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MR Outcome Parameters in Multiple Sclerosis: Comparison of Surface-Based Thresholding Segmentation and Magnetization Transfer Ratio Histographic Analysis in Relation to Disability (A Preliminary Note)

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BACKGROUND AND PURPOSES: **MR imaging is now widely used to monitor disease progression in patients with multiple sclerosis (MS). The purpose of this study was to explore the relationship between disability status and existing and new MR parameters in MS patients.**

METHODS: **Forty-one patients with clinically definitive MS were studied. MR imaging included T2- and T1-weighted imaging as well as gradient-echo imaging with and without magnetization transfer contrast. We used surface-based thresholding segmentation techniques to obtain T2 and T1 lesion load, T1/T2 ratio, and several magnetization transfer ratio (MTR) lesion load parameters. MTR histographic analysis included measurements of absolute peak height (aHp), relative peak height (rHp), MTR of the peak (MTRp), mean MTR (MTRm), and MTR_{25}, MTR_{50}, and MTR_{75}, relating to the integrals of the histogram at 25%, 50%, and 75%, respectively, of the total area under the curve. All MR parameters were correlated with Expanded Disability Status Scale (EDSS) score, disease duration, and patient's age.**

RESULTS: **Using surface-based thresholding segmentation techniques, we found relatively low correlations with EDSS. T1 lesion load and T1/T2 ratios correlated most strongly. Regarding MTR histographic parameters, EDSS correlated best with rHp but only weakly with others. Similar correlations were found with disease duration, but not with age.**

CONCLUSION: **The best MR correlations with disability were several MTR histographic parameters. Our findings may favor the use of these MR parameters over T2 lesion load to monitor disease progression in patients with MS, findings that should be explored further in longitudinal studies.**

In clinical trials involving patients with multiple sclerosis (MS), MR imaging parameters are now widely used as an alternative outcome, next to clinical parameters. In one such trial, the burden of disease (lesion load), as seen on T2-weighted MR images, was significantly affected by treatment with interferon-β (1). The clinical value of this finding remains uncertain, since the correlation between T2 lesion load and disability as measured by the Expanded Disability Status Scale (EDSS) has been shown to be moderate at best. This may be due to the histopathologic heterogeneity of MS lesions. Inflammation, edema, demyelination, axonal loss, and gliosis are all represented as hyperintense lesions on T2-weighted spin-echo (SE) MR images. Although this clinicoradiologic paradox exists, there seems to be a positive correlation between the percentage of change in burden of disease on T2-weighted images from baseline to exit and disability (1, 2).

Other MR techniques, like T1-weighted SE and magnetization transfer imaging, have been introduced, focusing on demyelination and axonal loss (3–5), which are the more likely pathologic substrates of persistent deficit. T1 lesion load correlates moder-

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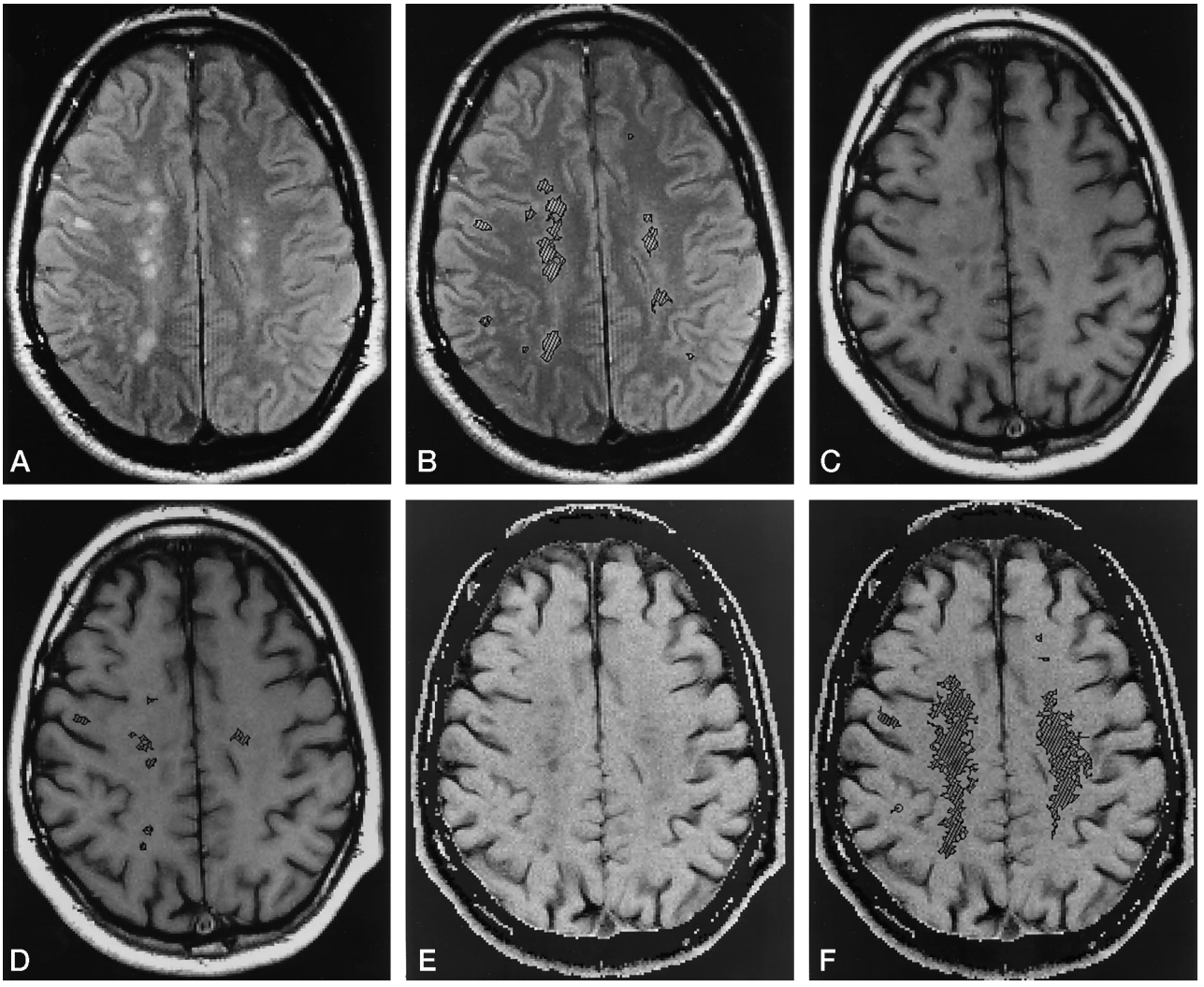

ately with clinical disability in cross-sectional studies and shows a good correlation with increase in disability over 3 years (in secondary-progressive MS patients) (6, 7). For magnetization transfer imaging, a moderate correlation was found between mean magnetization transfer ratio (MTR) in lesions and disability ($r = -.44$), which was stronger than for T2 lesion load ($r = .33$) (8). Recently, MTR histographic analysis has been introduced (9), which can provide a global disease estimation of the brain in MS patients, including lesion burden and subtle changes in white matter, and may be a promising single quantification technique for MS patients (10).

The purpose of this explorative study was to compare both surface-based thresholding segmented MR parameters and MTR histographic parameters in relation to disability in MS patients.

Methods

Forty-one patients (14 men and 27 women, 18 to 53 years old) with clinically definitive MS (eight relapsing-remitting and 33 secondary-progressive) were studied. Mean disease duration was 8.7 years (range, 1 to 20 years). EDSS scores ranged from 1.0 to 6.5 (mean, 4.5). Eleven patients were recruited in Milan and 30 in Amsterdam.

MR imaging was performed at 1.5 T (on the same model scanner at both sites) and included T2-weighted SE (2000/30–80/1 [TR/TE/excitations]), T1-weighted SE (500/15/2), and fast low-angle shot (FLASH) (600/12/2; flip angle 20°) MR imaging with and without a pulsed gaussian-shaped off-resonance (−1.5 kHz) presaturation pulse (duration, 12.8 milliseconds; bandwidth, 250 Hz; flip angle off-resonance pulse, 1000°), as described by Dousset et al (3). For all MR sequences, a section thickness of 5 mm and a pixel size of approximately 1 × 1 mm were used. Additionally, an interleaved scan mode with an intersection gap of 5 mm was used to obtain 2 × 12 sections, resulting in 24 contiguous sections covering the entire brain. Total acquisition time was 17.10 minutes, 8.38 minutes, and 20.36 minutes for the T2-weighted, T1-weighted, and MT imaging sequences, respectively.

Postprocessing of images with and without magnetization transfer contrast included derivation of MTR maps and computation of MTR histograms. MTR maps were calculated using the equation $(M_o - M_s)/M_o$, where M_o stands for signal intensity from unprepared sequences and M_s for signal intensity from MT-presaturated pulses. MTR histograms were computed by using 3DVIEWNIX software. The steps in this postprocessing operation, which has been described previously (10), result in an MTR histogram of the total brain parenchyma.

Surface-based thresholding segmentation techniques, using home-developed seed-growing software (6), included measurements of T2 lesion load, T1 lesion load, and MTR lesion load. T2 lesion load was obtained by measuring the total area of

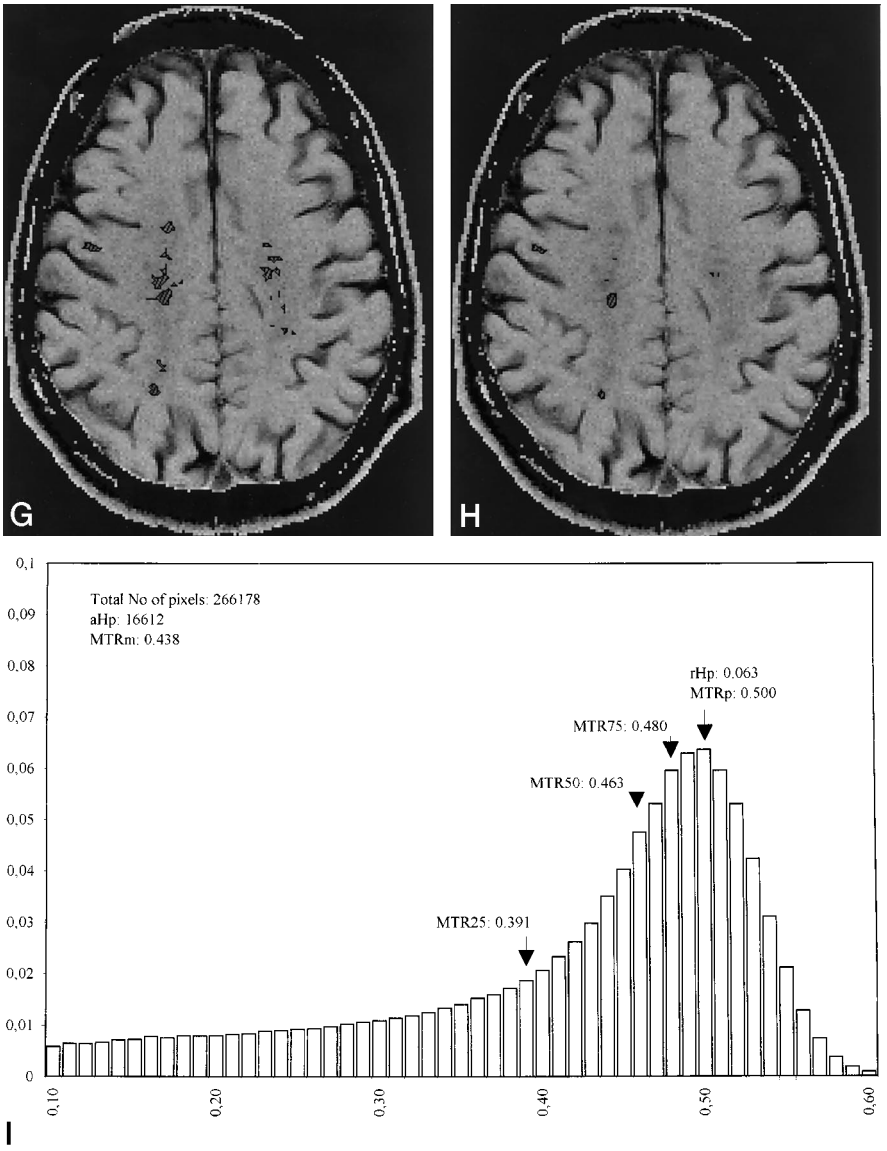

FIG 1. 43-year-old patient with secondary-progressive MS and an EDSS score of 5.5.

A–H, T2-weighted images (2000/30/1) without (*A*) and with (*B*) demarcation of T2 lesion load; T1-weighted images (500/15/2) without (*C*) and with (*D* demarcation of T1 lesion load; MTR_{subj} maps without (*E*) and with (*F*) demarcation of MTR_{subj}; and MTR_{85c} (*G*) and MTR_{75c} (*H*) lesion load.

I, Corresponding MTR histogram includes the following measured parameters: relative peak height (rHp) represents the percentage of the total number of brain pixels forming the highest bin. MTR value of the peak (MTRp) represents the MTR value on the *x*-axis of the highest bin. MTR_{25}, MTR_{50}, and MTR_{75} represent MTR values on the *x*-axis at which the integrals of the histogram are 25%, 50%, and 75% of the total area under the curve, respectively. Absolute peak height (aHp), which is the total number of pixels in the highest bin of the histogram, total number of brain pixels used for creating the histogram, and mean MTR (MTRm) of all brain parenchyma are not seen on the MTR histogram but are given separately. Note that only some T2 lesions appear hypointense on the T1-weighted image and that on the MTR map the NAWM surrounding the T2 lesions has decreased MTR values. In this patient, T2 lesion load (43.3 cm^3) was higher than both T1 lesion load (17.4 cm^3) and MTR_{85c} lesion load (21.4 cm^3), and lower than MTR_{subj} lesion load (54.0 cm^3). T1 lesion load was higher than MTR_{75c} lesion load (8.6 cm^3) and lower than MTR_{85c} lesion load. Relative peak height in this patient was 0.063, and MTR at the 25th percentile (MTR_{25}) was 0.39.

hyperintense MS lesions on the SE 2000/30/1 images. T1 lesion load was measured as the total area of hypointense lesions that showed equal or lower signal intensity than that of gray matter in the same section and that also appeared hyperintense on the corresponding T2-weighted image. In addition, a T1/T2 ratio was calculated per patient, defined as T1 lesion load divided by T2 lesion load. MTR lesion load was measured subjectively (MTR_{subj}) and by using two predefined cut-off levels below the MTR value of white matter in control subjects (mean MTR, 0.495). MTR_{subj} lesion load was measured as the total area of white matter that appeared hypointense on the MTR map, using the T2-visible lesions as a starting point. MTR_{85c} and MTR_{75c} lesion loads were obtained by the total area of hypointense pixels on the MTR map showing a decrease of at least 15% and 25%, in MTR, respectively, as compared with the mean MTR of normal white matter. Using T2-weighted images to confirm MS lesions, we placed a seed in the most hypointense pixel. The seed was automatically grown to include all pixels that showed an MTR equal to or less than 85% or 75% of MTR of white matter in control subjects.

From the MTR histogram (Fig 1I), the following parameters were obtained: absolute peak height (aHp) of the histogram (ie, total number of pixels representing the peak), relative peak height (rHp) of the histogram (ie, aHp divided by total number of pixels under the curve), MTR corresponding to the peak (MTRp), mean MTR (MTRm) of all pixels under the curve, and MTR_{25}, MTR_{50}, MTR_{75}, indicating the MT ratio values at which the respective integrals of the histogram are 25%, 50%, and 75% of the total area under the curve.

Scans from 10 patients were reanalyzed by the same readers after 2 months to evaluate intrarater reproducibility of all quantification techniques. The intrarater reproducibility was expressed as a coefficient of variation (CV), defined as the standard deviation in differences between consecutive measurements divided by the mean value of both measurements. A low CV indicates good intrarater reproducibility.

Because of nonparametric data distribution, the Spearman rank coefficient was used to assess correlations between MR parameters and disability, as measured by EDSS. In addition, all MR parameters were correlated with age and disease duration. Multiple regression analysis (forward and backward stepwise, F to enter = .05) was used to estimate the relative weight of MR parameters on disability.

Results

Mean values of all MR parameters and their range are reported in Table 1. T2 lesion load was higher than both T1 and MTR_{85c} lesion load, and lower than

TABLE 1: Mean values and range of all MR parameters studied, including parameters obtained from the volumetric MTR analysis

	Mean	Range
T2 lesion load (cm^3)	18.8	2.3–73.2
T1 lesion load (cm^3)	8.9	0–40.5
T1/T2 ratio	0.39	0.00–0.76
MTR_{subj} lesion load (cm^3)	29.8	1.0–121.2
MTR_{85c} lesion load (cm^3)	13.8	0.2–45.7
MTR_{75c} lesion load (cm^3)	4.5	0.1–16.9
aHp (cm^3)	17.2	11.5–21.6
rHp	0.073	0.047–0.098
MTRp	0.47	0.40–0.50
MTRm	0.43	0.40–0.46
MTR_{25}	0.39	0.32–0.43
MTR_{50}	0.46	0.42–0.49
MTR_{75}	0.49	0.47–0.53

Note.—MTR indicates magnetization transfer ratio; T1/T2 ratio, T1 lesion load divided by T2 lesion load; MTR_{subj}, MTR lesion load measured subjectively; MTR_{85c}, MTR lesion load using a 15% cut-off level; MTR_{75c}, MTR lesion load using a 25% cut-off level; aHp, absolute peak height; rHp, relative peak height; MTRp, MT ratio value corresponding to the peak; MTRm, mean MT ratio value; MTR_{25}, MTR_{50}, MTR_{75}, MTR values of the 25th, 50th, and 75th percentile of the histogram, which indicate the MT ratio values at which the respective integrals of the histogram are 25%, 50%, and 75% of the total area.

MTR_{subj} lesion load (all P values $< .01$, Wilcoxon) (Fig 1A–H). T1 lesion load was higher than MTR_{75c} lesion load and lower than MTR_{85c} lesion load (both P values $< .01$, Wilcoxon) (Fig 1A–H). The intrarater reproducibility, as expressed by CV, was 2.0% for T2 lesion load, 2.8% for T1 lesion load, 8.3% for MTR_{subj} lesion load, 8.0% for MTR_{85c} lesion load, and 5.1% for MTR_{75c} lesion load. For MTR histographic analysis, a CV of 0.6% was found.

TABLE 2: Correlations between all MR parameters and EDSS, disease duration, and patient's age (Spearman rank coefficient)

	EDSS Score	Disease Duration	Age
T2 lesion load	.17	.33*	−.03
T1 lesion load	.32*	.40*	.12
T1/T2 ratio	.40*	.35*	.23
MTR_{subj} lesion load	−.01	.17	.15
MTR_{85c} lesion load	.12	.30	−.01
MTR_{75c} lesion load	.30	.43*	.17
aHp	.24	−.29	−.19
rHp	−.47†	−.51†	−.25
MTRp	.11	−.13	−.18
MTRm	−.30	−.20	.13
MTR_{25}	−.46†	−.41†	−.01
MTR_{50}	−.23	−.12	.15
MTR_{75}	.23	.19	.16

* P value $< .05$, † P value $< .01$.

Note.—EDSS indicates expanded disability status scale; MTR, magnetization transfer ratio; T1/T2 ratio, T1 lesion load divided by T2 lesion load; MTR_{subj}, MTR lesion load measured subjectively; MTR_{85c}, MTR lesion load using a 15% cut-off level; MTR_{75c}, MTR lesion load using a 25% cut-off level; aHp, absolute peak height; rHp, relative peak height; MTRp, MT ratio value corresponding to the peak; MTRm, mean MT ratio value; MTR_{25}, MTR_{50}, MTR_{75}, MTR values of the 25th, 50th, and 75th percentile of the histogram, which indicate the MT ratio values at which the respective integrals of the histogram are 25%, 50%, and 75% of the total area.

Correlations between MR parameters and EDSS, disease duration, and age are reported in Table 2. T2 lesion load and all MTR lesion loads showed a weak correlation with EDSS ($r < .30$, $P > .05$). Only T1 lesion load correlated more strongly with EDSS ($r = .32$, P value $< .05$). Furthermore, the ratio of T1 lesion load over T2 lesion load (T1/T2) also correlated more strongly with EDSS ($r = .40$, ($P < .02$). Regarding histographic parameters (Fig 1I), EDSS correlated best with rHp ($r = -.46$, $P < .01$) (Fig 2) and MTR_{25} ($r = -.47$, $P < .01$).

Disease duration correlated moderately with T2 lesion load ($r = .33$), T1 lesion load ($r = .40$), T1/T2 ($r = .35$), and, best, with MTR_{75c} ($r = .43$) (all P values $< .05$); rHp ($r = -.51$, $P < .01$) and MTR_{25} ($r = -.41$, $P < .01$) showed the highest correlation with disease duration. None of the MR parameters we investigated correlated significantly with age.

Using multiple regression analysis, we found that only rHp was an independent contributor to disability ($r^2 = .31$, $P < .001$). No further independent contributors could be included in the model, probably because of the high correlation between all MR parameters (Table 3). By leaving rHp out of the analysis, T1/T2 became the only contributor ($r^2 = .26$, $P < .01$). By leaving both rHp and T1/T2 ratio out of the equation, MTR_{25} was included in the equation as the contributor to disability ($r^2 = .18$, $P = .01$). No further independent contributors could be included in the model when all three above-mentioned parameters were left out of the equation.

Discussion

As compared with T2 lesion load, a higher correlation with disability was found for T1 lesion load and T1/T2 ratio, in accordance with earlier studies (7, 11). T1 lesion load is reported to represent those lesions that have substantial myelin and axonal loss (5), although acute lesions may also show strong hypointense signal intensity, partly because of extracellular edema (12). The proportion of T2 lesions that appear hypointense on T1-weighted images (T1/T2 ratio) seems to be an important parameter for persistent deficit in case of similar burden of disease between MS patients (6, 7). Both MTR_{subj} lesion load and MTR_{85c} lesion load correlated poorly with disability. One explanation might be that these MR parameters are not yet well enough defined, as illustrated by the relatively poor intrarater reproducibility figures. The low intrarater reproducibility for MTR lesion load was partly related to difficulties in the demarcation of lesions at the border of the ventricles, owing to partial volume effects of brain tissue with ventricular CSF. Furthermore, MTR_{subj} lesion load represents both focal lesion load as well as diffuse abnormalities extending beyond the borders of focal lesions, and is higher than T2 lesion load. This may be due to the fact that MTR of normal-appearing white matter (NAWM), especially adjacent to lesions in secondary-progressive MS patients, is significantly reduced (13, 14), leading to less circumscribed lesions on MTR

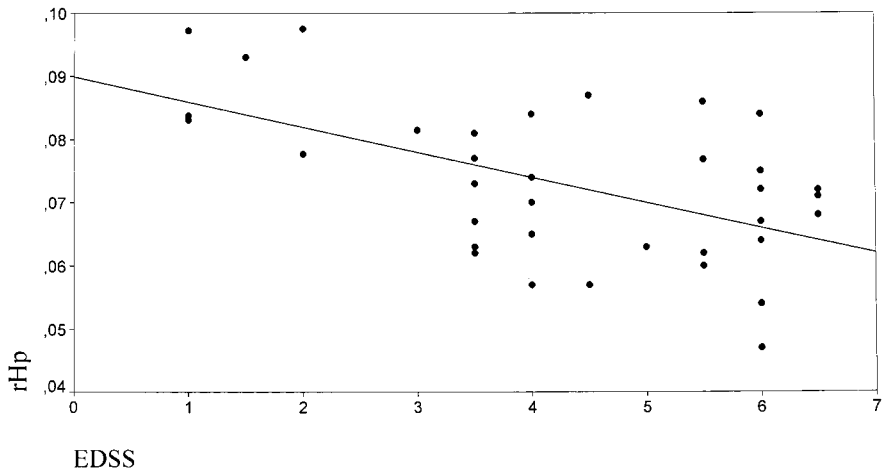

FIG 2. Relative peak height versus expanded disability status scale. The strongest correlation of all MR parameters with disability (EDSS) was found for rHp, $r = -.47$, $P < .01$).

maps and subsequently to lower reproducibility in outlining these lesions. MTR_{85c} lesion load was chosen to define lesions with substantial tissue destruction. MTR_{85c} lesion load was higher than T1 lesion load; MTR_{75c} lesion load was lower than the T1 lesion load, showed a better reproducibity than both other MTR lesion loads, and had a similar correlation coefficient as T1 lesion load. A more convenient way to explore different cut-off levels is of course the use of histographic analysis.

Using MTR histographic analysis, both rHp and the mean MTR at the 25th percentile of the histogram showed a good correlation with disability, which was higher than for T1 and T1/T2 lesion load. The relative peak height of a histogram represents the percentage of residual "normal" white matter in the brain. The higher the peak in a histogram, the smaller the amount of diseased brain tissue. With a decrease in rHp, MTR at the 25th percentile will decrease, as more pixels in the histogram will have lower MTR values. Consistent with earlier findings (9) of decreased peak height of the histogram in MS patients as compared with healthy control subjects, we observed a large range in rHp, which correlated well with EDSS. In contrast to this earlier study, we also found a large range in peak location, indicating that peak location may shift to lower MTR values in MS patients. Since in the normal situation the peak is constituted by the most abundant tissue class (ie, white matter), such a shift in MTR values can only be caused by diffuse changes in white matter, underlying the appropriateness of the term NAWM in MS. The change in peak location is in accordance with the finding of lowered MTR in NAWM in MS patients; especially in patients with secondary-progressive disease, in which lower MTR values have been reported in NAWM surrounding MS lesions than in patients with relapsing-remitting disease (13). In this study, the majority of patients had secondary-progressive MS, which may explain why we observed a large range in peak location, in contrast to an earlier study, in which the majority of patients had relapsing-remitting MS.

TABLE 3: Correlations between all MR parameters that showed a moderate to good association with EDSS or disease duration

	T1	T1/T2	rHp	MTR_{25}
T1/T2	.84	...	...	...
rHp	−.69	−.66	...	...
MTR_{25}	−.58	−.51	.73	...
T2	.90	.55	−.60	−.51

Note.—All P values <.01. MTR indicates magnetization transfer ratio; EDSS, expanded disability status scale; T1, T1 lesion load; T1/T2, ratio of T1 lesion load over T2 lesion load; rHp, relative peak height; MTR_{25}, MT ratio value at which the respective integral of the histogram is 25%; T2, T2 lesion load.

One might expect that the change in peak location is clinically relevant; however, no correlation was found between peak location and either EDSS or disease duration. Consequently, the significance of this change in peak location remains elusive. Given the poor correlation of both peak location and MTR_{subj} lesion load with disability, we suggest that diffuse involvement of white matter (only slightly decreased MTR and subsequently minor demyelination) in the brain may not have the same impact on disability as it seems to have in the spinal cord (15).

Because we found four different MR parameters that showed similar correlations with disability, the practical advantages and disadvantages of these parameters need to be considered. T1-weighted images are easy to obtain and require little time; and lesion load measurements are reproducible in trained hands. Conversely, T1 lesion load measurements are time-consuming (requiring 60 minutes per patient), observer-dependent (definition of hypointense lesion), sequence-dependent (the more T1-weighted, the more hypointense lesions), and, in this study, showed a lower correlation with disability than did T1/T2, rHp, and MTR_{25}. The ratio of T1 lesion load over T2 lesion load had a higher correlation with EPSS, but the ratio depends on two sequences, which require more imaging and analysis time.

MTR histographic analysis has the highest intrarater reproducibility, is less observer-dependent, and less time-consuming (15 minutes per patient). The histogram probably is influenced by both atrophy and overall disease burden. Although MTR histographic analysis disregards location and number of

lesions, it provides multiple parameters and allows the possibility of varying the cut-off levels for MTR values, which is impossible in one session of MTR lesion load measurements. Disadvantages of volumetric MTR analysis include the fact that two sequences (one with and one without magnetization transfer contrast) are needed and that derivation of MTR maps and MTR histograms will be influenced by any motion the patient makes between sequences. Furthermore, little information exists about reproducibility of histograms over time and among sites.

Conclusion

Although this is an explorative study and *P* values should not be interpretated simply by significance of correlation coefficients, we conclude that the correlation between MTR histographic parameters and disability seems to favor the use of these MR parameters over T2 lesion load to monitor disease progression and that MTR histographic parameters are well worth further testing in prospective longitudinal studies.

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References

1. Paty DW, Li, DK. **Interferon beta-1b is effective in relapsing-remitting multiple sclerosis: MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI study group and the IFNB multiple sclerosis study group.** *Neurology* 1993;43:641–643
2. Zhao GJ, Li DK, Wolinsky JS, et al. **Clinical and magnetic resonance imaging changes correlate in a clinical trial monitoring cyclosporine therapy for multiple sclerosis. The MS study group.** *J Neuroimaging* 1997;7:1–7
3. Dousset V, Grossman RI, Ramer KN, et al. **Experimental allergic encephalomyelitis and multiple sclerosis: lesion characterization with magnetization transfer imaging.** *Radiology* 1992;182:483–492
4. Dousset V, Brochet B, Vital A, et al. **Lysolecithin-induced demyelination in primates: preliminary in vivo study with MR and magnetization transfer.** *AJNR Am J Neuroradiol* 1995;16:225–231
5. van Walderveen MAA, Kamphorst W, Scheltens Ph, et al. **Hypointense lesions on T1-weighted SE MR images correlates with axonal loss in multiple sclerosis.** *Neurology* 1998;50:1282–1288
6. van Walderveen MAA, Barkhof F, Hommes OR, et al. **Correlating MR imaging and clinical disease activity in multiple sclerosis: relevance of hypointense lesions on short TR/short TE ("T1-weighted") spin-echo images.** *Neurology* 1995;45:1684–1690
7. Truyen L, van Waesberghe JHTM, Barkhof F, van Oosten BW, Hommes OR, Polman CH. **Accumulation of hypointense lesions ("black holes") on T1-weighted images of multiple sclerosis patients correlates with disease progression in secondary progressive MS patients.** *Neurology* 1996;47:1468–1476
8. Gass A, Barker GJ, Kidd D, et al. **Correlation of magnetization transfer ratio with clinical disability in multiple sclerosis.** *Ann Neurol* 1994;36:62–67
9. van Buchem MA, McGowan JC, Kolson DL, et al. **Quantitative volumetric magnetization transfer analysis in multiple sclerosis: estimation of macroscopic and microscopic disease burden.** *Magn Reson Med* 1996;36:632–636
10. van Buchem MA, Udupa JK, McGowan JC, et al. **Global volumetric estimation of disease burden in multiple sclerosis based on magnetization transfer imaging.** *AJNR Am J Neuroradiol* 1997;18:1287–1290
11. Lycklama à Nijeholt GJ, van Walderveen MAA, Castelijns JA, et al. **Brain and spinal cord abnormalities in multiple sclerosis: correlations between MR parameters, clinical subtypes amd symptomatology.** *Brain* 1998;121:687–697
12. Brück W, Bitsch A, Kolenda H, et al. **Inflammatory central nervous system demyelination: correlation of magnetic resonance imaging findings with lesion pathology.** *Ann Neurol* 1997;42:783–793
13. Filippi M, Campi A, Dousset V, et al. **A magnetization transfer imaging study of normal appearing white matter in multiple sclerosis.** *Neurology* 1995;45:478–482
14. Loevner LA, Grossman RI, Cohen JA et al. **Microscopic disease in normal appearing white matter on conventional MR images in patients with multiple sclerosis: assessment with magnetization-transfer measurements.** *Radiology* 1995;196:511–555
15. Lycklama à Nijeholt GJ, Barkhof F, Scheltens Ph, et al. **MR of the spinal cord in multiple sclerosis: relation to clinical subtype and disability.** *AJNR Am J Neuroradiol* 1997;18:1041–1048