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Subtle pathological changes in neocortical temporal lobe epilepsy☆

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ABSTRACT

This was a prospective observational study to correlate the clinical symptoms, electrophysiology, imaging, and surgical pathology of patients with temporal lobe epilepsy (TLE) without hippocampal sclerosis. We selected consecutive patients with TLE and normal MRI undergoing temporal lobe resection between April and September 2015. Clinical features, imaging, and functional data were reviewed. Intracranial monitoring and language mapping were performed when it was required according to our team recommendation. Prior to hippocampal resection, intraoperative electrocorticography was performed using depth electrodes in the amygdala and the hippocampus. The resected hippocampus was sent for pathological analysis. Results: Five patients with diagnosis with non-lesional TLE were included. We did not find distinctive clinical features that could be a characteristic of non-lesional TLE. The mean follow-up was 13.2 months (11–15 months); 80% of patients achieved Engel Class I outcome. There was no distinctive electrographic findings in these patients. Histopathologic analysis was negative for mesial temporal sclerosis. A second blinded independent neuropathologist with expertise in epilepsy found ILAE type I focal cortical dysplasia in the parahippocampal gyrus in all patients. A third independent neuropathologist reported changes in layer 2 with larger pyramidal neurons in 4 cases but concluded that none of these cases met the diagnostic criteria of FCD.

Subtle pathological changes could be associated with a parahippocampal epileptic zone and should be investigated in patients with MRI-negative TLE. This study also highlights the lack of interobserver reliability for the diagnosis of mild cortical dysplasia. Finally, selective amygdalo-hippocampectomy or laser ablation of the hippocampus may not control intractable epilepsy in this specific population.

1. Introduction

Temporal lobe epilepsy (TLE) is the most common form of epilepsy of focal origin. It is commonly associated with hippocampal sclerosis (HS) and other pathologies such as tumors and malformations of cortical development (MCD). In a study of 243 patients with TLE who underwent surgery published in 2009, only 5% had negative pathology [1]. These patients may have poor localization of their seizure focus and may be considered nonsurgical candidates. Lesional neocortical TLE (nTLE) cases are often not reported in the literature because they may be less likely to be admitted for video-EEG monitoring [2]

Nonetheless, nTLE has started has started to be a recognized as a different entity from mesial TLE, in which histopathological analysis reveals low grade or no sclerosis of hippocampal resections. In a small case series published in 2009, MCD was found in the parahippocampal gyrus of patients with only subtle but distinctive abnormalities on MRI [3]. In MRI-negative patients, the localization is more challenging, usually requiring intracranial monitoring for localization of the epileptogenic lesion. From the clinical presentation, including semiology and scalp EEG, TLE with HS and nTLE are difficult to differentiate. A study in 2010 compared the clinical features of patients with parahippocampal inferior temporal lesions and HS, finding that hypermotor and bilateral motor symptoms were more common in patients with lesions in the posterior parahippocampal gyrus group compared to patients with HS [4]. Another study reported typical TLE seizure semiology with preservation of memory and normal MRI; interestingly, hippocampal pathology reported in few of these patients was normal and MCD was found in the lateral temporal cortex [5]. Although TLE with HS is a thoroughly studied entity, the incidence, characterization, etiology, and pathophysiology of nTLE is not well documented in the literature. This study aimed to further investigate and analyze nTLE, including clinical symptoms, scalp EEG, intra-operative EEG,

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high-resolution MRI, surgical histopathology, and surgical outcome of patients with medically-intractable nTLE who underwent anterior temporal lobectomy.

2. Materials and methods

2.1. Subjects and patient selection

We selected consecutive patients evaluated at the University of South Alabama Comprehensive Epilepsy Program between April and September 2015. We targeted patients with medically-intractable epilepsy localized to either left or right temporal lobe by noninvasive methods and normal hippocampus on 3-T MRI, using T1, FLAIR, and T2 sequences with thin coronal cuts through the hippocampus. Diagnosis of TLE was reached through the normal epilepsy workup, including: seizure semiology, scalp EEG, brain PET, 3 T-MRI, EEG source imaging, Wada test, and neuropsychological evaluation. We only included patients with TLE without evidence of HS (nTLE) on 3T-MRI images who were scheduled for epilepsy surgery.

2.2. MRI protocol

Magnetic resonance imaging scanning was performed using a Philips Ingenia 3.0 Tesla MRI scanner (Philips Medical Systems, Best, The Netherlands) with a 16-channel head coil. The scans were performed using the non-contrast standard clinical seizure protocol to acquire coronal FLAIR, T1, and T2 weighted sequences to screen for possible underlying mesial temporal sclerosis or focal cortical dysplasias. Coronal FLAIR TE was 110, TR was 9000, TI was 2600, slice thickness was 3.0 mm, interslice gap 1.0 mm, matrix size 252 × 239, and the FOV = 200 mm. Coronal T2w turbo spin echo (TSE) sequence, echo time (TE) = 82, repetition time (TR) = 3325, TSE factor 21, single echo, slice thickness 2.5 mm without interslice gap, flip angle = 90° with 120° refocussing pulse, matrix size 400 × 301, and the FOV = 200 mm. For the coronal T1w 3D (TFE SENSE) sequence, TFE factor was 180, TE was 4.6, TR was 9.9, slice thickness was 0.8 mm without interslice gap, 0.8 mm isotropic resolution, matrix size 300 × 180, multishot single echo technique, flip angle = 8°, and the FOV = 240 mm Axial T1. Turbo spin echo T2w sequences as well as axial FLAIR images were also obtained.

2.3. Electroencephalographic evaluation and source analysis

The scalp EEG was recorded with a 10–20 lead placement, using a Neuvo amplifier (Compumedics), which acquires raw data at 10 kHz and then applies a software second-order Infinite Impulse Response (IIR) Butterworth low-pass filter at 40% of the sampling frequency, recorded at a sampling rate of 500 Hz. Ictal patterns were reviewed using a common average montage and standard filter setting (HFF 70 Hz, LFF 1 Hz, notch filter 60 Hz). Analysis of EEG source of interictal and ictal activity was performed with Curry 7 software. The EEG source was obtained using a moving dipole model and SLORETA, co-registered with the patient's own MRI.

2.4. Intracranial electroencephalographic recording

Patients who required intracranial monitoring for confirmation of the seizure-onset localization, as determined in our epilepsy surgery conference, were implanted with intracranial electrodes using subdural grids and/or strips covering the cortical areas that were suspected as potential epileptic zones based on non-invasive data. The seizure onset zone was determined by the presence of an electrographic seizure, which was defined as a sustained rhythmic change in the EEG background at a frequency of >2 Hz, not explained by level of arousal or artifacts, and clearly distinguished from background EEG and interictal activity, and correlated with the patient's typical clinical behavior [6].

The intracranial EEG recording setting was similar to the scalp EEG with the exception of the use of a wider filter band of 1–200 Hz to visualize high-frequency oscillations (HFO) associated within the ictal zone. The HFO power map distribution was displayed onto an image of three-dimensional (3D) reconstructed brain images using the patient's own co-registered MRI and computed tomography (CT) with the implanted electrodes (CURRY 7). Language mapping using cortical electrical stimulation through the implanted electrodes was performed in patients with language dominance ipsilateral to the epileptic zone (as determined by earlier WADA testing).

2.5. Surgery and electrocorticography (ECoG)

After intracranial electroencephalographic (ECoG) analysis was performed and the anatomic and cortical epileptogenic zone was identified, patients were scheduled for surgical resection (in all cases an anterior temporal lobectomy). The extent of the resection was planned pre-operatively based on localization of the ictal zones according to the available functional and imaging data. First, the lateral neocortex of the temporal lobe was resected, the temporal horn of the lateral ventricle was entered, and the hippocampus and amygdala were identified. Before any resection of the mesial temporal lobe structures, all patients underwent electrocorticography analysis using depth electrode placement under direct visualization and stereotactic placement in the amygdala, anterior, middle and posterior hippocampus, to assess the presence of ictal and interictal epileptic activity. The patients were anesthetized with sevoflurane during the recording at the lowest level of anesthesia possible to allow epileptic activity but avoiding movement or consciousness. After ECoG data were recorded for at least 20 min or until a seizure pattern was observed, the patient underwent hippocampal resection as posterior as the tectal plate.

2.6. Postoperative follow-up

The presence of seizure recurrence was closely monitored in both neurology and neurosurgery outpatient clinics, and surgical success was evaluated using Engel's classification. All antiepileptic drugs (AEDs) were continued in the post-operative period.

2.7. Histopathological analysis procedures

Each surgical specimen was comprised of multiple sections of the amygdala, hippocampus, and parahippocampal cortex which roughly correlated to the intra-operative depth electrode placement and recordings. The division of the tissue by sectors around the depth electrode recording areas was exclusive for the study patients. The specimens were fixed with 10% neutral buffered formalin. They received routine processing by our university pathology lab and then were sent for analysis to a well-known outside neuropathologist. All the histopathology samples without evidence of mesial temporal sclerosis were sent to an independent neuropathologist with extensive experience in analyzing epilepsy specimens since there is poor reliability for diagnosis of mild FCD among neuropathologists with low experience in epilepsy [7,8]. A typical sample slide of each case was sent to a third independent neuropathologist for review. Neither outside neuropathologist had access to clinical data — including MRI, electroencephalographic findings, or surgical outcome.

3. Results

3.1. Demographic characteristics

The study included five consecutive patients with TLE without evidence of mesial temporal lesions on MRI. Only subjects scheduled for epilepsy surgery between April and September 2015 were included in the study. Three patients with TLE operated within this period were