A WHOLE BRAIN MR SPECTROSCOPY STUDY FROM PATIENTS WITH ALZHEIMER’S DISEASE AND MILD COGNITIVE IMPAIRMENT

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We studied 25 patients with clinically probable Alzheimer’s disease (AD), 11 with mild cognitive impairment (MCI) and 16 sex- and age-matched controls, using a non-localized proton magnetic resonance spectroscopy to quantify the N-acetylaspartate in the whole brain (WBNAA). Compared to controls, AD patients showed significantly lower brain volumes (BV) and WBNAA concentrations while MCI patients had a significant reduction of WBNAA concentration without significant differences of BV. This suggest that axonal loss/dysfunction occurs at a early stage in AD. The magnitude of the reduction of WBNAA in MCI might be a strong predicting factor of subsequent clinical evolution to AD.

Purpose
Conventional magnetic resonance (MR) imaging typically shows a marked brain atrophy in patients with Alzheimer disease (AD) (1). Brain volume changes provide however a non-specific estimate of AD pathology. Since N-acetylasparate (NAA) is a metabolite almost exclusively closed to neurons, neuronal pathology can be measured by proton MR spectroscopy (1H-MRS) in vivo, which is able to evaluate changes of the NAA.

Localized MRS applied to AD previously showed a reduction of NAA amount in several brain regions (2). The application of localized MRS to AD is however challenged by its limited brain coverage. Such limitation might now be overcome by the use of an unlocalized sequence able to quantify the concentration of NAA in the whole brain (3). Whole brain NAA (WBNAA) measurement represents a novel 1H-MRS approach for the quantification of the presence and extent of neuronal pathology. Aims of the present study were: to quantify the WBNAA concentrations in a group of patients with AD and mild cognitive impairment (MCI), comparing these values to those found in a group of sex- and age-matched controls; to correlate them with brain volume (BV), with the final objective of gaining an insight into the nature of neuronal pathology in AD and MCI, improving our in-vivo monitoring of these pathological conditions.

Method
We studied 25 patients with clinically probable AD (median Mini-Mental State Examination [MMSE] score: 20; range=7-24), 11 patients with MCI (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) 1H-MRS pulse sequence based on a four-step cycle of non-selective 180° inversion pulses to obtain WBNAA measurement; b) dual-echo turbo spin echo (SE) (TR/TE/NEX=3300/16-98/1; number of slices: 24, contiguous, 5-mm thick); c) T1-weighted conventional SE (TR/TE=768/14; number of slices: 24, contiguous, 5-mm thick); d) fluid attenuated inversion recovery (FLAIR) (TR/TE=9999/105; TI=2340 ms; 20, 5-mm-thick, axial slices, interslice gap=0.3 mm). Acquisition procedures of the whole brain 1H-MRS were conducted, as extensively described elsewhere (3). Five separate acquisitions were obtained from each subject. Absolute WBNAA amounts (in mmoles) were calculated for each subject by averaging the NAA peak areas obtained from each of the five scans, and were then corrected for individual subjects’ BV in order to obtain WBNAA concentrations (mm) (3). The BV was measured on T1-weighted scans using SIENAX (4).

Macroscopic MR abnormalities were identified on the proton-density (PD) weighted scans, using T2-weighted and FLAIR images to increase the identification confidence. The number and the location of T2-hyperintense lesions were assessed.

Results
Within each group (AD, MCI patients and healthy controls) only 3 subjects did not present any macroscopic abnormality. In all the studied subjects ill-defined T2-hyperintensities were mainly located in subcortical regions (81.4% and 73.3% for patients and controls respectively). No significant difference regarding their number and distribution was found among the three groups. 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 MCI 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 MCI. 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 significantly correlated to MMSE score (r=0.40; p=0.06). Conversely, no significant correlations were found in controls and in the group of patients with MCI in isolation.

Conclusions
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 a early stage in the neuro-degenerative process of AD. The magnitude of the reduction of WBNAA concentrations in the patients with MCI might be a strong predicting factor of subsequent clinical evolution to AD.

References