Longitudinal Brain Volume Measurement in Multiple Sclerosis

Rate of Brain Atrophy Is Independent of the Disease Subtype

Nynke F. Kalkers, MD, PhD; Najim Ameziane, MSci; Joost C. J. Bot, MD; Arjan Minneboo, MD; Chris H. Polman, MD, PhD; Frederik Barkhof, MD, PhD

Background: In multiple sclerosis (MS), brain atrophy depicted by magnetic resonance imaging reflects overall tissue loss, including axonal loss.

Objective: To determine the course of atrophy by studying the rate of development of brain atrophy in patients who have different subtypes of MS.

Methods: Eighty-three patients with MS (42 with relapsing-remitting, 21 with secondary progressive, and 20 with primary progressive) were studied longitudinally, with an interval of 2 to 4 years. Magnetic resonance imaging included T1- and T2-weighted images to obtain 2 brain volume measurements: (1) the parenchymal fraction as a marker of global brain atrophy and (2) the ventricular fraction as a marker of central atrophy. The annualized rate of global and central brain atrophy was compared between those with different subtypes of MS and related to clinical characteristics, including sex, age, disease duration, and disability.

Results: There was a significant decrease of the parenchymal fraction ($-0.7\%$ per year; SEM, $0.11\%$ per year) and a significant increase of ventricular fraction ($3.7\%$ per year; SEM, $0.54\%$ per year) in the total group. Significant tissue loss was also seen in all 3 subtypes of MS; the decrease in parenchymal fraction was not different between subtypes, whereas the increase in ventricular fraction tended to be larger in patients with secondary progressive MS compared with patients with primary progressive MS. Marginal associations were found between clinical determinants and the rate of brain atrophy. Annualized increase in the ventricular fraction was correlated with age ($r = -0.26$) and duration of symptoms ($r = -0.22$): younger patients (mainly patients with relapsing-remitting MS who have a limited disability) displayed a larger increase in ventricular fraction compared with older patients.

Conclusions: The rate of development of brain atrophy is largely independent of the course of the disease and other clinical characteristics. The relentless loss of tissue occurring in MS is not restricted to later (progressive) phases of the disease, thereby stressing the need for early neuroprotective treatment in MS.

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gate for axonal damage, there is only a very small number of studies that have addressed the natural course of atrophy in MS. Most studies so far included patients with relapsing-remitting (RR) or secondary-progressive (SP) MS, reflecting the fact that these studies were incorporated in the analysis of large drug trials, in which restricted enrollment criteria were applied. So far, only 2 studies reported on the rate of cerebral atrophy in patients with primary progressive (PP) MS. Moreover, different automated segmentation techniques were used in the different studies, which hampers a meaningful comparison of the rate of atrophy between subgroups.

In this study we analyzed, in a larger cohort of patients with MS, not selected for disease type or EDSS score, the rate in brain volume over time using 2 markers for atrophy: (1) the parenchymal fraction (PF) defined as whole-brain parenchymal volume/intracranial volume (as a measure of global atrophy), and (2) the ventricular fraction (VF) defined as ventricular volume/intracranial volume (as a measure of central atrophy). Analyses were performed for different clinical subtypes. Moreover, different automated segmentation techniques were used in the different studies, which hampers a meaningful comparison of the rate of atrophy between subgroups.

Subjects and Methods

Subjects

Eighty-three patients with MS (42 with RR, 21 with SP, and 20 with PP MS) underwent an MRI scan and EDSS examination at baseline and after an interval of 2 to 4 years. Patients were recruited from natural history studies ongoing in our center. Data were retrospectively analyzed for this study. Twenty-two patients were receiving interferon-beta 1a treatment at the time of follow-up examination.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed at 1.0 T (Magnetom Impact; Siemens AG, Erlangen, Germany) and consisted of axial T1-weighted (repetition time, 620 milliseconds; echo time, 15 milliseconds; and number of excitations, 2) and T2-weighted (repetition time, 2500 milliseconds; echo time, 45 and 90 milliseconds; and number of excitations, 1) spin-echo MRIs. A slice thickness of 5 mm, with a 0.5-mm gap, and a pixel size of $0.98 \times 0.98$ mm was used to obtain 21 slices covering the whole brain.

MRI Analysis

All MRIs were analyzed on a computer workstation (Sun, Mountainview, Calif) using home-developed semiautomated seed growing software (Show_Images) based on a local threshold determined by a Canny edge-detection filter, which is designed to detect strong intensity gradients. When this failed, manual adjustment of the threshold was performed. Parenchymal and ventricular volumes were measured on T1-weighted MRIs and intracranial volume was measured on the corresponding slices of the heavily T2-weighted MRIs. Parenchymal volume consisted of combined supratentorial and infratentorial parenchymal volume (whole-brain parenchyma); MRIs below the level of the cerebellum, consisting of only medulla oblongata or spinal cord, were not considered. Ventricular measure included all 4 ventricles (including the choroid plexus). The fourth ventricle was measured until the slice below the foramen of Luschka (the Bochdalek flower basket). To correct for differences in skull size, 2 ratios were calculated (1) the PF or whole-brain parenchymal volume/intracranial volume, and (2) the VF or ventricular volume/intracranial volume. The PF was used as a marker of overall brain volume; the VF was used as a marker for central atrophy. Intrarater reliability of measurements was calculated, being 2% (SD, 1.7%) for PF and 5% (SD, 3.5%) for VF. All data were analyzed by a single, blinded rater (N.F.K.) and are presented as annualized percentages (annualized $\Delta$PF and annualized $\Delta$VF).

Statistical Analyses

Baseline data, annualized $\Delta$EDSS, annualized $\Delta$PF, and annualized $\Delta$VF were calculated for the total group and for each subtype of MS separately. When variables were not normally distributed (baseline VF and annualized $\Delta$VF), nonparametric analyses were used. Wilcoxon rank sum test was performed for the comparison of brain atrophy measurements between baseline and follow-up. The Kruskal-Wallis test was applied to analyze differences between the subtypes for baseline PF and VF and annualized $\Delta$PF and $\Delta$VF. Spearman rank correlation coefficients were calculated to analyze the relation between clinical characteristics (sex, age, duration of symptoms, baseline EDSS score, and annualized $\Delta$EDSS score) and the rate of annualized brain atrophy markers. Models for multiple linear regression analysis were created, using annualized $\Delta$PF or annualized $\Delta$VF as dependent variables, to analyze the influence of clinical characteristics (in which subtype of MS, sex, age, duration of symptoms, baseline EDSS score, and the interval between the 2 time points were used as predictors). To account for a possible effect of interferon-beta 1a treatment on the rate of brain atrophy analyses were repeated when patients who were receiving treatment were excluded. The Kruskal-Wallis test was repeated after dividing the patients into quartiles of age, to analyze whether group differences could be found post hoc. $P<.05$ was considered a trend; $P<.01$ was considered statistically significant in this exploratory analysis. All values are given as mean (SD).

Results

Forty-nine women (59%) and 34 men (41%) were studied. These patients had a mean age of 39.8 (10.5) years, a mean duration of symptoms of 6.4 (6.4) years, and a median EDSS score of 2.0 (range, 0-7.5). The mean interval between baseline and follow-up was 2 years 11 months. From 4 patients (3.3%), no EDSS score at follow-up was available; for analysis, in which annualized $\Delta$EDSS was used as a determinant, these patients were excluded. Patient characteristics and brain atrophy measurements are listed in the Table for the total group and 3 major disease subtypes.

Cross-sectional Data at Baseline

At baseline, patients with RR MS showed the highest PF ($P<.05$ vs patients with SP MS and $P<.01$ vs patients with PP MS), and the lowest VF ($P<.05$ vs patients with SP MS). Patients with SP or PP MS did not differ with regard to baseline PF and VF. Patients with RR MS differed significantly from patients with SP or PP MS on the baseline EDSS score.
Patient Characteristics and Values on Brain Atrophy Markers for Baseline and Follow-up in the Total Group and Subtypes of Multiple Sclerosis (MS)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Group (N = 83)</th>
<th>RR (n = 42)</th>
<th>SP (n = 21)</th>
<th>PP (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49</td>
<td>30</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Male</td>
<td>34</td>
<td>12</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>39.8 (10.5)</td>
<td>35.0 (6.6)</td>
<td>41.9 (8.8)</td>
<td>47.9 (10.3)</td>
</tr>
<tr>
<td>Duration of symptoms, mean (SD), y</td>
<td>6.4 (6.4)</td>
<td>4.2 (4.5)</td>
<td>5.2 (7.2)</td>
<td>7.1 (8.1)</td>
</tr>
<tr>
<td>EDSS baseline score</td>
<td>2.0 (1.4 to 4.0)</td>
<td>1.5 (1.0 to 2.0)</td>
<td>4.0 (2.5 to 5.5)</td>
<td>4.0 (2.5 to 6.0)</td>
</tr>
<tr>
<td>ΔEDSS scorey</td>
<td>0.28 (0 to 0.59)</td>
<td>0.27 (0 to 0.58)</td>
<td>0.32 (0 to 0.62)</td>
<td>0.16 (0 to 0.61)</td>
</tr>
<tr>
<td>PF baseline volume</td>
<td>0.64 (0.81 to 0.87)</td>
<td>0.86 (0.83 to 0.88)</td>
<td>0.82 (0.79 to 0.85)</td>
<td>0.82 (0.79 to 0.86)</td>
</tr>
<tr>
<td>ΔPF, %</td>
<td>-0.7 (-1.1 to -0.1)</td>
<td>-0.7 (-1.3 to -0.01)</td>
<td>-0.8 (-1.1 to -0.3)</td>
<td>-0.5 (-0.9 to -0.2)</td>
</tr>
<tr>
<td>VF baseline volume</td>
<td>0.023 (0.015 to 0.029)</td>
<td>0.018 (0.014 to 0.025)</td>
<td>0.024 (0.016 to 0.033)</td>
<td>0.022 (0.016 to 0.032)</td>
</tr>
<tr>
<td>ΔVF, %</td>
<td>3.7 (1.2 to 7.2)</td>
<td>3.9 (1.8 to 8.5)</td>
<td>3.9 (1.7 to 8.4)</td>
<td>2.4 (0.9 to 3.6)</td>
</tr>
</tbody>
</table>

*Data are given as median values (interquartile range) unless otherwise indicated. RR indicates relapsing remitting; SP, secondary progressive; PP, primary progressive; EDSS, Expanded Disability Status Scale; ΔEDSS, change in EDSS score; PF, parenchymal fraction: parenchymal volume/intracranial volume; ΔPF, decrease of PF per year; VF, ventricular fraction: ventricular volume/intracranial volume; and ΔVF, increase in VF per year.

COURSE OF ATROPHY DURING FOLLOW-UP: TOTAL GROUP AND SUBTYPES

Baseline measurements of brain atrophy markers differed significantly from follow-up; this was seen for both the total group and the subtypes (P<.001 for all comparisons, except P<.01 for VF in patients with PP MS). For the whole group, annualized ΔPF was −0.7% (SEM, 0.11%), and annualized ΔVF was 3.7% (SEM, 0.54%). Annualized ΔPF, annualized ΔVF, and an annualized ΔEDSS score were largest in the group with SP MS and smallest in the group with PP MS. Statistical analysis revealed that annualized ΔVF did not significantly differ between the subtypes; however, annualized ΔVF showed a trend for significance in difference between patients with PP and SP MS, with patients who have PP MS showing the largest increase in VF per year (P=.02). No difference on annualized ΔVF was found between patients with RR and PP MS and patients with SP MS. An annualized ΔEDSS score did not differ significantly between the 3 subtypes of MS.

RELATION BETWEEN CLINICAL DETERMINANTS AND RATE OF BRAIN ATROPHY

In the total group, no correlations were found between annualized ΔPF and clinical characteristics. A trend was observed in the correlation between age and the duration of symptoms and annualized ΔVF (r = −0.26 with age, and r = −0.22 with duration of symptoms). No correlation was found between the baseline EDSS score or the annualized ΔEDSS score with annualized markers of brain atrophy. When multiple linear regression analysis was performed using the stepwise method, a minor influence of age was found on annualized ΔVF (adjusted r² = 0.076), whereas subtype of MS, duration of symptoms, baseline EDSS score, and interval between 2 time points were excluded from the model. To further analyze the influence of age on annualized ΔVF, the total group was divided into quartiles according to age (median, 39.5 years). Post hoc comparison of annualized ΔVF between the lowest quartile (the youngest group aged < 31.1 years; consisting mainly of patients with RR MS and patients with low EDSS scores) and the highest quartile (the oldest group aged > 47.8 years; consisting mainly of patients with PP MS and patients with moderate to high EDSS scores) showed a significant difference, with the youngest group having a larger increase of VF (6.5%) per year than the oldest group (2.5%) per year.

INFLUENCE OF INTERFERON-BETA 1a TREATMENT ON THE RATE OF BRAIN ATROPHY

Twenty-two patients (26.5%) were receiving interferon beta treatment at follow-up. Data were reanalyzed for patients receiving treatment and those who were not, showing no significant difference in baseline data, follow-up data, and annualized Δ values on PF and VF. Both groups showed an annualized ΔPF of −0.7%, whereas the group who was not receiving interferon-beta 1a treatment showed an annualized ΔVF of 3.5% vs 4.4% for the group receiving interferon-beta 1a. The group with RR MS included the largest group of patients receiving interferon-beta 1a treatment at follow-up (n = 16). The annualized ΔPF was −0.7% for the group who was not receiving interferon-beta 1a treatment and −0.6% for those receiving interferon beta treatment; the annualized ΔVF was 3.9% vs 4.4%, respectively. These differences were not statistically significant (both r = 0.07). The trend in difference between patients with PP and SP MS on annualized ΔVF was no longer present after excluding the interferon-beta 1a–treated patients.

COMMENT

In this study, the rate of global brain atrophy and central atrophy per year was calculated for 83 patients with MS, representing all 3 major disease subtypes. The rate of global brain atrophy was 0.7% (SEM, 0.11%) per year in the total group, while central atrophy increased by 3.7%
The first major observation from this study is the fact that no significant difference in the rate of global brain atrophy between the subtypes of MS (including patients with PP MS) was found. So far, only 1 small study reported longitudinal brain atrophy data for different types of MS. In that study, Fox et al found a decrease in overall brain volume similar to our findings (0.8%). They used an image registration technique in a small group of patients with MS (n=26) and found the largest decrease (0.9% per year) of brain volume in patients with PP MS (n=9) and the smallest decrease (0.6% per year) in patients with SP MS (n=6). However, as in our study, these differences were not statistically significant. Other studies reporting on the percentage of decrease of brain volume ranged from 0.6% to 1.6% per year for patients with RR MS, age of decrease of brain volume reported values ranging from 0.6% to 1.7% for patients with SP MS. One large longitudinal study was performed in patients with PP MS (n=137), reporting a median decrease in overall brain volume of 0.95% per year. However, different intervals and different techniques have been used for these different studies. In some studies a few slices of the brain were measured, whereas in other studies, the whole brain was included; a correction for skull size was not always applied. A limitation of our study is the fact that we did not include longitudinal follow-up of healthy control subjects. In an earlier cross-sectional study, we did find a difference between PF and VF for all 3 subtypes of MS (including patients with RR MS) compared with healthy controls (P<.001 for PF and P<.01 for VF) using the same technique. Moreover, all patients in this study were examined in parallel using the same equipment.

New in this study is the inclusion of longitudinal measurement of central atrophy in different subtypes of MS. We found a median increase in VF of 3.7% for the total group. A trend for a difference between patients with PP or SP MS, with patients with SP MS having the largest increase in annualized ΔVF, was found. This trend was no longer present after the removal of patients who were receiving interferon-beta 1a treatment at follow-up. This may be caused by the fact that the subgroups were of limited size. Moreover, we did not consider the duration in treatment history. A study comparing patients with the clinically isolated syndrome with healthy controls already showed significant ventricular enlargement in those with the clinically isolated syndrome. So far, only 1 study measured central atrophy longitudinally in a large group of patients with RR MS; Simon et al reported an increase in third ventricle width of 4.5% and an increase in lateral ventricle width of 5.3% per year.

The second major observation in this study is the fact that most of the variance in central atrophy could not be explained by subtype of MS or other clinical determinants. Only for VF was a minor percentage of the variance explained by age. Interestingly, the larger increase was seen in the younger group, consisting mainly of patients with RR and of patients having EDSS scores below 2.0.

Apart from age as a (minor) predictor for atrophy, no other clinical characteristics (such as the duration of symptoms or annualized ΔEDSS) predicted the variance in the rate of global or central brain atrophy. The absence of a correlation between change in EDSS score and rate of global or central brain atrophy, might be caused by the fact that most patients had EDSS scores in the lower range, where minor loss in brain volume could easily be limited to symptoms and signs (eg, small changes in cognitive function) that are not picked up by the EDSS. Unfortunately, assessments of the MS functional composite (that is more strongly related to brain atrophy measurement) were excluded from the study at that time.

Other studies also failed to show a correlation between ΔEDSS score and the rate of brain volume loss over time, although others did find a correlation between the changes of brain volume and the change in EDSS score and cognitive deterioration. However, for these studies, in which a correlation was found, brain volumes were used without correction for skull size. Ge et al found no correlation between the change in brain volume (corrected for skull size) and the change in EDSS score in 27 patients with RR MS, whereas they did find this correlation in 9 patients with SP MS.

A potential confounder might be that about one fourth of our group was receiving interferon-beta 1a treatment at time of follow-up. However, we found no significant difference for both global and central brain atrophy between the group receiving treatment and the group not receiving treatment. This can be explained by the small sample size of the group using interferon-beta 1a, and by the fact that the duration of treatment was not similar for all patients.

Our main observations—the rate of brain atrophy being independent from clinical course (including both patients with RR MS and patients with PP MS) and the rate of central atrophy being larger in younger patients—suggest that MS should be considered a disease in which neurodegeneration is an early feature, thereby stressing the need for the study of early (neuroprotective) treatment in MS.

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**Author contributions:** Study concept and design (Drs Kalkers, Polman, and Barkhof); acquisition of data (Drs Kalkers, Bot, Minneboo, Barkhof, and Mr Ameziane); analysis and interpretation of data (Drs Kalkers, Minneboo, Polman, Barkhof, and Mr Ameziane); drafting of the manuscript (Drs Kalkers, Bot, Polman, Barkhof, and Mr Ameziane); critical revision of the manuscript for important intellectual content (Drs Polman, Barkhof, and Mr Ameziane); statistical expertise (Drs Kalkers and Barkhof); obtained funding (Dr Barkhof); administrative, technical, and material support (Drs Kalkers, Bot, Minneboo, Barkhof, and Mr Ameziane); study supervision (Drs Barkhof and Polman).

**Corresponding author:** Nynke F. Kalkers, MD, PhD, Department of Neurology, Vrije Universiteit Medical Center, De Boelelaan 1117, PO Box 7057, 1007 MB Amsterdam, the Netherlands (e-mail: nf.kalkers@vumc.nl).

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