Magnetic resonance imaging characteristics of children and adults with paediatric-onset multiple sclerosis

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The purpose of this study was to compare the clinical and quantitative magnetic resonance imaging metrics of paediatric-onset multiple sclerosis to adult-onset multiple sclerosis. It was a prospective comparison of clinical and magnetic resonance imaging characteristics of two paediatric onset multiple sclerosis and two adult onset multiple sclerosis groups that were matched for disease duration. The paediatric-onset-C group consisted of children with paediatric-onset multiple sclerosis with mean disease duration of 2.7 years, whereas the paediatric onset-A group consisted of adults with mean disease duration of 20 years. The adult onset multiple sclerosis-1 and adult onset multiple sclerosis-2 groups were matched to the paediatric onset-C and paediatric onset-A groups. The brain magnetic resonance imaging measures included: T1-, T2- and gadolinium contrast-enhancing volumes and the T2-lesion volume relative magnetization transfer ratio, global and tissue specific white and grey matter brain atrophy and normal appearing grey and white matter magnetization transfer ratio. Regression analyses were employed for magnetic resonance imaging measures. The paediatric onset multiple sclerosis-C (n=17) and adult onset multiple sclerosis-1 (n=81) groups had mean disease duration values of 2.7 ± standard deviation 2.0 and 2.6 ± 1.1 years, respectively. The paediatric onset multiple sclerosis-A group (n = 33) and adult onset multiple sclerosis-2 group (n = 300) had mean disease durations of 20 ± standard deviation 10.9 and 20 ± 9.3 years, respectively. In regression analysis, the T2- lesion volume of the paediatric onset multiple sclerosis-C and adult onset multiple sclerosis-1 groups were similar but there was a trend toward higher T1- lesion volume (P = 0.028) in the paediatric onset group. The brain parenchymal fraction and grey matter fraction in the paediatric-onset multiple sclerosis-C group were higher than those for the adult onset multiple sclerosis-1 group (both P < 0.001). The frequency of progressive multiple sclerosis in the paediatric onset multiple sclerosis-A group (27.3%) trended lower (odds ratio = 0.43, P = 0.042) than that in the adult onset multiple sclerosis-2 group (46.3%). The Expanded Disability Status Scale (median; inter-quartile range) in the paediatric onset multiple sclerosis-A group (2.25; 2.5) trended lower (P = 0.058).
compared with the adult onset multiple sclerosis-2 group (3.5; 4.0). There was a trend toward lower magnetization transfer ratio values in $T_2$-lesions, normal appearing grey matter and normal appearing white matter and higher grey matter fraction in the paediatric onset multiple sclerosis-A group compared with the adult onset multiple sclerosis-2 group. There was no evidence for differences on $T_2$-lesion volume, $T_1$-lesion volume, brain parenchymal fraction or white matter fraction. Paediatric-onset multiple sclerosis is characterized by a significant disease burden both early and later in the disease course. Despite this, disability is slower to accrue in paediatric onset multiple sclerosis than adult onset multiple sclerosis.

**Keywords:** multiple sclerosis; magnetic resonance imaging; paediatric; paediatric-onset multiple sclerosis, adult-onset multiple sclerosis

**Abbreviations:** EDSS = expanded disability status scale; MSSS = multiple sclerosis severity scale; MTR = magnetization transfer ratio

### Introduction and background

Paediatric onset multiple sclerosis may comprise up to 5% of all cases of multiple sclerosis. According to consensus definitions of the International Paediatric Multiple Sclerosis Study Group, paediatric-onset multiple sclerosis may be diagnosed after two distinct episodes of CNS demyelination that are disseminated in time and space, in individuals <18 years (Krupp et al., 2007). The consensus definition does not specify a lower age limit (Krupp et al., 2007).

MRI can enable earlier multiple sclerosis diagnosis and predict the conversion of clinically isolated syndrome to multiple sclerosis in the adult multiple sclerosis population. McDonald criteria, which employ conventional MRI measures, are widely accepted for the diagnosis of adult onset multiple sclerosis (McDonald et al., 2001; Polman et al., 2005). Although these criteria have been suggested for use in the diagnosis of paediatric onset multiple sclerosis, their value, particularly in children <10 years old, is not yet established (Banwell et al., 2007; Krupp et al., 2007). New MRI diagnostic criteria for establishing dissemination in space for paediatric-onset multiple sclerosis have recently been published, but further studies are necessary to confirm their predictive diagnostic value and utility for ascertaining dissemination in time (Callen et al., 2009).

It is widely accepted that in adult onset multiple sclerosis, conventional MRI lesion measures do not adequately predict progression of impairment and physical disability. Lesions identified on $T_2$-weighted images are non-specific and cannot adequately distinguish between inflammation, oedema and axonal loss (Zivadinov, 2004). The presence of contrast enhancement on $T_1$-weighted images may indicate active demyelination but this enhancement is transient, variable and does not reliably indicate permanent injury or disease progression (Lai et al., 1996; Filippi et al., 1997). Not surprisingly, lesion volume shows poor correlation with clinical findings in multiple sclerosis (Barkhof, 1999). For this reason, quantitative MRI measures of global and tissue specific atrophy have been widely employed to evaluate multiple sclerosis disease progression. Brain atrophy affecting both grey and white matter may occur early in adult onset multiple sclerosis (Chard et al., 2002; Tiberio et al., 2005) and grey matter atrophy has been shown to correlate with disease subtype and disability in patients with disease duration of 20 years. Indeed, grey matter atrophy may be greater than white matter atrophy in patients with longstanding multiple sclerosis (Fisniku et al., 2008). Nonetheless, clinical disease progression is sometimes difficult to correlate with MRI measures; patients with advancing neurologic disability may have only modest MRI lesion volume whereas patients with abundant or enlarging lesions on MRI may have minimal disability (Thompson et al., 1990; Zivadinov, 2009).

Although recent work on the diagnostic utility of brain MRI in paediatric onset multiple sclerosis has been published, little information on MRI progression is available. Clinical progression in paediatric-onset multiple sclerosis presents several paradoxical features differing from adult onset multiple sclerosis that are not fully understood. The annualized relapse rate may be up to 3-fold higher in paediatric-onset multiple sclerosis than in adult onset multiple sclerosis (1.13 versus 0.4), which suggests greater disease activity in this population (Gorman et al., 2009), but surprisingly the mean time to reach the secondary progressive phase of the disease is longer in children than in adults with multiple sclerosis (9–16 versus 7–9 years) (Simone et al., 2002; Renoux et al., 2007). Although the number of $T_2$ lesions at the time of first event is higher in children than in adults (Waubant, 2009), the mean time to reach certain milestones of disability progression [expanded disability status scale (EDSS) of 4.0] and conversion to the secondary progressive phase is almost 10 years longer in paediatric multiple sclerosis population than in the adults (Simone et al., 2002; Renoux et al., 2007).

Quantitative brain MRI measures can potentially provide a better understanding of the pathophysiological, lesional and neurodegenerative processes underlying the paradoxical features of paediatric onset multiple sclerosis, but have not been extensively investigated. In this study, our objective was to compare clinical outcomes and quantitative brain MRI studies in patients with early and longstanding paediatric-onset multiple sclerosis to those of adult onset multiple sclerosis of the same disease duration.

### Methods

#### Study population

This is a cross-sectional study of a cohort of patients entered in an ongoing prospective natural history study at the Paediatric Multiple Sclerosis Centre of the Jacobs Neurological Institute, part of the US National Paediatric Multiple Sclerosis Network.
Consensus-based diagnostic criteria for paediatric demyelinating disorders and multiple sclerosis were used (Krupp et al., 2007). The group of children with paediatric-onset multiple sclerosis was referred to as the paediatric-onset multiple sclerosis-C group and consisted of 17 children. All children in this cohort were tested for NMO IgG; no patients were seropositive.

Institutional review board approval was obtained from the University at Buffalo Children and Youth IRB.

The paediatric-onset multiple sclerosis adult (-A) group and two adult onset multiple sclerosis comparator groups (adult onset multiple sclerosis-1 and adult onset multiple sclerosis-2) were obtained by sampling an 800 subject MRI data set of consecutive individuals who had obtained quantitative MRI assessments at the Buffalo Neuroimaging Analysis Centre as part of a prospective clinical surveillance study. The MRI was obtained >1 month from any exacerbation or intravenous glucocorticosteroid treatments. The following criteria were applied for selection from the 800 subject MRI data set.

The paediatric onset multiple sclerosis-A group consisted of 33 adults who were identified using the criterion of age of onset <18 years and were confirmed to have paediatric-onset multiple sclerosis. The adult onset multiple sclerosis-1 subset was obtained by selecting cases that met the criteria: age of onset >18 and <45 years, relapsing–remitting multiple sclerosis disease course and disease duration of <4 years. The adult onset multiple sclerosis-1 comparator group consisted of 81 subjects and had mean disease duration similar to the paediatric onset multiple sclerosis-C group. The adult onset multiple sclerosis-2 comparator group consisted of 300 patients and was obtained by selecting cases with age of onset >18 years and matching to obtain a similar mean disease duration to the paediatric onset multiple sclerosis-A group.

**MRI analysis**

Patients underwent brain MRI using the same 1.5 T General Electric Signa 4x/Lx, scanner (version 12.0) at the Women and Children’s Hospital and Buffalo General Hospital. The MRI protocols were identical to two scanners and consisted of the following scans: axial dual fast spin-echo T2/proton density-weighted image, 3D spoiled-gradient recalled T1-weighted image, spin echo T1-weighted image with and without gadolinium contrast, fast attenuated inversion recovery and proton density with and without magnetization transfer pulse images. The acquisition parameters are summarized in the online Supplementary Data.

MRIs from children with braces at the time of MRI acquisition were excluded from analysis because of susceptibility artefacts.

Image analysis was performed at the Buffalo Neuroimaging Analysis Centre, Department of Neurology, SUNY Buffalo, Buffalo, NY. The following MRI measures were obtained: T1, T2- and gadolinium contrast-enhancing lesion volumes, measures of global and tissue specific brain atrophy.

The T2-lesion volume, T1-lesion volume and contrast-enhancing lesion volume were measured using a semi-automated edge detection contouring–thresholding technique previously described (Zivadinov et al., 2001).

For the global atrophy measures, Statistical Parametric Mapping (SPM5, Institute of Neurology, Queen Square, London, UK) was used (Ashburner and Friston, 2000). Because the presence of abnormal T1 hypointensities can cause tissue misclassification when performing automated segmentation, we use a dilution-based inpainting method to correct all areas of focal abnormality before proceeding with the analysis. The MRI scans were aligned, stripped of extracranial tissue (e.g. soft tissue, skull, orbit) and segmented into brain parenchyma and CSF compartments. The brain parenchymal fraction, a measure of normalized brain volume, was computed by dividing the total brain parenchyma by total intracranial volume. Similarly, grey matter fraction and white matter fraction were obtained by dividing each of these variables by total intracranial volume, as previously described (Zivadinov et al., 2009).

Magnetization transfer ratio (MTR) measurements were available for a subset of 29 patients in the paediatric onset multiple sclerosis-A, 59 patients in the adult onset multiple sclerosis-1 and 234 patients in the adult onset multiple sclerosis-2 groups. Although the magnetization transfer scanning protocol was included for the paediatric onset-C group, it was run only as an optional sequence at the end of the scanning session. Because motion artifacts increase at the end of MRI runs particularly in the paediatric population, the scans from the paediatric onset-C group were not analysable despite the availability of the magnetization transfer sequence in few paediatric onset-C cases. These data were not included in the statistical analyses.

The MTR post-processing was performed by an automated program previously described (Zivadinov et al., 2007). Initially, native acquisition fast attenuated inversion recovery, 3D spoiled-gradient recalled T1-weighted image, and proton density plus magnetization transfer images were co-registered to a native acquisition space proton density image. The fast attenuated inversion recovery and T1-weighted image lesion masks were used to nullify overt lesions, and the remaining proton density was algebraically combined with the co-registered proton density plus weighted image using the equation \[\% \text{MTR} = (PD - PD + MT)/PD \times 100\] to generate normal appearing grey matter, normal appearing white matter or T2-lesion volume maps. The mean MTR of the final image was calculated for each tissue class.

**Data analysis**

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, version 16.0) was used for all statistical analyses. Because of the multiple testing involved in the analysis of MRI and clinical data, we used a conservative \(\alpha = 0.01\) to assess significance. A statistical trend was assumed if the \(P \leq 0.05\).

The independent sample \(t\)-test was used for two-group comparisons to test for differences in means of continuous demographic variables such as age, age of onset and disease duration. The Fisher exact test was used for count variables such as female to male ratio and frequency of secondary-progressive multiple sclerosis. The Mann–Whitney test was used for the analysis of the EDSS.

The multiple sclerosis severity scale (MSSS) values were calculated from the EDSS and disease duration values with software from http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS/Readme.html. The global reference dataset provided with the software was employed. The T2-lesion volume, T1-lesion volume and contrast-enhancing lesion volume variables were cube root transformed (Benedict et al., 2006). These variables exhibited large deviations from normality in probability–probability plots and the transformation was effective at reducing the skewness of MRI parameters. For regression analysis, group status variables denoting the paediatric onset multiple sclerosis-C, paediatric onset multiple sclerosis-A, adult onset multiple sclerosis-1 and adult onset multiple sclerosis-2 groups were obtained using binary indicator variables.

The MSSS and MRI measures of interest were treated as dependent variables in univariate regression analysis with age and a group status variable for paediatric-onset multiple sclerosis as independent variables.
Results

Patient characteristics

The demographic and clinical characteristics of the paediatric onset multiple sclerosis-C, paediatric onset multiple sclerosis-A, adult onset multiple sclerosis-1 and adult onset multiple sclerosis-2 groups are summarized in Table 1. Figure 1 provides an overview of the inter-group comparisons that were assessed and the variables on which the paediatric onset multiple sclerosis-C, paediatric onset multiple sclerosis-A, adult onset multiple sclerosis-1 and adult onset multiple sclerosis-2 groups differed. There were no significant differences between comparison groups regarding treatment duration. The majority of the paediatric and adult onset subjects in our study were treated with disease modifying therapies; interferon-β 1a was the most frequent.

Comparison of children with paediatric onset multiple sclerosis to the early stages of adult relapsing–remitting multiple sclerosis

To compare the MRI characteristics of paediatric-onset multiple sclerosis children to adult onset multiple sclerosis with comparable mean disease duration, we used the paediatric onset multiple sclerosis-C and the adult onset multiple sclerosis-1 groups. As would be expected, the age of onset and age of the paediatric onset multiple sclerosis-C group were lower than the adult onset multiple sclerosis-1 group (both \( P < 0.001 \)). However, the mean disease duration (\( P = 0.85 \), t-test) and proportions of females and

Table 1 Clinical and demographic characteristics of the paediatric onset multiple sclerosis cohort and the adult onset multiple sclerosis comparator groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paediatric onset multiple sclerosis-C</th>
<th>Adult onset multiple sclerosis-1</th>
<th>Paediatric onset multiple sclerosis-A</th>
<th>Adult-onset multiple sclerosis-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>17</td>
<td>81</td>
<td>33</td>
<td>300</td>
</tr>
<tr>
<td>Females:males (% female)</td>
<td>12.5 (71%)</td>
<td>68:13 (84%)</td>
<td>35.8 (76%)</td>
<td>235:65 (78%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>13.8 ± 4.3</td>
<td>35.9 ± 6.9</td>
<td>36.5 ± 11.5</td>
<td>50.5 ± 9.1</td>
</tr>
<tr>
<td>Age of onset, years</td>
<td>11.1 ± 4.0</td>
<td>33.4 ± 6.6</td>
<td>16.3 ± 2.1</td>
<td>30.7 ± 8.0</td>
</tr>
<tr>
<td>Disease duration</td>
<td>2.7 ± 2.0</td>
<td>2.6 ± 1.1</td>
<td>20.0 ± 10.9</td>
<td>20.0 ± 9.3</td>
</tr>
<tr>
<td>Age ≤ 10 years</td>
<td>3:14 (18%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Onset age ≤ 10 years</td>
<td>6.11 (35%)</td>
<td>NA</td>
<td>1 (3%)</td>
<td>–</td>
</tr>
<tr>
<td>Treatment duration, years</td>
<td>1.2 ± 1.1</td>
<td>1.9 ± 1.5</td>
<td>5.0 ± 2.8</td>
<td>4.8 ± 3.1</td>
</tr>
<tr>
<td>Treatment in last 2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>18%</td>
<td>14%</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Interferon-β</td>
<td>71%</td>
<td>66%</td>
<td>76%</td>
<td>58%</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>6%</td>
<td>15%</td>
<td>6%</td>
<td>15%</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1%</td>
</tr>
<tr>
<td>Other therapiesa</td>
<td>6%</td>
<td>4%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Combination therapyb</td>
<td>–</td>
<td>1%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>EDSS</td>
<td>1.0 (2.25)</td>
<td>2.0 (1.5)</td>
<td>2.25 (2.5)</td>
<td>3.5 (4.0)</td>
</tr>
</tbody>
</table>

Data are mean ± SD except for proportions and EDSS, which is expressed as median (inter-quartile range).

a Other therapies includes intravenous immunoglobulin, mitoxantrone, azathioprine, methotrexate, intravenous glucocorticosteroids, etc.

b Combination therapy represents combination of other therapies with interferon-β or glatiramer acetate.
males ($P = 0.30$, Fisher Exact test) were similar in both groups. Both groups presented with a relapsing–remitting disease course. The EDSS of the paediatric onset multiple sclerosis-C group (median; inter-quartile range = 1.0; 2.5) was modestly lower ($P = 0.005$, Mann–Whitney test) than that in the adult onset multiple sclerosis-1 group (median; inter-quartile range = 2.0; 1.5).

Using regression analysis, the $T_2$-lesion volume values of the paediatric onset multiple sclerosis-C and adult onset multiple sclerosis-1 groups were similar but there was a trend toward higher $T_1$-lesion volume [$slope \pm standard error (SE) = 4.1 \pm 1.8$, $P = 0.020$] in the paediatric onset multiple sclerosis-C group (Table 2). No differences were observed for contrast-enhancing-lesion volume between the two groups. The brain parenchymal fraction [$slope \pm SE = 0.045 \pm 0.007$] and grey matter fraction [$slope \pm SE = 0.038 \pm 0.007$] in the paediatric-onset multiple sclerosis-C group were higher than those for the adult onset multiple sclerosis-1 group (both $P < 0.001$). This may be consistent with lack of evidence for atrophy. However, the exact significance of this finding is not clear because of the lack of normative brain parenchymal fraction and grey matter fraction values in children at different developmental stages.

Because the brain volume in children changes during development, we assessed the proportion of the brain that was occupied by $T_2$ and $T_1$ lesions by examining the ratios of $T_2$-lesion volume (and $T_1$-lesion volume) normalized to either the absolute intracranial volume or brain parenchymal volume and also the $T_1$-lesion volume to $T_2$-lesion volume ratio. There were no significant differences in the ratios involving $T_2$-lesion volume normalized to either absolute intracranial volume or brain parenchymal volume (Fig. 2). The $T_1$-lesion volume to $T_2$-lesion volume ratio was significantly higher in the paediatric onset multiple sclerosis-C group ($slope \pm SE = 0.22 \pm 0.039$, $P < 0.001$). The $T_1$-lesion volume to intracranial volume ratio ($slope \pm SE = 0.23 \pm 0.075$, $P = 0.004$) and $T_1$-lesion volume to brain parenchymal volume ratio ($slope \pm SE = 0.25 \pm 0.090$, $P = 0.006$) were also higher in the paediatric onset multiple sclerosis-C group.

These results indicate high levels of formation of $T_1$-hypointense lesions in children with multiple sclerosis, with the $T_1$-lesion volume in children with multiple sclerosis comprising a greater proportion of brain volume than in adults.

### Table 2 MRI parameters of the paediatric onset multiple sclerosis cohort and the adult onset multiple sclerosis comparator groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Paediatric onset multiple sclerosis-C</th>
<th>Adult onset multiple sclerosis-1</th>
<th>Paediatric onset multiple sclerosis-A</th>
<th>Adult onset multiple sclerosis-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE-lesion volume, mm$^3$</td>
<td>37 $\pm$ 98</td>
<td>127 $\pm$ 552</td>
<td>302 $\pm$ 1200</td>
<td>48 $\pm$ 140</td>
</tr>
<tr>
<td>T$_2$-lesion volume, ml</td>
<td>9.1 $\pm$ 15</td>
<td>8.0 $\pm$ 9.9</td>
<td>26.0 $\pm$ 31</td>
<td>17.0 $\pm$ 17</td>
</tr>
<tr>
<td>T$_1$-lesion volume, ml</td>
<td>3.9 $\pm$ 7.3</td>
<td>1.1 $\pm$ 2.2</td>
<td>2.6 $\pm$ 3.8</td>
<td>3.0 $\pm$ 4.7</td>
</tr>
<tr>
<td>GMF</td>
<td>0.460 $\pm$ 0.020</td>
<td>0.425 $\pm$ 0.026</td>
<td>0.402 $\pm$ 0.044</td>
<td>0.390 $\pm$ 0.033</td>
</tr>
<tr>
<td>WMF</td>
<td>0.403 $\pm$ 0.017</td>
<td>0.396 $\pm$ 0.021</td>
<td>0.392 $\pm$ 0.026</td>
<td>0.397 $\pm$ 0.025</td>
</tr>
<tr>
<td>BPF</td>
<td>0.864 $\pm$ 0.016</td>
<td>0.821 $\pm$ 0.027</td>
<td>0.794 $\pm$ 0.038</td>
<td>0.787 $\pm$ 0.033</td>
</tr>
</tbody>
</table>

Data are mean $\pm$ SD. CE = contrast enhancing; GMF = grey matter fraction; WMF = white matter fraction; BPF = brain parenchymal fraction.
Disease duration effects in adults with paediatric-onset multiple sclerosis versus adult-onset multiple sclerosis

We compared the clinical and MRI characteristics of the paediatric onset multiple sclerosis-A and adult onset multiple sclerosis-2 groups to assess the long-term impact of paediatric-onset multiple sclerosis after a mean disease duration of 20 years. The disease duration ($P = 0.99$, t-test) and proportions of females and males ($P = 0.82$, Fisher’s Exact test) were similar in both groups. As expected, the age of onset and age of the paediatric onset multiple sclerosis-A group was lower than in the adult onset multiple sclerosis-2 group (both $P < 0.001$).

We compared with the frequency of progressive disease in the paediatric onset multiple sclerosis-A group to that in the adult onset multiple sclerosis-2 comparator group. The adult onset multiple sclerosis-2 group had 126 (42%) secondary-progressive multiple sclerosis cases and 13 primary-progressive multiple sclerosis (4.3%) cases compared with nine (27.3%) secondary-progressive multiple sclerosis cases and no primary-progressive multiple sclerosis cases in the paediatric onset multiple sclerosis-A group. The frequency of progressive multiple sclerosis (includes both secondary-progressive and primary-progressive multiple sclerosis) trended lower in the paediatric onset multiple sclerosis-A group ($P = 0.042$, Fisher Exact test, odds ratio = 0.43).

The EDSS [median (inter-quartile range)] in the paediatric onset multiple sclerosis-A group was 2.25 (2.5) compared with 3.5 (4.0) in the adult onset multiple sclerosis-2 group indicating a possible trend toward lower EDSS in the paediatric onset multiple sclerosis-A group ($P = 0.058$, Mann–Whitney test). There was a trend toward lower MSSS (slope $\pm SE = -0.99 \pm 0.47$, $P = 0.035$) in the paediatric onset multiple sclerosis-A group [mean MSSS $\pm$ standard deviation (SD) = 2.63 $\pm$ 2.4] compared with the adult onset multiple sclerosis-2 group (3.60 $\pm$ 2.5).

As summarized in Fig. 3, there were trends toward lower MTR values in T2-lesions, normally appearing grey matter, as well as normally appearing white matter in the paediatric onset multiple sclerosis-A group compared with the adult onset multiple sclerosis-2 group. There was no evidence for significant differences between the paediatric onset multiple sclerosis-A and adult onset multiple sclerosis-2 groups on T2-lesion volume, T1-lesion volume, contrast-enhancing lesion volume, brain parenchymal fraction or white matter fraction (Table 2). There was a trend toward higher grey matter fraction in the paediatric onset multiple sclerosis-A group (slope $\pm SE = 0.013 \pm 0.006$, $P = 0.047$).

Effect of age in adults with paediatric-onset multiple sclerosis versus adult-onset multiple sclerosis

We compared the clinical and MRI characteristics of the paediatric-onset multiple sclerosis-A and adult onset multiple sclerosis-1 groups to determine whether the MRI characteristics of paediatric multiple sclerosis patients differed from that of adult multiple sclerosis patients of similar age. There was no evidence for differences in age ($P = 0.19$, t-test) and the proportions of females and males ($P = 0.62$, Fisher Exact test) between these groups were similar. As expected, the age of onset of the paediatric-onset multiple sclerosis-A group was lower than the adult onset multiple sclerosis-1 group and the disease duration was longer in the paediatric-onset multiple sclerosis-A group (both $P < 0.001$).

There was a trend toward higher EDSS ($P = 0.012$, Mann–Whitney test) in the paediatric-onset multiple sclerosis-A (median EDSS; inter-quartile range = 2.25; 2.5) group compared with the adult onset multiple sclerosis-1 group (median EDSS; inter-quartile range = 1.5; 1.1). In contrast to the EDSS, the MSSS of the paediatric-onset multiple sclerosis-A group (mean $\pm$ SD = 2.6 $\pm$ 2.4) was lower (slope $\pm SE = -2.0 \pm 0.51$, $P < 0.001$) than the MSSS for the adult onset multiple sclerosis-1 group (mean $\pm$ SD = 4.69 $\pm$ 2.4). This finding is consistent with a lower disability progression in paediatric-onset multiple sclerosis reported in natural history studies.

In regression analyses, the T2-lesion volume (slope $\pm SE = 8.0 \pm 1.6$, $P < 0.001$) and T1-lesion volume (slope $\pm SE = 3.4 \pm 1.2$, $P = 0.004$) were higher in paediatric onset multiple sclerosis-A group compared with the adult onset multiple sclerosis-1 group. No differences were observed for contrast-enhancing lesion volume between the two groups. The brain parenchymal fraction (slope $\pm SE = -0.023 \pm 0.006$, $P < 0.001$) and grey matter
fraction (slope ± SE = −0.016 ± 0.006, P = 0.006) were lower in paediatric onset multiple sclerosis-A group compared with the adult onset multiple sclerosis-1 group; we did not find evidence for differences in the white matter fraction (P = 0.12). The MTR values (Fig. 3) in T2-lesions, normally appearing grey matter, and normally appearing white matter (all P = 0.003) indicate greater extent of tissue injury in paediatric onset multiple sclerosis-A group. These MRI findings of increased lesion burden, atrophy and tissue injury are consistent with the longer disease duration in the paediatric-onset multiple sclerosis-A group.

Discussion

In this article, we have contrasted quantitative MRI metrics of lesion burden atrophy and MTR from brain MRI scans of patients with early and longstanding paediatric onset multiple sclerosis to those in a group of patients with adult onset multiple sclerosis of similar disease duration. Our data suggest that paediatric onset multiple sclerosis is characterized by a greater MRI disease burden both early on in the disease and at later stages, reinforcing previous studies that have suggested a higher frequency of relapses in paediatric onset multiple sclerosis than adult onset multiple sclerosis (Gorman et al., 2009).

Early on in the disease, children with paediatric-onset multiple sclerosis showed a trend towards higher T1-lesion volume compared with adults with similar disease duration. In addition, the ratio of T1-lesion volume to T2-lesion volume was greater in the paediatric onset multiple sclerosis-C group than the adult onset multiple sclerosis-1 group; T1-lesion volume to brain parenchymal volume was also higher in the paediatric onset multiple sclerosis-C group. Both of these findings suggest more aggressive disease in children early on. This corresponds with recent data that suggest a higher lesion burden in paediatric multiple sclerosis than adult onset multiple sclerosis (Waubant et al., 2009). These findings are somewhat surprising, considering that children have been generally assumed to have greater capacity for remyelination. A subset of T1-hypointense lesions can represent oedema or even remyelination and may resolve over 6 months (Zivadinov, 2007). In the present study, we did not have longitudinal data to assess whether any T1-hypointensities resolved over time. However, the higher T1-lesion volume to T2-lesion volume ratio in the paediatric onset multiple sclerosis-C group suggests that T1 hypointensities represent a greater proportion of the overall lesion burden. A limitation of this study is that we did not have MTR data in the paediatric onset multiple sclerosis-C group to measure capacity for remyelination.

Recent research suggests that grey matter atrophy can occur early in the course of paediatric onset multiple sclerosis (Mesaros et al., 2008): grey matter atrophy in the thalamus was found to be present in paediatric onset multiple sclerosis after a mean disease duration of three years. However, unlike the adult population where correlations between grey matter atrophy and disability have been found, there was no correlation found between the grey matter volume loss and disease duration or disability (Mesaros et al., 2008). This may be a function of the relatively short disease duration in the patients studied although other reasons related to reparative abilities in this age group (Chabas et al., 2008) or preserved functional reserve (Rocca et al., 2008) may be considered.

The brain parenchymal fraction was greater in the paediatric onset multiple sclerosis-C group compared the adult onset multiple sclerosis-1 group with similar disease duration. This may suggest better tissue preservation early in the paediatric onset multiple sclerosis disease course. However, comparisons between the groups are difficult because of the lack of normative data for brain parenchymal fraction in paediatric populations.

However, it is striking that, when contrasting adults in the paediatric onset multiple sclerosis-A group with longstanding paediatric-onset disease with adults in the adult onset multiple sclerosis-2 group with longstanding adult onset disease, no significant differences were found in the brain parenchymal fraction, grey matter fraction, white matter fraction, T1-lesion volume and T2-lesion volume. Evaluation of normal controls in the adult population has suggested a brain volume loss of 0.2% per year between the ages of 30–50 as part of the normal ageing process (Zivadinov and Bakshi, 2004). Because the average age of the paediatric onset multiple sclerosis-A group was 14 years younger (36.5 versus 50.5 years) than that of the adult onset multiple sclerosis-2 group, one would have expected to observe a greater brain parenchymal fraction for the paediatric onset multiple sclerosis-A group due to the adverse effects of normal ageing in the adult onset multiple sclerosis-2 group. This expectation was not borne out: the brain parenchymal fraction values were similar, again suggesting more aggressive disease in the paediatric onset multiple sclerosis group. The trends toward lower MTR values in T2-lesions, normally appearing grey matter as well as normally appearing white matter in the paediatric onset multiple sclerosis-A group compared with the adult onset multiple sclerosis-2 group suggest higher intrinsic damage and lower capacity for remyelination. In addition, individuals with longstanding paediatric onset disease had a significantly lower brain parenchymal fraction than adults with adult-onset disease who were similarly aged, but with shorter disease duration. The majority of damage was accounted for by loss in the grey matter volume tissue compartment. This too, reinforces the notion that paediatric onset multiple sclerosis is characterized with an accelerated micro- and macroscopic MRI disease progression. These findings are consistent with adult literature that suggests that gray matter atrophy is predominant in longstanding multiple sclerosis.

Longitudinal studies have demonstrated that white matter volume increases continually in the normal brain through adolescence, with evidence for a decline in grey matter from 12 years of age to post-adolescence (Giedd et al., 1999; Sowell et al., 2002). It is possible that the normal brain growth and development usually seen in this time period may be hampered by the disease process in multiple sclerosis, thus resulting in decreased brain volumes later on compared with individuals with adult onset disease, whose disease process did not start until after brain maturation was complete. As our MTR results show evidence for increased tissue injury in the paediatric groups, they corroborate this possibility.

Our adult and paediatric samples were obtained from a clinic-based cohort. A potential source of bias with clinic-based
samples is that these patients may have more severe disease activity when compared with population-based samples. The extent of the bias is difficult to assess. However, MSSS computations can provide an indirect assessment of the degree of severity of our patient population when compared with a large population-based sample. The global reference file of the MSSS is based on a collection of 9892 patients from 11 countries (Roxburgh et al., 2005). MSSS values are percentiles relating EDSS scores to the distribution of disability in patients with comparable disease durations. The percentile scores are scaled by a factor 10 to enable use of a 0–10 scale analogous to the EDSS. A representative patient with an average disease course would have an MSSS of 5.0 regardless of disease duration. The mean MSSS of the adult onset multiple sclerosis-2 group was 3.60 ± 2.5, and that of the adult onset multiple sclerosis-1 group was 4.69 ± 2.4. Thus, these MSSS values indicate that adult patients included in our study do not have more severe disease than in patients seen worldwide. This approach is not possible for the paediatric onset multiple sclerosis-C because global reference data for children are not available. However, other published studies including consecutive paediatric multiple sclerosis patients with similar disease duration have shown an average EDSS similar to that in our population (MacAllister et al., 2005; Amato et al., 2008; Mesaros et al., 2008). Further, our clinic is located in a regional children’s hospital and it is likely that most children in the region with demyelinating disease are evaluated at the centre. Comparison of the EDSS of local children included in the study to those referred from outside of our catchment area reveals similar EDSS scores, suggesting that disease severity in our patients may be similar to that in the larger population.

In the adult literature, there is a suggestion that measures of atrophy may correlate with disability (Zivadinov and Bakshi, 2004). There was a trend toward a greater EDSS in patients with adult onset disease with longstanding disease (adult onset multiple sclerosis-2) than those with paediatric onset multiple sclerosis with longstanding disease (paediatric onset multiple sclerosis-A). However, despite relatively greater grey matter atrophy in paediatric-onset cases, clinical progression was less likely to occur than in adults. This returns us to the issue of the paradoxical clinical features reported in natural history studies of paediatric onset multiple sclerosis. Our findings provide neuroimaging data that reinforce studies of paediatric onset multiple sclerosis that show that time to irreversible disability is longer in this group than in adult onset multiple sclerosis (Simone et al., 2002; Renoux et al., 2007). Further, they emphasize that despite very active and aggressive disease early on (as characterized by the accumulation of atrophy, MTR and T1 lesion volume measures), disability is slower to accrue in paediatric onset multiple sclerosis. The reasons for the slower accrual of disability in paediatric onset multiple sclerosis that have been suggested include heightened reparative abilities in the younger population, variability in the immunological mechanisms of disease in the young, the presence of greater tissue reserves, or the lack of co-morbidities that may contribute to brain atrophy.

Our study may contribute to resolution of the clinical paradox reported in natural history studies on paediatric onset multiple sclerosis (Simone et al., 2002; Renoux et al., 2007), suggesting that a slower clinical progression may depend on heightened reparative abilities or preserved functional reserve. Although we did not perform functional MRI to measure the preserved functional reserve, our T1 hypointense lesion and MTR findings suggest that patients with paediatric onset multiple sclerosis may have no greater capacity for remyelination compared with the adult onset multiple sclerosis group.

Recent studies have highlighted the concept of preserved functional reserve in paediatric onset multiple sclerosis; using functional MRI, children with paediatric multiple sclerosis were shown to maintain a selective and lateralized pattern of movement-associated brain activations, suggesting preserved functional reserve (Rocca et al., 2008). Other studies have shown that children who sustain brain insults between ages 10 and 16 may experience less severe outcomes than children experiencing earlier insults, giving rise to the hypothesis that vulnerability of the brain in childhood may vary, with later childhood and adolescence being a period of decreased vulnerability (Anderson et al., 2009). Most of the children in our study were in this age category. This may partially explain the favourable short/medium term clinical outcomes of children with paediatric multiple sclerosis in this and other studies (Rocca et al., 2008). Longitudinal studies that include functional MRI and magnetization transfer and compare paediatric onset multiple sclerosis to age-matched paediatric controls are required to examine the biological basis for these differences and to elucidate correlations between MRI findings and cognitive and physical outcomes in this population.

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Supplementary material
Supplementary material is available at Brain online.

References
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