Longitudinal Change in ^{1}H MRS Metabolites in Mild Cognitive Impairment and Alzheimer's Disease

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Background:

Non-invasive markers of disease progression are required for determining the effectiveness of putative disease modifying therapies that are under development in Alzheimer's disease (AD). Disease-modifying treatments will be most beneficial for patients who are at the earliest stages of the neurodegenerative process. Because people with amnestic mild cognitive impairment (MCI) have a higher rate of progressing to AD than cognitively normal elderly, MCI is an appropriate clinical group for evaluating neuroimaging markers of early AD pathology (1). MR- based volume measurements of atrophy are potential markers of disease progression in patients with MCI and AD, starting from the pre-clinical stages (2). The longitudinal change in ^{1}H MR spectroscopy (^{1}H MRS) metabolite markers in MCI and AD is not established (3, 4). The objectives of this study were:

1) To determine the longitudinal ^{1}H MRS metabolite changes in people with MCI, and AD;

2) To compare ^{1}H MRS metabolite ratios and ventricular volumes in tracking clinical disease progression in AD.

Methods:

We studied 85 cognitively normal elderly, 49 patients with MCI, and 60 with AD who underwent clinical evaluation, MRI, and single voxel ^{1}H MRS exams two times within a median of 13 months. The ^{1}H MRS voxel was positioned to include the posterior cingulate gyrus and precuneus. Annualized rate of change in ^{1}H MRS metabolite ratios, ventricular volumes, Mini Mental State Examination (MMSE), Dementia Rating Scale (DRS), and Clinical Dementia Rating Sum of Boxes (CDR) scores were measured. Eighteen of the patients with MCI progressed to AD, and 31 of them remained as MCI during follow-up.

Results:

Among patients with MCI and AD, the annual decline in N-acetylaspartate (NAA) /Creatine (Cr) was greater than controls ($p<0.05$) (Table). Controls and patients with MCI who were APOE ε4 carriers had a greater decline in NAA /Cr levels than controls and patients with MCI who were not carriers ($p<0.05$). Choline (Cho) /Cr declined in stable MCIs compared to MCI-converters and controls ($p<0.05$). The decline in NAA /Cr was correlated with the change in DRS and CDR scores in AD subjects about as strongly as the expansion of ventricular volumes ($p<0.05$). Elevation of Cho /Cr was correlated with the decline in DRS in controls and decline in MMSE in AD subjects ($p<0.05$).

Table: Annual percent change in metabolite ratios and ventricular volumes

	Control	All MCI	MCI-stable	MCI-converter	AD
N	85	49	31	18	60
NAA /Cr Mean (SD)	0.8 (4.6)	-1.4 (6.6)*	-1.2 (6.2)	-1.7 (7.4)	-1.8 (6.9)*
Cho /Cr Mean (SD)	2.8 (8.0)	-1.3 (10.8)	-3.7 (10.4)*	2.8 (10.5)	1.4 (9.9)
mI /Cr Mean (SD)	1.8 (8.0)	0.7 (10.1)	0.0 (10.0)	1.7 (10.6)	0.8 (7.6)
Ventricular volume Median (IQR)**	2.4 (1.2, 3.4)	3.1(1.6, 5.8)*	2.6 (1.2, 4.7)	5.0 (3.0, 6.2)*	5.7 (3.1, 8.0)*

* The annual percent change was different from normal ($p<0.05$, ANOVA followed by post hoc between group comparisons)

** Variables that were normally distributed are presented as mean (standard deviation (SD)), variables that were not normally distributed are presented as median (interquartile range (IQR)).

Conclusions:

1) The neuronal integrity marker NAA /Cr declines over time in subjects with MCI and AD. This is in agreement with a previous study showing a higher rate of gray matter NAA decline in AD subjects than controls (3). We identified a similar decline in NAA/Cr levels among MCI-stable, MCI-converter and AD subjects, suggesting a steady decline in NAA/Cr levels starting from the prodromal stages of AD.
2) The decline in NAA /Cr was greater in MCI subjects who were APOE ε4 carriers than noncarriers. A similar trend was present in the control group. APOE ε4 had no effect on the decline in NAA /Cr levels in patients with AD, which may indicate that the decline in NAA /Cr is mediated by APOE ε4 only during the prodromal stages of the disease.
3) The change in ^{1}H MRS metabolite ratios correlate with clinical progression about as strongly as the rate of ventricular expansion, suggesting that both ^{1}H MRS and MR volumetric markers may be equally useful in monitoring drug effects in patients with AD.
4) This study showed for the first time that Cho /Cr levels decline in patients with aMCI who remain stable, but not in patients with MCI who progress to AD, suggesting the presence of a compensatory cholinergic mechanism, that may be failing in those MCI patients who progress to AD. Understanding the possible relationship between the upregulation of choline acetyl transferase and the decline in Cho /Cr in MCI, may have important implications for monitoring compensatory cholinergic mechanisms during early progression of AD as well as other neurodegenerative syndromes such as DLB, that are characterized by cholinergic deficit (5).

References:

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