In vivo assessment of the brain and cervical cord pathology of patients with primary progressive multiple sclerosis

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Summary

In patients with primary progressive (PP) multiple sclerosis, brain MRI lesion activity and burden are low, despite the presence of severe neurological impairment. On the contrary, the degree of cord atrophy and diffuse tissue damage in the brain and cervical cord have been found to be associated with clinical disability. Against this background, this study aimed at providing an in vivo indirect assessment of brain and cervical cord pathology in a large cohort of PP multiple sclerosis patients, using conventional MRI and magnetization transfer imaging (MTI). Ninety-one PP multiple sclerosis patients, 36 secondary progressive (SP) multiple sclerosis patients and 30 healthy controls underwent brain and cervical cord MRI scans, using dual echo (brain) or fast short-tau inversion recovery (cervical cord) MTI and T1-weighted sequences. For the brain, T2 hyperintense and T1 hypointense lesion volumes were calculated and the volume of the whole of the brain tissue measured. For the cervical cord, the number and burden of lesions and the cross-sectional area were assessed. MTI scans were post-processed and analysed to obtain magnetization transfer ratio (MTR) histograms from the whole of the brain and cervical cord tissue and from the normal-appearing brain tissue in isolation. In PP multiple sclerosis patients, brain, normal-appearing brain tissue and cervical cord MTR histogram-derived metrics revealed the presence of diffuse tissue damage whose characteristics did not significantly differ from those of SP multiple sclerosis patients, even though SP multiple sclerosis patients had higher MRI-visible lesion burdens. None of the correlations between MRI or MTI measures obtained from the brain and the cord were significant. PP multiple sclerosis patients’ disability was significantly, albeit weakly associated with a composite MR model including measures of loss and intrinsic damage of cervical cord tissue. Our data indicate the presence of a diffuse tissue damage undetectable by conventional MRI in PP multiple sclerosis patients, whose extent seems to match that of SP multiple sclerosis patients with similar levels of disability. They also suggest that the severity of multiple sclerosis pathology in the cervical cord is one of the factors contributing to neurological impairment in PP multiple sclerosis.

Keywords: primary progressive multiple sclerosis; magnetic resonance imaging; magnetization transfer imaging; brain; cervical cord

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Introduction

Patients with primary progressive (PP) multiple sclerosis represent a subgroup with clinical and MRI characteristics that differ from those of patients with relapsing–remitting (RR) multiple sclerosis or secondary progressive (SP) multiple sclerosis (Thompson et al., 1997; Cottrell et al., 1999). Despite experiencing a progressive disease course from onset, the burden and activity of lesions on their T2-weighted and gadolinium-enhanced brain MRI scans are, on average, lower than in other multiple sclerosis phenotypes (Thompson et al., 1990, 1991; Kidd et al., 1996; Lycklama à Nijeholt et al., 1998; Stevenson et al., 1999; van Walderveen et al., 2001). The fact that the pathology of lesions in PP multiple sclerosis is characterized by a predominant loss of myelin and axons with only mild inflammatory components (Revesz et al., 1994) can explain, at least partially, the relative paucity of conventional MRI-detectable activity (Thompson et al., 1991; Kidd et al., 1996). However, unlike the case in other disease phenotypes, in PP multiple sclerosis patients the correlation between MRI abnormalities and clinical disease severity is not significantly ameliorated when measuring the load of brain T1-hypointense lesions (Stevenson et al., 1999; van Walderveen et al., 2001), which are thought to reflect the presence of severe tissue disruption (van Walderveen et al., 1998). Several pieces of evidence (Lycklama à Nijeholt et al., 1998; Filippi et al., 1999b; Leary et al., 1999; Stevenson et al., 1999; Tortorella et al., 2000) have suggested that two factors may explain the discrepancy between brain MRI and clinical findings in PP multiple sclerosis. First, the presence of diffuse tissue damage at a microscopic level (Filippi et al., 1999b; Leary et al., 1999; Tortorella et al., 2000). Secondly, a prevalent involvement of the cervical cord (Lycklama à Nijeholt et al., 1998; Stevenson et al., 1999), which might also explain the disproportion between the severity of locomotor disability and the less pronounced impairment of other functional systems (Thompson et al., 1997).

Against this background, this study aimed at investigating in vivo the macroscopic and microscopic aspects of brain and cervical cord pathology in a large cohort of PP multiple sclerosis patients, using conventional MRI and magnetization transfer imaging (MTI). Findings from PP multiple sclerosis patients were compared with those from age-matched healthy controls and SP multiple sclerosis patients with similar levels of disability. The correlations between MRI measures of brain and cervical cord pathology with PP multiple sclerosis patients’ disability were also investigated.

Material and methods

Patients

PP multiple sclerosis patients were consecutively selected from the populations attending multiple sclerosis clinics in the participating centres. The disease course was classified according to the criteria of Lublin and colleagues (Lublin et al., 1996) and other neurological conditions were carefully excluded by performing the appropriate investigations, as established by Thompson and colleagues (Thompson et al., 2000). Patients were classified as having definite, probable or possible PP multiple sclerosis, based upon laboratory and instrumental findings (Thompson et al., 2000). At study entry, all patients underwent a complete neurological examination, with rating of the Expanded Disability Status Scale (EDSS) scores (Kurtzke, 1983). This was done by a single observer, who was unaware of MRI results, on the same day as the MRI session.

Two control groups were identified. The first consisted of 30 sex- and age-matched healthy volunteers [female : male, 18 : 12; mean age 49.3 years (range 32–66 years)]. The second consisted of 36 clinically definite multiple sclerosis patients [female : male, 23 : 13] with a secondary progressive disease course (Lublin et al., 1996), who were consecutively referred to the multiple sclerosis clinics in the participating centres. To be included, SP multiple sclerosis patients had to be relapse- and steroid-free for at least 3 months prior to study entry. Their mean age was 48.2 years (range 31–61 years), median disease duration was 15.5 years (range 3–29 years) and median EDSS score, assessed by the same rater and with the same modalities as for PP multiple sclerosis patients, was 6.0 (range 3.5–8.0). At study entry, 18 SP multiple sclerosis patients were untreated, 10 were being treated with interferon beta 1b, six with pulses of intravenous mitoxantrone and two with glatiramer acetate. All the subjects signed a written informed consent prior to study entry and the study design was approved by the local ethical committees of the participating institutions.

Image acquisition

Using a 1.5 T system (Vision; Siemens, Erlangen, Germany), the following pulse sequences were acquired for brain imaging: (i) dual-echo turbo spin echo (TSE) [repetition time (TR) = 3300, echo time (TE) = 16/98, echo train length = 5]; (ii) 2D gradient-echo (GE) (TR = 640, TE = 12, flip angle = 20°), both with and without an MT saturation pulse (this was an off-resonance radio-frequency pulse centred 1.5 kHz below the water frequency with a Gaussian envelope.
of duration 7.68 ms and a flip angle of 500°); and (iii) 
T1-weighted conventional spin echo (SE) (TR = 768, TE = 14). Twenty-four contiguous axial slices with 5 mm thickness, 192 × 256 matrix size and 188 × 250 mm field of view (FOV) were obtained. Accurate scan positioning was achieved following published guidelines (Miller et al., 1991).

In the same scanning session, the following pulse sequences were acquired for cervical cord imaging, using a tailored cervical cord phased array coil for signal reception: (i) fast-short tau inversion recovery (fast-STIR) [TR = 2288, TE = 60, inversion time (TI) = 110, echo train length = 11, FOV = 280 × 280 mm, matrix size = 264 × 512]; (ii) 2D GE (TR = 640, TE = 10, flip angle = 20°, FOV = 250 × 250 mm, matrix size = 192 × 256), both with and without an MT saturation pulse (the saturation pulse had the same characteristics as that used for brain imaging); and (iii) 3D T1-weighted MP-RAGE (magnetization prepared rapid acquisition gradient echo) (TR = 9.7, TE = 4, slab orientation = sagittal, slab thickness = 160 mm, FOV = 280 × 280 mm, number of partitions = 128). For the fast-STIR scans, eight interleaved sagittal slices with a thickness of 3 mm and an interslice gap of 0.3 mm were obtained. For the GE scans, 20 contiguous interleaved axial slices with a thickness of 5 mm were obtained.

Brain scanning was completed for all the study subjects. Cord MRI and MTI data were not obtained from two PP multiple sclerosis patients as there was poor subject compliance owing to the relatively long scanning procedure and their severe disabilities.

Image analysis
Two experienced observers, without knowing to whom the scans belonged, identified by consensus the hyperintense lesions on proton density (PD)-weighted and the hypointense lesions on T1-weighted scans of the brain. T2-weighted images were always used to increase the confidence in lesion identification. On both PD-weighted and T1-weighted images, lesions were marked on the hard copies and brain total lesion volumes (LV) were measured by a single observer, unaware of patients’ clinical characteristics. A local thresholding technique was used for lesion segmentation, keeping the marked hard copies as a reference. Further details about this image analysis method are extensively reported elsewhere (Rovaris et al., 1997). On T1-weighted images, the volumes of the whole brain tissue were measured using a segmentation technique based on signal intensity thresholding and characterized by a high intra-observer reproducibility (Rovaris et al., 2000b).

On the hard copies of the fast-STIR scans, hyperintense multiple sclerosis lesions in the cervical cord were identified with agreement by two observers, without knowing to whom the scans belonged. The size of each lesion was assessed by counting the number of vertebral bodies over which the lesions extended. Reformattting of the original MP-RAGE data was performed using the standard, vendor-supplied multiplanar reformatting software available on the operator’s console of the scanner. For each subject, a set of five contiguous, 3-mm thick axial slices (perpendicular to the spinal cord) was reconstructed using the centre of the C2–3 disc as the caudal landmark. Then, a semi-automated technique developed by Losseff and colleagues was used to segment the cord tissue and to measure the cross-sectional cord area at the level of each slice (Losseff et al., 1996). Values from the five slices were averaged to obtain a single value for each subject. All the analysis was carried out by a single observer, blinded to the clinical status of the subjects. This approach proved to be highly reproducible (Losseff et al., 1996; Stevenson et al., 1999).

Brain and cervical cord magnetization transfer ratio (MTR) histograms were obtained as follows. First, the two GE images (i.e. with and without the magnetization transfer saturation pulse) were co-registered. Registration was performed using an automated technique based on pixel similarity measures (Studholme et al., 1997). Next, an MTR image was calculated from the co-registered GE images as previously described (Filippi et al., 1999b). Brain MTR maps were then co-registered with the dual-echo PD-weighted images (Tortorella et al., 2000). The entire brain and cervical cord tissues were segmented from the MTR images by a single observer, without knowing to whom the scans belonged, using a segmentation technique based on local thresholding (Rovaris et al., 1997). Finally, MTR histograms (with bins 1% in width) were produced. We excluded from the analysis all the pixels with MTR values <10%, to minimize partial volume effects from the CSF. To correct for the between-patient differences in brain and cord volumes, each histogram was normalized by dividing it by the total number of pixels included. MTR histograms were produced from the whole of the brain and cervical cord tissue and from the normal-appearing brain tissue in isolation. To obtain the MTR histograms of normal-appearing brain tissue, multiple sclerosis lesion outlines from PD-weighted scans were automatically transferred onto the co-registered MTR maps and then nulled out. The area of each lesion was also measured and, for individual patients, the average lesion MTR, weighted by lesion area, was calculated. The process of normal-appearing brain tissue MTR histogram creation and average lesion MTR computation is extensively described elsewhere (Tortorella et al., 2000). For each histogram, the average MTR and the peak height (i.e. the proportion of pixels at the most common MTR value) were measured. Given the strong correlation existing between average MTR and MTR histogram peak locations (Filippi et al., 1999b; Tortorella et al., 2000), the latter quantity was not considered for this study, in order to minimize the number of group comparisons and, therefore, reduce the risk of type I errors.

Statistical analysis
Group comparisons were assessed using the Mann–Whitney U test for non-parametric data or Student’s t-test for
parametric data. After Bonferroni correction, significant $P$ values were considered to be those $\leq 0.006$ for comparisons between PP multiple sclerosis patients and healthy controls, and those $\leq 0.004$ for comparisons between PP multiple sclerosis and SP multiple sclerosis patients, respectively. Univariate correlations were assessed using the Spearman rank correlation coefficient. A multivariable linear regression model was also used to generate a composite MR score. This score was computed using a linear combination of MR parameters, which were chosen a priori based on biological considerations. These parameters were cord lesion number and load, cross-sectional cord area, average MTR and histogram peak height, which were thought to reflect the severity of macroscopic lesion burden, atrophy and normal-appearing tissue damage in a critical site for the development of locomotor disability (which is the main aspect influencing the EDSS scores). The weight of each MR parameter resulted from the coefficients estimated by the regression model. The magnitude and the significance of the correlation between composite MR score and EDSS was evaluated by a non-parametric Spearman correlation analysis, as EDSS does not satisfy the assumptions of continuity and normality for a valid inference in linear regression models.

**Results**

Ninety-one PP multiple sclerosis patients (female : male, 56 : 35) were studied. Seventy-seven patients were affected by definite and 14 by probable PP multiple sclerosis (Thompson et al., 2000). Patients with probable PP multiple sclerosis had either negative CSF examination and positive MRI findings (12 cases), or negative CSF examination, equivocal MRI findings and abnormal visual evoked potentials (one case) or positive CSF examination, negative MRI findings and abnormal visual evoked potential (one case). Sixty-six PP multiple sclerosis patients had a spinal cord presentation at disease onset (i.e. progressive paraparesis), while 25 had a uni- (20 patients) or multi-focal (five patients) presentation with motor (eight patients), visual (three patients), cerebellar (12 patients), brainstem (four patients) or sensory (two patients) disturbances. Mean age was 50.2 years (range 25–69 years), median disease duration was 10.0 years (range 1–26 years) and median EDSS score was 6.0 (range 2.5–7.5). Sixty-nine PP multiple sclerosis patients were not undergoing any immunomodulatory or immunosuppressive treatment at study entry, 10 were being treated with methotrexate, seven with oral azathioprine and five with pulses of intravenous mitozantrone.

Nine or more $T_2$-hyperintense brain white matter lesions (Thompson et al., 2000) were seen on the scans from 83 PP multiple sclerosis (91.0%) (Fig. 1A and B) and all SP multiple sclerosis patients; fewer lesions (ranging from two to eight) were visible in the remaining PP multiple sclerosis patients. One or more cervical cord lesions were seen on the scans from 86 PP multiple sclerosis (96.6%) (Fig. 2) and 35 SP multiple sclerosis (97.2%) patients. Table 1 reports conventional MRI findings from multiple sclerosis patients, while Table 2 reports the values of brain and cervical cord MTR graph-derived quantities from normal controls and patients (Figs 3 and 4). The mean values (standard deviation) of brain volume and cervical cord cross-sectional area in healthy controls were 1169.7 (76.8) ml and 82.7 (3.4) mm$^2$, these values were significantly higher than those from PP multiple sclerosis patients ($P$ values $= 0.001$ and 0.002, respectively). All MTR histogram-derived metrics were significantly lower in PP multiple sclerosis patients than in controls. PP multiple sclerosis patients had significantly lower brain $T_2$ LV and higher cervical cord MTR histogram peak height than SP multiple sclerosis patients. The results of group comparisons for brain, normal-appearing brain tissue and cervical cord MTR histogram-derived metrics did not change when correcting for subjects’ brain volume and cord area, respectively. No significant differences were found between PP multiple sclerosis patients with cord or other presentations at the onset of the disease (data not shown).

Brain $T_2$ and $T_1$ LV were significantly correlated with average brain MTR ($r = -0.37$ and $-0.29$, $P < 0.001$ and 0.006, respectively). None of the remaining univariate correlations between brain and cord MRI- or MTI-derived metrics were statistically significant.

No significant univariate correlations were found between patients’ EDSS scores and any MRI- or MTI-derived variable. The multivariable analysis showed that a model including cord area and cord MTR histogram peak height was significantly associated with the level of disability in patients with PP multiple sclerosis; however, the strength of this correlation was relatively low ($r = -0.21$, $P = 0.04$).

**Discussion**

In PP multiple sclerosis patients, conventional MRI scans of the brain typically show a relatively low amount of white matter abnormalities, which are in contrast with their severe and irreversible disability (Thompson et al., 1990, 1991, 1997; Stevenson et al., 1999). Since previous studies have indicated that diffuse microscopic changes of the normal-appearing brain tissue (Leary et al., 1999; Tortorella et al., 2000) and spinal cord pathology (Kidd et al., 1996; Lycklama à Nijeholt et al., 1998; Stevenson et al., 1999) are relevant MRI aspects of patients with PP multiple sclerosis, we performed this study to indirectly assess the presence and extent of overall multiple sclerosis pathology in the brain and cervical cord from a large cohort of PP multiple sclerosis patients, and to compare these findings with those from healthy controls and from SP multiple sclerosis patients with similar levels of disability.

The clinical characteristics of the PP multiple sclerosis patients enrolled in this study are similar to those of other populations (Lycklama à Nijeholt et al., 1998; Stevenson et al., 1999), with the exception of a higher female : male ratio (1.6 versus average values close to 1.0) (Lycklama à Nijeholt et al., 1998; Cottrell et al., 1999; Stevenson et al.,...
Fig. 1 Axial PD-weighted (A), T₂-weighted (B) and T₁-weighted (C) images of the brain obtained from a patient with PP multiple sclerosis at the level of the lateral ventricles. On PD/T₂-weighted images, several hyperintense lesions are visible in the periventricular and deep white matter. The pattern of abnormalities is consistent with multiple sclerosis. On the corresponding T₁-weighted image, only one of these lesions appears as a mildly hypointense area.

1999). According to recently developed specific diagnostic criteria for PP multiple sclerosis (Thompson et al., 2000), ~85% of our patients were classified as having definite PP multiple sclerosis. This figure is even higher than that reported for another group of PP multiple sclerosis patients who underwent a recent, multicentre longitudinal MRI study (Stevenson et al., 2000) and it indicates that our sample was carefully selected in order to exclude other neurological disorders which have the potential to mimic PP multiple sclerosis on a clinical ground.

The high prevalence of patients with definite PP multiple sclerosis in our cohort is also likely to be the explanation for their relatively higher brain T₂ LV, compared with those reported by previous studies (Lycklama à Nijeholt et al.,
Brain and cervical cord tissue damage in PP multiple sclerosis

Fig. 2 Sagittal fast-STIR images of the cervical cord from a patient with PP multiple sclerosis. Multiple hyperintense lesions are visible within the cord.

Table 1 Brain and cervical cord MRI findings from PP multiple sclerosis and SP multiple sclerosis patients

<table>
<thead>
<tr>
<th></th>
<th>PP multiple sclerosis</th>
<th>SP multiple sclerosis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain T2 LV (ml)</td>
<td>19.8 (22.4)</td>
<td>31.2 (18.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>Brain T1 LV (ml)</td>
<td>5.2 (7.7)</td>
<td>7.4 (6.1)</td>
<td>0.28</td>
</tr>
<tr>
<td>T1 : T2 LV ratio</td>
<td>0.20 (0.13)</td>
<td>0.22 (0.08)</td>
<td>0.92</td>
</tr>
<tr>
<td>Brain volume (ml)</td>
<td>1097.4 (116.5)</td>
<td>1094.6 (115.9)</td>
<td>0.95</td>
</tr>
<tr>
<td>Number of cord lesions</td>
<td>3.6 (1.7)</td>
<td>4.0 (1.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Burden of cord lesions (no. of vertebral segments)</td>
<td>4.4 (1.8)</td>
<td>5.1 (1.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>Cord area (mm²)</td>
<td>67.4 (10.8)</td>
<td>64.5 (9.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are expressed as means (standard deviations). For abbreviations and statistical analysis, see the text.

Table 2 Average lesion MTR and MTR graph-derived metrics of the brain, normal-appearing brain tissue and cervical cord from all study subjects

<table>
<thead>
<tr>
<th></th>
<th>PP multiple sclerosis</th>
<th>Controls</th>
<th>P*</th>
<th>SP multiple sclerosis</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average lesion MTR (%)</td>
<td>37.4 (2.7)</td>
<td>-</td>
<td>-</td>
<td>36.7 (2.4)</td>
<td>0.13</td>
</tr>
<tr>
<td>Average MTR (%)</td>
<td>39.5 (1.3)</td>
<td>40.3 (0.9)</td>
<td>0.004</td>
<td>39.7 (1.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Peak height</td>
<td>102.7 (12.3)</td>
<td>114.5 (11.6)</td>
<td>&lt;0.001</td>
<td>98.9 (13.8)</td>
<td>0.10</td>
</tr>
<tr>
<td>Normal-appearing brain tissue Average MTR (%)</td>
<td>39.6 (1.2)</td>
<td>40.3 (0.9)</td>
<td>0.005</td>
<td>39.5 (1.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Peak height</td>
<td>103.6 (12.3)</td>
<td>114.5 (11.6)</td>
<td>&lt;0.001</td>
<td>99.5 (13.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Cord Average MTR (%)</td>
<td>41.9 (3.9)</td>
<td>45.8 (1.4)</td>
<td>&lt;0.001</td>
<td>41.7 (3.0)</td>
<td>0.49</td>
</tr>
<tr>
<td>Peak height</td>
<td>61.4 (13.1)</td>
<td>72.1 (12.9)</td>
<td>0.001</td>
<td>56.9 (11.6)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are expressed as means (standard deviations). For abbreviations and statistical analysis, see the text. *P values for group comparisons between PP multiple sclerosis patients and healthy controls; **P values for group comparisons between PP multiple sclerosis and SP multiple sclerosis patients.
decreased MTR values correspond to areas with significantly greater severity of multiple sclerosis-related disability better than metrics derived from conventional MRI (Filippi et al., 1999b; Tortorella et al., 2000). Although a large extent of the normal-appearing brain tissue is constituted of normal-appearing white matter and, as a consequence, diffuse normal-appearing white matter damage is likely to be the major contributor to the observed MTR histogram changes, recent studies suggest that grey matter pathology might also be an additional contributing factor (Bozzali et al., 2001; Cercignani et al., 2001; Miller et al., 2001). Contrary to a previous preliminary report based upon 13 PP multiple sclerosis patients (Tortorella et al., 2000), we did not find brain and normal-appearing brain tissue MTR histogram differences between PP multiple sclerosis and SP multiple sclerosis patients. This indicates that, in both PP multiple sclerosis and SP multiple sclerosis, the progressive reduction of cerebral tissue with ‘truly’ normal MTR values accompanies the accumulation of irreversible disability, independent of the concomitant accumulation of MRI-visible lesions. In PP multiple sclerosis, this agrees with the frequent finding of diffuse T2-signal abnormalities in the brain and cervical cord (Lycklama à Nijeholt et al., 1998). In addition, in our sample of PP multiple sclerosis patients, average brain MTR values were only in part correlated with T2 and T1 LV. The coefficients of the correlation were about −0.3, thus indicating that <10% of MTR variability was explained by the burden of macroscopic lesions. This agrees with the results of a recent study (Pelletier et al., 2001), showing that, in PP multiple sclerosis patients, brain atrophy and MR spectroscopic equivalents of axonal functioning are independent of the T2-hyperintense lesion load. All of this suggests that normal-appearing brain tissue pathology in PP multiple sclerosis does not merely reflect Wallerian degeneration of axons transversing macroscopic lesions (Evangelou et al., 2000), but it might be related to the occurrence of multiple, discrete lesions beyond the resolution of conventional scanning. This is consistent with the demonstration that, in PP multiple sclerosis (i) individual T2-hyperintense lesions tend to have, on average, a lower size than those seen in SP multiple sclerosis (Thompson et al., 1990) and (ii) a diffuse blood–brain barrier leakage can occur independently of focal enhancing lesions (Silver et al., 2001). The reason why, in PP multiple sclerosis patients, a diffuse brain tissue damage develops with an evident disproportion between MRI-visible lesion burden and normal-appearing tissue pathology still remains an unresolved issue.

We imaged the cervical cord using a fast-STIR sequence, which has been shown to maximize the MRI sensitivity for detecting multiple sclerosis-related macroscopic abnormalities (Rocca et al., 1999). Using such an approach, we found that the burden of cervical cord lesions is similar in PP multiple sclerosis and SP multiple sclerosis patients, in contrast to what is seen for the brain. This finding underpins the importance of multiple sclerosis pathology in the cords of patients with progressive accumulation of disability, independent of the way this occurs, i.e. with or without preceding or superimposed relapses. Our results also confirm
that cervical cord atrophy is present in patients with the two major progressive forms of multiple sclerosis (Losseff et al., 1996; Stevenson et al., 1996, 1999). Recent studies with animal models of chronic inflammatory demyelination (McGavern et al., 2000) and post-mortem specimens from SP multiple sclerosis patients (Lovas et al., 2000; Lycklama à Nijeholt et al., 2001) have confirmed that, in the cervical cord, axonal loss occurs both within visible lesions and in the normal-appearing white matter, and that its degree correlates with the severity of cord atrophy and neurological deficits. However, the modest inverse relationship we found between cord area and disease duration (r = -0.25, P = 0.01) suggests that the development of cord atrophy might also be dependent upon the time elapsed from the clinical onset of multiple sclerosis. This is also confirmed by the more pronounced degree of cord area reduction found in SP multiple sclerosis patients, who had longer disease duration than PP multiple sclerosis patients on average, but similar levels of disability.

Cord MTR histogram findings from both PP multiple sclerosis and SP multiple sclerosis patients are consistent with the presence of a diffuse and severe multiple sclerosis-related damage. However, the mechanisms leading to diffuse cord pathology might differ between PP multiple sclerosis and SP multiple sclerosis. In SP multiple sclerosis, cervical cord pathology may result from both local damage and a Wallerian degeneration of descending fibres from brain lesions. In patients with PP multiple sclerosis, the latter mechanism is likely to contribute to a lesser degree, due to the presence of a lower lesion burden in the brain (Thompson et al., 1990, 1991; Lycklama à Nijeholt et al., 1998; Stevenson et al., 1999; van Walderveen et al., 2001). The lack of significant correlations between MR measures of multiple sclerosis pathology in the brain and cord, which is consistent with the results of previous studies (Lycklama à Nijeholt et al., 1998; Rovaris et al., 2000a), also suggests that degenerative processes affecting fibre tracts descending from brain lesions play only a modest role in determining the severity of PP multiple sclerosis-related cervical cord pathology. As in a previous study (Lycklama à Nijeholt et al., 2000), we did not find a significant correlation between cord cross-sectional area and MTR histogram-derived quantities from the same region. This indicates that cord MTR histogram analysis encompasses both the loss of fibres leading to MRI-visible cord atrophy and the microscopic tissue damage affecting the remaining cord parenchyma (Bozzali et al., 1999; Filippi et al., 2000; Lycklama à Nijeholt et al., 2000; Rovaris et al., 2000a), without being influenced by partial volume effects from enlarged CSF spaces. The suggestion that microscopic changes may occur in addition to atrophy within CNS fibre tracts is supported by the study of Evangelou and colleagues, who found a decrease in both axonal density and tissue volume in the corpora callosa of patients with multiple sclerosis (Evangelou et al., 2000). The results of our analysis did not change after correcting for subjects’ cord size, which also supports this concept. Longitudinal studies are now needed to assess whether cervical cord MTR histogram analysis may be sensitive enough to detect the progression of multiple sclerosis pathology over time and to provide paraclinical measures of outcome for monitoring the evolution of PP multiple sclerosis.

Disappointingly, we did not find any correlation between individual MR-derived measures and patients’ EDSS scores. As far as brain metrics are concerned, this could mainly be due to the limitations of EDSS, including the fact that this scale is heavily weighted towards locomotor disability (Kurtzke, 1983). This is confirmed by the improved correlations obtained when cognitive scales (Camp et al., 1999) or composite scores (Tintore et al., 2001) are used to assess PP multiple sclerosis neurological disability. Only by combining cord measures reflecting the severity of atrophy and that of intrinsic pathology in the remaining tissue (MTR histogram peak height), we obtained a composite MR model with a relatively low, but significant correlation with PP multiple sclerosis patients’ EDSS score. In a recent study (Mainiero et al., 2001), we found that a multiparametric model including T1/LV, brain mean diffusivity and brain NAA/Cr (N-acetylaspartate/creatine) ratio was able to explain >50% of the variance of disability observed in a sample of RR multiple sclerosis and SP multiple sclerosis patients. Thus, the results of these two studies agree in suggesting that composite MR models have the potential to increase our understanding of multiple sclerosis pathophysiology.

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