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Detection of hippocampal atrophy in patients with temporal lobe epilepsy: A 3-Tesla MRI shape

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ABSTRACT

In patients with mesial temporal lobe epilepsy (MTLE), brain MRI often detects hippocampal sclerosis (HS). Almost half of patients with MTLE do not show any hippocampal damage on visual or volumetric assessment. Here, we wished to prospectively assess 65 patients with MTLE (41 women, mean age: 39 ± 10 years, range: 21–69; right (12/65 patients) (MRI-negative) nMTLE; right (14/65 patients) (MRI-positive with HS) pMTLE; left (24/65 patients) nMTLE; and left (15/65 patients) pMTLE) using shape analysis (SA). There were significant differences among pMTLE versus nMTLE for age at seizure onset (20.2 ± 12.8 vs. 31.8 ± 16.7 years; $p = .0029$), duration of epilepsy (14.6 ± 12.7 vs. 21.3 ± 9.6 years; $p = .0227$), risk of refractoriness ($p = .0067$), frequency of antecedent febrile convulsions (FCs) ($p < .001$), as well as a history of epilepsy or FCs ($p = .0104$). All the subjects underwent the same 3-Tesla MRI protocol. Shape analysis of hippocampal formation was conducted comparing each group versus 44 matched controls.
In all four subgroups, SA detected a significant atrophy in the corresponding hippocampus that coincided with the epileptogenic area. The damage was significantly more severe in patients with pMTLE (F value: 5.00) than in subgroups with nMTLE (F value: 3.50) and mainly corresponded to the CA1 subregion and subiculum. In the patients with MTLE, SA detects hippocampal damage that lateralizes with the epileptogenic area. Such damage is most prominent in the CA1 subregion and subiculum that are crucial in the pathogenesis of MTLE.

1. Introduction

In patients with mesial temporal lobe epilepsy (MTLE), high-resolution brain magnetic resonance imaging (MRI) study readily detects hippocampal sclerosis (HS) that is characterized by a loss of volume, increased signal intensity, and abnormal shape and positioning of the hippocampal formation [1–3]. Identifying HS on MRI strengthens the diagnosis and management of MTLE, as it strongly relates to the site of epileptogenicity. Magnetic resonance imaging findings of HS often imply refractory MTLE [4,5], even if it may be encountered in patients with drug-responsive MTLE [6].

Despite the advent of high-field MRI scanners, however, almost half of the patients with MTLE, especially those whose seizures are drug-responsive, do not show any hippocampal damage on standard MRI [7]. In such patients, quantitative MRI studies may yield data of reduced volumes of the hippocampus that strongly correlate with the epileptogenic focus [1,8]. Nonetheless, manual segmentation of the hippocampus requires a high degree of anatomical training, is observer-dependent, and is time-consuming [9]. The recent advent of computational anatomic techniques has overcome such disadvantages and biases [10]. However, previous whole brain voxel methods have failed to identify abnormalities within the hippocampus and the extent of this; thus, a new structural approach called shape analysis (SA) could be useful considering that it has proved reliability in detecting hippocampal atrophy in Alzheimer's disease [11].

Here, we aimed to assess the following: 1) the usefulness of SA to correctly confirm pathological volumes of the hippocampus and 2) the extraction of hippocampal shape descriptors capturing both global and local shape changes linked to MTLE, so as to improve the performance of disease classification using additional shape information.

Abbreviations: MTLE, mesial temporal lobe epilepsy; HS, hippocampal sclerosis; MRI, magnetic resonance imaging; pMTLE, positive MTLE (MTLE + HS); nMTLE, negative MTLE (MTLE no HS); FCs, febrile convulsions; SA, shape analysis.

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2. Methods

2.1. Study design

We compared 65 patients with MTLE versus 44 healthy controls. We divided the patients into four subgroups (left and right pMTLE and nMTLE) based on the convergence of electro-clinical, imaging, and volumetric features. Focusing on hippocampal structure, we performed a shape analysis of the hippocampus in each subgroup versus the control group, and we studied the pattern of regional atrophy detected.

2.2. Study participants

2.2.1. Patients

Demographic features of our population are summarized in Table 1. From March 2010 to March 2012, for 3-Tesla MRI scanning, we prospectively collected 65 consecutive unrelated patients (41 women, mean age: 39 ± 10, range: 21–69 years) who had received a diagnosis of mesial MTLE at least one year before the scanning. The mean follow-up in these patients was 6.2 ± 5.4 years (range: 1–20) after a comprehensive clinical and laboratory investigation. Data and evaluation procedures on our patients with MTLE have been extensively reported elsewhere [6,12]. In each patient, the diagnosis of MTLE was made on the basis of a range of clinical seizure semiology, typical mesio-temporal auras, interictal and ictal EEG, and automated volumetric MRI criteria [8,13–15]. Any suggestion of seizure onset outside the mesial temporal structures, by semiology or EEG findings, was an exclusion criterion. None of the patients had a mass lesion (tumor or vascular malformation), malformations of cortical development detected by MRI, or a history of traumatic brain injury. The only accepted MRI sign was HS, which was based on the characteristic MRI pattern of abnormalities [2]. Two independent neuroradiologists who were blinded to the study evaluated all MRIs. Conventional coronal FLAIR and IR images were visually inspected for the presence of HS. The MRI diagnosis of HS was based on the occurrence of at least one of the neuroimaging alterations that are considered reliable indicators of HS: the presence of atrophy on T1-weighted images, an increased mesial temporal signal intensity alteration on FLAIR or T2-weighted images, or both. Neurological examinations were unremarkable in all the patients. None of our patients had mental retardation.

Based on the convergence of clinical, EEG, and imaging investigation, these 65 patients with MTLE were classified into four subgroups: right MRI-negative (nMTLE): 12/65 patients; right MRI-positive with HS (pMTLE): 14/65 patients; left nMTLE: 24/65 patients; and left pMTLE: 15/65 mean. In each subgroup, the population was constituted either by patients with drug-refractory seizures (persistent seizures despite trials of two or three adequately tolerated and appropriate antiepileptic drugs) or patients with drug-responsive seizures (patients receiving the current antiepileptic drug regimen and who have been seizure-free for a minimum of 12 months).

Thirteen patients with MTLE without a clear lateralization were not included in the study; moreover, we excluded 10 additional patients affected by extra-temporal epilepsy based on electro-clinical features and neuroimaging findings. The patients were coded responders if they reached 12 months of seizure freedom.

2.2.2. Controls

Our control population consisted of 44 individuals comprising 21 males and 23 females (mean age: 50.5 ± 12.6) with no known neurological or psychiatric illness. The research ethic committee approved this study, and written informed consent was obtained from all the participants.

2.3. MRI acquisition

All the subjects underwent an MRI scan, using a 3-Tesla brain MRI, which was performed according to our routine protocol [16] by a 3-Tesla scanner with an 8-channel head coil (Discovery MR-750, GE, Milwaukee, WI, USA) at the Neuroimaging Research Unit, Institute of Neurological Sciences, National Research Council, Catanzaro, Italy. The study included conventional MR imaging techniques including standard T2-weighted and T1-weighted MRI, as well as fluid attenuation and inversion recovery (FLAIR), T2-weighted gradient echo (GRE), inversion recovery (IR), and diffusion-weighted imaging (DWI). Structural MRI data were acquired using a 3D T1-weighted spoiled gradient echo (SPGR) sequence with the following parameters: TE/TR = 3.7/9.2 ms, flip angle: 12°, and voxel-size: 1 × 1 × 1 mm3.

2.4. MRI postprocessing

Images were analyzed using FSL 4.1 (FMRIB Software Library) tools. Regions of interest (ROIs) and surface modelization were obtained automatically with the segmentation tool FIRST v1.2 [18]. The patients did not have major seizures for at least three months before scanning.

In this work, the hippocampi were segmented on each subject. Surface mesh for each structure was created using FIRST. The hippocampi were segmented on each subject using FIRST which, subsequently, created a surface mesh for the structure using a 3D deformable mesh model. The mesh is composed of a set of triangles, and the apex of adjoining triangles is called a vertex. The number of vertices for each structure is fixed so that cross-subject vertex correspondence (across individuals and between groups) can be obtained. Vertex correspondence is crucial for the FIRST methodology, as it allows the detection of local shape differences through the analysis of group differences in the spatial location of each vertex [17,18].

Subsequently, surfaces were aligned to a common space prior to investigating any group differences. The mean surface from the FIRST models (in MNI152 space) was used as the target to which surfaces from the individual subjects were aligned. Prior to statistical analysis, individual volume values were corrected with a multiplicative scaling factor derived from an affine transform calculated with the SIENAX

Table 1
Demographic and clinical features of 65 patients with MTLE.

	nMTLE right	pMTLE right	nMTLE left	pMTLE left	p value
No.	12	14	24	15	
Age (year)	44.7 + 12.8	39.4 + 10.7	47.3 + 13.5	43.2 + 14.1	n.s.
Age at onset (year)	25.5 + 12.3	17.4 + 9.7	34.9 + 17.8	22.8 + 14.9	*.0029*
Duration (year)	19.2 + 13.3	22.0 + 13.3	12.4 + 12.0	20.7 + 8.7	*.0227*
Antecedent FCs	0/12 (0%)	7/14 (50%)	2/24 (8.3%)	6/15 (40%)	*<0.0001*
Family history of FC/epilepsy	3/12 (25%)	6/14 (42.8%)	9/24 (37.5%)	6/15 (40%)	*.0104*
Drug control					
Responsive	7 (58.3%)	5 (35.7)	15 (62.5%)	6 (40%)	*.0069*
Refractory	5 (41.6%)	9 (64.3%)	9 (37.5%)	9 (60%)	*.0067*

FC = febrile convulsion; nMTLE = patients with MTLE without hippocampal sclerosis; pMTLE = patients with MTLE with hippocampal sclerosis on MRI.
The italic value represents the p value for statistical significance.