Plasma p-Tau181 Outperforms Cerebrospinal Fluid Total Tau in Terms of Alzheimer's Disease Diagnosis

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with dementia, and is a serious concern for the health of individuals and government health care systems worldwide. Gray matter atrophy and white matter damage are major contributors to cognitive deficits experienced by patients with AD, as seen through magnetic resonance imaging (MRI). Many of these brain changes associated with AD begin to occur about 15 years before the onset of initial clinical symptoms. Therefore, it is critical to find biomarkers reflective of these brain changes associated with AD to identify this disease and monitor its prognosis and development. The level of hyperphosphorylated tau 181 (p-Tau181) in the plasma has been recently considered as a novel biomarker for the presence of AD, with increased levels in patients with AD, preclinical AD, and those experiencing mild cognitive impairment (MCI). In the current study, we examined the association of cerebrospinal fluid (CSF) and plasma levels of p-Tau181 with structural brain changes pertaining to cortical thickness, cortical volume, surface area, and subcortical volume in MCI patients. In this cross-sectional study we included the information of 461 MCI patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. The results of voxel-wise partial correlation analyses showed a significant negative correlation between the increased levels of plasma p-Tau181, CSF total tau, and CSF p-Tau181 and structural changes in widespread brain regions. These results provide evidence for the use of plasma p-Tau181 as a diagnostic marker for structural changes in the brain associated with the early stages of AD and neurodegeneration.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disease characterized by dementia and progressive cognitive deficits, making it a serious healthcare concern worldwide (1). Clinical symptoms of AD such as memory impairment, anxiety, confusion, language difficulties, and mood swings (2) resulting from changes in multiple cognitive, functional, and behavioral domains served as the most utilized diagnostic indicator of AD for many years (3). However, use of imaging methods and assessment of cerebrospinal fluid (CSF) and plasma biomarkers have recently become more common (4). Hippocampal atrophy, a key characteristic of AD, as well as cortical and subcortical volume loss may occur several years prior to the onset of clinical symptoms, making the use of biomarkers critical for early detection, monitoring, and treatment of AD (3).

Gray matter atrophy and white matter (WM) damage are well-known contributors to cognitive impairment in AD patients (5). These structural brain changes are often measured using magnetic resonance imaging (MRI). Gray matter atrophy is mostly observed in the entorhinal cortex and hippocampus as part of the medial temporal lobe in AD patients when compared to healthy controls (6). This volumetric reduction is also associated with memory decline and impairment of executive functions which is one of the hallmarks for diagnosing AD pathology (7). As AD progresses, more brain areas are affected by atrophy and WM changes (8). The medial temporal lobe atrophy can predict the conversion of MCI to AD which can also be used to distinguish AD from other neurodegenerative diseases (6). Both MCI and AD patients

undergo brain structural changes, which can be a reliable indicator of the risk of developing AD in MCI patients (9).

The pathological features of AD are primarily identified in extracellular Amyloid beta (Aβ) deposition and intracellular tau-containing neurofibrillary tangles leading to neural system failure and cognitive decline (10). In the CSF analysis of AD patients, high levels of phosphorylated tau (p-tau) and total tau (t-tau) have been consistently found. Although CSF t-tau is a non-specific biomarker of neurodegeneration, p-tau in the brain may represent AD-related tauopathy. Immunoassays detecting tau phosphorylated at threonine 181 (p-tau181) have been used in the large number of CSF studies. Accordingly, CSF p-tau181 individually or in combination with 42-amino acid Aβ peptide ($Aβ_{1-42}$) can reliably differentiates AD in preclinical and subclinical stages from healthy subjects as well as predicts cognitive impairment. (11). As several clinical trials focused on Aβ immunotherapy have failed, researchers have turned their attention to tauopathy in order to explore both the diagnostic and therapeutic approaches of AD (12, 13).

Recent tau positron emission tomography (PET) investigations have found variable associations between imaging and CSF biomarkers of AD-related tau pathology. Tau PET is a measurement of insoluble paired helical filament (PHF) tau accumulation along AD progression, whereas P-tau levels in the CSF suggest impaired tau metabolism at the time of lumbar puncture (LP), such as increased phosphorylation and release of soluble tau from damaged neurons (14). Despite the utility of these approaches in detecting and monitoring AD, they have a range of drawbacks. In particular, the measurement of CSF tau protein is limited by its high financial cost, lack of accessibility, and invasiveness which requires LP collection. Thus, validated blood-based biomarkers could help in the less invasive evaluation and continuous disease monitoring of AD patients (15, 16). A significant correlation has recently been discovered between the plasma levels of $Aβ_{1-42}$ and $Aβ_{1-40}/Aβ_{1-42}$ ratios (17), as well as t-tau, and p-tau181 (18) with pathological changes in the brain.

The presence of higher levels of p-Tau181 in the plasma in patients with AD, preclinical AD, and MCI compared to healthy controls has recently emerged as a new biomarker (16, 19). According to recent investigations, the plasma level of p-Tau181 can discriminate AD from other neurodegenerative diseases, such as frontotemporal dementia, vascular dementia, and Parkinson's disease (15). Moreover, the amount of p-tau181 in the blood correlates with Aβ PET and tau PET uptake (20, 21). So, p-tau181 can be used to identify disease pathways involved in the pathology of AD. However, the correlation between brain regional neurodegeneration and blood p-tau181 levels has not been thoroughly investigated in AD (22).

In this study, we aimed to explore the association of CSF (T-tau and p-Tau181) and plasma p-Tau181 with brain structural changes (cortical thickness, cortical volume, surface area, and subcortical volume) in MCI patients. We hypothesized that higher CSF levels of t-tau and p-Tau181, as well as plasma p-Tau181, are correlated with brain structural changes such as volume reduction.

Materials And Methods

Participants

We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Principal Investigator Michael W. Weiner, MD, established the ADNI in 2003 as a public-private partnership. The primary aim of ADNI is to see whether serial MRI, PET, other biological imaging modalities, as well as clinical and neuropsychological tests, could be used to monitor MCI and early AD progression. In the current cross-sectional study, we included 461 patients which were diagnosed with MCI based on criteria (23, 24), with all required data, such as plasma p-Tau181 measurements and MRI processed, available at the baseline visit (adni.loni.usc.edu).. Of 461 participants with MCI, 248 (53.8%) were men and 213 (46.2%) were women with overall mean age 71.47 7.17. Mean AD Assessment Scale (ADAS)-11 and ADAS-13 scores of the participants were 8.79 4.47 and 14.06 6.78, respectively. Average FDG-PET of the angular, temporal, and posterior cingulate in our study group is ranged from 0.73 to 1.70. The mean MMSE (Mini-mental state examination) score of the study sample was 28.17 1.68. Baseline demographics with details are presented in Table 1.

Plasma p-Tau181 measurements

Plasma p-Tau181 was measured using the Single Molecule Array (Simoa) technique, by an in-house assay developed at the University of Gothenburg, Sweden, that uses a combination of two monoclonal antibodies (Tau12 and AT270) and measures N-terminal to mid-domain forms of P-tau181. The procedure is outlined in detail in (adni.loni.usc.edu).

MRI processing

Cortical reconstruction and volumetric segmentation using the FreeSurfer image analysis suite are freely available for download (http://surfer.nmr.mgh.harvard.edu/). Processing of images includes averaging of volumetric T1 weighted images and motion correction (25), using a procedure to remove non-brain tissue (26), automated Talairach transformation, intensity normalization, tessellation of the boundary between gray matter and white matter, automated topology correlation, and optimally placing the border between gray and white matter and gray matter and CSF.

The ADNI-GO clinical dataset and scans from the University of Southern California's Laboratory of Neuroimaging (LONI) data repository were used in this research (http://adni.loni.ucla.edu/). The image used in ADNI FreeSurfer is a T1 weighted image. An accelerated and non-accelerated T1 weighted images are acquired in ADNI-GO for each subject. Images are pre-processed at Mayo Clinic. Processing consisted of three main steps. The first step, autorecon-1, initiates motion correction, non-uniform intensity, Talairach transform computation, and intensity normalization skull strip. The Autoreckon-2 performs the creation of the white-matter and pial surfaces and segmentation of the gray and white matter. The autorecon-3 creates the cortical parcellation. The procedure is defined in detail at ADNI.

Cognitive measurements

The Mini-Mental State Examination (MMSE) is a 30-point questionnaire used in medicine to test for dementia and evaluate cognitive decline and thinking ability (27). Simple questions in some areas of the MMSE exam, such as repeating lists of words, language use and comprehension, and basic motor skills, are included (28). In the MMSE, scores of more than 24 indicate normal cognition, while scores of less than 9 indicate significant cognitive impairment. Additional information can be found on the oxford medical education website.

CSF Biomarkers assessments

CSF biomarkers were assessed by the electrochemiluminescence immunoassays (ECLIA) Elecsys beta-amyloid$_{1-42}$ CSF, phosphorylated Tau (181p) CSF, and Total-Tau CSF on an automated Elecsys cobas e 601 instrument. These immunoassays are available only for investigational uses. Analyses were performed in 36 runs, and each sample runs one time for the CSF biomarkers mentioned above. The analyte was ranging from the lower technical limit to the upper technical limit for each biomarker. Lower and upper limits were 200 to 1700 pg/mL for ABETA, 80 to 1300 pg/mL for t-tau, and 8 to 120pg/mL for CSF p Tau, respectively. Results with higher values than the upper limit are stated as “>” and results with lower values than the lower limit are stated as “<”.

APOE genotyping

APOE ε4 genotyping was performed on collected blood samples by ADNI. Subjects with at least one allele considered positive. More details about the procedure are described: http://adni.loni.usc.edu/methods/documents/.

Statistical analysis

We used SPSS16 for data analysis. First, we implement a partial correlation model for assessing the relation between demographical variables, including age, APOE genotyping, MMSE score, FDG-PET, and sex with each other. Next, to measure the relationship between all biomarkers, we used a partial correlation adjusted for age, sex, and APOE genotype. In the last partial correlation, models adjusted for age, sex, and APOE genotype were used to assess the correlation between CSF or plasma biomarkers with brain structural changes. We added each biomarker and structural values, including thickness, cortical and subcortical volume, and surface area, separately as variables in correlation models. We used the bootstrapping method set at 0.05 for significant results for address type I error due to multiple comparisons.

Results

Correlation analysis revealed a strong association between MMSE score with age (r: -0.214; *P*: 0.001) and APOE genotyping status (r: -0.186; *P*: 0.001). Also, we found a significant correlation between average glucose uptake in the angular, temporal, and posterior cingulate regions with plasma p-Tau181 (r: -0.130;

P: 0.007), CSF t-tau (r: -0.165; *P*: 0.001), and p Tau (r: -0.203; *P*: 0.000), which means that hypometabolism in these regions is associated with plasma p-Tau181, CSF t-tau and p Tau.

Examination of our partial correlations controlling for the effects of age, sex, and APOE genotype, we found a negative correlation between plasma p-Tau181 and thickness in the left bankssts, left entorhinal, left inferior temporal, and right entorhinal (Table 2). Also, there is a negative correlation between plasma p-Tau181, and cortical volume in the left entorhinal, left inferior temporal, left middle temporal. Moreover, the analysis revealed a negative correlation between p-Tau181 and surface area in the left middle temporal (Table 2).

Using the same model for total tau and p-Tau181 in CSF, we investigated the correlation between structural changes and these two biomarker. We found a significant negative correlation between total tau and thickness in the bilateral precuneus, left bankssts, left inferior temporal, left middle temporal, right entorhinal (Table 3).

Higher levels of CSF p-Tau181 was associated with the decreased thickness in the bilateral precuneus, Right Superior Parietal, left bankssts, left fusiform, left middle temporal, left inferior parietal, right middle temporal (Table 4).

Discussion

We herein investigated the relationship between the plasma level of p-Tau181 and structural parameters in the brain. We performed a cross-sectional study on the ADNI cohort, including 461 MCI patients using a partial correlation model, controlled for the effects of age, sex, and APOE genotype.

Recent studies have shown the importance of using plasma biomarkers to detect and monitor AD, and these measures hold a number of advantages over more invasive, expensive, and time-consuming CSF measures (29). Brain structural changes often occur prior to the onset of clinical symptoms of AD, and encompass alterations in gray and white matter cortical thickness, volume, surface area, and subcortical volume. The results of voxel-wise partial correlation analysis showed a significant correlation between the plasma levels of p-Tau181 and changes in structural parameters. Specifically, we observed a significant negative correlation between the plasma p-Tau181 level and cortical volume, surface area, and thickness of the left bankssts, bilateral entorhinal cortex, left inferior temporal gyrus, bilateral parahippocampal gyrus, and left middle temporal gyrus. The gray matter loss of this areas are believed to be a leading factor to cognitive impairments in AD development (30, 31). To the best of our knowledge, this is the first study demonstrating the correlation between the plasma p-Tau181 level and structural changes in the brain. Previous studies have demonstrated that p-Tau181 in the plasma predicts AD pathology, and can discriminate between AD and non-AD pathologies (32). It has been also reported that the plasma level of p-Tau181 significantly increases in AD, especially in symptomatic stages (33, 34). Here, we add to this literature by demonstrating that plasma p-Tau181 can also predict structural brain changes associated with many of the cognitive deficits experienced by those with AD.

Previous studies have revealed an association between layer 2 neurons in the entorhinal cortex of AD patients (35). In addition, reduced activity in the cingulo-frontal cortex and the ventral system often go undetected patients with AD (36). MRI findings have also shown structural differences in the amygdala, hippocampus, and entorhinal cortex between healthy controls and those with preclinical AD (32). Our findings in the entorhinal cortex are in line with these previous studies, showing that the entorhinal cortex is a crucial site for the development of neurodegeneration (37) due to the contribution of its superficial layer alterations in response to downstream changes in the hippocampus (38, 39).

The rostral and caudal sections of the hippocampus are functionally involved in learning and memory (40). Functional MRI (fMRI) studies have shown two sub-networks within the medial temporal lobe, involving the rostral hippocampus and the medial hippocampus in the memory system (41–44). Recent research has indicated the importance of reduced hippocampal volume as an indicator of the presence of AD (45). There is also evidence suggesting that AD is associated with the hippocampus, as well as superior and inferior lateral temporal regions atrophy (46). In the literature, the importance of the precuneus and inferior temporal regions in distinguishing physiological and pathological brain aging has been reported in terms of conducting preventing strategies (46, 47).

We also observed an association between CSF tau and p-tau levels with structural changes. Specifically, we found an overall negative correlation between the CSF tau and p-tau levels and the cortical volume, surface area, and thickness of the right prewcuneus, left bankssts, left caudal anterior cingulate gyrus, left inferior temporal gyrus, left middle temporal gyrus, left precuneus, right entorhinal cortex, left caudal middle frontal cortex, left inferior lobule, right superior parietal lobule, and left fusiform. These CSF biomarkers similar to plasma P-tau181, are also associated with atrophy within wide spread areas, a significant factor for developing cognitive decline. Dementias and neurodegenerative diseases, such as AD and Parkinson's disease, are associated with the hyperphosphorylated form of tau protein (48). In addition, the CSF levels of tau and Aβ42 can predict the development of AD in MCI patients with high sensitivity and have clinical utility for implementation in the early stages of AD (49, 50). These results are in agreement with the findings of other studies, in which the CSF tau and p-tau levels were associated with atrophy in pathological brain areas (51).

In contrast to earlier findings, we found a positive correlation between the CSF tau and p-tau levels and thickness of the left caudal anterior cingulate cortex (30, 31). Previous studies have reported significant atrophy in all four regions of the cingulate cortex, while atrophy was greater in the posterior region (52). We found that higher levels of CSF t-tau, p-tau, and plasma p-tau were correlated with atrophy in the left anterior and left middle temporal regions. The partial correlation model showed that the plasma level of p-tau and the CSF levels of t-tau and p-tau had strong correlations with the average fluorodeoxyglucose (FDG)-PET results in the angular, temporal, and posterior cingulate regions. Generally, PET is a neuroimaging technique used for measuring metabolic processes and other physiological activities (53). Plasma and CSF biomarkers are associated with hypometabolism in these regions. Hypometabolism of the cerebral cortex represents the loss of functional activity (54). This finding provides additional

evidence regarding the association of the plasma p-tau with hypometabolism and atrophy in the temporal region.

Conclusion

In the present study we assessed the correlation between level of CSF and plasma biomarkers including P-tau181 and total tau with volumetric parameters such as cortical and subcortical volume, surface area and thickness in the MCI patients. Our study revealed a significant correlation between the plasma p-tau level and structural changes in the brain, associated with AD physiopathology. These results provide evidence regarding the use of plasma p-Tau181 as a diagnostic marker for the early stages of AD and neurodegeneration.

Declarations

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Conflict of interest

The authors have no conflicts of interest to disclose.

Availability of data

The datasets analyzed during the current study are available upon request with no restriction.

Authors' contributions

FN, MP, and MB came up with the idea for the paper, FN, MB, and MRR analyzed data, and FN, MB, NA, RW, and MP helped to write it. All of the authors reviewed the article.

Ethical approval

Since the data in this paper obtained from the ADNI database (adni.loni.usc.edu), it does not include any research involving human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

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Tables

Tables 1-4 are not available with this version.