Quantitative T1 Measurements Suggest Sex-Dependent Gray Matter Involvement in MS

J. M. Njus[1], L. E. Vigeland[1], X. Li[1,2], C. S. Springer[1,2], M. Taylor[3], F. W. Telang[2,4], P. K. Coyle[3], W. D. Rooney[1,2]

[1]Advanced Imaging Research Center, Oregon Health and Science University, Portland, Oregon, United States, [2]Chemistry Department, Brookhaven National Laboratory, Upton, New York, United States, [3]Neurology Department, Stony Brook University, Stony Brook, New York, United States, [4]Medical Department, Brookhaven National Laboratory, Upton, New York, United States

Introduction

^1H_2O MRI T_1 mapping offers a precise way to characterize brain tissue *in vivo* and has potential for objective evaluation of intensive and extensive tissue properties. An intensive property of interest in multiple sclerosis (MS) is the tissue water concentration, since an increase in this quantity was found to precede new lesion development by many months.[1] Increased T_1 values in MS normal appearing white matter (NAWM) is an established finding,[2,3] and this could reflect a diffuse subtle edema or altered cellularity possibly related to microscopic disease activity. Although MS is traditionally classified as a white matter disease, gray matter involvement can be significant.[4-6] However, gray matter involvement in MS is difficult to quantify with traditional MRI techniques. Quantitative MR studies of MS normal appearing gray matter (NAGM) have found abnormal ^1H_2O magnetization transfer ratios (MTRs),[7] diffusion coefficients,[7,8] and metabolite concentrations (by water suppressed ^1H MRS).[9] Increased iron deposition in MS gray matter has also been reported.[10] The focus of this study is to determine whether the diffusely increased ^1H_2O T_1 values in MS are localized only to NAWM, or if they also extend into NAGM structures. Since ^1H_2O T_1 values are potentially different between men and women,[11] and with disease expression, we include disease comparisons separately between the sexes.

Methods

16 healthy control (HC) subjects [7 F and 9 M, mean age 33 (±10) y] and 17 MS subjects [10 F and 7 M, mean age 36 (±8) y] provided informed consent before participating in this study. All MR data were obtained using a 4 T Varian INOVA instrument, and employing a head birdcage RF transceiver coil. Quantitative T_1 maps were collected using a multislice inversion recovery (IR) sequence [sampling pulse flip angle (α) < 20°]. Each acquisition sampled a 192×80 matrix over a (192×80) mm^2 FOV. The 26 (3 mm thick) axial slices were centered on the lateral ventricles. The IR was sampled at 16 times (TI) post-adiabatic inversion, and the total acquisition time was 9 min. The voxel signal intensity, S(TI), was fitted to a two-parameter single exponential IR equation using a gradient expansion algorithm and T_1 values were corrected for sampling during IR.[12] ROIs were carefully selected from the interior areas of NAGM [putamen (PN), thalamus (TH), head of caudate nucleus (CH), and cortical gray matter (CGM)] and NAWM [centrum semiovale (CS), genu of corpus callosum (GCC), splenium of corpus callosum (SCC), forceps major (FMAJ), and forceps minor (FMIN)] structures.

Results

The results are summarized in **Table 1**, where regional ^1H_2O T_1 values are compared between HC and MS groups, and includes separate between group comparisons for men and women. The primary comparisons for NAWM and NAGM are summarized in the top two rows. We find T_1 values increased 6% in NAWM of MS compared to HC, with similar increases observed for both men and women. The average NAGM T_1 value was increased 3% in the MS group compared to the HC group, but sex differences are now apparent. The women showed a 5% NAGM T_1 increase, but no increase was found for the men.

Discussion

The finding of increased ^1H_2O T_1 for MS NAGM is consistent with a previous study reporting a similar increase in MS thalamus.[13] Our results suggest that T_1 changes in MS NAGM are sex-dependent. To our knowledge, this is the first report of sex-dependent regional T_1 increases in MS. Elevated T_1 values likely reflect an increased water to macromolecule ratio, perhaps due to edema or altered cellularity, and is consistent with MTR[7] and diffusion findings.[7,8] Increased iron deposition is thought to occur in MS basal ganglia.[10] An increase in iron would likely decrease ^1H_2O T_1 values, contrary to findings reported here. Sex-related differences in regional gray matter atrophy with age have been reported.[14,15] One notable finding is that substantial PN atrophy occurs in men, but not in women.[15] It could be that the main result of MS related damage to NAGM structures in men is decreased volume (an extensive property), whereas in women the main result is diffuse edema or changes in cellularity (an intensive property). These mechanisms are currently being investigated in our laboratory.

Table 1. Summary of average T_1 values (±SD[§]) from ROI analysis.

		All			**Men**			**Women**		
	ROI	**HC (n = 16)**	**MS (n = 17)**	P*	**HC (n = 9)**	**MS (n = 7)**	P*	**HC (n = 7)**	**MS (n = 10)**	P*
NAWM :	All	986 (±41)	1048 (±49)	0.0006	968 (±35)	1030 (±56)	0.0169	1010 (±37)	1061 (±40)	0.0202
NAGM:	All	1536 (±31)	1587 (±62)	0.0062	1543 (±29)	1564 (±81)	0.4828	1528 (±34)	1604 (±42)	0.0013
					Secondary	**Comparisons**				
NAGM:	PN	1424 (±26)	1477 (±64)	0.0046	1432 (±26)	1456 (±82)	0.4137	1414 (±23)	1492 (±49)	0.0014
	TH	1298 (±46)	1334 (±65)	0.0727	1289 (±27)	1295 (±77)	0.8313	1308 (±64)	1361 (±38)	0.0480
	CH	1546 (±37)	1571 (±71)	0.2133	1543 (±41)	1541 (±93)	0.9405	1549 (±35)	1593 (±46)	0.0519
	CGM	1878 (±81)	1967 (±121)	0.0195	1907 (±67)	1963 (±138)	0.3005	1840 (±86)	1969 (±116)	0.0245
NAWM:	CS	1025 (±40)	1093 (±50)	0.0002	1010 (±31)	1074 (±59)	0.0134	1045 (±43)	1107 (±41)	0.0089
	GCC	930 (±49)	985 (±68)	0.0131	910 (±52)	958 (±80)	0.1634	957 (±32)	1007 (±51)	0.0402
	SCC	956 (±51)	1021 (±53)	0.0013	929 (±34)	1002 (±51)	0.0042	990 (±50)	1036 (±53)	0.0985
	FMAJ	1020 (±42)	1097 (±57)	0.0001	1007 (±44)	1089 (±71)	0.0132	1037 (±34)	1104 (±47)	0.0069
	FMIN	999 (±46)	1045 (±51)	0.0120	983 (±39)	1026 (±50)	0.0721	1021 (±48)	1060 (±49)	0.1284

All T_1 values and SDs are given in units of msec * two-tailed *t* test for non-paired data § standard deviation

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