Quantitative DCE ^1H_2O R_1 Measurements Suggest Increased Fractional Blood Water in MS Normal Appearing Brain Tissue

J. M. Njus[1], L. Vigeland[1], X. Li[1], C. S. Springer[1], M. Taylor[2], F. W. Telang[3], P. K. Coyle[2], and W. D. Rooney[1]

[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, [2]Neurology Department, Stony Brook University, Stony Brook, New York, United States, [3]Medical Department, Brookhaven National Laboratory, Upton, New York, United States

Introduction

It is well known from ^1H_2O T_1 studies of subjects with multiple sclerosis (MS) that mean T_1 values in normal appearing white matter (NAWM) are elevated by about 5% with respect to healthy control (HC) subjects.[1-4] Likewise, ^1H_2O T_1 studies have reported increases of about 3% in MS normal appearing gray matter (NAGM) T_1 values,[3,4] though this increase may be due, primarily, to the women MS subjects.[4] The relatively greater T_1 values in MS NAWM and NAGM likely reflect an increased water to macromolecule ratio,[5] and may be associated with microscopic disease activity; such as diffuse inflammation and subtle edema. However, it is unclear whether this disease related rise in the fractional water of MS brain tissue represents an increase in the intravascular or extravascular compartments. Because angiogenesis likely occurs in MS lesions,[6] it may also occur microscopically in NAWM and NAGM. Insight into the extent or absence of increased vascular water content (via microscopic angiogenesis or vasodilatation[7]) in normal appearing MS brain tissue can only aid in the determination of appropriate treatment strategies.[6] In this report, we examine possible disease and sex related differences in fractional blood water (p_b) of 15 MS and 12 HC subjects by comparing mean NAWM and NAGM ^1H_2O R_1 (i.e. $1/T_1$) values with, and without, contrast reagent (CR).

Methods

12 HC subjects [7 W, mean age 33 (±12) y, and 5 M, mean age 33 (±9) y] and 15 MS subjects [8 W, mean age 35 (±7) y, and 7 M, mean age 40 (±8) y] provided informed consent before participating in this study. All MR data were obtained using a 4 T Varian INOVA instrument. The experimental details pertaining to data collection and quantitative R_1 mapping are as reported elsewhere.[4] R_1 maps were collected prior to, and seven min. after, CR injection (i.e. time between the injection and acquisition midpoints). A catheter placed within an antecubital vein was used to deliver 0.3 mmol/kg GdHPDO3A (Gadoteridol, Pro-Hance; Bracco) using a power injector (Spectris MR Injection System, MedRad, Inc.; Indianola, PA, USA). Bilateral regions of interest (ROIs) were carefully selected from the interior areas of three NAGM [putamen, thalamus, and the head of caudate nucleus] and five NAWM [centrum semiovale, genu of corpus callosum, splenium of corpus callosum, forceps major, and forceps minor] structures. All R_1 values and standard deviations (SD) are given in units of sec^{-1}. Fractional blood water values (p_b) were determined from the following equation for two-site-exchange[8] (transendothelial) and assuming no CR extravasation (i.e. K^{trans} is effectively zero):

$$R_{1t}(t) = \left(\frac{1}{2}\right)\left\{\left[R_{1b}(t) + R_{1e} + \tau_b^{-1} + \frac{p_b}{\tau_b(1-p_b)}\right] - \left[\left(R_{1e} - R_{1b}(t) - \tau_b^{-1} + \frac{p_b}{\tau_b(1-p_b)}\right)^2 + \frac{4p_b}{\tau_b^2(1-p_b)}\right]^{\frac{1}{2}}\right\} \quad (1)$$

where

$$R_{1e} = \frac{(R_{1t}(0) - p_b R_{1b}(0))}{(1-p_b)} \quad (2)$$

$R_1(t)$ is R_1 of normal appearing brain tissue (mean NAWM or NAGM values), and $R_{1b}(t)$ is the R_1 of blood (mean sagittal sinus ROI value),[9] at time t (post-CR injection). $R_1(0)$ and $R_{1b}(0)$ represent the pre-CR injection R_1 values (the latter in the absence of exchange), τ_b^{-1} is the unidirectional first-order rate constant for water extravasation, and p_b is the mole fraction of water in the blood. MATLAB 7.0 (MathWoks Inc., Natick, MA, USA) was used to determine p_b values from Eq. [1] (single-parameter fitting) with τ_b held constant at 300 msec.[10] Statistical analyses were performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). MANOVA was used to estimate the effects of disease and sex (main effects) on mean R_1 and p_b values. All P values were corrected for multiple comparisons. Corrected P values ≤ 0.05 were considered statistically significant.

Results

Group comparisons of mean NAWM and NAGM R_1 and p_b values are listed in **Table 1**, and the MANOVA results of these comparisons (including sex) are displayed in **Table 2**. Compared to the HC subjects, we find significantly ($P < 0.05$) decreased mean R_1 values of about 4% in MS NAWM, with similar decreases observed in both men and women. In the women, average R_1 values were decreased by about 4% in MS NAGM, whereas no significant differences were observed in the men, or between the total (both men and women) MS and HC groups. With respect to the HC subject, mean p_b values were significantly greater in MS NAGM by about 20%. The analysis did not reveal any significant sex differences in p_b values.

Discussion

The finding of significant sex-independent and sex-dependent decreases, respectively, in the mean MS NAWM and MS NAGM R_1 values, is similar to our results from a previous study.[4] However, unlike the R_1 values, there are no discernable sex-related differences in p_b values. Furthermore, while there is a significant (~4%) difference in NAWM R_1 values between the MS and HC subjects, there is no significant difference in p_b values; this finding is consistent with the literature.[11] On the other hand, despite not finding a statistical difference between the mean MS and HC NAGM R_1 values, our results indicate a significant increase in MS NAGM p_b values. This is surprising considering that the R_1 differences in NAWM are greater than NAGM.[1-4] The data suggests a notable increase in MS NAGM p_b due to microscopic angiogenesis or vasodilatation, and while similar changes likely take place in MS NAWM (nonsignificant ~13% increase), they appear to be proportionately less than the changes in NAGM. However, because our results are based on the assumption of no CR extravasation and a single, fixed τ_b time constant for both the MS and HC groups, a more thorough analysis of differences in p_b values is necessary to substantiate these results.

Table 1. MS vs. HC group comparisons of mean ^1H_2O R_1 and p_b values.

		HC	MS	% Diff.
		(n = 12)	(n = 15)	HC > MS
R_1 (±SD):	NAWM	1.015 (±0.036)	0.974 (±0.032)	4%
	NAGM	0.692 (±0.022)	0.685 (±0.028)	1%
				MS > HC
p_b:	NAWM	0.013 (±0.003)	0.015 (±0.005)	13%
	NAGM	0.023 (±0.003)	0.027 (±0.007)	20%

Table 2. P-values for Disease (MS) × Sex interactions and main effects.

		MS*Sex	MS	Sex
			P values	
R_1 (sec^{-1}):	NAWM	NS	0.002	0.02
	NAGM	0.04	NS	0.03
p_b:	NAWM	NS	NS	NS
	NAGM	NS	0.04	NS

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