Medial temporal lobe atrophy in patients with refractory temporal lobe epilepsy

L Bonilha, E Kobayashi, C Rorden, F Cendes, L M Li

METHODS

Subjects

We studied 30 healthy adult subjects (19 women) without previous medical history of epilepsy. All subjects were contacted in the local community and were volunteers for this study. We also studied 25 consecutive patients with chronic refractory MTLE. All patients were referred from the outpatient epilepsy clinic of our institution, where they were diagnosed by a detailed neurological evaluation. The nature of the epileptic syndrome was determined based on ILAE criteria.13 Seizures were lateralised according to the medical history, a comprehensive neurological examination, interictal EEG, and prolonged video EEG monitoring of seizure onset. Visual inspection of the MRI scans following a standard protocol revealed unilateral HA in all the patients. Each patient was diagnosed with drug refractory MTLE, with unilateral seizure onset. The ethics committee of our institution approved the study.

MR image acquisition

We acquired diagnostic MRI using a standardised protocol.14 T1 weighted images with 1 mm isotropic voxels were acquired on a 2 Tesla Elscint Prestige scanner (Haifa, Israel) using a spoiled gradient echo sequence (TR = 22 ms, TR = 22 ms, TE = 19 ms).

Abbreviations: Amy, amygdala; Hip, hippocampus; ERC, entorhinal cortex; PHC, parahippocampal cortex; PRC, perirhinal cortex; ROI, regions of interest; TPC, temporopolar cortex
RESULTS

Thirteen patients had left HA and left MTLE and twelve patients had right HA and right MTLE. There was no significant difference in age or sex distribution between controls and patients with MTLE.

Control subjects

The volumes of the different structures in the control subjects are shown in table 1. There was no significant side to side difference in any of the structures analysed (PRC \( l_{58, 2} = 0.57 \), \( p = 0.53 \); TPC \( l_{58, 1} = 0.29 \), \( p = 0.59 \); ERC \( l_{58, 1} = 0.59 \), \( p = 0.44 \); PHC \( l_{58, 1} = 0.84 \), \( p = 0.36 \); Amy \( l_{58, 1} = 1 \), \( p = 0.32 \); Hip \( l_{58, 1} = 0.04 \), \( p = 0.84 \).

Patients with MTLE

The volumes of the studied structures in patients with MTLE are shown in table 1. Multivariate analysis of variance with Tukey post hoc comparison between patients and controls showed a significant reduction in the volumes of the left PRC, left ERC, and left Hip in patients with left MTLE, and significant reduction in the volumes of the right PRC and right ERC in patients with right MTLE (fig 1). Patients with left MTLE exhibited a larger right amygdala compared to controls and patients with right MTLE: \( l_{52, 2} = 4.6 \), \( p<0.05 \).

Asymmetry

Group differences on asymmetry were significant for all analyses, as follows: PRC \( l_{52, 2} = 36.5 \), \( p<0.001 \) Tukey’s: left MTLE<control<right MTLE. TPC \( l_{52, 2} = 11.4 \), \( p<0.001 \), left MTLE = control<right MTLE: ERC \( l_{52, 2} = 106.9 \), \( p<0.001 \), left MTLE<control<right MTLE: PHC \( l_{52, 2} = 22.3 \), \( p<0.001 \), left MTLE = control<right MTLE; Amy \( l_{52, 2} = 8.5 \), \( p<0.01 \), left MTLE = control<right MTLE; Hip \( l_{52, 2} = 274.1 \), \( p<0.001 \), left MTLE<control<right MTLE.

Individual analysis

The analysis of the Z score revealed that the degree of atrophy was significantly different among the medial temporal lobe structures in patients with left MTLE \( F_{13, 11} = 26.45 \), \( p<0.001 \) and in patients with right MTLE \( F_{12, 11} = 22.22 \), \( p<0.001 \) (fig 2). Tukey post hoc comparison did not show difference between the Z scores of the ERC and the PRC in patients with left and patients with right MTLE.

Correlation and simple regression

Linear correlation and simple regression analysis were performed with the data from similar structures ipsilateral to HA—that is, left perirhinal cortex in patients with left MTLE and right perirhinal cortex in patients with right MTLE, grouped together. All structures were analysed simultaneously in the search for significant inter-structure correlation. There was no significant linear correlation between the volumes of structures analysed—that is, there was no inter-dependent variability between the volumes of the different structures of the medial temporal lobe.

Simple regression analysis revealed \( R^2 = 0.3 \) for the comparison between the entorhinal and perirhinal cortices. All other comparisons revealed smaller values of \( R^2 \).

DISCUSSION

Volumetric analysis of the amygdala and hippocampus has been successfully used to determine tissue damage in patients with temporal lobe epilepsy.\(^{14}\) Currently, few studies have examined the other temporal lobe structures, particularly the cortical structures of the medial temporal lobe, as reviewed below. As there is a large and intricate network of connections involving all structures in the medial temporal lobe, it is possible that damage to the medial temporal lobe

\[ TE = 9 \text{ ms}, \text{ flip angle} = 35^\circ, \text{ matrix} = 256 \times 220, \text{ field of view} = 25 \times 22 \text{ cm}, 1 \text{ mm thick sagittal slices}. \]
may extend beyond the amygdala and the hippocampus, which may contribute to the symptoms of temporal lobe epilepsy.

It is not yet established to what extent damage to the medial temporal lobe involves the cortical structures. Jutila et al examined patients with unilateral MTLE and reported that patients with right HA have ipsilateral damage in the entorhinal and temporopolar cortices, whereas patients with left HA have ipsilateral damage only in the entorhinal cortex. Salmenpera et al observed that in patients with MTLE the mean volumes of the entorhinal cortex ipsilateral to the side of seizure onset did not differ from controls. However, they found that the entorhinal volume correlated with hippocampal volume and that patients with right MTLE with HA had a 19% volume reduction of the ipsilateral entorhinal cortex. In their study, the volume of the entorhinal cortex correlated with the duration of MTLE. They also found that none of the patients showed additional atrophy in the hippocampus, amygdala, or the entorhinal and perirhinal cortices at a 1 year follow up. However, Bernasconi et al have found volume reduction of the entorhinal cortex ipsilateral to the seizure focus in all MTLE patients studied, reduction of the perirhinal cortex in 33% of the patients, and contralateral reduction of the entorhinal cortex in 50% of the patients. The same group also found bilateral reduction of the entorhinal cortex volume in patients with MTLE, the atrophy being greater ipsilateral to the epileptic focus, and observed that it was possible to lateralise the seizure focus in patients with MTLE and normal hippocampal volumes based on the entorhinal cortex volume. Recently, they examined a group of 25 patients with drug refractory MTLE and observed that the entorhinal cortex was more severely reduced than the perirhinal cortex. In summary, we analysed medial temporal lobe structures in consecutive patients with unilateral chronic refractory MTLE defined and documented by video EEG, along with unilateral HA. Our findings demonstrated that patients with MTLE have significant reduction of the volume of the cortical structures closer to the hippocampus—that is, the entorhinal and perirhinal cortices. Other structures, such as the

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R, right; L, left; PRC, perirhinal cortex; TPC, temporopolar cortex; ERC, entorhinal cortex; PHC, parahippocampal cortex; Hip, hippocampus; Amy, amygdala; Max, maximum; Min, minimum

In summary, we analysed medial temporal lobe structures in consecutive patients with unilateral chronic refractory MTLE defined and documented by video EEG, along with unilateral HA. Our findings demonstrated that patients with MTLE have significant reduction of the volume of the cortical structures closer to the hippocampus—that is, the entorhinal and perirhinal cortices. Other structures, such as the

Figure 1: Box and whiskers plot showing the distribution of the volumes of the structures significantly atrophied in MTLE: the entorhinal cortex (ERC), the perirhinal cortex (PRC) and the hippocampus (Hip). (A) Distribution between groups (control, right MTLE (Rtle) and left MTLE (Utle)) of the volumes of the ERC, PRC and Hip on the right side; and (B) distribution between groups of the left sided structures.

Right hippocampus
\( \lambda = 84.05, p < 0.001 \).
Tukey’s: Rtle < Control = Utle
Right perirhinal cortex
\( \lambda = 6.55, p = 0.01 \).
Tukey’s: Rtle < Control = Utle
Right entorhinal cortex
\( \lambda = 18.84, p < 0.001 \).
Tukey’s: Rtle < Control = Utle

Left hippocampus
\( \lambda = 10.95, p < 0.001 \).
Tukey’s: Utle < Control = Rtle
Left perirhinal cortex
\( \lambda = 6.55, p = 0.01 \).
Tukey’s: Utle < Control = Rtle
Left entorhinal cortex
\( \lambda = 24.76, p < 0.001 \).
Tukey’s: Utle < Control = Rtle
parahippocampal and temporopolar cortices, are less affected. For all medial temporal lobe structures, there was a significant difference in the asymmetry index between patients with right MTLE and controls, while patients with left TLE exhibited significant difference of the asymmetry indexes of the Hip, PRC, and ERC. This information can be used as additional information for lateralisation of seizures.

We did not observe significant correlations between the volumes of any of the structures analysed, nor did we observe significant difference between the degree of damage to the entorhinal and perirhinal cortex. These null results may reflect both the relatively small number of patients examined in this study and the variability found when studying an unselected set of consecutive patients rather than a more homogenous group matched for other factors. Nevertheless, as there is a large neural network involved in the generation and propagation of seizures in MTLE, it is also possible that MTLE reflects a heterogeneous population composed of different patterns of atrophy beyond the hippocampus according to the different sub-pattern of network most intensively activated.

In conclusion, our work extends the understanding of the extent of atrophy of the medial temporal lobe in patients with MTLE. Some issues related to the pattern of medial temporal lobe volumetric alterations require further studies. For instance, it is not currently possible to define the role of the cortical structures in the symptom presentation of medial MTLE, neither is it possible to predict which clinical factors may influence the presence and extent of medial temporal lobe damage. However, the observation and quantification of damage extending beyond the hippocampus may be helpful for understanding the lateralisation of seizures in patients with MTLE and may provide clues to further investigation of the role of temporal lobe cortical structures in the pathophysiology of medial temporal lobe epilepsy.

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