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Gray Matter Atrophy Correlates With MS Disability Progression Measured with MSFC But Not EDSS

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Abstract

Background—Gray matter (GM) pathology is an important component of the multiple sclerosis (MS) disease process. Accelerated gray matter atrophy has been observed in MS patients, but its relationship to neurological disability is not defined. This study was done to determine the relationship between whole brain, GM, and white matter (WM) atrophy and MS disability progression.

Methods—Patients with MS and Clinically Isolated Syndromes (CIS), and age- and gender-matched healthy controls were entered into an observational protocol. Baseline brain parenchymal fraction (BPF), GM fraction, and WM fraction, and change over 4 years were correlated with sustained disability progression over the entire study duration. Disability progression was measured using the multiple sclerosis functional composite (MSFC) and the expanded disability status scale (EDSS).

Results—Seventy MS and CIS patients and 17 HCs were studied for an average of 6.6 years (range, 3.6-7.8 years). At the final visit, 7 patients were classified as CIS, 36 as relapsing-remitting MS (RRMS), and 27 as secondary progressive MS (SPMS). Baseline whole brain, GM, and WM atrophy predicted EDSS $\geq$ 6.0 at the last study visit. Twenty-one (33%) patients worsened using the EDSS to define disability progression; 29 (46%) worsened using MSFC to define disability progression. Patients with MSFC progression had significantly higher GM atrophy rates compared with patients who were stable on MSFC. White matter atrophy was similar in patients with and without disability progression. Atrophy rates were not different in patients with or without disability progression defined using EDSS.

Conclusions—Whole brain, GM, and WM atrophy predicted MS disability progression observed over the next 6.6 years. Gray matter atrophy rates over 4 years correlated with disability progression measured with the MSFC, but not EDSS. This indicates that MSFC defined disability progression is more closely linked to brain atrophy than EDSS defined disability progression, and provides important new insight into the poor correlation between MRI and clinical disability in MS. The findings confirm the clinical relevance of gray matter atrophy in MS.

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Introduction

Multiple sclerosis has historically been classified as a white matter disease. Conspicuous foci of demyelination are evident post-mortem, and are easily visualized by magnetic resonance imaging (MRI), explaining why MS has long been perceived as a white matter disease. Recently, many studies have demonstrated prominent pathological changes in GM in MS brains as well. These changes include widespread demyelination, activated microglia, apoptotic neurons, and atrophy affecting the cortex, and deep GM structures(1-4). Focal GM lesions are not well visualized by conventional MRI scanning, however. Therefore, the time course and relevance of GM pathology has not been fully elucidated.

Magnetic resonance imaging studies have documented that GM volumes are lower in MS patients than in healthy age-matched controls, and some studies have suggested that GM atrophy may begin early in the course of disease.(5-11) Evolution of GM atrophy over the course of MS, its relationship to disability, and the pathogenesis of GM pathology remain important questions in the MS field. The objective of this study was to determine the clinical relevance of GM atrophy in a spectrum of MS patients, by correlating correlate whole brain, GM, and WM atrophy with sustained disability progression.

Methods

Research Subjects

Patients and age- and gender-matched HC subjects were recruited from the Mellen Center. The study was approved by the Cleveland Clinic Institutional Review Board and each subject provided informed consent. Subjects with MS met the International Panel criteria(12) and each had a cranial MRI demonstrating lesions consistent with MS. Patients were classified as RRMS if they had 2 or more relapses with significant neurologic recovery in the prior 3 years, or as SPMS if they reported continued deterioration for at least 6 months, with or without relapses, and a history of at least 2 prior relapses. Subjects with CIS had an episode of neurological dysfunction typical for an initial MS presentation. Disease therapy with interferon β, glatiramer acetate, methotrexate, or azathioprine was allowed. Age- and gender-matched healthy controls were required to have a normal neurological examination, a normal brain MRI, and no history of symptoms suggestive of MS. Patients and controls were excluded if they received corticosteroid therapy within 2 months, were on bimonthly corticosteroid pulses, required therapy for hypertension, or had a history of TIA or stroke, heart disease, pulmonary disease, diabetes, or chronic renal insufficiency.

Visit Schedule

Healthy control subjects were evaluated annually; CIS and MS patients were evaluated bi-annually for 4 years, and annually thereafter. Demographic information, date of disease onset, and clinical pattern of disease were recorded at baseline. Kurtzke Extended Disability Status Scale (EDSS), timed ambulation, 9-hole peg test, 3-second Paced Auditory Serial Addition Test (PASAT), relapse history, and medications were recorded at each visit. The timed ambulation, 9-hole peg test, and PASAT scores were transformed into the Multiple Sclerosis Functional Composite (MSFC) by normalization to a published MS reference group.(13) Subjects had standardized MRI exams using the same protocol throughout the study. For subjects requiring corticosteroids for relapses, study visits were postponed at least 6 weeks. Disease worsening among the MS subjects was defined in two ways: 1) Disability progression using the MSFC was defined as a sustained change of ≥ 20% from baseline for any of the 3 components of the MSFC, sustained for two successive visits. 2) Disability progression using EDSS was defined as worsening from baseline by 1.0 EDSS point (or 0.5 point for those who

started the study with EDSS >= 5.5), sustained at two successive visits. For both MSFC and EDSS disability progression, worsening was required to persist for ≥ 6 months.

MRI Exams

Images were acquired on a 1.5T Siemens MR scanner. The standardized protocol included T2-weighted fluid attenuated inversion recovery (FLAIR) and T1-weighted spin echo (SE) images that were used for volumetric measurements. Acquisition parameters for the FLAIR sequence were: repetition time 6000ms, echo time = 105ms, inversion time = 2000ms; and for the T1 SE: repetition time 800ms, echo time = 35ms. Both images had in-plane resolution = 0.9mm × 0.9mm; and slice thickness = 5mm. MRIs were analyzed to calculate brain parenchymal fraction (BPF), gray matter fraction (GMF), and white matter fraction (WMF) using fully-automated software developed at the Cleveland Clinic, as previously described(11;14;15). Partial volume effects were accounted for in the calculation of all volumes using linear mixture models and GM volumes were adjusted for the effects of T2 lesions. The scan-rescan coefficient of variability for BPF, GMF, and WMF were determined to be 0.19%, 1.1%, and 1.4%, respectively.

Statistical Analyses

Magnetic resonance imaging data was available for the initial 4 years of the study; clinical data was available for a mean of 6.6 years. Baseline and on-study changes in atrophy measures were compared among disease subgroups and healthy controls using analysis of variance (ANOVA). T-test was used to compare groups in MSFC and EDSS progression status. For categorical variables, a chi-square test or Fisher's exact test was performed. Spearman Rank correlation was used for correlations between GM atrophy, WM atrophy and clinical disability. All analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, NC).

Results

One hundred six research subjects were enrolled in the original study. Nineteen subjects discontinued the protocol for various reasons; this report provides information on the remaining 87 subjects. These 87 research subjects were observed for a mean of 6.6 years (range: 3.6-7.8 years). Eight of 15 subjects who initially entered with a diagnosis of CIS transitioned to MS during the course of the study; 7 to RRMS, and 1 to SPMS. The remaining 7 CIS patients remained stable and were still classified as CIS at the final visit. In the 7 cases transitioning to RRMS, conversion was based on a second relapse. Seven of the 36 patients initially categorized as RRMS transitioned to SPMS.

Baseline characteristics for the research subjects are listed in Table 1, grouped according to disease classification at the final visit. There were no significant differences between BPF, GMF, or WMF in HCs compared with CIS patients who did not convert to MS during the study (all p-values > 0.79). Brain parenchymal fraction was significantly lower in RRMS patients compared with HCs ($p<0.01$), and significantly lower in SPMS patients compared with RRMS patients ($p <0.0001$). Similarly, GMF and WMF were significantly lower in MS patients compared with HCs (all p-values <0.01), and lower in SPMS compared with RRMS ($p<0.001$). Figure 1 shows the percent difference at baseline between HCs and the patients groups at baseline. Patients with RRMS had average BPF values 2.2% lower than HCs; SPMS had average baseline values 6.8% lower than HCs.

Subsequent analyses excluded the 7 CIS cases who did not convert to MS during the study, and focused on 63 MS patients and the HCs. At baseline, GMF and WMF were both moderately correlated to EDSS, MSFC, and all 3 components of the MSFC. Baseline correlations with disability were generally stronger for WM atrophy than GM atrophy for each disability measure

except for the PASAT. The strongest disability correlate of WMF was 9HT ($r = 0.63$, $p < 0.0001$) and for GMF it was the overall MSFC ($r=0.49$, $p<0.0001$).

Baseline BPF, GMF and WMF for the MS patients correlated with EDSS status at the last visit. Twenty of 63 patients (32%) had EDSS scores ≥ 6.0 at the last visit. Compared with the less disabled group, the group with EDSS ≥ 6.0 had lower baseline GM fraction (0.521 +/- 0.029 vs 0.537 +/- 0.022, $p<0.05$), and WM fraction (0.281 +/- 0.014 vs 0.300 +/- 0.018, $p<0.01$). Baseline BPF, GMF and WMF were correlated with last visit EDSS status as illustrated in Figure 2. For each of the 3 atrophy measures, there was significantly increased likelihood of being in the EDSS ≥ 6.0 category at the follow up visit in the quartile with the highest amount of atrophy at baseline compared to the quartile with the lowest amount. Patients in the worst quartile of baseline atrophy scores had ≥ 50% likelihood of being in the EDSS ≥ 6.0 group at the final visit; patients in the best quartile of baseline atrophy scores had ≤ 13% risk of being in the EDSS ≥ group at the final visit.

Disability progression defined using MSFC occurred more frequently than disability progression defined using EDSS. Forty-six percent of the MS patients had disability progression measured by MSFC, compared with 33% measured by EDSS. Characteristics of patients with disability progression defined using MSFC are shown in Table 2. Patients with disability progression were older, had longer disease duration, were more likely to be classified as SPMS at baseline, had higher baseline EDSS, more EDSS change, worse baseline atrophy, and higher annual rates of GMF decline during the study. Figure 3 shows the rate of GMF and WMF decline for patients with MSFC-defined disability progression compared with MSFC-stable patients, shown as fold-increases compared with concurrently studied HCs. White matter fraction decline was similar in the two groups (2.8-fold increase in patients with MSFC-progression vs 3.9-fold increase in MSFC-stable patients). In contrast, the GMF decline was 14.2-fold higher in patients with MSFC -progression compared with 6.3-fold increase in MSFC-stable patients.

Accelerated GM atrophy was observed in both RRMS and SPMS patients with MSFC-defined disability progression. Annual GM fraction decline for RRMS and SPMS with MSFC -progression was -0.311% and -0.423%, respectively. Annual GM fraction decline for RRMS and SPMS who were MSFC-stable was -0.174% and -0.183%, respectively. This finding indicates that the relationship between MSFC disability progression and GM fraction decline was constant across disease categories, and not driven by the higher proportion of SPMS patients with MSFC disability progression.

In contrast, there were no differences in GM fraction or WM fraction change in patients with EDSS disability progression compared with EDSS-stable patients. Characteristics of patients with EDSS disability progression are shown in Table 3. They were less likely to be classified as SPMS at the baseline, indicating that the EDSS scale identifies more patients with disability progression at earlier stages of the disease than at later stages. This suggests that the scale becomes less sensitive in SPMS patients. Otherwise, the characteristics of patients with EDSS disability progression were similar to EDSS-stable patients. In particular, there were no differences in BPF, GM fraction, or WM fraction at baseline, or in atrophy progression during the study.

The data in tables 2 and 3 demonstrate that MSFC progression correlated with whole brain and gray matter atrophy, while EDSS progression did not. This finding emphasized the fact that different patients were classified as having progressed on disability by use of the two measures, as shown in Table 4. Only 62% of the patients were classified the same by both MSFC- and EDSS-based definitions of disability progression, while 38% were classified as disability progression by one but not the other measure. Twenty-five percent worsened on MSFC but

not EDSS, and 13% worsened on EDSS but not MSFC. Twenty-one percent worsened on both MSFC and EDSS, and 41% were stable on both measures.

Characteristics of patients classified as discordant for MSFC and EDSS progression are compared in Table 5. Compared with subjects who progressed only by EDSS criteria, patients who progressed only by MSFC criteria had longer disease duration, were more likely to be SPMS patients, had higher baseline EDSS, and worse baseline atrophy scores. These results indicate that disability defined by EDSS but not confirmed by MSFC occurs largely in patients at low levels of the EDSS scale, and in patients with low levels of brain atrophy and low rates of brain atrophy progression. Subjects who progressed only by MSFC criteria had higher EDSS scores, higher levels of brain atrophy, and greater brain atrophy progression. Taken together, these results suggest that EDSS misclassifies MS disability progression in patients at the low end of the EDSS scale. In those cases, function is stable as measured by MSFC, and brain atrophy rates are low. The data further suggests that EDSS is an insensitive measure of disability progression in more severely affected patients. In those cases, EDSS is stable, but patients worsen as measured by MSFC and have high rates of brain atrophy. The combination of these two problems probably accounts for lack of correlation between EDSS progression and rates of brain atrophy, and suggests that MSFC progression has more biological meaning than EDSS progression.

Discussion

Accelerated rates of brain volume loss have been reported in MS patients.(16-18) Over the years, brain volume declines 5-8 times faster in MS patients than healthy, age-matched controls, leading to the obvious interpretation that loss of brain volume is an end stage consequence of the pathologic processes operating in the disease.

However, measures of brain volume are pathologically nonspecific. Fluid shifts may increase or decrease brain volume; gliosis may increased brain volume; and pathological processes unrelated to MS, such as drug toxicity or co-existing brain conditions, may reduce brain volume. Despite these complexities and nuances, the consistent observation that MS patients lose brain volume at an accelerated rate over the long course of the disease must be explained by loss of axons and myelin as a result of the MS disease process. Therefore, in this paper, we use the terms “brain volume loss” and “brain atrophy” interchangeably.

As was previously observed by other investigators(19), accelerated brain atrophy was observed in patients with CIS who converted to MS, indicating that brain atrophy begins early in the disease process. Brain atrophy in RRMS often occurs with a very weak relationship to relapses or EDSS, suggesting that brain atrophy can be clinically silent during the early stages of the disease. However, brain atrophy during early disease stages is clinically relevant. The rate of brain atrophy during the RRMS stage was shown to strongly correlate with future clinical disability and with development of SPMS(20). Anti-inflammatory drugs slow brain atrophy during the RRMS disease stage(14;21), but not in the SPMS stage.(22;23) In some prior studies, brain atrophy rates were similar in RRMS and SPMS patients,(24-26) in our prior report of 4-year atrophy rates in a spectrum of MS patients(11) we observed higher rates of atrophy in SPMS compared with RRMS. In nearly all prior studies, the extent of whole brain atrophy correlated better with disability than did lesions.(18)

Reports about gray matter pathology have accumulated in recent years. Based on pathologic studies, tissue damage in gray matter appears to be a large component of overall MS disease burden.(2;27) Previous studies demonstrated GM atrophy during the course of MS.(7-10) However, because conventional MRI techniques are not sensitive to lesions in gray matter, (28) atrophy measures are one of the only current method that can be used to quantify gray

matter pathology in MS patients without the need for specialized image acquisitions. We recently reported that the rate of gray matter atrophy increased substantially in later stages of MS, and that gray matter atrophy correlated with measures of white matter pathology in RRMS but not SPMS(11), suggesting an evolution in the pathological basis for gray matter pathology as the disease evolves.

Numerous prior reports have documented correlations between whole brain atrophy and neurological disability,(16-18) but most prior studies have shown weak or no correlations between gray matter atrophy and disability.(9;29;30) A recent report, however, documented good correlations between GM atrophy and neurological disability 20 years after CIS.(31) In the current study, we measured gray matter atrophy at all stages of MS to determine its relationship to disability progression. A limitation of this and other observational studies relates to variable use of disease modifying drugs during the follow up, which could affect both progression rates, atrophy rates, and the relationship between atrophy and disability progression.

Despite that limitation, there were a number of interesting findings. First, we found that baseline levels of brain atrophy correlated with EDSS $\geq$ 6.0 at a follow up 6.5 years later. This replicates in a separate population our prior report that BPF and the rate of BPF worsening in RRMS predicted EDSS $\geq$ 6.0 status after an 8 year interval(32). The new findings further demonstrate that both GM and WM atrophy predict the EDSS 6.0 milestone. Second, we observed a significant correlation between brain atrophy and disability progression measured using MSFC. Patients with disability progression measured with MSFC had significantly higher rates of whole brain atrophy, and gray matter atrophy, but not white matter atrophy. Gray matter atrophy was increased 14.1 fold over HCs in patients with MSFC disability progression, compared with 6.3 fold increased in patients stable by MSFC. White matter atrophy was similar in patients with MSFC disability progression (2.8-fold increased) and MSFC stable patients (3.9-fold increased). These data suggest that gray matter pathology underlies disability progression measured by MSFC. This is the first report defining sustained disability progression using the MSFC, although 20% worsening on quantitative measures of neurologic function, including components of the MSFC, have been suggested by others(33).

An important and unique finding in this study was that disability progression measured by EDSS did not correlate with whole brain, GM, or WM atrophy, while MSFC disability progression did. This was explained by relatively low concordance between disability progression defined by the two measures. The rate of concordance between MSFC and EDSS progression was 62%, indicating that the two scales indentified overlapping but distinct patient populations. The question arises as to why atrophy correlations were evident with MSFC but not EDSS. Conceivably, patients with disability progression from spinal cord disease were identified using EDSS but missed by MSFC. EDSS is known to be sensitive to ambulation, and insensitive to other dimensions including cognition. Also, one study showed minimal correlation between spinal cord atrophy and brain atrophy(34). However, it seems unlikely that EDSS would identify progressive spinal cord dysfunction but MSFC would not, since MSFC progression is largely determined by changes in walking and arm function, two dimensions that are measured by MSFC components. Our data suggests that EDSS incorrectly classifies disability progression in two ways. First, EDSS was less sensitive than MSFC in identifying disability progression in patients with higher levels of disability. This is consistent with a prior finding that patients with SPMS had stable EDSS scores but deteriorated on quantitative tests of walking and arm function(33). EDSS appears to be insensitive to disease worsening in SPMS patients, obscuring the relationship between disability progression and brain atrophy. Secondly, EDSS classified a number of patients as having disability progression who had stable MSFC scores, and mild MS with low EDSS scores. This would have the effect of further diluting atrophy correlations, by incorrectly classifying patients who had changes on

neurological exam but no disability. Presumably, imprecision in the EDSS instrument at this level of the scale contributed to incorrect classification, as suggested by the finding that sustained improvement in EDSS occurs very frequently in RRMS(35). MSFC progression was more closely related to brain atrophy, suggesting that MSFC is more suited as an outcome measure for clinical trials. The data raise concerns about the use of EDSS progression as a disability measure in RRMS because it misclassifies patients as disability progression, and also raise concerns about using EDSS to define disability progression in SPMS, where it appears to be insensitive to disease progression measured using brain atrophy or MSFC.

The results of this study further document the relevance of brain atrophy progression, demonstrate that GM atrophy but not WM atrophy correlates with disability progression, and suggest that MSFC should be used to define disability progression. The results imply that therapeutic interventions should be tested for their effects on the rate of GM atrophy progression.

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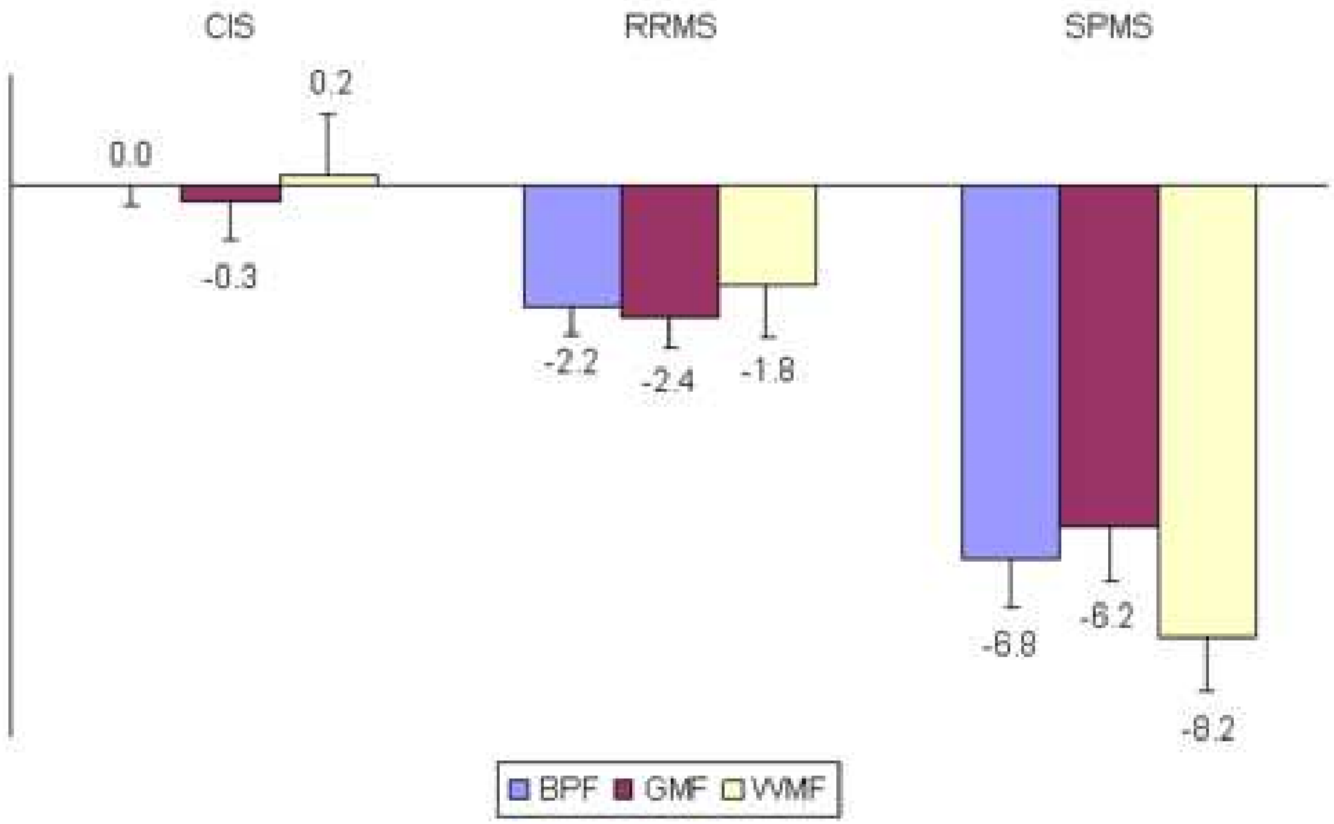

Figure 1. Percent Difference From Healthy Controls At Start Of Study

Mean percent difference in BPF, GMF, and WMF compared with healthy controls at the study baseline. Error bars are standard error of the mean. Corrected for disease duration, the average annual deviation from healthy controls for BPF was calculated as about -0.40% for both RRMS and SPMS patients.

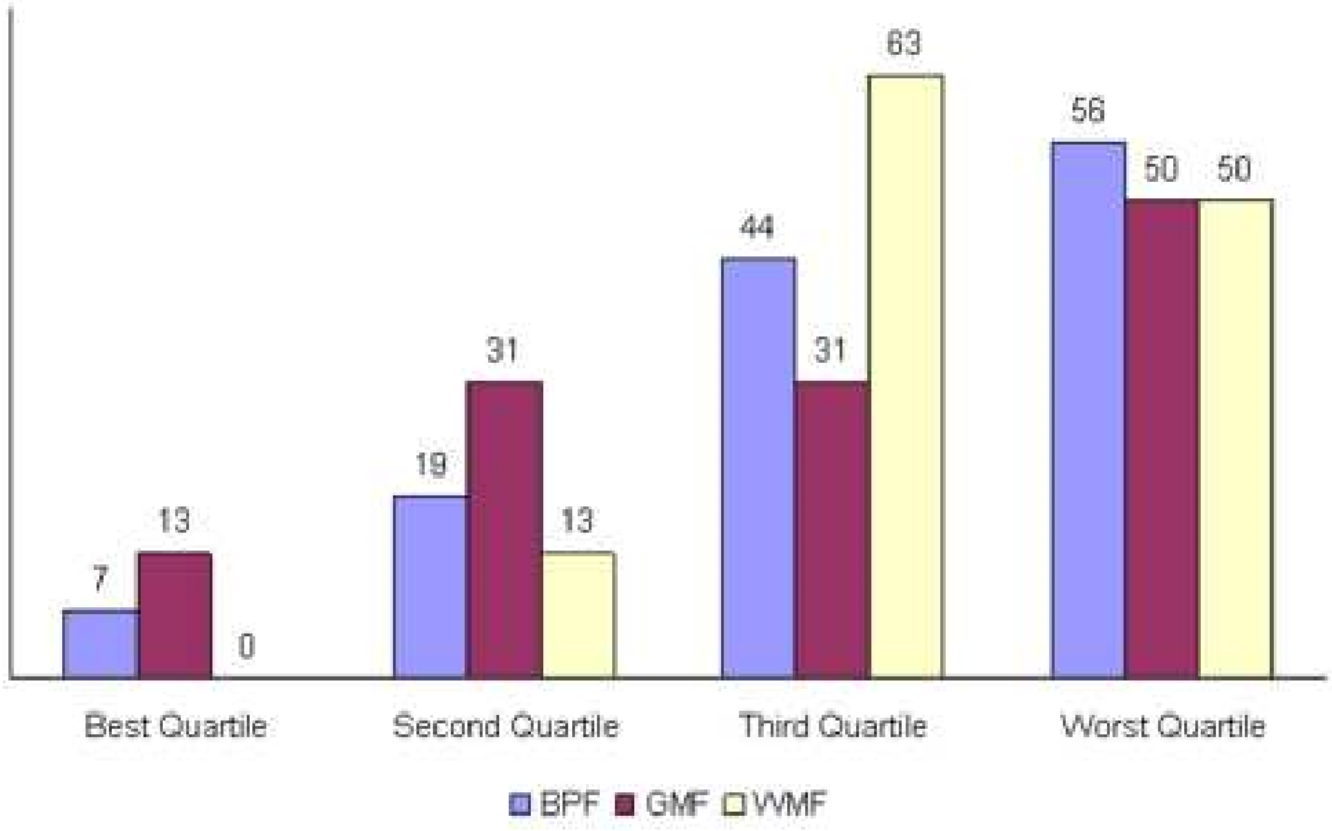

Figure 2. Percent EDSS ≥ 6.0 At Last Visit According To Atrophy At Baseline Visit

Percentage of patients at different baseline atrophy scores who were classified as EDSS ≥ 6.0 at the last visit. Patients with MS were divided into quartiles of BPF, GMF, and WMF at study entry, and the proportion at the EDSS milestone at the last visit shown. Patients in the worst quartile had significantly higher risk of poor clinical outcome compared with subjects in the most favorable quartile.

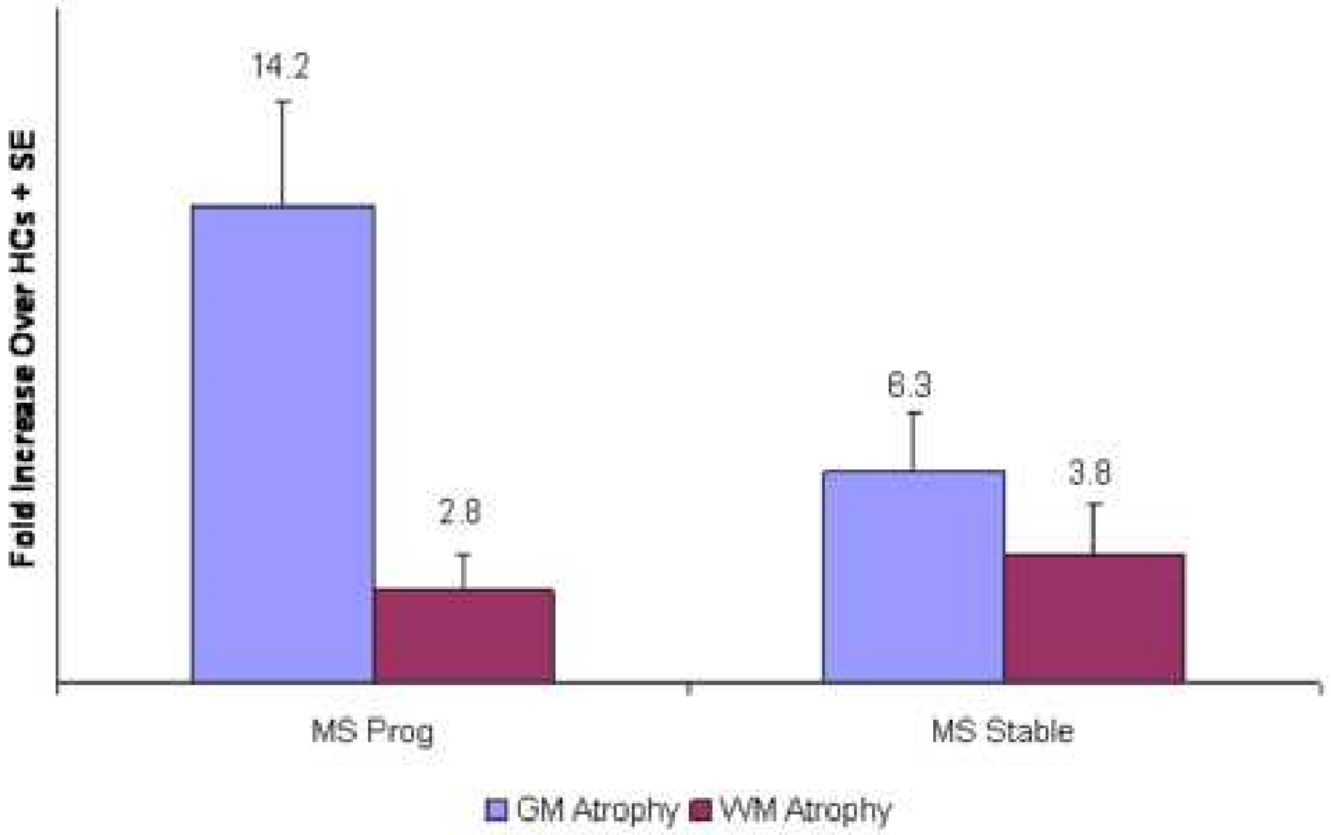

Figure 3. Fold Increase In Atrophy Rates Compared With Healthy Controls By Disability Progression[1]

[1]Progression Defined Using MSFC

Plot of the mean fold-increase over healthy controls in the annual rates of gray matter and white matter atrophy in MS patients with MSFC progression compared with stable patients. Gray matter atrophy was defined as the annualized percentage decline in the gray matter fraction. White matter atrophy was defined as the annualized percentage decline in the white matter fraction. Error bars are standard error of the mean. Compared to healthy control rates, gray matter atrophy was higher than white matter atrophy in both groups. In contrast to white matter atrophy, gray matter atrophy was higher in patients with disability progression measured with the MSFC.

Table 1

Baseline Characteristics

	HC (n=17)	CIS (n=7)	RRMS (n=36)	SPMS (n=27)
Mean (sd) Age, years	41.6 (8.1)	44.2 (10.9)	39.4 (8.4)	47.5 (7.8)
n Female (%)	10 (59%)	6 (86%)	28 (78%)	18 (67%)
Mean (sd) symptom duration, years	(na)	0.25 (0.1)	5.7 (5.4)	17.0 (7.6)
Mean (sd) EDSS	(na)	1.0 (0.76)	1.9 (1.5)	5.1 (1.5)
Mean (sd) MSFC	0.55 (27)	0.36 (0.35)	0.43 (0.58)	-0.82 (1.34)
Mean (sd) T2 lesion volume, ml	(na)	2.5 (2.3)	18.1 (17.2)	42.7 (24.9)
Mean (sd) T1 lesion volume, ml	(na)	0.15 (0.22)	1.72 (2.89)	8.30 (8.31)
% GD Positive	(na)	14.3%	22.2%	18.5%
Mean (sd) BPF	0.862 (0.012)	0.862 (0.008)	0.843 (0.026)	0.804 (0.04)
Mean (sd) GMF	0.554 (0.015)	0.553 (0.010)	0.541 (0.019)	0.520 (0.028)
Mean (sd) WMF	0.308 (0.011)	0.309 (0.009)	0.302 (0.017)	0.283 (0.016)

Abbreviations: sd = standard deviation; HC = Healthy controls; CIS = patients who had a clinically isolated syndrome and did not meet the criteria for a diagnosis of clinically definite MS over the course of 6.5 years; RRMS = relapsing-remitting MS patients (throughout study); SPMS = secondary progressive MS patients (throughout study); EDSS = Expanded Disability Status Score; MSFC = Multiple Sclerosis Functional Composite; % GD Positive = percent of patients with gadolinium-enhancing lesions; BPF = brain parenchymal fraction; GMF = gray matter fraction; WMF = white matter fraction

Table 2
Characteristics of Study Subjects by MSFC Progression Status

Clinical and MRI Characteristics	Worse (n=29)	Not Worse (n=34)	p-value
Age	44.64 (9.65)	41.30 (8.34)	0.15
Symptom Duration at Baseline	15.04 (8.90)	6.75 (6.0)	<0.001
Time In Longitudinal Study (Months)	6.63(0.95)	6.65(0.70)	0.93
% Time on DMT During Study	63.8%(37.7)	79.7%(35.0)	0.093
MS Classification at Baseline			
CIS	2(7%)	6(18%)	<0.01
RR	12(41%)	24(71%)	
SP	15(52%)	4(11%)	
EDSS at Baseline	4.35 (2.05)	2.35(1.91)	<0.001
EDSS Δ Baseline to Last Visit	0.69 (1.07)	0.09 (0.79)	0.016
MSFC at Baseline	-0.51(1.34)	0.24(0.84)	0.012
MSFC Δ Baseline to Last Visit	-0.47 (1.38)	-0.024(0.81)	0.14
BPF at Baseline	0.813 (0.042)	0.838 (0.030)	0.01
GMF at Baseline	0.526 (0.030)	0.537 (0.019)	0.08
WMF at Baseline	0.286 (0.017)	0.301 (0.019)	<0.01
BPF % Δ/year	-0.380 (0.242)	-0.196 (0.22)	0.01
GMF % Δ/year	-0.396 (0.469)	-0.175 (0.279)	0.03
WMF % Δ/year	-0.215 (0.435)	-0.296 (0.678)	0.57

Abbreviations = See Table 1; Also, DMT = Disease Modifying Therapy; Δ = Change

Table 3
Characteristics of Study Subjects by EDSS Progression Status

Clinical and MRI Characteristics	Worse (n=21)	Not Worse (n=42)	p-value
Age	44.36 (7.24)	42.07 (9.83)	0.30
Symptom Duration at Baseline	10.81 (8.89)	10.45 (8.38)	0.88
Time In Longitudinal Study (Months)	6.64(0.78)	6.64(0.84)	0.99
% Time on DMT	68.1%(33.3)	74.6%(38.58)	0.50
MS Classification at Baseline			
CIS	3(14%)	5(12%)	0.86
RR	11(53%)	25(59%)	
SP	7(33%)	12(29%)	
EDSS at Baseline	3.10 (2.56)	3.36(2.02)	0.69
EDSS Δ Baseline to Last Visit	1.17(1.00)	-0.04(0.67)	<0.001
MSFC at Baseline	-0.33(1.36)	0.004(1.04)	0.33
MSFC Δ Baseline to Last Visit	-0.63 (1.51)	-0.028(0.83)	0.10
BPF at Baseline	0.827 (0.040)	0.826 (0.036)	0.92
GMF at Baseline	0.532 (0.028)	0.532 (0.024)	0.91
WMF at Baseline	0.293 (0.020)	0.294 (0.019)	0.84
BPF % Δ/year	-0.300 (0.260)	-0.264 (0.242)	0.65
GMF % Δ/year	-0.339 (0.399)	-0.246 (0.388)	0.38
WMF % Δ/year	-0.276 (0.468)	-0.251 (0.629)	0.86

Abbreviations = See Table 1; Also, DMT = Disease Modifying Therapy; Δ = Change

Table 4

Relationship Between MSFC and EDSS Progression

	EDSS Progressed	EDSS Stable	Total
MSFC Progressed	13	16	29 (46%)
MSFC Stable	8	26	34 (54%)
Total	21 (33%)	42 (67%)	

Table 5
Characteristics of Patients By MSFC and EDSS Progression

Characteristics	MSFC Progressed EDSS Stable n=16 (25%)	EDSS Progressed MSFC Stable n=8 (13%)	p-value	ALL MS n=63
Age	45.5(11.3)	45.6(7.1)	0.98	42.8(9.1)
Symptom Duration	16.4(8.5)	6.6(6.3)	< 0.01	10.6(8.5)
% Time on DMT	64.5(40.3)	76.0(30.1)	0.48	72.5%(36.8)
MS Classification at Baseline				
CIS	1(6%)	2(25%)	0.10	8(13%)
RR	6(38%)	5(63%)		36(57%)
SP	9(56%)	1(13%)		19(30%)
EDSS at Baseline	4.53(1.78)	1.44(1.99)	< 0.001	3.27(2.20)
EDSS Δ Baseline to Last Visit	0.22(0.68)	1.0(0.60)	0.012	0.37(0.97)
MSFC at Baseline	-0.41(1.29)	0.17(1.12)	0.29	-0.11(1.15)
MSFC Δ Baseline to Last Visit	0.01(0.68)	0.07(0.33)	0.83	-0.23(1.13)
BPF at Baseline	0.812(0.040)	0.848(0.020)	0.03	0.826(0.037)
GMF at Baseline	0.525(0.027)	0.543(0.011)	0.10	0.532(0.025)
WMF at Baseline	0.286(0.018)	0.305(0.021)	0.04	0.294(0.019)
BPF % Δ/year	-0.344(0.252)	-0.128(0.191)	0.07	-0.277(0.246)
GMF % Δ/year	-0.361(0.514)	-0.177(0.313)	0.37	-0.277(0.391)
WMF % Δ/year	-0.116(0.397)	-0.175(0.487)	0.75	-0.259(0.576)