MRI Correlates of Hippocampal Demyelination in Multiple Sclerosis Brains

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Background: Recent histopathologic studies have demonstrated extensive demyelination in the hippocampus in multiple sclerosis brains.[1,2] However, there have been few reports of MRI evidence of hippocampal pathology *in vivo,*[2] even though a majority of MS patients develop cognitive impairment, and 30-40% suffer from episodic memory dysfunction indicative of hippocampal involvement.[3]

Objective: To investigate whether hippocampal pathology can be detected using commonly available MRI sequences.

Methods: MRI data were acquired *in situ*, just prior to autopsy, from MS patients who had consented to donate CNS tissue post-mortem. MPRAGE (TR/TE/TI = 9700/4/350ms; α=10; 1x1x1mm^3), 2D FLAIR (TR/TE/TI = 6000/105/2000; 0.9x0.9mm^2; slice thickness=3.0mm), and 3D gradient echo magnetization transfer images (TR/TE = 35/6ms; flip angle=3°; MT pulse: 7.68ms 250Hz Gaussian applied 1.5kHz off resonance once per TR; H1=8.8μT; 0.9x0.9x3.0mm^3) were acquired on a 1.5T scanner. Brains were fixed in 4% paraformaldehyde for 4 weeks and re-imaged in a custom-designed slicing box for co-registration purposes, as previously described.[4] Hippocampal tissue samples were blocked and stained with proteolipid protein (PLP) for myelin. The degree of demyelination was assessed in each hippocampus, and only normally myelinated or completely demyelinated hippocampi were selected for comparison of imaging characteristics (Figure 1). From the MPRAGE images, left and right hippocampi were manually segmented using a co-registered brain atlas as a guide. Mean T2, T1, and MTR contrast ratios were determined as the mean intensity within the hippocampus mask divided by the mean intensity of normal-appearing white matter (Figure 2). MTR histograms were calculated within each hippocampus, smoothed, and normalized to correct for volume differences.

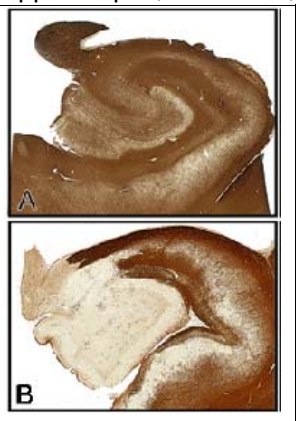

Figure 1: Examples of PLP-stained hippocampi (a) normally myelinated; (b) deymyelinated.

Results: Four hippocampi from 2 brains were rated as normally myelinated and 5 hippocampi from 4 brains were rated as severely demyelinated. There were no focal T2 hyperintensities or T1- or MTR-hypointensities visible within the hippocampi, even in the severely demyelinated samples, which is consistent with the low sensitivity of conventional MRI for gray matter pathology. Mean T2-, T1-, and MTR contrast ratios were not different between the groups, but MTR histograms from severely demyelinated hippocampi were shifted downward compared to MTR histograms from normally myelinated hippocampi (Figure 3). The mean MTR peak position for normally myelinated hippocampi was 96.3 (range = 95 – 100) whereas the mean MTR peak position for demyelinated hippocampi was 92.4 (range = 91 – 95).

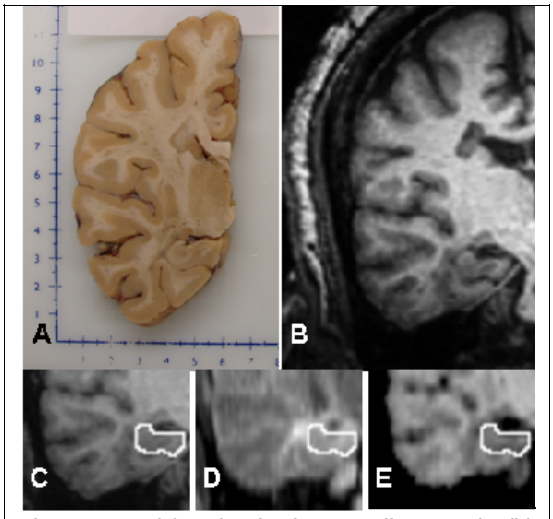

Figure 2: (a) Fixed tissue slice and (b) corresponding MPRAGE slice after image-to-tissue registration; hippocampal tracing superimposed on (c) MPRAGE, (d) FLAIR, and (e) MTR images

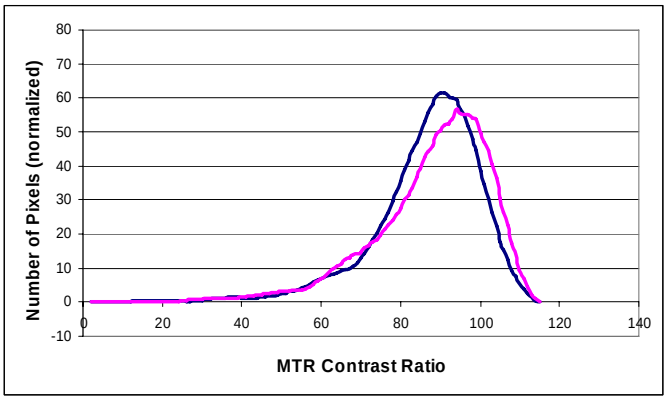

Figure 3: Composite histograms of MTR contrast ratio in hippocampi from MS brains. Pink: normally myelinated (n=4). Blue: demyelinated (n=5)

Conclusion: These data suggest that MTR histogram peak may be a sensitive and useful marker of hippocampal pathology in MS patients. Additional hippocampal tissue samples will be analyzed, including those with intermediate degrees of demyelination, to determine the robustness of the association. Hippocampal MTR peak position will be measured in live MS patients with and without memory dysfunction to determine the clinical usefulness of this measurement.

References:

[1] Geurts JJG, et al. J Neuropathol Exp Neurol 2007; 66:819-827. [2] Sicotte NL, et al. Multiple Sclerosis 2007;13:S14. [3] Rao SM, et al. Neurol 1991;39:161-166. [4] Fisher E, et al. Ann Neurol 2007; 62:219-228.

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