T1rho ($T_{1\rho}$) MRI and CSF analysis in prediction of Alzheimer's disease at early stage

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Introduction:

Alzheimer's disease (AD) is the most common form of disabling cognitive impairment in older people. For treatment to be most effective, there is a need for an early clinical diagnosis of AD, particularly in mild cognitive impairment (MCI) patients who possess a greater risk in AD. While there are no established biochemical markers to identify early AD, a number of studies suggest that cerebral spinal fluid (CSF) markers in combination with MRI and neuropsychological tools, adds to the accuracy of AD diagnosis[1]. Recently a new MRI technique called $T_{1\rho}$ MRI has shown some sensitivity in distinguishing between AD and age-matched controls[2]. Higher $T_{1\rho}$ values were observed in the medial temporal lobe (MTL) in the brain of AD patients compared to MCI and control[2]. In the current study, we measure $T_{1\rho}$ in the MTL in the brain of AD, MCI and control, via MRI and to evaluate the diagnostic performance of $T_{1\rho}$ alone as well as in combination with CSF biomarkers of tau and amyloid protein.

Materials and Methods:

Subjects: The Institutional Review Board approved the study protocols. In the current study, we included 28 AD patients (mean age±SD = 74.1±8.4 years), 17 MCI patients (mean age±SD = 70.7±7.9 years), and 22 age-matched controls (mean age±SD = 70.6±9.8 years). The Mini-Mental State Examination (MMSE) was used as a measure of general cognitive function. The control group consisted of patients, who presented to our memory clinic with subjective complaints, and underwent exactly the same diagnostic work-up as the MCI and AD patients.

CSF Study: CSF samples were obtained by lumbar puncture following an overnight fast. Spinal fluid was withdrawn through an atraumatic 25-gauge sprotte needle and immediately transferred to bar code-labeled polypropylene vials and placed in a -80°C freezer. The 42B-amyloid (Aβ-42), t-tau and p-tau181p were measured in sample aliquots using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics immunoassay kit-based reagents (INNO-BIA AlzBio3, Ghent, Belgium). Full details of this combination immunoassay have been previously published[3].

MRI protocol: All these patients underwent a standard MRI protocol on a 1.5 Tesla Siemens Sonata clinical scanner using the vendor-supplied head coil. The written informed consent was obtained from each patient before they underwent for MRI. For $T_{1\rho}$ MRI, a fluid-attenuated $T_{1\rho}$ pre-encoded Turbo Spin-Echo pulse sequence was used. The imaging parameters were: TE/TR = 12/2000 ms, TSL (duration of spin lock pulse) = 10, 20, 30, 40 ms, with a spin lock frequency of 500Hz, slice thickness = 2mm, FOV = 22 cm, Matrix size=256x128, bandwidth= 130Hz/pixel, echo train length = 4 and inversion time (TI) = 860 ms. An oblique coronal $T_{1\rho}$ weighted image of a slice perpendicular to the anterior/posterior commissure (AC/PC) plane was obtained. Immediately after $T_{1\rho}$ MRI, the entire volume of each subject's brain was imaged in the coronal plane using a T_1-weighted 3D volumetric MPRAGE pulse sequence with 124 continuous slices. The parameters were TR/TE= 3000 ms/3.5 ms, slice thickness= 1.2 mm, FOV of 24 cm and 192 phase encode steps, and flip angle =8°.

Data Processing: $T_{1\rho}$ maps were generated by fitting each pixel's intensity as a function of the duration of the spin-lock pulse (TSL) by a linear least-squares algorithm[2]. Pixels whose intensities correlated poorly (R^2<0.95) with the fitting equation were set to zero. $T_{1\rho}$ values were automatically calculated from the gray matter (GM) and white matter (WM) of right and left MTL by an algorithm described previously. For GM and WM segmentation a previously developed method was used to partition the volumetric MPRAGE scans into 92 ROIs incorporating all major cortical and sub-cortical regions[4].

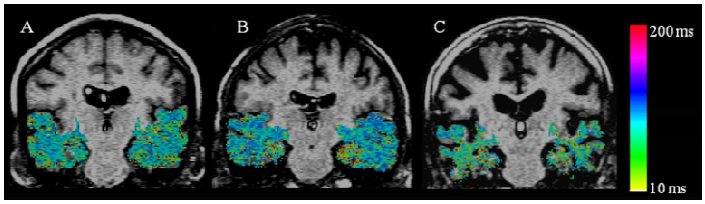
Statistical analyses: For statistical analysis the $T_{1\rho}$ value from left and right side were averaged for MTL (separately for GM and WM). Logistic regression was performed to measure the prediction rate of $T_{1\rho}$ and CSF biomarkers in differentiation of AD, MCI and control. Pearson correlations between $T_{1\rho}$ versus CSF biomarkers, $T_{1\rho}$ versus age and between $T_{1\rho}$ versus MMSE score were performed.

Results:

The value of MMSE, $T_{1\rho}$ and CSF biomarkers in the three cohorts (AD, MCI and control) are reported in table 1. The MCI individuals showed increased WM $T_{1\rho}$ compared to control. On comparing to control the AD individuals showed a significant increase in WM $T_{1\rho}$, T-tau and significant decreased Aβ-42 concentration. No significant difference for the $T_{1\rho}$ and CSF biomarkers was observed between MCI and AD. The binary logistic regression showed that both the $T_{1\rho}$ (GM and WM) and CSF biomarkers (T-tau, P-tau and Aβ-42) were able to predict 77.3% control and 44.8% MCI. Using the combination of $T_{1\rho}$ and CSF biomarkers we were able to predict 77.3% control and 60.6% MCI accurately. $T_{1\rho}$ predicted 46.7% control and 71.4% AD accurately while the CSF biomarkers alone or in combination with $T_{1\rho}$ the prediction rate was 77.3% for control and 82.1% for AD. On comparing the MCI with AD, the $T_{1\rho}$ predicted only 43.8% MCI and 85.7% AD, while the prediction rate was 56.2% for MCI and 89.3% for AD using the CSF biomarkers. We did not find any significant correlation between $T_{1\rho}$, CSF biomarkers and MMSE score. No significant correlation between $T_{1\rho}$ and age was observed. In case of control the T-tau (r=0.534, p=0.027) and P-tau (r=0.487, p=0.045) level showed a positive significant correlation with age of individuals.

Discussion:

We found an increase in CSF-tau and a decrease in CSF-Ab42 levels in AD, in agreement with results of several previous studies[1,5]. The WM $T_{1\rho}$ in MCI and AD were significantly increased compare to control. The current data suggests that by combining $T_{1\rho}$ MRI and CSF measures, an early (sensitive) and more specific diagnosis of AD is at hand. One of the limitations of the present study is the cross-sectional design, in which the value of two different diagnostic methods was compared in subjects with the clinical diagnosis as gold standard. Further study with larger sample sizes is needed to properly assess these differences. In conclusion, both CSF biomarkers and $T_{1\rho}$ MRI seem to be of incremental value for the diagnosis AD. By applying both disease markers together, diagnostic accuracy is increased.



Group	MMSE	GM $T_{1\rho}$	WM $T_{1\rho}$	t-tau	p-tau	Aβ42
Control	29.8±1.8	86.9±1.8	80.5±2.1	56.9±7.0	26.1±3.6	230.4±11.2
MCI	24.9±2.6	89.9±1.3	85.8±1.9	71.9±11.6	30.1±4.8	192.8±15.7
AD	18.9±4.7	90.9±0.8	88.3±1.3	96.9±9.7	35.2±4.3	151.3±9.8

Table 1. Values of MMSE score $T_{1\rho}$ and CSF biomarkers in control, MCI and AD cohorts. The values are given in mean ± standard error.

References:

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