ORIGINAL CONTRIBUTION

Normal-Appearing Brain T1 Relaxation Time Predicts Disability in Early Primary Progressive Multiple Sclerosis

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Objective: To investigate whether patients with early primary progressive multiple sclerosis show changes in T1 relaxation time (T1-RT) in normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM) during 2 years and whether T1-RT at baseline predicts disability.

Methods: Twenty-one patients and 12 control subjects were studied at baseline and after 2 years. Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores were assessed. T1 relaxation time histograms of NAWM and NAGM were obtained in all subjects, and mean, peak height, and peak location of the histograms were measured. Paired *t* tests were used to compare baseline and 2-year histogram values in patients and control subjects. To investigate whether T1-RT predicted clinical changes, multiple linear regression analysis was used.

Results: Patients showed increases in NAWM and NAGM T1-RT mean and peak location during follow-up, and significant decreases in NAWM and NAGM peak height. Baseline NAWM T1-RT mean values and peak height predicted disability at 2 years, as measured with the Multiple Sclerosis Functional Composite score.

Conclusion: T1 relaxometry is a good marker of disease progression and has prognostic potential in primary progressive multiple sclerosis.

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Nonconventional quantitative magnetic resonance (MR) imaging measures in multiple sclerosis (MS) correlate with disability better than do conventional MR imaging measures. Among conventional measures, T1 lesion load has a stronger relationship to disability than does T2 lesion load[1] and reflects axonal loss and matrix destruction.[2] In addition to T1 lesion load, whole brain T1 relaxation time (T1-RT) can be mapped. The T1-RT reflects the amount of free water, and, therefore, pathologic processes such as edema, inflammation, gliosis, and axonal loss that cause increased extracellular space lead to an increase in T1-RT. Changes in normal-appearing (NA) brain tissues contribute to disability in MS,[3] and histogram analysis of T1-RT in the NA brain tissues enables us to examine pathologic change outside of lesions and to improve clinicoradiologic correlations.

Previous cross-sectional studies of NA white matter (NAWM) T1-RT reported increased T1-RT in patients with relapsing remitting MS (RRMS) and secondary progressive MS (SPMS) compared with control subjects.[4-6] Two longitudinal studies of T1-RT in both NAWM and NA gray matter (NAGM) have been published. The first study by Parry et al[7] detected a decrease in T1-RT in both the total white matter and neocortical gray matter in RRMS and SPMS. The second study, from Davies et al,[8] did not find significant changes in T1-RT histogram measures for either NAWM or NAGM in patients with early RRMS. To our knowledge, no longitudinal study of primary progressive MS (PPMS) has been performed to date. Therefore, we investigated a homogeneous cohort of patients with PPMS within 5 years of disease onset. Primary progressive MS is a subtype of MS in which prognosis is generally poor; however, the rate of progression differs among patients.[9] We hypothesized that patients who demonstrated more deterioration at 2 years have greater changes in NA brain tissue T1-RT measures at baseline.

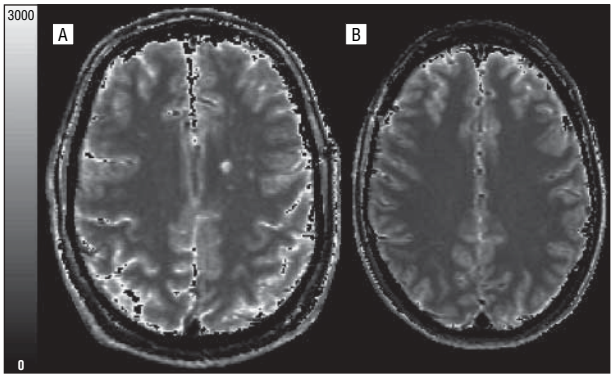

Figure 1. T1 mapping in patients (A) and control subjects (B).

The purposes of this study were to investigate whether T1-RT differs in patients with early PPMS compared with control subjects, whether T1-RT changes during 2 years in patients with NAWM or NAGM, whether this change correlates with progression of disability with time, and whether NAWM and NAGM T1-RT at baseline predict clinical outcomes at 2 years.

METHODS

SUBJECTS

Twenty-one patients with PPMS (11 men and 10 women; mean age, 44 years [age range, 26-56 years] and mean disease duration, 3.0 years [range, 2-5 years]) and 12 control subjects (6 men and 6 women; mean age, 34 years [age range, 27-52 years]) were studied at baseline and after 2 years. Patients with PPMS[10] and clinical progression for less than 5 years were enrolled at the National Hospital for Neurology and Neurosurgery and other hospitals in southeast England. The study was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology; all subjects gave informed written consent.

Patient Expanded Disability Status Scale (EDSS) was calculated at each time point.[11] A 1-step deterioration was defined as an increase of 1 if the EDSS was 5 or less or as an increase of 0.5 if it was greater than 5. The Multiple Sclerosis Functional Composite (MSFC) subtests (9-hole peg test, timed 25-ft walk test [TWT], and Paced Auditory Serial Addition Test) were also performed. Mean *z* scores were obtained for each subtest and used to calculate MSFC score using our own sample as a reference.[12] One patient at baseline and 3 patients at 2 years were too disabled to complete the TWT and were scored with the maximum time allowed for that test (180 seconds).[13]

MR IMAGING

The following MR images were acquired with a 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, Wis):

1. Dual-echo, fast spin-echo; echo time 1/echo time 2/repetition time, 19/95/2000 ms; number of signals acquired, 1; and field of view, 24×24 cm, with three quarter field of view in the phase-encoding direction
2. Proton-density–weighted gradient-echo; echo time/relaxation time, 1/1500 ms; flip angle, 45°; number of signals acquired, 1.5; and field of view, 24×24 cm
3. T1-weighted gradient-echo; echo time/relaxation time, 11/50 ms; flip angle, 45°; number of signals acquired, 3; and field of view, 24×24 cm

All images were acquired at the same 28 axial locations with a matrix size of 256×256 pixels, giving a reconstructed resolution of 0.94×0.94 mm^2; the section thickness was 5 mm.

Once acquired, the images from sequence 1 were registered to those from sequence 2 using the Automated Image Registration package (version 3.08; http://bishopw.loni.ucla.edu/AIR).[14] In addition, the images from sequence 3 were registered to those from sequence 2 using a mutual information algorithm.[15] Lesions were then contoured using a local thresholding technique[16] on the registered T2-weighted images by an observer (F.M.) blinded to the patient data (coefficient of variation, 2.5%). The lesion mask was then used to exclude lesions in the images from sequence 2, which was segmented into NAWM and NAGM using statistical parametric mapping 2 (SPM2; Wellcome Department of Cognitive Neurology, London, England). Similar segmentation of sequences in the control subjects produced segments of normal white matter and normal gray matter. These segments were then eroded by 1 pixel to reduce the effect of partial volume. Maps of T1 (**Figure 1**) were then produced from sequences 2 and 3 using the validated method of Parker et al.[17] Random noise was added to the raw data to prevent spikes in the histograms.[18] The white and gray segments obtained were then used as masks to produce T1 maps of the 2 tissues, from which T1 relaxation histograms of NAWM and NAGM or normal white and normal gray matter were calculated.

The histograms were normalized for brain volume and had a bin width of 1 millisecond; a 7-millisecond moving average window was used to smooth the histograms. Mean T1 relaxation values, peak height, and peak location were then extracted from each histogram.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software (version 11.5; SPSS Inc, Chicago, Ill). The Wilcoxon signed rank test was used to compare baseline and 2-year clinical changes in scores on the EDSS, and the MSFC and its subtests. A multiple linear regression model was used to compare differences in histogram measures between patients and control subjects at baseline and at 2 years, adjusting for age and sex. The paired *t* test was used to compare baseline and 2-year histogram values within the patient and control groups. The Spearman correlation coefficient was used to assess the relationship between histogram changes and clinical changes. Multiple linear regression analysis was used to investigate whether T1 relaxation histogram measures of NAWM and NAGM at baseline predict scores for the EDSS and the MSFC and its subtests at 2 years, correcting for age and sex. $P<.05$ was considered significant.

RESULTS

CLINICAL CHANGES

There was borderline statistical significance in the median EDSS score changes between baseline and 2 years (4.5 vs 6.0; $P=.06$). Twelve patients (57%) had at least 1-step deterioration on the EDSS, 8 patients (38%) showed no change, and 1 patient (5%) improved by 1 step. Although mean MSFC score decreased at 2 years, this was not statistically significant, and only the TWT mean *z* score decreased significantly with time (0.004 vs −0.88; $P<.001$).

Table 1. Comparisons of T1-RT Histogram Measures Between Control Subjects and Patients, and Changes in Patients at 2 Years

T1-RT Histogram Measure	Baseline			2 Years			Changes in Patients During 2 Years
	Control Subjects	Patients	*P* Value	Control Subjects	Patients	*P* Value	*P* Value
NAWM							
Mean	652	734	.009	657	881	<.001	.002
Peak height	0.009	0.007	<.001	0.008	0.006	<.001	.006
Peak location	629	646	.79	637	707	.02	.02
NAGM							
Mean	1140	1227	.02	1130	1438	<.001	.004
Peak height	0.002	0.002	.03	0.002	0.002	.003	.004
Peak location	1120	1179	.35	1127	1291	.005	.03

Abbreviations: NAGM, normal-appearing gray matter; NAWM, normal-appearing white matter; RT, relaxation time.

COMPARISONS BETWEEN PATIENTS AND CONTROL SUBJECTS, AND CHANGES DURING 2 YEARS

At baseline, NAWM and NAGM T1-RT mean was significantly higher and peak height was significantly lower in patients than in control subjects, and peak location was not significantly different (**Table 1**). At 2 years, NAWM and NAGM mean difference between the groups became more prominent, and peak height remained significantly lower and peak location became significantly higher in patients. No significant T1-RT changes between baseline and 2 years were found in control subjects, whereas patients showed significant changes in all histogram measures, causing the histogram shapes to broaden, flatten, and shift toward the right (**Figure 2**).

CORRELATIONS BETWEEN T1-RT CHANGES WITH TIME AND CLINICAL CHANGES

Significant correlations between NAWM T1-RT changes and clinical changes were found (**Table 2**). An increase in NAWM mean and peak location during 2 years correlated with a decrease in TWT mean *z* score and an increase in the EDSS score, and a reduction in NAWM peak height correlated with a decrease in TWT mean *z* score and an increase in the EDSS score. Similar correlations were found between NAGM and clinical changes.

PREDICTIVE VALUE OF BASELINE T1-RT MEASURES

Higher NAWM mean and lower peak height at baseline predicted greater EDSS, lower MSFC, and lower TWT mean *z* score at 2 years (**Table 3**). There was no association between NAGM measures at baseline and disability at 2 years.

COMMENT

This study demonstrates that T1-RT changes are noted during 2 years in the early stages of PPMS and are clinically meaningful. Baseline T1-RT predicted disability at 2 years.

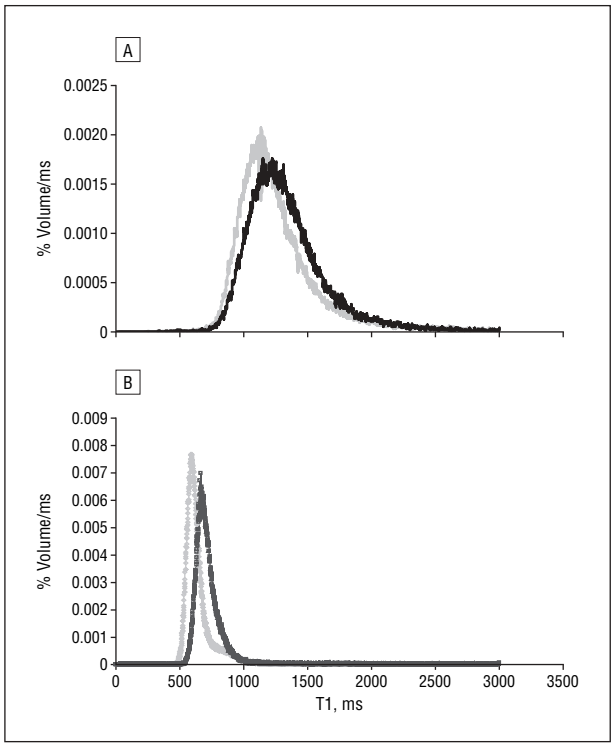

Figure 2. Averaged histograms of normal-appearing gray matter (A) and normal-appearing white matter (B) in patients. Baseline histograms are shown in gray; 2-year histograms, in black.

COMPARISONS BETWEEN PATIENTS AND CONTROL SUBJECTS

There were differences in NAWM and NAGM mean and peak height between patients and control subjects at baseline, whereas NAWM and NAGM peak location differed between groups only at 2 years. This suggests that mean and peak height are the most sensitive detectors of pathologic changes in NA brain tissues in early PPMS and that peak location becomes a sensitive marker as the disease progresses.

Table 2. Significant Correlations Between T1-RT Histogram Changes and Clinical Changes During Follow-up

	TWT Mean *z* Score		EDSS Score	
T1-RT Histogram Measure	*P* Value	*r* Value	*P* Value	*r* Value
NAWM				
Mean	.005	–0.67	.001	0.67
Peak height	.02	0.50	.006	–0.58
Peak location	.01	–0.54	.002	0.63
NAGM				
Mean	.025	–0.49	.001	0.68
Peak height	.003	0.61	.002	–0.64
Peak location	.01	–0.54	.005	0.63

Abbreviations: EDSS, Expanded Disability Status Scale; NAGM, normal-appearing gray matter; NAWM, normal-appearing white matter; RT, relaxation time; TWT, timed 25-ft walk test.

Table 3. T1-RT Histogram Measures at Baseline That Significantly Predict Clinical Outcome at 2 Years

	2-Year Follow-up					
	TWT Mean *z* Score		MSFC Score		EDSS Score	
T1-RT Histogram Measure	*P* Value	r^2 Value	*P* Value	r^2 Value	*P* Value	r^2 Value
NAWM at baseline						
Mean	.04	0.24	.04	0.25	.03	0.28
Peak height	.002	0.51	.04	0.22	<.001	0.58

Abbreviations: EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; NAWM, normal-appearing white matter; RT, relaxation time; TWT, timed 25-ft walk test.

T1-RT CHANGES DURING 2 YEARS

All T1-RT histogram measures in both NAWM and NAGM significantly changed in 2 years in patients (ie, increased mean and peak location and decreased peak height) but not in control subjects. For NAWM, our results were different from those reported by Parry et al,[7] who studied 4 patients with SPMS and 9 with RRMS for a median of 19.5 months using a 3-T scanner and found only a reduction in peak height. This discrepancy might be because we studied a homogeneous cohort of patients with early PPMS using a 1.5-T MRI scanner, where T1 is shorter and, therefore, the same absolute change corresponds to a larger percentage of baseline T1,[19] and performed a slightly longer follow-up. Our results also differ from those reported in our early cohort with RRMS,[8] who, although analyzed with a similar method, showed stable abnormalities in T1-RT histogram measures during a mean follow-up of 26 months. This supports the hypothesis that progressive subtypes of MS show greater abnormalities in T1-RT and a more marked change with time when compared with RRMS, reflecting greater damage to NA tissues.[6]

In our study, NAGM included both the cortex and the deep gray matter. Although caution should be used in interpreting the 2 studies because different techniques were used and different types of patients were studied, Parry et al[7] found increased T1-RT mean values in the thalamus of patients with SPMS and decreased mean T1-RT in the neocortical gray matter in patients with SPMS or RRMS.[7] Davies et al[8] did not detect longitudinal changes in the NAGM in patients with early RRMS. This difference is again mainly owing to the different subtypes of patients and different underlying pathologic processes.

T1 abnormalities in NAWM and NAGM likely reflect pathologic processes that occur in these tissues, such as inflammation, gliosis, and axonal loss.[2] Therefore, T1-RT might prove to be a sensitive and comprehensive measure of tissue damage that can readily be determined in any MR imaging center and be quantified with an automated method. However, it does not provide pathologic specificity because it is impossible to differentiate an increase in water content from inflammation or tissue matrix loss. We are performing a multiparametric analysis in this cohort of patients to investigate whether a combination of measures is more sensitive in assessing disease progression. The finding of similar changes in NAWM and NAGM are in agreement with those reported in PPMS using different MR imaging techniques such as magnetization transfer imaging and diffusion.[20]

A possible limitation of our study is that we did not measure the progression of atrophy during follow-up. In theory, a reduction in brain volume could cause an increase in T1 values because of the contribution of pixels at the brain–cerebrospinal fluid interface. However, we believe we can be confident about our results because during the segmentation we eroded the brain segments by 1 pixel to reduce this partial-volume effect and normalized the individual histograms by brain volume.

CORRELATIONS BETWEEN T1-RT CHANGES WITH TIME AND CLINICAL CHANGES

The T1-RT increase in the NAWM and NAGM in patients with early PPMS was associated with greater disability, as measured with the EDSS, and, in particular, with reduced ability to walk, as measured using the TWT, during follow-up. This suggests that T1-RT might be a marker of disease progression in PPMS. In our cohort, lower limb function was the only clinical variable to deteriorate significantly, and the deterioration in walking is reflected in the higher EDSS score at 2 years (EDSS is weighted toward locomotor disability). This is not surprising if we consider that most patients had a spinal cord syndrome at onset, and their walking ability deteriorated. In addition, the Paced Auditory Serial Addition Test and 9-hole peg test are sensitive to training effects[21] that may have occurred in our cohort, masking some of the clinical deterioration.

PREDICTIVE VALUE OF BASELINE T1-RT MEASURES

Higher T1-RT mean values and lower peak height of NAWM at baseline were moderate predictors of future disability. The EDSS and TWT scores were the clinical measures best predicted by NAWM mean and peak height, and this is relevant because in our cohort the disability with time mainly involved walking ability. This result suggests that T1-RT enables early detection of the pathologic process that will have an effect on future disability. Although the NAGM changes mirrored the NAWM at baseline, NAGM histograms did not show any predictive value, perhaps because the NAWM damage has a greater clinical effect on the progression of locomotor function than gray matter changes do.

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