Rate of Brain Atrophy in Benign vs Early Multiple Sclerosis

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Background: Benign multiple sclerosis (MS) is defined by minimal or no disability after many years of observation, therefore a less degenerative disease process is suspected to be present in this subset of patients.

Objective: To compare brain atrophy rates in patients with long-standing benign MS vs typical early MS.

Design: A longitudinal prospective cohort study and a retrospective database review.

Setting: An academic MS center.

Patients: Thirty-nine patients with clinically defined benign MS and an age-matched group of 40 patients with early relapsing-remitting MS.

Main Outcome Measures: Baseline demographic, treatment, brain magnetic resonance imaging measures, and annualized atrophy rates, derived from serial brain parenchymal fraction measurements across 2 years, were compared.

Results: In the baseline analysis, patients with benign MS were matched to the early MS group on age, sex, treatment with immunomodulatory therapy, T2 lesion volume, and brain parenchymal fraction. The mean (SD) annualized brain atrophy rate in patients with benign MS (−0.16% [0.51%]) was lower than that in patients with early MS (−0.46% [0.72%]) (P = .02). The difference remained significant after controlling for age, sex, and treatment (P = .04).

Conclusions: Serial magnetic resonance imaging revealed a low 2-year rate of brain atrophy in patients with clinically benign MS, suggesting a less prominent degenerative component in its pathogenesis than in patients with typical early MS. Identification of patients with a low rate of brain atrophy may indicate a benign course.


Original Contribution

Benign multiple sclerosis (MS) has been recognized and defined as engendering minimal or no disability after many years of observation. Longitudinal studies have identified cohorts of patients with benign MS, but a method for early identification of these patients is still lacking, and benign MS remains a retrospective diagnosis. Early and accurate identification of patients with benign MS could help limit patient anxiety, prevent the need to initiate immunomodulatory therapy, and avoid the associated adverse effects and expense of treatment.

The pathogenesis of benign MS has been postulated to relate to differences in the mechanism of irreversible disability or the ability for remyelination compared with the standard course of MS, although a clear understanding as to why these patients have a milder disease course is lacking. The brain parenchymal fraction (BPF) has been used to measure brain atrophy in MS; more importantly, early measurements of BPF change were predictive of long-term irreversible disability. The aim of this study is to determine whether the rate of brain atrophy, as measured by the change in the BPF in 2 years, differs in a cohort of patients with benign MS compared with an age-matched cohort with early MS. This study addresses the need to identify magnetic resonance imaging (MRI) markers that predict benign MS and to provide further insight into the pathologic differences between this cohort and other patients with MS.

Methods

Data were collected as part of the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women’s Hospital (CLIMB) study and the research database at the Partners Multiple Sclerosis Center. A computerized research database approved by the

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We identified 39 patients with benign disease and 40 with early MS, according to the criteria set forth. The baseline comparison between the 2 groups is outlined in Table 1. Both groups included treated and untreated patients, and the proportion of patients treated with different MS therapies, such as interferon-β-1b, high- or low-dose interferon-β-1a, glatiramer acetate, pulse monthly methylprednisolone, and combination therapy, was similar (P = .19). In addition, the interval between treatment initiation and baseline MRI was similar between cohorts.

**RESULTS**

The annualized brain atrophy rate calculated across 2 years was significantly slower in patients with benign MS compared with patients with early MS (P = .02) (Table 2). The association of a lower atrophy rate with benign disease remained significant in the multivariable analysis after controlling for age, sex, and treatment with immunomodulatory therapy (odds ratio, 0.39; P = .04). For every 1% increase in yearly atrophy rate, the odds of being categorized as having benign MS decreased by a factor of 0.39. After separating treated vs untreated patients, atrophy rates in patients with benign MS remained lower compared with those in patients with early MS (Table 2), although these groups were no longer age matched and the association did not remain significant in the multivariable analysis. The association between annualized BPF change and baseline demographic, clinical, and MRI characteristics was evaluated in the combined cohort of patients with benign and early MS (Table 3). Neither the baseline BPF nor T2 lesion volume was associated with the annualized atrophy rate; however, patients receiving immunomodulatory therapy had a higher rate of brain atrophy compared with untreated patients. This relationship remained significant in the multivariable analysis (P = .03).

**COMMENT**

Loss of brain volume is affected by factors such as inflammation, edema, and gliosis, although it is thought to predominantly reflect axonal loss and demyelination.4,5 In this study, serial MRI revealed a lower 2-year rate of brain atrophy, as measured by the BPF, in patients with clinically defined benign MS compared with an age-matched cohort of patients with early MS. These results suggest that benign MS may have a less destructive pathologic pro-
Table 2. Annualized Brain Atrophy Rates*

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign MS (n=39)</td>
<td>-0.16 (0.51)</td>
<td>-0.20</td>
<td>-1.6 to 0.95</td>
<td>.02</td>
</tr>
<tr>
<td>Early MS (n=40)</td>
<td>-0.46 (0.72)</td>
<td>-0.43</td>
<td>-3.5 to 1.17</td>
<td>.02</td>
</tr>
<tr>
<td>Untreated patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign MS (n=11)</td>
<td>0.02 (0.68)</td>
<td>0.17</td>
<td>-1.6 to 0.95</td>
<td>.25</td>
</tr>
<tr>
<td>Early MS (n=13)</td>
<td>-0.19 (0.63)</td>
<td>-0.20</td>
<td>-1.5 to 1.17</td>
<td>.25</td>
</tr>
<tr>
<td>Treated patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign MS (n=28)</td>
<td>-0.22 (0.42)</td>
<td>-0.21</td>
<td>-1.5 to 0.49</td>
<td>.01</td>
</tr>
<tr>
<td>Early MS (n=27)</td>
<td>-0.64 (0.77)</td>
<td>-0.51</td>
<td>-3.5 to 0.5</td>
<td>.01</td>
</tr>
</tbody>
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Abbreviation: MS, multiple sclerosis.

*Percentage change in brain parenchymal fraction per year.

Table 3. Association of Baseline Variables and the Annualized 2-Year Atrophy Rate in the Combined Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted R²</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>0.004</td>
<td>.25</td>
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<tr>
<td>Disease duration²</td>
<td>0.021</td>
<td>.11</td>
</tr>
<tr>
<td>Sex</td>
<td>0.003</td>
<td>.27</td>
</tr>
<tr>
<td>EDSS score</td>
<td>-0.002</td>
<td>.37</td>
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<tr>
<td>T2 lesion volume</td>
<td>-0.012</td>
<td>.80</td>
</tr>
<tr>
<td>BPF</td>
<td>-0.012</td>
<td>.79</td>
</tr>
<tr>
<td>Treatment²</td>
<td>0.043</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: BPF, brain parenchymal fraction; EDSS, Expanded Disability Status Scale.

²Disease duration was calculated from the first neurologic symptom consistent with multiple sclerosis.

*Received treatment at some point during the 2-year follow-up.

cess and, thus, a less prominent or slower degenerative component. Studies using magnetization transfer imaging and magnetic resonance spectroscopy in benign MS have also suggested that a less destructive pathologic process may underlie benign MS, although others, including those using a global measure such as the BPF, have not found differences between benign and other subgroups of MS. A direct comparison of these studies is challenging due to technical MRI differences that exist among them. As had other researchers, we found that the cross-sectional BPF was similar between benign and relapsing-remitting MS, but unique to the present study was the slower rate of longitudinal cerebral atrophy in patients with benign disease. Taken together, these results suggest that a degenerative process still remains but may occur at a slower rate in some patients with clinically defined benign disease. Furthermore, the rate of atrophy in patients with early MS in the present study corresponds to the expected annualized rate for relapsing-remitting MS and validates this BPF method to previously published methods.

The decision to use the early MS group as a comparative one in the present study was an attempt to compare benign MS with minimally disabled relapsing-remitting MS, as opposed to comparing patients with a similar disease duration, for whom differences would be expected. However, the rate of cerebral atrophy cannot be assumed to be a linear process, and differences in atrophy rates could be a reflection of disease duration. Therefore, an additional comparative nonbenign group with a long disease duration would have strengthened the study. Ideally, early cerebral atrophy rates of benign and nonbenign MS of similar durations should be compared; however, these data are not available and will eventually be studied in the context of the CLIMB study. A less active disease process in benign MS is further supported in the present study by the finding that patients with benign MS and those with early MS have similar T2-hyperintense lesion loads, although the benign group had a disease duration 7 times longer. Similarly, recent studies have demonstrated that higher T2 lesion volume early in the disease is associated with higher subsequent irreversible disability and that baseline T2 lesions correlated with the BPF 13 years later. The present selection criterion for benign MS was based on clinical criteria alone to minimize the effect of a potential MRI selection bias regarding either lesion volume or BPF.

Specific definitions of benign disease have varied among studies and, recently, an EDSS score of 2 or less and a disease duration of 10 years have been proposed to redefine benign MS; however, other researchers have found that a low EDSS score at 10 years could not accurately predict patients whose disease would remain benign at 20 years. In an attempt to identify patients with truly benign MS, we used a conservative definition of benign disease. In this study, patients at 10 years of disease lacked noticeable disability and had at 15 years had only minimal disability in 1 functional system (EDSS score ≤2). In addition, it was required that these EDSS levels were sustained throughout multiple semiannual visits to ensure the accuracy of patients’ disease status. Although this definition is conservative, it has yet to be validated. A unified validated definition of benign MS would allow for a more accurate comparison between studies.

Because benign disease is mainly a retrospective diagnosis, it is possible that a small percentage of patients in the early MS group would ultimately witness their disease following a benign course and contribute to the observed variability. In addition, to not include a measure of cognitive function in the analysis could also affect the variability of the results. A measure of cognitive function is lacking in all definitions of benign disease; however, cognitive dysfunction has been found in a cohort of patients with clinically defined benign MS. Inclusion of cognitive function would be of interest because brain atrophy has been shown to be related to cognitive impairment in patients with MS.
Acceptance of Acceleration in brain volume loss, known as pseudoatrophy, has been shown to occur in the first few months after the initiation of immunomodulatory therapy and is likely to be related to the anti-inflammatory effect of therapy. Because this was an open-label observational study, there were several untreated patients and patients who initiated treatment at various time points. Although the cohorts were matched regarding these treatment variables, we further attempted to address pseudoatrophy as a possible effect on the results and analyzed treated and untreated patients separately. The benign group was consistently found to have lower atrophy rates, although the groups were no longer age matched; therefore, this finding should be interpreted with caution. With both cohorts combined, we found that treatment had an effect on brain atrophy rate such that patients undergoing treatment had a higher atrophy rate than untreated patients. A possible explanation for this observation is that patients with more active disease have a higher likelihood of being treated with an immunomodulatory agent; however, pseudoatrophy may also be a contributing factor. These results reinforce the need to control for treatment in any analysis of brain atrophy.

The present results do not show an association between the baseline BPF or T2-hyperintense lesion load and the subsequent annualized brain atrophy rate in the combined cohorts, indicating that a cross-sectional MRI measurement may not accurately reflect the ongoing biological process compared with the measurement of the longitudinal rate of change. Because clinical characteristics of MS have not accurately predicted a benign disease course, the quest for biological markers is of particular importance. These results indicate that the rate of BPF change may provide an indication of subsequent disease course and should be further evaluated for its predictive potential.

REFERENCES