Magnetic Resonance Imaging and Spectroscopy Measures of Cognitive Decline in Mild Cognitive Impairment and Alzheimer's Disease Converters.

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Introduction: The early identification of patients with an increased probability of developing Alzheimer's disease (AD) is an important factor in a successful intervention that may slow disease progression. Magnetic resonance imaging (MRI) has identified structural correlates of mild cognitive impairment (MCI) and the development of AD [(1,2,3)]. Changes in cerebral metabolism measured by magnetic resonance spectroscopy (MRS) has identified decreases in the N-acetyl-aspartate (NAA)/creatine (Cr) metabolite ratio that predicts the conversion of MCI to mild AD [(4.5)]. The objective of this study was to compare global brain, white and gray matter volumes as well as cerebral metabolite levels and ratios in tracking cognitive decline in MCI and mild AD converters.

Methods: Twenty MCI and 13 cognitively normal control subjects were classified using the Mini Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scale. Structural 3D T1-weighted MRI images (MPRAGE, TR/TE = 11.4/4.4 ms, 128 slices, 2mm thick slices) and T2-weighted MR images (TR/TE = 4000/120 msec, echo train length of 15, 4 mm thick slices) were obtained on a Siemens Vision 1.5T scanner. Single voxel (STEAM TR/TE/TM = 3000/20/13ms) ^{1}H MRS measurements were taken from the posterior cingulated gyrus (PCG). Whole brain tissue segmentation, volume measurements and tissue segmentation within the MRS voxel were performed using Statistical Parametric Mapping software (SPM5). LCmodel was used to obtain quantitative N-acetylaspartate (NAA), creatine (Cr), choline (Cho), myo-inositol (Ins), and glutamate/glutamine (Glx) metabolite levels and ratios. MCI and control subjects were followed over a 2-year period (2.03 ± 0.6 years) with MRI/MRS studies approximately every 12 months and neurocognitive testing of executive function, word fluency, and episodic memory every 6 months. To account for variations in inter-study duration, cognitive, imaging and spectroscopy measures were analyzed as the annual percent change (APC). Statistical significance was measured using one-way ANOVA. Correlations between MRI, MRS and cognitive data were determined using Pearson partial correlations controlling for age and education. Discriminate analysis was used to determine the accuracy of the MRI or MRS measures associated with the conversion to mild AD.

Results: In the initial study, MCI subjects had significantly lower GM volume, NAA level and NAA/Cho ratio in addition to an increased Cho/Cr metabolite ratio compared to controls ($p < 0.05$). Follow-up MRI/MRS studies showed that subjects that converted to mild AD ($n = 9$) had a significantly lower GM volume and NAA level, compared to controls ($p < 0.05$). Mild AD subjects showed significantly higher APC in CSF volume increase and decrease in NAA and Glx levels, compared to controls ($p<0.05$). Baseline NAA and Glx metabolite levels predicted the conversion to mild AD with a 78% accuracy, which was not improved by the inclusion of GM volume in the analysis. GM, WM and total brain volume measurements predicted the conversion to mild AD with 67% accuracy. While WM volume alone predicted the conversion with a 56% accuracy, the APC in WM volume of MCI subjects was strongly associated with changes in executive function (Boston Naming test, $r = 0.994$, $p = 0.006$ and perseverative errors, $r = 0.981$, $p = 0.019$) and decreasing NAA/Cr ($r = 0.993$, $p = 0.007$), NAA/Cho ($r = 0.9996$, $p = 0.004$) and Glx/Cr ($r = 0.954$, $p = 0.046$) metabolite ratios.

Conclusions: The conversion to AD is associated with an increased rate of GM loss and decreases in NAA and Glx levels, compared to cognitively normal aging adults. Baseline NAA and Glx levels had a higher predictive accuracy than tissue or CSF volume. While tissue volume loss and decreases in cerebral metabolite levels and ratios were not significant in stable MCI subjects, the decrease in WM volume in this population was significantly associated with changes in neurocognitive function, findings not seen in the AD converter group, which may reflect compromised neuronal circuitry resulting from the degeneration of cortical neurons.

References:
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