T2 hyperintense signal in patients with temporal lobe epilepsy with MRI signs of hippocampal sclerosis and in patients with temporal lobe epilepsy with normal MRI

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ABSTRACT

Background: Increased MRI T2 signal is commonly present not only in the hippocampus but also in other temporal structures of patients with temporal lobe epilepsy (TLE), and it is associated with histological abnormalities related to the epileptogenic lesion.
Objective: This study aimed to verify the distribution of T2 increased signal in temporal lobe structures and its correlations with clinical characteristics of TLE patients with (TLE-HS) or without (TLE-NL) MRI signs of hippocampal sclerosis.
Methods: We selected 203 consecutive patients: 124 with TLE-HS and 79 with TLE-NL. Healthy controls (N = 59) were used as a comparison group/comparative group. T2 multiecho images obtained via a 3-T MRI were evaluated with in-house software. T2 signal decays were computed from five original echoes in regions of interest in the hippocampus, amygdala, and white matter of the anterior temporal lobe. Values higher than 2 standard deviations from the mean of controls were considered as abnormal.
Results: T2 signal increase was observed in the hippocampus in 78% of patients with TLE-HS and in 17% of patients with TLE-NL; in the amygdala in 13% of patients with TLE-HS and in 14% of patients with TLE-NL; and in the temporal lobe white matter in 22% of patients with TLE-HS and in 8% of patients with TLE-NL. Group analysis demonstrated a significant difference in the distribution of the T2 relaxation times of the hippocampus (ANOVA, $p < 0.0001$), amygdala ($p = 0.003$), and temporal lobe white matter ($p < 0.0001$) ipsilateral to the epileptogenic zone for patients with TLE-HS compared with controls but only for the amygdala ($p = 0.029$) and temporal lobe white matter (ANOVA, $p = 0.025$) for patients with TLE-NL compared with controls. The average signal from the hippocampus ipsilateral to the epileptogenic zone was significantly higher in patients with no family history of epilepsy (two-sample *T*-test, $p = 0.005$).
Conclusion: Increased T2 signal occurs in different temporal structures of patients with TLE-HS and in patients with TLE-NL. The hippocampal hyperintense signal is more pronounced in patients without family history of epilepsy and is influenced by earlier seizure onset. These changes in T2 signal may be associated with structural abnormalities related to the epileptogenic zone or to the nature of the initial precipitating injury in patients with TLE.

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1. Introduction

In patients with temporal lobe epilepsy (TLE), the quantification of MRI T2 signal can add information about structural abnormalities related to the epileptogenic zone [1,2]. Classically, the T2 signal quantification with relaxometry analysis can increase the detection of signs of hippocampal sclerosis (HS), which is confirmed by histopathology [1,2].

The increase in T2 signal in the images is related to the increase of free water in the tissues as a consequence of gliosis, which is characteristic of HS [3].

It is currently known that the structural damage of TLE extends beyond the hippocampus [4]. Although the contribution of this network of atrophy to seizure generation is not fully understood, there is a high possibility that the epileptogenic zone may encompass the structural damage localized in the temporal structures other than the hippocampus [5]. Although different studies have focused on the contribution of hippocampal T2 signal increase to the detection of HS and lateralization of the epileptic hippocampus, fewer efforts have been put on the evaluation of T2 signal increase in extrahippocampal structures [6]. Some studies have demonstrated, however, that the T2 relaxometry of white matter of the temporal lobe is abnormal in patients with drug-refractory TLE, and it can add information to the lateralization of

the epileptogenic zone [7]. Also, in patients with TLE and no signs of HS (MRI-negative TLE), T2 relaxometry could be an additional tool to detect the lesions associated with the epileptic network.

Therefore, the aim of this study was to verify the distribution of T2-increased signal in temporal lobe structures and its correlations with clinical characteristics of TLE patients with (TLE-HS) or without (TLE-NL) MRI signs of HS.

2. Methods

2.1. Ethical aspects

The Ethics Committee of Human Research at the University of Campinas (UNICAMP) approved the study, and all patients signed informed consent prior to the acquisition of MRI.

2.2. Identification and selection of patients

We evaluated 203 consecutive patients with clinical and electroencephalographic diagnosis of TLE according to the ILAE criteria [8] followed in a tertiary epilepsy center (Epilepsy Clinic of Campinas University). Only patients with MRI signs of HS or normal MRI were selected. At the moment of their inclusion in the present study, none of these patients had been submitted to surgery, and those with seizures drug-refractory to AEDs were under investigation or refused surgery for personal reasons. It is important to point out that a significant number of patients in this cohort had good seizure control with medication, and for these patients, we did not record seizures. In order to make the data homogeneous among the patients, the laterality of the epileptogenic zone of each patient was defined according to a comprehensive clinical and EEG evaluation. All patients underwent prolonged scalp EEG recordings.

From 124 patients with TLE-HS, we excluded 18 patients with bilateral or undefined side of the epileptogenic zone. For the remaining 106 patients, 42 (40%) had the epileptogenic zone defined by ictal video-EEG recordings, with clear seizure onset in one of the anterior temporal lobes. Patients without ictal EEG recordings had either unilateral anterior temporal epileptiform discharges (42 patients, 66%) or bilateral but asymmetrical anterior temporal lobe discharges (more than 80% of the discharges lateralized to one side) (22 patients, 34%). All patients with TLE-HS had the side of the epileptogenic zone concordant with the MRI signs of HS.

From the 79 patients with TLE-NL, we excluded eight with bilateral or undefined epileptogenic zone. For the remaining 71 patients, 19 (27%) had the epileptogenic zone defined by ictal EEG recordings, with clear seizure onset in one of the anterior temporal lobes. Patients without ictal EEG recordings had either unilateral anterior temporal epileptiform discharges (31 patients, 60%) or bilateral but asymmetrical anterior temporal lobe discharges (more than 80% of the discharges lateralized to one side) (21 patients, 40%). In summary, all patients included in the present study had concordant seizure semiology, EEG findings, and side of MRI signs of HS when present.

Having family history of epilepsy was considered as having at least one first- or second-degree relative with any type of epilepsy. Patients with up to three complex partial seizures and no generalized tonic–clonic seizures in the last 12 months were classified as having infrequent seizures; those who did not fulfill these criteria were considered as having frequent seizures [9].

2.3. MRI acquisition

Magnetic resonance imaging (MRIs) of patients and controls were obtained via a 3-Tesla scanner (Philips Achieva, Best, Netherlands), with acquisitions in the coronal, sagittal, and axial planes, parallel to the long axis of the hippocampus. T1 and T2-weighted images were used for visual analysis and classification of patients with or without signs of HS. According to the MRI visual analysis, patients were classified

as having TLE-HS (124 patients; 42 men, median age = 43 years) or having TLE-NL (79 patients; 33 men, median age = 43 years).

Coronal T2 multiecho images (five different echo times: 30/60/90/120/150; 3 mm thick, repetition time = 3300 ms; matrix, 200 × 176; FOV, 1802 × 180) were used for T2 relaxometry analysis.

2.4. Signal analysis (T2 relaxometry)

The T2 multiecho images of patients and controls were postprocessed with Aftervoxel software (http://www.liv.ic.unicamp.br/~bergo/aftervoxel). T2 signal values of the hippocampus, amygdala, and white matter were obtained by manual definition of a region of interest (ROI) of each individual (Fig. 1). The T2 signal decay was computed from the six original echoes. A group of 59 healthy controls (22 men, median age = 42 years) was used for normality comparison.

The hippocampus was manually defined in three different MRI slices, (one in the head, one in the body, and one in the tail of the hippocampus). The head of the hippocampus was defined as the first image in which it was possible to see the temporal horn of the lateral ventricle and, therefore, to appropriately separate the hippocampal formation from the amygdala. The body of the hippocampus was defined in the fourth coronal section after the region of interest of the hippocampus head, and the tail was defined in the third coronal section after the hippocampus body, in which it was also possible to visualize the quadrigeminal plate. The amygdala was demarcated in two different MRI slices and was defined as the first and second images before the hippocampus head. The temporal lobe white matter was also marked in two different MRI slices located in the same sections of the amygdala. We opted to evaluate the anterior part of the temporal lobe white matter because this is the region in which the majority of focal cortical dysplasias are seen concomitantly with hippocampal sclerosis, and it is included in the postoperative histopathological analyses in most centers.

The ROIs were manually drawn not only to include the larger area of the hippocampus, amygdala, and white matter in that section, in a consistent fashion, but also to carefully avoid interference in signal values caused by incorrect demarcation of cerebrospinal fluid in the structures. (Fig. 1). Images in which all sections of the hippocampus, amygdala, or white matter were not visible were not considered for the analysis of the specific structure. The mean T2 signal from the three sections of each hippocampus and the two sections of each amygdala and white matter was used as the final result.

The determination of signal abnormality of each structure (hippocampus, amygdala, and temporal white matter) was defined by calculating the Z-score (Z-score = $z = (x - \mu) / s$ — where "x" is the value of the T2 signal obtained from each patient, "μ" is the average value of the T2 signal in the control group, and "s" is the standard deviation for "μ"). Signals above or equal to two standard deviations from the mean signal of the control group were considered as abnormal.

2.5. Statistical analysis

Statistical analysis was performed with the software Systat 9.0. Different statistical tests were used in order to answer the following questions: i) Are there differences in T2 signal intensity of the hippocampus, amygdala, temporal lobe white matter between the group with TLE-HS, the group with TLE-NL, and the control group?; ii) Could the clinical differences between the two groups of patients influence the differences of distribution of T2 signal intensity?; and iii) Independent of the subgroup of patients, is there any clinical aspect associated with the T2 hyperintense signal in any of these structures?

ANOVA, with Tukey's pairwise post hoc comparisons, was used to access the differences of T2 signal intensity among groups of individuals. General linear model, including the clinical variables that were significantly different between groups, was used to evaluate if the T2 signal differences between patients with TLE-HS and patients with TLE-NL