Disease Duration Influences the Relationship between Brain Axonal Injury, Spinal Cord Atrophy and Disability in Multiple Sclerosis

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Introduction

Proton MR spectroscopy (MRS) studies of patients with multiple sclerosis (MS) monitoring resonance intensities of N-acetylaspartate (NAA) (a marker of neuronal integrity) have shown that clinically relevant axonal damage or dysfunction occurs in brain lesions and in white matter which appears normal (NAWM) on conventional MRI (1). The NAA signal from a large, central volume of interest (VOI) predominantly including NAWM can be used as a global index of brain axonal injury. Spinal cord atrophy has also been shown to correlate strongly with disability scores (2). In this study, we examined the effect of disease duration on the correlation of NAA and spinal cord atrophy with disability.

Methods

Patient population:

Fifty five patients (36 women and 20 men) aged 20 to 61 years [39.6 (8.8) years, mean (standard deviation)] with definite MS were selected from the Multiple Sclerosis Clinic of the Montreal Neurological Hospital to span the entire range (0-9) of the Expanded Disability Status Scale (EDSS). Patients with either relapsing-remitting (RR) or secondary-progressive (SP) disease underwent magnetic resonance examination and concurrent clinical evaluation. Examinations were timed to be at least 1 month after an attack. A group of 17 healthy laboratory and hospital workers of similar mean age [35.3 (9.2), p=0.1] served as normal control subjects.

Proton MRI/MRSI of brain:

MRI and MRSI examinations were performed using a 1.5T, Philips Gyroscan ACS II (Philips Medical Systems, Best, The Netherlands). MRI data were acquired using a transverse dual-echo TSE sequence (TR/TE1/TE2=2075/32/90, 256×256, 1 SA, 250mm FOV) yielding two sets of 50 contiguous 3mm slices parallel to the AC-PC line. These images were used to select a VOI for spectroscopic imaging of approximately 90×90×20mm^3 centered on the corpus callosum. MRSI data were acquired using a double spin-echo excitation method (TR 2000, TE 272ms, 32×32 phase-encodes, field of view 250×250mm, slice thickness 20mm), and post-processed as previously described (3). Metabolite resonance intensities were determined automatically from fitted peak areas using in-house software. Signals from NAA were expressed as ratios to creatine (Cr) in the same voxel and then averaged over the entire VOI to obtain mean NAA/Cr ratios for each examination.

Measurement of spinal cord atrophy:

T1W images of the cervical spine at the level of C2 were obtained with a quadrature neck coil, using a 3D T1W-FFE sequence (TR=27ms, TE=7.5ms, 256×256 matrix, 150mm FOV, 20° flip angle, and 6 SA). Twenty-five transverse slices (0.6 mm × 0.6 mm × 1 mm) were acquired perpendicular to the cord, with the level of the most inferior slice positioned at the top of C3. Post-processing consisted of rotating and resampling this volume data set to be sliced truly perpendicular to the cord and applying a box filter of dimensions 1×1×4 mm to improve the signal-to-noise ratio. The data were then resampled and cropped to yield three 4 mm thick slices, with the bottom of the most inferior slice aligned with the inferior margin of C2. The cord was labeled on each slice by applying a threshold equal to the signal intensity halfway between the average intensity of CSF and cord. The cross-sectional areas were then averaged to yield the final result.

Statistics

We examined group differences of NAA/Cr and spinal cord cross-sectional area using analysis of variance (ANOVA) followed by Tukey's post-hoc testing.

Spearman rank-order correlations of NAA/Cr and spinal cord cross-sectional area with EDSS were performed for patients grouped by duration of disease.

Results

Group Differences:

Brain NAA/Cr ratios of the patient group with RR [2.7 (0.3), mean (SD)] and SP [2.6 (0.3)] disease both were significantly lower than normal controls [3.1 (0.20), p=0.002]. NAA/Cr was not significantly lower in SP patients than in RR patients (p=0.1). Spinal cord cross-sectional area was not significantly reduced in the RR group [77.8 (10.3)] compared to controls [81.0 (6.9), p = 0.58], but was significantly low in SP patients [59.5 (14.8)].

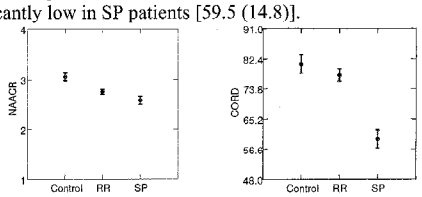

Figure 1: NAA/Cr (left) and spinal cord area (right) for normal controls, RR patients and SP patients.

Correlations

Over the entire EDSS range, EDSS correlated with both NAA/Cr and spinal cord atrophy (see Table and Figure 2). The correlation between NAA/Cr and EDSS was stronger earlier in the disease than later, while the initially weak correlation between spinal cord area and EDSS became stronger with increasing disease duration.

	Dur < 5	5≤ Dur ≤ 20	Dur ≥ 20	Overall
NAA/Cr	-0.75	-0.44	-0.30	-0.53
Cord	-0.29	-0.53	-0.84	-0.58
N	15	33	8	56

Table:Correlation (SRCC) with EDSS as a function of disease duration

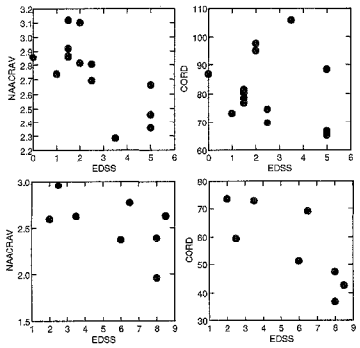

Figure 2: NAA/Cr and spinal cord area vs. EDSS for MS patients with disease duration < 5 yrs (top pair) and > 20 years (bottom pair).

Conclusions

Cerebral axonal damage begins early in the course of MS and contributes significantly to the clinical disability from disease onset. In patients with long disease duration, however, decreases of cerebral NAA explain less of the changes in EDSS. Conversely, atrophy of the cervical spinal cord does not feature prominently early in the disease, but correlates strongly with disability in patients with longstanding disease. Possible explanations for this include: 1) the fact that EDSS in the later stages of MS is based on gait which is particularly sensitive to spinal pathology and 2) that cerebral axonal dysfunction reported by decreased NAA/Cr is not initially accompanied by significant axon loss. As the disease progresses, axonal degeneration and loss become more marked and are associated with more spinal cord atrophy.

References

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