MRI Evidence For Primary Degeneration of Myelin and Axons in Patients with Multiple Sclerosis

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Synopsis Cross-sectional study of 73 MS patients examined relationship between disease duration and abnormalities in MR surrogates of *(i)* NAWM myelin integrity (tissue-specific magnetisation transfer ratios), *(ii)* peri-ventricular axonal integrity (^{1}H-MRSI NA/CR values), and *(iii)* cerebral atrophy (brain to intra-cranial capacity ratios). Found: *(i)* significant myelin disturbance in patients' NAWM present even prior to disease onset that remained constant with disease duration; *(ii)* significant axonal disturbance was also present well before disease onset – but that became even more severe with disease duration; and *(iii)* cerebral atrophy was not present at disease onset – but that developed over the duration of the disease.

Introduction

Although the pathology and chronic disability that is seen in patients with multiple sclerosis (**MS**) has traditionally been linked with the hallmark focal inflammatory white matter lesions that are present in the CNS of patients with this disease, there is mounting clinical and MRI evidence to suggest that findings in patients with MS may also be associated with a primary degenerative process. In the present, cross-sectional study we examined the relationship between disease duration and abnormalities in MR surrogates of *(i)* myelin integrity in normal-appearing white-matter (**NAWM**) [as measured with tissue-specific magnetisation transfer ratios (**MTr**)], *(ii)* peri-ventricular axonal integrity [as measured with peri-ventricular ^{1}H-MRSI-measured NA/CR values, and *(iii)* cerebral atrophy [as measured using Collins' **BICCR** (brain to intra-cranial capacity ratio)].

Methods

MRI data were acquired in 73 patients with clinically-definite MS (59 RR, 14 SP; 51 females). Using a z-transformation approach, these data were normalized relative to similar findings in 38 normal control (**NC**) subjects (21 females): for each normalized-to-NC patient value, a z-score of 0 is equal to the mean of the NCs and a z-score 1 unit away from 0 signifies 1 NC standard deviation away from that mean. See tables for demographics and imaging results from NCs.

Image Acquisition: MRI was performed on a 1.5T, Philips Gyroscan ACS II using a body coil transmitter and a quadrature head-coil receiver. Fifty 3-mm thick, contiguous proton-density-weighted (**PD**) and T_2-weighted images were acquired parallel to the AC-PC line using a dual turbo spin-echo sequence (TR 2075 ms, TE 30/90 ms, 256×256 matrix, 250 mm field of view). T_1-weighted images were acquired with the same matrix using a 3D gradient-echo sequence (TR 35 ms, TE 10.2 ms, 40°excitation angle). This T_1-weighted sequence was repeated with 1-2'-1 on-resonance MT pulse, and standard MTr values were generated. 2D ^{1}H-MRSI from a large VOI of approximately 90 x 90 x 20 mm^3 centered on the corpus callosum was obtained using a PRESS sequence (TR = 2000 ms, TE = 272 ms, 250 x 250 mm FOV, 32 x 32 phase encodes, 1 SA); areas under the NA and Cr metabolite peaks were obtained using in-house software.

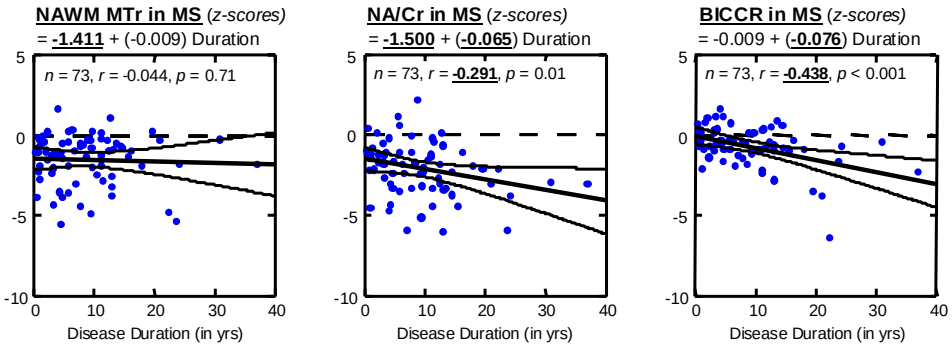
Image Processing: Each MRI volume was corrected for image-intensity inhomogeneity and the T_2/PD image pair was registered to the T_1 volume using mutual information. The T_1 volume was registered into stereotaxic space to facilitate model-based structure segmentation. The resampled image volumes were input to an Expectation-Maximization algorithm to identify white matter (**WM**), grey matter tissue (**GM**), cerebrospinal fluid (**CSF**), and lesions (**L**) using T_1, T_2, and PD volumes. Morphological operators were also applied to the same data to identify the intra-cranial space and create a mask (**ICM**). BICCR was defined as the ratio (GM+WM+L)/(GM+WM+L+CSF) within the ICM. Furthermore, a separate, Bayesian tissue-classification algorithm was used to generate NAWM tissue masks that were used to calculate NAWM-specific median MTr values for each individual.

Results

As shown in the figures below (bold and underlined values in the regression equations and correlations are statistically-significant different from 0 with $p < 0.01$; straight line is the linear-regression best fit +/- 95% confidence intervals), our normalized-to-NC median-MTr measures suggested a significant myelin disturbance in the patients' NAWM that was present prior to disease onset and that remained constant with disease duration. On the other hand, our normalized-to-NC NA/Cr findings suggested a significant axonal disturbance that was also present well before disease onset – but that became even more severe with disease duration. Finally, our normalized-to-NC BICCR findings suggested that cerebral atrophy was not present at disease onset – but, rather, developed over the duration of the disease.

MS Patient Information (n=73)	Mean	StDev	Min	Max
Age (yrs)	38.94	9.53	14.21	57.42
Onset (yrs)	29.97	8.07	11.06	48.40
Duration (yrs)	8.97	7.28	0.32	36.95
EDSS	3.08	2.40	0.0	9.0

Normal Control Information (n=38)	Mean	StDev	Min	Max
Age (yrs)	35.37	9.27	23.51	57.05
WM MTr	36.568	1.163	32.903	38.334
NA/Cr	3.248	0.195	2.890	3.680
BICCR	0.847	0.025	0.786	0.894



Discussion

The presence of abnormal MTr and NA/Cr values at the time of symptom onset (*i.e.* at the time of the so-called CIS or first demyelinating event) suggests a primary abnormality of the myelinated-axon unit in patients with MS – a finding that is consistent with the finding of abnormal MTr values in first degree relatives of patients with familial MS. On the other hand, the presence of normal brain volumes at symptom onset suggests that cerebral atrophy may have a different pathogenesis – possibly secondary to the development of focal, inflammatory lesions. Our findings suggest that abnormalities in the integrity of MS patients' myelin and axons go back in time long prior to disease onset. Furthermore, given that most patients are known to have low lesion volumes at disease onset, the present findings also suggest that these abnormalities are present even long before the accumulation of focal inflammatory lesions.