Increased brain metabolite T_2 relaxation times in patients with Alzheimer's disease

M. Dumoulin[1], E. Zimmerman[2], R. Hurd[3], I. Hancu[4]

[1]McGill University, Montreal, Quebec, Canada, [2]Albany Medical College, Albany, NY, United States, [3]GE Healthcare Technologies, Menlo Park, CA, United States, [4]GE Global Research Center, Niskayuna, NY, United States

Introduction

Many *in vivo* magnetic resonance spectroscopy studies on Alzheimer's disease (AD) have focused on measuring brain metabolite concentrations. General observations include a decrease in N-acetyl aspartate (NAA) and an increase in myo-inositol (mI) levels [1] of AD patients. In contrast, little attention has been paid to measuring the transverse relaxation times of these metabolites. Studies done at 1.5T to compare metabolite T_2 values in AD patients and controls have been inconclusive; one study found no significant differences between AD patients and normal age-matched controls [2], while another observed a statistically insignificant trend toward longer NAA T_2 values in AD [3]. We present here the results of a large study conducted at 3T on AD patients, mild cognitive impairment (MCI) patients and age-matched normal controls (NC's). T_2 values for NAA, creatine (Cr) and choline (Cho) were computed for all the subjects. Significant differences between the transverse relaxation times were observed between NC's and AD, as well as between NC's and MCI patients. As all of these metabolites reside within cell boundaries, these results offer valuable insight into the evolution of the intracellular environment in neurodegenerative diseases.

Methods

Scanning was performed on a 3T, whole body GE scanner. 40 AD patients (mean age 72.3±10 years), 17 MCI patients (mean age 70.8±7.7 years), and 40 normal controls (mean age 70.5±9.0 years) participated in the study. All the subjects underwent a scanning session, comprised of a whole brain localizer, followed by one PRESS-J MRS acquisition [4]. A total of 128 spectra were collected, with TE values varying from 35ms to 355ms in steps of 2.5ms (2 averages per step). The repetition time for the sequence was 2s. The 2cmx2cmx2cm voxel was located in the posterior cingulate gyrus, following reports about this brain region's early involvement in AD.

Each of the 128 individual spectra was reconstructed in SAGE, and mono-exponential fits were performed to peak height values to obtain T_2 values for NAA, Cr and Cho. A Lorentzian fit was also performed to the unsuppressed water frames to extract water linewidths and T_2's.

T_2 values for water and metabolites were then binned in 3 categories, and analysis for statistical significance was done using one-way ANOVA tests in Minitab 12. Post-hoc corrections were not performed; however, post-hoc adjustments for multiple comparisons could be made by comparing p-values to a Bonferroni adjusted threshold.

Results and Discussion

Mean T_2 values for metabolites and water are shown in Table 1. NAA, Cho, and Cr T_2 values reported here are on the same scale with values reported in the literature [4,5]. Table 2 presents the p values comparing the T_2 values of the three groups studied. Note the significant differences in T_2 values between the AD and the normal control groups for both creatine ($p<0.02$) and N-acetyl aspartate ($p=0.007$). There was also a statistically significant difference ($p<0.02$) in NAA T_2 relaxation times between NC's and patients with MCI. There was no statistically significant difference in T_2 values of the AD and MCI groups ($p>0.05$); choline T_2 values also did not differ between the control and MCI groups ($p>0.05$). Water T_2 values showed no significant difference between AD, MCI, and control patients. The slight decrease in water T_2 values moving from NC's to AD patients is not contradictory to the increases that we see in metabolite T_2 values; the metabolite signals only come from the intracellular space, while the water signal comes from both intra- and extracellular space. The increases in the T_2 relaxation times of the 3 metabolites studied indicate a change in the metabolite environments. More precisely, the intra-neuronal localization of NAA and Cr indicates that the interior of the neuronal cells may be becoming more fluid; Cr can also be found in glial cells, indicating that the intra-glial environment may be undergoing similar changes. Immunohistochemistry studies have shown that activated caspase-3 is localized in vacuoles of AD neurons undergoing granulovacuolar degeneration [6], indicating that the presence of the vacuoles acts to stall the mechanisms of programmed cell death that are activated in AD. The activation of apoptotic pathways accompanied by the compensatory expression of antiapoptotic proteins has also been reported in microglia [7]. Caspases act to cleave many proteins within the cell, including many cytoskeleton proteins, and may do so in AD neurons before being sequestered into vacuoles [6] and in AD glial cells undergoing apoptosis. Rearrangement and disruption of the cytoskeleton of neurons and glial cells would alter their cytoplasmic viscosity, which could account for the observed lengthening of NAA and Cr T_2 values in individuals with AD.

	Creatine T_2 (3.05 ppm)	Choline T_2 (3.24 ppm)	NAA T_2 (2.01 ppm)	H_2O T_2 (4.7 ppm)
Normal	140.80±16.40	176.38±36.67	235.40±23.96	63.51±29.21
MCI	147.06±15.55	182.76±42.72	254.18±33.76	62.75±10.05
AD	151.05±20.72	189.70±42.72	254.05±35.58	60.71±11.20

Table 1. Mean T2 values in milliseconds for *in vivo* creatine, choline, NAA, and water in the posterior cingulate gyrus ± 1 SD

	Creatine	**Choline**	**NAA**	**H_2O**
Normal v AD	**0.016**	0.122	**0.007**	0.543
Normal v MCI	0.186	0.508	**0.016**	0.913
MCI v AD	0.479	0.547	0.99	0.571

Table 2. One-way ANOVA p-values comparing AD, MCI, and normal control T_2 values

Conclusion

The changes in metabolite T_2 values observed in our study provide valuable insight into the progression of Alzheimer's disease on a cellular level. These changes are compatible with a decrease in the viscosity of the intracellular environment. Previous studies have failed to obtain these findings [2,3], but this does not contradict our results due to the higher field strength and larger sample sizes used in this study. Considerable overlap is observed between the three groups of subjects studied; consequently, it is improbable that this measure of disease can lend itself to being a single diagnostic test for AD.

References

1. Valenzuela et al, Neurology **56**:592-598 (2001). 2. Moats et al, Magn Reson Med **32**, 110-5 (1994). 3. Christiansen et al, Magn Reson Imaging; **13**, 457-62 (1995). 4. Hurd et al, Magn Reson Med; **51,** 435-40 (2004). 5. Träber et al, J Magn Reson Imaging; **19**, 537-45(2004). 6. Stadelmann et al, Am J Pathol; **155**, 1459-66 (1999). 7. Streit, J Neurosci Res **77**:1-8 (2004).