Determinants of Cerebral Atrophy Rate at the Time of Diagnosis of Multiple Sclerosis

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Objective: To identify determinants visible on magnetic resonance imaging of the brain that explain the subsequent rate of cerebral atrophy in patients with recently diagnosed multiple sclerosis.

Design: Magnetic resonance imaging of the brain was performed at baseline and after 2 years. T2 hyperintense lesion load, black hole lesion load, presence of contrast-enhancing lesions, and normalized brain volume were derived from the baseline magnetic resonance imaging and considered as possible explanatory variables for the subsequent annualized percentage of brain volume change (PBVC/y) using forward stepwise multiple linear regression analysis.

Setting: MS center Amsterdam, Department of Neurology, VU University Medical Center, Amsterdam, the Netherlands.

Patients: Eighty-nine patients recently diagnosed as having multiple sclerosis were included at the time of diagnosis from our outpatient clinic.

Main Outcome Measure: Annualized percentage of brain volume change.

Results: The mean (SD) annualized rate of cerebral atrophy was −0.9 (0.8) PBVC/y. Baseline normalized brain volume (standardized coefficient, 0.426; \( P = .001 \)) and baseline T2 lesion load (standardized coefficient, −0.244; \( P = .02 \)) were identified as explanatory variables for subsequent PBVC/y and yielded a regression model that explained 31.2% of the variance in PBVC/y.

Conclusions: In patients with recently diagnosed multiple sclerosis, the extent of accumulated brain tissue loss and overall lesion load partly explain the subsequent rate of cerebral atrophy.

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implications for the interpretation of clinical trials that use atrophy rate as an outcome measure.

Therefore, the aim of this study was to identify MRI variables at the time of diagnosis that explain the subsequent rate of brain atrophy in patients with MS. Explanatory models for cerebral atrophy rate were constructed using preselected variables that could explain the rate of cerebral atrophy. Whole-brain volume measurement was used because this measure reflects the net resultant effect of destructive processes in MS. Clinical variables were only considered as descriptives and covariates in the eventual regression models.

PATIENTS

Eighty-nine patients were selected from a cohort of 133 from an ongoing natural history study of patients with recently diagnosed MS. Forty-four patients were excluded because either the baseline and/or follow-up MRI was not available or because a pre gadolinium T1-weighted sequence was not available, which is obligatory for our current protocol for brain volume analysis. Patients were included at the time of diagnosis from our outpatient clinic at the MS center Amsterdam at the VU University Medical Center. Multiple sclerosis was diagnosed according to the Poser criteria. Patients were classified into 2 groups according to disease course: relapse-onset and progressive-onset MS (onset type). Decisions to start disease-modifying therapy (DMT) were made by the treating neurologist according to guidelines for standard clinical practice and in dialogue with the patient. Informed consent was obtained from all participating patients and our local ethics committee approved the study.

Patients underwent assessment of disability using the Expanded Disability Status Scale (EDSS), performed by trained raters. When patients had a relapse, clinical and MRI evaluations were delayed for a minimum of 6 weeks.

MAGNETIC RESONANCE IMAGING OF THE BRAIN

Magnetic resonance imaging of the brain was performed at baseline and at a median follow-up time of 2.2 years (interquartile range, 2.0 to 2.4 years) on a 1.0-T MRI scanner (Magnetom Impact; Siemens, Erlangen, Germany) and consisted of axial pre gadolinium and post gadolinium T1-weighted (repetition time, 700 milliseconds; echo time, 15 milliseconds; 5-mm slice thickness) sequences and T2/proton density–weighted (repetition time, 2700 milliseconds; echo time, 90 milliseconds and 45 milliseconds; 5-mm slice thickness) sequences. Baseline T1 hypointense or black hole lesion load (BHLL) and T2 lesion load (T2LL) were quantified using locally developed, semiautomated seed growing software based on a local thresholding technique after intensity normalisation. Lesions were quantified using locally developed, semiautomated seed growing software based on a local thresholding technique after intensity normalisation.

The atrophy rate in PBVC/y in patients receiving DMT at any time during the study (mean [SD], −1.24 [0.76] PBVC/y) was significantly (P = .04) more pronounced than in patients not receiving DMT (mean [SD], −0.86 [0.74] PBVC/y), which underlines the need to correct all models for DMT. There were no significant differences in PBVC/y between men and women or between relapse-onset or progressive-onset MS.

RESULTS

Clinical and MRI characteristics at baseline of the 89 patients included are given in Table 1. No differences in disease duration, age, EDSS score, or use of DMT were observed between the studied group and the 44 excluded patients.

CORRELATIONS BETWEEN STUDY VARIABLES AND PBVC/y

The atrophy rate in PBVC/y in patients receiving DMT at any time during the study (mean [SD], −1.24 [0.76] PBVC/y) was significantly (P = .04) more pronounced than in patients not receiving DMT (mean [SD], −0.86 [0.74] PBVC/y), which underlines the need to correct all models for DMT. There were no significant differences in PBVC/y between men and women or between relapse-onset or progressive-onset MS.

The PBVC/y correlated significantly with the annualized change in EDSS score (r = −0.232; P = .03), showing that a higher brain atrophy rate was associated with an increase in clinical disability. Significant correlations with PBVC/y were found for baseline NBV (r = 0.403; P < .001) and baseline ln(T2LL) (r = −0.441; P < .001). Atrophy rate in PBVC/y was more pronounced in patients with contrast-enhancing lesions at baseline (mean [SD], −1.21 [0.71] PBVC/y) compared with patients without contrast-enhancing lesions at baseline (mean [SD], −0.79 [0.74] PBVC/y) (P = .01). Baseline BHLL correlated significantly with PBVC/y (r = −0.244; P = .02) and there was a signifi-
cantly higher atrophy rate (median, −1.36 [interquartile range, −1.67 to −0.65]) in patients in the highest tertile of BHLL compared with patients in the lowest tertile of BHLL (median, −0.83 [interquartile range, −1.27 to −0.22]) (P = .009).

**MULTIVARIATE MODELS EXPLAINING SUBSEQUENT ATROPHY RATE**

In the first model, considering only lesion measures, baseline lnT2LL was the only significant explanatory variable of subsequent PBVC/y. This model (Table 2) explained 21.3% (adjusted $R^2$) of variance in PBVC/y.

In the second model, considering lesion measures and NBV, baseline NBV and lnT2LL were both significant explanatory variables for subsequent PBVC/y. This model (Table 2) explained 31.2% (adjusted $R^2$) of variance in PBVC/y. Note that the regression coefficient for lnT2LL in model 2 (with NBV) is substantially lower than in model 1 (without NBV), indicating that NBV and lnT2LL are partly interrelated in explaining variance of PBVC/y.

**COMMENT**

In this study, we attempted to identify MRI variables that explain the subsequent rate of cerebral atrophy early in the disease course of MS. The annual atrophy rate of 0.9% in this cohort of patients with early MS is very similar to what has been found previously.6-10 Previous studies, using different techniques for brain volume measurement, have found that inflammatory lesions and the presence of new T2 lesions are predictive of the subsequent rate of brain atrophy in patients with relapsing-remitting MS,7 secondary progressive MS,17 and clinically isolated syndrome.6 These studies were performed on patient data from various clinical trials, using strict inclusion criteria. Patients with clinically isolated syndrome typically had very short disease duration in weeks, without a diagnosis of clinically definite MS. The studies on patients with relapsing-remitting MS and secondary progressive MS typically showed a disease duration of more than 6 years. The cohort in the current study consisted of patients with a recent diagnosis of clinically definite MS in a regular hospital setting, providing a unique view on the broader spectrum of patients with MS early in the disease course.

The main finding in the current study is that baseline T2LL and baseline NBV partly explain subsequent cerebral atrophy rate in a cohort of patients with MS early in the disease course. Lower NBV was a strong explanatory variable of higher cerebral atrophy rate. Cross-sectional brain volume can be regarded as a measure of accumulated tissue loss in the preceding years and may therefore reflect patients with a disease phenotype char-

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**Table 1. Baseline Characteristics in Patient Subgroups According to Onset Type**

<table>
<thead>
<tr>
<th></th>
<th>Relapse Onset (n = 74)</th>
<th>Progressive Onset (n = 15)</th>
<th>Total (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>36.2 (9.2)</td>
<td>43.6 (8.9)</td>
<td>37.5 (9.5)</td>
</tr>
<tr>
<td>Male/female, No.</td>
<td>23/51</td>
<td>11/4</td>
<td>34/55</td>
</tr>
<tr>
<td>Time since first symptoms, y, median (IQR)</td>
<td>1.7 (0.6 to 4.4)</td>
<td>1.5 (0.3 to 3.0)</td>
<td>1.6 (0.7 to 4.1)</td>
</tr>
<tr>
<td>EDSS score, median (IQR)</td>
<td>2.9 (1.9 to 2.5)</td>
<td>3.0 (2.5 to 4.0)</td>
<td>2.0 (2.0 to 3.0)</td>
</tr>
<tr>
<td>DMT yes/no, No.</td>
<td>21/53</td>
<td>0/15</td>
<td>21/68</td>
</tr>
<tr>
<td>T2LL, cm³, median (IQR)</td>
<td>3.89 (1.68 to 12.34)</td>
<td>4.15 (0.94 to 9.75)</td>
<td>3.94 (1.54 to 11.90)</td>
</tr>
<tr>
<td>Patients with/without black holes, No.</td>
<td>54/20</td>
<td>11/4</td>
<td>65/24</td>
</tr>
<tr>
<td>BHLL, cm³, median (IQR)</td>
<td>0.30 (0 to 0.88)</td>
<td>0.25 (0 to 1.51)</td>
<td>0.30 (0 to 0.93)</td>
</tr>
<tr>
<td>Patients with/without contrast-enhancing lesions, No.</td>
<td>31/43</td>
<td>3/12</td>
<td>34/55</td>
</tr>
<tr>
<td>Contrast-enhancing lesion load, cm³, median (IQR)</td>
<td>0 (0 to 0.21)</td>
<td>0 (0 to 0)</td>
<td>0 (0 to 0.20)</td>
</tr>
<tr>
<td>NBV, cm³, mean (SD)</td>
<td>1476 (72)</td>
<td>1447 (69)</td>
<td>1471 (72)</td>
</tr>
<tr>
<td>PBVC/y, mean (SD)</td>
<td>−1.0 (0.8)</td>
<td>−0.9 (0.8)</td>
<td>−0.9 (0.8)</td>
</tr>
</tbody>
</table>

**Table 2. Multiple Linear Regression Results for Baseline MRI Variables Explaining Subsequent PBVC/y**

<table>
<thead>
<tr>
<th>Model*</th>
<th>Baseline Variable</th>
<th>Adjusted $R^2$ Total Model</th>
<th>Standardized Regression Coefficients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lesions only</td>
<td>LnT2LL</td>
<td>0.213</td>
<td>−0.447</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2. Lesions and NBV</td>
<td>NBV</td>
<td>0.312</td>
<td>0.426</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>LnT2LL</td>
<td></td>
<td>−0.244</td>
<td>.02</td>
</tr>
</tbody>
</table>

**Abbreviations:** BHLL, black hole lesion load; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IQR, interquartile range; NBV, normalized brain volume; PBVC/y, annualized percentage brain volume change; T2LL, T2 lesion load.

*Both models were corrected for age, disease duration, onset type, sex, and use of disease-modifying therapy during study.
acterized by a higher propensity to decline in brain volume, which probably explains our findings.

Higher T2LL at baseline explains a higher rate of subsequent brain atrophy. Lesions lead to local and remote tissue damage and therefore may contribute directly or indirectly to cerebral atrophy. There are at least 2 ways to interpret the relation between baseline T2LL and the rate of atrophy found in this study. First, baseline T2LL reflects accumulation of tissue damage due to past disease activity. Patients who have a high T2LL early in the disease course may therefore have a more aggressive disease course leading to a higher rate of cerebral atrophy. Second, part of the T2 lesions may be actively inflicting tissue damage at baseline, which will lead to atrophy at a later point due to local and more remote (for instance, due to Wallerian degeneration) tissue loss at a later stage.

In univariate models, a higher BHLL and the presence of contrast-enhancing lesions were associated with a higher cerebral atrophy rate. These variables did not survive in the eventual regression models, whereas T2LL did. Black hole lesion load partly represents lesions with a high degree of tissue destruction, although cross-sectionally T1 hypointensity cannot be differentiated from edematous inflammatory lesions. Contrast enhancement of lesions is a specific finding for lesions exhibiting inflammatory activity. T2-weighted images are very sensitive for detecting lesions but not very specific. T2 lesion load can therefore be regarded as a global measure of lesions with a wide range of destructive properties and inflammatory activity. The reason BHLL and contrast enhancement did not survive in the eventual models is probably because their predictive properties are “taken over by” or “included in” T2LL. This does not exclude that BHLLs and contrast enhancement do have predictive properties. One previous study reported a relationship between change in T1 hypointense lesion load and cerebral atrophy rate concurrently. Some, but not all, studies have shown a relationship between contrast-enhancing lesions and subsequent brain atrophy. Our findings suggest that, with regard to lesion measures, baseline T2LL is more relevant for the development of cerebral atrophy in an early stage of MS.

Our model could only explain approximately one third of the variance in atrophy rate, leaving approximately two thirds unexplained. Inevitably, part of the unexplained variance is due to technical limitations of lesion measurement and brain volume assessment. Previous studies using quantitative MRI techniques have shown that diffuse abnormalities are present in the normal-appearing brain tissue. These abnormalities could be a reflection of more diffuse and global destructive processes in the normal-appearing brain tissue of patients with MS, contributing to the development of brain atrophy. Thus, it seems likely that part of the remaining variance in atrophy rate is attributable to a more diffuse and subtle destructive process in the normal-appearing brain tissue of patients with MS.

The use of DMT at any time during the 2-year follow-up period was associated with a higher rate of brain atrophy, which supports our strategy to correct all models for DMT. The explanation why patients with DMT have a higher brain atrophy rate is 2-fold. First, DMT is given to patients who show evidence of higher disease activity (based on relapse activity after disease onset and MRI variables), which may lead to a selection bias of patients with a more aggressive disease course associated with a higher rate of brain atrophy despite DMT. Second, start of DMT between the baseline and follow-up MRI could lead to a higher rate of brain atrophy because of resolution of edema.

This study is the first, to our knowledge, to provide longitudinal data on brain atrophy in a relatively unselected cohort of patients with newly diagnosed MS. Patients who have acquired more brain tissue loss and more T2 lesions are prone to have a higher rate of subsequent brain atrophy. In this relationship, the extent of brain tissue loss seemed more important than lesional activity. Because a higher rate of cerebral atrophy is predictive of worse clinical functioning at a later stage in the MS disease course, our findings suggest that these 2 baseline variables could have prognostic value for clinical functioning in early MS. These findings also indicate that T2LL and brain volume should be taken into account when designing and interpreting clinical trials that use cerebral atrophy rate as outcome measure.

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Author Contributions: Dr Jasperse had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Jasperse, de Groot, Uitdehaag, Barkhof, and Polman. Acquisition of data: Jasperse, Minneboo, de Groot, and van Heldén. Analysis and interpretation of data: Jasperse, de Groot, Kalkers, Uitdehaag, Barkhof, and Polman. Drafting of the manuscript: Jasperse, Kalkers, Barkhof, and Polman. Critical revision of the manuscript for important intellectual content: Jasperse, Minneboo, de Groot, van Heldén, Uitdehaag, Barkhof, and Polman. Statistical analysis: Jasperse, de Groot, and Uitdehaag. Administrative, technical, and material support: Jasperse, Minneboo, de Groot, Kalkers, and van Heldén. Study supervision: Barkhof and Polman.
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