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Temporal pole abnormalities in temporal lobe epilepsy with hippocampal sclerosis: Clinical significance and seizure outcome after surgery

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ABSTRACT

Purpose: To assess the clinical significance of temporal pole abnormalities (temporopolar blurring, TB, and temporopolar atrophy, TA) in patients with temporal lobe epilepsy (TLE) and hippocampal sclerosis (HS) with a long post-surgical follow-up.
Methods: We studied 60 consecutive patients with TLE–HS and 1.5 preoperative MRI scans who underwent surgery and were followed up for at least 5 years (mean follow-up 7.3 years). Based on findings of pre-surgical MRI, patients were classified according to the presence of TB or TA. Groups were compared on demographic, clinical, neuropsychological data, and seizure outcome.
Results: TB was found in 37 (62%) patients, while TA was found in 35 (58%) patients, always ipsilateral to HS, with a high degree of overlap (83%) between TB and TA ($p < 0.001$). Patients with TB did not differ from those without TB with regard to history of febrile convulsions, GTCSs, age of epilepsy onset, side of surgery, seizure frequency, seizure outcome, and neuropsychological outcome. On the other hand, they were significantly older, had a longer duration of epilepsy, and displayed lower preoperative scores on several neuropsychological tests. Similar findings were observed for TA. Multivariate analysis corroborated the association between temporopolar abnormalities and age at onset, age at surgery (for TB only), and lower preoperative scores on some neuropsychological tests.
Conclusions: Temporopolar abnormalities are frequent in patients with TLE–HS. Our data support the hypothesis that TB and TA are caused by seizure-related damages. These abnormalities did not influence seizure outcome, even after a long-term post-surgical follow-up.

1. Introduction

The clinical entity of temporal lobe epilepsy (TLE) may be considered fairly well defined [1] and hippocampal sclerosis (HS) plays a leading role in the genesis of seizures in most patients with TLE [1,2]. Surgery is currently accepted as an effective and safe therapeutic approach when seizures are not adequately responsive to medical treatment [2]. It is well established that short-term seizure outcome after epilepsy surgery for TLE–HS is favourable****, with a high percentages of seizure freedom, ranging from 70 to 90% [3–5]. Although less good, data coming from 5 years-follow-up studies are fairly similar, showing a seizure freedom rate of 50–75% in different series [6–8]. However, recent data suggest that the long-term seizure outcome after surgery is less encouraging, with many studies reporting seizure freedom rates of 40–55% at 10 years [6,9,10]. In the largest and longest prospective study of epilepsy surgery, in which the cohort consisted mainly of TLE patients who underwent temporal resections, the probability of being entirely seizure free after 5 and 10 years was 52% and 47%, respectively [11]. A few other studies found better results, with sustained long-term seizure

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freedom after surgery of 71–72% [7,8]. Moreover, late seizure recurrence is not uncommon [6,9] and little is known about its risk factors, prognosis, and management. Therefore, correct prediction of postoperative seizure outcome is of prime importance in selecting patients with drug-resistant TLE. Several papers reported that HS is frequently associated with other temporal lobe abnormalities beyond the hippocampus [12–14], which suggests, in some cases, a more widespread anatomical substrate for the epileptogenesis. Several authors reported that ipsilateral temporal atrophy (TA) with temporopolar grey/white matter abnormalities (also called 'temporopolar blurring', TB), are often found in brain MRI images of many patients with TLE–HS [15–20]. TB is described as hyperintensity of signal in the white matter together with loss of grey/white matter demarcation on T2-weighted and fluid attenuation inversion recovery (FLAIR) sequences [15–20]. Although TB may be a neuroradiological marker of a focal cortical dysplasia [21], a recent study, using high-field (7 T) MRI combined with light and electron microscopy of surgical specimens resected from nine drug-refractory patients with TLE and HS, provided evidence that TB is caused by the degeneration of fibre bundles, suggesting a slowly evolving chronic degeneration with the redistribution of the remaining fibres [22].

The clinical significance of TB has not yet been fully elucidated. On one hand, some studies reported a significantly higher success rate of surgery in patients with TLE–HS with TB than in patients without this abnormality [15,23], or no TB-related differences in preoperative and postoperative scores on neuropsychological tests [24]. On the other hand, several studies showed that the proportion of seizure-free patients was the same in those with and without TB [22,24], or that patients with TB showed lower scores on neuropsychological tests than those without TB [22]. Moreover, no study, to our knowledge, investigated the clinical significance and prognostic value of TA in terms of seizure outcome after surgery. With the aim to shed further light on these issues, we investigated the clinical and neuropsychological characteristics of patients with TLE–HS with temporopolar abnormalities who had surgery due to drug-resistant epilepsy, and we examined the association between these abnormalities and long-term postoperative seizure outcome.

2. Methods

2.1. Patient population

The study was performed at the Epilepsy Surgery Center of the Neuromed-IRCCS neurological institute, Pozzilli, IS, Italy. We retrospectively included all patients affected by drug-resistant TLE and radiological evidence of hippocampal sclerosis who undergone resective surgery (anterior temporal lobectomy, ATL) between January 2004 and December 2008, had histologically proven HS, and were followed up for at least 5 years. All these patients had 1.5 T MRI scans available for revision. The patients operated on before January 2004 could not be included in the study because their MRI images were not available for revision. In order to work on a homogeneous sample, we did not include in the present study the small number of patients operated on after December 2008 who had at least 5 years of follow-up, because from January 2009 onwards all MRI scans were performed by using a 3 T MRI magnet. Before surgery, all patients underwent a non-invasive diagnostic work-up described in detail elsewhere [4,25], including, synthetically: (1) detailed medical history and neurological examination; (2) continuous long-term intensive, diurnal and nocturnal Video-EEG monitoring (Telefactor Corp, Conshohoken, PA, USA); (3) neuropsychological evaluation; (4) psychiatric evaluation; and (5) 1.5 T brain MRI scan. For each case, the decision for ATL was made after discussion in a multidisciplinary case conference, with the aim of evaluating the concordance between electro-clinical and anatomical data.

2.2. Histology

The removed brain tissue was submitted for pathological examination in all cases. The resected temporal pole and hippocampus were fixed in 4% paraformaldehyde buffered solution. After 24 h, the temporal pole and neocortex were cut into 4–6 coronal sections and post-fixed in the same solution for 4–5 days. Alternate sections were embedded in paraffin. For routine histological examination, 7-μm thick sections were cut and stained with haematoxylin and eosin and/or luxol fast blue. Additional serial sections were processed for immunohistochemistry using antibodies against glial fibrillary acidic protein (GFAP; 1:200 Roche), non-phosphorylated neurofilaments (Roche, prediluted), and neuron-specific nuclearprotein (NeuN; 1:500; Millipore). The immunoistochemistry was performed automatically by Benchmark XT (Roche). Quantification of the degree of gliosis and possible inflammatory changes in the white matter of all the samples was performed. The white matter neuronal density was estimated by counting NeuN-positive neurons in the depth of the white matter. Finally, the hippocampus was kept separate and processed for neuropathological examination to confirm the presence of HS, defined as a loss of neuronal cells of 30% or more in the CA1 region of hippocampal formation with or without neuronal loss or gliosis involving other mesial temporal structures [26].

Patients with histological evidence of HS associated with other gross lesions (tumors, Taylor's focal dysplasia, vascular malformation and scar, etc.) were excluded from the study.

2.3. Preoperative 1.5 T magnetic resonance imaging

All of the MRI studies were performed using 1.5 T instrument (G.E. HDXt). The MRI protocol included: transverse spin-echo T2-weighted images of the entire brain (repetition time: 5100 ms, echo time: 102 ms, number of averages: 2, matrix: 450 × 256, field of view: 240 mm, slice thickness: 4 mm); coronal and transverse spin-echo FLAIR images (repetition time: 11,000 ms, echo time: 160 ms, inversion time: 2250 ms, number of averages: 2, matrix: 224 × 320, field of view: 240 mm, thickness: 4 mm) and coronal fast spin-echo inversion recovery T1-weighted images (repetition time: 4000 ms, echo time: 50 ms, inversion time: 288 ms, number of averages: 1, matrix: 224 × 256, field of view: 240 mm, thickness: 4 mm). SPGR isovoxel (flip angle: 13; echo time: MIN FULL, inversion time: 450 ms, number of averages: 1, matrix: 320 × 320, field of view: 256 mm, thickness: 1.6 mm). The transversal and coronal sections were acquired parallel and perpendicular, respectively, to the axis of the hyppocampal formation. No contrast medium was used.

The exams were visually and qualitatively reviewed independently by two experienced observers (A.D.A and G.G.) who were masked to the patient's clinical data and postoperative seizure outcome. In absence of agreement, MRI images were reviewed and discussed until consensus was reached. HS was qualitatively diagnosed by means of the comparative visual detection of atrophy and loss of definition of the internal structures of the hyppocampal formation and increased signal intensity in the T2-weighted images. According to Garbelli et al. [22] and Naves et al. [24], the criteria for TB definition were increased signal intensity in the white matter together with loss of grey/white matter demarcation of the temporal pole on coronal T2-weighted and FLAIR images (Fig. 1). Also, the presence of TB atrophy was also assessed. The boundaries of the temporal pole on MRI were defined according to Coste et al. [18] and Naves et al. [24], with the posterior limit