Impact of Inflammation on Brain Volume in Multiple Sclerosis

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Objective: To study changes in brain volume measured monthly in patients treated for relapsing multiple sclerosis due to loss of tissue and the appearance of inflammation.

Design and Patients: The results from T2/fluid-attenuated inversion recovery axial images from 13 consecutive monthly 3-T brain magnetic resonance imaging tests conducted on 74 patients diagnosed with relapsing multiple sclerosis in the BECOME study were used to calculate whole brain volumes using automated software analysis tools. The patients had been randomized to receive treatment with interferon beta-1b or glatiramer acetate. Ongoing inflammation was studied by counting the number of combined active lesions and measuring the volume of gadolinium enhancement. A mixed-effects model was used to analyze brain volumes over time.

Results: There was a significant decrease in brain volume over time but there was no difference in its rate of change by age, sex, frequency of ongoing inflammation, multiple sclerosis type, or randomized treatment assignment. The mean rate of brain volume change per month from multivariable models was -1.1 cm³ (95% CI, -1.5 to -0.6) and during times of magnetic resonance imaging activity, it increased transiently by an average of 1.2 cm³/lesion (95% CI, 0.7 to 1.7) and 7.1 cm³/1 cm³ of gadolinium volume. In a model with both measures, combined active lesions were independent predictors of brain volume but gadolinium volume was not.

Conclusion: Two major changes in brain volume occur in patients with relapsing multiple sclerosis, a steady decrease likely due to tissue loss with overlapping transient increases due to the appearance of inflammation.

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ORIGINAL CONTRIBUTION

METHODS

STUDY PARTICIPANTS

Inclusion and exclusion criteria, baseline characteristics, and the brain MRI protocol used in the BECOME study were previously reported. Following approval by the associated institutional review boards, 75 patients with RRMS (n=61) or clinically isolated demyelinating syndromes at risk of MS (n=14) provided informed consent and were randomized to subcutaneous treatment with interferon beta-1b (230 mg every other day) or glatiramer acetate (20 mg daily). The study used monthly brain MRI scans at 3-T with cumulative triple-dose gadolinium-diethylenetriaminepentaacetic acid and postinjection delay (30-40 minutes from a single-dose injection and 15-20 minutes from a double-dose injection). All scans were performed at 3-mm sections on a single 3-T head unit (Allegra; Siemens Medical Solutions). Compliance with monthly MRI scanning during the first year was very high.

MEASUREMENT OF BRAIN VOLUME

Brain volumes from baseline and months 1 to 12 after randomization were measured using the axial fluid-attenuated inversion recovery (FLAIR) sequences with BrainSuite version 2.0 software (http://users.loni.ucla.edu/~shattuck/brainsuite/). Digital Imaging and...
Communications in Medicine (National Electrical Manufacturers Association) images were converted into SPM Analyze (Wellcome Trust Centre for Neuroimaging) format and underwent the 3-stage BrainSuite surface modeling sequence. The first stage removes the nonbrain tissue with the Brain Surface Extractor method, which uses anisotropic diffusion filtering, Marr-Hildreth edge detection, and mathematical morphology. Spatial gain variation in the MRI is compensated by the Bias Field Correction technique, which computes local estimates of gain variation in the image using an adaptive partial-volume tissue model. The estimates are spaced uniformly throughout the volume and used by the Bias Field Correction technique to compute a tricubic B-spline that estimates the gain variation throughout the entire brain volume. The Bias Field Correction technique fixes the extracted brain image using the values of the spline. In the second stage, voxel-based partial-volume tissue classification assigns each remaining voxel into white matter, gray matter, cerebrospinal fluid, or partial-volume mixtures. In the third stage, label volumes are computed using a label painter tool to obtain the cumulative whole brain volume in cubic centimeters at 16 bits. Brain volumes could not be determined for times without FLAIR scan results. One participant had only 1 postbaseline MRI and brain volumes were not calculated; results for the remaining 73 participants (43 taking interferon beta-1b and 38 taking glatiramer) are presented. Participants had 839 brain volumes estimated from visits at baseline or months 1 to 12, of which 37 were discarded owing to severe motion or tilt during scans.

ANALYSIS OF PATTERN OF FOCAL INFLAMMATORY ACTIVITY ON MONTHLY BRAIN MRI SCANS

We used data from scans taken during months 1 to 12 (excludes screening and baseline) to categorize whether the focal inflammatory activity entered remission completely, temporarily, or not at all. The presence of active focal inflammatory activity was defined by the presence of any enhancing new T2/FLAIR lesions or gadolinium lesions (either newly or persistently enhancing). Such lesions were referred to as combined active lesions (CALs). Only participants who had at least 2 valid MRIs in each of months 1 to 6 and months 7 to 12 were included in this analysis, resulting in the exclusion of 5 additional participants. Participants who had at least 2 consecutive months with no CALs were considered to have achieved partial remission, participants who never had 2 consecutive months with no CALs were considered to have never reached remission, and participants in whom all available scans had no CALs were considered in complete remission. A full description of the rationale for the 3 categories was previously published.11

MEASUREMENT OF THE VOLUME OF GADOLINIUM ENHANCEMENT

The volume of all gadolinium-enhancing lesions previously identified in scan results from months 0 to 12 by a neuroradiologist (L.J.W.) was measured by a blinded reader (J.C.) using Analyze software (Mayo Clinic) with a pixel contiguity threshold detection tool. Only T1 fat-suppressed axial images were used. The area of gadolinium enhancement on each slice of every lesion was multiplied by the slice thickness of 3 mm to calculate the volume using the LogStat application and then summed to get the total volume of gadolinium enhancement per scan. Scans without gadolinium-enhancing lesions had zero volume of gadolinium enhancement.

STATISTICAL ANALYSES

Baseline comparisons used Wilcoxon rank sum or Kruskal-Wallis tests, and age was assessed using simple linear regression. The mixed procedure in SAS software (SAS Institute Inc) was used to estimate the brain volume over time and evaluate predictors, while taking into account correlation between measures for the same individual. We used random intercept and slope models, which allowed individual-specific initial brain volumes and rates of change, and restricted maximum likelihood methods for estimation. In addition to taking into account treatment, age, sex, MS type, and MRI pattern of inflammatory activity, we tested whether the number of CALs and the gadolinium-enhancing lesion volume from the same scan results were associated with brain volume. Tests for treatment and MRI pattern differences used only postbaseline brain volume measurements. We identified some outlying brain volume measurements but did not exclude them; instead, we performed sensitivity analysis excluding outliers and found that the conclusions were unchanged. All statistical testing was 2-sided at the 5% significance level. SAS version 9.1 software was used for all analyses.

RESULTS

BASELINE BRAIN VOLUMES

Seventy-three of the 74 participants underwent brain scans at baseline. The median baseline brain volume was 1253 cm³ (range, 1046-1547 cm³) (Table 1). We found a significant difference in brain volume by sex at baseline, with women having a smaller median volume (P=.001) estimated at 107 cm³. Age was also associated with brain volume, with participants having an estimated average of

Table 1. Brain MRI Volumes Prerandomization to Interferon Beta-1b or Glatiramer in Patients With RRMS or CIS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Median Brain Volume, cm³ (Range)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>73</td>
<td>1253 (1046-1547)</td>
<td>.001</td>
</tr>
<tr>
<td>By sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>1329 (1131-1514)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>51</td>
<td>1222 (1046-1547)</td>
<td></td>
</tr>
<tr>
<td>By randomized treatment</td>
<td></td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>Interferon beta-1b</td>
<td>36</td>
<td>1239 (1066-1529)</td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>37</td>
<td>1264 (1046-1547)</td>
<td></td>
</tr>
<tr>
<td>MS type</td>
<td></td>
<td></td>
<td>.64</td>
</tr>
<tr>
<td>RRMS</td>
<td>60</td>
<td>1254 (1046-1529)</td>
<td></td>
</tr>
<tr>
<td>CIS</td>
<td>13</td>
<td>1235 (1096-1547)</td>
<td></td>
</tr>
<tr>
<td>MRI activity postrandomization</td>
<td></td>
<td></td>
<td>.60</td>
</tr>
<tr>
<td>Never in MRI remission</td>
<td>21</td>
<td>1266 (1131-1547)</td>
<td></td>
</tr>
<tr>
<td>Intermittent MRI remission</td>
<td>32</td>
<td>1244 (1046-1514)</td>
<td></td>
</tr>
<tr>
<td>Complete MRI remission</td>
<td>16</td>
<td>1246 (1096-1541)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CIS, clinically isolated demyelinating syndrome suggestive of MS; MRI, magnetic resonance imaging; MS, multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis.

a One participant (male, glatiramer; CIS) had no baseline or screening MRI and was excluded from baseline summaries. Five participants (or 4 additional) had insufficient MRIs to classify their remission status in the first year.

b P values from Wilcoxon rank sum test (2 categories) or Kruskal-Wallis test (more than 2 categories). The MRI pattern testing for a trend by examining whether Spearman correlation = 0 gave P = .38.
3.1-cm³ smaller volume (P = .03) each successive year after study entry. In contrast, there was no difference in brain volume by treatment with interferon beta-1b or glatiramer (P = .54), regardless of whether participants had been diagnosed with RRMS or clinically isolated demyelinating syndrome at risk of MS at entry (P = .64) or of the pattern of brain inflammatory activity (CALs) post-randomization (always in remission, never in remission, or intermittent remission) (P = .60).

LONGITUDINAL ANALYSIS OF BRAIN VOLUME

Brain volume measurements were calculated at baseline and monthly during months 1 to 12. Examples of brain volumes for 4 randomly selected participants are shown in the Figure. Longitudinal models with random intercepts and slopes were used to assess changes in brain volume over time and covariates potentially associated with brain volume and differences in the rate of change (Table 2). A model with a fixed effect for each month showed brain volume decreased significantly over time (P < .001), with an average loss of 1.3 cm³ per month. Although women had a smaller estimated mean brain volume, they did not have a different rate of change (P = .96). Age at entry was associated with brain volume, with volume decreasing over the study period by 2.82 cm³ (P = .046) each successive year after study entry. However, the rate of change in volume did not differ by age (P = .84). Treatment assignment did not impact brain volume (P = .34) or the rate of change (P = .26) nor did MRI pattern of focal inflammatory activity in the year following randomization (P = .33 and P = .49 for volume and change in volume, respectively).

Figure. Actual and fitted brain volumes at baseline and months 1 to 12 in 4 randomly selected patients with relapsing-remitting multiple sclerosis or clinically isolated demyelinating syndrome at risk of multiple sclerosis assigned to treatment with interferon beta-1b or glatiramer acetate. The cohort was stratified by quartiles of estimated change in brain volume, and a single participant was selected at random from each quartile. A-D, Participants from first through fourth quartiles, from fastest to slowest decline. The number of combined active lesions (CALs) and gadolinium volume are shown on the horizontal axis. A multivariable model was fit to the data, which included a random intercept and slope and fixed effects for CALs, visit month, age at baseline, and sex. The model showed CALs were positively associated with brain volume, with each lesion corresponding to a 1.2-cm³ (95% CI, 0.7 to 1.7) higher brain volume. Actual brain volume was calculated from the axial fluid-attenuated inversion recovery sequences. The expected brain volume trajectory was based on the multivariable model setting CALs to zero. The expected brain volume was based on the model with actual observed number of CALs.
EFFECT OF THE PRESENCE OF ACTIVE INFLAMMATORY LESIONS ON BRAIN VOLUME

To measure active focal inflammatory brain activity, we first measured the number of CALs per scan (Table 3). Of the 802 brain MRI scans during months 0 to 12 from 74 participants, 393 scans (49%) corresponding to 61 individuals had at least 1 CAL. Among scans with CALs, the median (range) number of CALs per scan was 2 (0–43) CALs. A mixed model using a random intercept and slope adjusted for fixed effects for visit month, age at baseline, and sex found that the brain volume was increased by an estimated mean of 1.2 cm³ (95% CI, 0.7 to 1.7) per CAL during scans with focal inflammatory activity (P < .001) (Table 4, model 1). The number of CALs for the 4 randomly selected participants are shown in the Figure.

RELATIONSHIP BETWEEN THE VOLUME OF GADOLINIUM ENHANCEMENT AND BRAIN VOLUME

We next measured focal-brain inflammation using the volume of gadolinium enhancement. Thirteen of the 74 participants (17.6%) included in this analysis had gadolinium-enhancing volumes of zero at all times from baseline through the first year of study follow-up. The median gadolinium-enhancing lesion volume at baseline was 82 mm³. For every additional CAL, gadolinium-enhancing lesion volume increased by an average of 106 mm³ (95% CI, 100 to 112 mm³). We found no significant differences in baseline gadolinium volumes by sex (P = .94), MS type (P = .29), or treatment assignment (P = .43) (Table 3). Instead of CALs, we used gadolinium-enhancing lesion volume (which was highly correlated with the number of CALs, Spearman rank correlation = 0.96, P < .001) in the adjusted model (Table 4, model 2) to estimate the mean increase in brain volume, yielding 7.1 cm³ (95% CI, 3.8 to 10.4 cm³) per cubic centimeter increase in gadolinium volume (P < .001). When using both the number of CALs and the gadolinium-enhancing lesion volume with brain volume in a single model (Table 4, model 3), we found that CALs were an independent predictor of brain volume (P = .003) while gadolinium volume was not (P = .58). Gadolinium volumes for the 4 randomly selected participants are also shown in the Figure.

### Table 2. Evaluating the Effects of Covariates on Brain Volume and on the Rate of Change in Brain Volume Using Longitudinal Models in Patients With RRMS or CIS Using Measures at Baseline and During the First Year After Randomization to Treatment With Interferon Beta-1b or Glatiramer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Estimated Mean Difference in Brain Volume, cm³ (95% CI)</th>
<th>P Valuea</th>
<th>Estimated Mean Difference in Rate of Change of Brain Volume, cm³/mo (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit month</td>
<td>−1.3 (−1.7 to −0.8)</td>
<td>&lt;.001</td>
<td>−0.04 (−0.77 to 0.68)</td>
<td>.91</td>
</tr>
<tr>
<td>Female vs male</td>
<td>−96.8 (−147.3 to −46.3)</td>
<td>&lt;.001</td>
<td>0.09 (−0.01 to 0.19)</td>
<td>.07</td>
</tr>
<tr>
<td>Age per y</td>
<td>−2.82 (−5.60 to −0.04)</td>
<td>.046</td>
<td>0.77 (−0.50 to 2.04)</td>
<td>.26</td>
</tr>
<tr>
<td>RRMS vs CIS</td>
<td>9.2 (56.0 to 74.4)</td>
<td>.78</td>
<td>0.8 (0.3 to 1.4)</td>
<td>.57</td>
</tr>
<tr>
<td>Randomized to interferon beta-1b vs glatiramer acetate</td>
<td>−24.8 (−75.6 to 26.0)</td>
<td>.34</td>
<td>0.06 (−1.00 to 2.29)</td>
<td>.84</td>
</tr>
<tr>
<td>MRI activity postrandomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never in MRI remission</td>
<td>37.7 (−33.3 to 108.8)</td>
<td>.33</td>
<td>−0.20 (−1.97 to 1.57)</td>
<td>.49</td>
</tr>
<tr>
<td>Intermittent MRI remission</td>
<td>−6.9 (−72.5 to 58.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete MRI remission</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAL per lesion</td>
<td>1.2 (0.8 to 1.7)</td>
<td>&lt;.001</td>
<td>−0.04 (−0.77 to 0.68)</td>
<td>.91</td>
</tr>
<tr>
<td>Per cubic centimeter gadolinium enhancement</td>
<td>7.2 (3.9 to 10.5)</td>
<td>&lt;.001</td>
<td>0.09 (−0.01 to 0.19)</td>
<td>.07</td>
</tr>
</tbody>
</table>

Abbreviations: CALs, combined active lesions; CI, confidence interval; CIS, clinically isolated demyelinating syndrome suggestive of MS; MRI, magnetic resonance imaging; RRMS, relapsing-remitting multiple sclerosis.

aFrom models with random intercepts and slopes plus fixed effects for visit month (continuous), the covariate, and interaction between visit month and the covariate. The first model included a fixed effect for the visit month only.

bFrom models with random intercepts and slopes plus fixed effects for visit month (continuous), the covariate, and interaction between visit month and the covariate. Only estimated interaction effects and tests are shown.

The optimized monthly MRI scanning protocol used in the BECOME study allowed us to measure in great detail the changes in brain volume that occur in patients with relapsing MS on a monthly basis and how brain volume is affected by the presence of active inflammatory lesions. The main findings include: (1) a significant decrease in brain volume occurs monthly in patients with relapsing MS that is independent of age, sex, treatment with interferon beta-1b or glatiramer, and pattern of MRI inflammatory activity; (2) at times of active MRI inflammatory activity, the brain volume transiently increases by an average of 1.2 cm³/lesion and 7.1 cm³/cubic centimeter increase in gadolinium volume (both P < .001); and (3) the increase in brain volume at times of active MRI inflammatory activity is not fully explained by the volume of gadolinium enhancement; in fact, in models that use both gadolinium volume and number of CALs, only the number of CALs independently predicts brain volume.

To accurately assess changes in brain volume in patients with MS, serial quantitative volumetric measurements are needed. Although there have been several previous studies of the longitudinal changes in the brain volume in patients with MS, most have used infrequent MRI scanning, most often yearly scans. It is difficult to determine the impact of ongoing inflammatory activity on brain
volume using infrequent brain MRI scanning. A few studies have used frequent brain MRI scans but for short duration and did not study volume changes. 

One exception was a study using monthly brain MRI scanning for 9 months followed by quarterly scans for an additional 9 months that found no differences in the rate of brain volume change in patients with RRMS randomized to glatiramer acetate or placebo. To our knowledge, ours is the first MS study that measures the change of brain volume on a monthly basis for a full year and quantifies the impact of ongoing inflammatory activity (CALs) on brain volume. We found that on any given month, having active focal lesions in the brain is associated with an increase in brain volume in MS was not influenced by age, sex, treatment with interferon beta-1b or glatiramer acetate, or the MRI pattern of ongoing focal inflammatory activity. This is consistent with true loss of brain tissue rather than reduced brain water content. Others have previously reported that brain atrophy occurs early in patients diagnosed with RRMS and is the most significant MRI predictor of disability at long-term follow-up. A large study of patients with MS who went untreated demonstrated that brain atrophy proceeds relentlessly throughout the course of the disease at a rate that seems largely independent of the MS subtype when adjusting for baseline brain volume. This steady loss of brain volume may be the MRI signature of sustained disease progression and may correspond to the pathological finding of extensive axonal transection and demyelination at sites of active inflammation at all stages of MS.

We found that on any given month, having active focal inflammation (CALs) increases brain volume associated with blood-brain barrier breakdown likely due to an influx of water due to vasogenic edema and entry of inflammatory cells from the circulation. The finding that CALs were independent predictors of brain volume while gadolinium volume was not could be explained by the fact that the counting of CALs by an expert neuroradiologist is more accurate than estimating gadolinium volume using automatic software analysis tools. This suggests there is more volume increase per CAL than one can measure with gadolinium. Alternatively, as brain MRI analysis methods improve, we might find that gadolinium volumes might be as good or better predictors of brain volume changes than CALs. The average increase in brain volume due to the presence of focal inflammation (1.3 cm³/CAL with a median [range] of 2 [1 to 43] CALs/scan) is of similar magnitude to the average monthly loss of brain volume (1.2 cm³/mo). This finding highlights the difficulty of making true assessment of brain atrophy in patients with MS in the setting of the appearance and disappearance of CALs. This is especially problematic for studies that use yearly scans because of the inability to compare brain volumes at times.
with and without CALs as we were able to do in our modeling based on 13 scans during 1 year. Simple differences in CALs between the baseline and subsequent scans will result in an apparent change in brain volume simply because of the change in CALs. Based on these findings, it can be predicted that drugs that can control vasogenic edema and inflammatory cell influx will cause a reduction of brain volume during the initial treatment period. This reduction of brain volume secondary to resolution of active inflammation has been referred to as pseudoatrophy and has been well documented with treatments such as natalizumab, and intramuscular interferon beta-1a. Pseudoatrophy explains the lack of protective effect on brain atrophy reported during the first year of treatment with interferon beta-1b experienced a loss of brain volume of 1.39% at 6 months (average 0.23% per month) and 2.91% at 3 years (average 0.08% per month).

There are several methods available to study changes in brain volume, most of them use highly reproducible semi-automated quantitative techniques with coregistration of images. The methods include the Bragance Basic Skills Inventory test, Structural Image Evaluation using Normalization of Atrophy, and ventricular enlargement. One frequently used method is the brain parenchymal fraction, which divides the brain parenchymal volume by the total volume within the brain-surface contour, resulting in reduced variability. More recently, there has been increased interest in measuring segmented volumes, including gray and white matter volumes, central brain volume, and the upper cervical spinal cord area. One long-term follow-up study of patients who presented with optic neuritis revealed that gray matter atrophy is more marked than white matter atrophy and reflects MS disease subtype and disability to a greater extent. We preferred to use whole brain volume because it is the most responsive to change over time and less variable than the measures currently available to assess cortical volume or cortical thickness.

We conclude that a steady decrease in brain volume not explained by transient changes in inflammation is detectable on a monthly basis in patients with relapsing MS that is of similar degree during treatment with interferon beta-1b or glatiramer acetate. Many additional factors do influence the total brain volume of a patient with MS at any given time, including the presence of focal inflammatory activity (CALs), age, and sex.

There have been several previous studies of the yearly loss of brain volume that occurs in patients with MS, including subjects with clinically isolated demyelinating syndromes at risk of MS, RRMS, and progressive MS. The annual rate of volume loss in progressive MS was estimated at about 6.5 cm³, which corresponds to about 0.5 cm³ per month, consistent with the 0.59% per year loss reported in patients with secondary progressive MS in another study. A review of a subgroup of 95 patients from the European interferon beta-1b secondary progressive MS study measured the volume of 4 contiguous brain slices and reported that a significant loss of about 0.9% was already apparent after only 6 months of treatment in the placebo group; it reached 3.9% after 3 years, corresponding to an average monthly loss of approximately 0.1%. In this study of 4 brain slices, patients treated with interferon beta-1b experienced a loss of brain volume of 1.39% at 6 months (average 0.23% per month) and 2.91% at 3 years (average 0.08% per month).

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Acquisition of data: Cheriyan, Wolansky, Cook, and Cadavid.
Drafting of the manuscript: Cheriyan, Kim, and Cadavid.
Critical revision of the manuscript for important intellectual content: Cheriyan, Kim, Wolansky, Cook, and Cadavid.
Administrative, technical, and material support: Cheriyan, Wolansky, Cook, and Cadavid.
Study supervision: Wolansky and Cadavid.
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