Platelet-derived growth factor-BB and white matter hyperintensity burden in *APOE4* carriers

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ABSTRACT

Background: The apolipoprotein-e4 (*APOE4*) gene increases risk for developing late-onset Alzheimer's disease (AD) and has been linked to increased microvascular dysfunction, including pericyte degeneration and blood-brain barrier breakdown. Platelet-derived growth factor-BB (PDGF-BB) is a glycoprotein involved in blood-brain barrier and pericyte maintenance. Increased PDGF-BB levels have been reported in white matter in AD brain tissue. However, the association between circulating levels of PDGF-BB and cerebral white matter damage in older adults remains unknown.

Methods: Participants included community-dwelling older adults (age range 55–90 years, $M = 73.1$ years; SD $= 7.5$; 61.0% male) from the Alzheimer's Disease Neuroimaging Initiative who underwent venipuncture and blood plasma immunoassay for PDGF-BB, brain MRI scanning with T2-FLAIR for volumetric quantification of white matter hyperintensities (WMH) and *APOE4* genotyping ($N = 64$). Linear regression analyses examined the relationship between plasma PDGF-BB levels and WMH volume, adjusting for age, sex, intracranial volume (ICV) and stratifying by *APOE4* status.

Results: Greater levels of circulating PDGF-BB were related to greater WMH volume, even after accounting for age, sex, ICV and *APOE4* carrier status ($p = 0.040$). Nineteen (29.2%) were *APOE4* carriers. When stratified by *APOE4* status, the relationship between PDGF-BB and WMH volume was only significant for *APOE4* carriers ($p = 0.007$), but not non-carriers ($p = 0.448$), after adjusting for age, sex and ICV.

Discussion: These findings reveal a differential relationship between PDGF-BB and WMH volume for *APOE4* carriers versus non-carriers. The *APOE4* variant leads to accelerated cerebrovascular injury and cognitive decline. Elevated levels of PDGF-BB in carriers may suggest a role for pericytes and blood-brain barrier dysfunction in white matter damage, vascular cognitive impairment and AD. Additional studies will elucidate the role of PDGF ligands and receptors in these conditions.

1. Introduction

The apolipoprotein-e4 (*APOE4*) allele is the strongest genetic risk factor for developing late-onset Alzheimer's disease (AD) [1,2]. The presence of *APOE4* is linked to increased cerebral amyloid beta levels [3], but is also important in a variety of other mechanisms of potential relevance to AD, including changes in lipid metabolism, inflammation and vascular health [4–7]. Recently, it has been hypothesized that *APOE4* causes cognitive decline due to effects on brain capillary pericytes that lead to neurovascular inflammatory pathway activation and pericyte degeneration, thinning of the microvascular basement membrane, breakdown of the blood-brain barrier and small vessel damage [8–15].

Platelet-derived growth factor receptor-beta (PDGFRβ) and its ligand PDGF-BB are involved in maintaining the integrity of the blood-brain barrier [16]. Elevated cerebrospinal fluid levels of soluble PDGFRβ (sPDGFRβ) have been observed in individuals with cognitive dysfunction, independent of amyloid and tau changes [17,18], implicating pericyte degeneration in cognitive impairment. Increased sPDGFRβ levels are also observed in *APOE4* carriers relative to non-carriers, even among cognitive unimpaired individuals, suggesting pericyte injury may be caused by *APOE4* and could represent an early stage biomarker

of cognitive impairment in *APOE4* carriers [14]. To date, few studies have examined PDGF-BB, a PDGFRβ ligand in the context of *APOE4* and cerebral microvascular injury.

In the current study, we aimed to investigate the association between levels of circulating PDGF-BB and small vessel damage, specifically white matter hyperintensities (WMH) of presumed vascular origin. Given prior evidence suggesting a role for PDGF-BB in maintaining the integrity of the vasculature, we hypothesized that greater levels of circulating PDGF-BB will be associated with greater WMH burden in older adults.

2. Methods

This was a cross-sectional analysis utilizing data obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which is a longitudinal multicenter study designed to identify early-stage clinical, imaging, genetic, and biochemical biomarkers for early detection of AD. The complete study aims, design and method are available through the ADNI website (adni.loni.usc.edu/about/). This study was approved at the local Institutional Review Boards of the participating organizations and all participants gave written informed consent.

2.1. Participants

All participants were community-dwelling older adults between the ages of age 55–90 years, required to have a study partner who could accompany the participant to visits, had Geriatric Depression Scale score less than 6, Hachinski Ischemic score less than or equal to 4, with adequate visual and auditory acuity, good general health, 6 grades of education or work history equivalent, and ability to speak English or Spanish fluently. In this analysis, we included participants from ADNI 1, ADNI-GO, ADNI-2 and ADNI-3 and did not restrict the analysis to a specific baseline diagnosis. Baseline diagnosis of cognitively normal (CN), mild cognitive impairment (MCI) or Alzheimer's disease (AD) was based on subjective memory complaints, Logical Memory II subscale from the Wechsler Memory Scale, Mini-Mental State Exam, Clinical Dementia Rating, and the NINCDS/ADRDA criteria for probable AD. For more information regarding inclusion and exclusion, please see adni. loni.usc.edu/methods/document.

In the current analysis, we were specifically interested in examining the relationship between circulating levels of PDGF-BB and WMH burden and therefore, only included participants who underwent venipuncture and blood plasma immunoassay for PDGF-BB and brain MRI scanning with T2-FLAIR for volumetric quantification of WMH($N = 64$). Demographics data and *APOE4* carrier status was also obtained.

2.2. Brain magnetic resonance imaging

Participants underwent the standardized magnetic resonance imaging (MRI) protocol for the ADNI study. All data was acquired on either Siemens, GE, or Phillips scanners at 1.5T or 3T. The complete imaging protocol and details have previously been published [19,20]. For the current study, we utilized WMH volumes quantified using the ADNI protocol [21,22]. This method uses 3D T1 and FLAIR structural magnetic resonance (MR) sequences to reliably segment WMH using a Bayesian approach [22]. The complete methods and pipeline have been published elsewhere [22]. The first WMH volume determined for each participant was examined. Total intracranial volume (ICV) was calculated by combing cerebrospinal fluid, white matter, and gray matter volumes. WMH as a percent of ICV was determined.

2.3. Fluid biomarkers

Plasma samples from a subset of participants in the ADNI cohort were obtained after overnight fast and analyzed by Rules Based Medicine (RBM) based on the ADNI Biomarkers Consortium Project protocol,

Table 1
Patient characteristics.

	All(N = 64)	*APOE4/4*Carrier (N = 3)	*APOE3/4*Carrier (N = 16)	*APOE4*Non-Carrier(N = 45)	*p*-value
Age (Years), M (SD)	73.1 (7.5)	69.7 (4.8)	70.8 (7.9)	74.2 (7.3)	.23
Education (Years), M (SD)	15.0 (3.2)	14.0 (2.0)	15.3(3.6)	15.0 (3.2)	.83
Sex (Male), N (%)	39 (60.9)	3 (100)	9 (56.3)	27 (60.0)	.35
Baseline Diagnosis, N (%) Cognitively Normal Mild Cognitive Impairment	18 (28.1) 46 (71.9)	0 (0.0) 3 (100)	2 (12.5) 14 (87.5)	16 (35.6) 29 (64.4)	.11
ADAS-13, M (SD)	13.8 (6.7)	21.0 (8.0)	16.5 (6.5)	12.3 (6.3)	.01
MMSE, M (SD)	27. 9 (1.6)	27.0 (2.0)	27.6 (1.4)	28.1 (1.6)	.28
Plasma PDGF-BB (pg/mL), M (SD)	3.2 (0.5)	2.9 (0.7)	3.2 (0.5)	3.2 (0.4)	.69
WMH/ICV (%), M (SD)	0.6 (0.8)	0.2 (0.1)	1.0 (1.2)	0.5 (0.6)	.04

which aimed to utilize proteomic strategies to identify plasma-based biomarkers (adni.loni.usc.edu/methods/). Values for PDGF-BB were determined using a multiplex (151 analyte) plasma-based immunoassay panel based on Luminex immunoassay technology created by Rules Based Medicine (RBM). Additional details of the assay are available here: Biomarkers Consortium Data Primer. The lower assay limit and least detectable dose for PDGF-BB was 43 pg/mL and 139 pg/mL, respectively.

In addition, ADNI participants underwent venipuncture and blood samples were analyzed for *APOE4* carrier status [23]. DNA extraction was conducted by Cogenics. Two SNPs (rs429358, rs7412) which determine epsilon 2, 3, and 4 alleles were examined. Participants with one or two copies of the *APOE4* variant were considered *APOE4* carriers.

2.4. Statistical analysis

All analyses were performed using R Version 3.6.1 and IBM SPSS Statistics 28. Multiple linear regression analyses were utilized to examine the relationship between PDGF-BB levels (independent predictor) and WMH (outcome), adjusting for age, sex and ICV. WMH values were log transformed, with a constant of 1 added to each value. The analysis was stratified by *APOE4* carrier status. Significance threshold was set at $p < 0.05$ for all analyses.

3. Results

A total of 64 participants with complete WMH volume and PDGF-BB levels were included in the current analysis. Age of study participant in this analysis ranged from 55.1 to 89.6 ($M = 73.1$, $SD = 7.5$) and education ranged from 8 to 20 years ($M = 15.0$, $SD = 3.2$). Additional demographic characteristics are reported in Table 1. *APOE4* carriers were significantly more likely to meet mild cognitive impairment (MCI) criteria as defined by the ADNI study and performed worse on the Alzheimer's Disease Assessment Scale (ADAS).

In multiple linear regression analysis, older adults with higher plasma PDGF-BB levels exhibited greater WMH volume after adjusting for age, sex, ICV and *APOE4* carrier status (β = 0.218, $p = 0.040$, 95% CI [0.010, 0.426]) (Table 2). Older adults with one or more copies of *APOE4* also showed higher WMH volume in multiple regression analyses (β = 0.361, $p = 0.001$, 95% CI [0.149, 0.572]). Therefore, we stratified the analysis by *APOE4* status. In *APOE4* carriers, PDGF-BB levels

Table 2

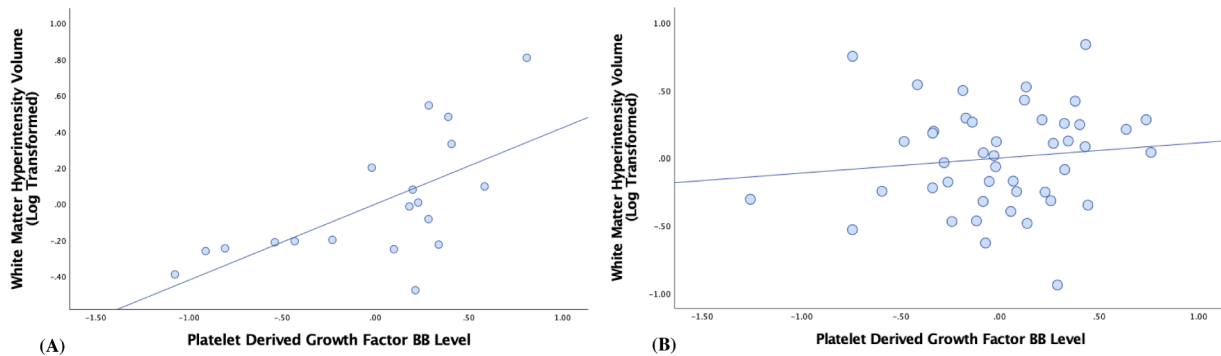Association between PDGF-BB levels and WMH volume.

Variable	Multivariable (all variables entered in the model)						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	β			Lower Bound	Upper Bound
Age (Years)	0.023	0.007	0.393	3.38	0.001	0.009	0.036
Sex (Male)	-0.167	0.128	-0.193	-1.31	0.195	-0.424	0.089
APOE4 (Carrier)	0.361	0.106	0.388	3.41	0.001	0.149	0.572
PDGF-BB (pg/mL)	0.218	0.104	0.232	2.10	0.040	0.010	0.426
ICV (cm^3)	0.000	0.000	0.077	0.52	0.606	-0.001	0.001

Note: APOE4 = apolipoprotein-e4 (APOE4) allele carrier; PDGF-BB = platelet-derived growth factor BB; ICV = intracranial volume. Bold values indicate significant predictors of WMH volume. B represents the unstandardized regression coefficient and β represents the standardized regression coefficient.

Table 3

Association between PDGF-BB levels and WMH volume in *APOE4* carriers.

Variable	Multivariable (all variables entered in the model)						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	β Beta			Lower Bound	Upper Bound
Age (Years)	0.028	0.012	0.540	2.31	0.037	0.002	0.055
Sex (Male)	-0.622	0.315	-0.793	-1.98	0.068	-1.297	0.053
PDGF-BB (pg/mL)	0.421	0.133	0.585	3.16	0.007	0.135	0.707
ICV (cm^3)	0.001	0.001	0.427	1.17	0.261	-0.001	0.003

Note: APOE4 = apolipoprotein-e4 (APOE4) allele carrier; PDGF-BB = platelet-derived growth factor BB; ICV = intracranial volume. Bold values indicate significant predictors of WMH volume. B represents the unstandardized regression coefficient and β represents the standardized regression coefficient.

Fig. 1. Partial regression plot of association between WMH volume and PDGF-BB in *APOE4* carriers and non-carriers.

Table 4

Association between PDGF-BB levels and WMH volume in *APOE4* non-carriers.

Variable	Multivariable (all variables entered in the model)						
	Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
	B	Std. Error	β			Lower Bound	Upper Bound
Age (Years)	0.025	0.008	0.432	2.98	0.005	0.008	0.042
Sex (Male)	-0.123	0.148	-0.144	-0.83	0.412	-0.422	0.176
PDGF-BB (pg/mL)	0.112	0.146	0.111	0.77	0.448	-0.183	0.406
ICV (cm^3)	0.000	0.001	0.073	0.42	0.678	-0.001	0.001

Note: APOE4 = apolipoprotein-e4 (APOE4) allele carrier; PDGF-BB = platelet-derived growth factor BB; ICV = intracranial volume. Bold values indicate significant predictors of WMH volume. B represents the unstandardized regression coefficient and β represents the standardized regression coefficient.

remained a significant predictor of WMH volume (β = 0.421, p = 0.007, 95% CI [0.135, 0.707], Table 3, Fig. 1). However, in non-carriers, there was no relationship between PDGF-BB levels and WMH volume (Table 4, Fig. 1).

We also stratified the analysis by diagnosis and conducted the same analysis in MCI participants only, which yielded the same results.

4. Discussion

In the present study, we observed that circulating levels of PDGF-BB are selectively related to small vessel damage in *APOE4* carriers, suggesting activation of platelet-derived growth factors in the context of

cerebrovascular injury, specifically in individuals at genetic risk of AD. These findings are consistent with prior studies showing elevated cerebrospinal fluid levels of sPDGFRβ in *APOE4 carriers* and among individuals with cognitive dysfunction and AD [17,18,24]. Increased PDGF-BB levels and loss of PDGFRβ in the precuneus and underlying white matter in AD brains post-mortem has previously been observed [25]. Elevated levels of sPDGFRβ in CSF are further associated with cognitive decline in *APOE4* carriers, and to a lesser degree in non-carriers [14,18], suggesting a role for pericytes and blood-brain barrier dysfunction in cognitive decline and AD.

Platelet-derived growth factors are actively involved in blood vessel formation, and binding of PDGF-BB to the receptor PDGFRβ triggers

pathways which augment blood-brain barrier integrity [26,27]. PDGF proteins are also known to be involved in angiogenesis after stroke, and found to be expressed on brain microvascular endothelial cells and specifically in white matter [28]. Similar angiogenic processes—such as increased levels of circulating endothelial progenitor cells (EPCs) and vascular endothelial growth factor D (VEGF-D)—are known to be activated in response to cerebral small vessel disease [29,30]. Prior studies have also supported a role for aberrant angiogenesis in the development of AD [31–33]. It remains unclear whether elevated levels of PDGF-BB in *APOE4* carriers indicate a compensatory mechanism to trigger angiogenesis and rescue the vasculature or an abnormal mechanism causing further damage. For example, Aβ may prevent binding of PDGF-BB to PDGFRβ [25,34], leading to increased levels of circulating PDGF-BB. *APOE4* knock-in mice studies have also shown that the *APOE4* isoform does not bind low-density lipoprotein receptor-related protein 1 (LRP-1), which is known to be involved in numerous biological processes such as removal of excess amyloid beta [35,36]. This further triggers the proinflammatory cyclophilin A–matrixmetalloproteinase-9 (CypA–MMP9) pathway in brain pericytes, leading to pericyte injury, MMP-9 mediated blood-brain barrier breakdown and ultimately, neuronal dysfunction [10,14,15]. This process results in increased levels of pericyte-injury marker sPDGFRβ, as observed in CSF in *APOE4* carriers [14]. Greater shedding of sPDGFRβ receptor as well as pericyte degradation may therefore lead to higher levels of circulating PDGF-BB ligand levels.

PDGFs are known to induce migration of pericytes and maintain microvascular integrity [37,38]. Prior *in vitro* studies have shown shredding of sPDGFRβ in response to hypoxia and Aβ [37] and increased sPDGFRβ levels in the CSF in AD may represent a biomarker suggesting microvascular damage [24]. Disruptions in PDGF signaling may occur due to loss of PDGFRβ on the cell surface due to shedding and potentially subsequent increases in circulating PDGF-BB. Given that PDGF-BB and PDGFRβ likely act as paracrine growth factors, Sagare et al. [37] suggest that disruption of this signaling pathway could influence communication with neighboring neurovascular unit cell types and downstream signal transduction events. This could ultimately influence blood brain barrier integrity, angiogenesis, cerebral blood flow and cognition. Further longitudinal studies evaluating the association between the PDGF signaling pathway and small vessel disease, AD related pathology and cognitive decline could also elucidate the role of angiogenesis in the development of dementia.

Limitations of this study include the cross-sectional design and limited sample size. In addition, given that *APOE4* carriers were more likely to have MCI, future studies are warranted to examine if these findings are consistent in those with and without cognitive impairment. Nonetheless, we observed a novel association between PDGF-BB and WMH in *APOE4* carriers. CSF levels of PDGF-BB were unavailable for the current analysis; however, a prior study has shown elevated levels of PDGFRβ in CSF in *APOE4* carriers [24]. Future studies should evaluate CSF levels of PDGF-BB as well. Numerous drugs treatments that target the PDGF pathway are already available [39]. Understanding the role of this pathway and of angiogenesis in the development of small vessel disease and AD could uncover potential treatment opportunities.

Declaration of Competing Interest

None.

Acknowledgments

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