precentral (Y11-14) and inferior postcentral (S12-16) gyrus. These changes evolved and spread bilaterally (*figure 6*).

Subclinical electrographic seizures were also recorded in the left orbital-frontal region and remained restricted only to electrode E' whilst on AEDs. Following cessation of AEDs, these electrographic seizures then evolved into LVFA with slow DC shift that then engaged the right inferior pre and postcentral gyrus (Y, S), progressing into his typical clinical seizures (*figure 7*). This clinical phenomenon ceased immediately upon re-introduction of his AEDs. Cortical stimulation (50 Hz with 0.3-msec stimulus interval) of the right inferior postcentral gyrus (S) at 3 mA provoked his typical aura. Cortical stimulation of the right inferior precentral gyrus (Y) at 3 mA provoked his typical seizure without aura. Cortical stimulation at other electrodes including E' did not provoke seizure.

A focal resection of the epileptogenic tuber that straddled both the pre and post central gyrus (Y, S) was performed during craniotomy whilst awake. Post-resection ECoG did not show any epileptiform

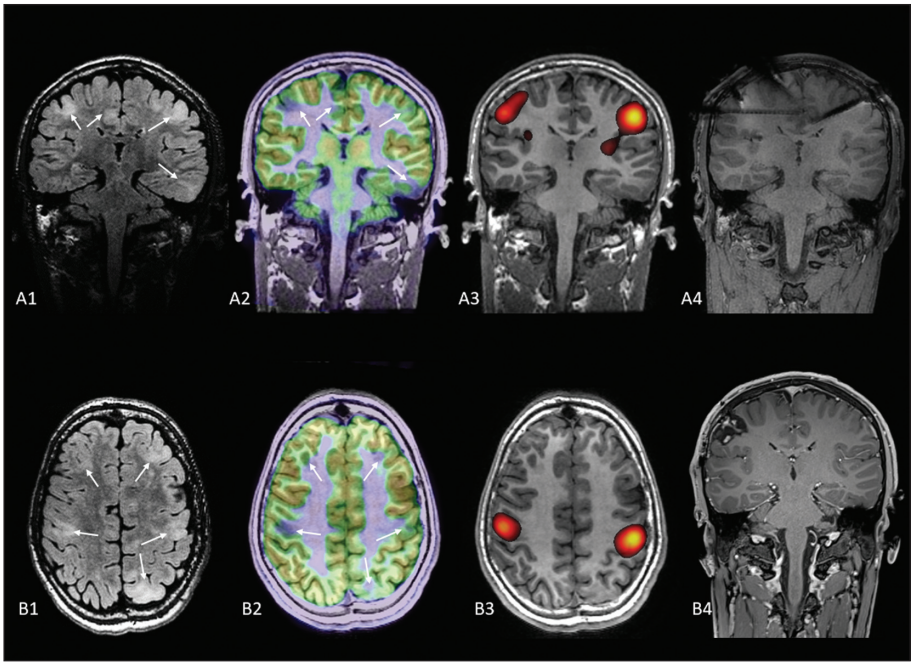

Figure 2. Coronal and axial MRI (A1, B1) co-registered with interictal PET (A2, B2), ictal SPECT (A3, B3) and SEEG electrode (A4). (A2, B2) Interictal PET shows multiple focal areas of hypometabolism coinciding with each of the tuber (arrows). (A3, B3) Ictal SPECT with HMPAO injection given at 3 seconds after the start of a 52-second long seizure showing hyperperfusion over bilateral central regions. (A4) Example multiple SEEG electrode trajectories inserted orthogonally and obliquely targeting the multiple tubers over both hemispheres. (B4) MRI postresection.

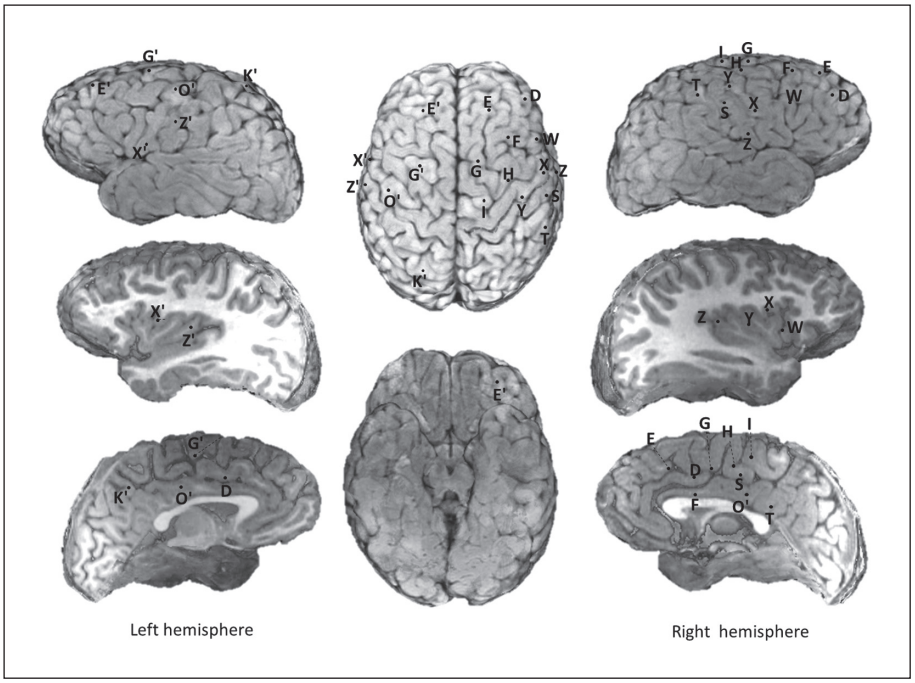

Figure 3. SEEG implantation scheme with 18 electrodes.

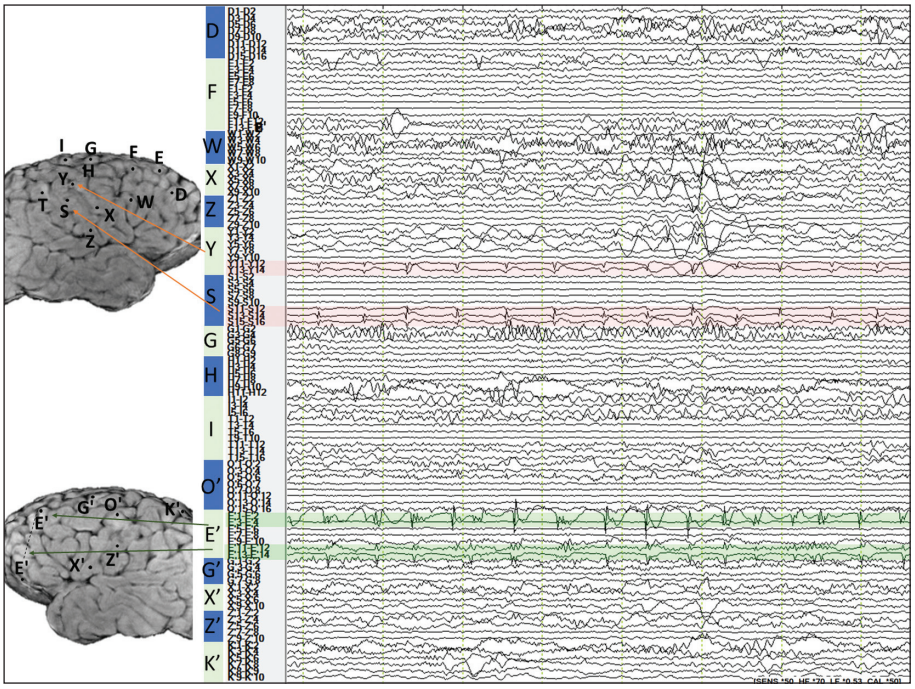

Figure 4. Interictal EEG showing two populations of periodic spike-wave discharges over the right inferior pre-central (Y11-14; BA 4) and post-central region (S12-16, BA 1) (highlighted in red), and left orbitofrontal (E'1-3; BA 11) and left anterior middle frontal gyrus (E'12-14, BA 46) (highlighted in green).

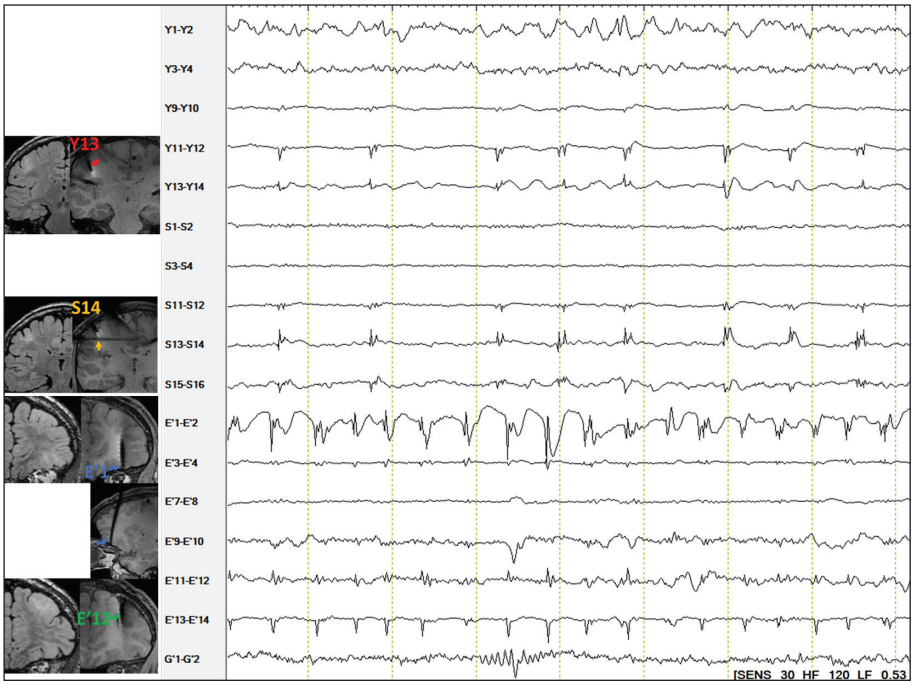

Figure 5. Interictal EEG on selected electrode montage with SEEG electrode placement on coronal MRI showing the two populations of interictal epileptiform discharges. In the right pre-central (Y11-14; BA 4) and post-central region (S12-16; BA 1), continuous spike/polyspike discharges are seen. An independent continuous spike/polyspike discharge is seen interictally in the left orbitofrontal (E'1-3: BA 11) and left middle frontal gyrus (E'12-14; BA 46). The epileptiform discharges on E' electrode show a higher amplitude and more polyspike activity in the left orbitofrontal gyrus (E'1-3: BA 11). Note that the left frontal tuber is complicated by a large tuberal complex encompassing BA 46, BA 10 and BA 11.

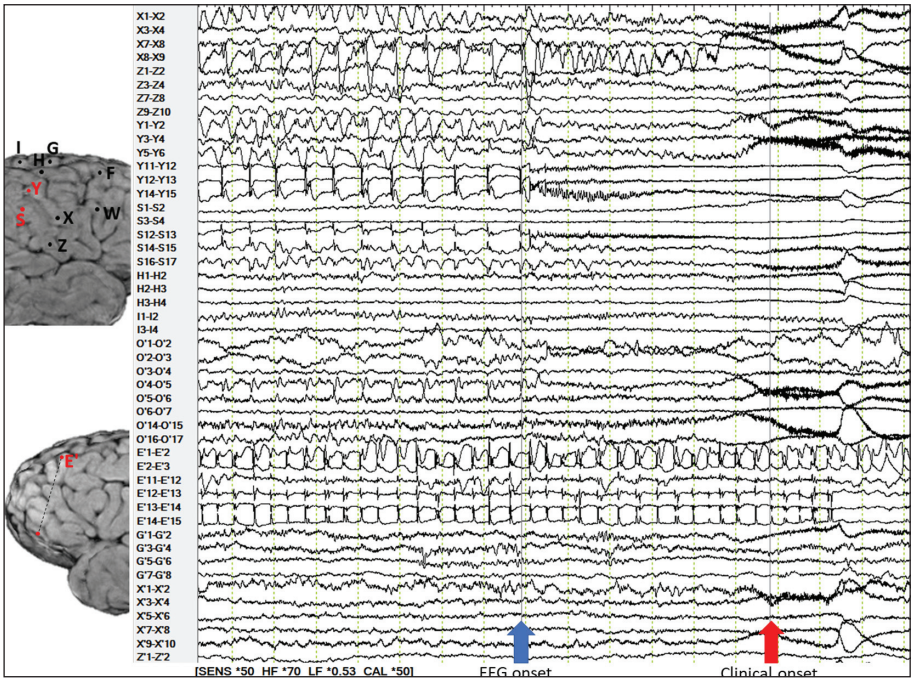

Figure 6. Ictal EEG showing repetitive spike-wave discharges over Y11-14 and S12-16 which attenuate and evolve into low-voltage fast activity (blue arrow), followed by clinical seizures (red arrow). The interictal continuous periodic spike-wave discharge over E'12-14 remains unchanged.

discharges from the cortex surrounding the resection cavity or from the walls of the resection cavity itself. Postoperatively, there was transient hand weakness that resolved completely. Histology showed features of cortical tuber with focal cortical dysplasia type 2b. The patient has been followed for over two years post-operatively and has remained seizure-free since surgery. He was successfully weaned off vigabatrin and remains on carbamazepine at 1,000 mg daily and zonisamide at 50 mg nocte.

Discussion

We present a TSC patient with intractable focal epilepsy, with multiple tubers over both hemispheres and inconclusive non-invasive investigations for localisation of the epileptogenic tuber. The ictal scalp EEG and SPECT might have been expected to provide at least consistent lateralisation but were inconclusive. Even the very early ictal SPECT injection showed bilateral activation, as might be expected in the central regions and considering the rapid and multiregional propagation shown during the SEEG.

Whilst there are published reports describing intraoperative or multistage extraoperative invasive grid and depth recordings for TSC patients, to our knowledge, there is only one publication describing the usefulness of SEEG for epilepsy surgical evaluation in TSC patients (Neal *et al.*, 2020). With a sound pre-implantation hypothesis, SEEG can be invaluable in determining which potential candidate tuber is responsible for the clinical seizures. Our case reiterates that removal of a single tuber generating the electroclinical seizure network can provide seizure freedom.

The mechanisms leading to epileptogenesis in TSC are complex with multiple inter-related factors that include dysfunction in the mTOR signalling pathway and the presence of abnormal neuropathological substrates (Wong, 2008; Feliciano *et al.*, 2013). These factors interact causing potential alteration in cerebral architecture, neurotransmitter receptor expression and / or cellular proliferation resulting in epileptogenesis at either the primary circuit or at the molecular-cellular level (Curatolo, 2015). Our patient illustrates this complex interaction showing that cerebral tubers can have different degrees of epileptogenicity. Tuber Y,S was proven to be the 'drug-resistant' epileptogenic tuber, tuber E' the 'drug-controlled' epileptogenic tuber, and the other tubers were epileptogenically 'inert'. Our case illustrates the importance of more studies evaluating the interaction of neuronal circuits between tubers at both the molecular-cellular and network level.

Identifying the primary epileptogenic tuber in TSC can be challenging. Some studies suggest that at a cellular level, the abnormal cells in tubers act as the intrinsic 'pacemaker' which can initiate and be the primary generator of epileptogenesis (Cepeda *et al.*,

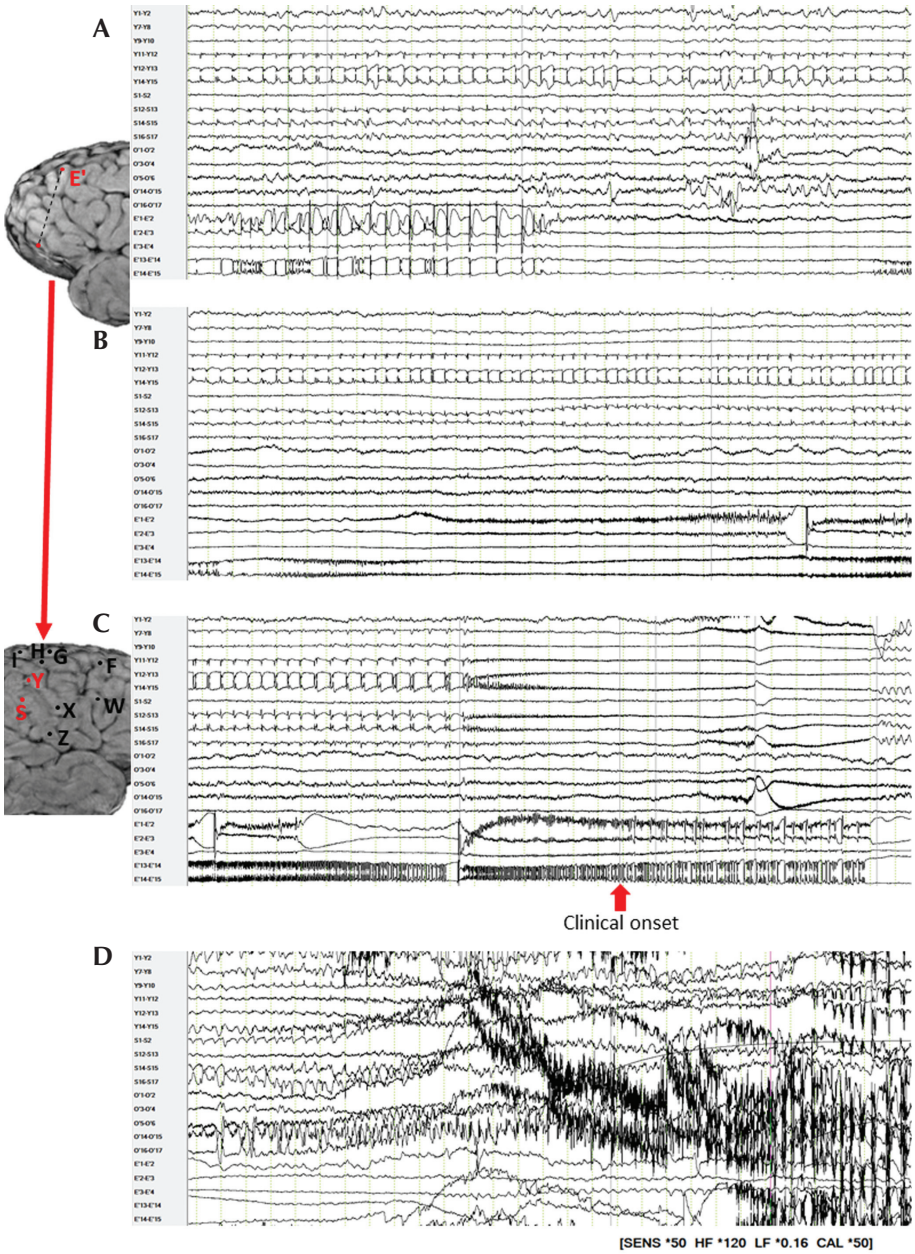

Figure 7. Following cessation of all antiepileptic medications, EEG seizures were seen arising from the left frontal region and spreading to the right central region, causing a clinical seizure. (A-D) Ictal seizure evolution in a 30-second epoch showing an electrographic seizure over E'1-3 (BA 11) and E'13-15 (BA 46) which attenuates to low-voltage fast activity (B), subsequently spreading to the external Y (BA 4) and S (BA 1) electrodes causing a clinical seizure (C, D). Note that during the "provoked" seizure (A 1), the pre-ictal activity at E' differs between E'1-3 and E'13-15, showing a more polyspike appearance and more fast and tonic activity at the E'13-15 contacts.

2003; Cepeda *et al.,* 2005). Various morphological definitions of the ictal discharges from an epileptogenic tuber have been described; these include:
– a tuber producing ictal discharges or frequent (>50% of an epoch) interictal discharges (Koh *et al.,* 2000; Jansen *et al.,* 2005);
– a tuber producing continuous or periodic sharp waves on an attenuated background providing the 'pacemaker activity' out of which a seizure onset occurs (Mohamed *et al.,* 2012; Kannan *et al.,* 2016);
– and fast ripples localised to the epileptogenic tuber (Okanishi *et al.,* 2014; Fujiwara *et al.,* 2016)
However, despite using invasive EEG recording, identification of these rhythms can remain difficult. This is because different ictal rhythms can be present simultaneously and rapidly propagate to tubers in distinct

locations (Kannan *et al.,* 2016). Our SEEG data show interictal discharges of the 'seizure-generating' tuber and the 'subclinical' tuber can be indistinguishable morphologically. Our case emphasises the need for careful correlation of ictal clinical manifestation with spatiotemporal organisation of the ictal epileptic discharges to identify the primary epileptogenic tuber. Our patient showed an ictal EEG onset pattern of LVFA associated with DC-shift and supports the findings of other studies that have shown ictal fast activity as a biomarker of epileptogenicity (Di Giacomo *et al.,* 2019). Other factors unique to TSC that make delineation of the epileptogenic zone challenging include focal seizures in TSC that may demonstrate inter-tuberal activation causing ictal discharges to propagate rapidly to other tubers. Some studies have suggested that tubers showing intra-ictal tuber activation should also be resected (Kannan *et al.,* 2016). In our case, we have shown that an electrographic seizure can remain very localised to a tuber at the E' electrode without propagation and remains subclinical. We decided to spare removal of E' even though electrographic seizure discharges started at E' and activated the Y,S network and triggering his clinical seizures only occurred when he was weaned off AEDs. We suggest, as demonstrated by the SEEG analysis, that all his clinical seizures originated from the Y,S network, which defined the region as the primary epileptogenic zone.

FDG-PET can reveal cortical tubers, including smaller ones that are not easily visualised on MRI. Although it is not possible to distinguish between epileptogenic and non-epileptogenic tubers based on the extent and severity of FDG-PET hypometabolism (Rintahaka and Chugani, 1997), preliminary studies combining quantitative analysis of FDG-PET with MRI and diffusion-tensor imaging (DTI) suggested larger volumes of FDG-PET hypometabolism relative to MRI tuber size, and higher DTI apparent diffusion coefficients in the subtuber white matter showed promise for detecting epileptogenic tubers (Cahndra *et al.,* 2006).

Successful epilepsy surgery is possible in intractable focal epilepsy patients with multiple bilateral tubers. A strong preimplantation hypothesis, based on careful analysis of seizure semiology and all non-invasive investigations, is crucial. In some patients, repeating the VEEG study or performing an early ictal SPECT could provide additional information to localize the epileptogenic zone or generate an implantation strategy and improve outcome (Muniz, 2010; Ahnlide, 2007; Barba *et al*., 2007; von Oertzen, 2011). Our case shows the potential important role of SEEG when evaluating selected TSC cases with multiple bilateral potential epileptogenic tubers. Our patient remains classified as Engel Class 1A with complete seizure freedom, two years after epilepsy surgical resection. □

Legend for video sequences

Video sequences 1, 2

A seizure with typical aura followed by stiffening of the jaw with axial tonicity and neck extending forward. The patient was fully aware during the seizure and able to obey commands but post-ictally had some dysarthria.

Video sequence 3

A seizure showing progression of a typical seizure to a right facial clonic seizure.

Key words for video research on www.epilepticdisorders.com

Phenomenology: axial tonic seizure
Localisation: perisylvian epilepsy
Syndrome: genetic, structural
Aetiology: tuberous sclerosis complex

Supplementary data.
Summary didactic slides are available at www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

References

Ahnlide JA, Rosen I, Linden-Mickelsson TP, Kallen K. Does SISCOM contribute to favorable seizure outcome after epilepsy surgery? *Epilepsia* 2007; 48: 579-88.

Barba C, Di Giuda D, Policicchio D, Bruno I, Papacci F, Colicchio G. Correlation between provoked ictal SPECT and depth recordings in adult drug-resistant epilepsy patients. *Epilepsia* 2007; 48(2): 278-85.

Cepeda C, Hurst RS, Flores-Hernandez J, *et al*. Morphological and electrophysiological characterisation of abnormal cell types in pediatric cortical dysplasia. *J Neurosci Res* 2003; 72: 472-86.

Cepeda C, Andre VM, Vinters HV, Levine MS, Mathern GW. Are cytomegalic neurons and balloon cells generators of epileptic activity in pediatric cortical dysplasia? *Epilepsia* 2005; 46(5): 82-8.

Chandra PS, Salamon N, Huang J, *et al*. FDG-PET/MRI coregistration and diffusion-tensor imaging distinguish epileptogenic tubers and cortex in patients with tuberous sclerosis complex: a preliminary report. *Epilepsia* 2006; 47(9): 1543-9.

Chu-Shore CJ, Major P, Camposano S, *et al*. The natural history of epilepsy in tuberous sclerosis complex. *Epilepsia* 2010; 51: 1236-41.

Curatolo P. Mechanistic target of rapamycin (mTOR) in tuberous sclerosis complex-associated epilepsy. *Pediatr Neurol* 2015; 52: 281-9.

Di Giacomo R, Uribe-San-Martin R, Mai R, *et al*. Stereo-EEG ictal/interictal patterns and underlying pathologies. *Seizure* 2019; 72: 54-60.

Fallah A, Guyatt GH, Snead III OC, *et al*. Predictors of seizure outcomes in children with tuberous sclerosis complex and intractable epilepsy undergoing resective epilepsy surgery: an individual participant data meta-analysis. *PLoS One* 2013; 8: e53566.

Fallah A, Rodgers SD, Weil AG, *et al*. Resective epilepsy surgery for tuberous sclerosis in children: determining predictors of seizure outcomes in a multicentre retrospective cohort study. *Neurosurgery* 2015; 77: 517-24.

Feliciano DM, Lin TV, Hartman NW, *et al*. A circuitry and biochemical basis for tuberous sclerosis symptoms: from epilepsy to neurocognitive deficits. *Int J Dev Neurosi* 2013; 31: 667-78.

Fujiwara H, Leach JL, Greiner HM, *et al*. Resection of ictal high frequency oscillations is associated with favourable surgical outcome in pediatric drug resistant epilepsy secondary to tuberous sclerosis complex. *Epilepsy Res* 2016; 126: 90-7.

Jansen FE, van Huffelen AC, Bourex-Swart M, van Nieuwenhuizen O. Consistent localisation of interictal epileptiform activity on EEGs on patients with tuberous sclerosis complex. *Epilepsia* 2005; 46: 415-9.

Jansen FE, van Huffelen AC, Algra A, van Nieuwenhuizen O. Epilepsy surgery in tuberous sclerosis: a systematic review. *Epilepsia* 2007; 48: 1477-84.

Jeong A, Wong M. Systemic disease manifestations associated with epilepsy in tuberous sclerosis complex. *Epilepsia* 2016; 57: 1443-9.

Kannan L, Vogrin S, Bailey C, Maixner W, Harvey AS. Centre of epileptogenic tubers generate and propagate seizures in tuberous sclerosis. *Brain* 2016; 139: 2653-67.

Koh S, Jayakar P, Dunoyer C, *et al*. Epilepsy surgery in children with tuberous sclerosis complex: presurgical evaluation and outcome. *Epilepsia* 2000; 41: 1206-13.

Krueger DA. Management of CNS-related disease manifestations in patients with tuberous sclerosis complex. *Curr Treat Options Neurol* 2013; 15: 618-33.

Mohamed AR, Bailey CA, Freeman JL, Maixner W, Jackson GD, Harvey AS. Intrinsic epileptogenicity of cortical tubers revealed by intracranial EEG monitoring. *Neurology* 2012; 79: 2249-57.

Muniz J, Benbadis SR. Repeating video/EEG monitoring: why and with what results? *Epilepsy Behav* 2010; 18: 472-3.

Neal A, Ostrowsky-Coste K, Jung J, *et al*. Epileptogenicity in tuberous sclerosis complex: a stereoelectroencephalographic study. *Epilepsia* 2020; 61: 81-95.

Okanishi T, Akiyama T, Tanaka S, *et al*. Interictal high frequency oscillations correlating with seizure outcome in patients with widespread epileptic networks in tuberous sclerosis complex. *Epilepsia* 2014; 55: 1602-10.

Rintahaka PJ, Chugani HT. Clinical role of positron emission tomography in children with tuberous sclerosis complex. *J Child Neurol* 1997; 12: 42-52.

von Oertzen TJ, Mormann F, Urbach H, *et al*. Prospective use of subtraction ictal SPECT coregistered to MRI (SISCOM) in presurgical evaluation of epilepsy. *Epilepsia* 2011; 52(12): 2239-48.

Weiner HL, Carlson C, Ridgway EB, *et al*. Epilepsy surgery in young children with tuberous sclerosis: results of a novel approach. *Pediatrics* 2006; 117: 1494-502.

Wong M. Mechanisms of epileptogenesis in tuberous sclerosis complex and related malformations of cortical development with abnormal glioneuronal proliferation. *Epilepsia* 2008; 49: 8-21.

TEST YOURSELF

(1) Are tuberous sclerosis patients with focal epilepsy and multiple tubers suitable candidates for epilepsy surgery?

(2) Should all tubers with frequent interictal discharges and electrographic seizures be removed to achieve seizure freedom?

(3) In patients with seizures arising either within or in close proximity to eloquent cortex, what procedures could be performed to achieve optimal seizure outcome with minimal neurological deficits?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".