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Localization of the epileptogenic tuber with electric source imaging in patients with tuberous sclerosis

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Summary
Purpose: Patients with tuberous sclerosis complex (TSC) often suffer from medically refractory epilepsy. Despite the multifocality of the disease, resection of the most epileptogenic tuber can lead to major improvement of seizure control. Therefore, non-invasive imaging methods are needed for detecting epileptogenic sources. We assessed the utility of electric source imaging (ESI) in the presurgical work-up of TSC patients and its combination with Positron Emission Tomography (PET) and ictal/interictal Single Photon Emission Computed Tomography (SISCOM).
Methods: Thirteen patients underwent high density ESI (8/13) and/or low density ESI (13/13). We investigated the concordance between ESI, PET, SISCOM and the resection area in the 11 operated patients (nine seizure-free).
Results: High resolution ESI was partially or completely concordant with the resected area in 5/5 seizure free patients. Low resolution ESI was partially or completely concordant in 7/9 seizure free patients. PET and SPECT were concordant (partially or completely) in 8/9 and 6/9 cases, respectively. We found multifocal ESI sources in 2/9 seizure free patients, marked

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multifocal PET hypometabolism in 3/9 and multifocal SISCOM in 4/9. The region of concordant ESI and PET accurately predicted the dominant epileptogenic source in 6/9 patients. The same was true for concordant ESI and SISCOM in 4/9 patients, whereas the coregistration of only PET and SISCOM was insufficient in 3/9 successfully operated cases. The combination of all three imaging modalities could successfully identify the resection area in all but one patient with a favorable post-operation outcome.

Conclusion: ESI is an important tool for the pre-surgical evaluation of TSC patients. It complements PET and SPECT results and can improve the management of candidates for surgery when integrated with electro-clinical information.

Introduction

Tuberous sclerosis complex (TSC) is a rare multi-organic genetic disorder with a typical early-life symptomatic onset that is inherited in an autosomal dominant pattern; however, spontaneous mutations are frequent (van Slegtenhorst et al., 1998). The most common presenting symptom is epileptic seizures, which often commence in infancy under the form of spasms or later in childhood as focal seizures (Devlin et al., 2006). These seizures are often pharmaco-resistant since they are triggered by multiple epileptogenic foci that are either activated simultaneously or are shifting between them (Ohmori et al., 1998).

Epilepsy management is crucial for proper cognitive development and the overall quality of life, including that of the caregivers. Epilepsy onset at a young age correlates with a decline in adaptive functioning; whereas developmental delay is associated with the amount of antiepileptic drugs and interictal epileptic discharges (IEDs) (van Eeghen et al., 2012). Despite the multifocal presentation of epilepsy in TSC, these patients could benefit from surgery, since one tuber is usually more epileptogenic than others (Asano et al., 2000). Surgical treatment with a satisfactory seizure outcome improves mental and behavioral development (Karenfort et al., 2002; Jansen et al., 2007a). A meta-analysis of 177 surgically treated TSC patients demonstrated a favorable post-operative outcome, with a 57% seizure free rate (mean follow up 3.7 years, range: 0.1—47 years) and 18% experiencing >90% seizure frequency reduction (mean follow up 4.2 years, range: 0.5—20 years) (Jansen et al., 2007b). Another independent recent meta-analysis reported similar results (Fallah et al., 2013). In addition, multiple or bilateral epileptogenic foci are not necessarily a contraindication to epilepsy surgery and do not preclude a favorable post-surgical outcome (Weiner et al., 2006).

Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) and ictal/interictal Single Photon Emission Computed Tomography (SPECT) are useful tools to localize epileptic activity. However, their use in TSC is often characterized by multifocal abnormalities that may preclude their utility (Rintahaka and Chugani, 1997; Asano et al., 2000; Aboian et al., 2011; Koh et al., 1999). Electric source imaging (ESI) is a technique that estimates the localization of the cortical generators of epileptic activity recorded with scalp electroencephalogram (EEG) (Michel et al., 2004b; Plummer et al., 2008; Vulliemoz et al., 2010; Sperli et al., 2006). A large prospective study has recently highlighted the utility of ESI for the pre-surgical evaluation of epilepsy, particularly when using a high number of electrodes (Brodbeck et al., 2011). In the present study, we examined the utility of ESI as a source imaging tool in the specific group of TSC patients. We aimed to identify the dominant epileptogenic sources with ESI and to combine these results with ^{18}F-Fluorodeoxyglucose PET (FDG-PET) and perfusion SPECT. Moreover, for those patients receiving surgical treatment, we co-registered the source maxima identified by ESI, ictal/interictal SPECT, and PET with the post-operative MRI (post-op MRI).

Methods

Patients

We included 13 patients (age range: 1—32 years, median: 7 years) from our database diagnosed with TSC who underwent pre-surgical evaluation for pharmaco-resistant epilepsy by means of long-term video-EEG including the study of seizure onset symptomatology, ESI imaging, neuropsychological tests, ictal/interictal SPECT and PET. Ten patients received surgical treatment; one patient was operated twice, and we considered each intervention as a separate case, leading to a total of 11 surgically treated cases. Eight patients were additionally evaluated with high resolution ESI, among which 6 of them were operated. The resection zone was determined through a multidisciplinary approach and by taking into account the prementioned presurgical evaluation modalities and additionally the data from the intracranial recordings available in 5 patients. The post-surgical outcome was favorable (Engel class I or II) in all but one patient who was eventually re-operated without success. Mean follow up was 2.17 years (range 1—7 years). Table 1 shows the patients' clinical details.

Electroencephalogram recordings

Conventional long-term video-EEG recording was performed on all patients with a standard clinical EEG setup of 31 electrodes (10/10 system, reference FCz). Impedances were kept below 10 kΩ, the sampling rate was 256 Hz. Ictal scalp recordings were obtained in all patients and their origin, as well as the localization of the IEDs are shown in Table 1. Eight of 13 patients had multifocal IED and 4/12 had multifocal seizures. In one patient, the ictal pattern was obscured by motion artifacts.

High-resolution EEG was also recorded in 8 patients at the end of the long-term EEG monitoring (Table 2). In the other patients, lack of equipment or logistical issues