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Neurobiology of Aging 33 (2012) 1253–1257

NEUROBIOLOGY OF AGING

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Brief communication

CSF tau markers are correlated with hippocampal volume in Alzheimer's disease

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Received 9 September 2010; received in revised form 4 February 2011; accepted 24 February 2011

Abstract

Hippocampal atrophy as assessed by magnetic resonance imaging (MRI) and abnormal cerebrospinal fluid (CSF) biomarkers are supportive features for the diagnosis of Alzheimer's disease (AD) and are assumed to be indirect pathological markers of the disease. In AD patients, antemortem MRI hippocampal volumes (HVs) correlate with the density of neurofibrillary tangles (but not with senile plaques) at autopsy suggesting that HVs may better correlate with CSF tau and hyperphosphorylated tau (P-tau) levels than CSF amyloid beta protein $(A\beta)_{42}$ level. Here, we tested this hypothesis in a well-defined AD group. Patients were selected according to the New Research Criteria for AD, including specific episodic memory deficit and CSF AD profile (defined as abnormal ratio of $A\beta_{42}$:tau). MRI was performed within 6 months of lumbar puncture. HVs were obtained using automated segmentation software. Thirty-six patients were included. Left HV correlated with CSF tau ($R = -0.53$) and P-tau ($R = -0.56$) levels. Mean HVs correlated with the CSF P-tau level ($R = -0.52$). No correlation was found between any brain measurement and CSF $A\beta_{42}$ level. The CSF tau and P-tau levels, but not the CSF $A\beta_{42}$ level, correlated with HV, suggesting that CSF tau markers reflect the neuronal loss associated with the physiopathological process of AD.

Keywords: Alzheimer's disease; CSF biomarkers; Hippocampus

1. Introduction

In Alzheimer's disease (AD), both hippocampal volumes (HVs) and cerebrospinal fluid (CSF) tau markers were associated with neurofibrillary tangles deposits: (1) antemortem HVs assessed by using magnetic resonance imaging (MRI) volumetry significantly correlated with the density of neurofibrillary tangles at autopsy (Csernansky et al., 2004; Jack et al., 2002) but not with amyloid beta protein (Aβ) plaque load (Csernansky et al., 2004), and (2) CSF tau levels correlated with the presence of neocortical neurofibrillary tangles (Tapiola et al., 2009). Therefore, levels of CSF tau and CSF hyperphosphorylated tau (P-tau) should correlate with HV. However, conflicting results have been observed in neuroimaging studies (Apostolova et al., 2010; Fagan et al., 2009; Herukka et al., 2008; Schoonenboom et al., 2008; Thomann et al., 2009) and a recent study (Fagan et al., 2009) showed no correlation between CSF biomark-

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10.1016/j.neurobiolaging.2011.02.022

ers and HV in AD patients. We wanted to analyze the correlations between CSF biomarkers and whole brain volume or HV in order to test the hypothesis that the levels of CSF tau and P-tau, but not CSF $A\beta_{42}$, are associated with hippocampal atrophy in AD patients.

2. Methods

2.1. Subjects

Patients were retrospectively recruited from the database of the Memory and Alzheimer Institute of the Pitié-Salpêtrière Hospital from May 2007 to February 2010. Inclusion criteria were: (1) AD (either at prodromal or dementia stage) defined according to the New Research Criteria (Dubois et al., 2007, 2010); and (2) complete clinical and neuropsychological evaluations, brain MRI using standardized protocol and CSF marker measurements (for $A\beta_{42}$, total tau [T-tau], and P-tau) performed less than 6 months from 1 to another.

The New Research Criteria for AD (Dubois et al., 2007, 2010) included: (1) progressive episodic memory impairment, characterized by a low free recall not normalized with cueing; (2) CSF AD profile, defined as score below 1, calculated with the formula $A\beta_{42}/(240 + [1.18 \times \text{T-tau}])$ (Visser et al., 2009); and (3) Clinical Dementia Rating (CDR) greater than 0. We did not include patients who presented: (1) clinical or neuroimaging evidence of focal lesions; (2) severe cortical or subcortical vascular lesions; or (3) severe depression.

All imaging and clinical data were generated during routine clinical workups of the patients in the Neurology and Neuroradiology departments and retrospectively extracted for the purpose of this study. According to French legislation, explicit informed consent was waived. However, the regulation concerning electronic filing was followed, and both patients and their relatives were informed that individual data may be used in retrospective clinical research studies.

2.2. Measurement of CSF biomarkers

CSF samples obtained by lumbar puncture (LP) were centrifuged for 10 minutes at 1500 rpm at 4 °C to remove cells, aliquoted into 0.4-mL polypropylene tubes, and stored at -80 °C until analysis. CSF biomarkers T-tau, tau phosphorylated at threonine 181 (P-tau), and $A\beta_{42}$ were measured in duplicate using a double-sandwich enzyme-linked immunosorbent assay (ELISA) method (Innogenetics, Gent, Belgium) according to the manufacturer's instructions.

2.3. MRI acquisition

T1-weighted magnetic resonance images were acquired with standard 3-dimensional sequences (please see Supplementary data for details).

2.4. Automated hippocampal volumetry

Segmentation of the hippocampus was performed using an automated method, as previously described (Chupin et al., 2009). Gray matter, white matter, and whole-brain volumes (WBV) were derived from SPM5 segmentations (Wellcome Trust Centre for Neuroimaging, London, UK). HVs were adjusted for head size by correcting for total intracranial volume, derived from SPM5 segmentations.

2.5. Statistical analysis

All statistical analyses were performed with Statistica 5.5A (StatSoft©, Tulsa, OK, USA). Descriptive statistics were used to characterize the population. All variables tested positive for normality by the Shapiro-Wilk test. The statistical analyses were performed with parametric tests. Statistical analyses of correlations between CSF data and volumetric brain measurements were performed using Pearson correlation test and were confirmed by partial correlations controlling for age and Mini Mental State Examination (MMSE) score. The Bonferroni correction for multiple correlations was applied ($\alpha < 0.002$). Only results for Pearson correlation test are presented below. Values are presented as means ± standard deviations.

3. Results

Thirty-six patients were included (mean age = 62.6 ± 8.1 years; Mini Mental State Examination [MMSE] score = 19.2 ± 6.3; CDR = 0.5 for n = 6 subjects, CDR = 1 for n = 10, CDR = 1.5 for n = 10, and CDR = 2 for n = 10; please see Supplementary data for table). The mean time interval between MRI scan and LP was 15 ± 59 days. All selected patients had decreased CSF $A\beta_{42}$ concentrations (261 ± 100.23 pg/mL). Mean CSF concentrations were 506.52 ± 160.22 pg/mL for T-tau (increased >450 pg/mL in 23/36 patients) and 82.42 ± 19.59 pg/mL for P-tau (increased >60 pg/mL in 32/36 patients). There was no asymmetry between left and right mean HVs (left HV = 2.22 ± 0.49 cm^3; right HV = 2.21 ± 0.50 cm^3). The mean WBV was 1021 ± 140.47 cm^3.

Significant negative correlations ($p < 0.001$) were found between left HV and concentrations of T-tau ($R = -0.53$) and P-tau ($R = -0.56$). Mean left + right HV correlated negatively with P-tau levels ($p < 0.001$; $R = -0.52$) (Fig. 1) but not with T-tau levels. No significant correlation was found between HV and $A\beta_{42}$ concentration.

There was no correlation between normalized whole-brain volume and any CSF biomarker ($A\beta_{42}$, T-tau, or P-tau) (Table 1) or between neuroimaging parameters and CSF ratios (T-tau/$A\beta_{42}$ or P-tau/$A\beta_{42}$).

4. Discussion

This study explored correlations between CSF biomarkers and measurements of hippocampal atrophy in a well-