Creatine and myo-Inositol are Increased in Multiple Sclerosis Normal Appearing White Matter

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Introduction

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system resulting in white matter lesions which are detectable by MRI. However, a limitation of MRI is that it does not detect abnormalities of lesion free white matter (i.e. normal appearing white matter, NAWM). Considerable evidence from pathological studies suggests that there is often extensive microscopic disease in white matter devoid of visible lesions. In an effort to develop more sensitive measures for the diagnosis of MS in patients with few or no MRI-detectable lesions, MRSI has been used to study MS. Previous studies have reported increased Cr ^{1}H MRS signal in MS NAWM (1-3). This increase could be due to a change in cellular composition, such as gliosis or inflammation, or a non-specific relaxation time change. Myo-inositol (mI) is a putative marker of glia (4), so an increased mI would support the hypothesis that increased Cr is associated with gliosis in MS NAWM. Previously Destefano et al. (5) reported increased mI in MS lesion, but to the best of our knowledge there are no reports on mI in MS NAWM.

Therefore, the purpose of this study was to perform short TE ^{1}H MRSI studies of MS NAWM to 1) replicate the findings of increased Cr in NAWM, and 2) determine if mI is increased in NAWM.

Methods

Eleven patients with clinically definite relapsing remitting MS and 10 age matched controls were studied by ^{1}H MRSI.

All data were acquired on a Siemens Vision 1.5T system with a quadrature head coil. ^{1}H MRSI data were acquired with STEAM (TE30/TM55/TR1000) to select a volume of interest (VOI) with typical dimensions of 100mm (anterior-posterior), 80mm (left-right), and 60mm (cranio-caudal) with the axial plane angulated parallel to the AC-PC line and located completely within the brain including as much white matter as possible. Applying a spherical k-space acquisition scheme this VOI was phase encoded with 20 x 20 x 12 steps over a field of view (FOV) of 180 × 180 × 108 mm^3. Total acquisition time was 42 minutes. The spectroscopy data was apodized in the spatial frequency domains using a Gaussian filter that produced an effective voxel size of 2.6 cm^3. The time domain data was apodized with a Gaussian function that provided effective broadening of 4 Hz in the frequency domain. NAWM spectra were selected from two locations (left and right hemisphere) within centrum semiovale white matter of each subject. To avoid signal contamination from MS lesions, regions of interest were at least 10 mm distant from the edge of identified lesion and abnormal white matter regions. Absolute intensities of MRSI data, corrected for coil loading, receiver gain, and processing factors, were calculated from spectral peak fittings to the mI, Ch (choline), Cr, AA (amino acids, “marker peaks”), and NAA resonances and normalized to the proton density intensity of CSF within the lateral ventricles.

Proton density and T2-weighted MRI were acquired using a double spin echo sequence (TE20, 80/TR 2500). Fifty-one 3 mm axial slices, without gap, were acquired in 16 minutes with a 192 x 256 matrix and a 180 mm x 240 mm FOV. The MRI studies were collected with full brain coverage to ensure that all lesion areas could be properly assigned.

Results

Results are summarized in the table below. The first major finding was that Cr was significantly ($p<0.05$) increased from 1.71 ± 0.10 in white matter of controls to 2.06 ± 0.10 in MS NAWM. This result confirms the previous finding of Rooney et al. (2). The second major finding was that mI was significantly ($p<0.05$) increased from 0.78 ± 0.07 in controls to 0.99 ± 0.09 in MS NAWM.

There was no significant difference in Cho, NAA, or AA intensity between MS NAWM and white matter of controls.

Discussion

The major findings of this study were: 1) Cr was increased in MS NAWM, and 2) mI was increased in MS NAWM compared to white matter of controls. The finding of increased Cr replicates the previous observations (1-3) which were performed with different TE, TR and Bo._. Furthermore, the magnitude of increased Cr in MS NAWM in this study (20.5%) is greater than that reported by Rooney et al. (15.4%) at TE 135 ms. This suggests that the Cr increase is not due to a change in relaxation time. More likely, the increased Cr is due to a change in the cellular composition of NAWM, either increased inflammatory cells or increased glial cells. Other studies in this lab by Suhy et al. (6) on primary progressive MS (PPMS) also show increased Cr. Since PPMS has much less inflammation and more gliosis than RRMS, this suggests that the increased Cr is due to an increase in glial cells. The finding of increased mI in NAWM is similar to a previous report of increased mI in MS lesions (5). Furthermore, increased mI has been found in a number of other brain diseases including Alzheimers disease. It has been previously suggested that increased mI is a marker of gliosis (4). This would be consistent with findings of gliosis in MS NAWM.

In conclusion the finding of increased Cr and increased mI is most consistent with the presence of gliosis in MS NAWM. Therefore, an increase in Cr and mI signal intensity may serve as a marker of gliosis in MS NAWM and may be useful in the diagnosis of patients without MRI-detectable lesions. Finally, these findings demonstrate that ^{1}H MRSI at short TE provides additional information not only to MRI but also to ^{1}H MRSI at long TE in the evaluation of MS.

	Control n=10	**MS n=11**	**p**
mI	0.78 ± 0.07	0.99 ± 0.09	< 0.05
Ch	1.68 ± 0.08	1.63 ± 0.08	ns
Cr	1.71 ± 0.10	2.06 ± 0.10	< 0.05
AA	2.29 ± 0.28	2.50 ± 0.28	ns
NAA	2.67 ± .014	2.68 ± 0.11	ns

Mean ± SE; p determined from Mann-Whitney rank test.

References

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