ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2022;32(1):4-8
DOI:10.5152/pcp.2022.21206

The Relationship of Plasma Transthyretin Level with Global or Regional Amyloid Beta Burden in Subjects with Amnestic Mild Cognitive Impairment: Cross-Sectional Amyloid PET Study

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ABSTRACT

Background: To investigate the relationships of plasma transthyretin levels with amyloid beta deposition and medial temporal atrophy in amnestic mild cognitive impairment.

Methods: This is a cross-sectional study of association of subjects with amnestic mild cognitive impairment. Plasma transthyretin levels, brain magnetic resonance imaging, and ^{18}F-florbetaben positron emission tomography were simultaneously measured in subjects with amnestic mild cognitive impairment.

Results: Plasma transthyretin levels were positively associated with amyloid beta deposition in global (r=0.394, P=.009), frontal cortex (r=0.316, P=.039), parietal cortex (r=0.346, P=.023), temporal cortex (r=0.372, P=.014), occipital cortex (r=0.310, P=.043), right posterior cingulate (r=0.350, P=.021), left precuneus (r=0.314, P=.040), and right precuneus (r=0.398, P=.008). No association between plasma transthyretin level and medial temporal sub-regional atrophies was found.

Conclusions: Our findings of positive association of plasma transthyretin levels with global and regional amyloid beta burden suggest upregulation of transthyretin level as a reactive response to amyloid beta deposition during the early stages of the Alzheimer's disease process.

ARTICLE HISTORY

Received: August 30, 2021
Accepted: January 1, 2022

KEYWORDS: Amnestic mild cognitive impairment, amyloid beta deposition, medial temporal atrophy, positron emission tomography, transthyretin

INTRODUCTION

Alzheimer's disease (AD) is now one of the most common neurodegenerative diseases in the elderly population and has 2 definitive pathological features, which are neurofibrillary tangles (NFTs) of intracellular aggregation of abnormal hyperphosphorylated tau and amyloid plaques of extra-neuronal aggregation of amyloid beta peptide (Aβ) in the brain.

The amyloid cascade hypothesis[1] suggests that the consequent accumulation of Aβ peptides mediates the pathogenesis of AD through synaptic injury, gliosis, and NFTs. Amyloid beta loads are associated positively with clinical cognitive severity and faster cognitive decline in people with subjective memory impairment (SMI),[2] mild cognitive impairment (MCI),[3] and early AD.[4] Mild cognitive impairment patients with amyloid-positive deposition have a significantly greater risk of progression to dementia compared with people with amyloid-negative deposition,[5] and faster converters have higher Aβ load than slower converters.[6] Considering that Aβ deposition is progressively initiated 15-20 years before cognitive decline in AD, identifying blood-based biomarkers for Aβ deposition is critical for prediction of cognitive decline and early diagnosis of dementia in the future.

Transthyretin (TTR), a 55-kDa homotetrameric protein, is related to the transfer of retinol and thyroid hormones and is mainly produced in choroid plexus and liver. Previous studies showed that TTR was a protective protein for AD, which is associated with Aβ deposition. In vitro,[7] TTR binds Aβ and keeps it in a soluble form, preventing Aβ aggregation and fibrillation. In an in vivo AD transgenic mouse model,[8] only

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Cite this article as: Lee K, Lee Y-M, Park J-M, et al. The relationship of plasma transthyretin level with global or regional amyloid beta burden in subjects with amnestic mild cognitive impairment: cross-sectional amyloid PET study. *Psychiatr Clin Psychopharmacol*. 2022;32(1):4-8.

1 copy of the TTR gene showed higher Aβ levels compared to both copies of the gene. Cerebrospinal fluid (CSF)[9] and plasma[10-12] biomarker studies of AD showing decreased TTR level strengthen the idea of neuroprotection by TTR.

Although it is interesting that TTR is involved in protection against Aβ deposition, the association of plasma TTR levels with Aβ deposition in subjects with amnestic-MCI (aMCI) is unclear. The purpose of this study was to investigate the cross-sectional association of plasma TTR level with Aβ deposition and medial temporal atrophy in subjects with aMCI. For the purpose of this study, plasma TTR levels, brain magnetic resonance imaging (MRI), and ^{18}F-florbetaben positron emission tomography (PET) were simultaneously measured in subjects with a clinical diagnosis of aMCI.

METHODS

Participants

Forty-seven aMCI patients who had completed both blood samples for TTR plasma level and ^{18}F-florbetaben PET for amyloid deposition at baseline were obtained from a memory impairment clinic cohort during the period from August 2015 to July 2019. A diagnosis of aMCI was made using the following Petersen's criteria[13]: (1) reporting of subjective memory complaints by caregivers or patients, (2) objective memory impairment based on a verbal learning test (Seoul Verbal Learning Test delayed recall)[14] with a cut-off score of 1.5 SD under a population mean standardized for age and education, (3) normal function in activities of daily living (ADL) based on the ADL scale (Seoul-instrumental activities of daily living, S-IADL),[15] and (4) the absence of dementia.

Participants were excluded from this study if they had: (1) a significant psychiatric condition causally linked to cognitive impairment (e.g., substance abuse, delirium, major depressive disorder, bipolar disorder, schizophrenia, and other psychotic disorder), (2) a significant cerebrovascular or intracranial disease (e.g., cerebral hemorrhages), multiple (more than 5) lacunes, brain tumors, or severe white matter hyperintensities equivalent to the Fazekas scale, (3) other significant neurodegenerative diseases (e.g., frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease), (4) a significant medical condition causally linked to cognitive impairment (e.g., clinically significant abnormal laboratory findings, metabolic or hematologic disorders, and severe organ failure). All subjects with minor medical illnesses (e.g., hypertension, diabetes, hyperlipidemia, mild arthritis, or others) were included. The Institutional Review Board of the Pusan National University Hospital (1908-006-081) approve this study and all participants gave their informed consent.

MAIN POINTS

- Plasma transthyretin (TTR) levels was associated with amyloid-beta (Aß) deposition in amnestic mild cognitive impairment (aMCI).
- No association between plasma TTR levels and medial temporal sub-regional atrophies was found.
- The upregulation of TTR levels in aMCI may be a reactive response to Aß deposition.

Study Design and Clinical Evaluation

This cross-sectional study was conducted to investigate the association of plasma TTR level with Aβ deposition and medial temporal atrophy in subjects with aMCI. At baseline, all subjects had a standardized cognitive test for the diagnosis of aMCI, including a clinical interview, laboratory tests, The Korean version of mini mental status examination,[16] the clinical dementia rating Sum of Boxes,[17] the SIADL,[15] and the Seoul Neuropsychological Screening Battery (SNSB).[14] We also measured plasma TTR levels, ^{18}F-florbetaben PET, and brain MRI to investigate cross-sectional association of plasma TTR levels with Aβ deposition or medial temporal volume at baseline.

Transthyretin Measurements

At baseline, venous blood samples were collected in ethylenediaminetetraacetic acid tubes. The samples from each participant were then centrifuged and stored at −80°C until chemical analysis for plasma TTR level. We used a noncompetitive enzyme immunoassay method (ELISA Assaypro LLC, prealbumin AssayMAX Human ELISA Kit Assaypro, 3400 Harry S Truman Blvd St. Charles, MO 63301 USA) to measure the plasma TTR level. We also measured plasma TTR level on the same plate to avoid plate-to-plate variation. The samples showed a coefficient of variance of less than 20%.

Florbetaben Positron Emission Tomography Acquisition and Imaging Analysis

Amyloid PET data were acquired using a Biograph 40 PET/CT scanner (Siemens, Knoxville, Tenn, USA). Each participant underwent PET scans between 90 and 110 minutes after injection of 185 MBq of ^{18}F-florbetaben. An ordered subset expectation-maximization algorithm was used to reconstruct PET data.

All MRI images were normalized to a T1-weighted MRI template, and then each PET image was co-registered with each normalized MRI image. The automated anatomic labeling atlas[18] was used to obtain volume of interest (VOI) quantitative values. Standardized uptake value ratio (SUVR) is calculated as the degree of radiotracer uptake of a region of interest relative to a reference region and is the most common quantitative method used to calculate amyloid deposition levels in AD. We calculated SUVR using whole cerebellum as a reference region to determine the level of Aβ deposition in each VOI region.

Magnetic Resonance Imaging Data Acquisition and Image Analysis

All T1-weighted MRI images were acquired using a Siemens 3-T Trio TIM scanner (Erlangen, Bavaria, Germany). To estimate cortical thickness or volume, 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence was obtained. The parameters for MPRAGE are: field of view = 250 × 250 mm^2, repetition time = 1800 milliseconds, slice thickness = 1 mm, and acquisition matrix = 256 × 256. The FreeSurfer version 5.1 software package was used to calculate cortical volume or thickness on MPRAGE MRI images.[19] The Desikan-Killiany atlas[20] was used to acquire cortical thickness or volume of medial temporal sub-regions (entorhinal, hippocampus, and parahippocampus) as regions of interest. All images were examined visually by a neuroradiologist to ensure segmentation accuracy.

Statistical Analysis

Pearson's correlation analysis was performed to examine the association of plasma TTR level with SUVR for Aβ deposition in aMCI subjects. Multiple regression analysis was used to investigate the association of plasma TTR level with medial temporal sub-regional atrophies after adjusting for age, gender, education level, CDR Sum of Boxes (CDR-SOB), and total intracranial volume (TIV) since these variables can influence medial temporal volume. The statistical analyses were performed with Statistical Package for the Social Sciences software (version 26.0, IBM, Inc., Armonk, NY, USA) and statistical significance was determined at $P < .05$.

RESULTS

Demographic and Clinical Characteristics

Of the 47 initial subjects, 2 aMCI patients were excluded. One subject was excluded because he withdrew his consent to the study, the other was excluded because his MRI data were too noisy to be analyzed in FreeSurfer pipeline. This left us with the last group of 43 MCI patients (mean age = 72.13±6.78 years; females = 29 (67.4%); mean education = 9.65±4.51 years; CDR-SOB = 1.68±0.84; plasma TTR levels = 24.91±6.09 μg/mL; total intracranial volume = 1429.16±151.77 cm^3).

Association of Plasma TTR Levels with Global and Regional Standardized Uptake Value Ratio for Amyloid Beta Deposition

The correlation between plasma TTR levels and SUVR values were analyzed in global and regional area using Pearson's correlation tests (Table 1). Plasma TTR levels were positively associated with Aβ deposition in global cortex (r=0.394, P=.009), frontal cortex (r=0.316, P=.039), temporal cortex (r=0.372, P=.014), parietal cortex (r=0.346, P=.023), occipital cortex (r=0.310, P=.043), right posterior cingulate (r=0.350, P=.021), left precuneus (r=0.314, P=.040), and right precuneus (r=0.398, P=.008). In caudate, putamen, pallidum, thalamus, and hippocampus, however, no correlations with plasma TTR levels were found.

Table 1. The Association of Plasma TTR Levels with Regional Aβ SUVR Values

Brain Region	SUVR Value	Pearson's Correlation Coefficient	*P*
Global	1.14±0.13	0.394**	.009
Frontal cortex	1.06±0.14	0.316*	.039
Parietal cortex	1.26±0.17	0.346*	.023
Temporal cortex	1.05±0.16	0.372*	.014
Occipital cortex	1.19±0.17	0.310*	.043
Anterior cingulate, left	1.27±0.32	0.218	.159
Anterior cingulate, right	1.29±0.28	0.211	.175
Posterior cingulate, left	1.40±0.31	0.286	.063
Posterior cingulate, right	1.34±0.32	0.350*	.021
Precuneus, left	1.29±0.25	0.314*	.040
Precuneus, right	1.34±0.24	0.398**	.008
Caudate, left	1.36±0.25	0.213	.170
Caudate, right	1.38±0.27	0.170	.277
Putamen, left	1.34±0.30	0.068	.663
Putamen, right	1.37±0.29	0.062	.692
Pallidum, left	1.19±0.38	-0.009	.953
Pallidum, right	1.21±0.35	0.005	.972
Thalamus, left	1.47±0.22	0.033	.837
Thalamus, right	1.46±0.23	-0.006	.970
Hippocampus, left	1.11±0.20	0.120	.443
Hippocampus, right	1.18±0.24	0.107	.495

**$P < .01$; *$P < .05$.
TTR, transthyretin; Aβ, amyloid beta; SUVR, standardized uptake value ratio.

Association of Plasma TTR Level with Sub-Regional Atrophies of Medial Temporal Lobe

After controlling for age, gender, education, CDR-SOB, and TIV by a multiple regression model, none of sub-regional

Table 2. The Association Between Plasma TTR Level and Sub-Regional Thickness (or Volume) of Medial Temporal Lobe

Sub-regions	B	SE	*P*
Hippocampal volume, left	-0.001	0.005	.822
Hippocampal volume, right	-0.003	0.004	.474
Entorhinal thickness, left	-6.581	3.518	.124
Entorhinal thickness, right	-3.482	3.338	.309
Parahippocampal volume, left	-6.376	4.138	.140
Parahippocampal volume, right	-5.666	4.695	.242

P-value was adjusted for age, gender, education, CDR-SOB, and TIV.
SE, standard error; TIV, total intracranial volume; TTR, transthyretin; B, unstandardized beta (this value represents the slope of the line between the predictor variable (TTR) and the dependent variable (sub-regional thickness)).

atrophies of medial temporal lobe were associated with plasma TTR levels (Table 2).

DISCUSSION

The question addressed by this study was to investigate the cross-sectional association of plasma TTR levels with Aβ deposition and medial temporal atrophy in subjects with aMCI. In an attempt to answer this question, we measured plasma TTR levels, MRI, and ^{18}F-florbetaben PET at the same time. The present study demonstrates a positive correlation between plasma TTR levels and global or regional Aβ deposition burden. Higher levels of plasma TTR were associated with higher values of SUVR in right posterior cingulate, both precuneus, global, frontal, temporal, parietal, and occipital cortices.

Many studies of AD patients[9-12] have shown that lower TTR levels in CSF or plasma were associated with more severe cognitive impairment or faster cognitive decline. However, results of previous studies of MCI patients on association of TTR level with Aβ load have been inconsistent. While some studies[10,11] demonstrated that MCI patients had significantly lower levels of plasma TTR compared to the elderly with normal cognition, another study[21] conflictingly reported higher levels of plasma TTR in the MCI group. Such inconsistent results mean that the association of plasma TTR with Aβ load may differ between AD and MCI. In this study, we investigated the association of plasma TTR level with Aβ deposition in subjects with aMCI. Our study indicated that plasma TTR levels were associated positively with global or regional Aβ load. Notably, high correlations between plasma TTR levels and Aβ burden were found in precuneus and posterior cingulate, where Aβ deposition occurs first. This finding suggests that in subjects with aMCI, the decreased TTR level is not the cause of the increase in Aβ load but rather the greater Aβ load may increase TTR level. Therefore, increased TTR levels in subjects with aMCI may be associated with upregulation in the reactive response to the Aβ deposition.

Such a hypothesis is supported by an in vivo study[22] which reported that the production of Aβ or its precursors can induce an increase of neuronal TTR transcription.

In the amyloidogenic pathway,[23] amyloid precursor protein (APP) is first cleaved by β-secretase, releasing a C-terminal fragment β (CTFβ) and a soluble ectodomain of APP (sAPPβ). The CTFβ is then further cleaved by γ-secretase to generate Aβ and the APP intracellular domain (AICD). Kerridge et al[24] reported that in particular, the AICD fragment derived from the APP695 isoform is involved in the mechanism of TTR upregulation. They suggested increased levels of AICD through the amyloidogenic pathway cause TTR upregulation and eventually decrease Aβ levels. A recent longitudinal study[21] of the temporal relationship of the plasma TTR level with the progression from the MCI to the AD showed that TTR levels continue to increase during MCI stage, and higher TTR levels are related to increased risk of progression to dementia. After progression to AD stage, however, the TTR levels keep decreasing and lower TTR levels are associated with faster cognitive decline. This result strengthens our hypothesis that in aMCI, TTR upregulation is the result of a reactive response to the Aβ deposition. In this study, we did not find any association between plasma TTR level and medial temporal sub-regional volumes. These findings imply that many other factors besides TTR may be involved in medial temporal volumes.

Our study has several limitations. First, this study is a cross-sectional design that correlates the findings to a specific disease stage. Therefore, further longitudinal studies will be needed to examine the effect of TTR on deposition of Aβ across the AD continuum. Second, this is a hospital-based study, which may not represent the general population with aMCI. In addition, the aMCI group was relatively small sample. Although this sample size allowed us to detect the effect, a larger sample may be required to increase power and find an association. Third, in this study, we did not make any adjustment of a significance level for multiple statistical comparisons because this study was an exploratory one. Thus, our exploratory analyses could have increased type I error inflation from the multiple regional variables. Finally, we did not include some potential confounders that affect plasma TTR levels, such as liver function and thyroid hormones. Because liver is a major site for metabolism of TTR, dysfunction in liver may affect plasma TTR level. Despite these limitations, to the best of our knowledge, this is the first amyloid PET study of plasma TTR to find blood-based biomarkers that can reflect Aβ pathogenesis of AD in subjects with aMCI.

In conclusion, we have found that plasma TTR levels were associated positively with global or regional Aβ burden. Considering the previous studies reporting that TTR levels in cognitive healthy elderly[21] and AD patients[10-12] were decreased, our findings of Aβ-related increased TTR level and a positive correlation between TTR level and Aβ deposition levels in the state of aMCI suggest that the increased plasma TTR level in subjects with aMCI may be associated with reactive upregulation of TTR for Aβ deposition during the early cognitive impairment stage. Prospective longitudinal studies focusing on the regulatory mechanism of TTR in different cognitive stages should be explored to determine its usefulness as a blood biomarker.

Ethics Committee Approval: Ethics committee approval waa received from the Institutional Review Board of the Pusan National University Hospital (1908-006-081).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept - K.L., Y.M.L., J.M.P.; Design - K.L., Y.M.L., J.M.P.; Supervision - Y.M.L., J.M.P.; Resource - Y.M.L, H.J.K, K.P., K.U.C.; Materials - Y.M.L, H.J.K, K.P., K.U.C.; Data Collection and/or Processing - Y.M.L.,

H.J.K., K.P., K.U.C.; Analysis and/or Interpretation - K.L., Y.M.L., J.M.P.; Literature Search - K.L., Y.M.L.; Writing - K.L., Y.M.L.; Critical Reviews - B.D.L., E.M., H.J.J., H.S.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was supported by Biomedical Research Institute Grant (2018B039) from Pusan National University Hospital.

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