Quantitative T2 Relaxation of White Matter Hyperintensities in Probable Alzheimer Patients

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INTRODUCTION

White matter hyperintensities (WMH) on T_2-weighted images are a common finding in a variety of central nervous system disorders. The physical interpretation of WMHs is challenging, since many different pathologies may produce similar changes in the average transverse T_2 relaxation times, resulting in equivalent T_2-weighted intensities. Quantitative T_2 (qT_2) has been proposed to provide more specific information about brain anatomy and pathology, including the relative sizes of the different water compartments (myelin, intra and extracellular water) [1]. Recent studies have shown that it is possible to distinguish the processes of demyelination and inflammation using qT_2 [2]. The short T_2 component (10-30ms) of the T_2 spectra of white matter scales linearly with myelin content and can be used as a indirect measure of the processes of demyelination or remyelination in the CNS [2]. Conversely, the position of the intra/extracellular (I/EW), long T_2 component (~90 ms in normal appearing white matter, NAWM) is thought to be indicative of processes related to inflammation and/or axonal loss [3]. Alzheimer's disease (AD) is the most common cause of dementia in the elderly. It is a progressive, irreversible neurodegenerative disease that results in a gradual deterioration in cognition, function, and behavior. AD is mostly considered to be a disease of the gray matter because of the presence of amyloid plaques and neurofibrillary tangles. However, damage to white matter tracts may also occur due to Wallerian degeneration accompanying neuronal loss. Additionally, white matter pathology in subjects with probable AD is often visible in the form of WMH on T_2 weighted images [4]. The goal of this study was to determine the underlying pathology of WMH in AD, and is the first attempt in the literature to characterize WMHs in AD and aging subjects using quantitative T_2 techniques.

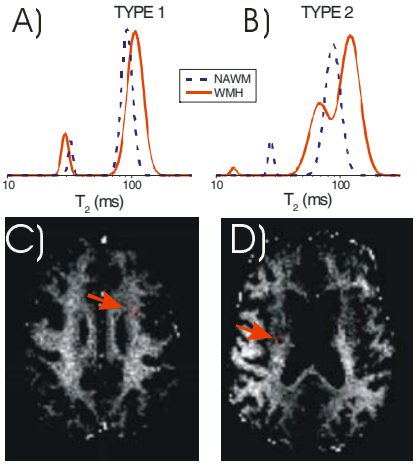
METHODS

WMHs in 3 subjects with probable AD and 4 normal controls were studied. AD subjects met the NINCDS-ADRDA [5] criteria for probable AD. Normal controls had no previous history of neurological or psychiatric disease, and no memory complaints. MRI was performed on a 1.5T GE Signa. A set of axial proton density (PD) and T_2-weighted images were simultaneously acquired (TR 2500ms, TE 30/80ms, BW 10.42/5.68, matrix 128x128, FOV 24cm, slice thickness 4mm, NEX 0.5) to determine the locations of WMH. A single slice, qT_2 pulse sequence was used (TE=10ms, matrix 128x128, FOV 24cm, slice thickness 4mm, NEX 6, 96 echoes collected). Analysis of the T_2 relaxation decay curves was performed using the Gaussian model of T_2 decay [6, 7]. This model assumes that the T_2 spectrum has three different components, each with a Gaussian distribution on a logarithmic time scale. The T_2 spectrum shows the relative signal amplitude per logarithmic interval as a function of T_2 relaxation. As a single-parameter summary of the T_2 spectra, an average T_2 relaxation time, $\langle T_2 \rangle$, was also calculated. Regions of normal appearing white matter (NAWM) and WMH were chosen for all subjects. The typical ROI consisted of ~10 voxels. In most cases, the NAWM ROI was located in the same anatomical location as the WMH, but in the contralateral hemisphere. If this was not possible, the ROI was placed in frontal or adjacent NAWM. For the WMH, the ROIs included approximately 90% of voxels in focal WMHs, and a similar number of PVH voxels were analyzed. Additionally, the T_2 spectra were calculated for each voxel providing myelin maps, where voxel intensity is related to the area of the short T_2 component or myelin water fraction (MWF).

RESULTS

In NAWM, the MWF (8 ± 1%) and location of the I/EW component (90 ± 4 ms) were similar in all subjects. Based on the appearance of the T_2 spectra, two different types of WMH were identified (Fig.1). Type 1 WMHs exhibited a MWF on the order of 10%, and a single I/EW component (Fig.1a). Type 2 hyperintensities were characterized by a very small MWF (less than 3%), and a splitting of the I/EW component into two peaks (Fig.1b). Type 1 WMHs were observed only in normal control subjects, while Type 2 WMHs were observed in all AD subjects and in two NC subjects,

Subject	NAWM			WMH			
NC	MWF [%]	Long T2 position [ms]	<T2> [ms]	MWF [%]	Long T2 position [ms]	<T2> [ms]	WMH type
1	9 ± 1	92 ± 1	87 ± 1	11 ±1	106 ± 1	98 ± 1	1
2	8 ± 1	85 ± 1	79 ± 1	12 ± 1	95 ± 1	112 ± 1	1
2				9 ± 1	165 ± 1	153 ± 1	1
3	9 ± 1	95 ± 1	90 ± 2	1 ± 1	135 ± 2	134 ± 2	2
4	8 ± 2	93 ± 1	87 ± 1	10 ± 1	102 ± 1	95 ± 1	1
4				0	108 ± 9	107 ± 9	2
AD							
5	10 ± 1	91 ± 1	85 ± 1	1 ± 1	141 ± 32	139 ± 32	2
6	6 ± 1	87 ± 1	83 ± 1	1± 1	106 ± 34	105 ± 34	2
6				2 ± 1	220 + 15	216 ± 15	2
7	9 ± 1	88 ± 1	82 ± 1	2 ± 2	99 ± 11	98 ± 11	2



DISCUSSION

The results of this study demonstrated that similar looking WMHs may represent different pathologies. The Type 1 WMH seen in the normal control subjects were the result of inflammation only. Their T_2 spectra showed amounts of myelin comparable to those seen in regions of NAWM. The hyperintense appearance was the result of a rightwards shift in the I/EW component, indicative of inflammation. The small within-subject variability (<1%) for both NAWM and WMH in these subjects indicates homogeneous tissue compartments within the ROI, and the normal-appearing shape of the I/EW component suggests a single mechanism for the shift in I/EW T_2. The Type 2 WMH seen in all three subjects with a diagnosis of probable AD indicate multiple mechanisms produced the WMH. All showed a decrease in myelin in addition to either inflammation or axonal loss. These changes were also reflected in the myelin water fraction (MWF) intensity maps (Fig.1c.d). This type of WMH was also seen in two of the four normal controls. Additionally, the I/EW component appeared to be split into two peaks. The splitting of the I/EW peak into two components has not previously been reported in any animal or human study. Two possibilities are that two different populations of cells experiencing differing degrees of inflammation were measured. Alternatively, it is also possible that in some cases the lower peak reflects a structural difference in the myelin sheath and therefore increased exchange of water between myelin and I/E compartments [8], and thus a very different underlying pathology.

REFERENCES

1) Whittall KP et al MRM, 2002. 47: 403. 2) Odrobina, E. et al NMR in Biomed, 2005. 18:277 3) Stanisz, G. et al MRM, 2004. 51: 473-9.
4) Brun, A et al Ann Neurol, 1986. 19: 253 5) McKhann, G. et al Neurology, 1984. 34: 939 6) Webb, S. et al MRM, 2003. 49: 638 7) Stanisz, G. et al MRM, 1998. 40: 405 8) Stanisz, G. et al MRM, 1999. 42: 112