Eight-year follow-up study of brain atrophy in patients with MS

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Abstract—Objective: To characterize whole-brain atrophy in relapsing-remitting MS (RRMS) patients over an 8-year period. The specific goals of this study were to determine if brain atrophy is related to subsequent disability status and to identify MRI correlates of atrophy progression. **Methods:** A follow-up study was conducted to reassess patients from a phase III trial of interferon β -1a (IFN β -1a) 8 years after randomization. Clinical and MRI data from 172 patients followed over 2 years in the original trial were used as baseline data. Follow-up data were obtained on 160 patients, including 134 patients with follow-up MRI examinations. Brain atrophy was estimated by automated calculation of brain parenchymal fraction. The relation between atrophy during the original trial and disability status at follow-up was determined. Correlations were also determined between lesion measurements from the original trial and the brain parenchymal fraction at follow-up. **Results:** Brain atrophy was correlated with subsequent disability status. Atrophy rate during the original trial was the most significant MRI predictor of disability status at follow-up. Brain atrophy at follow-up was related to lesion volumes measured during the original trial. **Conclusions:** The relation between atrophy progression and subsequent neurologic disability status suggests that atrophy progression during RRMS is clinically relevant. Therefore, atrophy progression may be a useful marker for disease progression in clinical trials. The relation between lesions and subsequent atrophy indicates that brain atrophy may be related to focal tissue damage at earlier points in time, but important predisposing or other factors contributing to atrophy remain undefined.

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MRI has fallen short of expectations in terms of providing a surrogate marker in MS. The lack of robust correlations between conventional MRI measures of pathology and clinical measures of disability has been attributed to various shortcomings of both MRI and clinical assessments. At least part of the discrepancy may be due to the use of MRI measurements that include both reversible and irreversible components of MS pathology. Conventional MRI lesion measurements also neglect to account for diffuse abnormalities in normal-appearing tissue in MS. One of the alternative MRI measures that have been proposed to monitor MS progression is the estimation of CNS atrophy.^{1–11} In contrast to MRI-visible lesions, CNS atrophy is believed to reflect the net effect of severe and potentially irreversible processes such as demyelination and axonal loss. Measurement of the size of CNS structures may provide an indication of the total amount of tissue damage that has occurred up to a given point in time. New computer-assisted methods have been developed to precisely and reli-

ably quantify tissue loss in MRI,^{5–13} and atrophy has been shown to occur even in the early stages of MS.^{3,4,6–9} However, previous longitudinal studies in MS^{3,6–9,14–16} have not shown very strong or consistent relations between brain atrophy and disability. These studies have been limited to relatively short follow-up periods of 6 months to 3 years.

The goals of this study were to determine if brain atrophy was related to progression of disability over a longer period of time and to identify MRI correlates of atrophy progression in patients with relapsing-remitting MS (RRMS). To address these questions, we analyzed data that had previously been acquired during a phase III trial of IFN β -1a in conjunction with new data that were acquired as part of an 8-year follow-up study to validate the MS Functional Composite (MSFC).¹⁷ Initial results from this follow-up study on the significant cross-sectional correlations between brain atrophy and disability have been recently reported.^{17,18} This report presents a more complete analysis of the longitudinal and pre-

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dictive relations between brain atrophy, MRI lesion measurements, and disability. Three specific questions are addressed: 1) Is the rate of atrophy in RRMS predictive of the subsequent development of disability? 2) What are the characteristics of atrophy progression over the course of 8 years? and 3) Are MRI lesion measurements in RRMS related to the subsequent progression of brain atrophy?

Methods. *Clinical trial (1990 through 1994).* Clinical and MRI data for the first 2 years were collected during the MS Collaborative Research Group (MSCRG) phase III trial of IFN β -1a (AVONEX, Biogen, Cambridge, MA). Three hundred one patients with RRMS were enrolled at four sites (Buffalo, NY; Cleveland, OH; Portland, OR; and Washington, DC). To meet the inclusion criteria, patients had to score between 1.0 and 3.5 on the Kurtzke Expanded Disability Status Score (EDSS)¹⁹ and had to have had at least two relapses in the prior 3 years. Details of the trial design have been reported elsewhere.²⁰ Clinical measures of disability included (among others) the EDSS, a timed 25-foot walk, the Nine-Hole Peg test, and the 3-second Paced Serial Addition Test. The MSFC²¹ was computed as described.¹⁷ MRI examinations included a dual-echo, proton density, T2-weighted spin-echo series (repetition time [TR] = 2000 ms, echo time [TE] = 30 and 90 ms) and T1-weighted spin-echo series (TR = 600 ms, TE = 20 ms) acquired before and after injection of contrast. Images were acquired with 192 $\times$ 256 matrix size, 240 mm field of view, and 5-mm-thick contiguous slices on 1.5-T scanners. MRI lesion measurements included T2-hyperintense lesion volume, contrast-enhancing lesion number and volume, and T1-hypointense lesion volume.²² The number of new and enlarging T2 lesions at year 2 and the cumulative number of contrast-enhancing lesions over 2 years were also determined. Lesion measurements were performed as part of the original trial at the University of Colorado Health Sciences Center in Denver. Brain parenchymal fraction (BPF) was calculated blindly with automated segmentation software developed at The Cleveland Clinic Foundation, as previously described.⁷

Follow-up study (1999). The follow-up study protocol was reviewed and approved by the Institutional Review Board (IRB) of each of the four participating sites. Patients who were enrolled for at least 2 years in the phase III study were eligible for this study. This requirement was included to ensure baseline, year 1, and year 2 data for the MSFC for each subject in the follow-up study. All patients who agreed to participate signed an IRB-approved informed consent form. Follow-up study visits consisted of a neurologic examination (EDSS, relapse history, current disease category, and history of disease-modifying drugs), an examination by a trained technician (MSFC, visual contrast letter acuity), a patient quality-of-life questionnaire (Sickness Impact Profile²³), and an MRI examination. Patients who were not able to participate in a clinic visit were asked to complete an EDSS self-report,¹⁹ disease-modifying therapy questionnaire, and Sickness Impact Profile questionnaire. Family members of patients who had died in the interim were interviewed to record the cause of death and EDSS prior to death.

Image acquisition and analysis. As in the original clinical trial, a dual-echo, proton density, T2-weighted spin-

echo image series was acquired (TR = 2000 ms; TE = 30 and 90 ms) with 256 $\times$ 256 matrix size, 240 mm field of view, and 5-mm-thick contiguous slices on 1.5-T scanners at each of the original sites. The images were sent in digital format to the Cleveland Clinic, transferred to a UNIX file server, and converted to an internal image format (BIP, Whitaker Biomedical Imaging Lab, Cleveland Clinic Foundation). All images were visually inspected and compared to images acquired during the phase III trial to verify consistency.

Brain atrophy was assessed with the same method that was used for the retrospective analysis of the phase III trial images.⁷ In summary, a program was used to automatically measure the brain parenchymal volume (BV) and the total volume within the outer contour of the brain (TCV) using a knowledge-based, three-dimensional segmentation algorithm.²⁴ The BPF was calculated as the ratio BV/TCV to provide a size-normalized measure of whole-brain atrophy. Previous validation studies showed that the accuracy is approximately 99% for brain volume measurement and the scan-rescan variability is approximately 0.2% for BPF.⁷ To process dual-echo image sets, the complete analysis pipeline included the following steps in one program: 1) correct intensity nonuniformities; 2) normalize the gray levels; 3) perform optimal linear combination of the early and late echo images to null the signal from cerebral spinal fluid; 4) filter out noise if necessary; 5) perform the segmentation; and 6) calculate volumes accounting for partial volume effects. Following segmentation, the image results were visually verified using custom display software. In cases where the segmentation failed with the default program settings, the process was repeated with adjustments to parameters that control the filtering operations. BPF analysis was fully automated and performed blinded to clinical disability scores and other clinical information. Lesion analysis was not included in the follow-up study because it was considered to be outside the scope of the study (which was primarily to validate the MSFC and, secondarily, to study the predictive value of atrophy measurements for disability).

Analysis subgroups. The numbers of patients with available MRI measurements were different at each point in time. The numbers varied because some patients did not have MRI scans at the 8-year follow-up, and images from the original trial were omitted from analysis if the electronic data were corrupted or lost in transfer or if the images were not acquired according to protocol—that is, with gaps between the slices or varying pixel sizes. Therefore, two different subgroups of patients were considered to address the specific questions of this study.

For the first question regarding the relation between atrophy and subsequent disability, we used the subgroup of all patients who had at least two analyzable MRI scans during the original trial and an EDSS measurement at the 8-year follow-up. This subgroup was chosen so that the results would not be biased by only including patients who were well enough at follow-up to have an MRI examination. The requirement of at least two MRI scans during the original trial ensured that atrophy rate during the original trial could be estimated. The 2-year atrophy rate was estimated as the percent change in BPF from baseline to year 2 or, for cases with only two consecutive MRI scans avail-

Table 1 Brain volume and disability measurements at each time point

Measure	Baseline	Year 1	Year 2	8-Year follow-up
EDSS	2.35 (0.84) [172]	2.71 (1.37) [168]	2.84 (1.57) [170]	4.38 (2.33) [160]
MSFC	0.0 (0.71) [171]	−0.10 (1.18) [163]	−0.11 (1.25) [150]	−1.05 (2.19) [135]
BPF	0.830 (0.017) [137]	0.824 (0.021) [152]	0.821 (0.021) [148]	0.804 (0.028) [134]

Values are expressed as mean (SD) [no. of patients].

EDSS = Expanded Disability Status Scale; MSFC = MS Functional Composite; BPF = brain parenchymal fraction.

able ($n = 13$), the 2-year atrophy rate was estimated as twice the annual percent change in BPF.

For the second two questions on the progression of atrophy, the subgroup of all patients who had analyzable MRI scans at all four time points was considered. This subgroup was defined to ensure that all patients would have BPF measurements from the original trial and from the 8-year follow-up examination. MRI lesion measurements were also available for the majority of these patients during the original trial.

Statistical analyses. Correlations were calculated between BPF and disability measurements at each time point using Spearman rank statistics. Patients were categorized into two outcome groups based on whether their EDSS score at 8-year follow-up was less than 6.0 or greater than or equal to 6.0. This particular cutoff value was selected because it is a clinically meaningful and relatively objective milestone: EDSS 6 is the point at which a patient needs assistance to walk. Patients were subclassified into quartiles based on percent BPF change during the 2-year phase III trial. The percent of patients in each quartile who reached EDSS 6 or greater were determined. Mean BPF at each time point was compared between the two EDSS outcome groups using the Mann–Whitney test. Logistic regression analyses were performed to determine which variables during the original trial were significant predictors of disability status at the 8-year follow-up. The following demographic and disease-related variables were considered in all models: age, sex, treatment group, disease duration, number of relapses during the trial, time from baseline to the 8-year follow-up, and total percent time on treatment over the 8-year period. In addition, specific disability and MRI variables were also considered for inclusion in each model. Continuous factors considered for the logistic regression models were plotted using a locally weighted smoothing scatterplot technique to assess linearity on the logit scale. A forward stepwise selection procedure was used with a p value of 0.15 required to enter the model and a p value of 0.05 required to remain in each model.

Spearman correlations were also calculated to determine the relation between MRI lesion measurements from the phase III trial and subsequent atrophy. Multiple regression analysis was performed to determine which parameters from the original trial were significant predictors of the change in BPF from year 2 to the 8-year follow-up. The same demographic and disease-related variables as those used for the logistic regression analyses were considered for inclusion in all models, in addition to model-specific disability and MRI variables. Linearity between each independent variable and the dependent variable was confirmed. A forward stepwise selection procedure was

used with p values of 0.15 to enter and 0.05 to remain in the model.

Results. *Descriptive statistics.* Follow-up clinical data were obtained on 160 (93%) of the 172 patients who were eligible for the study, including 3 patients who returned for a neurologic examination but refused MRI, 16 patients who completed self-reports for EDSS but did not have neurologic or MRI examinations, and 7 patients who died. EDSS scores prior to the terminal event for these seven patients were assigned by the neurologist after interview with the family and record review. The mean follow-up time was 8.1 years (SD 0.4, range 7.2 to 8.8 years) and disease duration at follow-up was 14.3 years (SD 5.5, range 8.5 to 39.0 years). MRI scans at the 8-year follow-up were acquired on 134 patients. All images were analyzable with the BPF software.

As a whole, the group worsened in terms of both disability and brain atrophy. The mean disability level, measured with either the EDSS or MSFC, and the severity of brain atrophy worsened significantly between baseline and the 8-year follow-up point (table 1). At baseline, the mean EDSS was 2.4 (SD 0.9) and at follow-up it had increased to 4.1 (SD 2.0). Fifty-seven (35%) patients had progressed to EDSS ≥ 6.0 by the 8-year follow-up. Similarly, mean MSFC worsened from 0.0 (SD 0.7) at baseline to -1.1 (SD 2.2) at the 8-year follow-up. The mean BPF decreased 3.1% from 0.83 (SD 0.02) at baseline to 0.80 (SD 0.03) at the 8-year follow-up.

During the placebo-controlled 2-year trial, 49% of the patients in the follow-up group were taking IFN treatment. Treatment was uncontrolled and variable in the 6-year interim between the end of the phase III trial and the follow-up examination. Patients were taking disease-modifying drugs (IFN, glatiramer acetate, pulsed steroids, methotrexate, cyclophosphamide, or azathioprine) during the interim time from the end of the phase III trial until follow-up. The percent time on treatment during the year 2 to follow-up interval was 54.2% for the original treatment group and 46.5% for the original placebo group.

Available images. As described in the Methods section, two different subgroups of patients were considered to address the specific questions of this study. There were 138 patients who had at least two analyzable MRI scans during the original trial and an EDSS measurement at the 8-year follow-up (including 5 of the patients who died). This subgroup was considered for the first question regarding the relation between atrophy and subsequent disability. For the second two questions on the progression of atrophy, there were 106 patients who had analyzable MRI scans at all four time points. Baseline demographic and

Table 2 Baseline characteristics of patient subgroups

Measure	All patients eligible for the follow-up study, n = 172	Patients with $\geq$ two MRIs in original trial and EDSS at 8-year follow-up, n = 138	Patients with MRIs at all four time points, n = 106
Age, y, mean (SD)	36.1 (6.8)	36.0 (6.9)	35.9 (7.2)
Female, %	77	76	77
Disease duration, y, mean (SD)	6.3 (5.6)	6.1 (5.5)	6.1 (5.1)
EDSS, mean (SD)	2.3 (0.84)	2.3 (0.84)	2.3 (0.84)
MSFC, mean (SD) [no. of patients]	0.0014 (0.71) [171]	0.055 (0.65) [137]	0.079 (0.59) [106]
T2 lesion volume, mL, mean (SD) [no. of patients]	15.5 (15.7) [163]	14.8 (15.3) [137]	14.7 (15.4) [106]
T1 lesion volume, mL, mean (SD) [no. of patients]	1.51 (2.03) [150]	1.49 (2.02) [127]	1.44 (1.44) [98]
Gadolinium + lesion number, mean (SD) [no. of patients]	2.8 (6.7) [170]	2.3 (5.1) [136]	2.1 (4.9) [104]
BPF, mean (SD) [no. of patients]	0.830 (0.017) [137]	0.830 (0.018) [127]	0.832 (0.016) [106]

EDSS = Expanded Disability Status Scale; MSFC = MS Functional Composite; BPF = brain parenchymal fraction.

disease-related characteristics of these patient subgroups are given in table 2. There were no substantial differences between the subgroups at baseline for any of the variables measured.

Question 1: Relations between atrophy and disability. As previously reported,^{17,18} BPF was correlated with concurrent disability measurements at each of the four time points (baseline, year 1, year 2, and the 8-year follow-up). The concurrent correlations ranged from -0.27 (BPF and EDSS at year 1) to 0.51 (BPF and MSFC at year 1). The correlation between BPF and MSFC was consistently stronger than the magnitude of the correlation between BPF and EDSS at each time point. The change in BPF from year 2 to 8-year follow-up was correlated with change in EDSS in the same period ($r = -0.31$, $p = 0.0005$) and with change in MSFC in the same period ($r = 0.30$, $p = 0.001$).

The relation between brain atrophy during the original trial and subsequent progression of disability progression was studied in the subgroup of patients ($n = 138$) with at least two analyzable MRI scans from the original trial and an EDSS measurement at the 8-year follow-up. In this subgroup, the mean EDSS at baseline was 2.3 (SD 0.8) and at the 8-year follow-up it had increased to 4.2 (SD 2.3). Forty-four (32%) of these patients had progressed to EDSS ≥ 6.0 by follow-up. The mean MSFC had decreased from 0.055 (SD 0.65) at baseline to -0.95 (SD 2.1) at the 8-year follow-up. The mean percent change in BPF during the original trial was -1.1% (SD 1.3%) over 2 years.

Brain atrophy during the original phase III trial was related to EDSS, MSFC, and disability status at the 8-year follow-up. Percent change in BPF from baseline to year 2 was correlated with EDSS at the 8-year follow-up ($r = -0.27$, $p = 0.001$) and with MSFC at the 8-year follow-up ($r = 0.35$, $p < 0.0001$). Quartile analysis showed that the patients with the least amount of atrophy during the trial were less likely to have reached EDSS 6.0 at the 8-year follow-up than those with the most amount of atrophy (figure 1). In the quartile of patients with little or no atrophy from baseline to year 2 (change in BPF $+1.3\%$ to -0.26%), only 14.3% (SE 6.0%) had reached EDSS ≥ 6.0

by the 8-year follow-up, whereas in the quartile of patients with the largest amount of atrophy during the 2-year trial (change in BPF -0.7 to -6.5%), 55.9% (SE 8.4%) had reached EDSS ≥ 6.0 by the 8-year follow-up. BPF change remained a significant predictor of disability status after adjusting for baseline EDSS score in a logistic regression model. The mean BPF at baseline, year 2, and the 8-year follow-up for each of the two EDSS outcome groups are shown in figure 2. In addition to the significant difference in the rate of atrophy during the original 2-year trial, the mean BPF was also significantly different at each time point for the group who reached EDSS ≥ 6.0 by the 8-year follow-up as compared with those who did not.

Logistic regression analysis was performed to determine which variables from the original trial were independently related to disability status at the 8-year follow-up. Since correlations were stronger between year 2 values

Figure 1. Patients ($n = 138$) were categorized into quartiles based on the amount of atrophy during the phase III trial, i.e., change in brain parenchymal fraction (BPF) from baseline to year 2. Bars represent the percent of patients in each quartile who had reached Expanded Disability Status Scale (EDSS) score ≥ 6.0 by the follow-up examination. Error bars indicate the SEs. There were a total of 44 patients of 138 who reached EDSS ≥ 6.0 .

Figure 2. Mean brain parenchymal fraction (BPF) over the course of 8 years for all patients who had BPF measurements at all time points (diamonds, $n = 106$), for the subgroup of these patients who had reached $EDSS \geq 6.0$ by the follow-up examination (squares, $n = 32$) and for the subgroup who had not reached $EDSS \geq 6.0$ by the follow-up examination (circles, $n = 74$). Error bars indicate $\pm SEM$. Differences in mean BPF between the outcome groups were significant at each point in time. The rate of BPF change during the original 2-year trial was also significantly different between the outcome groups.

and follow-up than between baseline values and follow-up (data not shown), only the year 2 values were considered. The results are summarized in table 3. The following disability and MRI variables were considered for inclusion in the first model (in addition to the demographic and disease-related variables): EDSS at year 2, MSFC at year 2, T2 lesion volume at year 2, T1 lesion volume at year 2, number of enhancing lesions at year 2, and BPF at year 2. A forward stepwise selection procedure was used. None of the demographic or MRI variables at year 2 was an independent predictor of disability status at the 8-year follow-up. Only EDSS and MSFC at year 2 were significant predictors of reaching $EDSS \geq 6$ at the 8-year follow-up.

A second model consisting of changes during the original 2-year trial was also tested. In addition to the demographic and disease-related variables, the following disability and MRI variables were considered for inclusion in this model: EDSS change from baseline to year 2, MSFC change from baseline to year 2, number of new and enlarging T2 lesions at year 2, change in T1 lesion volume from baseline to year 2, cumulative number of enhancing lesions from baseline to year 2, and BPF change from baseline to year 2. MSFC change and percent BPF change from baseline to year 2 were the only significant predictors of reaching $EDSS \geq 6$ at the 8-year follow-up.

Finally, both models were rerun without EDSS and MSFC in order to determine significant MRI predictors. For the first model (with year 2 values as independent variables), BPF at year 2 and number of relapses during the trial were the only significant predictors of reaching $EDSS \geq 6$ at the 8-year follow-up. For the second model (with baseline to year 2 changes as independent variables), percent change in BPF from baseline to year 2 and number

Table 3 Logistic regression results for predicting $EDSS \geq 6$

Model no./variable	Regression coefficient	SE	p Value
1*			
Intercept	-2.75	0.74	
EDSS (year 2)	0.64	0.24	0.0070
MSFC (year 2)	-0.98	0.39	0.012
2†			
Intercept	-1.51	0.34	
BPF change	-0.42	0.22	0.056
MSFC change	-2.21	0.53	<0.0001
3‡			
Intercept	24.39	8.06	
BPF (year 2)	-31.95	9.89	0.0012
No. of relapses	0.50	0.12	<0.0001
4§			
Intercept	-2.15	0.37	
BPF change	-0.45	0.18	0.0107
No. of relapses	-0.42	0.11	0.0001

* All risk factors at year 2, $n = 126$.

† All on-study changes, $n = 125$.

‡ Year 2 MRI, $n = 126$.

§ MRI on-study changes, $n = 125$.

EDSS = Expanded Disability Status Scale; MSFC = MS Functional Composite; BPF = brain parenchymal fraction.

of relapses during the trial were the only significant predictors of reaching $EDSS \geq 6$ at the 8-year follow-up.

Questions 2 and 3: Progression of atrophy over 8 years. The progression of brain atrophy over the course of 8 years was studied in the subgroup of patients ($n = 106$) with analyzable MRI scans at all four time points (baseline, year 1, and year 2 of the original trial and the 8-year follow-up). The severity of brain atrophy worsened significantly between baseline and the 8-year follow-up. The mean percent change in BPF over the 6 years from the end of the phase III trial to the 8-year follow-up was -2.0% (SD 1.9%). Patients who were originally in the placebo group of the phase III trial ($n = 52$) had a mean BPF change of -3.0% from baseline to follow-up, whereas patients who were originally in the treated group ($n = 54$) had a mean BPF change of -2.5% from baseline to follow-up. This difference was not significant ($p = 0.18$). BPF and BPF percent change were not related to the total time on disease-modifying therapies from baseline to the 8-year follow-up.

In general, baseline BPF, follow-up BPF, and percent change in BPF were not correlated with age, sex, or disease duration. The exceptions were that baseline BPF was weakly correlated to age ($r = -0.18$, $p = 0.039$) and disease duration ($r = -0.29$, $p < 0.001$), but these correlations were not observed at the 8-year follow-up. There was a weak correlation between the percent change in BPF from baseline to 8-year follow-up and the number of relapses during the 2-year controlled study ($r = -0.26$, $p = 0.007$). There was a strong correlation between baseline BPF and 8-year follow-up BPF ($r = 0.71$, $p < 0.0001$).

Table 4 BPF/lesion correlations (Spearman rank correlation coefficients)

Parameter	Baseline BPF	Year 2 BPF	Follow-up BPF	BPF change (year 2 to follow-up)
Baseline T2 lesion volume (n = 106)	−0.41 (<0.0001)	−0.47 (<0.0001)	−0.54 (<0.0001)	−0.31 (0.001)
Year 2 T2 lesion volume (n = 106)	−0.37 (<0.0001)	−0.45 (<0.0001)	−0.55 (<0.0001)	−0.35 (0.0002)
Year 2 new and enlarging T2 lesions (n = 106)	NS	NS	−0.20 (0.04)	−0.36 (0.0002)
Baseline T1 lesion volume (n = 98)	−0.41 (<0.0001)	−0.50 (<0.0001)	−0.52 (<0.0001)	−0.25 (0.01)
Year 2 T1 lesion volume (n = 98)	−0.35 (0.0005)	−0.43 (<0.0001)	−0.54 (<0.0001)	−0.36 (0.0003)
Baseline no. of gadolinium- enhancing lesions (n = 104)	0.25 (0.01)	NS	NS	−0.19 (0.056)
Year 2 no. of gadolinium-enhancing lesions (n = 103)	NS	NS	−0.17 (0.087)	−0.31 (0.002)
Cumulative no. of gadolinium lesions at year 2 (n = 103)	0.21 (0.03)	NS	NS	−0.26 (0.008)

p Values are indicated in parentheses.

BPF = brain parenchymal fraction; NS = not significant.

BPF was correlated to lesion measurements from the phase III trial (table 4). The volumes of T2 lesions and T1-hypointense lesions were significantly correlated with BPF concurrently and at subsequent time points, with Spearman *r* values ranging from −0.35 to −0.55. The number and volume of enhancing lesions were only very weakly associated with BPF, if at all. However, in terms of predicting the rate of atrophy over the long term, expressed as the change in BPF from year 2 to the 8-year follow-up, the number of enhancing lesions at year 2 was correlated with subsequent BPF change (*r* = −0.31, *p* = 0.002). Other lesion measures, especially at year 2, were also correlated with long-term atrophy rate, including the number of new and enlarging T2 lesions (*r* = −0.36, *p* < 0.0001), the volume of T2 lesions (*r* = −0.35, *p* = 0.0002), the volume of T1-hypointense lesions (*r* = −0.36, *p* = 0.0003), and the cumulative number of enhancing lesions during the trial (*r* = −0.26, *p* = 0.008).

Multiple regression analysis was performed to determine which variables at year 2 were independent predictors of subsequent atrophy (i.e., change in BPF from the end of the original trial to the 8-year follow-up). The results are summarized in table 5. The following disability and MRI variables were considered for inclusion in the first model (in addition to the demographic and disease-related variables): EDSS at year 2, MSFC at year 2, T2 lesion volume at year 2, T1 lesion volume at year 2, and number of enhancing lesions at year 2. A forward stepwise selection procedure was used. The only significant predictors of subsequent atrophy were the number of enhancing lesions at year 2 and the volume of T2 lesions at year 2 ($R^2 = 0.29$, adjusted $R^2 = 0.27$).

A second model including changes during the original trial was also tested. In this model, the following disability and MRI variables were considered for inclusion (in addition to the demographic and disease-related variables): EDSS change from baseline to year 2, MSFC change from baseline to year 2, number of new and enlarging T2 lesions at year 2, change in T1 lesion volume from baseline to year 2, and cumulative number of enhancing lesions from baseline to year 2. The only significant predictors of subsequent

atrophy were the number of new and enlarging T2 lesions at year 2 and the MSFC change from baseline to year 2 ($R^2 = 0.29$, adjusted $R^2 = 0.28$).

Discussion. The follow-up study showed that brain atrophy continued to progress in this group of patients with RRMS during the 6 years after the original trial. The degree of brain atrophy was related to disability, measured by both EDSS and MSFC, as well as to T1, T2, and enhancing lesion volumes. Atrophy rate during the phase III trial was the only significant MRI predictor of disability status at the 8-year follow-up, and it was more strongly related to disability than were lesion volumes. Several important aspects of brain atrophy in RRMS were noted in the course of this work.

One of the main questions addressed by this study is the relation between brain atrophy and subse-

Table 5 Linear regression results for predicting percent change in BPF from year 2 to year 8 follow-up

Model no./variable	Regression coefficient	SE	<i>p</i> Value
1*			
Intercept	−1.24	0.21	
No. of enhancing lesions	−0.36	0.07	<0.0001
T2 lesion volume	−0.026	0.009	0.003
2†			
Intercept	−1.12	0.22	
No. of new and enlarging T2 lesions	−0.23	0.04	<0.0001
MSFC change	0.49	0.19	0.011

* All risk factors at year 2, n = 115.

† All on-study changes, n = 10%.

BPF = brain parenchymal fraction; MSFC = MS Functional Composite.

quent progression of disability. BPF is a proposed marker of disease progression that, unlike lesion measurements, does not fluctuate over time and primarily reflects severe tissue damage. However, the rate of tissue loss may not be strongly related to concurrent changes in disability in RRMS due to compensatory mechanisms at this early stage of disease. One hypothesis is that the rate of irreversible tissue damage in the relapsing-remitting stage of disease will be predictive of *later* disability. There have not been any previous studies on the long-term predictive value of brain atrophy in MS. In this study, the relation between BPF change and disability measured at subsequent time points indicate that patients with more atrophy during the original trial had greater disability at the 8-year follow-up. The quartile of patients with the largest amount of atrophy during the phase III trial were approximately four times as likely to reach EDSS 6 or greater by the time of the follow-up examination than the quartile of patients with the smallest amount of brain atrophy during the original trial. The logistic regression analysis showed that the amount of atrophy during the original trial was an independent predictor of EDSS status at the 8-year follow-up, whereas the MRI lesion measurements and change in EDSS during the original trial were not. Logistic regression analysis with MRI variables demonstrated that BPF and change in BPF were the only significant MRI predictors of later disability status. Therefore, BPF appears to be useful for predicting which patients with RRMS have more aggressive disease. However, because this study does not provide information between year 2 and year 8, the optimal time for assessing the relation between progression of BPF and disability remains unknown.

A second objective of this study was to characterize atrophy progression in patients with RRMS over time. The retrospective analysis of images acquired for the clinical trial in conjunction with the image analysis for this follow-up study have allowed us to observe atrophy progression in a relatively large group of patients with RRMS over the course of 8 years. Previous studies have looked at atrophy over shorter periods of time—up to 3 years. In our study, the amount of atrophy over the interim period (-2.0% over approximately 6 years) is lower than the atrophy rate during the phase III trial^{3,7} and lower than atrophy rates in several other serial MS studies.^{6,8,9,14-16} In the placebo and treated groups combined, there was a mean BPF change of -1.1% over 2 years, or -0.55% per year during the original trial. The estimated rate of atrophy during the interim was only -0.33% per year. One possible explanation for the apparent decrease in atrophy rate over time may be related to natural history. It is conceivable that the rate of atrophy may decrease over time in MS,^{4,14} just as the frequency of enhancing lesions decreases over time. A second explanation may be the introduction of disease-modifying drugs that

have immediate effects on inflammation but delayed effects on atrophy rate. BPF analysis of the phase III trial showed that atrophy progressed at essentially equal rates in the placebo and treated groups during the first year of the trial, but progressed at a significantly slower rate in the treated group in the second year.⁷ Although this follow-up study did not demonstrate a significant difference in treatment effect on atrophy at the time of the 8-year follow-up, there was a trend toward less atrophy in the original treated group as compared with the original placebo group. The finding that BPF was weakly correlated to age and disease duration only at baseline and not at the 8-year follow-up may also be related to treatment. At baseline all patients were untreated, whereas by the follow-up examination many of the patients had been treated with disease-modifying drugs, which may have slowed the rate of atrophy progression and therefore decoupled BPF and disease duration. Sustained treatment effects are difficult to discern owing to the 6 years of uncontrolled therapy in the interim period. Statistical modeling will be necessary to account for the different treatments during this period. These studies are in progress.

It is also possible that the slower rate of atrophy may be partly artifactual. Although care was taken to acquire images with the same pulse sequence parameters and spatial resolution, scanner upgrades are unavoidable and may have an effect on the absolute numbers for BPF. There is no way to accurately track acquisition-related changes that may effect the calculation of long-term atrophy rates in this study because of the 6-year time gap between the end of the clinical trial and the follow-up examination. However, the data indicate that if there is error due to scanner drift and upgrades, it is mainly a systematic error because the 8-year follow-up BPF was strongly correlated with baseline BPF. Furthermore, estimated atrophy rates in individual patients were consistent with what was qualitatively observed in the images when compared over time. Therefore, we do not believe technical limitations had a significant effect on the results.

Another potential explanation is informative censoring. That is, the patients who experienced the greatest progression in atrophy were not included in the calculation of long-term atrophy rate and therefore the mean decline was underestimated because of the absence of these patients. There were seven patients who died; many of these patients had experienced significant disease progression in terms of disability. There were also 12 people who could not be located or who refused to participate, and they may have contributed to differential effects on the mean BPF change. Conversely, the overall ascertainment rate (93%) was high for such a long-term study and it is unlikely that the seven deaths fully explain the shift in decline.

The final question addressed in this study is the relation between lesions and subsequent brain atro-

phy. The exact pathologic mechanisms that contribute to atrophy in MS are unknown; however, it is possible that some mechanisms can be inferred by the relations between specific lesion types and atrophy. We anticipated that tissue damage evident as lesions on MRI scans in the original trial would become progressively worse over time and eventually lead to brain atrophy. There were moderate correlations between BPF and T2 lesions and between BPF and T1-hypointense lesions concurrently, as in previous studies of cerebral volumes.^{4,25} There were no correlations between gadolinium-enhancing lesions and BPF; however, enhancing lesions, particularly at year 2, were predictive of the change in BPF from year 2 to the 8-year follow-up. The multiple regression analysis confirmed that the number of enhancing lesions and the volume of T2 lesions at year 2 were independent predictors of subsequent brain atrophy. Similar relations between MRI markers of inflammation and atrophy have previously been reported.^{3,6,16} The observed relations between different types of lesions and BPF are consistent with the interpretation of BPF as an indicator of all the previous severe and irreversible tissue damage that has occurred up to a given point in time. To varying degrees, T2 and T1 lesions also reflect previously damaged tissue and, therefore, were expected to correlate with concurrent BPF, subsequent BPF, and change in BPF. In comparison to T2 and T1 lesions, enhancing lesions are much more transient and only reflect active inflammation at a single point in time. The finding that enhancing lesions are related to subsequent change in BPF is additional evidence for a cascade of potentially irreversible tissue damage that may follow inflammation and ultimately result in atrophy.³ However, the multiple regression analysis showed that lesion measurements (number of enhancing lesions and volume of T2 lesions) only accounted for 27% of the variance in subsequent atrophy, suggesting that most of the pathology contributing to atrophy was not detected by conventional lesion measurements at a single point in time.

The correlations between BPF, disability, and different types of lesions over the 8-year follow-up study help to clarify the clinical and biological relevance of brain atrophy in RRMS. The relation between brain atrophy and subsequent disability status indicate that brain atrophy is an important marker of tissue destruction in patients with RRMS. Brain parenchymal fraction may be useful in identifying patients with more aggressive disease. Furthermore, this study suggests that brain atrophy may be due in part to focal tissue damage evident as MRI lesions at earlier points in time, but other factors contributing to atrophy remain undefined. Additional work is needed to determine optimal methods for the use of atrophy measurements in combination with clinical and MRI measures to monitor individual patients and the effects of new treatments.

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Neuro Images

Figure. (A) Representative T2-weighted MRI. There is a well demarcated lesion at the lower thoracic level compressing the spinal cord. A histopathological section of the tumor (B) showed fascicles of spindle cells with elongated nuclei and eosinophilic cytoplasm, which reacted strongly with S-100, consistent with a low-grade schwannoma.

Spinal schwannoma mimicking lower limb SMA

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A 60-year-old man presenting with a 30-year history of progressive, painless weakness and atrophy of the lower limb muscles requested new treatment options for peroneal type of spinal muscular atrophy (SMA), which had been diagnosed 25 years previously at another institution. On examination, knee and ankle reflexes were absent, and

there were no signs of sensory or autonomic involvement. Motor and sensory nerve conduction studies were normal, but needle EMG showed “neurogenic” changes in lower limb muscles. MRI revealed an extramedullary, ventrolaterally located mass lesion almost completely filling the spinal canal (figure, A) that histopathologically was diagnosed as WHO grade I schwannoma (figure, B). This case illustrates that longstanding spinal schwannoma can be painless and can selectively affect motor fibers thereby presenting as lower limb SMA.¹

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