Epilepsy Research 127 (2016) 50–54

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Clinical and electrophysiological findings in mesial temporal lobe epilepsy with hippocampal sclerosis, based on the recent histopathological classifications

F. Irsel Tezer (M.D. Ph.D.) (Professor)[a,*,1], Farid Xasiyev (M.D.)[a,1], Figen Soylemezoglu (M.D.) (Professor)[b], Burcak Bilginer (M.D.) (Assoc. Professor)[c], Kader Karli Oguz (M.D.) (Professor)[d], Serap Saygi (M.D.) (Professor)[a]

[a] Hacettepe University, Faculty of Medicine, Dept. of Neurology, Ankara, Turkey
[b] Hacettepe University, Faculty of Medicine, Dept. of Pathology, Ankara, Turkey
[c] Hacettepe University, Faculty of Medicine, Dept. of Neurosurgery, Ankara, Turkey
[d] Hacettepe University, Faculty of Medicine, Dept. of Radiology, Ankara, Turkey

ARTICLE INFO

Article history:
Received 17 May 2016
Received in revised form 4 July 2016
Accepted 14 August 2016
Available online 16 August 2016

Keywords:
Epilepsy
Seizure
Hippocampal sclerosis
Temporal lobe epilepsy
Pathology
Types of hippocampal sclerosis

ABSTRACT

Background: Hippocampal sclerosis (HS) is a common pathology in MTLE, patients may show different surgical outcomes and clinical features. The 2013 ILAE classification subdivides HS into 3 types (HS type 1: severe neuronal loss and gliosis predominantly in CA1 and CA4 regions; – HS type 2: CA1 predominant; HS type 3: CA4 predominant) and includes "gliosis only, as no-HS". The association of clinical and electrophysiological findings with different HS types has not been reported previously in detail.
Methods: 48 patients who had undergone temporal lobectomy with amygdalohippocampectomy due to mesial TLE-HS between February 2014 and February 2016 were included. The patients were divided into five groups: patients with HS ILAE type 1, HS ILAE type 2, HS ILAE type 3, FCD type IIIa, or gliosis/no HS. The correlation between HS ILAE types and clinical/EEG findings in patients with MTLE due to HS was investigated.
Results: Of the 48 patients 30 were male. In 23 patients, the resection was on the left side (48%). Three patients had only gliosis, 25 patients had HS ILAE type 1, 7 had HS ILAE type 2, and 4 had HS ILAE type 3. Nine of the 48 patients had cortical lamination abnormalities in the temporal lobe associated with HS (FCD type IIIa). All patients were seizure free for early follow up. There was no association between type of HS in terms of duration of epilepsy, onset age of epilepsy, lateralized or localized semiological findings, or interictal/ictal EEG findings. Family history of epilepsy or SGTCSs were statistically more frequent in patients with types 2 and 3 HS and status epilepticus was more frequent in patients with HS-FCD type IIIa.
Conclusion: The patients with HS types 2 and 3 have more frequent SGTCS or status epilepticus as well as increased family history of epilepsy. These findings can be helpful in understanding the epileptogenicity-prognoses of HS.

1. Introduction

Approximately one third of patients with epilepsy have drug-resistant epilepsy, and epilepsy surgery is the treatment of choice for refractory epilepsy. Mesial temporal lobe epilepsy (MTLE) pathologically characterized by hippocampal sclerosis (HS) is the prototype for surgically remediable epileptic syndromes. Tailored resection strategies, including selective amygdalohippocampectomies and standard temporal lobectomies with amygdalohippocampectomy, are established. Up to 80% of patients with MTLE-HS will become seizure-free after surgery but this will decrease to approximately 60% in long-term follow-up (Janszky et al., 2005; Sperling et al., 1996; Tezer et al., 2008; Wiebe et al., 2001). Although HS is a common pathology in MTLE, patients may show different surgical outcomes. Possible causes of these include the presence of different pathological types of HS besides other

* Corresponding author at: Hacettepe University Faculty of Medicine, Department of Neurology, Sihhiye 06100 Ankara, Turkey.
E-mail addresses: irseltezer@yahoo.com.tr, irsel@hacettepe.edu.tr (F.I. Tezer).
[1] These authors are equally contributed in this manuscript.

http://dx.doi.org/10.1016/j.eplepsyres.2016.08.012
0920-1211/

reasons such as incomplete resection and the presence of dual pathology (Barba et al., 2015; Lopez-Gonzalez et al., 2012; Wyler et al., 1989).

The hippocampus includes the CA1–CA4 subfields, dentate gyrus, fimbria, subiculum, parasubiculum, and entorhinal cortex. Neuron loss can be detected within different hippocampal subfields (CA1–CA4, dentate gyrus); therefore, neuropathological investigations indicate that HS is not a single entity. The International League Against Epilepsy (ILAE) has reported a new classification of HS (Blumcke et al., 2013). The 2013 ILAE classification subdivides HS into three types (typical – type 1 and atypical – types 2 and 3) and includes a term "gliosis only, no-HS" groups, based on the histological patterns of subfield neuronal loss and gliosis (Blumcke et al., 2013). Different patterns of HS may be a manifestation of distinct pathways of epileptogenesis leading to different clinical findings and outcomes. To support that, there is evidence suggesting atypical HS may be predictive of poorer outcome (Blumcke et al., 2007; de Lanerolle et al., 2003). Furthermore, later ages of onset of habitual seizures have been reported in patients having atypical HS (Thom et al., 2010; de Lanerolle et al., 2003). In addition, a history of febrile seizures was less common in those atypical groups (Blumcke et al., 2007). Therefore, the extent of hippocampal damage or type of HS and clinical features related to these pathologies can provide predictive information for surgical outcome. The association of clinical and electrophysiological findings with different HS types has not been reported previously. In this report, our aim was to assess the correlation between HS ILAE types and clinical/EEG findings in patients with MTLE due to HS.

2. Methods

Patients who had undergone temporal lobectomy with amygdalohippocampectomy due to mesial TLE-HS between February 2014 and February 2016 were included. The diagnosis of mesial TLE-HS was discussed in a multidisciplinary case conference including neurologists, neurosurgeons, neuroradiologists, neuropathologist, and neuropsychologists. The clinical and electrographic features of seizures, magnetic resonance imaging (MRI) findings and positron emission tomography (PET), and ictal or interictal single photon emission computerized tomography (SPECT) when available were evaluated. Additionally all patients underwent a preoperative evaluation including neuropsychological testing. Patients' seizure types and epilepsy syndromes were determined according to the ILAE classifications (ILAE, 1981).

Each patient was monitored for 3–10 days in a video-EEG monitoring unit using a 32-channel EEG system (Grass-Telefactor). T1 and T2 scalp electrodes were placed according to the standard 10–20 system. There was no standard procedure for withdrawal of the antiepileptic drug during monitoring. The location and frequency of interictal epileptiform discharges were assessed by visual analysis of interictal EEG samples. Unilateral interictal epileptiform discharges were defined if at least 70% of interictal discharges appeared over one temporal lobe. Seizures were defined by an EEG pattern that represents a clear change from background frequencies and evolves in frequency and amplitude. Remontaging assists in distinguishing epileptic seizures from artifacts.

MRIs were obtained using either 1.5 or 3.0 T scanners and the MRI protocol included coronal 3D T1-weighted (W) gradient echo imaging (MPRAGE) obtained parallel to the brainstem, and fluid-attenuated inversion recovery (FLAIR) and T2-W turbo spin-echo and T1-W inversion recovery images obtained perpendicular to the hippocampi in addition to routine brain imaging. Hippocampal atrophy/sclerosis was defined by the presence of abnormal hippocampal MRI signals, including hippocampal atrophy and temporal horn dilatation on coronal T1-weighted images and increased signal intensity within the hippocampus on T2-weighted images and fluid attenuated inversion recovery (FLAIR) images.

Patients in whom HS was present on imaging and/or temporal lobe abnormality was revealed on PET-SPECT underwent an operation when interictal and ictal EEG findings were concordant with these. Patients with extratemporal and temporal dual pathologies (i.e. tumors, Rasmussen's encephalitis, dysplastic findings in the extratemporal area) were not included. Our standard procedure for treating MTLE was anterior temporal lobectomy with removal of the medial structures including the amygdala, hippocampus, and parahippocampal gyrus. We performed standard anterior temporal lobe resection in all patients. We resected 3.5 cm of the lateral temporal lobe from the anterior temporal tip for the dominant hemisphere and 5 cm for the nondominant one. Patients who underwent epilepsy surgery were re-examined every 6 months subsequently, with assessment of seizures. The type of AEDs may change or the dosage may decrease after 1 year.

A retrospective chart review was performed to extract patients' demographic details and potential preoperative risk factors. The following variables were investigated: sex; age at epilepsy onset (onset of habitual seizures, excluding febrile seizures); presence of family history; history of natal or perinatal injury; history of febrile seizures, trauma, and status epilepticus; history of secondarily generalized tonic–clonic seizures (SGTCS); age at operation; duration of epilepsy; propagation of ictal EEG changes to the contralateral side; presence of bilateral interictal EEG findings (>30% of epileptiform discharges on the contralateral temporal lobe); and presence of lateralized/localized semiological findings (dystonic hand posturing, figure 4 sign, forced head and eye deviation, postictal aphasia) during video-EEG monitoring.

The latest available seizure outcomes of patients were described in detail by using the classification system of Engel's classes I–IV (Engel et al., 1993). Patients were categorized as seizure-free (Engel's class I) or not (Engel's classes II–IV). Moreover, the patients who were completely free from both seizures and auras at the last available outcome (Engel's class IA) were determined. Postoperative data were obtained from patient interviews during the postoperative outpatient visits or by telephone interviews.

En bloc surgical resections were orientated and cut perpendicular to the ependymal surface. 4–7 μm thick sections were obtained from formalin fixed paraffin embedded blocks and stained for appropriate histochemical (H&E, cresyl violet) and immunohistochemical (NeuN, phosphorylated and nonphosphorylated neurofilament protein, synaptophysin, GFAP) stains. The patients were divided into five groups according to pathological findings as follows: patients with HS ILAE type 1, HS ILAE type 2, HS ILAE type 3, FCD type IIIa, or gliosis/no HS (Blumcke et al., 2011, 2013).

The hippocampal specimens of these patients were collected for pathological investigation. The hippocampal subfields and dentate gyrus were examined for neuronal loss and gliosis. The ILAE classification system was employed to identify the HS types in our study (Blumcke et al., 2013): HS ILAE type 1 = classical hippocampal sclerosis with pronounced neuronal cell loss in all hippocampal subfields (in particular CA1 >80% cell loss; CA4 >40% neuronal cell loss); HS ILAE type 2 = hippocampal sclerosis with predominant neuronal cell loss in CA1 (>78%) and less severe neuronal cell loss in all other subfields (<25%); and HS ILAE type 3 = hippocampal sclerosis with predominant neuronal cell loss in CA4 (>45%). Hippocampal specimens with gliosis only (no-HS) and cortical lamination abnormalities in the temporal lobe associated with HS, called FCD IIIa, were also reported (Blumcke et al., 2011).

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 17.0). Categorical variables were examined by the chi-square test and Fisher's exact test as appropriate. The Mann–Whitney *U* test, Kruskal–Wallis test, and Pearson's