MRI Evidence For A Strong Relationship Between Total Cerebral White-Matter Lesion Load And Clinical Disability In Patients With Multiple Sclerosis

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INTRODUCTION Focal, inflammatory, demyelinating white-matter (**WM**) lesions of the CNS are the hallmark pathology in patients with multiple sclerosis (**MS**). Such lesions are typically visible as hyperintensities on T_2-weighted MRI (**T2**) and lesions that are associated with greater tissue destruction also appear as chronic hypointensities on T_1-weighted MRI (**T1**). Recent evidence has suggested that the clinical disability seen in patients with MS may be associated with widespread neuroaxonal disturbance (*e.g.,* as measured with peri-ventricular ^{1}H-MRSI-measured NA/CR values) and ongoing CNS atrophy. The results of recent clinical trials as well as those of other studies have suggested that the relationship between patients' total WM lesion-load (**LL**) and their level of clinical disability [as is typically-measured on the Expanded Disability Status Scale (**EDSS**)] is not as strong as might have been expected. However, such studies have *(i)* not sampled the entire range of the EDSS scale and/or *(ii)* been based on relatively-small sample sizes. The present work consists of two sets of analyses: *(i)* the first set examined the relationships between patients' EDSS scores and their cerebral LLs, both *(a)* within a limited range of EDSS values (0-6, n = 78), as has typically done in most other studies, and *(b)* across the entire range of the EDSS (0-9.5, n = 98); *(ii)* the second set examined – in a smaller sample of patients that underwent additional MRI investigation (n = 60) – the relationships between their EDSS scores and MR measures of their total cerebral-WM LLs, their central-brain neuroaxonal integrity, and their CNS atrophy.

METHODS ***Subjects:*** The first set of analyses included data from 98 patients with clinically-definite MS [70 (51 ♀) relapsing-remitting (**RR**) and 28 (14 ♀) secondary-progressive (**SP**) patients]. The second set included data from 60 such patients [40 RR (28 ♀); 10 SP (10 ♀)]. All patients were untreated and relapse-free at the time. Data from RR patients with benign disease (*i.e.*, duration > 15 yrs, but EDSS < 3.0) were excluded. These patients' ages, disease durations, and EDSS scores are shown below. ***Image Acquisition:*** For all patients, brain MRI was performed on a 1.5T, Philips Gyroscan ACS II using a body-coil transmitter and a quadrature head-coil receiver. For patients included in the second set of analyses, brain ^{1}H-MRSI and spinal cord MRI were also carried out. Brain MRI: Fifty contiguous, 3-mm-thick proton-density-weighted (**PD**) and T_2-weighted images were acquired parallel to the AC-PC line using a dual turbo-spin-echo sequence (TR 2075 ms, TE 30/90 ms, 256×256 matrix, 250 mm FOV). T_1-weighted images were acquired with the same matrix using a 3D gradient-echo sequence (TR 35 ms, TE 10.2 ms, 40°excitation angle). Each MRI volume was corrected for image-intensity inhomogeneity and the T_2/PD image pair was registered to the T_1 volume using mutual information. Cerebral T2- and T1-LLs were segmented using a manually-corrected, Bayesian tissue classification (S.J.F.). Normalized brain volumes (**NBV**) were generated using SIENAX (NeuroImage **17**, 479; 2002). Brain ^{1}H-MRSI: 2D data from a large VOI of 90 x 90 x 20 mm^3 centered on the corpus callosum was obtained using a PRESS sequence (TR 2000 ms, TE 272 ms, 250 x 250 mm FOV, 32 x 32 phase encodes, 1 signal average). Data were post-processed, and NA and Cr metabolite peaks were obtained using in-house software as detailed elsewhere (Arch Neurol **58**, 65; 2001). Spinal Cord MRI: T_1-weighted images of the cervical spine were obtained with a quadrature neck coil using a 3D FFE sequence (TR 27 ms, TE 7.5 ms, 256×256 matrix, 150 mm FOV, 20° flip angle, and 6 signal averages). Twenty-five transverse slices (0.6 mm × 0.6 mm × 1 mm) were acquired perpendicular to the cord. Data were post-processed and the mean cervical-cord cross-sectional areas at the level of C2 (**Cord**) were determined as detailed elsewhere (Proc Int Soc Magn Reson Med **8**, 297; 2000). ***Statistical Analyses:*** Relationships between EDSS scores and other single measures were evaluated both *(i)* parametrically using Pearson product-moment correlations (**PPMC**) and *(ii)* non-parametrically using Spearman rank-order correlations (**SROC**). In the second set of analyses, multivariate linear regressions were used to evaluate the relationships between patients' EDSS scores and combinations of values on their other measures. For purposes of parametric analysis and graphing, 0.1 was added to each patients' T2- and T1-LL values and these values were logged before analysis (or were plotted on a semi-log scale). SYSTAT for Windows, version 10.2, was used for all statistical analyses.

RESULTS ***Part I: Relationship between patients' EDSS scores and their total cerebral-WM lesion loads:*** As shown in the Figure and in Table 1, in this large, representative sample of patients with MS, EDSS scores were strongly related to T2-LLs, and even more so to T1-LLs. Importantly, the strength of these relationships seemed to increase when data from patients that encompassed the entire range of the EDSS were examined. Interestingly, disease duration was also very strongly related to EDSS, especially across the entire EDSS.

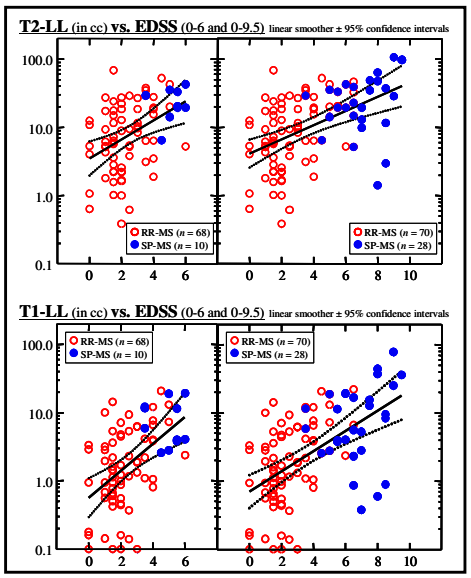

Table 1	EDSS	Age (yrs)	Duration (yrs)	T2-LL (cc)	T1-LL (cc)
Median (Range), (n = 98)	3 (0 - 9.5)	39.4 (14.2 - 66.5)	8.3 (0.3 - 41.9)	11.5 (0.3 - 105.7)	2.6 (0 - 78.1)
Mean (SD), (n = 98)	3.59 (2.52)	39.9 (10.3)	10.1 (8.5)	17.8 (19.4)	6.4 (11)
PPMC (p): EDSS 0-6 (n = 78)	-	0.336 (0.00261)	0.468 (0.00002)	0.432 (0.00008)	0.512 (< 0.00001)
SROC (p): EDSS 0-6 (n = 78)	-	0.346 (0.00192)	0.407 (0.00022)	0.431 (0.00008)	0.495 (< 0.00001)
PPMC (p): EDSS 0-9.5 (n = 98)	-	0.403 (0.00004)	0.593 (< 0.00001)	0.491 (< 0.00001)	0.562 (< 0.00001)
SROC (p): EDSS 0-9.5 (n = 98)	-	0.392 (0.00006)	0.584 (< 0.00001)	0.499 (< 0.00001)	0.539 (< 0.00001)

Part II: Relationship between patients' EDSS scores and their total cerebral-WM lesion loads and other MR measures: As shown in Table 2, in the second, somewhat-smaller sample of patients that had the additional MR measures, EDSS scores were still strongly related to T2-LLs, and even more so to T1-LLs. Patients' EDSS scores seemed to be even-more-strongly related to their disease durations, mean cervical-spinal-cord cross-sectional areas, and NBV values. Interestingly, over the entire EDSS range, patients' EDSS scores seemed to be more strongly related to their cerebral LLs than to their central-brain NA/Cr values. The linear-multiple-regression combination of these patients' sexes, ages, and disease durations; their T2- and T1-LLs; and their Cord, NBV, and NA/Cr values was able to account for 64.5% of the variance in their EDSS scores ($F_{8, 51} = 11.57$, $p < 0.00001$). Importantly, both forward- and backward-stepwise-regression analyses agreed that, of these variables, the optimal model for predicting EDSS values in these patients (a model that accounted for 63.4% of the variance in their EDSS scores with $F_{4, 55} = 23.81$ and $p < 0.00001$) included T1-LL ($p = 0.001$), Cord value ($p = 0.002$), disease duration ($p = 0.02$), and sex ($p = 0.08$) – further suggesting that total cerebral-WM T1-LL is importantly related to clinical disability in patients with MS.

Table 2	EDSS	Age (yrs)	Duration (yrs)	T2-LL (cc)	T1-LL (cc)	Cord (mm^2)	NBV (x 10^{-6})	NA/CR
Median (Range), (n = 60)	2.8 (0 - 9)	38.8 (14.2 - 61.7)	9.4 (0.7 - 26)	12.2 (0.9 - 105.7)	2.3 (0 - 52.5)	72.9 (34.5 - 104.4)	1.578 (1.284 - 1.762)	2.83 (1.99 - 3.59)
Mean (SD), (n = 60)	3.6 (2.6)	39.3 (9.9)	10 (6.3)	18.1 (19.4)	6.1 (9.9)	71 (14.6)	1.565 (0.097)	2.81 (0.33)
PPMC (p): EDSS 0-9.5 (n = 60)	-	0.403 (0.00141)	0.674 (< 0.00001)	0.470 (0.00015)	0.581 (0.00001)	-0.643 (< 0.00001)	-0.634 (< 0.00001)	-0.369 (0.00370)
SROC (p): EDSS 0-9.5 (n = 60)	-	0.406 (0.00128)	0.580 (< 0.00001)	0.478 (0.00011)	0.582 (< 0.00001)	-0.537 (0.00001	-0.528 (0.00001)	-0.364 (0.00423)

DISCUSSION The present findings suggest that total cerebral-WM T1-LL, which is indicative of the extent of severe tissue pathology, is strongly related to clinical disability in patients with MS, and that this relationship is strengthened when the entire range of clinical disability is sampled. Furthermore, patients' T1-LL, cervical-cord cross-sectional area, disease duration, and sex can be combined to explain most of the variance in such patients' clinical disability; interestingly, the addition of their T2-LL, brain volume, and central-brain NA/Cr values to this model did not seem to account for any additional variance in these patients' clinical disability.