Long-T_2 Imaging: Evidence of a New Water Reservoir in Multiple Sclerosis

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Introduction

In normal human white matter, water protons can be separated into three pools based on their T_2 relaxation times [1,2]. The longest T_2 component (2s) is due to cerebrospinal fluid, an intermediate component (80-100ms) arises from intra/extracellular (IE) water and the shortest T_2 component (20ms) is due to water trapped between the myelin bilayer (myelin water). Previous T_2 relaxation work in multiple sclerosis has shown abnormalities in the T_2 distribution in terms of total water content and myelin water fraction (MWF) for both normal appearing white matter (NAWM) and lesions [3]. Two previous studies using spectroscopy [4] and multi-echo T_2 relaxation (TE=30ms) [5] reported the presence of an additional longer T_2 component in MS lesions. The purpose of this study was to better define the T_2 distribution in MS lesions and NAWM with particular emphasis on identifying potential long T_2 components, by lengthening the total acquisition time of the multi-echo T_2 relaxation sequence from 320ms to 1.120s, with the ultimate aim being to better characterize lesions on the basis of their pathology.

Methods

Subject Information: Twenty subjects with clinically definite MS underwent MR examinations (14 relapsing-remitting, 3 secondary-progressive, 2 relapsing-progressive, 1 benign; 15 female, 5 male; median EDSS = 2.5 (range 1.0-8.0); mean age = 38yrs (range 23-54yrs); mean disease duration = 10.5yrs (range 1-35yrs)).
MR Experiments: MR experiments were conducted on a 1.5T GE Echo Speed scanner operating at the 5.7 software level. Localizers, proton density and T_2 images (TR 2500 ms, TE 30/80 ms) were followed by a 48 echo modified Carr-Purcell-Meiboom-Gill (CPMG) sequence with variable TR, consisting of a 90° slice selective pulse followed by 48 rectangular composite 180° pulses flanked by slice-selective crusher gradient pulses for elimination of stimulated echoes [6]. For the CPMG T_2 relaxation measurement, a single transverse slice was acquired (TR = 2120-3800ms, TE = first 32 echoes @ 10ms, last 16 echoes @ 50ms, 5 mm thick, 256×128, 4 averages). A post Gd-DTPA T_1-weighted spin echo series (TR 550ms, TE 8ms, 22 slices, matrix 256x192) was also collected.
Data Analysis: Regions of interest (ROIs) were outlined around lesions and contralateral NAWM. T_2 relaxation decay curves were decomposed into an unspecified number of exponentials using a regularized non-negative least squares algorithm using 120 input relaxation times spaced logarithmically from 15ms to 2s [7]. Both χ^2 and solution roughness were minimized such that χ^2 fell between 1.02 and 1.025 times the minimum χ^2 from the non-regularized least-squares solution. Results were displayed as a T_2 distribution plot of component amplitude as a function of T_2. Geometric mean T_2 (GMT_2) and peak width (analogous to the variance on a logarithmic scale) of the IE component from 50ms to 200ms and the potential Long-T_2 component from 200ms-800ms were calculated. The MWF was defined as the fraction of the T_2 signal below 50ms relative to the total signal in the T_2 distribution. Similar to the MWF, a "Long-T_2" component fraction was calculated by dividing the T_2 signal between 200 and 800 ms by the total signal in the T_2 distribution. MWF and Long-T_2 maps were created for each subject by calculating the fraction of each component for every pixel in the image. Statistical analysis was carried out using a two-tailed Student's t test with a p value of <0.05 considered significant. All errors are expressed as standard errors.

Results

A total of 92 lesions and 92 contralateral NAWM areas were examined in the 20 subjects with MS. On average, MWF for all lesions was 0.046 (0.004), 39.2% less ($p<0.0001$) than average NAWM MWF, 0.076 (0.006). IE GMT_2 for all lesions was on average 119ms (3ms), 38.5% longer ($p<0.0001$) than average NAWM GMT_2, 86ms (1ms). The average width of the IE peak for lesions was 0.17 (0.04), 40% wider (not significant, $p=0.16$) than average NAWM peak width of 0.12 (0.02). Signal from a Long-T_2 peak between 200ms and 800ms was identifiable in 28 lesions from 11 subjects. The average MWF of those Long-T_2 lesions was 0.039 (0.007), less, although not significantly different ($p=0.14$) from, the average MWF of those 64 lesions which had no Long-T_2 component 0.049 (0.004). The average IE GMT_2 for Long-T2 lesions was 132ms (6ms), longer ($p=0.0009$) than the average IE GMT_2 of the lesions with no Long-T_2 signal, 113ms (2ms). The average GMT_2 of the Long-T_2 peak itself was 280ms (23ms). A wide heterogeneity was observed in Long-T_2 peak fraction for each lesion, with a median value of 0.076 (0.058). A Long-T_2 peak (average fraction 0.029 (0.011)) was also observed in 3 NAWM areas in 2 different subjects. Of the 92 lesions, 5 were gadolinium enhancing. 2 of the 5 enhancing lesions showed a Long-T_2 peak and average values for MWF, IE GMT_2 and peak width were not different from non-enhancing lesions. Figure 1 shows a PD, Gad-T_1, myelin map and Long-T_2 map for an MS patient with an enhancing lesion. Three ROIs with corresponding T_2 distributions are shown for the enhancing core of the lesion, non-enhancing periphery and NAWM. Figure 2 shows images from 2 other subjects demonstrating the Long-T_2 component.

Conclusions

Our goal was to better characterize the T_2 distribution in MS white matter. As expected, decreased myelin water, increased GMT_2 and increased peak width of the intra/extracellular (IE) peak were observed in MS lesions. Of particular interest, a new water reservoir with a markedly prolonged T_2 peak (200-800ms) was also identified in 30% of lesions and several NAWM regions. This peak is possibly due to increased extracellular water and has also been identified in PKU [8]. Those lesions with a Long-T_2 peak also exhibited longer IE GMT_2 than those lesions without a Long-T_2 signal.

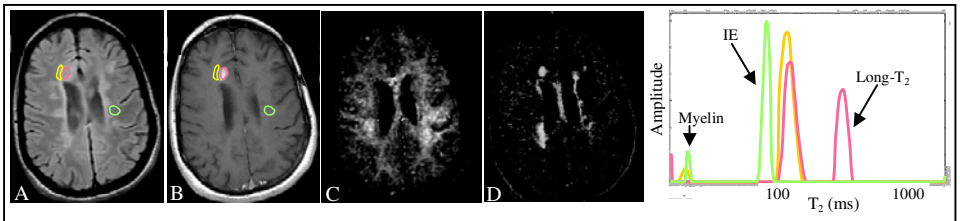

Figure 1 – (A) PD, (B) Gad-T_1, (C) myelin map and (D) Long-T_2 map for an MS patient with an enhancing lesion. Three ROIs with corresponding T_2 distributions are shown: enhancing core of lesion (pink), non-enhancing periphery of lesion (yellow) and NAWM (green)

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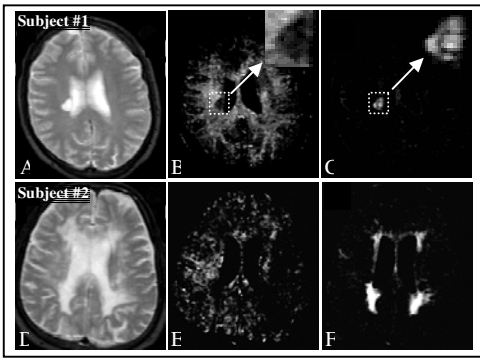

Figure 2 – Two more MS patients demonstrating the Long-T_2 component: (A) and (D) show T_2 weighted images; (B) and (E) show myelin water maps; (C) and (F) show Long-T_2 maps. Insets in B and C show a larger view of the lesion of interest for subject #1. Note the ring like appearance of the lesion. Extensive demyelination and Long-T_2 signal is observed in subject #2.