

CSF total tau, plasma and CSF p tau 181 associated with structural changes in the early stage of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most important cause of dementia and is a serious concern for individuals and governments worldwide. Changes in the brain appear about 15 years before the first clinical symptoms; with this in mind, it can clear the role of biomarkers in monitoring Alzheimer's development. P tau 181 level in plasma recently emerged as a new biomarker and rises obviously in AD patients, preclinical AD, and MCI patients. The role of gray matter atrophy and white matter damages in cognitive decline is well established, which is detectable by magnetic resonance imaging (MRI). In this investigation, we measured the association between CSF (total tau, and p tau 181) and plasma p tau 181 with structural changes (cortical thickness, cortical volume, surface area, and subcortical volume) in MCI patients. We performed a cross-sectional study on the ADNI cohort between 461 MCI patients. Results of voxel-wise partial correlation analysis in our participants showed a significant correlation between plasma p tau 181, CSF total tau and p tau 181 with changes in structural values in different regions. Our study revealed a significant correlation between plasma p tau and structural changes in the brain regions associated with Alzheimer's disease physiopathology. These results provide evidence for using plasma p tau 181 as a diagnostic factor in the early onset of AD patients and neurodegeneration.

Introduction

Alzheimer's disease (AD) is the most important cause of dementia and is a serious concern for individuals and governments worldwide (1). Clinical symptoms were the most common diagnosis option of Alzheimer's disease for many years. Still, recently we rather use imaging markers and biological methods, for example, assessments of fluid (CSF, Plasma) biomarkers (2). Changes in the brain appear about 15 years before the first clinical symptoms; with this in mind, it can clear the role of biomarkers in monitoring Alzheimer's development (3). Important cerebrospinal fluid (CSF) biomarkers that are commonly measured for AD diagnosis contain 42 amino acid long amyloid-beta peptide ($A\beta_{1-42}$), total tau protein (T-tau), and tau phosphorylated at threonine 181 (p-tau181) (4). CSF $A\beta_{1-42}$ level decreases in AD subjects; meanwhile, t-tau and p-tau181 levels in CSF start to increase (5). There are six types of tau protein that exist in CNS neurons axons with an important effect on maintaining of microtubules stability (6-8). The PKN (a serine/threonine kinase) phosphorylates tau causes a disruption in microtubule organization, and the Aggregation of the hyperphosphorylated form of tau interacted with neurofibrillary degeneration and could responsible for microtubule network disruption (9, 10). $A\beta$ is the predominant component of extracellular deposition called amyloid plaques, which are observed in AD patient's brains (11). On the other hand, There is a neuroimaging method designed to determine the molecular process in the brain called positron emission tomography (PET), which is able to measure the $A\beta$ burden, tau and deposition, and neuroinflammation, and also provide remarkable acumen to underlying pathophysiological process in AD and mild cognitive impairment (MCI) (12).

However, there are problems in the extensive use of these biomarkers as diagnostic factors because of costs and invasiveness of the CSF collection and some imaging tools, so the use of blood-based biomarkers strongly reflect the levels of the biomarkers in CSF is more efficient (13, 14). P tau 181 level in

plasma recently emerged as a new biomarker and rises obviously in AD patients, preclinical AD, and MCI patients (14, 15). Plasma p tau 181, according to recent investigations, could discriminate AD from any longer neurodegenerative diseases as in frontotemporal dementia, vascular dementia, and Parkinson's disease (13).

The role of gray matter atrophy and white matter damages in cognitive decline is well established, which is detectable by magnetic resonance imaging (MRI) (16). Atrophy mostly observed in the entorhinal cortex and hippocampus as part of the medial temporal lobe Compared to healthy controls (17). In the progression of AD, the pattern of atrophy and white matter changes become wider and involve more regions (18). Medial temporal lobe atrophy can predict the conversion of MCI to AD and also can differentiate AD from other neurodegenerations (17). Structural changes occur in both MCI and AD patients and could be a reliable marker for the risk of developing AD in MCI patients (19).

As our search, there is no study assessed the relation between plasma p tau 181 and structural changes, including cortical thickness, cortical volume, surface area, and subcortical volume. In this investigation, we measured the association between CSF (total tau, and p tau 181) and plasma p tau 181 with structural changes (cortical thickness, cortical volume, surface area, and subcortical volume) in MCI patients. We hypothesized that there is a correlation between this plasma and CSF biomarkers with structural changes in the early stages of AD.

Materials And Methods

Participants

We used data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). We enrolled 461 patients diagnosed with mild cognitive impairments according to criteria (20, 21) which all required data, including plasma p tau 181 measurements and MRI processed, were available for baseline visit (adni.loni.usc.edu).

Plasma p tau 181 measurements

Plasma p tau 181 was analyzed at the University of Gothenburg, Sweden, using the single-molecule array technique. The detailed procedure is described in (adni.loni.usc.edu).

MRI processing

Cortical reconstruction and volumetric segmentation with 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 (22), using a procedure to remove non-brain tissue

(23), 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.

In our study, ADNIGO data available on LONI was used. The image used in ADNI FreeSurfer is a T1 weighted image. An accelerated and non-accelerated T1 weighted images are acquired in ADNIGO 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 1skull 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.

Cognitive measurements

The Mini-Mental State Examination is a 30-points questionnaire used to assess cognitive impairment and thinking ability in medicine for screening dementia (24). The MMSE test includes simple questions in some areas such as repeating lists of words, language use, and comprehension, and basic motor skills (25). Scores more than 24 in MMSE indicate normal cognition but, scores below 9 points(can show severe cognitive impairment. Additional information can be found on the oxford medical education website.

CSF Biomarkers assessments

CSF biomarkers 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 Total-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 ϵ 4 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. In the next, to measure the relation between all biomarker with each other, 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 changes. We add 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

Of 461 participants with MCI, 248 (53.8%) were men and 213 (46.2%) were women with age 71.477.17. Mean ADAS 11 and ADAS 13 scores of the participants were 8.794.47 and 14.066.78, respectively. Average FDG-PET of angular, temporal, and posterior cingulate in our study group is ranged from 0.734 to 1.701. THE mean MMSE score of the study group was 28.171.68. Baseline demographics with details are presented in Table 1.

Correlation analysis revealed a strong association between MMSE score with age and APOE genotyping status (P value<0.001). Also, there is a significant correlation between plasma p tau 181, CSF total tau, and p tau with average glucose uptake in the angular, temporal, and posterior cingulate regions (P value<0.05).

Investing partial correlation controlled for the effect of age, sex, and APOE genotype, we found a negative correlation between plasma p tau 181 and thickness in the left bankssts, left entorhinal, left inferior temporal, and right entorhinal (Tab2). Also, there is a negative correlation between plasma p tau 181, and cortical volume in the left entorhinal, left inferior temporal, left middle temporal. Moreover, the analysis revealed a negative correlation between p tau 181 and surface area in the left middle temporal. (P value<0.05) (Tab2).

Using the same model for total tau and p tau 181 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. (P value<0.05) (Tab3).

Higher levels of CSF p tau 181 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. (P value<0.05) (Tab4).

Discussion

We performed a cross-sectional study on the ADNI cohort between 461 MCI patients. Recent studies showed the importance of plasma biomarkers due to the advantage of blood tests over invasive, expensive, and time-consuming tests (26), so we investigated whether plasma p tau 181 has a significant correlation with structural changes of the brain. We used partial correlation controlled for the effect of

age, sex, and APOE genotype. Our study also aimed to determine the correlation between total tau and p tau 181 in the CSF with structural changes in the brain regions.

Results of voxel-wise partial correlation analysis in our participants showed a significant correlation between plasma p tau 181 and changes in structural parameters. Due to our findings, there is a significant negative correlation between plasma p tau 181 and cortical volume, surface area, and thickness in the left bankssts, bilateral entorhinal, left inferior temporal, bilateral Para hippocampus, and left middle temporal. To our knowledge, this is the first study that demonstrates the correlation between plasma p tau and structural changes in the areas, as mentioned earlier.

In accordance with the present results, previous studies have demonstrated that tau phosphorylated at threonine-181 (p-tau181) in plasma predicts AD pathology and can accurately discriminate between AD and non-AD pathologies (27). Also, it has been reported that plasma levels of p tau 181 have been significantly increased in AD, especially at symptomatic stages (28, 29).

Previous studies revealed an association between layer two neurons in AD patients' entorhinal cortex (30). There are functional impairments at the level of the cingulofrontal region and ventral system in unaware patients with AD (31). Also, significant differences between the control group and patients with preclinical AD in the amygdala, hippocampus, and entorhinal cortex based on MRI measures were observed (32). our findings in the entorhinal cortex are in line with previous studies demonstrating that the entorhinal cortex is a crucial site for the development of neurodegeneration (33) due to the contribution of entorhinal superficial layer alterations to downstream changes in the hippocampus (34, 35).

Our study found a negative correlation between plasma levels of p tau and changes in the structural feature, including volume, surface area, and thickness in pathological brain areas such as entorhinal, temporal, and hippocampus. These results match those observed in earlier studies. The rostral and caudal hippocampus are functionally involved in learning and memory, and functional MRI studies showed two subnetworks within the medial temporal lobe, involving the rostral hippocampus and the medial hippocampus in the memory system (36-39). Recent research demonstrated the importance of the hippocampus volumetric reduction as an indicator of AD (40). there is evidence that AD is associated with the hippocampus and superior and inferior lateral temporal regions (41). the importance of the precuneus and inferior temporal regions in pathological brain aging was proven previously (42).

Another finding of our research was the correlation between CSF tau and p tau with structural changes. We found that there is a significant correlation between CSF tau and p tau and cortical volume, surface area, and thickness in right precuneus, left bankssts, left caudal anterior cingulate, left inferior temporal, left middle temporal, left precuneus, right entorhinal, left caudal middle frontal, left inferior parietal, right superior parietal and left fusiform. CSF levels of t tau and p tau can discriminate AD and non-AD with high sensitivity (43). CSF levels of t tau have a potential role in the prognosis of AD patients (44). Dementias and neurodegenerative diseases such as AD and Parkinson's disease are associated with the hyperphosphorylated form of tau protein (45). CSF levels of tau and A β 42 could predict AD in MCI

patients with high sensitivity and have clinical value in the early phase of AD (46, 47). These results agree with other studies' findings, in which CSF tau and p tau are associated with atrophy in the pathological brain areas (48).

In contrast to earlier findings, however, we found a positive correlation between CSF tau and p tau with the left caudal anterior cingulate's thickness. previous studies revealed significant atrophy in all four regions of the cingulate lobe while the atrophy in the posterior region was greater (49).[22]

We found that higher amounts of CSF t tau, p tau, and plasma p tau are correlated with atrophy in the left anterior and left middle temporal regions. Investigation partial correlation, we found that plasma levels of p tau and CSF levels of t tau and p tau have a strong correlation with the average fluorodeoxyglucose (FDG)-positron emission tomography (PET) values in the angular, temporal and posterior cingulate regions. PET is a neuroimaging technique used for measuring metabolic processes and other physiologic activities (50). plasma and CSF biomarkers are associated with hypometabolism in these regions. Hypometabolism of the cerebral cortex represents a loss of functional activity (51). This finding provides additional evidence for the association between plasma p tau and hypometabolism and atrophy in the temporal region.

Conclusion

Our study revealed a significant correlation between plasma p tau and structural changes in the brain regions associated with Alzheimer's disease pathophysiology. These results provide evidence for using plasma p tau 181 as a diagnostic factor in the early onset of AD patients and neurodegeneration.

Declarations

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http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

The declaration of interest: none

We have no conflict of interest

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Tables

TABLE1. participant characteristics

MCI(N=461)	
Sex(M/F)	248/213
Average Age	71.47(7.17)
Education in years	16.23
Mean MMSE score	28.17(1.68)

MMSE: Mini-Mental state exam

TABLE2.significance results of partial correlation analyses brain regional structural changes and plasma ptau₁₈₁

Brain regions	Thickness Average	Cortical Volume	Surface Area	Subcortical Volume
RightParacentral	0.060	0.027	-0.009	–
LeftAccumbensArea	–	–	–	-0.130**
LeftBankssts	-0.136**	-0.055	-0.011	–
LeftEntorhinal	-0.098*	-0.103*	-0.037	–
LeftInferiorTemporal	-0.139**	-0.100*	-0.065	–
LeftMiddleTemporal	-0.149	-0.132**	-0.098*	–
LeftParacentral	0.013	-0.022	-0.048	–
LeftRostralAnteriorCingulate	0.043	0.006	-0.044	–
RightEntorhinal	-0.124**	-0.030	0.048	–
FifthVentricle	–	–	–	-0.124*
RightIsthmusCingulate	-0.053	0.016	0.049	–

*p<0.05

**p<0.01

Partial correlation coefficient of brain regional structural changes and plasma PTAU protein values controlled for age, sex and APOE.

TABLE3. significance results of partial correlation analyses brain regional structural changes and CSF tau

Region	Thickness Average	Surface Area	Cortical Volume	Subcortical Volume
RightPrecuneus	-0.114*	0.011	-0.057	–
LeftAccumbensArea	–	–	–	-0.108*
LeftBankssts	-0.136**	-0.006	-0.076	–
LeftCaudalAnteriorCingulate	0.097*	-0.055	0.010	–
LeftCaudalMiddleFrontal	-0.094	0.102*	0.062	–
LeftCaudate	–	–	–	-0.115*
LeftCerebellumCortex	–	–	–	0.119*
LeftHippocampus	–	–	–	-0.096*
LeftInferiorLateralVentricle	–	–	–	-0.101*
LeftInferiorTemporal	-0.129**	0.008	-0.059	–
CorpusCallosumCentral	–	–	–	0.160**
LeftMiddleTemporal	-0.135**	-0.030	0.063	–
CorpusCallosumMidAnterior	–	–	–	0.102*
LeftPrecuneus	-0.142**	-0.005	-0.082	–
RightAmygdala	–	–	–	-0.098*
RightCaudate	–	–	–	-0.174**
RightChoroidPlexus	–	–	–	-0.201**
RightEntorhinal	-0.122*	-0.012	-0.090	–
RightHippocampus	–	–	–	0.167**

*p<0.05

**p<0.01

Partial correlation coefficient of brain regional structural changes and TAU protein values controlled for age, sex and APOE

TABLE4. significance results of partial correlation analyses brain regional structural changes and CSF ptau

Regions	Cortical Volume	Surface Area	Thickness Average	Subcortical Volume
RightPrecuneus	-0.072	-0.009	-0.148**	–
RightSuperiorParietal	-0.077	-0.034	-0.097*	–
LeftAccumbensArea	–	–	–	-0.111*
LeftBankssts	-0.091	-0.022	-0.150**	–
LeftCaudalAnteriorCingulate	0.019	-0.053	0.107*	–
LeftCaudate	–	–	–	-0.119*
LeftCerebellumCortex	–	–	–	0.121*
LeftFusiform	-0.034	0.039	-0.102*	–
LeftHippocampus	–	–	–	-0.098*
LeftInferiorParietal	-0.162**	-0.129**	-0.102*	–
CorpusCallosumCentral	–	–	–	0.153**
LeftMiddleTemporal	-0.104	-0.046	-0.140**	–
LeftPrecuneus	0.052	-0.025	-0.143**	–
RightCaudate	–	–	–	-0.184**
RightHippocampus	–	–	–	-0.169**
RightLateralVentricle	–	–	–	-0.191**

*p<0.05

**p<0.01

Partial correlation coefficient of brain regional volumetrics and TAU protein values controlled for age, sex and APOE