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ABSTRACT

BACKGROUND AND PURPOSE: **Two common approaches for measuring disease severity in multiple sclerosis (MS) are the clinical exam and brain magnetic resonance imaging (MRI) scan. Although most patients show similar disease severity on both measures, some patients have clinical/MRI dissociation.**

METHODS: **Subjects from a comprehensive care MS center who had a concurrent brain MRI, spinal cord MRI, clinical examination, and patient reported outcomes were classified into three groups based on the Expanded Disability Status Scale (EDSS) and cerebral T2 hyperintense lesion volume (T2LV). The first group was the low lesion load/high disability group (LL/HD) with T2LV $<$ 2 ml and EDSS $\geq$ 3. The second group was the high lesion load/low disability group (HL/LD) with T2LV $>$ 6 ml and EDSS $\leq$ 1.5. All remaining subjects were classified as not dissociated. The three groups were compared using regression techniques for unadjusted analyses and to adjust for age, disease duration, and gender.**

RESULTS: **Twenty-two subjects were classified as LL/HD (4.1%; 95% CI: 2.6%, 6.2%), and 50 subjects were classified as HL/LD (9.4%; 95% CI: 7.0%, 12.2%). Subjects in the LL/HD group were more likely to have a progressive form of MS and had significantly lower physical quality of life in adjusted and unadjusted analysis. Subjects in HL/LD had significantly more gadolinium-enhancing lesions, and subjects in the LL/HD group had significantly more cervical spinal cord lesions.**

CONCLUSIONS: **Our results indicate that dissociation may occur between physical disability and cerebral lesion volume in either direction in patients with MS. Type of MS, brain atrophy, and spinal cord lesions may help to bridge this dissociation.**

Keywords: clinical/MRI dissociation, lesion volume, brain atrophy, quality of life, gadolinium-enhancing lesions, spinal cord lesions, multiple sclerosis.

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Introduction

One of the hallmark traits of multiple sclerosis (MS) is the heterogeneity of the disease process. Some patients have a benign disease course in which they develop limited disability even after having the disease for many years.[1] Other patients have a rapidly progressive course with significant disability early in their disease.[2] In addition, clinical symptoms and magnetic resonance imaging (MRI) parameters (eg, number, location, and severity of lesions) vary dramatically among patients. This heterogeneity complicates the management of MS because a given patient's disease course cannot be predicted at the time of diagnosis or presentation.

Beyond differences between patients, disease heterogeneity also exists within some patients. More specifically, patients may appear to have severe disease according to one metric and mild disease according to another metric. The two most commonly used measures of disease activity and severity are the clinical exam and the brain MRI scan. For the clinical exam, the Expanded Disability Status Scale (EDSS) is the most widely used measure of physical disability.[3] Higher scores on the EDSS correspond to more disease severity clinically. For the brain MRI scan, the T2 hyperintense lesion volume (T2LV) and brain parenchymal fraction (BPF) are two common measures of disease severity, representing inflammatory events, and whole brain atrophy, respectively.[4] Most patients with low disability on EDSS have relatively low disease burden on MRI, and vice versa. The correlation between BPF and EDSS is generally stronger (range: .4–.6) than the correlation between T2LV and EDSS (range: .2–.4),[5–9] but the T2LV may be a better predictor of progression on the EDSS.[10] Interestingly, this correlation does not occur for all patients, giving rise to the so-called "clinical/MRI dissociation" that is often encountered in clinical practice.[11] This dissociation can have two forms: a rapidly progressive clinical course leading to severe disability in spite of a

relatively low lesion load (LL) on brain MRI, as is commonly seen in primary progressive (PP) or early secondary progressive (SP) MS with incomplete recovery from relapses; and a clinical course with little or no physical disability despite a striking T2LV accumulation on brain MRI.

In the first scenario, one potential explanation is that the disease may affect the spinal cord, rather than the brain, through increased prevalence of spinal cord lesions.[12] A second potential explanation is that although these patients have limited lesion load, they have severe brain atrophy that causes the physical disability.[13] In the second scenario, the high brain T2LV appears to not affect the patient clinically, at least in terms of physical disability as measured by the EDSS. Potential explanations for this could be that the lesions have an effect on the cognitive functioning, mood, or fatigue of the patients as opposed to the physical functioning.

The focus of this paper was to compare patients with either form of clinical/MRI dissociation with a nondissociated MS sample at a single large academic MS center. Characteristics of these groups were compared to determine the distinguishing features of each group, and several explanations for the dissociation were investigated. Finally, the stability of the dissociation over time was also assessed.

Methods

Subjects

The Comprehensive Longitudinal Investigation of Multiple Sclerosis at Brigham and Women's Hospital and Partners MS Center (CLIMB) has been enrolling patients since 2000[14] and currently has more than 2,000 subjects at various points in their disease course. CLIMB participants have clinical visits every 6 months during which the EDSS is measured. The Multiple Sclerosis Severity Scale (MSSS) is also calculated based on the EDSS and the disease duration at the time of the visit.[15] Starting in 2002, participants completed an annual patient reported outcomes (PROs) battery that includes measures of depression and health-related quality of life (HRQOL). In 2006, a brief cognitive screening test and a fatigue rating scale were added to the battery. The specifics regarding the PRO battery are provided below. In addition to the clinical and PRO data, all patients had MRI scans of the brain every year and MRI of the cervical and thoracic spine every other year. To be enrolled in this study, patients needed to have a visit with a clinical exam, brain MRI, and cervical spine MRI prior to 2010. Given these constraints, our final sample consisted of 533 patients. This study was approved by the Partners Human Research Committee.

Patient-Reported Outcomes

CLIMB participants in this analysis completed several PRO measures. The Multiple Sclerosis QOL-54 (MSQOL-54) instrument was used to assess HRQOL. It is an extension of the commonly used SF-36 and includes 18 additional MS-specific questions.[16] The responses to the questions were combined to calculate the physical health composite (PHC) score and the mental health composite (MHC) score. If patients missed a question in a specific domain, the average of the remaining questions in the domain was used to calculate the domain score. If a complete domain was missing (ie, the sexual functioning domain), the component scores could not be calculated, and the patient was removed from the analysis. The Center for Epidemiologic Studies Depression scale (CES-D) was used to measure depressive symptoms.[17] A subset of patients ($n = 423$) also completed the Modified Fatigue Impact Scale (MFIS), which is used to measure fatigue in patients with MS.[18]

Cognitive Functioning

To assess a patient's cognitive functioning, the Symbol Digit Modalities Test (SDMT) was administered.[19] The SDMT is a measure of speed of information processing that requires subjects to substitute numbers for symbols as part of a set code. This test is short and easy to administer but has been shown to be very sensitive to cognitive impairment in MS patients.[20]

MRI Acquisition

All patients underwent brain and spinal cord MRI using a similar acquisition protocol. Nearly all (531 scans, 99.6%) were acquired on the Signa 1.5 T (General Electric [GE], Milwaukee, WI) fleet of scanners at Brigham and Women's Hospital; the remaining two scans were acquired on a Signa 3 T (GE) scanner. Brain 1.5 T imaging relevant to the quantitative analysis included an axial T2-weighted conventional spin-echo dual-echo covering the whole head with the following acquisition parameters: (1) TR (mean [range]) = 2,980 (1,800–3,000) ms, TE1/TE2 = 30/80 ms, pixel size = .9246 (.7812−.9375) mm, slice thickness = 3 mm (no interslice gaps). Regarding the consistency of scanning, 450 patients (84.4%) had MRI scans performed on the same scanner utilizing the same protocol (TR 3,000 ms, TE 30/80 ms, voxel size .9375 × .9375 × 3 mm). The slice thickness and TE were consistent among the 1.5 T scans. MRI of the cervical and thoracic spinal cord was acquired on the same scanners using clinically-routine T2-weighted sagittal and axial fast spin-echo images. Cervical MRI was performed on all subjects; thoracic MRI was not available in 11 patients (2.1%). After infusion of intravenous gadolinium (GD) contrast (.1 mmole/kg), and a minimum of a 5-minute delay, axial T1-weighted spin-echo images of the brain and sagittal T1-weighted spin-echo images of the spinal cord were repeated.

MRI Analysis

Using automated template-driven segmentation (TDS+) from the cerebral dual echo images, T2LV and BPF were measured, the latter of which was used as an estimate of whole brain atrophy.[21] No manual correction of the data was performed. In addition to these measures, the total number of GD-enhancing (GD+) lesions was counted on nearly all of the scans ($n = 507$), and the presence or absence of spinal cord lesions in the cervical and thoracic cord was ascertained by a trained observer (FK) under the supervision of a senior observer (ST) for the subjects in the two dissociation groups.

Identification of Clinical/MRI Dissociation Groups

In order to identify patients with clinical/MRI dissociation, the EDSS and T2LV were chosen as markers for each aspect of the disease. Patients were placed into one of three categories: low lesion load/high disability (LL/HD), high lesion load/low disability (HL/LD), and nondissociated (ND). LL/HD patients were defined as patients with <2 ml in T2LV and ≥ 3 on the EDSS. HL/LD patients were defined as patients with >6 ml in T2LV and <2 on the EDSS. All remaining patients were classified as ND. Since patients could change from one category to

Table 1. Characteristics of Patients in the Clinical/MRI Dissociation Groups

	LL/HD	HL/LD	ND	*P*-Value
Number of patients	22	50	461	
EDSS (median (Interquartile range))	3.5 (3.0, 5.875)	1 (0,1.5)	1.5 (1.0, 2.5)	
T2LV (ml)	1.4 ± .42	10.4 ± 6.2	3.7 ± 3.1	
Age (years)	53.0 ± 10.7	40.9 ± 13.0	43.8 ± 10.1	<.0001
Disease duration (years)	12.5 ± 6.4	9.5 ± 7.9	9.1 ± 7.2	.097
Gender (F/M)	14/8	36/14	358/103	.26
On treatment (Y/N)	15/7	37/13	345/116	.79

For T2LV, Age and Disease duration, data are presented as mean ± standard deviation. LL/HD = low lesion load/high disability group; HL/LD = high lesion load/low disability group; ND = nondissociated group; EDSS = Expanded Disability Status Scale; T2LV = cerebral T2 hyperintense lesion volume.

Table 2. Clinical, MRI, Cognitive, and Quality of Life Characteristics of Patients in the Clinical/MRI Dissociation Groups

	LL/HD	HL/LD	ND	Unadjusted *P*-Value	Adjusted *P*-Value*
Clinical Characteristics					
SP, PP/RR	16/6	1/49	58/403	<.0001	<.0001
MSSS	5.33 ± 2.29	1.16 ± 1.13	2.54 ± 2.35	<.0001	<.0001
MRI Characteristics					
BPF	.836 ± .046	.853 ± .049	.864 ± .048	.011	.068
Total GD+	0 ± 0	.98 ± 4.24	.19 ± 1.03	.0003	.029
Cognition/Quality of Life					
SDMT	53.6 ± 14.3 (17)	51.8 ± 12.7 (36)	53.9 ± 11.5 (312)	.59	.082
CES-D	30.6 ± 6.2 (22)	29.6 ± 8.1 (49)	29.6 ± 8.5 (452)	.85	.81
MFIS	33.7 ± 12.7 (18)	21.0 ± 13.9 (41)	27.0 ± 17.0 (364)	.017	.059
MSQOL-54 PHC	58.8 ± 17.6 (18)	80.6 ± 12.8 (44)	73.0 ± 17.9 (418)	<.0001	.0004
MSQOL-54 MHC	72.5 ± 14.8 (22)	76.9 ± 17.5 (48)	75.2 ± 17.7 (450)	.62	.75

Data are presented as mean ± standard deviation. For Cognition/Quality of Life measures, the value in parentheses is the sample size of patients who contributed to the analysis. LL/HD = low lesion load/high disability group; HL/LD = high lesion load/low disability group; ND = nondissociated group; RR = relapsing remitting; PP = primary progressive; SP = secondary progressive; MSSS = Multiple Sclerosis Severity Scale; BPF = brain parenchymal fraction; GD+ = number of cerebral gadolinium-enhancing lesions; SDMT = Symbol Digit Modalities Test; CES-D = Center for Epidemiologic Studies Depression scale; MFIS = Modified Fatigue Impact Scale; MSQOL-54 = Multiple Sclerosis Quality of Life-54 instrument; PHC = physical health composite; MHC = mental health composite. *P-values are from regression adjusting for age, disease duration, and gender.

another over time, patients were all classified into one of the groups at the last visit. For patients in the LL/HD group, all subjects were not considered as having a current relapse by the treating neurologist at the visit, which ensured that the dissociation was not solely due to a temporary elevation in the EDSS.

Statistical Analysis

The proportion of subjects in each of the dissociation groups was calculated, and a Clopper–Pearson 95% confidence interval was created for each proportion. The three groups were compared in terms of clinical, MRI, PRO, and cognitive measures. For continuous variables, linear regression was used to compare the groups. For the dichotomous variables, logistic regression was used. For GD+ lesion count, negative binomial regression was used. In addition to the univariate comparisons, the same regression models were used to estimate the difference between the groups adjusting for age, disease duration, and gender. The difference between the LL/HD group and the HL/LD group in terms of presence and number of cervical and thoracic spinal cord lesions was assessed using Fisher's exact test and Poisson regression with robust standard errors, respectively. In addition, the clinical/MRI dissociation status after the start of the study was investigated for all patients. All statistical analyses were completed in the statistical package R (www.r-project.org). A two-sided alpha level of .05 was used to assess statistical significance.

Results

Subjects with Clinical/MRI Dissociation

Of the 533 subjects who contributed to our analysis, 22 were in the LL/HD group (4.1%; 95% CI: 2.6%, 6.2%), and 50 were in the HL/LD group (9.4%; 95% CI: 7.0%, 12.2%). The demographic characteristics of the patients in each group are provided in Table 1. The patients in the LL/HD group were significantly older than the other two groups ($P < .01$ for each comparison), but the groups were not significantly different in terms of disease duration, gender, or treatment status. In terms of clinical characteristics, patients in the LL/HD group had significantly higher disability as measured by the MSSS (Table 2). The LL/HD group was also significantly more likely to be progressive than the other groups ($P < .0001$), while all subjects in the HL/LD group were relapsing patients except for one.

Brain MRI

In terms of brain MRI metrics, the GD-enhancing lesion count was significantly different across the groups after adjusting for age, disease duration, and gender ($P = .029$). The HL/LD group had the highest GD+ lesion count, and no subjects in the LL/HD group had GD+ lesions. Although the BPF was significantly different across the groups in unadjusted analysis, the difference was smaller after accounting for age, disease duration, and gender (Table 2). The BPF was lowest (ie, most

atrophy) in the LL/HD group, followed by the HL/LD group and highest in the ND group.

Patient-Reported Outcomes/Cognition

The comparisons of the groups in terms of HRQOL showed that groups significantly differed in terms of physical HRQOL (adjusted $P = .0004$), but there was no significant difference in terms of mental HRQOL (adjusted $P = .75$). The differences in physical HRQOL were not surprising given the differences between the groups in terms of physical functioning. In terms of fatigue, the LL/HD group had the highest mean score, and the difference was statistically significant in the unadjusted analyses (Table 2); the difference did not remain statistically significant after adjusting for age, disease duration, and gender. The groups did not differ significantly in terms of depression. Finally, the groups did not significantly differ in terms of mean SDMT score but the HL/LD group did have the lowest mean cognitive score.

Spinal Cord Lesions

The presence of T2 hyperintense lesions in the cervical and thoracic spinal cord was also examined in the two dissociation groups. In the LL/HD group, 21 out of 22 patients (95%) had at least one cervical spinal cord lesion, and the mean (SD) number of cervical cord lesions was 3.1 (2.0). Further, 15 out of these 19 patients (79%) had at least one thoracic spine lesion, and the mean (SD) number of lesions was 1.8 (1.3). In the HL/LD group, 41 out of the 50 patients (82%) had at least one cervical spinal cord lesion, and the mean (SD) number of cervical cord lesions was 2.0 (1.6). Further, 22 out of these 42 patients (52.4%) had at least one thoracic spinal cord lesion, and the mean (SD) number of thoracic cord lesions was 1.4 (1.8). When the presence of lesions in both regions was compared using Fisher's exact test, there was no significant difference between the groups ($P = .16$ for cervical, $P = .088$ for thoracic). There was a significant increase in the number of cervical cord lesions based on the Poisson regression model ($P = .011$), but there was no significant difference for thoracic cord lesions ($P = .40$).

Persistence of Dissociation over Time

To assess the stability of the dissociation over time, the patients with multiple observations were classified in groups at each previous visit using our rule. The majority of patients did not have the clinical/MRI dissociation at any time during follow-up. In each dissociation group, the proportion of patients who always had the dissociation or had only one visit was less than 50% (Table 3).

Table 3. Persistence of the Dissociation between Clinical and MRI Measures over Follow-Up

Group at Last Visit	Persistence of Group Assignment	Number of Patients
LL/HD	Only one visit	3
	Always LL/HD	7
	LL/HD and ND	12
HL/LD	Only one visit	7
	Always HL/LD	15
	HL/LD and ND	28
ND	Only one visit	38
	Always ND	380
	LL/HD and ND	14
	HL/LD and ND	29

LL/HD = low lesion load/high disability group; HL/LD = high lesion load/low disability group; ND = nondissociated group.

Discussion

In this paper, we have shown that a total of 13.5% of patients have a clinical/MRI dissociation using our definition with 4.1% having low lesion load and high disability and 9.4% having a high lesion load and low disability. The subjects in the low lesion load and high disability group were more likely to be progressive and had lower physical HRQOL in adjusted and unadjusted analyses. Further, this group had significantly more cervical cord lesions compared to the other dissociation group. There was no significant difference in terms of the presence of any lesions in part because such a large proportion of subjects had at least one cervical cord lesion. In addition, the LL/HD group had a lower mean BPF that was not statistically significant in adjusted analysis, but this result may be confirmed in studies with larger sample size.

In terms of the characteristics of the high lesion load and low disability group, we investigated several potential features that might be impacted by the high lesion load despite the low EDSS score including cognition, depression and fatigue. Although there was no statistically significant difference between the groups in terms of the mean SDMT score, the HL/LD group had the lowest mean SDMT score, and the difference between the groups approached statistical significance in adjusted analyses. Therefore, larger sample sizes or a more comprehensive cognitive battery assessing multiple cognitive domains might be required to determine whether the high lesion load is impacting cognition in this group of patients. The HL/LD groups did not appear to have impairment in terms of fatigue or depression based on our sample.

The classification of patients into groups was completed using cutoffs determined by the investigators. The cutoffs for the EDSS, <2 for low disease burden and ≥ 3 for high disease burden, were chosen to ensure that the patients in each dissociation group were clinically either low disease burden or high disease burden. For the high disability cutoff, an EDSS of ≥ 6 could also have been used, but only 6 patients would have met the criteria for dissociation. The cutoffs for the cerebral T2LV were approximately one standard deviation above and below the mean T2LV on the log scale using all of the available data. The log scale was used because of the heavy right skew in the lesion volume data. These T2LV cutoffs are in line with our previous studies evaluating disease severity.[13] Patients who met this criterion were somewhat extreme in either a positive or negative manner in terms of the T2LV.

In most analyses, a drawback of using cutoffs to classify patients as opposed to using the original continuous data is the reduction in information on each patient. In our case, the data reduction is actually of benefit because the focus of our analysis was the extreme patients, not the entire patient population. If we combined the T2LV and EDSS into a single measure, we would be treating all patients equally. Since the majority of patients were ND, the differences in the ND patients would likely dominate any comparison involving a measure that combines EDSS and T2LV, which would not provide information regarding the extreme patients. Therefore, by classifying patients

using cutoffs, our analysis was focused on the comparisons of interest.

Our study has limitation that should be considered when interpreting our results. First, our focus in the analysis of the spinal cord was the use of spinal cord lesions as the outcome as opposed to spinal cord atrophy given that the presence of spinal cord lesions is not an appropriate surrogate of spinal cord atrophy.[12] The present analysis did not investigate the potential of spinal cord atrophy to explain the difference between the patients. At the same time, accurate estimation of spinal cord atrophy was not feasible from our clinically obtained 2-dimensional MRI scans. Second, our study did not measure cortical lesions or diffuse damage that can be more reliably measured using high resolution and higher field MRI, and these features might show important differences between the dissociation groups. Future work with more advanced imaging will be required to assess the impact of these measures. Third, the focus of this study was structural MRI, and the lesion volume on structural MRI was used to classify subjects in groups. One possible explanation for subjects having high lesion load on structural MRI and low clinical disability (ie, HL/LD group) is that the patient has compensatory mechanisms that allow the patient to retain physical functioning despite a large amount of structural damage. One potential explanation is brain or cognitive reserve,[22] and future work with alternative imaging modalities will be required to investigate whether brain reserve or other aspects of the brain not visible on structural MRI might explain this type of dissociation. Finally, we assessed cognition based on a single measure of processing speed, but a more comprehensive cognitive battery would be required to assess the difference between the groups.

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