MAGNETIZATION TRANSFER CHANGES IN THE NORMAL-APPEARING WHITE MATTER PRECEDE THE APPEARANCE OF ENHANCING LESIONS IN PATIENTS WITH MULTIPLE SCLEROSIS

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Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the CNS of unknown etiology (1). It is currently believed that CNS antigen-specific T cells provide the organ specificity of the pathogenic process and regulate the recirculation within the CNS of non-specific lymphocytes which may act as effector cells by releasing myelinotoxic substances. It is, therefore, conceivable that a primary immunological sensitization against myelin antigens may occur within the CNS before perivascular infiltrations and demyelination become evident. In MS, lesions seen to enhance on magnetic resonance imaging (MRI) scans after gadolinium (Gd) injection represent areas with a damaged blood-brain barrier and intense inflammation. At present, this abnormality is considered the first step of MS lesion formation which is visible with MRI. Using magnetization transfer imaging (MTI), there is, however, evidence that tissue changes may occur in MS lesions and in the normal-appearing-white matter (NAWM) independently from enhancement. This longitudinal MTI study was designed to evaluate whether any abnormality in the NAWM from MS patients can be detected before enhancing lesion appearance.

Patients and methods

Ten patients with clinically definite MS entered the study. MRI examinations were performed on all patients every 28 (± 5) days on four separate occasions using a scanner operating at 1.5 T. On each scanning occasion, we obtained the following scans: a) dual echo conventional spin echo (CSE) (TR=2400, TE=30-80); b) 2D GE (TR=600, TE=12) with and without a saturation pulse. The saturation pulse was an off-resonance RF pulse centered 1.5 kHz below the water frequency and with a Gaussian envelope of duration of 16.4 ms, a bandwidth of 250 Hz and an amplitude of 3.4×10^4 T; c) pre-contrast T1-weighted CSE (TE=768, TE=15); d) post-contrast T1-weighted CSE, with the same acquisition parameters as before Gd injection, 20 minutes after the injection of Gd (0.3 mmol/kg). For all the scans, 24 contiguous interleaved axial slices were acquired with 5 mm slice thickness, 256x256 matrix and 250 mm field of view. We also obtained MT scans from five age-matched healthy volunteers at the beginning and at the end of the study. The MTR values obtained from gray matter, white matter and CSF were stable over the study period (scan-rescan variation < 3%).

New enhancing lesions, with no corresponding abnormalities on the dual-echo or pre-contrast T1-weighted scans of the previous months, were identified and marked on the hard copies by two observers by agreement. Then, a single observer displayed the post-contrast images on a computer screen and outlined the enhancing lesions, using a semi-automated segmentation technique based on local thresholding, with the marked hard copies as a reference. The regions of interest (ROIs) outlined on the enhanced scans were then mapped on to the co-registered MT images, and the MT ratio (MTR) and areas of the regions measured. The MTR values of the same ROI on the corresponding co-registered MT scans before the appearance of enhancement were also measured. Using the same method and square ROIs of 8.6 mm², MTR values of four NAWM areas away from the areas of enhancement were measured in the same slices where new enhancing lesions were identified.

Differences in MTR values between areas of NAWM corresponding to areas of new enhancement on subsequent scans and NAWM areas outside visible MS lesions on any of the scans was performed using the Student t Test for paired data. One-way ANOVA was used to evaluate the evolution of MTR in NAWM which subsequently enhanced.

Results

A total of 40 post-contrast scans was obtained and analyzed. Forty-eight new enhancing lesions with no evidence of any previous MRI abnormalities were identified. For each of them, at least one previous MRI scan was available, while for 29 of them two previous MRI scans and for 17 of them three previous MRI scans were available. The average MTR of all the areas of NAWM studied outside visible MS lesions was 50.0 (SD=1.6) % and that of new enhancing lesions at the time of their appearance was 33.1 (8.4) %.

At each time point the mean MTR for NAWM in areas of future enhancement was significantly lower than the mean MTR in the other NAWM (Table). There was a progressive and significant reduction in MTR in areas of NAWM which subsequently enhanced, from the time the patients were enrolled in the study until the point when enhancement was seen (F=51.7; p < 0.000001). During the follow-up period, there was no significant change of the MTR in NAWM outside areas of subsequent enhancement in any of the ROIs studied.

Table. Mean MTR in NAWM corresponding to areas of future enhancement and in NAWM outside visible MS lesions.

<table>
<thead>
<tr>
<th>N. of ROIs studied</th>
<th>NAWM in areas of future enhancement</th>
<th>NAWM outside visible MS lesions</th>
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<tbody>
<tr>
<td>Mean MTR (SD) 3 months prior to enhancement</td>
<td>17</td>
<td>45.0 (6.1)%</td>
</tr>
<tr>
<td>p</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Mean MTR (SD) 2 months prior to enhancement</td>
<td>29</td>
<td>44.5 (6.2)%</td>
</tr>
<tr>
<td>p</td>
<td>0.0005</td>
<td></td>
</tr>
<tr>
<td>Mean MTR (SD) 1 month prior to enhancement</td>
<td>48</td>
<td>42.5 (7.1)%</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.00001</td>
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</tbody>
</table>

Conclusions

In this study, we found a progressive MTR reduction in areas of NAWM which were subsequently involved in the formation of enhancing MS lesions. MTR reduction reflects increased unbound water content in the diseased brain tissue. We believe that the most likely pathological substrate of our finding is increased water content in reactive astrocytes participating in the demyelinating process (2). In response to a local inflammatory reaction, which possibly represents the initial phase of the immune-activation leading to demyelination (3), a switch may occur in the differentiation of common glial cell progenitors leading to preferential differentiation of these cells into type II astrocytes resulting in astrocyte hyperplasia, which is a prominent feature of ‘established’ MS lesions (1) and might explain an increased content of unbound water in the areas we studied.

References