Hypointense Lesions on T1-Weighted Spin-Echo Magnetic Resonance Imaging

Relation to Clinical Characteristics in Subgroups of Patients With Multiple Sclerosis

Marianne A. A. van Walderveen, MD; Geert J. Lycklama a` Nijeholt, MD; Herman J. Ad`r, PhD; Peter J. H. Jongen, MD; Chris H. Polman, MD; Jonas A. Castelijns, MD; Frederik Barkhof, MD

Context: Hypointense lesions on T1-weighted spin-echo magnetic resonance images (T1 lesions) represent destructive multiple sclerosis (MS) lesions, consisting of axonal loss and matrix destruction. These lesions are being used as a secondary outcome measure in phase III clinical trials. Clinical determinants of T1 lesions may differ between subgroups of patients with MS and subsequently may have implications for the selection of patients for clinical trials.

Objective: To determine if clinical characteristics of patients with MS are related to T1 lesion volume.

Design: A survey of 138 patients with MS (52 with relapsing-remitting MS, 44 with secondary progressive MS, and 42 with primary progressive MS).

Setting: The Magnetic Resonance Center for Multiple Sclerosis Research, University Hospital “Vrije Universiteit,” Amsterdam, the Netherlands.

Main Outcome Measures: Type of MS, Expanded Disability Status Scale (EDSS) score, sex, age at first symptoms, and T1 lesion volume.

Results: Patients with secondary progressive MS have the highest T1 lesion volume. Patients with relapsing-remitting MS have a lower T1/T2 ratio than patients with secondary progressive MS and patients with primary progressive MS. In patients with relapsing-remitting MS and secondary progressive MS, T1 lesion volume relates to disease duration and EDSS score, while in patients with primary progressive MS sex is important. A trend toward higher T1 lesion volume was found with age at onset in patients with relapsing-remitting MS and in patients with primary progressive MS.

Conclusions: In patients with MS different clinical characteristics associate with T1 lesion volume, suggesting a more destructive type of lesions in certain subgroups. A possible sex difference in (destructive) lesion development on magnetic resonance imaging should be evaluated in more detail, preferably in a cohort.

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Change in hypointense lesion load on T1-weighted magnetic resonance images (MRIs) (T1 lesions) is recommended as a secondary outcome measure in definitive (phase III) clinical trials in multiple sclerosis (MS). This is based on the observation that T1 lesion volume correlates more strongly with clinical disability in patients with MS than does the overall lesion volume on T2-weighted MRIs (T2 lesions). The histopathologic correlate of T1 lesions includes axonal loss and matrix destruction; implying that in vivo monitoring of progressive tissue destruction may be possible.

A recent study showed that increase in T1 lesion volume relates more strongly to baseline T1 lesion volume in patients with relapsing-remitting (RR) MS and in patients with secondary progressive (SP) MS than to the degree of inflammatory activity seen on MRIs. Thus, while in some patients new lesions remain hypointense on T1-weighted MRIs (and probably have axonal damage), in other patients lesions remain or become isointense, indicating a more favorable outcome.

This suggests that some patients with MS may be genetically prone to develop destructive lesions. A combination of—so far unknown—genetic factors may well be reflected in certain clinical characteristics of patients with MS. The frequency of blood-brain barrier disruption on contrast-enhanced MRI has already been shown to correlate with an earlier age at onset and a more aggressive disease course in patients with RR MS or SP MS, support-
PATIENTS AND METHODS

PATIENTS

One hundred thirty-eight patients with clinically definite MS were recruited from the outpatient clinic of the Department of Neurology, University Hospital "Vrije Universiteit," Amsterdam, the Netherlands. Informed consent was obtained from each patient after the nature of the procedures had been explained. Clinical evaluation consisted of assessment of the duration of the disease (ie, the interval between the date of first symptoms and the date of examination [measured in years]), patient's age at first symptoms, disease course, and the Expanded Disability Status Scale (EDSS) score. Fifty-two patients had RR MS, 44 patients SP MS, and 42 patients PP MS.

MAGNETIC RESONANCE IMAGING

Brain MRI was performed at 1.0 T (Magnetom Impact; Siemens, Erlangen, Germany) and consisted of postcontrast (0.1 mmol/kg of gadolinium-DTPA [diethylenetriamine pentaacetic acid dimeglumine]) dual echo T2-weighted spin-echo (2300/45, 90/1 [repetition time/echo time/excitations]) and T1-weighted spin-echo series (600/15/2 [repetition time/echo time/excitations]). Twenty-one axial slices with an in-plane resolution of 1 mm, slice thickness of 5 mm, and an interslice gap of 0.5 mm, were obtained.

DATA ANALYSIS

Hypointense lesions on T1-weighted spin-echo MRI and hyperintense lesions on T2-weighted spine-echo MRI were analyzed and marked on hard copies (M.A.A.W., G.J.L.a N.). T1 lesions were defined as regions with a signal intensity similar to or reduced to the signal intensity of gray matter and corresponding to a hyperintense region on T2-weighted MRI. Hyperintense–T2 lesions were defined as sharply demarcated regions of high signal intensity compared with surrounding brain tissue. All data were transferred to a computer (Sparc 5; SUN, Palo Alto, Calif). A single observer, using home-developed, semiautomated local thresholding software, quantified the areas of previously identified brain lesions. T1 and T2 lesion volumes (in cubic centimeters) were calculated by adding the area of all lesions multiplied by interslice distance.

STATISTICAL ANALYSIS

The median and (interquartile) range were used to describe clinical and MRI characteristics for subgroups of patients. Since RR MS and SP MS may be considered as 2 phases of the same disease, analyses were also performed for the subgroup of patients with RR and SP MS.

The Mann-Whitney test was used to test for differences in the T1 and T2 lesion volumes between men and women; between patients with mild disability (EDSS score, $<2.5$) and moderate to severe disability (EDSS score, $>3.0$); and between patients whose age at first symptoms was 25 years or younger or older than 25 years (cutoff levels based on findings in the literature). In patients with SP MS and PP MS, few patients had mild disability and patients were therefore reclassified with those with an EDSS score of 5.5 or less and an EDSS score greater than 6.0 (this level of disability is obvious since patients need support to walk) to provide a homogeneous division. In patients with PP MS the first symptoms usually occur at an older age. In our study only 3 patients experienced their first symptoms when they were aged 25 years or younger: patients with PP MS, therefore, were classified with those who were 39 years or younger at first symptoms and with those who were older than 40 years at first symptoms to provide a homogeneous division.

Multiple linear regression analysis was performed to determine the relationship between T1 and T2 lesion volume and the clinical characteristics in the subgroup of patients. A forward stepwise procedure was used to find out which clinical characteristics were most influential (probability of F to enter, .05), the residuals of the final models were tested for normality. Average T1 and T2 lesion volume were transformed to a natural logarithmic scale (ln [T1 lesion volume +10] and ln [T2 lesion volume +10]) to satisfy the assumptions underlying regression analysis. Independent variables included were age at first symptoms before or after the age of 25 years, EDSS score (high or low disability variables included were age at first symptoms before or after the age of 40 years, EDSS score (high or low disability scores), sex, and disease duration. Age at first symptoms before or after the age of 40 years was used as an independent variable in patients with PP MS, and the cutoff level for EDSS scores was 5.5 in patients with PP MS or SP MS.

A Spearman rank correlation coefficient ($r_s$) was used to determine the associations between MRI parameters and clinical characteristics. To correct for multiple comparisons, a 2-sided significance level of P $\leq$ .01 was considered statistically significant and a P value between .01 and .05 was considered a trend.

RESULTS

Clinical (Table 1) and MRI characteristics (Table 2) of the patients are listed. T1 and T2 lesion volumes were significantly ($P < .01$) higher in patients with SP MS compared with patients with RR MS or PP MS. A trend toward a higher ratio of T1 lesion volume over T2 lesion volume (T1/T2 ratio) was found in patients with SP MS compared with patients with RR MS ($P = .03$). The T1/T2 ratio in patients with PP MS was similar to that in patients with SP MS, but not significantly different from the
T1/T2 ratio in patients with RR MS. Since a large variance in T1 lesion volume is present between the subgroups of patients with MS, only subgroup analysis was performed to evaluate the clinical characteristics of T1 lesions.

Table 3 gives the T1 lesion volume for patients with RR MS, SP MS, and PP MS. A division has been made according to sex, level of disability, and age at first symptoms. A similar division has been made for T2 lesion volume and the T1/T2 ratio (data are described).

SEX

In patients with RR MS, SP MS, or RR and SP MS no statistically significant differences in T1 lesion volume, T2 lesion volume, or T1/T2 ratio were noted between male or female patients. In patients with PP MS, a trend toward a higher T1 lesion volume (1.0 vs 0.3, P = .03) and a higher T1/T2 ratio (0.22 vs. 0.08, P = .02) was shown for male patients compared with female patients.

LEVEL OF DISABILITY

In patients with RR MS, the difference in T1 lesion volume (0.2 cm³ vs 0.7 cm³), T2 lesion volume (4.0 cm³ vs 6.8 cm³), and T1/T2 ratio (0.08 vs 0.07) was not statistically significant between male or female patients. In patients with PP MS, a trend toward a higher T1 lesion volume (0.2 cm³ vs 1.1 cm³), T2 lesion volume (12.9 cm³ vs 7.0 cm³), or T1/T2 ratio (0.19 vs 0.12). In patients with PP MS, the T1 lesion volume did not differ between patients with an EDSS score of 5.5 or less (0.4 cm³) and an EDSS score higher than 6.0 (0.3 cm³); also no differences were present in T2 lesion volume or T1/T2 ratio.

AGE AT FIRST SYMPTOMS

In patients with RR MS, a trend toward a higher T1 lesion volume (0.3 cm³ vs 0.0 cm³, P = .02) and a higher T1/T2 ratio (0.09 vs 0.0, P = .01) was shown for patients who had their first symptoms after the age of 25 years. No difference was shown for T2 lesion volume.

In contrast, a trend toward a higher T1 lesion volume was found (3.2 cm³ vs 0.8 cm³, P = .03) in patients with SP MS who had their first symptom before the age of 25 years. T2 lesion volume was higher for patients with an earlier onset of disease (15.3 cm³ vs 10.2 cm³, P = .06), but not significantly. No difference in T1/T2 ratio was present (0.21 vs 0.12, P = .1). For patients with RR and SP MS, no difference in MRI parameters was present regarding age at onset.

A trend toward a significant difference in T1 lesion volume (0.1 cm³ vs 0.6 cm³, P = .04) and in T1/T2 ratio (0.04 vs 0.17, P = .02) was shown between patients with PP MS who were aged 39 years or younger at the onset of first symptoms compared with those who were aged older than 40 years at the onset of first symptoms. No significant difference was present for T2 lesion volume (2.5 cm³ vs 4.3 cm³, P = .7).

MULTIPLE LINEAR REGRESSION

In the subgroups with RR MS, no meaningful model could be found. A weak model (R² = 0.16) was present in patients with SP MS, including being younger than 25 years at the onset of first symptoms as a variable (β = −0.40). In patients with RR and SP MS, a model with R² = 0.19 was found including disease duration (β = 0.28, P = .008) and EDSS score (β = 0.24, P = .02). In patients with PP MS, sex (β = 0.40, P = .008) was the only variable included in the model (R² = 0.16), indicating a higher preponderance of T1 lesions in male patients with PP MS. All patients showed abnormalities on T2-weighted MRI. Mul-

Table 1. Clinical Data Classified by Clinical Disease Course*

<table>
<thead>
<tr>
<th>Clinical Disease Course</th>
<th>RR (n = 52)</th>
<th>SP (n = 44)</th>
<th>PP (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>36 (22-58)</td>
<td>43 (30-65)</td>
<td>48 (20-69)</td>
</tr>
<tr>
<td>M/F</td>
<td>17/35</td>
<td>17/27</td>
<td>11/31</td>
</tr>
<tr>
<td>Disease duration, y†</td>
<td>5.0 (0.0-30)</td>
<td>10 (1-40)</td>
<td>7.0 (1.0-35.0)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>1.0 (0.0-7.0)</td>
<td>5.0 (1.5-7.5)</td>
<td>6.0 (2.0-7.5)</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td>29 (17-50)</td>
<td>32 (15-58)</td>
<td>39 (18-62)</td>
</tr>
</tbody>
</table>

* All values are expressed as medians (ranges) unless otherwise specified. MS indicates multiple sclerosis; RR, relapsing-remitting; SP, secondary progressive; PP, primary progressive; and EDSS, Expanded Disability Status Scale.

† Disease duration is the time between the date of the first symptoms and the date of the physical examination.

Table 2. Magnetic Resonance Imaging Characteristics Classified by Clinical Disease Course*

<table>
<thead>
<tr>
<th>All Patients (N = 138)</th>
<th>Clinical Disease Course</th>
<th>RR (n = 52)</th>
<th>SP (n = 44)</th>
<th>PP (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 lesion volume</td>
<td>0.4 (0.0-17.3)</td>
<td>0.3 (0.0-7.6)†</td>
<td>2.0 (0.0-17.3)‡</td>
<td>0.3 (0.0-11.5)</td>
</tr>
<tr>
<td>T2 lesion volume</td>
<td>4.9 (0.0-49.2)</td>
<td>4.7 (0.0-49.1)†</td>
<td>11.7 (0.14-49.2)‡</td>
<td>3.8 (0.4-32.1)</td>
</tr>
<tr>
<td>T1/T2 ratio</td>
<td>0.11 (0.0-0.71)</td>
<td>0.07 (0.0-0.53)§</td>
<td>0.16 (0.0-0.71)</td>
<td>0.15 (0.0-0.54)</td>
</tr>
</tbody>
</table>

* All values are expressed as medians (ranges) unless otherwise specified. MS indicates multiple sclerosis; RR, relapsing-remitting; SP, secondary progressive; and PP, primary progressive.

† Patients with RR MS vs patients with SP MS, P < .01, Mann-Whitney test.

‡ Patients with SP MS vs patients with PP MS, P < .01, Mann-Whitney test.

§ Patients with RR MS vs patients with SP MS, P < .01 vs P < .05, Mann-Whitney test.

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In patients with RR MS, a trend toward significant correlation was found between age at symptoms and T1 lesion volume ($r_c=0.34$, $P=0.02$), whereas age at first symptoms correlated significantly with T1/T2 ratio ($r_c=0.42$, $P<0.01$); T2 lesion volume did not correlate with any clinical parameter. In patients with SP MS, a trend toward significant correlation was found between T1 lesion volume and disease duration ($r_c=0.34$, $P=0.03$) and age at first symptoms ($r_c=-0.31$, $P=0.04$), and between T2 lesion volume and disease duration ($r_c=0.33$, $P=0.03$) and age at first symptoms ($r_c=-0.32$, $P=0.04$), disease duration being interrelated with age at first symptoms ($r_c=0.49$, $P=0.001$) and EDSS score ($r_c=0.43$, $P<0.01$). No correlation was found for T1/T2 ratio.

When patients with RR MS and SP MS were grouped together, T1 lesion volume correlated with EDSS score ($r_c=0.32$, $P=0.001$), and with disease duration ($r_c=0.33$, $P=0.001$), disease duration again being interrelated with EDSS score ($r_c=0.41$, $P<0.001$) and age at first symptoms ($r_c=-0.31$, $P=0.002$). T2 lesion volume correlated with EDSS score ($r_c=0.34$, $P=0.001$). A trend toward significant correlation was shown between disease duration and T2 lesion volume ($r_c=0.24$, $P=0.02$) and T1/T2 ratio ($r_c=0.23$, $P=0.03$). In patients with PP MS, T1 or T2 lesion volume did not correlate with any clinical parameter although a trend toward a significant correlation was found between T1/T2 ratio and age at first symptoms ($r_c=0.33$, $P=0.04$).

**COMMENT**

Previous reports examining T1 lesions in patients with MS have been based on small longitudinal studies with a limited range of disabilities. To our knowledge, this is the first large cross-sectional examination of the relationship of a range of clinical characteristics of patients with MS (including a range of EDSS scores, 0-7.5) to T1 lesion volumes. The clinical characteristics of the patients in this study are typical and—except for the female preponderance in patients with PP MS—in line with previous reports, suggesting that the sample under consideration is more or less representative of patients with RR MS, SP MS, and PP MS in general and that no selection bias (eg, selection of patients with extraordinary disease courses or with high EDSS scores) has occurred.

Patients with PP MS develop fewer T2 lesions in the brain and have a lower frequency of MRI–detected inflammatory lesions compared with patients with SP MS, although their EDSS scores are often comparable. Compared with patients with RR MS, patients with PP MS have less histologically demonstrable inflamma-

**Table 3. Hypointense T1–Lesion Volume, Subdivided According to Patient Characteristics for Patients With Relapsing-Remitting (RR), Secondary Progressive (SP), and Primary Progressive (PP) Multiple Sclerosis (MS)**

<table>
<thead>
<tr>
<th>Clinical Disease Course</th>
<th>No. of Patients</th>
<th>Median</th>
<th>IQR†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RR (n = 52)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
<td>0.3</td>
<td>0.0-0.6</td>
<td>.51</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>0.3</td>
<td>0.0-2.4</td>
<td>.03</td>
</tr>
<tr>
<td>EDSS score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$2.5</td>
<td>42</td>
<td>0.2</td>
<td>0.0-0.6</td>
<td>.30</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>10</td>
<td>0.7</td>
<td>0.0-1.6</td>
<td>.04</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$25</td>
<td>14</td>
<td>0.0</td>
<td>0.0-0.3</td>
<td>.02</td>
</tr>
<tr>
<td>&gt;25</td>
<td>38</td>
<td>0.3</td>
<td>0.1-0.9</td>
<td></td>
</tr>
<tr>
<td><strong>SP (n = 44)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>27</td>
<td>2.2</td>
<td>0.3-3.1</td>
<td>.88</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>2.0</td>
<td>0.2-3.6</td>
<td>.03</td>
</tr>
<tr>
<td>EDSS score§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$5.5</td>
<td>27</td>
<td>1.1</td>
<td>0.3-3.9</td>
<td>.57</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>17</td>
<td>2.1</td>
<td>0.3-6.9</td>
<td>.03</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$25</td>
<td>12</td>
<td>3.2</td>
<td>1.2-9.4</td>
<td>.03</td>
</tr>
<tr>
<td>&gt;25</td>
<td>32</td>
<td>0.8</td>
<td>0.3-3.0</td>
<td></td>
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<tr>
<td><strong>PP (n = 42)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
<td>0.3</td>
<td>0.0-1.2</td>
<td>.03</td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>1.0</td>
<td>0.3-8.1</td>
<td>.34</td>
</tr>
<tr>
<td>EDSS score§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$5.5</td>
<td>21</td>
<td>0.4</td>
<td>0.0-2.4</td>
<td>.43</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>21</td>
<td>0.3</td>
<td>0.1-1.1</td>
<td>.04</td>
</tr>
<tr>
<td>Age at first symptoms, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq$39</td>
<td>21</td>
<td>0.1</td>
<td>0.0-1.2</td>
<td>.04</td>
</tr>
<tr>
<td>&gt;40</td>
<td>21</td>
<td>0.6</td>
<td>0.3-1.9</td>
<td></td>
</tr>
</tbody>
</table>

*The patient characteristics are sex, level of disability measured using the Expanded Disability Status Scale (EDSS) score, and patient age at the sign of first symptoms of MS.
†IQR indicates interquartile range.
‡Values based on Mann-Whitney test.
§The level of disability was chosen as an EDSS score of 5.5 or less and greater than 6.0 in patients with SP MS or PP MS, respectively, to provide a homogeneous division.
∥For similar reasons, patients with PP MS were reclassified into those with age at first symptoms of 39 years or younger and those older than 40 years.
patients with RR and SP MS. In subgroups of patients with RR and SP MS, T1 lesion volume does not differ significantly between patients with mild disability or with moderate to severe disability. This may be due to a combination of factors. Patients with RR MS showed little variance in EDSS scores (in our study only 10 patients were included with an EDSS score >3.0) in addition to limited variance in T1 lesion volume (18 patients [35%] did not show any lesion on T1-weighted MRI). In patients with SP MS, the opposite holds true, only 4 patients having an EDSS score of 2.5 or less. After reclassifying patients with SP MS with those who had EDSS scores below or above 6.0, patients with severe disability showed more lesions on T1-weighted MRI, but the values were not statistically significant. These circumstances may have contributed to the lack of a correlation between EDSS and T1 lesion volume in individual subgroups, also shown by others,24,25 since a correlation was present when patients with RR MS and SP MS were grouped together. Further, involvement of normal-appearing white matter,20-25 atrophy of brain and spinal cord,12,23 and perhaps even a chronic “low-grade” inflammation of the whole brain30 may all have contributed—in addition to T1 lesions—to disability to some extent in this subgroup of patients.

In patients with RR and PP MS, a trend toward a higher T1 lesion volume was found for patients who have their first symptoms after the age of 25 (or 40) years. This result agrees with clinical studies, showing that an older age at onset relates to a more unfavorable outcome.30,31,34 Apart from the higher chance of following a progressive disease course from onset, patients with RR MS have an increased risk of a rapid shift to the SP phase and the time to reach EDSS score of 6.0 tends to be shorter.31-39 A contradictory trend was assessed in patients with SP MS, suggesting that in this clinical subgroup, accumulation of T1 lesions is a consequence of longer disease duration and the age at which the first symptoms occur cannot be used as a prognostic indicator.

We showed a trend toward higher T1 lesion volume (and a higher T1/T2 ratio) in male patients with PP MS compared with female patients with PP MS. Previous studies have shown that, in general, male patients with MS are prone to have a more unfavorable clinical outcome than female patients,18,35,36,40,41 although other studies have failed to detect a sex difference in the rate of clinical disease progression.17,37,38 Experimental studies emphasize that expression of autoimmune diseases differs between male and female patients, possibly related to susceptibility modulation by the sex hormones—estrogen, progesterone, and testosterone.42 Estriol treatment has been shown to reduce the severity of experimental autoimmune encephalomyelitis in an animal model of MS, whereas treatment with progesterone did not yield a substantial effect.43 Also, inflammatory activity on MRI has been shown to relate to the estrogen-progesterone ratio; a low ratio appeared to diminish the number of active lesions on MRI.44,45 Preliminary results of the clinical trial with interferon beta-1a (Rebif) in SP MS indicate that the response to treatment may differ according to sex (Lance D. Blumhardt, oral communication, June 5-9, 1999, at the European Neurological Society’s Ninth meeting); remarkably, females, who according to our observations may develop less destructive lesions, responded better to treatment in this study. Our observation of a possible sex difference in T1 lesion volume in patients with PP MS is in line with these observations and should be evaluated in more detail in other longitudinal studies, preferably in relation to other MRI parameters such as spinal cord pathologic features, enhancing lesion rate, and development of atrophy.

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Corresponding author and reprints: Marianne A. A. van Walderveen, MD, Magnetic Resonance Center for Multiple Sclerosis Research, University Hospital “Vrije Universiteit,” PO Box 7057, 1007 MB Amsterdam, the Netherlands (e-mail: m.vanwalderveen@azvu.nl).

REFERENCES


