Title

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Journal

Annals of neurology, 85(5)

ISSN

0364-5134

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Publication Date

2019-05-01

DOI

10.1002/ana.25463

Silent Progression in Disease Activity–Free Relapsing Multiple Sclerosis

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Objective: Rates of worsening and evolution to secondary progressive multiple sclerosis (MS) may be substantially lower in actively treated patients compared to natural history studies from the pretreatment era. Nonetheless, in our recently reported prospective cohort, more than half of patients with relapsing MS accumulated significant new disability by the 10th year of follow-up. Notably, "no evidence of disease activity" at 2 years did not predict long-term stability. Here, we determined to what extent clinical relapses and radiographic evidence of disease activity contribute to long-term disability accumulation.
Methods: Disability progression was defined as an increase in Expanded Disability Status Scale (EDSS) of 1.5, 1.0, or 0.5 (or greater) from baseline EDSS = 0, 1.0–5.0, and 5.5 or higher, respectively, assessed from baseline to year 5 (±1 year) and sustained to year 10 (±1 year). Longitudinal analysis of relative brain volume loss used a linear mixed model with sex, age, disease duration, and *HLA-DRB1*15:01* as covariates.
Results: Relapses were associated with a transient increase in disability over 1-year intervals ($p = 0.012$) but not with confirmed disability progression ($p = 0.551$). Relative brain volume declined at a greater rate among individuals with disability progression compared to those who remained stable ($p < 0.05$).
Interpretation: Long-term worsening is common in relapsing MS patients, is largely independent of relapse activity, and is associated with accelerated brain atrophy. We propose the term *silent progression* to describe the insidious disability that accrues in many patients who satisfy traditional criteria for relapsing–remitting MS.

ANN NEUROL 2019;85:653–666

One of the defining clinical features for many multiple sclerosis (MS) patients is relapses—episodes of neurological worsening that evolve over hours or days and then last for days or weeks, followed by varying degrees of recovery.[1] MS relapses are typically accompanied by radiographic changes on magnetic resonance imaging (MRI) such as the development of new lesions on T2-weighted imaging or new contrast-enhancing lesions.[2] Relapses contribute to meaningful neurological disability over the short term[3]; however, whether relapses also contribute substantially to long-term disability is controversial. Some observational studies found no substantial impact of relapses on long-term disability

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.25463

Received Sep 26, 2018, and in revised form Mar 5, 2019. Accepted for publication Mar 6, 2019.

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progression in participants who had reached specific MS milestones.[4–7] In contrast, natural history studies suggest that relapse frequency and recovery from relapses within the first few years of disease onset contribute to long-term disability.[8–12] A recent study using the large MSBase dataset found that relapses contribute, at least in part, to long-term disability.[13] The generally accepted model of MS disability proposes a 2-stage process in which poor recovery from relapses underlies disability progression during the relapsing phase of MS, which is followed by insidious decline in function caused by neurodegeneration in the secondary progressive disease phase.[14] Whether the radiographic counterparts of MS relapses documented by the occurrence of new T2 lesions or gadolinium-enhancing lesions seen on brain MRI also contribute to long-term disability is also controversial. Some studies have showed that the number of lesions seen on initial brain MRI or evolution of new lesions following relapsing disease onset correlate with long-term disability,[15,16] whereas others point to a clinicoradiological paradox inherent in MS—that the radiographic burden of tissue injury correlates poorly with disability worsening.[17,18] A methodological limitation to studies that have investigated the contributions of relapsing activity to long-term disability is patient retention. Many studies, including long-term follow-up studies from clinical trial cohorts, are difficult to interpret because substantial proportions of participants are lost to follow-up (33–59% retention)[19–25] or because interval data are missing. We sought to test the 2-stage hypothesis of disability progression by defining the contribution of relapses and radiographic disease activity to long-term disability and brain atrophy using a well-phenotyped, University of California, San Francisco (UCSF) MS-EPIC (expression/genomics, proteomics, imaging, and clinical) dataset.

The MS-EPIC dataset is a single-center prospective observational cohort of contemporary, actively treated MS patients who have been evaluated annually since July 2004 with long-term data ascertained in 91% of study participants. We previously reported that rates of worsening and evolution to secondary progressive MS (SPMS) were substantially lower when compared to natural history studies from the pretreatment era. Nonetheless, more than half of patients with relapsing MS accumulated significant new disability after 1 decade of follow-up.[26] Notably, no evidence of disease activity (NEDA) at 2 years did not predict long-term stability. Because over half of the relapsing–remitting (RRMS) patients in the EPIC dataset developed clinically significant disability worsening by 10 years, but were still considered by their treating physicians to have relapsing MS (ie, they had not been reclassified as having developed secondary progressive disease), we sought to determine whether ongoing relapse activity, assessed clinically as relapses or radiographically as new or enlarging focal white matter lesions, might be the primary contributor to this long-term disability worsening. We also sought to determine to what extent relapsing activity contributes to evolution of brain atrophy—an in vivo measure of irreversible tissue injury that correlates with long-term disability.

Patients and Methods

The UCSF EPIC cohort is a prospective, longitudinal, actively treated, single-center cohort of patients, now in its 14th year of follow-up. The UCSF Institutional Review Board reviewed and approved the study protocol. Written informed consent was obtained for all participants. This study was conducted in accordance with the Declaration of Helsinki. The 10-year, postbaseline follow-up of this cohort was previously reported.[26] Although the cohort enrolled participants with clinically isolated syndrome (CIS), RRMS, SPMS, and primary progressive MS, here we considered only those participants who had either CIS or RRMS at entry. For baseline data, the annualized relapse rate (ARR; life-time) was calculated from when the first relapse occurred to baseline in the patient self-reported database. At end of study, the ARR was calculated from baseline to last visit. If missing data were due to MS disability in Multiple Sclerosis Functional Composite (MSFC) assessment, then 99 seconds was used in the Timed 25-Foot Walk (T25FW), 300 seconds was used in the 9-Hole Peg Test (9HPT), and 0 scores were used for the 3-second Paced Auditory Serial Addition Test (PASAT) and the Symbol Digit Modalities Test (SDMT). R median algorithm (type 7) was used to calculate median and interquartile scores. Some patients had partial visits due to missing MSFC at last follow-up. In this case, the most recent available MSFC visit was used.

As previously reported,[26] clinically significant disability was defined as worsening by an increase in the Expanded Disability Status Scale (EDSS)[27] of 1.5 points if the baseline EDSS score was 0, 1.0 point if the baseline EDSS score was between 1.0 and 5.0, and 0.5 point for baseline EDSS scores of 5.5 or higher. Relapses were patient-reported and assessed systematically for the year prior at each annual visit. Relapses were defined as new, focal neurological symptoms evolving over days to weeks that lasted for >24 hours, were not associated with an intercurrent infection, and were typically followed by at least partial recovery of function over time. Examples of relapses included vision loss, double vision, weakness in one or more limbs, sensory disturbances including paresthesias, or loss of coordination including imbalance. Symptoms that were nonspecific such as headache, malaise, and generalized weakness or were insidious and progressive in nature were not considered relapses. To assess the effect of relapses on disability, we compared 1-year intervals, with disability assessments performed annually. For each 1-year

interval, a short-term impact of relapse on MS disability was defined as an increase in EDSS between the 2 annual visits during a year in which a relapse occurred. As such, each subject was considered serially for annual assessment of the impact of relapses on MS disability. Confirmed disability was defined as worsening maintained for 2 consecutive annual visits. Lastly, long-term worsening was defined as increase in disability between baseline and the midpoint of the study (median years = 5, range = 4–6), with confirmation of worsening 5 years thereafter (sustained worsening).

Disability was also assessed using the T25FW, 9HPT, and PASAT. Because the SDMT became generally available for MS studies during the course of the study, this test of cognitive function was performed after the 5th study year. Clinically meaningful worsening was defined as a 20% increase in the T25FW (average of 2 trials), a 20% increase in the 9HPT time for either arm (single trial), an increase in the reliable change index for the PASAT, and a 4-point worsening in the SDMT. The contribution of relapse to disability was determined by Pearson chi-squared test with Yates continuity correction or Fisher exact test.

To simplify the analysis of treatment on relapses, we grouped therapies into 2 tiers: "platform" (eg, interferons, glatiramer acetate) and "high-potency therapy" (eg, natalizumab, mitoxantrone, rituximab, cyclophosphamide).[26] We also considered a 3-tiered model grouping together therapies by relative relapse rate reduction: modest (interferons, glatiramer acetate, teriflunomide), moderate (fingolimod, dimethyl fumarate), and high (natalizumab, anti-CD20 monoclonal antibodies, alemtuzumab) efficacy. However, because oral treatment options and other monoclonal antibodies were not generally available during the first 6 years of the study, we present the simpler, 2-tiered model. Multivariate logistic regression was used to model the impact of treatment tier on relapses, with disease duration, disease course, and *HLA-DRB1*15:01* included as covariates. *HLA-DRB1*15:01* was included in this and other analyses because we previously reported an effect of this allele on certain clinical features of MS.[28,29] Age-adjusted baseline brain volume was calculated by regression (baseline brain volume ~ age + sex + disease duration) and was divided into quartiles. Logistic regression was used to assess relationships between long-term disability worsening and age-adjusted brain volume. A linear mixed model was developed to consider the impact of relapses and disability worsening on relative brain volume loss. Four subject groups were considered: (1) participants with increased disability but without relapses, (2) participants without increased disability and without relapses, (3) participants with increased disability and with relapses, and (4) participants without increased disability but with relapses. The annual percentage change in relative brain volume is defined as the slope of follow-up year divided by the relative brain volume at baseline. If brain volume is a_0 and cerebrospinal fluid (CSF) is b_0 at time 0, and brain volume is a_{10} and CSF is b_{10} at time 10, then the percentage change of brain volume is $(a_{10} - a_0) / 10 / a_0 = \frac{a10-a0}{10a0}$. The percent change of relative brain volume is $(a_{10} / [a_{10} + b_{10}] - a_0 / [a_0 + b_0]) / 10 / (a_0 / [a_0 + b_0]) = \frac{a10b0-a0b10}{10a0(a10+b10)}$. The ratio of percentage change of brain volume to the percentage change of relative brain volume is $(a_{10} - a_0)(a_{10} + b_{10}) / (a_{10}b_0 - a_0b_{10})$. In this dataset, the ratio of relative brain volume to percentage change in brain volume is 5- to 6-fold.

To assess the effect of new brain lesions on silent progression and on brain atrophy in treated and untreated participants, 4 subgroups were identified: (1) treated participants without new lesions (new T2 or Gd^+), (2) treated participants with new lesions, (3) untreated participants without new lesions, and (4) untreated participants with new lesions. Logistic regression was used to identify influences on disability and a linear mixed model for brain atrophy.

The MRI acquisition protocol and analytic pipelines were previously published.[26] Briefly, Lesion Segmentation Tool[30] was used to segment lesion on fluid-attenuated inversion recovery images and corrected using the Mind Control platform.[31] These lesions were used as input to SIENAX[32] using optibet[33] for brain extraction. Registration and multinormal segmentation methods were used to propagate lesions backward and forward within a subject over time (unpublished methods). Gadolinium-enhancing lesions were visually assessed on postcontrast T1-weighted MRI. Gadolinium was not routinely administered for all brain MRI studies at long-term follow-up.

Results

Relapses Are Associated with Short-Term but Not Confirmed or Long-Term Disability Worsening

The baseline characteristics of this cohort are described in Table 1. Of 480 RRMS or CIS participants assessed at baseline, 407 completed visits through year 5 ± 1 year (43 participants missed this visit, 28 withdrew from the study, 2 participants died). Of the 43 participants who missed the year 5 visit ±1 year, 33 returned to complete the year 10 visit. Of the 407 participants who completed visits through year 5 ± 1 year, 372 subjects completed the year 10 visit ±1 year (19 participants missed this visit, EDSS was not performed in 1 participant, 14 participants withdrew from the study, 1 participant died). Therefore, the percentage of RRMS/CIS participants with baseline through year 5 and year 10 data was 77.5%. Of 372 long-term patients with long-term follow-up, 28 (8%) patients did not have MRI after follow-up year 5 (most recent

TABLE 1. Baseline Demographic, Clinical, and MRI Features of Relapsing MS at Entry

Characteristic	CIS, n = 88	RRMS, n = 392	Total, n = 480
Demographic			
Age at entry, yr, mean ± SD	41.5 ± 9.6	41.6 ± 9.7	41.6 ± 9.7
Sex, n (%)			
Women	59 (67.0)	279 (71.2)	338 (70.4)
Men	29 (33.0)	113 (28.8)	142 (29.6)
Clinical			
Disease duration, yr, mean ± SD	1.8 ± 3.6	8.9 ± 8.4	7.6 ± 8.2
EDSS score, MIR	1.0 [0.0–1.5] {0–4.0}	1.5 [1.0–2.5] {0–6.5}	1.5 [1.0–2.0] {0–6.5}
MSSS, mean ± SD	3.0 ± 2.4	2.5 ± 2.1	2.6 ± 2.2
MSFC, mean ± SD			
T25FW	11.7 ± 2.2	12.7 ± 2.8	12.5 ± 2.8
9HPT, DH	19.6 ± 4.5	21.2 ± 4.6	20.9 ± 4.7
9HPT, NDH	20.2 ± 3.8	21.8 ± 4.8	21.5 ± 4.7
PASAT-3	49.3 ± 10.8	46.9 ± 10.7	47.3 ± 10.7
Relapse history			
ARR, mean ± SD	0.5 ± 0.3	0.6 ± 0.5	0.6 ± 0.4
Treatment history, n (%)			
Never treated	31 (35.2)	37 (9.4)	68 (14.2)
Not actively treated	29 (33.0)	89 (22.7)	118 (24.6)
Platform therapy	27 (30.7)	261 (66.6)	288 (60.0)
High-potency therapy	1 (1.1)	5 (1.3)	6 (1.2)
MRI, mean ± SD			
T2 lesion volume, mm^3	9.9 ± 14.2	22.8 ± 36.4	20.4 ± 33.8
Number of Gd^+ lesions	0.1 ± 0.4	0.4 ± 1.1	0.3 ± 1.0
Total brain volume, cm^3	1,550.3 ± 78.2	1,508.1 ± 87.1	1,515.8 ± 87.0
GM volume, cm^3	813.6 ± 57.0	797.7 ± 57.9	800.7 ± 58.0
WM volume, cm^3	734.9 ± 39.6	708.3 ± 41.9	713.2 ± 42.7
Ventricular CSF volume, cm^3	21.7 ± 8.5	27.4 ± 12.5	26.4 ± 12.0
Cortical GM volume, cm^3	667.1 ± 48.6	654.3 ± 49.3	656.6 ± 49.4
Genetics			
*HLA-DRB1*15:01*, n (%)			
0 copies	52 (59.1)	210 (53.6)	262 (54.6)
1 or 2 copies	36 (40.9)	182 (46.4)	218 (45.4)

Relapsing MS subjects in the EPIC study recruited from July 2004 to December 2008. Subjects were divided into CIS and RRMS categorized at baseline (2 columns). Treatment type is presented for the year prior to baseline.

9HPT = 9-Hole Peg Test; ARR = annualized relapse rate; CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; DH = dominant hand; EDSS = Expanded Disability Status Scale; GM = gray matter; MIR = median [interquartile range] {range}; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSSS = Multiple Sclerosis Severity Scale; NDH = nondominant hand; PASAT-3 = Paced Auditory Serial Addition Test, 3-second interval; RRMS = relapsing–remitting MS; SD = standard deviation; T25FW = Timed 25-Foot Walk; WM = white matter.

scans: baseline only, n = 5; year 1, n = 4; year 3, n = 8; year 4, n = 10; year 5, n = 1).

Relapse occurrence was associated with clinically meaningful EDSS worsening at the next annual examination; 29.7% of yearly intervals in which participants experienced relapses were associated with disability worsening at the next visit, compared to 22.7% of yearly intervals during which participants did not relapse (odds ratio = 1.44, 95% confidence interval = 1.09–1.90, $p = 0.012$). However, there was no impact of relapses on confirmed disability worsening, defined as disability worsening at the visit following the relapse and confirmed at the subsequent year; 12.9% of yearly intervals with relapse, and 14.4% without relapse, were associated with confirmed worsening ($p = 0.551$; Fig 1). Similarly, there was no association between relapses during the first 6 study years and long-term disability worsening. For this analysis, long-term follow-up was assessed at a median of 11 years after baseline (mean = 10.68, standard deviation = 0.65, minimum = 9 years, maximum = 11 years). In patients with clinically significant long-term disability worsening, there was no difference in the proportion of patients who experienced relapses during the first 6 years of the study (38.1%) and those who were relapse-free (35.9%, $p = 0.736$). The long-term outcomes of the relapsing population are summarized in Table 2. Pyramidal and cerebellar functional scale scores worsened in participants with increased long-term disability independently of relapse occurrence. Baseline scores in these scales were not predictive of long-term outcomes (Supplementary Table 1).

Relapses were associated with short-term worsening of the T25FW (20% increase) with borderline statistical significance ($p = 0.039$; see Fig 1); 9.1% of yearly intervals in which participants experienced a relapse were associated with this increase in the T25FW, compared to 5.7% of yearly intervals without relapses. Relapses were not associated with a significantly confirmed change in the T25FW or with long-term worsening of the T25FW.

Relapses were not associated with clinically significant worsening (20% increase) of the 9HPT (see Fig 1); 15.5% of yearly intervals in which participants experienced a relapse were associated with a clinically significant increase in the 9HPT, compared to 11.7% of yearly intervals without relapse ($p = 0.091$). Similarly, there was no association between relapses and confirmed change in the 9HPT (increased in 4.2% of those with relapses vs 3.2% in those without, $p = 0.475$) or long-term worsening ($p = 0.228$).

For the PASAT, 12.6% of annual intervals during which participants relapsed also experienced short-term worsening on this outcome compared to 11.1% of intervals without relapse ($p = 0.500$; see Fig 1). There was no discernible effect of relapses on confirmed worsening of the PASAT ($p = 0.902$) or long-term worsening ($p = 1.000$). Data on the SDMT were limited to assessments performed after the 5th study year, and no correlation between relapses and subsequent worsening on this test was found in the near term ($p = 0.819$) or for confirmed worsening ($p = 0.755$).

Clinical and Genetic Factors Associated with MS Relapses

Binomial logistic regression was used to assess the association of treatment with MS disease-modifying therapies and relapse occurrence (Table 3). The comparison of SPMS to RRMS subjects showed a numerically lower risk for relapse occurrence in SPMS patients, although this comparison was not statistically significant. Similarly, the relatively small group of subjects classified with an unclear disease course (RRMS patients suspected of transitioning to SPMS) had a similar risk of relapse as SPMS subjects. Platform

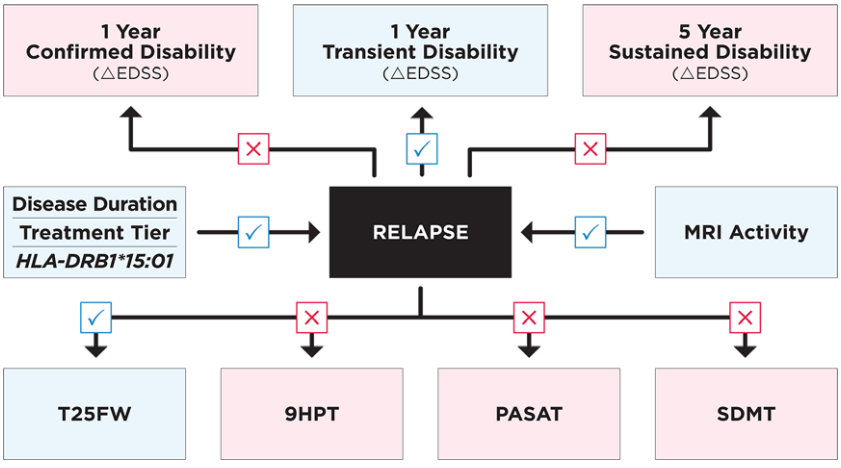

FIGURE 1: Factors that contribute to or correlate with relapse occurrence and the subsequent impact of relapses on disability. Check marks indicate significant associations, and x marks indicate that associations were not identified. 9HPT = 9-Hole Peg Test; EDSS = Expanded Disability Status Scale; MRI = magnetic resonance imaging; PASAT = Paced Auditory Serial Addition Test; SDMT = Symbol Digit Modalities Test; T25FW = Timed 25-Foot Walk.

TABLE 2. Demographic, Clinical, and MRI Features of Relapsing MS Cohort at Last Visit

Characteristics	CIS, n = 13	RRMS, n = 285	SPMS, n = 60 + Transitional MS, n = 14	Total, n = 372
Demographic				
Age at follow-up, mean yr ± SD	56.3 ± 8.3	52.5 ± 9.3	59.2 ± 9.1	54.0 ± 9.6
Sex, n (%)				
Women	9 (69.2)	199 (69.8)	50 (67.6)	258 (69.4)
Men	4 (30.8)	86 (30.2)	24 (32.4)	114 (30.6)
Years in study, mean ± SD	10.5 ± 0.9	10.7 ± 0.7	10.8 ± 0.6	10.7 ± 0.7
Clinical				
Disease duration, mean yr ± SD	13.8 ± 2.0	19.2 ± 7.8	24.4 ± 9.0	20.1 ± 8.3
EDSS score, MIR	1.5 [1.0–2.5] {0–4.0}	2.0 [1.5–3.0] {0–7.0}	5.0 [3.5–6.5] {2.0–8.0}	2.5 [1.5–3.5] {0.0–8.0}
Δ EDSS mean ± SD	0.6 ± 0.7	1.0 ± 1.2	2.5 ± 1.6	1.3 ± 1.4
MSSS, mean ± SD	1.5 ± 1.4	1.7 ± 1.2	4.3 ± 2.1	2.2 ± 1.8
MSFC, mean ± SD				
T25FW	13.1 ± 4.9	12.0 ± 2.1	20.4 ± 14.4	13.6 ± 7.4
9HPT, DH	21.6 ± 8.5	19.7 ± 3.5	28.2 ± 14.3	21.4 ± 7.9
9HPT, NDH	21.0 ± 3.3	20.8 ± 3.4	29.0 ± 13.5	22.4 ± 7.4
PASAT-3	50.6 ± 7.5	51.2 ± 10.6	45.4 ± 13.4	50.1 ± 11.3
SDMT	54.3 ± 11.0	51.2 ± 10.4	40.4 ± 11.4	49.2 ± 11.5
Relapse history				
ARR, mean ± SD	0.0 ± 0.0	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2
Treatment at last follow-up, n (%)				
Never treated	10 (76.9)	32 (11.2)	7 (9.5)	49 (13.2)
Not actively treated	3 (23.1)	107 (37.5)	36 (48.6)	146 (39.2)
Platform therapy	0 (0.0)	76 (26.7)	16 (21.6)	92 (24.7)
High potency	0 (0.0)	70 (24.6)	15 (20.3)	85 (22.9)
MRI, mean ± SD				
T2 lesion volume, mm^3	12.1 ± 17.9	14.3 ± 17.8	19.5 ± 29.5	15.3 ± 20.7
Total brain volume, cm^3	1,459.8 ± 70.8	1,433.2 ± 77.0	1,397.5 ± 55.3	1,427.0 ± 74.5
GM volume, cm^3	744.8 ± 33.4	734.4 ± 47.6	712.6 ± 33.7	730.5 ± 45.6
WM volume, cm^3	715.1 ± 44.5	698.5 ± 41.1	684.7 ± 34.5	696.4 ± 40.4
CSF volume, cm^3	28.5 ± 10.0	36.4 ± 16.2	44.0 ± 16.8	37.7 ± 16.5
Cortical GM volume, cm^3	593.2 ± 29.5	590.2 ± 41.1	574.2 ± 29.5	587.1 ± 39.2
Genetics				
*HLA-DRB1*15:01*, n (%)				
0 copies	6 (46.2)	153 (53.7)	38 (51.4)	197 (53.0)
1 or 2 copies	7 (53.8)	132 (46.3)	36 (48.6)	175 (47.0)

Subjects were divided into CIS, RRMS, SPMS, or transitional categories at last follow-up. The transitional category refers to patients who remain classified as having RRMS and in whom transition to SPMS is suspected but has not been confirmed. Δ EDSS was calculated from baseline to last visit. Treatment type is shown for the year preceding the last follow-up visit.

9HPT = 9-Hole Peg Test; ARR = annualized relapse rate; CIS = clinically isolated syndrome; CSF = cerebrospinal fluid; DH = dominant hand; EDSS = Expanded Disability Status Scale; GM = gray matter; MIR = median [interquartile range] {range} calculated using R median algorithm, type 7; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSSS = Multiple Sclerosis Severity Scale; NDH = nondominant hand; PASAT-3 = Paced Auditory Serial Addition Test, 3-second interval; RRMS = relapsing–remitting MS; SD = standard deviation; SDMT = Symbol Digit Modality Test; SPMS = secondary progressive MS; T25FW = Timed 25-Foot Walk; WM = white matter.

TABLE 3. Binomial Logistic Regression of Relapse: Relapse Occurrence ~ Disease Duration + Disease Course + Treatment + *HLA-DRB1*15:01*

	Odds Ratio	95% CI	*p*
Intercept	0.11	0.06–0.20	<0.001
Disease duration	0.96	0.94–0.98	<0.001
Disease course			
Disease course, SPMS/RRMS	0.59	0.26–1.18	0.167
Disease course, UNC/RRMS	0.62	0.03–3.18	0.647
Treatment, platform/high potency	2.41	1.45–4.27	0.001
*DRB1*15:01*, 1 or 2 copies/none	1.33	1.01–1.76	0.041

Binomial logistic regression was performed with relapse occurrence as the outcome and with disease duration, disease course, treatment, and *HLA-DRB1*15:01* as predictors. For disease duration, the odds ratio is for each year; the longer the disease duration, the lower the relapse risk. Subjects classified with CIS at baseline who remained CIS at the last observation were not analyzed, because by definition, these subjects experienced only one relapse.

CI = clinically isolated syndrome; CIS = clinically isolated syndrome; MS = multiple sclerosis; RRMS = relapsing remitting MS; SPMS = secondary progressive MS; UNC = unclear, subjects who were transitioning from RRMS to SPMS.

therapies were 2.4-fold more likely to be associated with relapses compared to high-potency therapies. The major MS susceptibility allele, *HLA-DRB1*15:01*, was associated with an increased risk of relapse albeit with marginal statistical significance, suggesting a potential genetic contribution to relapses, although the relatively small sample size limited analysis of copy number. Thus, a longer disease duration, a secondary progressive versus relapsing disease course, treatment with disease-modifying therapies, and absence of the *HLA-DRB1*15:01* allele were associated with lower relapse risk (see Fig 1), although the overall model accounts for only a fraction of relapse variance (McFadden pseudo-R^2 = 0.034). Remarkably, factor analysis (analogous to principal component analysis but with both continuous and categorical variables contributing to individual clusters) of these mixed data showed that participants clustered together by annual relapse frequency based on the clinical and genetic factors listed in Table 3 (Fig 2). That subjects who are grouped together by commonality of these factors also share similar numbers of relapses suggests that the variables identified in the binomial logistic regression are biologically relevant contributors to relapse occurrence.

White Matter Lesions Contribute to MS Relapses

As expected, radiographic disease activity as defined by new brain lesions on T2-weighted imaging correlated strongly with clinical relapses (see Fig 1). New lesions (defined as T1 gadolinium–diethylenetriamine pentaacetic acid enhancing lesions or new T2 lesions) were detected in 47.1% of annual intervals during which participants relapsed, compared with 25.3% of annual intervals without relapse ($p = 4.0 \times 10^{-16}$). However, the development of new T2 lesions did not correlate with EDSS worsening measured at the next annual visit ($p = 0.521$), with confirmed worsening ($p = 0.430$), or with long-term worsening ($p = 0.116$).

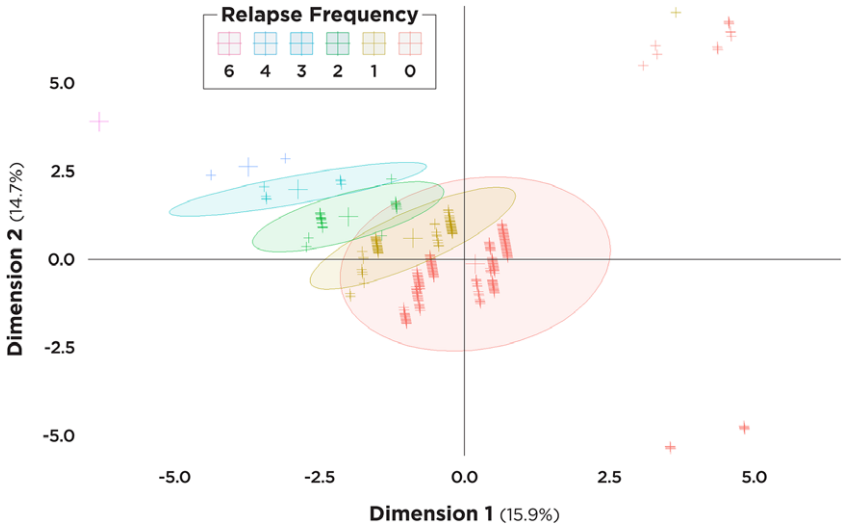

FIGURE 2: Factor analysis for mixed data clustering individuals by shared clinical and genetic attributes (from Table 3) that contribute to relapse frequency. Participants appear to cluster together based on annual relapse frequency. Participants with no relapses cluster separately from participants with more than one relapse. Even participants with a single relapse appear to cluster together as a subset of participants with no relapses.

Long-Term Brain Volume Loss and Disability Progression

The relationship between relapses, disability progression, and changes in relative brain volume was assessed using a linear mixed-effects model in the 4 subject groups that were defined by the presence or absence of relapse and/or increased disability (Table 4). At baseline, a significant effect on relative brain volume loss was observed only in the group of subjects with worsening disability and relapses. Age at baseline, disease duration at baseline, male sex, and years of follow-up were all associated with decline in relative brain volume loss. The interaction term of subject group with years of observation in the study was significant for all 3 groups relative to the reference group of clinically stable participants (without disability worsening and without relapses). This interaction term indicates that each subject group modifies the impact of time on relative brain volume loss. That the interaction terms for all groups relative to clinically stable patients (those without worsening disability and without relapses) was significant indicates that patient group modifies the effect of time on relative brain volume loss. Therefore, the rates of relative brain volume loss for participants with either relapses or increasing disability are significantly greater than the rate found in clinically quiescent participants (Fig 3, Table 5). Significant differences were found for comparisons between the "stable disability without relapse" and "increased disability without relapse," "increased disability with relapse," and "stable disability with relapse" groups, but no differences were observed for other comparisons. The most statistically significant comparison is for the group of subjects who experienced increased disability without relapse in comparison to the group of subjects who were clinically stable. Nonsignificant p values suggest that there is no difference between the 2 groups being compared on rates of relative brain volume loss. Although relapses may contribute to relative brain volume loss in subjects without increasing disability ($p = 0.027$), there was no apparent additional impact of relapses in the group of subjects with worsening disability ($p = 0.486$). Similarly, there was no apparent additional impact of increased disability in the group of subjects with relapses ($p = 0.999$).

TABLE 4. Multivariate Regression Model of Relative Brain Volume over Time: Relative Brain Volume ~ Group + Year of Follow-up + Group * Year of Follow-up + Sex + *HLA-DRB1*15:01* + Age at BL + Disease Duration at BL

Effect	Estimate	SE	*p*
Intercept	0.9952	0.001717	<0.0001
Increased disability without relapse	−0.00064	0.001003	0.5253
Stable disability with relapse	−0.00100	0.000837	0.2310
Increased disability with relapse	−0.00215	0.000950	0.0245
Year of follow-up	−0.00066	0.000042	<0.0001
Year of follow-up * increased disability without relapse	−0.00018	0.000069	0.0094
Year of follow-up * stable disability with relapse	−0.00013	0.000058	0.0267
Year of follow-up * increased disability with relapse	−0.00013	0.000064	0.0470
Age at BL	−0.00021	0.000038	<0.0001
Disease duration at BL	−0.00021	0.000044	<0.0001
Sex, men	−0.00195	0.000668	0.0038
*DRB1*15:01*	−0.00093	0.000625	0.1388

Linear mixed model of measures of relative brain volume over time. The group of patients with stable Expanded Disability Status Scale and without prior relapses is used as reference for the other 3 groups. Relative brain volume is defined as brain volume/(brain volume + cerebrospinal fluid volume). *HLA-DRB1*15:01*: either 1 or 2 copies.
BL = baseline; SE = standard error.

The baseline brain parenchymal fraction was not significantly different between the 4 groups, and, over the course of the study, brain volume declined in each group. In considering the group of patients who did not experience relapses during the first 6 years of the study, relative brain volume declined at a more pronounced rate in participants whose disability progressed compared to those who remained stable (see Fig 3). Among these nonrelapsing participants, CSF volume marginally increased in participants who experienced long-term increased disability ($p = 0.022$, nonsignificant following multiple comparison correction). Changes in T2 lesion volume, white matter volume, gray matter volume, cortical gray matter volume, and brain volume were similar between these 2 groups.

Baseline Brain Volume and Disability Progression

Several models were developed to determine whether greater baseline age-adjusted brain atrophy placed participants at greater risk for disability. Results indicated that age-adjusted baseline brain atrophy was associated with both an increased risk of long-term disability (Supplementary Table 3) and silent progression (Supplementary Table 4). By contrast, the occurrence of relapses did not appear to worsen the risk of long-

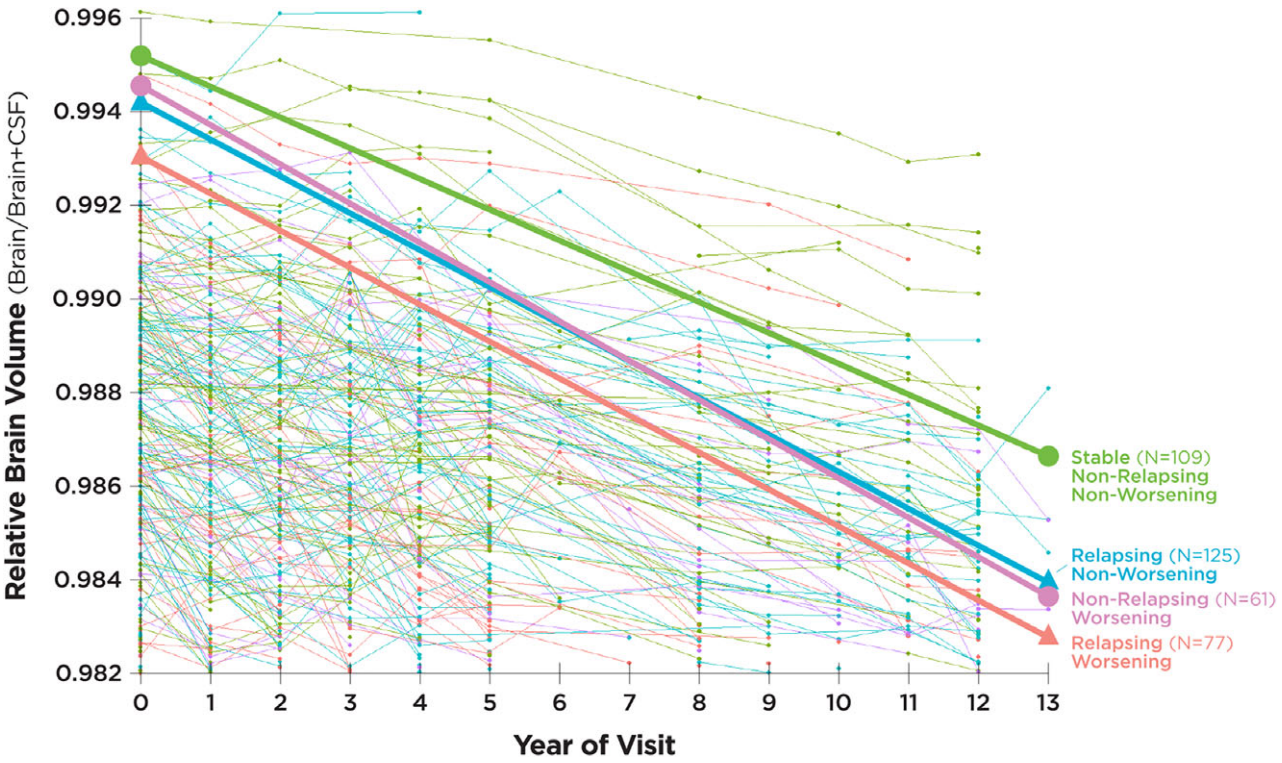

FIGURE 3: Relative brain atrophy is attenuated in clinically stable patients. Longitudinal response plots show the impact of relapses and disability on relative brain volume loss. Plots of individual data are depicted in addition to the regression lines that are adjusted for covariates (sex, disease duration, age, and *HLA-DRB1*15:01*). CSF = cerebrospinal fluid.

term disability (see Supplementary Table 3) or recovery from relapses (Supplementary Table 5).

Associations with Treatment

To control for potentially deleterious effects of treatment on brain volume loss, we first assessed the impact of platform therapies versus no treatment on brain volume loss (Supplementary Table 2a) and then assessed the impact of treatment escalation to natalizumab (Supplementary Table 2b), the most commonly used escalation therapy in this dataset, on brain volume loss using linear mixed models. These analyses showed that treatment with platform therapy reduced brain atrophy and that escalation to natalizumab is potentially associated with further stabilization of brain volume loss despite natalizumab-treated participants having lower baseline brain volumes, which we interpret as a marker of disease severity.

Of the 138 participants who experienced disability worsening, 46 were clinically recognized as having developed or developing SPMS, whereas the remaining 92 were considered still having a RRMS disease course at the time of the last observation. Of these 92 RRMS participants, 34 experienced long-term disability worsening without relapse. In comparison to these 34 participants who experienced progression that was not clinically recognized, the patients who developed clinically recognized SPMS scored higher on the EDSS and Multiple Sclerosis Severity Score and had longer disease durations at baseline (Table 6). However, there was no difference in rates of brain volume

TABLE 5. Comparison of Relative Brain Loss by Group

	Increased Disability without Relapse	Stable Disability without Relapse	Increased Disability with Relapse	Stable Disability with Relapse
Increased disability without relapse	—	—	—	—
Stable disability without relapse	0.009	—	—	—
Increased disability with relapse	0.486	0.047	—	—
Stable disability with relapse	0.449	0.027	0.999	—

Pairwise comparisons of slopes of relative brain volume loss across the 4 groups.

TABLE 6. Comparison of SPMS versus RRMS with Silent Progression: MRI Markers ~ Group (SPMS vs Silent Progression) + Visit Type + Group * Visit Type + Sex + *HLA-DRB1*15:01* + Age at BL + Disease Duration at BL

	SPMS	Silent Progression	*p*
Brain atrophy (95% CI)	−7.432 (−8.965, −5.899)	−8.595 (−10.316, −6.874)	0.322
WMV atrophy (95% CI)	−1.715 (−2.240, −1.189)	−1.984 (−2.566, −1.401)	0.501
GMV atrophy (95% CI)	−6.142 (−7.200, −5.084)	−6.950 (−8.126, −5.774)	0.316
CGMV atrophy (95% CI)	−5.823 (−6.753, −4.894)	−6.691 (−7.719, −5.663)	0.219
CSF increase (95% CI)	1.270 (1.072, 1.468)	1.140 (0.925, 1.356)	0.385
T2LV increase (95% CI)	−0.321 (−0.741, 0.099)	0.057 (−0.423, 0.537)	0.244
Relative brain atrophy (95% CI)	−0.100% (−0.115%, −0.085%)	−0.087% (−0.103%, −0.070%)	0.247
EDSS at BL	2.13 ± 1.24	0.60 ± 0.82	3.16×10^{-8}
Disease duration at BL, yr	12.72 ± 9.57	7.76 ± 8.03	0.019
MSSS at BL	2.49 ± 2.11	1.25 ± 1.63	0.006
Age at onset, yr	34.38 ± 9.92	34.26 ± 8.40	0.956

Linear mixed model of measures of brain and lesion volume over time comparing participants who developed clinically definite SPMS versus those RRMS participants with silent progression. The values presented are the coefficients of the effect of time on the parameter observed. For brain atrophy, WMV, GMV, CGMV, CSF, and T2LV, the unit of measure is cm^3 per year. For relative brain volume, the percentage change is presented.

BL = baseline; CGMV = cortical gray matter volume; CI = confidence interval; CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; GMV = gray matter volume; MRI = magnetic resonance imaging; MS = multiple sclerosis; MSSS = Multiple Sclerosis Severity Scale; RRMS = relapsing–remitting MS; SPMS = secondary progressive MS; T2LV = T2 lesion volume; WMV = white matter volume.

loss or T2 burden of disease between the participants with disability worsening who were classified as having SPMS versus those who remained classified as having RRMS, suggesting an underlying physiologic/anatomic similarity. In contrast, participants with silent progression had lower EDSS scores at baseline and a shorter disease duration, yielding a difference in the baseline Multiple Sclerosis Severity Score.

Logistic regression was used to analyze whether the development of new lesions in treated and untreated participants was associated with long-term disability worsening (Supplementary Table 6a). Although statistically significant effects were not observed for any subgroup, this analysis suggested that participants with new lesions could be at increased risk for long-term disability independent of treatment.

A linear mixed model was used to assess whether new brain lesions in treated and untreated participants influenced brain atrophy. Rates of relative brain volume loss were comparable across these 4 groups without a trend to suggest that new lesions influenced long-term brain atrophy (Supplementary Table 6b).

Sensitivity Analyses

To address potential confounding by inclusion of CIS subjects who remained stable over the long term, we repeated our analyses excluding these subjects. Excluding stable CIS subjects (n = 13) did not significantly alter the observations regarding the short-term and long-term impact of relapses on disability (Supplementary Table 7a). Similarly, excluding stable CIS participants did not influence the multivariate regression model of relative brain volume over time (Supplementary Table 7b).

Discussion

These data reveal that long-term worsening is common in RRMS patients and is largely independent of relapses or new lesion formation on brain MRI. Thus, insidious progression accrues in many early RRMS patients who remain classified as having relapsing MS. The current definition of SPMS is worsening of disability independent of relapses over at least a 6-month interval. Our data suggest that this process occurs earlier than is clinically recognized by either patients or physicians; 92 of the 138 patients who experienced insidious worsening of clinically meaningful disability in this dataset were still considered by their clinicians to have RRMS. It is possible that the loss of function over time is so gradual as to be unnoticed by the patient or physician. Typically, these patients have low EDSS scores and are for the most part fully functional. Many clinicians do not consider a diagnosis of SPMS in patients with EDSS scores of 3 or less. The recently

suggested MSBase definition of SPMS requires a minimum EDSS score of 4.0.[34] The EDSS is nonlinear, and patients with scores <3 are less likely to show more year-to-year changes than those with scores between 3 and 6. Moreover, during the relapsing phase, disability measures are confounded by clinical attacks followed by variable recovery. All of these factors can obscure recognition of an underlying neurodegenerative process that we labeled *silent progression* to highlight its subtle emergence over the course of RRMS. It seems likely that the same underlying process that causes silent progression is responsible for SPMS when the march of clinical worsening is more evident. In this regard, it is notable that patients experiencing silent progression had accelerated brain atrophy over the long-term course of the EPIC study, as well as more age-adjusted brain atrophy at the time of their initial enrollment.

Our data are consistent with 2 simultaneous processes; one results in the appearance of new focal demyelinating lesions visible on brain MRI that correlate with relapses, and the other is more diffuse and contributes to brain atrophy. This second process of global tissue injury is largely independent of relapses or focal lesion formation and appears to represent the most important contributor to long-term MS disability. That brain volume loss occurs early in MS and correlates with long-term disability was shown in prior studies.[35–37] However, uncertainty remains as to whether this process is dependent or independent of the development of new focal lesions. Because we found no correlation of new brain MRI lesions with long-term disability, our data are more consistent with the hypothesis that either diffuse injury or perhaps focal lesions too small to be detected by current methods lead to irreversible tissue loss.

The pathologic substrate responsible for progressive tissue injury in MS is likely to result from some combination of a white matter axonopathy and direct neuronal injury. Slowly enlarging white matter lesions associated with chronic inflammation at the leading edge is one possible mechanism for progressive symptoms, and more diffuse injury might also play a role.[38] Histopathological studies in chronic MS show that focal inflammatory changes, microglial activation, and astrocytosis typically accompany axonopathy and myelin injury.[39–41] Furthermore, chronic demyelination appears to predispose axons to early death.[42] In addition, ectopic B-cell–containing immune aggregates located in the overlying meninges and in Virchow–Robin perivascular spaces could contribute to progressive cortical injury. Thus, histopathological studies support a model in which both microscopic and macroscopic tissue injury occur with CNS inflammation.

These data also indicate that silent progression is not an invariable accompaniment of RRMS, and that measurement of whole brain atrophy might serve as a surrogate marker to identify patients with insidiously progressive ongoing disability. Incorporating a threshold for preservation of brain volume was proposed as a component for no evidence of disease activity (NEDA-4).[43] For fingolimod-treated patients, incorporating a minimal acceptable threshold for preservation of brain volume reduced the proportion of patients meeting the NEDA criteria from 31% for NEDA-3 to 19.7% for NEDA-4, underscoring the remaining unmet need for therapies that are more effective in arresting axonopathy and brain volume loss than current treatments.

Regulatory agencies have approved more than a dozen therapies for treatment of RRMS. All are proven, with varying degrees of efficacy, to reduce the occurrence of clinical relapses and prevent development of focal lesions measured on brain MRI. For the most part, the selection of which treatment to use is based on these measures of efficacy as well as consideration of safety and tolerability. Our observation that tissue injury distinct from focal white matter lesions underlies long-term disability in RRMS suggests that treatment selection should also consider the impact on silent progression and on associated measures of brain atrophy. Importantly, recent studies indicate that the high-efficacy therapies natalizumab[44] and ocrelizumab[45] reduce progression independent of relapse activity in RRMS, although these effects were partial. Additional studies are needed to determine whether long-term benefits on disability prevention are mediated by prevention of brain volume loss.

Our conclusions in regard to the impact of relapses on long-term disability are consistent with those from the British Columbia cohort[7] but appear to diverge from the observations from MSBase.[13] One explanation for this difference could be sample size. The MSBase group drew their conclusions from a larger dataset of 2,466 relapsing onset participants and has greater power to detect predictors of long-term disability with small effect sizes. However, advantages of the current EPIC study are its prospective ascertainment, systematic MRI acquisition and analysis, and a high rate of retention that reduces the impact of bias introduced by missing information from participants lost to follow-up. The mean annual relapse frequency was slightly higher in MSBase than EPIC (0.36 compared with 0.25, $p < 0.001$), possibly increasing the long-term effect of attacks on disability. Differences in prescribing practice between these datasets could also play a role, as treatment likely influences not only relapse frequency but also relapse severity. The methods used for assessing the impact of relapses on long-term disability between these 2 studies are also different; in EPIC we used a minimal threshold for disability worsening from our baseline observation and correlated relapse occurrence with both short-term and long-term disability worsening, whereas MSBase used a linear-regression model that considered the impact of the ARR over the 10 years of study on median 10-year EDSS change.

The 16-year follow-up study of the pivotal interferon β-1b trial[46] also found an impact of relapses on long-term disability. Participants in this study had higher relapse rates (1.2 ARR) and baseline EDSS scores (3.0), indicating that this cohort was more clinically active and had worse disability compared to the EPIC dataset. At the time of the pivotal interferon β-1b trial, therapeutic options for escalation treatment were limited. Perhaps even more importantly, these studies used different analytic methods: the interferon β-1b long-term follow-up study assessed whether the ARR during the first 2 years of the study correlated with increased EDSS by year 16.

When relapses have been correlated with long-term disability, their impact typically was observed primarily during the first 2 to 5 years from disease onset.[8–12] With earlier diagnosis of MS based on evolving diagnostic criteria and hence earlier treatment, it seems likely that many patients with high relapse frequency would be treated with disease-modifying therapies, thereby attenuating the association between early frequent relapses and long-term disability. Given that the mean disease duration at baseline in the EPIC dataset was 7.6 years (see Table 1), the majority of the observations regarding relapses in this dataset occur after the first 5 years of disease onset. Therefore, due to differences in the windows of observation, our finding that relapses do not contribute to long-term disability may be consistent with these prior studies. Lastly, our findings should not be interpreted to suggest that MS relapses are without clinical significance. Within this dataset, in addition to the impact of relapses on short-term disability, there are circumstances in which severe relapses caused permanent disability (data not shown). Rather, our results argue that long-term disability in RRMS is not primarily driven by cumulative injury from relapses.

Our study has several limitations. We were not able to identify a statistically significant impact of treatment on long-term disability or brain volume loss; however, this dataset is likely underpowered to detect small treatment effects mediated through reduction of new white matter lesions detected by MRI. In addition to the relatively small size of our dataset, information on relapses was patient-reported and thus is not directly comparable to clinician-validated relapses obtained from controlled clinical trials. In the clinical trial setting, participants are assessed within a defined window of relapse onset, and relapses are defined by an objective change in EDSS score. Such rigorous relapse assessment was beyond the scope of our study, which was designed for long-term characterization of the MS phenotype. We therefore relied on patient-reported relapses that were assessed through structured interview. When our participants were clustered by factor analysis of mixed data (see Fig 2), participants with the same relapse frequency grouped together, suggesting validity of self-reported relapses. Moreover, in the CombiRx study, the impact of treatment on patient-reported relapses was similar to that of protocol-defined relapses, suggesting that patient-reported relapses are likely valid.[47] Another potential limitation is the possibility that focal gray matter lesions or spinal cord lesions, not quantified in this study, could contribute to long-term disability. Finally, results obtained from any single-center design may not be replicated in other datasets. Work is underway to address this issue; we have partnered with other groups who have similar deeply phenotyped long-term datasets for the purpose of increasing statistical power and performing validation studies for these and other observations.[48] Despite these limitations, the characteristics of this dataset are consistent with previously published observations in that MS relapses were associated with new lesions on brain MRI and were associated with increased short-term MS disability.[2,3] The consistency of our findings regarding short-term outcomes lends credence to our longer-term observations.

In summary, the high degree of effectiveness of MS therapies against clinical attacks and new white matter lesions made it possible to prospectively assess long-term outcomes in RRMS when these elements of focal disease were silenced. The appearance of silent progression during the RRMS phase and its association with brain atrophy suggest that the same process that underlies SPMS likely begins far earlier than is generally recognized and support a unitary view of MS biology, with both focal and diffuse tissue destructive components, and with inflammation and neurodegeneration occurring throughout the disease spectrum. In addition to brain atrophy, other markers of neural degeneration, such as quantitative spinal cord imaging,[49] optical coherence tomography,[50] and serum neurofilament light chains,[51] may also prove useful in identifying patients with silent progression. Moreover, as relapses and focal white matter lesions are brought under excellent control by disease-modifying therapies for RRMS, the effectiveness of these agents against silent progression is likely to represent a key determinant of their relative value.

Acknowledgment

The National Institute of Neurological Disorders and Stroke (R01NS26799 to S.L.H. and J.R.O.), the Valhalla Foundation, and gifts from Friends of the Multiple Sclerosis Research Group at UCSF supported this study.

We thank the patients for their long-term participation in this ambitious study and A. Barnecut for helping with graphics and formatting.

Author Contributions

Study concept and design: B.A.C.C., J.A.H., C.Z., S.E.B., J.R.O., R.G.H., and S.L.H. Data acquisition and analysis:

all authors. Drafting the manuscript and figures: B.A.C.C., J.A.H., C.Z., and S.L.H. All authors edited and approved the final version of the manuscript.

Potential Conflicts of Interest

Companies that make MS disease-modifying therapies mentioned in this article include Bayer, Biogen, EMD Serono, Novartis, Pfizer, F. Hoffman La Roche, Sanofi Genzyme, and Teva. The following authors disclosed financial relationships with these companies. B.A.C.C.: consultancy, Biogen, EMD Serono, Novartis. R.B.: consultancy, F. Hoffmann-La Roche, Novartis, Sanofi Genzyme. J.M.G.: consultancy, Biogen. J.G.: speaker honoraria, Biogen, Sanofi Genzyme. D.S.G.: consultancy, Novartis; speaker honoraria, EMD, Serono, Novartis, Sanofi Genzyme. M.R.W.: grant support, F. Hoffman La Roche, Genentech. A.J.G.: consultancy, Novartis. S.S.Z.: consultancy, Biogen, F. Hoffman La Roche, Novartis, Sanofi Genzyme, Teva; grant support, Biogen, Teva. S.E.B.: speaker honoraria, Bayer, Biogen, EMD Serono, Novartis, Pfizer, F. Hoffman La Roche, Sanofi Genzyme, Teva. R.G.H.: grant support, F. Hoffman La Roche, Sanofi Genzyme; advisory boards, F. Hoffman La Roche, Novartis; educational programs, Sanofi Genzyme, Teva. S.L.H., travel reimbursement and writing assistance, F. Hoffmann-La Roche for CD20-related meetings and presentations. The other authors have nothing to report.

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