Epilepsy & Behavior 26 (2013) 67–70

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

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

Morphological variations of hippocampal formation in epilepsy: Image, clinical and electrophysiological data

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ARTICLE INFO

Article history:
Received 4 October 2012
Revised 12 October 2012
Accepted 15 October 2012
Available online 7 December 2012

Keywords:
Hippocampal formation
Hippocampal sclerosis
Malformation of cortical development
Magnetic resonance imaging
Morphological variations
Epilepsy

ABSTRACT

Morphological variations of hippocampal formation (MVHF) are observed in patients with epilepsy but also in asymptomatic individuals. The precise role of these findings in epilepsy is not yet fully understood. This study analyzes the hippocampal formation (HF) morphology of asymptomatic individuals (n = 30) and of patients with mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) (n = 68), patients with malformations of cortical development (MCD) (n = 34), or patients with pure morphological variations of hippocampal formation (pure MVHF) (n = 12). Main clinical and electrophysiological data of patients with MVHF were also analyzed. Morphological variations of hippocampal formation are more frequently observed in patients with MCD than in patients with MTLE-HS or in asymptomatic individuals. Patients with pure morphological variations of hippocampal formation showed higher incidence of extratemporal seizure onset. Refractoriness seems to be more associated with other abnormalities, like HS or MCD, than with the HF variation itself. Thus, although morphological HF abnormalities might play a role in epileptogenicity, they seem to contribute less to refractoriness.

1. Introduction

Temporal lobe epilepsy (TLE) is the most frequent focal epileptic syndrome in adults [1], and hippocampal sclerosis (HS) its most common pathological substrate [2]. Mesial temporal lobe epilepsy associated with hippocampal sclerosis (MTLE-HS) is a well-defined syndrome with seizures originating in the hippocampal formation (HF) and, occasionally, in the amygdala [3].

Some authors have also reported that variations in shape, orientation, and position of the HF can be observed in patients with malformations of cortical development (MCD), corpus callosum agenesis, congenital hydrocephaly, chromosomal disorders, or MTLE-HS [4–6]. Lehéricy et al. previously suggested that HF abnormalities might be the consequence of cortical developmental disorders in some patients [7]. This hypothesis was later reconsidered by other authors who observed that MVHF could be seen in patients with MTLE-HS, MCD, or even in healthy subjects [8–14]. However, the impact of these structural variations on clinical and neurophysiological aspects has been poorly explored.

The objective of the present study was to observe the HF morphology of healthy individuals, of patients with MTLE-HS, of patients with MCD, and of patients with morphological HF variation without any other structural signs (pure MVHF). We also analyzed clinical and neurophysiological findings in patients with MVHF in order to improve our understanding of epilepsy associated with this HF variation.

2. Methods

2.1. Patients

We analyzed the neuroimaging findings of 114 consecutive patients with MTLE-HS (n = 68), MCD (n = 34), or pure MVHF (n = 12), focusing on HF morphology. Data were also seen in a voluntary group of 30 healthy controls. From the selected group of patients with MVHF, we also analyzed the neurophysiological and clinical findings and compared them to those of patients with MTLE-HS. Patients and controls were selected at the Epilepsy Outpatient Clinic

Abbreviations: MVHF, morphological variations of hippocampal formation; HF, hippocampal formation; MTLE-HS, mesial temporal lobe epilepsy associated with hippocampal sclerosis; MCD, malformations of cortical development; PHFD, pure hippocampal formation dysmorphism; TLE, temporal lobe epilepsy; HS, hippocampal sclerosis; MRI, magnetic resonance imaging.

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http://dx.doi.org/10.1016/j.yebeh.2012.10.028

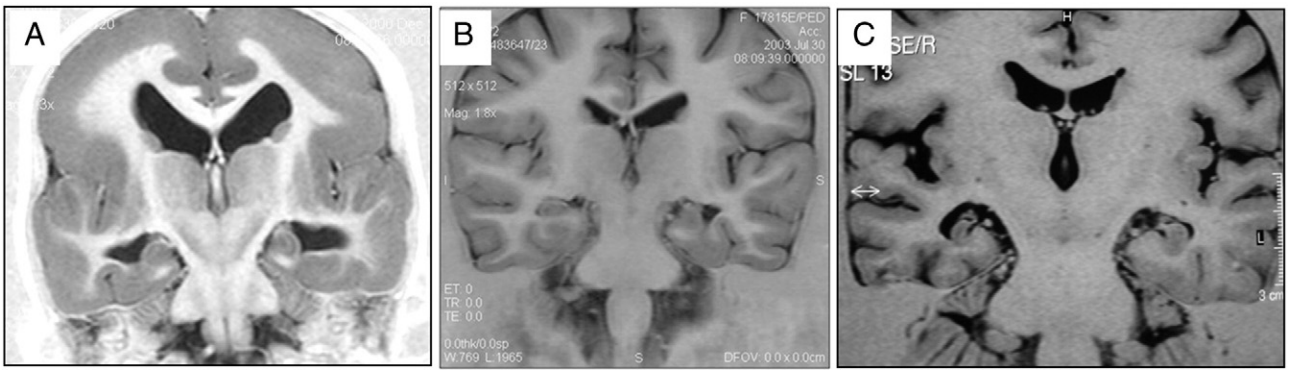

Fig. 1. Variations of HF morphology among different groups. A) Bilateral abnormalities of the hippocampal formations with globular shape, verticalization, and position, in the presence of malformation of cortical development — lissencephaly. B) The right side is normal, but there is left-sided abnormal hippocampal formation: a rounded, medially displaced left side of the hippocampus, a vertical collateral sulcus and an enlarged-appearing temporal horn. C) Bilateral abnormalities of the hippocampal formations with globular shape and verticalization, in the presence of a right hippocampus sclerosis.

of Hospital São Paulo, Universidade Federal de São Paulo. The study was approved by the Ethics Committee of our institution.

2.2. Neuroimaging data

All patients were scanned using 1.5-T MRI equipment (Gyroscan; Philips Medical System, Eindhoven, The Netherlands or Magneton Sonata; Siemens, Erlangen, Germany). Acquisition protocol included FLAIR, sagittal T1 and axial T2 sequences as well as coronal T2, FLAIR and IR sequences with slices perpendicular to the longest axis of the hippocampus. Images were independently analyzed by two neuroradiologists with expertise in epilepsy neuroimaging. Patients were defined as having MVHF when they presented at least one of the criteria previously suggested by Baulac et al. [8] and also used by Bernasconi et al. [10] — round or pyramidal in shape, in vertical orientation or medial positioning with respect to the temporal horn (Fig. 1). Patients were classified in four groups according to the etiology and the presence of MVHF: 1) MTLE-HS plus MVHF; 2) MCD plus MVHF; 3) pure MVHF; and 4) MTLE-HS without MVHF. Patients with MCD without MVHF were excluded from further analyses.

2.3. Clinical and neurophysiological data

Demographic and clinical data were obtained from hospital charts. Interictal and ictal EEG findings and seizure data were collected from video-EEG recordings, lasting from 12 to 120 h, with scalp plus sphenoidal electrodes.

2.4. Statistical analysis

Categorical variables were assessed by the chi-square test or Fisher's exact test. The magnitudes of associations were measured by the odds ratio with the respective confidence intervals (O.R., 95% CI). Mean differences of numerical variables were analyzed by ANOVA with Tukey's honestly significant difference as a *post hoc* test. All data were analyzed using SPSS, Windows® (SPSS Inc.) and GraphPad Instat®, Windows® (GraphPad Software Inc.). In order to avoid type I error due to the large number of comparisons, results were considered significant only if $p<0.01$.

3. Results

Table 1 shows the demographic data of the patients. Patients with MCD were significantly younger ($p<0.0001$) when compared to the other patients.

Variations of HF morphology among different groups are presented in Table 2. Variations of HF were observed in 30 (20.8%) of the 144 epilepsy patients. Of these, five were MTLE-HS patients (16.7% of the patients with MVHF and 7.4% of all MTLE-HS patients) and 13, MCD patients (43.3% of the patients with MVHF and 38.2% of all patients with MCD). The other 12 cases presented MVHF without any other structural abnormality (40% of all patients with MVHF). None of the 30 controls showed HF abnormalities. The frequency of each aspect of HF dysmorphism (shape, orientation or positioning) differed among groups. Morphological variations of hippocampal formation were significantly more frequent in the MCD group when compared to controls (Table 2).

When the side of MVHF was evaluated, we noted a trend to a higher frequency of abnormalities in the left when compared to the right temporal lobe, although this did not reach statistical significance. Regarding the five patients with MTLE-HS plus MVHF, one presented HF abnormalities ipsilateral to the side of HS, one presented HF abnormalities contralateral to the side of HS, and the remaining three patients had unilateral HS but bilateral HF abnormalities.

3.1. Clinical characteristics of patients with MVHF

Patients with all forms of MVHF (MTLE-HS plus MVHF, MCD plus MVHF, or pure MVHF) were compared to patients with MTLE-HS without MVHF. This later group of patients was chosen for comparison since MTLE-HS represents the most frequent epileptic syndrome in adults. Clinical data are presented in Table 3. Patients with MCD plus MVHF were younger, and their seizures started earlier. Twenty-one patients in the MTLE-HS without MVHF group (33.3%)

Table 1
Demographic data.

	Control (n = 30)	MTLE-HS (n = 68)	MCD (n = 34)	Pure MVHF (n = 12)	Total (n = 144)
Age — mean (SD)	32.80 (8.90)	35.16 (9.53)	16.03 (11.10)*	28.92 (13.85)	29.63 (12.75)
Sex (M/F), n	15/15	28/40	15/19	6/6	64/80

MTLE: mesial temporal lobe epilepsy; HS: hippocampal sclerosis; MCD: malformations of cortical development; MVHF: morphological variations of hippocampal formation; M: male; F: female.
* Statistically significant ($p<0.0001$).