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Associations between electroencephalographic and magnetic resonance imaging findings in tuberous sclerosis complex

Anne Gallagher[a,b,1], **Catherine J. Chu-Shore**[a,b,1], **Maria A. Montenegro**[a,b], **Philippe Major**[a,b], **Daniel J. Costello**[a,b], **David A. Lyczkowski**[a], **David Muzykewicz**[a], **Colin Doherty**[c], **Elizabeth A. Thiele**[a,b,*]

[a] *Carol and James Herscot Center for Tuberous Sclerosis Complex, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA*
[b] *Harvard Medical School, Boston, MA, USA*
[c] *Trinity College, School of Medicine, St James' Hospital, UK*

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Summary Nearly 90% of patients with tuberous sclerosis complex (TSC) develop epilepsy; however the mechanisms of epileptogenesis remain unclear. Some cortical tubers are thought to be epileptogenic while others are not. This study aimed to evaluate whether tuber burden, size or type seen on magnetic resonance imaging (MRI) co-registers with interictal epileptiform discharges on electroencephalogram (EEG). EEG and MRI data from 69 patients with TSC were reviewed by dividing the cerebrum into four quadrants. Quadrants containing greatest tuber burden, largest tuber, calcified tubers, cyst-like tubers, and no tubers were identified on MRI. For EEG analysis, spikes and sharp waves were counted and averaged to a value per minute, and each quadrant was assigned a score. MRI and EEG findings were compared in each patient. The presence of a cyst-like tuber in a quadrant correlated with a higher incidence of epileptiform activity in the same quadrant ($p = 0.002$). This finding supports the notion that cyst-like cortical tubers may contribute to the more severe epilepsy profile seen in TSC patients with these lesions. Quadrants containing greatest tuber burden, largest tubers, and calcified tubers were not predictive of regional interictal epileptiform activity. Furthermore, quadrants without any apparent tuber co-registered with interictal epileptiform discharges in two patients, suggesting a multifactorial component of epileptogenicity in TSC.

* Corresponding author at: Carol and James Herscot Center for Tuberous Sclerosis Complex, 175 Cambridge Street, Suite 340, Boston, MA 02114, United States. Tel.: +1 617 726 6540; fax: +1 617 726 0230.
E-mail address: ethiele@partners.org (E.A. Thiele).
[1] These authors contributed equally to the preparation of this manuscript.

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Introduction

Tuberous sclerosis complex (TSC) is a dominantly inherited genetic disorder affecting multiple organ systems. The disease is caused by a mutation in one of the two tumor-suppressor genes, *TSC1* on 9q34 and *TSC2* on 16p13.3, which code for the proteins hamartin and tuberin, respectively (van Slegtenhorst et al., 1997; European Chromosome 16 Tuberous Sclerosis Consortium, 1993). Although the phenotype is variable, hamartomas most commonly develop in brain, skin, kidneys, heart, liver, retinas, and lungs. The neurological manifestations of TSC are typically of greatest concern, and include cognitive impairment in approximately 50%, and epilepsy in approximately 80—90% of the patients (Crino et al., 2006). Epilepsy in TSC is intractable to pharmacotherapy in two-thirds of patients, and has significant impact on cognitive outcome and quality of life (Goh et al., 2005).

Brain involvement in TSC can include cortical and subcortical tubers, subependymal nodules, and subependymal giant-cell tumors (SGCTs) (DiMario, 2004; Roach et al., 1998). Cortical tubers are areas of disrupted cortical architecture composed of a heterogeneous mixture of glial cells and poorly differentiated neuroastrocytes, some of which develop into cytomegalic giant cells in an irregular and dysplastic matrix (Curatolo and Verdecchia, 2003). Tubers vary widely in size, location and appearance (Ridler et al., 2004), and some but not others appear to be epileptic foci (Crino et al., 2006; Doherty et al., 2005; Schwartz et al., 2007). It is well known that tuber resection, guided by multimodal identification of seizure foci can provide excellent seizure control (Koh et al., 2000; Jansen et al., 2007). Neuroimaging studies using positron emission tomography suggested a variability of epileptogenicity among tubers and surrounding cortex by an increased uptake of α-[^{11}C]methyl-L-tryptophan by epileptogenic compared to nonepileptogenic cortical tubers in TSC patients (Asano et al., 2000; Chugani et al., 1998; Fedi et al., 2003). However, intracranial electrocorticography suggests that tubers themselves may be electrically silent while adjacent disrupted tissue is epileptogenic (Major et al., 2009). Some factors such as calcification, size, and tuber burden may have an effect on local epileptic activity (Holmes et al., 2007). We have recently shown a strong association between cyst-like tubers and a more aggressive seizure phenotype (Chu-Shore et al., 2009). However, the relationship between tuber morphology and associated cortical neurophysiology remains unclear (Thiele, 2004; Holmes et al., 2007). The aim of the present study is to determine whether the presence and frequency of epileptiform discharges co-registers with tuber location and with some tuber characteristics, such as size, burden, and the presence of calcification and cyst-like components.

Methods

Participants

Clinical records, MRI images, and EEG recordings of all patients who met clinical diagnostic criteria for TSC (Roach et al., 1998) seen at the Carol and James Herscot Center for Tuberous Sclerosis Complex at Massachusetts General Hospital from January 2002 to June 2005 were reviewed. 166 patients were identified. Patients were included if they had at least one EEG recording and one brain MRI scan (including axial three-dimensional spoiled gradient-recalled with steady-state acquisition [3D-SPGR], fast spin-echo [FSE] axial T2, and axial fluid attenuation inversion recovery [FLAIR] sequences) available for review. Of 75 patients with available imaging and EEG data, 6 patients with evidence of a large SGCT associated with hydrocephalus or mass effect into the adjacent parenchyma on neuroimaging were excluded. 69 patients were included, resulting in 276 brain quadrants for analysis.

EEG recordings and analyses

EEG data from routine 30 to 60 min EEGs or long-term monitoring (LTM) recordings (1—3 days) were reviewed by a neurophysiologist blinded to MRI data using a 16-channel referential montage using the standard 10—20 electrode placement system, with the reference electrode placed over the second cervical vertebra. For patients who had multiple EEG recordings, data acquired closest in time to an available MRI were selected for review. Moreover, if a patient had a LTM EEG and a routine EEG, the latter was selected for review. For routine EEGs, the entire recording was reviewed. For patients with LTM recordings, 30 min of awake-state EEG and 30 min of drowsiness and sleep recorded during the first day of recording prior to reduction in medication were reviewed.

For EEG analysis, the brain was divided into four quadrants (left anterior, right anterior, left posterior and right posterior). The anterior quadrants included the F, Fp, and C electrodes and the anterior temporal electrodes T3 and T4. The posterior quadrants included the P and O electrodes and the posterior temporal electrodes T5 and T6. Interictal epileptiform activity, including either spikes (duration < 70 ms) or sharp waves (duration > 70 ms), was manually identified by quadrant. EEG tracings were repeatedly reviewed focusing on one quadrant at a time switching between montages to avoid inclusion of epileptiform discharges elicited in a different region. When an epileptiform discharge appeared to lie on a midline (z) electrode, laterality was assigned to the quadrant where the discharge was of highest amplitude. The distribution of epileptiform discharges was allocated based on interpretation of the non-cephalic referential montage. When interictal discharges were broadly distributed, only unequivocal epileptiform discharges were noted. Low amplitude reflections (less than 50% of the maximal spike/sharp wave amplitude) of broadly distributed epileptiform discharges were not included. Distinct populations of discharges within the same quadrant were not distinguished. Where possible, a distinction was made based on configuration, morphology and distribution between separate populations of epileptiform discharges arising from different quadrants and broadly distributed discharges arising from a single focus.

For discharge frequency quantification, within each quadrant, epileptiform discharges were counted and averaged to a value per minute. The highest number of interictal discharges in 1 min was noted and a score was allocated to each quadrant using the following semi-quantitative rating scale: 1 = maximum of $\leq$2 epileptiform discharges in 1 min; 2 = maximum of 3—6 epileptiform discharges in 1 min; 3 = maximum of >6 epileptiform discharges in 1 min. If no epileptiform discharges were observed in a particular region, a score of 0 was assigned.

Since ictal data were not available for most patients, only interictal epileptic discharges were reviewed. Non-epileptiform abnormalities were not analyzed.

MRI acquisition and image analyses

MRI scans were acquired on a 1.5 T GE Signa system (GE Signa, Madison, WI). Sequences included axial 3D-SPGR (TR 32, TE 8, NEX 1, flip

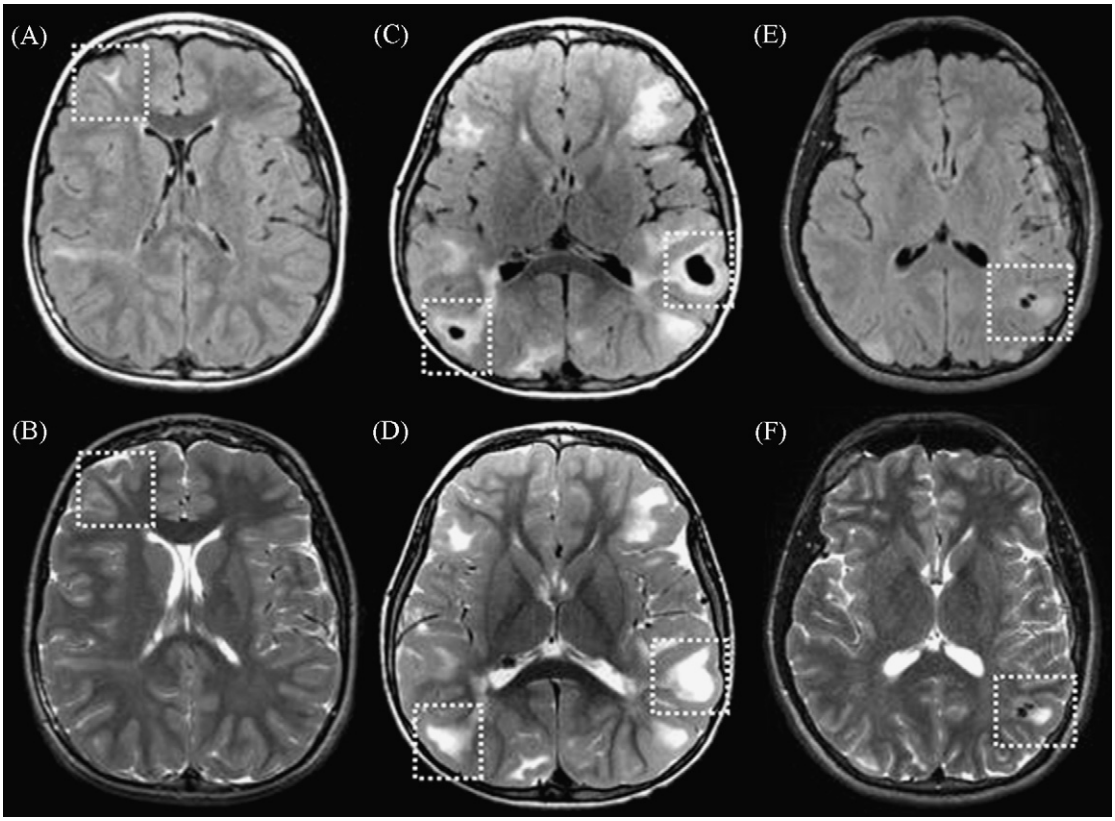

Fig. 1 Axial MRIs showing in dotted boxes a cortical tuber on (A) FLAIR, and (B) T2 FSE sequences; cyst-like tubers on (C) FLAIR, and (D) T2 FSE images; and a calcified tuber on (C) FLAIR, and (D) T2 FSE sequences.

angle 25, matrix 256 × 192, 1.2 mm slice thickness, 0 mm gap), FSE axial T2 (TR 6000, TE 102, NEX 2, ETL 12, matrix 320 × 256, 3 mm slice thickness, 0 mm gap), and axial FLAIR (TR 10,000, TE 126, TI 2200, NEX 0.5, matrix 256 × 192, 3 mm slice thickness, 0 mm gap).

Images were reviewed by two neurologists with experience in neuroimaging and TSC and blinded to EEG data. Discordant findings were reviewed together in order to establish a consensus. For patients who had multiple MRI scans including the three required sequences (axial 3D-SPGR, axial T2, and axial FLAIR), the scan acquired closer in time to the EEG was chosen.

For MRI analysis, the cerebrum was divided into four quadrants (left anterior, right anterior, left posterior and right posterior), which grossly co-register with EEG quadrants above. The plane containing the central fissure defined the left—right boundary and the plane containing the central sulcus defined the anterior—posterior boundary. Each brain quadrant was analyzed for the presence or absence of at least one cortical tuber, cyst-like tuber, and calcified tuber by visual inspection of all MRI sequences for each patient. Diagnostic criteria for cortical tuber identification were in accordance with prior reports (Braffman et al., 1992; Doherty et al., 2005; Jurkiewicz et al., 2006; Pinto Gama et al., 2006). Tubers were defined as areas of cortical gray matter distortion with decreased or isointense subcortical signal intensity on 3D-SPGR images and increased signal intensity on T2 FSE and FLAIR sequences. Cyst-like tubers were identified as hypointense on 3D-SPGR, hyperintense on T2 FSE, and heterogeneous on FLAIR characterized by a hypointense central region surrounded by a hyperintense rim. Calcified tubers were seen as hypointense on 3D-SPGR, hypointense on T2 FSE, and heterogeneous on FLAIR characterized by a hypointense central region surrounded by a hyperintense rim. Fig. 1 shows an example of all types of lesion. The quadrant containing the greatest tuber burden (proportion of abnormal cortex compared to normal-appearing parenchyma) and the quadrant with the largest single tuber were also identified for each patient using all MRI sequences. Multiple quadrants were chosen when no difference in burden or tuber size could be visually identified. Size of tubers and tuber burden were visually estimated by following the lesions through several subsequent MRI images. No tuber count technique or quantitative measurements of single tuber or tuber burden were performed.

Statistical analyses

Chi-square analyses were performed to evaluate for an association between brain quadrants with greatest tuber burden, biggest tuber, cyst-like tuber, and calcified tuber and co-registered regional interictal epileptiform discharges. Among quadrants with interictal epileptiform activity on EEG ($N = 106$ brain quadrants), we evaluated the relationship between the frequency of interictal epileptiform discharges and each of the above MRI findings. For this analysis, independent Student's *t*-tests were performed using Statistic Package for the Social Sciences Version 15.0.0.1 (SPSS, Inc., Chicago, IL). All reported *p* values used two-tailed tests of significance with α set at 0.05.

Results

Participants

Of 166 patients with TSC seen at the Herscot Center from January 2002 to June 2005, 69 patients were included allowing for the analysis of 276 brain quadrants. The patients included 38 men and 31 women aged between 0.4 and

Table 1 Co-registration of interictal epileptiform discharges and tuber characteristics by cerebral quadrant.

Co-registered findings	Fraction	(%)	*P* value
1. Quadrants with interictal epileptiform discharges among quadrants containing at least one tuber	106/267	(39.7%)	[a]
Quadrants with interictal epileptiform discharges among quadrants with no tubers	2/9	(22.2%)	
2. Quadrants with interictal epileptiform discharges among quadrants containing cyst-like tubers	26/44	(59.1%)	0.002[*]
Quadrants with interictal epileptiform discharges among quadrants containing no cyst-like tubers	80/232	(34.5%)	
3. Quadrants with interictal epileptiform discharges among quadrants containing calcified tubers	11/21	(52.4%)	0.171
Quadrants with interictal epileptiform discharges among quadrants containing no calcified tuber	95/255	(37.3%)	
4. Quadrants with interictal epileptiform discharges among quadrants containing the largest tuber	31/77	(40.3%)	0.694
Quadrants with interictal epileptiform discharges among quadrants without the largest tuber	75/199	(37.7%)	
5. Quadrants with interictal epileptiform discharges among quadrants containing the greatest tuber burden	33/81	(40.7%)	0.607
Quadrants with interictal epileptiform discharges among quadrants without the greatest tuber burden	73/195	(37.4%)	

[a] Comparison not performed due to small sample size.
[*] Statistically significant association using chi-square analyses.

39 years (mean = 10.2; median = 7; standard deviation = 8.8). Thirty-four out of 69 patients (49%) had a history of infantile spasms. Sixty-five patients (94%) had a history of seizures. Neuropsychological evaluation was available for 54 patients, and IQ or developmental quotient was below the normal range in 31 of them (57%). 49 patients had a routine EEG and 20 patients had long-term monitoring. Twelve patients had undergone epilepsy surgery prior to the date of the EEG recordings that have been analyzed in this study. EEG data acquired before surgery were not available for review.

MRI and EEG findings

EEG was recorded during wakefulness in 61 patients, drowsiness in 61 patients, and sleep in 58 patients. Data recorded in all three states were available in 52 out of 69 patients (75%). 23 out of 69 patients (33%) showed no interictal epileptiform activity including the four patients with no history of epilepsy and 13 patients who were seizure free at the time of the EEG.

MRI data showed that all patients included in this study had at least one cortical tuber in at least one quadrant. Moreover, 64 patients out of 69 (93%) had at least one tuber in each of the 4 quadrants. Of the 69 individuals, 22 (32%) had at least one cyst-like tuber, whereas 17 (25%) had at least one calcified tuber.

The temporal interval between MRI acquisition and EEG evaluation ranged from 0 to 33 months (mean = 4.4; median = 7). Spatial associations between EEG data and MRI findings were investigated. Although interictal epileptiform discharges were usually recorded over quadrants with tubers, two patients presented epileptiform discharges in quadrants without any apparent tuber.

Presence of cyst-like tubers was associated with interictal epileptiform activity in the same brain quadrant ($p = 0.002$). There was no statistical association between regional interictal epileptiform activity and the presence of calcified tubers ($p = 0.171$), the greatest tuber burden ($p = 0.607$), and the largest single tuber ($p = 0.694$) [see Table 1]. Furthermore, among cerebral quadrant with interictal epileptiform activity, there was no association between interictal epileptiform discharge frequency and the presence of a cyst-like tuber ($t(104) = -0.501$; $p = 0.619$), a calcified tuber ($t(104) = 0.566$; $p = 0.582$), the greatest tuber burden ($t(104) = -0.098$; $p = 0.922$), and the largest single tuber ($t(104) = -0.064$; $p = 0.949$) in the corresponding brain quadrant. Comparison between quadrants with and without tuber and interictal epileptiform discharges was not performed because of the small sample size of quadrant without tuber.

Discussion

Seizures in TSC are generally thought to originate either from tubers or from the adjacent normal-appearing cortex (Holmes et al., 2007; Major et al., 2009). It is therefore unsurprising that, in the present study, most epileptic discharges were recorded on EEG over cerebral quadrants that showed cortical tubers on MRI. However, two patients presented epileptic discharges in quadrants without apparent

tuber. This interesting finding has been previously reported by Cusmai et al. (1990) who found EEG epileptic foci in cerebral regions that did not contain tubers in 4 of their 26 patients (15%). The association between epileptic discharges and normal-appearing cortex may reflect limited resolution for identifying tubers using standard neuroimaging techniques (Ridler et al., 2001) or suggest a physiological disruption in these patients on an ultrastructural or biochemical level (Wang et al., 2007). In further studies, the use of more powerful scanners, such 3 or 7 T magnets could reveal MRI abnormalities that are not visible on images acquired on 1.5 T scanners.

Some factors, such cyst-like changes, calcification, edema, and vascular abnormalities, have been reported to have an effect on the epileptic activity (Holmes et al., 2007). We have recently shown a strong association between the presence of a cyst-like tuber on MRI and a more aggressive seizure phenotype in patients with TSC (Chu-Shore et al., 2009). Neuropathological evaluation of a cyst-like tuber suggested a chronic process of substantial subcortical white matter loss in addition to the typical pathological features seen in classic tubers (Chu-Shore and Thiele, 2009). Here we have found that cyst-like cortical tubers co-localize with the presence of epileptiform activity on EEG, suggesting a spatial relationship between these altered morphological and neurophysiological processes. It remains unknown whether the cyst-like changes associated with some tubers contribute to or result from locally altered neurophysiologic activity, however we have previously observed that cyst-like changes on MRI may precede the appearance of epileptiform activity on EEG (Chu-Shore and Thiele, 2009).

The significance of the frequency of interictal epileptiform discharges is unclear, though some have suggested that frequency may correlate with cognitive performance, seizure frequency and duration of epilepsy (Aarts et al., 1984; Janszky et al., 2005). In this study, focal imaging findings were not predictive of the frequency of interictal epileptiform discharges among patients with known epileptiform activity.

Previous studies reported that the localization of the largest MRI identified tuber would be less accurate in identifying epileptogenic regions compared to localization of large tubers exhibiting calcified component (Koh et al., 2000) or to some neuroimaging characteristics such increased volume of FDG-PET hypometabolism, and increased ADC values (Chandra et al., 2006). In the present study, we found no association between quadrants containing greatest tuber burden, largest tuber, and calcified tubers and interictal epileptiform abnormalities. Thus, the relationship between epileptogenicity and some tubers characteristics such tuber size and the presence of calcification component remain unclear.

Several methodological and technical considerations can be reported. First, as Cusmai et al. (1990), we decided to visually estimate the size of the tubers and tuber burden in contrast to the tuber count method. The latter has been reported to undercount tubers as well as underestimate the impact of large cerebral lesions and overestimate the effect of small tubers. The qualitative aspect of the measures used in this study can be raised as a methodological drawback, and a quantitative technique, such as tuber segmentation on brain MRI which was recently described by Jansen et al. (2008), would allow a quantitative measure of the greatest tuber burden and tuber/brain proportion and could be used in further studies. However, since the aim of this study was to investigate the spatial relationship between EEG abnormalities and MRI findings in TSC, we consider our method appropriate.

Another methodological characteristic of the present study refers to statistical analyses that have been conducted on cerebral quadrants, instead of smaller regions such cerebral lobes. This technique allows a more precise definition of anatomical boundaries and therefore a better co-registration of EEG and MRI modalities. However, such large subdivisions may tend to overestimate the association between tubers and epileptiform abnormalities.

Finally, EEG has a lower spatial resolution than MRI, but remains the more commonly used noninvasive technique to detect and localize the epileptic focus. Although it is not always accessible, the use of high-density EEG and, corroboration of EEG findings with invasive electrocorticography would allow a more precise localization of the epileptiform discharges.

Conclusions

We have demonstrated that although most epileptiform discharges are recorded over quadrants containing cortical tubers, some patients with TSC present epileptiform activity in cerebral areas without cortical tubers. Thus, epileptogenicity in TSC seems to be multifactorial, perhaps involving some combination of aberrant neurochemical and ultrastructural changes in radiographically normal-appearing cortex. Quadrants containing cyst-like tubers are more likely to be associated with epileptiform discharges than other quadrants. However, the greatest tuber burden, the largest cortical tuber, and the presence of calcified tuber do not appear to predict the presence of epileptiform discharges. Accessibility to higher resolution neuroimaging and EEG techniques, as well as comparison with intraoperative electrocorticography would help clarify how tubers, perituberal cortex, and apparently normal cortex contribute to epileptogenicity in patients with TSC.

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