Whole Brain MR Spectroscopy Study from Patients with Alzheimer’s Disease and Mild Cognitive Impairment

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Purpose
Conventional MR imaging typically shows a marked brain atrophy in patients with Alzheimer’s disease (AD) (1). Brain volume (BV) changes, however, provide a nonspecific estimate of AD pathology. Localized proton MR spectroscopy (1H-MRS) applied to AD previously showed a reduction of N-acetylaspartate (NAA) amounts in several brain regions (2). Such technique is, however, challenged by its limited brain coverage. This limitation might now be overcome by the use of a nonlocalized sequence able to quantify the whole brain NAA (WBNAA) (3). Using such technique, we evaluated the presence and the extent of neuronal loss/dysfunction in patients with AD and mild cognitive impairment to gain an insight into the nature and evolution of these pathologic conditions.

Materials & Methods
We studied 25 patients with clinically probable AD (median Mini-Mental State Examination [MMSE] score: 20; range = 7-24), 11 patients with mild cognitive impairment median MMSE score: 25; range = 22-27) and 16 sex- and age-matched healthy subjects. During a single MR session, the following brain sequences were collected from every subject: a) nonlocalized 1H-MRS pulse sequence based on a four-step cycle of nonselective 180° inversion pulses to obtain WBNAA measurement (5 separate acquisitions); b) dual-echo turbo spin-echo (SE) (TR/TE = 3300/16-98); c) T1-weighted conventional SE (TR/TE = 768/14). Acquisition procedures of the whole brain 1H-MRS were conducted, as extensively described elsewhere (3). Absolute WBNAA amounts (in mmoles) were calculated for each subject by averaging the NAA peak areas obtained from each of the five scans, and, with a replacement phantom method, they were corrected for individual subjects’ BV in order to obtain WBNAA concentrations (mM) (3). The BV was measured on T1-weighted scans using SIENAX (4). The number and the location of macroscopic MR abnormalities were assessed.

Results
In all the studied subjects the macroscopic abnormalities were located mainly in
subcortical regions, without significant differences regarding their number and distribution. The entire cohort of 36 patients, on average, showed significantly lower BV 
(p = 0.02) and WBNAA concentration (p = 0.001) (mean values: 883 ml and 10.8 mM, respectively) than healthy volunteers (mean values: 961 ml and 14.6 mM, respectively). Similar results were found between the subgroup of patients with AD and controls (p < 0.001 for WBNAA concentration and p = 0.01 for BV comparison). Conversely, patients with mild cognitive impairment had a significant reduction of WBNAA concentration (p = 0.003) but no significant differences of BV (p = 0.11) when compared to healthy subjects. No statistically significant difference was found for any of the analyzed quantities between patients with AD and patients with mild cognitive impairment. In the entire group of patients, a moderate correlation between WBNAA concentration and disease duration (r = -0.33; p = 0.05) was found. In patients with AD, WBNAA concentration was correlated significantly to MMSE score (r = 0.40; p = 0.03).

**Conclusion**
This study presents a novel MR approach to assess in vivo the pathology of the brain tissue in AD. Our findings suggest that MR-measurable axonal loss/dysfunction occurs at an early stage in the neurodegenerative process of AD. The magnitude of the reduction of WBNAA concentrations in the patients with mild cognitive disorder might be a strong predicting factor of subsequent clinical evolution to AD.

**References**