Seizure 25 (2015) 141–146

Contents lists available at ScienceDirect

Seizure

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

Long-term seizure outcome for international consensus classification of hippocampal sclerosis: A survival analysis

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ARTICLE INFO

Article history:
Received 21 June 2014
Received in revised form 5 September 2014
Accepted 8 October 2014

Keywords:
Mesial temporal lobe epilepsy
Hippocampal sclerosis
International consensus classification
Long-term seizure outcome

ABSTRACT

Purpose: Surgery is regarded as a common treatment option for patients with mesial temporal lobe epilepsy (MTLE) as a result of hippocampal sclerosis (HS). However, approximately one-third of patients with intractable epilepsy did not become seizure-free after tailored resection strategies. It would be compelling to identify predictive factors of postoperative seizure outcomes. Our aim was to assess the correlation between HS classification and long-term postoperative seizure outcome in patients with MTLE due to HS.

Methods: To investigate HS classification, semi-quantitative analysis and immunohistochemical staining of neuronal nuclei (NeuN) were performed on 100 postoperative hippocampal specimens. All patients had a 1–7 year postoperative follow-up. The postoperative seizure outcome was evaluated using International League Against Epilepsy (ILAE) outcome classification.

Results: Three types of HS were recognized. The highest incidence of initial precipitating injury (IPI) was noted in the HS ILAE type 1 group (53.1%). The most favorable long-term seizure outcome was also noted in the HS ILAE type 1 group. The shortest epilepsy duration was recorded in the HS ILAE type 2 group (mean epilepsy duration = 6.64 ± 5.83 years). The completely seizure free rate of patients in all groups declined with an increase in time.

Conclusions: Our study for the first time demonstrated a significant correlation between HS ILAE types and long-term postoperative seizure outcome in patients with MTLE due to HS. Therefore, HS ILAE types have predictive value in long-term seizure outcome following epilepsy surgery.

1. Introduction

Patients with epilepsy respond differently to medications. Approximately 20–30% of patients with epilepsy have drug-resistant epilepsy, and epilepsy surgery is the treatment of choice for the refractory epilepsy. However, after a follow-up of 5 years, the number of patients remaining seizure-free begins to decline,[1–4] consistent with our recent results.[4] In addition, not all patients with similar seizure types and epileptogenic focus localizations become seizure-free after surgery. This indicates that the mechanisms underlying poor postoperative outcomes are unclear. Therefore, it would be compelling to identify predictive factors of postoperative seizure outcomes.

The hippocampus is a highly sophisticated structure, including CA1–CA4 subfields, dentate gyrus (DG), fimbria, subiculum (SUB), parasubiculum, and entorhinal cortex (ERC).[5] Hippocampal sclerosis (HS) is a pathological hallmark of mesial temporal lobe epilepsy (MTLE). MTLE due to HS are more frequently drug resistant. Tailored resection strategies, including selective amygdalohippocampectomies and standard temporal lobectomies, are established treatment modalities. The postoperative seizure freedom rate in patients with MTLE due to HS is approximately 56–91%.[1,3,6,7] Neuropathological investigations indicate that HS is

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http://dx.doi.org/10.1016/j.seizure.2014.10.006
1059-1311/

not a single entity. Neuron loss can be detected within different hippocampal subfields (CA1–CA4, DG). Thus, HS can be separated into distinct pathological subgroups according to its subtle differences.[8,9] International League Against Epilepsy (ILAE) has reported a new classification of HS.[10] Different types of HS may be associated with different clinical phenotypes and postoperative outcomes.[11,12] However, the association of long-term postoperative seizure outcomes with different HS types has never been reported. Our aim was to assess the correlation between HS ILAE types and postoperative seizure outcome in a cohort of 100 patients with MTLE due to HS.

2. Methods

2.1. Study population

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Harbin Medical University, and the participants gave informed consent. For the minors/children enrolled in our study, we obtained the written informed consent from the next of kin, caretakers, or guardians on behalf of them. A total of 100 patients were included in the Department of Neurosurgery at the First Affiliated Hospital of Harbin Medical University between 2006 and 2013. All cases were considered to have refractory epilepsy, after at least two first-line anti-epileptic drugs failed. The preoperative evaluation included cognitive and neuropsychological testing, electroencephalogram (EEG), video-electroencephalographic monitoring, high-resolution hippocampal 1.5 T or 3 T magnetic resonance imaging (MRI), and fluoro-deoxy glucose positron emission tomography combined with computed tomography (FDG-PET/CT). The mesio-temporal foci were diagnosed with EEG and 24 h video-electroencephalographic monitoring. 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, could be shown in some patients. However, the other patients indistinctively showed abnormal signals on their hippocampal MRI. Indeed, it is difficult to distinguish the slight atrophy of a single hippocampal subfield on MRI by naked eyes. According to the abnormal spike wave and sharp wave in mesio-temporal lobe on EEG and 24 h-video EEG (VEEG), we performed FDG-PET/CT in patients who had indistinctive abnormal signals on their hippocampal MRI. The low metabolism of mesio-temporal lobe could be detected. The senior author, who has had nearly 15 years of experience in the surgical treatment of intractable epilepsy, was responsible for identifying these findings and the criteria used for diagnosing HS. All patients underwent selective amygdalohippocampectomies or standard anterior temporal lobectomies with amygdalohippocampectomies by the senior author. During operation, cortical electroencephalogram (ECoG) and deep electrodes were used to further identify the abnormal electrical activity. The hippocampal specimens of these patients were collected for pathological and histological research. Postoperative data were obtained from patients' interviews during the postoperative outpatient visits or by telephone interviews at least once per year. The postoperative seizure outcome was evaluated using ILAE outcome classification[13] after 7-year follow-up. The clinical characteristics of patients were categorized (Table 1). The patients were divided into three groups according to their histological results. Seven hippocampal specimens served as controls. Three hippocampal control specimens were obtained from neurologically healthy autopsies and the written consents were given by the next of kin. The other control specimens were obtained from patients who were diagnosed with intracranial space-occupying lesions (tumors or cerebral cavernous malformations) next to the hippocampus and who had only one or two seizures. Hippocampectomies were performed in these patients to avoid postoperative secondary epilepsy. All the procedures were standardized in the framework of the study. The first author participated in all the procedures, and verified by the corresponding author.

Table 1
Demographic and clinical characteristics of 100 patients.

Demographic and clinical characteristics	Data
Mean age at surgery (means ± SD, (min–max) years)	27.72 ± 10.67 (2–61)
Gender (female/male) (*N* (%))	35 (35%)/65 (65%)
Epilepsy duration (means ± SD, (min–max) years)	13.31 ± 10.18 (0.42–43)
With IPI (*N* (%))	31 (31%)
EEG (abnormal *N* (%))	100 (100%)
24 h-VEEG (abnormal *N* (%))	100 (100%)
Hippocampal MRI (abnormal *N* (%))	82 (82%)
Head FDG-PET/CT (abnormal *N* (%))	23 (23%)
Intro-operation ECoG (abnormal *N* (%))	100 (100%)
Intro-operation deep electrodes (abnormal *N* (%))	100 (100%)
Side of operation (left/right) (*N* (%))	59 (59%)/41 (41%)
Bilateral abnormalities (*N* (%))	2 (2%)

SD: standard deviation, *N*: number of patients, IPI: initial precipitating injury, EEG: electroencephalogram, VEEG: video-EEG, FDG-PET/CT: fluoro-deoxy glucose positron emission tomography combined with computed tomography, and ECoG: cortical electroencephalogram.

2.2. Tissue preparation

Hippocampal specimens were dissected into 3-mm-thick slices along the long axis. All tissues were fixed with 10% formalin overnight, and then cut at 4 μm with a microtome (Leica). The sections were mounted onto charged slides, air-dried in an oven at 70 °C for 2 h, cleared in xylene, and deparaffinized in descending alcohol concentrations. The hippocampal pyramidal neurons and granule cells of the DG were immunostained for the neuronal core antigen NeuN. The staining was performed with the streptavidin-peroxidase method, and 3,3′-diaminobenzidine was added as a chromogen. Hematoxylin counterstaining was finally conducted.

2.3. The quantitative measurement method

The quantitative measurement of neuronal cell numbers was employed as previously described.[9] Neuronal cell bodies immunohistochemically stained (NeuN) could be clearly tagged on the computer screen. The neurons were manually counted separately within different hippocampal subfields with a microcomputer imaging system (Leica Application Suite, Version 4.3.0) coupled to a microscope (Leica DM 4000B). The number of neurons was calculated in 4 visual fields in CA4 region and in 10 visual fields in CA1 region at 200× objective magnification, representing 1.21 mm^2. The mean number of neurons/mm^2 was calculated, and the values were transformed into *z*-scores [z = (score − mean of the population)/standard deviation of the population]. The pathological features of neurons loss within CA1 and CA4 regions were categorized (Fig. 1 and Table 2).

2.4. The clinicopathological classification system for HS

The ILAE classification system was employed to identify the HS types in our study.[10] According to the semi-quantitative methods, 3 types of HS were classified. HS ILAE type 1 refers always to severe neuronal cell loss and gliosis predominantly in CA1 and CA4 regions, HS ILAE type 2 shows predominant neuronal cell loss and gliosis in CA1 region, HS ILAE type 3 demonstrates predominant neuronal cell loss and gliosis in CA4 region.