Diffusion-Weighted Imaging in Chronic Temporal Lobe Epilepsy: sensitivity analysis of the B-value and ability to detect hippocampal sclerosis.

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***Abstract* – Hippocampal sclerosis (HS) is a common lesion encountered in patients with temporal lobe epilepsy (TLE). Studies with quantitative magnetic resonance (MRI) and chemical-shift imaging (CSI) have found widespread structural and metabolic changes along the entire length of the hippocampus. The aim of this study was to investigate diffusion changes interictally in patients with chronic TLE carrying structural/metabolic pathological changes in the hippocampus and to test the hypothesis that HS would be associated with abnormalities of diffusion.**

I. INTRODUCTION

Diffusion-weighted imaging (DWI) is a relatively new magnetic resonance imaging (MRI) technique that can be used to probe the microenvironment of water. Contrast in DWI depends on properties different from traditional T1 and T2 contrast, and is derived from the translational motion of water molecules. Since it is reasonable to think that a change in the microenvironment of water might be reflected in a change in water diffusion characteristics, the quantitative assessment of the (apparent) diffusion coefficient of water (ADCw) may represent a unique means of assessing tissue status.

In experimental temporal lobe epilepsy, DWI studies have shown that apparent diffusion coefficients of water are reduced during the acute seizure state (*status epilepticus*) and maintained or increased in later stages [1,2]. This effect may be caused by the initial cytotoxic edema induced by excitotoxicity [3].

In humans, most reports have addressed only focal DWI abnormalities in the course of the ictal state, discarding the analysis of the chronic TLE phase where there is evidence of established hippocampal sclerosis. This work aims to report and discuss the DWI findings in chronic, refractory TLE patients with histological and quantitative structural MRI and metabolic CSI evidence of HS using different levels of diffusion weighting.

II. METHODS

Eight age-matched healthy controls, and fifteen TLE patients enrolled for amygdalo-hippocampal resection were selected from the local surgery for epilepsy program.

Both were studied with a diffusion-weighted sequence, using three different weightings (b1=1000, b2=1500, b3=3000 s/mm2) obtained along identical hippocampal planes, on the coronal axis (figs.1 and 2).

All MRI examinations were performed with a 1.5 T GE CV/i-NV/i and included conventional routine MR images for clinical diagnosis (T1-weighted sagittal spin-echo, T1-weighted coronal gradient-echo, T2-weighted coronal and axial fast spin-echo, and fluid-inversion recovery sequences). DW imaging was performed with a echo-planar imaging sequence with the following parameters: 10000/Min.full (TR/TE), matrix size of 128 x 128, 320 mm field of view, 5 mm slice thickness with no gap.

For each subject, three sets of tilted coronal DW images were obtained with application of b1, b2, b3, along the three axes simultaneously.

Additionally, quantitative MR-based coronal T1 volumetry (3D) and T2 relaxometry (T2-r), and axial chemical-shift imaging were performed prior to surgery as part of our comprehensive multimodal epilepsy evaluation (for details see [4,5,6,7]).

To eliminate artifacts due to the T2 component of the original acquisition, images were post-processed using the manufacturer's software to create ADCw maps of the whole slices. To obtain each individual mean hippocampal isotropic diffusion map, ADCw values were averaged from four rostro-caudal orthogonal DWI partitions using ROIs of constant size ($20mm^2$), located bilaterally. ROIs were drawn by two observers, according to each subject's anatomical landmarks obtained from the original T2-DWI image and the 3D data set (fig.2). ADCw data was correlated with histological observations of HS, quantitative structural MRI and metabolic CSI data.

The overall acquisition time for the combined MRI/CSI data was 35 min. The DWI sequence added 5 min. to the total scan time.

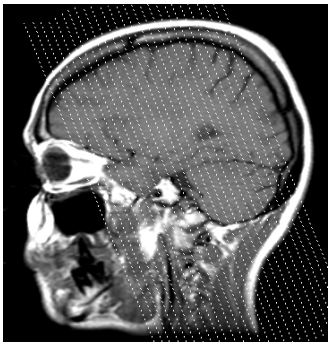

Fig 1 - Oblique coronal slices perpendicular to the main axis of the temporal lobe.

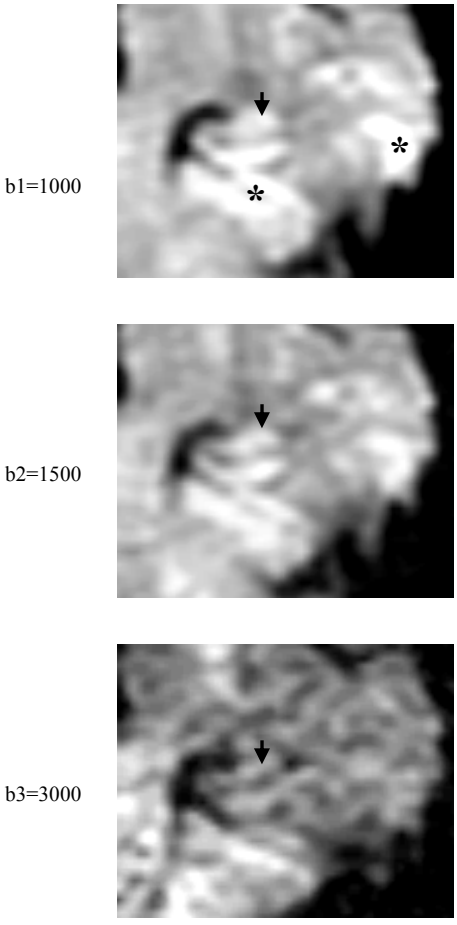

Fig 2 - Hippocampal (arrow) T2-DWI images from a control subject with the 3 different DWI weightings (b1=1000, b2=1500, b3=3000 s/mm2) used. It should be noted how the anatomical detail blurs with b3 and how the image artifacts are more evident with b1 (*).

III. RESULTS

To date, 12 patients underwent the surgical mesio-temporal resection. All had a clear cut diagnosis of histological HS, with neuronal loss and gliosis in hippocampal sectors dentate gyrus, CA3 and CA1 with relative sparing of CA2 and subiculum.

In all fifteen patients, ipsilateral ADCw increased a mean 23% (b1), 18% (b2) and 12% (b3) interictally in the ipsilateral hippocampus, where the side of seizure focus was determined electrographically and confirmed by quantitative MRI (tables 1 and 2).

No difference in the mean ADCw was observed between the contralateral hippocampus in the group with HS and the control group, while a clear asymmetry was quantified between the ipsilateral and contralateral hippocampus in the patients group (table 3).

Individually, all ipsilateral hippocampi data from b1 and b2 showed ADCw values 2,5 SD higher than controls, while 5 patients from the b3 study fell below this limit. Moreover, ADCw values correlated best with both hippocampal volume decrease (r=0.75), T2-r increase (r=0.81) but not with CSI NAA/(Cho+Cre) (r=0.31) with the b1 protocol (figs. 4 and 5).

DWI	b 1000	b 1500	b 3000
Control (8)	0.86±0.025	0.81±0.034	0.68±0.026
Right TLE (7)	0.99±0.137	0.91±0.065	0.74±0.035

Table 1 - DWI values (ms/mm^2 x10^3) in the right hippocampus of controls and TLE patients, with right EEG focus.

DWI	b 1000	b 1500	b 3000
Control (8)	0.87±0.028	0.80±0.033	0.69±0.035
Left TLE (8)	1.13±0.174	0.99±0.108	0.79±0.062

Table 2 - DWI values (ms/mm^2 x10^3) in the left hippocampus of controls and TLE patients, with left EEG focus.

Δ	b 1000	b 1500	b 3000
Control (8)	1.87±1.7	2.92±2.0	2.47±0.9
Right TLE (7)	16.28±12.7	10.0±6.0	6.98±4.9
Left TLE (8)	22.63±15.7	18.47±10.3	12.98±5.2

Table 3 – Asymmetry indexes (Δ) of DWI values (ms/mm^2 x10^3) between right and the left hippocampus of controls and TLE patients.

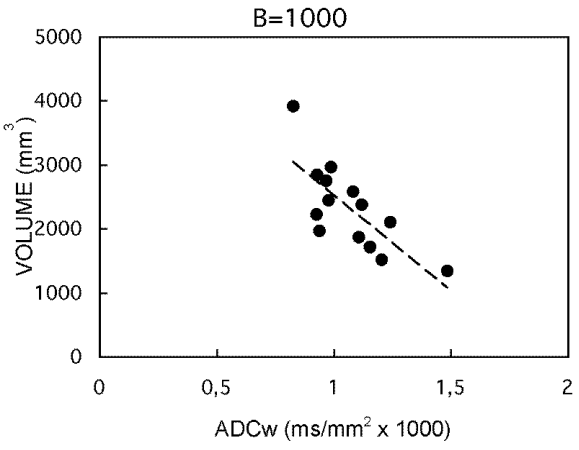

Fig 3 - Correlation data between hippocampal volume and ADCw (r=0.75).

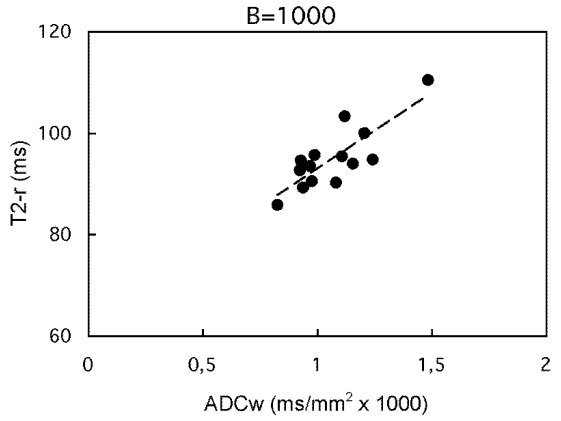

Fig 5 - Correlation data between hippocampal T2 relaxometry values and ADCw (r=0.81).

IV. DISCUSSION

While diffusion changes have been reported in humans with *status epilepticus* [7], there is a paucity of reports concerning the chronic phases of TLE with histopathological correlations. When we were undertaking this study, S.Y.Yoo and co-workers [9], published a report showing an increase in ADCw values in sclerotic hippocampus of 19 TLE patients (mean of 19% increase). In this work, HS was diagnosed by means of qualitative MRI.

Our study, used a recent functional MR technique to examine water diffusion changes in a selected group of patients undergoing mesial temporal resection for intractable epilepsy and its correlation with other quantitative MRI variables of disease: volume and signal. The quantitative histological analysis is ongoing.

In animal models of TLE, diffusion changes occur sequentially in regions of seizure activity, usually accompanied by hyperintense signal changes on long-TR images (high T2). The regions with altered ADCw correspond to regions of transient, increased perfusion and EEG abnormalities. The most affected regions are the hippocampus, the amygdala and the piriform cortex. In these models [1,2], decreases in ADCw occur as early as 1 hour after *status epilepticus*, become most pronounced at 24 hours and tend to return to baseline values over the first week.

Eventually, these diffusion changes correlate with the seizure-induced abnormalities in cellular membrane permeability and normal ion exchange, resulting in an elevation of extracellular potassium and an influx of sodium and calcium. Following this altered osmotic gradient, cell swelling occurs as water enters the neurons and glia. In these circumstances, ADCw values (ms/mm^2) would increase due to the rapid shift of free moving water into a more restrictive intracellular environment. Swelling of cells may lead to irreversible cellular edema, resulting in selective cell death by activation of apoptotic or necrotic pathways. As the cell lyses and the acute seizure activity ends, ADCw values normalize over time and MR imaging frequently reveals atrophic changes within that epileptogenic brain area.

In the human situation, the chronic phase of refractory TLE is characterized by recurrent seizure events and patients frequently present with a damaged, atrophic and hyperintense hippocampus in MRI.

In this sclerotic region, there is a permanent impairment of the metabolic and structural organization of both extracellular and intracellular compartments. The remaining cells are probably more prone to develop a bursting activity but the extracellular space is also diminished by the overall destruction of the original structure. Thus, the chronic state of TLE can be associated with critical changes in the intra/extracellular balance, reflection of a permanent metabolic impairment.

Although we have tailored the shape of our ROIs to each measured hippocampus, we do not discard the possibility that some factors could alter the accuracy of the measurements (i.e. partial volume averaging of blood and cerebrospinal fluid or the occurrence of exchange of water between compartments with different diffusion and relaxation properties). This is particularly important with the b3 study, where the anatomical details are difficult to interpret.

The study of S.Y.Yoo and c-workers [9], performed with b=0/500/1000 were able to identify also increased ADCw values in the contralateral hippocampus (by a mean of 6%), although they were not significant when compared to controls. Our research work did not obtain any relevant increase in the contralateral hippocampus (mean ± SD = 0.86 ± 0.054 ms/mm^2x10^3, with b1). S.Y.Yoo et al used a single measurement, over an axial plane to place a large ROI (3.75 cm^2) in the most anterior aspect of the hippocampal formation. The possibility to include portions of the amygdala (which is not clearly separated from the head of the hippocampus in the axial MRI view) and, above all, the likelihood to average the cerebrospinal fluid from the anterior horn of the lateral ventricle may account for this effect.

Our present results were obtained by averaging measurements from four rostro-caudal tilted coronal slices from patients in which we obtained qualitative histological assessment of the surgical specimen. The findings of increased ADCw values in patients with ipsilateral HS, and the correlations with quantitative MRI volumetry and T2 relaxometry are consistent with a chronic epileptogenic hippocampus.

One limitation in this study was that only patients with evident MRI criteria of HS were enrolled. To further determine the importance of ADCw measurements in the pathophysiology of TLE and it's potential ability to lateralize seizure activity, we are now conducting DWI

experiments on TLE patients without imaging evidence of damage in the hippocampus.

V. CONCLUSIONS

Increased ADCw can identify pathology associated with the impairment of the structural organization in sclerotic hippocampi and confirm seizure lateralization.

Brain tissue with interictally increased ADCw may represent an epileptogenic region with neuronal loss, gliosis, and expanded extracellular space. Quantitative measurements of diffusion can be used as a rapid and efficient MR technique to highlight a damaged hippocampus for pre-surgical screening of chronic, refractory temporal lobe epilepsy patients.

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