Annual Decrease in N-acetylaspartate /Creatine Correlates with the Progression of Alzheimer's Disease

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Background and objective: Advances in treatments targeting the pathologic process of Alzheimer's disease (AD) created a need for biologic markers that can accurately measure the effectiveness of therapeutic interventions. Major beneficiaries of disease-modifying treatments will be those patients who are at the earliest stages of the neurodegenerative disease. One such clinically characterized group is people with amnestic mild cognitive impairment (aMCI). Most people with aMCI progress to AD in the future, and therefore can be regarded as having prodromal AD. Brain N-acetylaspartate/creatine (NAA/Cr) levels are decreased, and *myo*-inositol (mI)/Cr is elevated in people with AD. We previously identified elevated mI/Cr levels also in people with aMCI. The objective of the current study was to determine if annual change in ^{1}H MRS measurements correlate with clinical disease progression and neuropsychological measures of cognitive function along the whole spectrum of cognitive performance from cognitively normal elderly to people with aMCI and AD.

Methods: We studied 69 cognitively normal elderly controls 42 patients with aMCI, and 41 patients with AD who underwent a single voxel ^{1}H MRS exam from the posterior cingulate gyri with TR/TE=2000/30ms and a battery of neuropsychological tests annually. Clinical group membership was determined through a comprehensive clinical examination in each subject at baseline and again at annual follow-up visits, creating five clinical groups after longitudinal assessment: Control-stable, control-converter to aMCI, aMCI-stable, aMCI-converter to AD, and patients with AD. All subjects were followed at least one year with an average period of 16±6 months. We also performed ^{1}H MRS scans TR/TE=2000/30ms on a phantom that contained the major brain metabolites in order to determine scanner dependent changes in metabolite measurements. We calculated the annual change in Mini-Mental State Exam (MMSE), Dementia Rating Scale (DRS), Clinical Dementia Rating sum of boxes (CDR), Auditory Verbal Learning Test (AVLT)-delayed recall, Logical Memory subtest of the Wechsler Memory Scale-Revised (LMP) test scores, NAA/Cr, MI/Cr and choline (Cho)/Cr ratios in the five clinical groups (Table). We compared the % annual change in metabolite ratios of the clinical groups using ANOVA and post hoc rank sum tests. The association between the annual change in metabolite measurements and neuropsychological test scores were determined with regression analysis.

Results: Five of the 69 normals converted to aMCI, and 15 of the 42 patients with aMCI converted to AD during follow-up. There was no difference between the average age, male/female ratios of the clinical groups. The interval between the first and second ^{1}H MRS scan was longer in control stables than other clinical groups ($p<0.05$). Annual change in metabolite intensities from the phantom was not significant (paired t-tests $p>0.05$). The annual decrease in NAA /Cr measurements was greater in patients with AD than control-stables ($p=0.004$). A similar trend was observed in control-converters ($p=0.09$), and aMCI converters ($p=0.11$). The % annual change of mI/Cr and Cho/Cr was not different between the groups.

Table: Annualized rates of change (mean ± SD) of ^{1}H MRS metabolite ratios

	Control stable	Control converter	aMCI stable	aMCI converter	AD
N	64	5	27	15	12
NAA /Cr	1.02% ± 4.37%	-1.96% ± 3.29%**	0.35% ± 6.35%	-1.57% ± 6.78%*	-2.33% ± 6.33%***
Cho /Cr	3.96% ± 8.01%	15.40% ± 14.35%	2.15% ± 12.37%	1.87% ± 7.63%	1.35% ± 8.54%
mI /Cr	2.38% ± 8.41%	6.71% ± 8.17%	3.25% ± 9.90%	0.96% ± 10.54%	1.71% ± 7.31%

*Rate of change is different from the rate of change in control stables on rank sum tests *p=0.11, **p=0.09, ***p=0.004.*

In cognitively normal elderly, the annual change in metabolite measurements was not associated with the annual change in MMSE and the neuropsychological test scores. In the whole group of patients who were cognitively impaired, (control-converter, aMCI stable, aMCI converter and AD), annual decrease in NAA/Cr ratios was associated with the annual decrease in DRS and CDR scores (regression analysis $p<0.05$). In patients with AD, annual decrease in NAA/Cr ratios was associated with the annual decrease in DRS and CDR scores, and the annual increase in mI/Cr ratios was associated with the annual decrease in MMSE scores (regression analysis $p<0.05$).

Conclusion: Posterior cingulate gyri NAA/Cr ratios longitudinally decline in people with AD with respect to cognitively normal elderly who are stable. The association between the decline in NAA/Cr ratios and the decline in CDR and DRS test scores across the whole spectrum of cognitive dysfunction from control-converters, to people with aMCI and AD, suggests that serial measurements of NAA/Cr may be a valid bio-marker of disease progression in AD.