A Preliminary Diffusion Tensor and Magnetization Transfer Magnetic Resonance Imaging Study of Early-Onset Multiple Sclerosis

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Background: Early-onset multiple sclerosis (MS) typically has a more favorable course than adult-onset disease.

Objective: To assess the extent of microscopic tissue damage in the brain and cervical cord of patients with early-onset MS.

Design: During a single magnetic resonance imaging session, images of the brain and spinal cord were obtained using diffusion tensor and magnetization transfer magnetic resonance imaging.

Patients: We studied 13 patients with early-onset MS and 10 healthy volunteers.

Results: Compared with control subjects, patients with early-onset MS showed only a slight increase of the average mean diffusivity of the normal-appearing brain tissue.

Conclusion: The relatively modest central nervous system damage detected in these patients might explain why early-onset MS typically has a more favorable clinical course than adult-onset MS.

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In about 3% to 12% of cases, multiple sclerosis (MS) has an onset before 16 years of age. Several natural history studies have demonstrated that early-onset MS typically has a more favorable clinical course than the more common adult-onset disease. A plausible explanation for such a finding might be that the overall amount of tissue damage occurring in the central nervous systems of patients with early-onset MS is only mild. Previous studies, however, did not show any difference between early- and adult-onset MS in terms of conventional magnetic resonance imaging (MRI) metrics. This is likely owing to the poor specificity of conventional MRI to the heterogeneous substrates of MS and to its limited accuracy in estimating the actual amount of central nervous system tissue damage. In adult-onset MS, diffusion tensor (DT) and magnetization transfer (MT) MRI have enabled researchers to obtain reliable estimates of tissue damage, and show that it is not limited to lesions visible in T2-weighted images, but that it involves diffusely the normal-appearing brain tissue (NABT). To our knowledge, no previous study has attempted to quantify tissue damage in the brain and spinal cord of patients with early-onset MS. In this study, we obtained MT- and DT-MR images from these patients, with the goal of improving our understanding of the pathophysiology of early-onset MS.

METHODS

We studied 10 girls and 3 boys with early-onset MS (mean age, 14.1 years [range, 7-16 years]; mean disease duration, 17.6 months [range, 8-36 months]; median Expanded Disability Status Scale score, 1.5 [range, 1.0-2.5]; and mean number of relapses per patient, 2.7 [range, 2-4]). Ten healthy volunteers (7 girls and 3 boys; mean age, 14.8 years [range, 9-16 years]) served as control subjects. At the time MRI was performed, all patients had been relapse- and steroid-free for at least 6 months. Eight patients were taking disease-modifying treatments ( interferon beta-1a [n=5] and glatiramer acetate [n=3]). Local ethical committee approval and written informed consent from all patients were obtained before study initiation.

Using a 1.5-T scanner, we obtained the following sequences in the brain: (1) dual-echo turbo spin echo (repetition time/echo time, 3300/16-98 milliseconds; 24 axial 5-mm-thick sections with 256 × 256 matrix; and 250 × 250-mm² field of view); (2) 2-dimensional gradient echo (repetition time/echo time, 600/12 milliseconds; flip angle, 20°; 20 axial 5-mm-thick sections with 256 × 256 matrix; and 250 × 250-mm² field of view) with and
without a saturation pulse (off-resonance radio-frequency pulse centered 1.5 kHz below the water frequency, with a gaussian envelope of duration of 7.68 milliseconds and $\alpha=500\degree$); and (3) pulsed gradient spin echo planar (interecho spacing, 0.8; echo time, 123 milliseconds; 10 axial 3-mm-thick sections with $128 \times 128$ matrix; and $250 \times 250$-mm$^2$ field of view), with diffusion gradients applied in 8 noncollinear directions. Additional information about this sequence is given elsewhere.3 For the cervical cord, we obtained the following sequences: (1) fast–short-time inversion recovery (repetition time/echo time/inversion time, 2288/60/110 milliseconds; echo train length, 11, 8; 3-mm-thick sagittal sections with an intersection gap of 0.3 mm; matrix size, 264 × 512; field of view, 280 × 280 mm$^2$; and number of signal averages, 4); and (2) 2-dimensional gradient echo with the same acquisition parameters used for the brain.

All MRI postprocessing was performed by a single observer (D.M.M.) masked to the subjects’ identity. Lesions were identified on the dual-echo scans, and lesion volumes were measured using a segmentation technique based on local thresholding. Alter coregistration of the 2 gradient-echo scans using a surface-matching technique based on mutual information, the MT ratio (MTR) images were derived pixel by pixel, as described elsewhere.4 Extracerebral tissue was removed from MTR maps, and the resulting images were coregistered with the T2-weighted images. The pulsed gradient spin echo images were first corrected for distortion induced by eddy currents using an algorithm that maximizes mutual information between the diffusion-unweighted and -weighted images. Then, we calculated the DT and mean diffusivity (MD) derived for every pixel, as previously described.5 The diffusion images were interpolated to the same image matrix size as the dual echo, and then the $b=0$ step of the pulsed gradient spin echo scans were coregistered with the dual-echo T2-weighted images.6 The final step consisted of automatic transfer of lesion outlines onto the MTR and MD maps to calculate the average lesion MTR and MD. To study the MTR and MD of NABT, pixels inside lesion outlines were masked out, and MTR and MD histograms of the NABT were produced.7 Cervical cord lesions were identified by the same observer on the fast–short-time inversion recovery scans. From the 2 gradient-echo images, with and without the saturation pulse, MTR maps and histograms were derived, as previously described.8 For each histogram, the average MTR and MD and the peak height were measured. Given the strong correlation existing between average histogram measures and the histogram peak location, the latter quantity was not considered for this study, to reduce the risk for type I errors.

We used a 2-tailed $t$ test for unpaired data to compare MTR and MD histogram-derived metrics from the 2 groups of subjects. Univariate correlations were explored using the Spearman rank correlation coefficient.

### RESULTS

In patients with early-onset MS, mean T2-weighted volume of brain lesions was 11.1 mL (range, 0.0–61.5 mL), average lesion MTR was 39.2% (SD, 2.0%), and average lesion MD was $1.01 \times 10^{-3}$ mm$^2$/s (SD, $0.08 \times 10^{-3}$ mm$^2$/s). The median number of cervical cord lesions was 1.6 (range, 0–6).

In the Table, MTR and MD histogram-derived metrics of the NABT and MTR histogram-derived metrics of the cervical cord from patients and controls are reported. Compared with controls, patients with MS had significantly increased average MD of the NABT only. No correlation was found between dual-echo lesion load and MD and MTR histogram-derived metrics.

### MTR and MD Histogram-Derived Metrics of the NABT and MTR Histogram-Derived Metrics of the Cervical Cord

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Controls</th>
<th>Early-Onset MS Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain NABT average MD, x10^{-3} mm$^2$/s</td>
<td>0.97 (0.02)</td>
<td>1.02 (0.05)</td>
<td>.03</td>
</tr>
<tr>
<td>Brain NABT MD histogram peak height</td>
<td>103.1 (11.2)</td>
<td>98.1 (15.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Brain NABT average MTR, %</td>
<td>37.8 (1.8)</td>
<td>37.7 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Brain NABT MTR histogram peak height</td>
<td>83.9 (7.6)</td>
<td>82.4 (8.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical cord average MTR, %</td>
<td>41.2 (4.0)</td>
<td>39.6 (6.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Cervical cord MTR histogram peak height</td>
<td>63.1 (7.4)</td>
<td>64.6 (12.2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Abbreviations: MD, mean diffusivity; MS, multiple sclerosis; MTR, magnetization transfer ratio; NABT, normal-appearing brain tissue. *Data are given as mean (SD).**

### COMMENT

Several studies have shown a more favorable course in patients with an onset of MS before 16 years of age than those with a typical onset in adulthood.1,2 However, the reasons for such a difference have not been fully elucidated yet. Cerebrospinal fluid3 and conventional MRI findings4 at disease onset have been found to be similar in both populations. Longitudinal MRI studies have also shown that the accumulation of disease burden on brain dual-echo scans is similar between these 2 groups of patients.4 In this preliminary study, we used MT- and DT-MRI to quantify the extent of NABT damage in patients with early-onset MS. Previous quantitative MRI studies5,6 showed significant and widespread NABT damage in adult patients with MS and clinical characteristics similar to those of our patient cohort (relapsing-remitting course, number of relapses, Expanded Disability Status Scale score). On the contrary, the present study shows that the brain and cervical cord of patients with early-onset MS are relatively spared, because these patients did not differ from matched controls in terms of relative proportions of free and bound water (as measured by MTR), and had only modest increase of average MD. These findings are in agreement with those of a previous study showing a lower rate of development of hypointense lesions and brain atrophy in early-onset MS.7 We also quantified the number of cervical cord lesions and the extent of microscopic cord damage. We found no MT histogram abnormalities in patients with early-onset MS, confirming that spinal cord damage has a major role in the development of disability in MS. Another factor that might contribute to the modest central nervous system damage found in this cohort of patients with early-onset MS is the relatively short disease duration. However, this factor is likely to have only a marginal role, because significant MTR abnormalities have been found in the NABT of patients with relapsing-remitting MS or patients with clinically isolated syndromes, and disease durations that were even shorter than those of the present study.8,9
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REFERENCES


Correction

Error in Table References. In the Original Contribution by Honig et al titled “Stroke and the Risk of Alzheimer Disease,” published in the December issue of the ARCHIVES (2003;60:1707-1712), an error occurred in the table references. On page 1710, there is a reference to Table 4. This should have referred to Table 3. The journal regrets the error.