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Plasma NT1 tau is associated with hypometabolism in Alzheimer's disease continuum

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Abstract

Objectives: There is a pressing demand for highly sensitive and easily accessible blood-based screening assessments to identify individuals in the preclinical stages who are likely to develop Alzheimer's disease (AD). We aimed to investigate the association between plasma NT1 tau and metabolism in meta-ROI regions including cingulate, angular, and inferior temporal gyrus across the AD continuum.

Methods: We retrieved the data of 182 cognitively unimpaired (UC), 339 MCI patients, and 160 AD subjects from Alzheimer's Disease Neuroimaging Initiative (ADNI). We analyzed the potential association between plasma NT1 tau levels and FDG-PET SUVR in (MetaROIs) including right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus using simple linear regression models adjusted for age, sex, and APOE ε4 genotype.

Results: We found a negative correlation between plasma NT1 tau concentration and FDG-PET SUVR in meta-ROI demonstrating that subjects with a higher level of plasma NT1 tau have hypometabolism in right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus. In the next, we conducted the models in each of the clinical groups. We found a negative association in CU and AD subjects between plasma NT1 tau concentration and FDG-PET SUVR in meta-ROI. However, there was no association among MCI participants.

Conclusion: In conclusion, our findings highlight the value of plasma NT1 tau as a biomarker for AD pathobiology. Based on our findings, plasma NT1 tau is significantly associated with hypometabolism in common AD-affected regions.

Keywords: Alzheimer's disease, tau, hypometabolism, NT1

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Introduction

Recent clinical trials in Alzheimer's disease (AD) have emphasized the necessity for enhanced screening of trial participants and the identification of individuals in the early stages of the disease (1, 2). The development of a cost-effective blood test that can be conducted at various time points would represent a transformative advancement in the field. While most research efforts have been focused on Aβ, the outcomes have generally been disappointing (3, 4). When evaluating the relative utility of measuring Aβ and tau in plasma, it is important to note that although Aβ is expressed in both the brain and

periphery, tau is primarily found in the central nervous system (CNS) (5, 6). Additionally, emerging data suggest that measuring specific forms of tau in plasma may offer better differentiation between individuals with mild cognitive impairment (MCI) and healthy controls (7).

In the CSF, elevated levels of tau and phospho-tau are widely recognized parameters utilized for the confirmation of AD diagnoses and the detection of presymptomatic AD cases (8, 9). The enzyme-linked immunosorbent assays (ELISAs) employed for CSF tau detection are commonly known as total tau assays; however, there is an increasing recognition that extracellular tau primarily consists of N-terminal and mid-region fragments, and conventional immunoassays may not capture all tau forms (10-13).

Recently, a highly sensitive immunoassay called NT1 tau, was designed to quantify tau forms captured by the mid-region antibody BT2 (amino acids 194–198) and detected using the N-terminal antibody Tau12 (amino acids 6–13) (14). The designation NT1 is not a registered trademark but serves to differentiate our assay from other N-terminal tau assays, highlighting that not all N-terminal tau assays target the same molecular tau forms. The complex molecular diversity of tau poses challenges in comparing outcomes from assays utilizing different combinations of anti-tau antibodies (14-16). In a previous investigation, the NT1 assay demonstrated superior discrimination between AD and AD with mild cognitive impairment (AD-MCI) cases compared to an in-house assay utilizing the same monoclonal antibodies as the Quanterix assay. Moreover, in two distinct study groups, NT1 tau effectively distinguished AD cases from controls (14, 17).

Here we aimed to investigate the association between plasma NT1 tau and metabolism in meta-ROI regions including cingulate, angular, and inferior temporal gyrus across the AD continuum.

Materials and Methods

Data Collection

The data utilized in this study was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, accessible at adni.loni.usc.edu. Established in 2003, ADNI operates as a collaborative effort between public and private sectors under the leadership of Principal Investigator Michael W. Weiner, MD. The primary objective of ADNI is to monitor the progression of MCI and early AD by integrating longitudinal PET, MRI, biomarkers, clinical assessments, and neuropsychological evaluations. For the most current information, please refer to www.adni-info.org.

Participant Selection

All essential data from the baseline assessments of participants in the ADNI-2 and ADNI-GO cohorts were provided for individuals with available plasma NT1 tau levels and FDG-PET data. The study included 182 cognitively unimpaired (UC), 339 MCI patients, and 160 AD subjects. Diagnosis of MCI in the subjects was based on specific criteria: Mini-Mental State Examination (MMSE) scores ranging from 24 to 30, self-reported memory concerns, objectively measured memory decline using education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating (CDR) of 0.5, absence of significant impairment in other cognitive domains, intact activities of daily living, and no diagnosis of dementia. All data extracted for analysis pertained to the baseline visit.

NT1 tau measurement

NT1 tau measured in a 3-step assay designed to identify tau forms encompassing residues 6 to 198. The original version of the assay had been validated previously, but modifications were made to the protocol due to changes in two proprietary reagents by Quanterix. The assay procedure involved activating paramagnetic beads with a specific agent before incubating them with BT2 and using biotinylated Tau12 for detection. Plasma samples were processed by thawing, centrifuging, transferring supernatant, diluting with a sample diluent reagent, and preparing a standard curve for analysis. The lower limit of quantitation (LLOQ) was determined based on specific criteria, and the assay's performance was evaluated over multiple runs and days, showing consistent results.

Imaging

FDG-PET data were acquired for 30-min dynamic emission scan, six 5-min frames, 30–60 min post-injection of 5.0 mCi of [18F]FDG. PET data underwent extensive quality control protocols and standardized image preprocessing correction steps to produce uniform data across the ADNI centers. These steps included frame co-registration, averaging across the dynamic range, and standardization with respect to the orientation, voxel size, and intensity [21]. Detailed information on the imaging protocols and standardized image preprocessing steps for MRI and PET can be found at http://adni.loni.usc.edu/methods. The dataset provided FDG-PET SUVR of a set of pre-defined regions of interest (MetaROIs) including right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus.

Statistical Analysis

The SPSS software (Statistical Package for the Social Sciences, version 16, USA) was used to analyze the data. All analyses were performed while adjusting for APOE ε4 genotype, age, and sex (18). First, we conducted several simple linear regression models for assessing the association of plasma NT1 and FDG-PET values (meta-ROI) in brain regions using simple linear regression models. Multiple comparisons caused type I errors; hence the Benjamini-Hochberg method was utilized to address it. Results at P value <=0.05 are considered significant.

Results

Patient's characteristics

Table1. Participants characteristic

Demographic and health characteristics	CU(182)	MCI(339)	AD(160)	P value
Age, years	72.9(±6.2)	72.8(±6.8)	74.0 (±8.6)	0.655
Education, years	16.4(±2.6)	16.0(2.6)	15.2(±2.9)	0.084
MMSE score	28.8(±1.4)	27.9(±1.9)	23.4(±1.8)	0
APOE genotype				0
Without ε4	88	101	31	
One ε4	48	175	68	
Two ε4	52	63	61	

Values are shown as mean(±SD), Mini-Mental State Examination(MMSE), results of ANOVA analysis between groups noted as p-value

The mean age of the studied population was 72.76 ± 7.34 years, while the mean MMSE score was 26.39. The details of demographical characteristics are described in Table 1.

Plasma NT1 tau and clinical status

We found that plasma NT1 was negatively associated with MMSE score in each of three clinical groups ($p<0.001$). Also, we found a significant association between higher age and higher concenteration of plasma NT1 tau in each of groups. Furthermore, comparing the level of plasma NT1 tau among APOE ε4 carriers and non-carriers showed a higher level in APOE ε4 carriers.

Plasma NT1 tau and metabolism in meta-ROI

We performed linear regression models to assess the association between plasma NT1 tau and FDG-PET SUVR in meta-ROI first across all subjects (Figure 1). As shown in Figure 1, we found a negative correlation between plasma NT1 tau concentration and FDG-PET SUVR in meta-ROI demonstrating that subjects with a higher level of plasma NT1 tau have hypometabolism in right and left angular gyri, bilateral posterior cingulate gyrus, and left middle/inferior temporal gyrus.

In the next, we conducted the models in each of the clinical groups. We found a negative association in CU and AD subjects between plasma NT1 tau concentration and FDG-PET SUVR in meta-ROI (Figure 1). However, there was no association among MCI participants.

Discussion

The main outcomes of this study are: (1) plasma NT1 tau can reflect hypometabolism in participants with AD dementia and healthy individuals; (2) plasma NT1 tau cannot reflect the hypometabolism of commonly affected regions of AD among individuals with MCI.

Previous studies have consistently documented increased plasma neurofilament light (NfL) levels in AD when compared to cognitively intact individuals (19, 20). Nonetheless, plasma NfL elevation is not exclusive to AD but is also observed in various neurological disorders (21-23). In this study, it was observed that plasma NfL levels were increased not only in AD but also in non-AD dementias, encompassing individuals with Frontotemporal Dementia (FTD), Dementia with Lewy Bodies (DLB), and Vascular Dementia (VaD). The observed rise in plasma NfL across certain conditions is unlikely to stem from inherent differences in disease mechanisms or NfL release but is more likely attributed to differences in disease stage and the extent of ongoing neurodegeneration in individual patients.

While there is general consensus on the elevated levels of NfL in both AD and other neurodegenerative conditions, the measurement of tau in plasma has produced conflicting findings (21, 24). This discrepancy is likely attributed to the intricate molecular composition of extracellular tau and the utilization of assays targeting different tau populations. Recently, an ultra-sensitive immunoassay was developed to detect tau forms captured by the mid-region antibody BT2 (amino acids 194–198) and identified with the N-terminal antibody Tau12 (amino acids 6–13). The evaluation of plasma NT1 tau in this study, employing a slightly modified version of the NT1 assay, validated previous findings that NT1 tau effectively distinguishes individuals with AD from controls. Furthermore, the comparison of 62 plasma and 50 CSF samples using both the original and revised NT1 assays demonstrated consistent relative values and similar differentiation of AD from controls (25). Additionally, both iterations of the assay are specific to tau forms immunoprecipitated with the well-established Tau5 monoclonal antibody and exhibit satisfactory specimen dilution linearity (26).

Omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential nutrients known for their neuroprotective properties (27, 28). They play a critical role in maintaining cell membrane integrity, reducing inflammation, and promoting synaptic plasticity. Anti-seizure medications, such as levetiracetam, are being explored for their potential benefits in AD beyond controlling seizures (29). Seizures and subclinical epileptic activity are increasingly recognized in AD, particularly in the later stages. Resveratrol, a natural polyphenol compound, has shown promise in potentially reducing the risk and slowing the progression of AD by inhibiting the aggregation of amyloid-beta proteins and improving cognitive function (30).

The prediction of long-term cognitive decline holds significant importance in the planning of clinical trials for early AD and in the clinical care of individuals at risk of cognitive impairment (11, 23, 31). Consistent with findings from recent observational cohort studies, our research revealed a notable correlation between elevated plasma NfL levels and the increased risk of developing all-cause dementia, encompassing both AD and

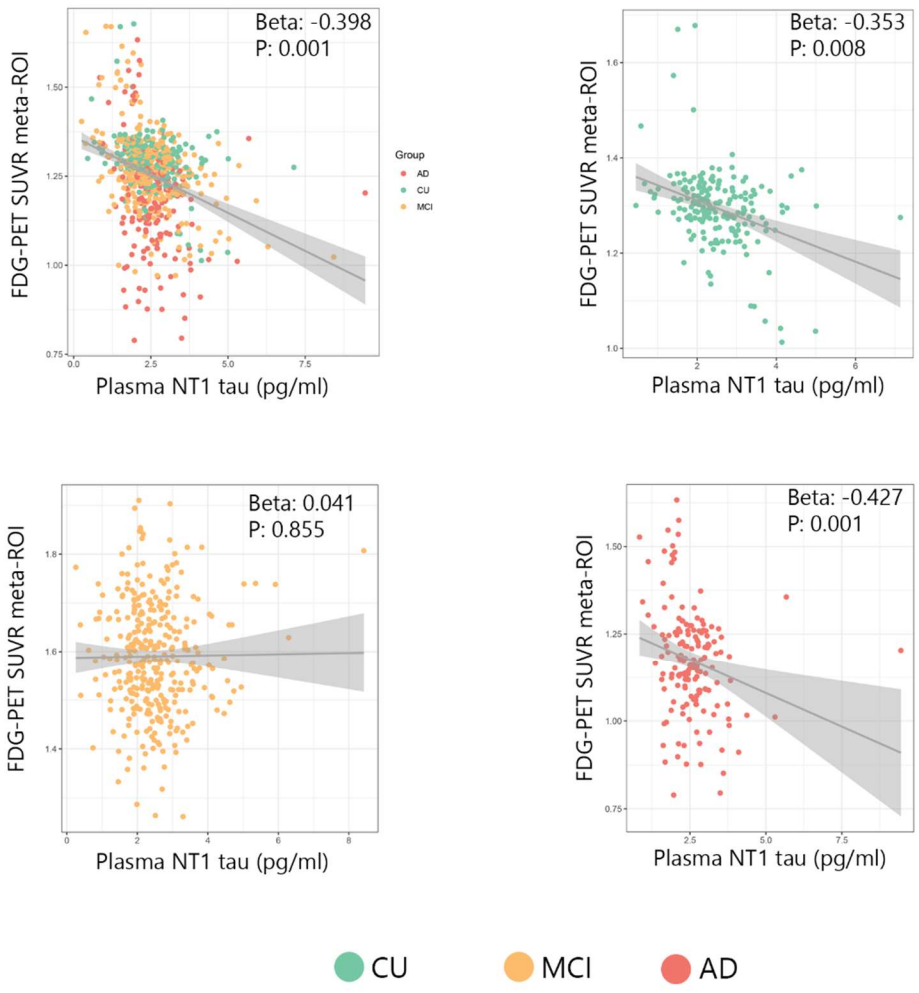

Figure1. Association between plasma NT1 and FDG-PET SUVR in meta-ROIs

non-Alzheimer's dementias (NADD). Conversely, plasma NT1 tau specifically indicated the progression to AD but not NADD (32-34). These longitudinal findings suggest that assessing NT1 levels in plasma could serve as a valuable screening tool to aid in the current diagnosis and future prediction of AD dementia (27, 33). Consequently, the measurement of NT1 tau may facilitate the selection of participants for clinical trials by identifying individuals most appropriate for subsequent confirmatory CSF analysis or PET imaging. A previous study revealed that plasma NT1 tau is a specific marker of AD, which is elevated early in the disease and may prove useful as a first-round screen to identify individuals at risk of developing AD (32, 35).

COVID-19 has accelerated AD research, revealing potential connections between the virus and neurodegeneration (36). Studies indicate that COVID-19-induced inflammation and vascular damage may exacerbate Alzheimer's pathology, necessitating urgent exploration of therapeutic strategies targeting both conditions for improved patient outcomes.

Conclusion

In conclusion, our findings highlight the value of plasma NT1 tau as a biomarker for AD pathobiology. Based on our findings, plasma NT1 tau is significantly associated with hypometabolism in common AD-affected regions. While additional validation of NT1 is necessary, it is anticipated that utilizing NT1 tau measurement as a screening tool will support the diagnosis and prediction of AD progression. This approach is expected to aid in clinical care planning and the timely initiation of treatment with emerging AD therapies.

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Declarations

Funding

We do not have any financial support for this study.

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.

Code availability

Not applicable

Ethical approval

The data in this paper were obtained from the ADNI database (adni.loni.usc.edu). It does not include any examination of human or animal subjects.

Consent for publication

This manuscript has been approved for publication by all authors.

Authors contribution

Z.GH and A.M designed and collected data. Y.P and D.E wrote the draft and analyzed the data.

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