Atrophy Is Detectable Within a 3-Month Period in Untreated Patients With Active Relapsing Remitting Multiple Sclerosis

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Background: Atrophy is recognized as a measure of destructive changes in multiple sclerosis (MS). The time course and pathologic mechanisms of atrophy development are not well understood. Significant atrophy was reported to occur within 9 to 12 months in relapsing remitting MS.

Objectives: To test whether atrophy can be detected over short time intervals, and to evaluate its relationship to inflammation.

Design and Methods: Prior to randomization to a treatment trial, 138 untreated patients with relapsing remitting MS had 3 magnetic resonance imaging scans within a mean±SD follow-up of 76±20.2 days. Brain parenchymal fraction (BPF), a normalized measure of whole brain volume, the proportion of active (gadolinium-enhancing) scans, and the volume of T1-weighted gadolinium-enhancing and T2-weighted hyperintense lesions were determined at all time points. An annualized atrophy rate was estimated by calculating a regression slope.

Results: The median Expanded Disability Status Scale (EDSS) score was 3.5, the mean disease duration was 7.6, and the mean age was 38.5 years. The BPF decreased significantly by –0.229% from scan 1 to scan 3, while the proportion of active scans remained high (65%, 63%, and 67%). The BPF change was only weakly correlated to the volume of T1-weighted gadolinium-enhancing lesions in scan 1 ($r = -0.185$). The estimated annualized atrophy rate was –1.06% (95% confidence interval, −1.50% to −0.62%).

Conclusions: The annualized atrophy rate found in this study is comparable with rates reported previously. Measurements of BPF allow detection of atrophy over short time intervals in active disease. The short-term relationship of inflammation to atrophy development was weak. Brain parenchymal fraction might be a promising measure in future phase 2 studies of agents, with an expected effect on tissue-destructive pathologic mechanisms of MS.

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ease duration was 7.6 ± 5.4 years, and the mean age was 38.5 ± 7.1 years. Ten subjects were treated with intravenous methylprednisolone for a relapse during the study.

IMAGE ACQUISITION

Magnetic resonance imaging was performed at 3 time points before randomization: scan 1 was performed a mean ± SD of 76.0 ± 20.2 days, and scan 2, 42.6 ± 18.1 days, before scan 3. A double echo T2-weighted image and a T1-weighted image obtained before and after intravenous injection of gadolinium pentetic acid, with 23 axial, contiguous 5-mm slices, were acquired. Repositioning was achieved using standardized anatomic landmarks. The complete MRI protocol is described elsewhere.8

IMAGE ANALYSIS

Brain parenchymal fraction is a normalized measure equivalent to the ratio of the volume of the brain parenchyma to the volume within the outer contour of the brain. It is automatically calculated using Autoseg MS (Cleveland Clinic Foundation, Cleveland, Ohio). The measurement has previously been shown to have a high reproducibility (mean scan-rescan coefficient of variation of 0.19%).3 The T1Gd on T1-weighted images and T2LL on T2-weighted images were measured using a semiautomated seed-growing technique based on local thresholding (for details, see Clanet et al).8

STATISTICAL ANALYSIS

The Wilcoxon rank sum test was used to compare median BPF, T1Gd, and T2LL between scans. Absolute and relative changes were calculated. To estimate an annualized atrophy rate, the mean and the 95% confidence interval (CI) of the regression slope was calculated for each subject having 3 BPF values (n = 128). The inclination of the slope was used to extrapolate the change to 360 days (mean annualized atrophy rate and 95% CI). The difference to zero was assessed by a 1-sample t test. In addition, a sensitivity analysis was performed based on imputation: missing follow-up values were replaced with the last and missing baseline values with the first BPF value available (n = 137). Correlation was assessed by the Spearman rank correlation test. Tests were regarded as significant at a 2-sided level of P < .05, if not indicated otherwise. Data are given as mean ± SD unless otherwise indicated.

RESULTS

The correlations between clinical data and MRI measures were weak. BPF at baseline correlated to EDSS score (r = −0.242) and disease duration (r = −0.216) (both P < .05) and T2LL correlated to EDSS score (r = 0.222) (P < .05). The time interval between scans 1 and 2 was significantly (P < .001) shorter than between scans 2 and 3. In 12 scans, BPF could not be measured because of segmentation errors caused by image artefacts. For scans 1, 2, and 3, BPF was evaluable in 131, 134, and 136 subjects, respectively. Values for BPF, T1Gd, and T2LL are presented in the Table. There was no significant difference between BPF 1 and BPF 2, whereas BPF 3 was significantly lower than BPF 1 and BPF 2. This corresponds to a mean relative BPF change of −0.229% from scan 1 to scan 3. In 69% of the subjects, a decrease in BPF was found; 53% showed a decrease of at least −0.2%. Considering complete cases only (n = 128), BPF 2 (0.8276 ± 0.028) showed a trend (P = .10) of being lower than both BPF 1 (0.8281 ± 0.028) and BPF 3 (0.8263 ± 0.028) was significantly (P < .001) lower than the earlier measurements.

The estimated annualized atrophy rate was −1.06% (95% CI, −1.50% to −0.62%) for complete cases (n = 128), as shown in the Figure. The slope differed significantly (P < .01) from zero. The slope, based on imputation analysis, was not significantly different (−1.099%; 95% CI, −1.53% to −0.67 [n = 137]). Correlation between number and volume of Gd-enhancing lesions was high and significant (P < .001) at all time points (r = 0.851, r = 0.749, r = 0.860); therefore, only volumes are reported (T1Gd). The T1Gd did not change significantly between scans. Sixty-five percent, 63%, and 67% of the subjects had an active scan at time points 1, 2, and 3, respectively. Eighty-three percent of subjects had at least 1 active scan. The T2LL significantly increased between scans 1 and 2 (P < .001) and 2 and 3 (P < .01), corresponding to a median change of 4.3% (interquartile range, −1.6 to 10.1) and 3.5% (interquartile range, −4.2 to 8.8), respectively.

Cross-sectionally, BPF showed a strong negative, significant (P < .001) correlation to T2LL at all time points (r = −0.668, r = −0.622, and r = −0.650). The T2LL was sig-
significantly ($P<.001$) correlated to T1Gd at all time points ($r=0.371$, $r=0.461$, and $r=0.406$), and a weak significant ($P<.05$) correlation was found between BPF and T1Gd for scan 3 ($r=-0.17$).

Longitudinally, no significant correlation between changes in BPF and changes in other MRI or clinical measures was found. Change in BPF showed a weak negative correlation to T1Gd and T2LL for scan 1 ($r=-0.185$ and $r=-0.219$, respectively; $P<.05$). A subgroup analysis excluding subjects who had received intravenous methylprednisolone for a relapse ($n=10$) did not yield different results.

**COMMENT**

We found a small but highly significant ($P<.001$) change in BPF in this group of untreated RRMS patients within a mean follow-up period of 76 days. More than 50% of the patients showed a decrease in BPF of at least −0.2%. Up to now, 2 published studies have yielded conflicting results: in a small patient sample ($n=12$), a decrease in brain fractional volume was described during a 3-month period preceding a relapse. However, with another, probably less sensitive, method with higher variability of measurements, no significant change in the volume of 4 central slices was found during a 6-month period. The change found in our study corresponds to an overall mean estimated yearly atrophy rate of $−1.06\%$, which is at the higher end of the range reported in other studies. Longitudinal, no significant correlation between changes in BPF and changes in other MRI or clinical measures was found. Change in BPF showed a weak negative correlation to T1Gd and T2LL for scan 1 ($r=-0.185$ and $r=-0.219$, respectively; $P<.05$). A subgroup analysis excluding subjects who had received intravenous methylprednisolone for a relapse ($n=10$) did not yield different results.

A decrease in brain volume can be due to (1) resolution of inflammatory edema or (2) destructive tissue loss. The former is unlikely, since there was ongoing inflammatory activity as depicted by a high proportion of active scans, persistent Gd enhancement, and an increase in T2LL. There was no correlation between change in T1Gd and change in BPF. Intravenous methyl-prednisolone treatment has been reported to result in higher variability in BPF $^{11}$ and a significant reduction in brain fractional volume 1 month later. However, exclusion of the 10 subjects treated with intravenous methyl-prednisolone in our cohort did not have an effect on the results. Therefore, the decrease in BPF observed during the study period more likely reflects an ongoing destructive process rather than reversible volume changes.

Extrapolating short-term changes to yearly rates assumes linearity of the time course of the measure. In untreated RRMS patients, the atrophy rate measured with the same method was reported to be not significantly different in the second year $^{6}$ compared with the first year. During treatment with recombinant interferon $\beta$-1a, atrophy rates remained unchanged between the second and third year of treatment. $^{12}$ Two small studies reported a considerable amount of intrasubject short-term variability. $^{13,14}$ However, in RRMS, 40% of the patients showed a significant regression slope for monthly increasing ventricle size. $^{14}$ In our setting, the extrapolation of the mean regression slope to an annualized rate seems to be justified. Since the regression is based on all 3 time points, it better reflects the trend of BPF change than extrapolating the relative change between scans 1 and 3.

The high atrophy rate we found most likely reflects natural history in a very active group of RRMS patients with well-established disease (EDSS score, 2.0-5.5). Most other studies included patients with a mean EDSS score ranging from 1.2 to 2.6. $^{1,4,10,14}$ In our sample, activity is shown by the high percentage of active scans and persistent T1Gd enhancements during the study period. This may be a result of the study design, which did not include a placebo but only 2 active treatment arms. Therefore, investigators might have included patients they would not have put at risk to receive a placebo.

Studies about the relationship of other MRI measures with the development of atrophy have not yielded uniform results. During a 2-year period, the width of the third ventricle was predicted only by Gd enhancement at baseline $^{15}$; in a very similar sample, whole brain atrophy was only correlated with baseline T2LL. $^{3}$ In our short-term study, there was a weak relationship of T1Gd and T2LL in the first scan to subsequent BPF change. Cross-sectionally, we found a strong correlation between BPF and T2LL. While these findings imply that inflammation has a relationship to atrophy development, the contribution of other mechanisms, such as changes in the normal-appearing white matter, has to be elucidated.

In conclusion, BPF measurements allow detection of whole brain atrophy, even in intervals of less than 3 months in groups of patients with active disease. Therefore, BPF might be a promising measure in future phase 2 studies of agents with an expected effect on the tissue-destructive pathologic mechanism of MS.

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