Serum detection of blood brain barrier injury in subjects with a history of stroke and transient ischemic attack

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ABSTRACT

Objective: Stroke and transient ischemic attack may have long-term negative effects on the blood-brain barrier (BBB) and promote endothelial inflammation, both of which could increase neurodegeneration and dementia risk beyond the cell death associated with the index event.

Methods: Serum from 88 postmortem subjects in the Arizona Study of Aging and Neurodegenerative Disorders were analyzed by sandwich ELISA for specific biomarkers to investigate the effects of cerebrovascular accidents (CVAs) on BBB integrity and endothelial activation. Statistical analyses were performed using the Mann-Whitney *U* Test, Spearman rank correlation, and linear/logistic regressions adjusted for potential confounders; a *P*-value $< .05$ was considered significant for all analyses.

Results: Serum PDGFRß, a putative biomarker of BBB injury, was significantly increased in subjects with vs without a history of CVA who had similar cardiovascular risk factors ($P < .01$). This difference was stable after adjusting for age, hypertension, and other potential confounders in regression analysis (odds ratio, 27.02; 95% confidence interval, 2.61-411.7; $P < .01$). In addition, PDGFRß was positively associated with VCAM-1, a biomarker of endothelial inflammation ($\rho = 0.42$; $P < .01$).

Conclusions: Our data suggest that patients with stroke or transient ischemic attack have lasting changes in the BBB. Still more, this demonstrates the utility of PDGFRß as a serum-based biomarker of BBB physiology, a potentially powerful tool in studying the role of the BBB in various neurodegenerative diseases and COVID infection sequelae.

Clinical Relevance: Our data demonstrate the utility of serum PDGFRß, a putative biomarker of BBB integrity in the setting of stroke and TIA (CVA). A serum biomarker of BBB integrity could be a useful tool to detect early BBB damage and allow prospective work to study how such damage affects long-term neurodegenerative risk. Since BBB disruption occurs early in ADRD development, it could be monitored to help better understand disease progression and involvement of vascular pathways in ADRD. (JVS—Vascular Science 2024;5:100206.)

Keywords: Blood-based biomarkers; Blood-brain barrier; Endothelial inflammation; Ischemic attack; Stroke; Transient

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Stroke, and, to a lesser extent, transient ischemic attacks (TIAs), are increasingly recognized as independent risk factors for Alzheimer's disease and related dementias (ADRDs).[1,2] In addition to acute tissue loss by infarction, patients with these disease processes could have increased risk for ADRD development by disrupting blood-brain barrier (BBB) integrity through various mechanisms including embolic events that are clinical (ie, stroke and TIA) and/or subclinical, such as microemboli. BBB injury is a prominent characteristic of both ischemic and hemorrhagic stroke.[3-5] BBB injury is characterized by endothelial inflammation and the disruption of BBB cellular components, including tight junctions, pericytes, astrocytes, endothelial cells, and other cell types.[6,7] The time course of BBB dysfunction after stroke may occur in two phases: acute and delayed. In the acute phase following a cerebrovascular accident (CVA), cerebral micro vessels are obstructed by large clots or microemboli, leading to hypoxia and release of cytokines and matrix metalloproteases from astrocytes.[8-10] Additionally, the accumulation of peripheral inflammatory molecules post-event exacerbates the progression of delayed BBB dysfunction and cerebral injury secondary to stroke.[11]

Platelet-derived growth factor receptor (PDGFRß) is a marker of pericyte injury, and increased levels of PDGFRß have been associated with disruption of the BBB in both animal models and humans.[12,13] Pericytes are the only contractile components present on capillaries of the brain and greatly affect overall cerebral blood flow.[14-16] PDGFRß increases as pericyte death/stress occurs because pericytes shed PDGFRß in response to unfavorable conditions such as hypoxia,[17,18] which is common with CVAs.[19,20] Recent evidence has shown that PDGFRß can be quantified in cerebrospinal fluid (CSF) and has implications in neurodegenerative diseases such as Alzheimer's Disease.[21-25] However, serum biomarkers are less invasive, less expensive, and more accessible than current imaging or CSF biomarkers. A serum biomarker of BBB integrity would have meaningful clinical and experimental potential. Pericytes are primarily found in the central nervous system at an approximately 30- to 100-fold higher concentration compared with other areas of the body, increasing the likelihood that serum PDGFRß is reflective of BBB physiology.[26] Additionally, recent work has identified a significant association between serum and CSF PDGFRß.[17,27]

In this cross-sectional analysis, we evaluate the effect of stroke and TIA on the BBB and the interplay between endothelial inflammation and BBB dysfunction utilizing a novel serum biomarker; this could be a highly valuable tool in exploring the role of the BBB in the pathogenesis of various neurodegenerative pathologies and COVID infection sequalae.

ARTICLE HIGHLIGHTS

- **Type of Research:** Human study
- **Key Findings:** Eighty-eight participants in the Arizona Brain and Body Donation Program were split based on their history of stroke or transient ischemic attack (cerebrovascular accident [CVA]). Serum PDGFRß, a putative biomarker of blood-brain barrier (BBB) injury, was elevated in subjects with CVA and was associated with VCAM-1, a marker of endothelial inflammation.
- **Take Home Message:** These data indicate that CVAs may have lasting negative effects on the BBB and demonstrate the utility of a serum-based biomarker of BBB integrity in the context of cerebrovascular disease.

METHODS

Patient subset. Eighty-eight participants enrolled in the Brain and Body Donation Program at Banner Sun Health Research Institute, and the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND) from 1997 to 2019 were included in this cross-sectional study. These participants are followed annually through a standardized clinical assessment. The subjects' clinical diagnoses were assigned post-mortem, after a final review of all clinical data, medical records, and neuropathological examination findings.[28] A diagnosis of CVA was defined as a history of stroke or TIA. Subjects were eligible for inclusion if they had at least 500 µl of postmortem serum available for analysis. The clinical and neuropathological data from participants in the Arizona Brain and Body Donation program are available at http://www.brainandbodydonationprogram.org. The enzyme-linked immunosorbent assay (ELISA) data utilized in this study will be made available upon reasonable request to the corresponding author (C.W.).

ETHICS APPROVAL

All experiments were conducted in accordance with the Declaration of Helsinki. The operations of the Brain and Body Donation Program (AZSAND) are approved by Institutional Review Boards and all participants, or their legal representatives gave informed consent.

CONSENT TO PARTICIPATE

All subjects or their legal representatives signed written informed consent.

Collection of serum samples. The median time that passes between death and the initiation of autopsy is 3 hours across all participants in AZSAND.[28] The postmortem serum collection procedure for AZSAND has been previously described in detail by Beach et al.[28] In

Table I. General and clinical demographics split by the presence of cerebrovascular accident (*CVA*)

Characteristic	No CVA (n = 40)	CVA (n = 48)	*P*-value[a]
Age at death, years			
Median (IQR)	84.0 (12.5)	87.5 (10.0)	.06
Min, Max	64, 100	70, 103	
Gender			
Male	25 (62.5)	25 (52.1)	.39
Female	15 (37.5)	23 (47.9)	
Last MMSE score[b]			
Median (IQR)	24.0 (15.0)	22.0 (12.75)	.55
Diabetes			
Yes	20 (50.0)	13 (27.1)	.05
Hyperlipidemia			
Yes	26 (65.0)	32 (66.7)	1
HTN			
Yes	20 (50.0)	38 (79.2)	<.01
CAD			
Yes	14 (35.0)	28 (58.3)	.03
ECAD			
Yes	18 (45.0)	24 (50.0)	.67
Atrial fibrillation			
Yes	7 (17.5)	13 (27.1)	.32
Cancer			
Yes	20 (50.0)	16 (33.3)	.13

CAD, Coronary artery disease; *ECAD*, extracranial carotid artery disease; *HTN*, hypertension; *IQR*, interquartile range; *Max*, maximum; *Min*, minimum; *MMSE*, Mini-Mental State Exam; *TIA*, transient ischemic attack.
Data are presented as number (%) unless otherwise indicated.
[a]Based on Mann-Whitney *U* test for continuous variables and Fisher exact test for categorical variables.
[b]One subject from the No CVA group had a missing MMSE score.

summary, the blood was drawn prior to removing the brain during autopsy by a transthoracic puncture of the heart using an 18-gauge needle connected to a 30 mL polyethylene syringe. The blood is placed into standard serum separator vacuum tubes (7 mL) and were given time to clot prior to centrifugation. After centrifugation, the samples were frozen and stored at −80 °C, in 500 μg or 1000 μg aliquots. Upon collection of the serum samples from the AZSAND, the samples were thawed and were split into separate aliquots each containing 50 μl and then refrozen at −80 °C until experimentation.

Detection of PDGFRß and VCAM-1 in serum. Sandwich ELISA technology was utilized to detect PDGFRß and VCAM-1 in serum. ELISA analysis was performed using commercially available and validated test kits (Invitrogen). Before the assay, the samples were diluted with a kit-provided diluent buffer at 100× for PDGFRß and 50× for VCAM-1. The samples, standards, and blanks were all run in duplicate. The mean absorbance values from the duplicate wells were used to interpolate the concentrations of PDGFRß and VCAM-1 using the standard curve generated during each experiment. Each experiment was performed twice, and the mean concentrations were used for the analysis. The detailed procedures and research materials utilized for detection of PDGFRß and VCAM-1 are described in the Extended Methods and Major Resources Table of the Supplementary Appendix (online only).

Statistical analysis. Subject general and clinical demographics (Table I) and comparisons between groups were analyzed using the Mann-Whitney *U* test or Fisher Exact test, as applicable, to test the significance of the differences with continuous and categorical variables. Serum PDGFRß was $\log_{10}$ transformed for all analyses.

The relationship between PDGFRß and VCAM-1 was analyzed using the Spearman correlation. Associations between PDGFRß and CVA and subtypes of CVA were analyzed using the Mann-Whitney *U* Test. For the secondary analysis, logistic and linear regression models were run to adjust for relevant cardiovascular risk factors as follows: (1) a multiple logistic regression model with any CVA as the dependent variable and multiple cardiovascular risk factors as predictors; and (2) a multiple linear regression model with PDGFRß as the dependent variable. Conditions associated with cerebrovascular physiology and BBB dysfunction, including age, sex,

hypertension (HTN), hyperlipidemia, coronary artery disease (CAD), atrial fibrillation, diabetes, cancer, and extracranial carotid artery disease (ECAD) were selected as covariates. These covariates were selected because of their role in BBB/pericyte pathophysiology along with CVA development.[13,22,29-37]

A *P*-value $< .05$ was considered statistically significant. Statistical tests were conducted using GraphPad Prism Version 10.1.2 (324).

Supplementary analysis. In the supplementary analysis, the effect of potential confounding variables on the relationship between PDGFRß and CVA was explored. These potential confounding variables were defined as clinical or general demographic data that differed between the groups in our primary analysis, as noted in Table I. The subjects with a diagnosis of HTN were identified and split into two groups based on their CVA status, similar to the primary analysis (HTN + CVA vs HTN − CVA), resulting in groups with a similar distribution of age, hypertension, and CAD.

RESULTS

Primary analysis. For the primary analysis, our 88 subjects were split into two groups, determined by CVA status. The CVA group was slightly older than the no CVA group ($P = .06$), with a similar distribution of males and females ($P = .39$). Additionally, the CVA group contained a higher prevalence of HTN and CAD ($P < .05$). The no CVA group contained more subjects with diabetes than the CVA group ($P = .05$). The two groups were of similar cognitive status, as determined by Mini-Mental State Exam (MMSE) scores ($P = .55$). The general and clinical demographics of our subjects are summarized in Table I.

There was a significant increase observed in PDGFRß concentration in the serum of subjects with a history of CVA compared with those without CVA ($P < .01$) (Fig 1). Subjects with TIA had slightly higher levels of PDGFRß compared with those with stroke, but without reaching statistical significance ($P = .52$) (Fig 2, *A*). When stratifying by type of CVA, subjects with a history of stroke and TIA had elevated serum PDGFRß compared with those without ($P < .01$) (Fig 2, *B* and Fig 2, *C*). Additionally, PDGFRß was positively associated with VCAM-1 ($\rho = 0.42$; $P < .01$) (Fig 3, *A*), which was elevated in the presence of CVA, but without significance ($P = .16$) (Fig 3, *B*).

Secondary analysis. Figs 4 and 5 summarize regression models that were fit to examine the relationship between CVA and PDGFRß, adjusting for other clinical variables. In the multiple logistic regression model, PDGFRß was the only variable associated with increased odds for any CVA (odds ratio [OR], 27.02; 95% confidence interval [CI], 2.61-411.7; $P < .01$) (Fig 4). In the multiple linear regression model, the only variable associated with increased odds for elevated PDGFRß was the presence of any CVA (ß = 0.14; 95% CI, 0.04-0.25; $P < .01$) (Table II).

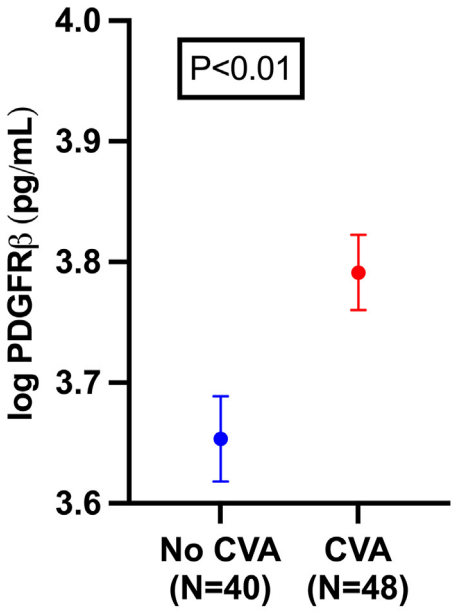

Fig 1. Serum platelet-derived growth factor receptor-ß (*PDGFRß*) is elevated in the serum of subjects with cerebrovascular accident (*CVA*) using the Mann-Whitney *U* test. The data are shown as means with error bars representing the standard error of the mean (SEM).

Supplementary analysis. To control for the possibility of HTN driving the effect on PDGFRß in CVA vs no CVA cohorts, we did an additional comparison by including only hypertensives in each group. The resulting groups were of similar age and sex, with an equal distribution of clinical variables as summarized in the Supplementary Table (online only). Similar to our primary analysis, the +HTN+CVA group had increased PDGFRß compared with the +HTN−CVA group ($P < .01$). A summary of demographic information and results from this analysis is available in the Supplementary Materials, online only (Supplementary Fig, online only).

DISCUSSION

This project utilized commercially available ELISA kits to explore potential biomarkers of cerebrovascular physiology in the serum of participants with and without CVA. Our data demonstrate that PDGFRß is increased in the serum of patients with CVA, independent of covariates. Because the serum was obtained months to years after the events, this implies that stroke and TIA could have lasting negative effects on the BBB. In addition, these data are important because they indicate that serum PDGFRß can be used as a biomarker of this damage, in agreement with mouse data[12] and data showing a correlation between PDGFRß in the serum and CSF[17,27] in humans. The mechanism of this potential long-term effect is unknown, but it could be related to sustained inflammatory pathways resultant from the CVA event, ongoing subclinical microembolic events occurring in

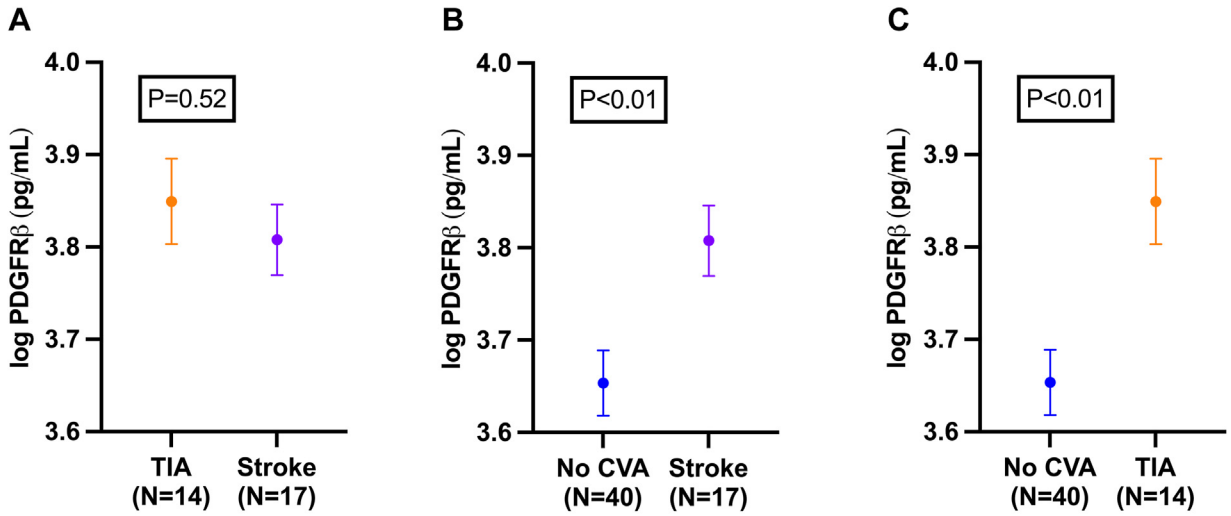

Fig 2. Platelet-derived growth factor receptor-ß (*PDGFRß*) is elevated in cerebrovascular accident (*CVA*) subtypes using the Mann-Whitney *U* test. The data are shown as means with error bars representing the standard error of the mean (SEM). **A**, No significant differences were observed related to PDGFRß between stroke and transient ischemic attack (*TIA*). **B**, Serum PDGFRß was elevated in stroke compared with subjects without CVA. **C**, Serum PDGFRß was elevated in TIA compared with subjects without CVA.

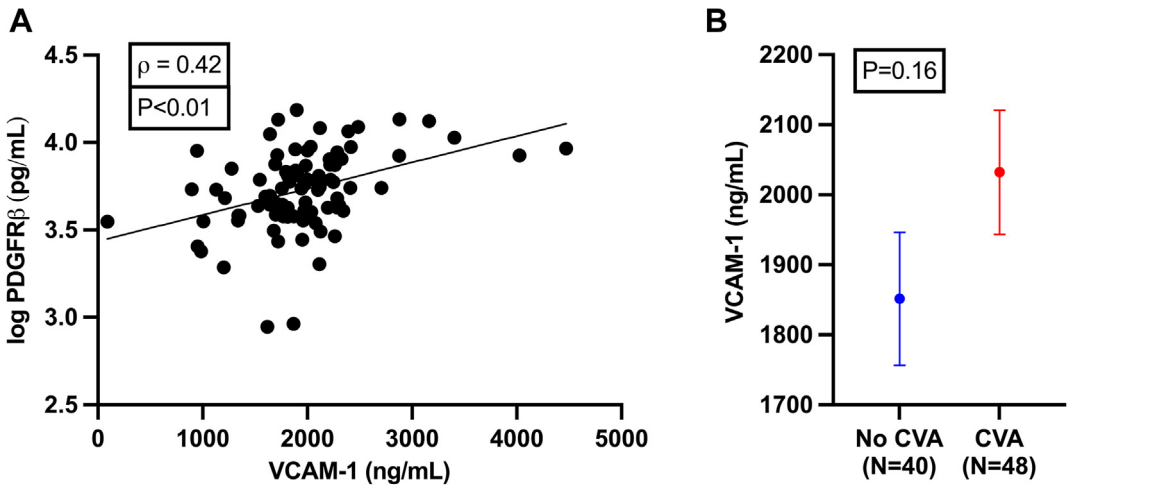

Fig 3. Association of vascular cell adhesion molecule (*VCAM*)-1 with platelet-derived growth factor receptor-ß (*PDGFRß*) and cerebrovascular accident (*CVA*) physiology. **A**, Association of PDGFRß and VCAM-1 in the serum using Pearson correlation. The plot includes a simple regression line for visual reference. **B**, VCAM-1 is modestly elevated in subjects with CVA using the Mann-Whitney *U* test. The data are shown as means with error bars representing the standard error of the mean (SEM).

these patients who have proven risk, or other unknown reasons or possible confounders, beyond those for which we were able to control.

Although BBB damage in the setting of stroke has been previously demonstrated,[38,39] we found that PDGFRß was also elevated in subjects with a history of TIA alone. This finding is in agreement with the results reported by Serlin et al,[40] who found that patients with a minor stroke or TIA have an increased brain volume containing BBB damage compared with age-matched controls using dynamic contrast-enhanced magnetic resonance imaging. In addition, TIA subjects with a larger brain volume containing BBB damage at baseline were at increased risk for developing future stroke and neurological impairment.[40] These data highlight that even minor events (TIAs) have lasting correlations with BBB physiology and quantification of this damage via a serum-based test would have great utility.

In addition to demonstrating the relationship between the BBB and CVAs, our data also show a positive relationship between endothelial inflammation and BBB damage, as measured by PDGFRß and VCAM-1 in

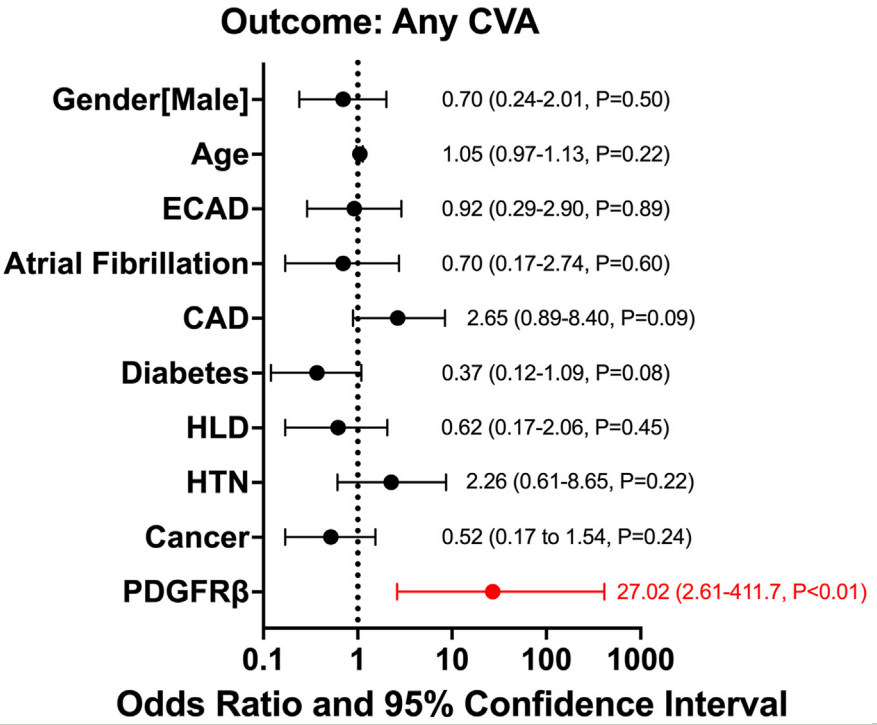

Fig 4. Platelet-derived growth factor receptor-ß (*PDGFRß*) is associated with increased odds for having any cerebrovascular accident (*CVA*) in multiple logistic regression analysis. The odds ratio, 95% confidence interval, and respective *P*-value for each variable is summarized in the given table. *CAD*, Coronary artery disease, *ECAD*, extracranial carotid artery disease, *HLD*, hyperlipidemia, *HTN*, hypertension.

Table II. Cerebrovascular accidents (CVAs) are associated with increased odds for elevated platelet-derived growth factor receptor-ß (*PDGFRß*) in multiple linear regression analysis

Outcome: PDGFRß			
Variable	ß estimate	95% CI	*P*-value
Gender, male	0.02	−0.08 to 0.12	.70
Age, years	0.003	−0.004 to 0.01	.39
ECAD	−0.06	−0.17 to 0.05	.30
Atrial fibrillation	−0.01	−0.14 to 0.13	.92
CAD	−0.04	−0.15 to 0.07	.50
Diabetes	0.01	−0.10 to 0.12	.85
HLD	0.05	−0.07 to 0.16	.42
HTN	0.04	−0.09 to 0.17	.56
Cancer	0.07	−0.03 to 0.18	.19
Any CVA	0.14	0.04 to 0.25	<.01

CAD, Coronary artery disease; *CI*, confidence interval; *ECAD*, extracranial carotid artery disease; *HLD*, hyperlipidemia; *HTN*, hypertension.

postmortem serum. This is in direct agreement with a recent antemortem study performed by Butts et al, who found an association at baseline and at 2-year follow-up between PDGFRß and VCAM-1 in CSF after adjusting for age, sex, race, and education.[25] Endothelial inflammation is characterized by the binding of leukocytes to receptors on endothelial cells and triggering the release of pro-inflammatory signaling molecules.[41] VCAM-1, a member of the immunoglobulin family, is a cell adhesion molecule allowing for the endothelial regulation of immune cell extravasation and inflammatory pathways.[42] It is upregulated in carotid endothelium in patients with unstable atherosclerotic plaque,[43] which may provide a link between CVA and inflammatory pathways that could affect BBB integrity/damage. Our data support the hypothesis that endothelial inflammation and BBB dysfunction have associated neuroinflammatory pathways. In our study, VCAM-1 was elevated in the serum of subjects with CVA compared with those without; however, this relationship was not statistically significant. This lack of a significant association may be due to a small sample size. Future studies of larger sample sizes in living patients are needed to confirm or deny this preliminary finding.

The results of the present study show the utility of PDGFRß as a biomarker of BBB physiology. Serum biomarkers indicative of cerebrovascular pathology are being increasingly sought due to their accessibility, noninvasive nature, and potential to detect and differentiate neurodegenerative processes.[44] A serum biomarker of BBB integrity could be a valuable tool to detect early injury to the BBB and facilitate prospective work to determine how such damage affects long-term

neurodegenerative risk. BBB disruption occurs early in ADRD development, and it could be monitored to help better understand disease progression and involvement of vascular pathways in ADRD. In addition, PDGFRß may also be a beneficial tool to explore downstream effects of the COVID-19 infection on the BBB. BBB dysfunction is observed in patients with a history of COVID-19 infection and may contribute to the neuropsychological deficits seen in these patients.[45-47] Therefore, a serum biomarker of BBB dysfunction such as PDGFRß could help to identify patients who may be at an increased risk for developing cognitive impairment after COVID-19 infection.

There were some key limitations to this study. The first limitation is the postmortem serum collection; it is difficult to know how hypoxia at the time of death affects PDGFRß release from the BBB, but we presume that all enrolled patients (with or without CVA) would be affected similarly. Future prospective studies in living patients will be needed to confirm our results. The second limitation of this study is the relatively small sample size, which could result in type I or II errors. It also limited our ability to exhaustively control for potential confounders. However, we were able to control for key differences between the groups (age, sex, HTN, hyperlipidemia, CAD, diabetes, cancer, and ECAD). Additionally, when the CVA group was further stratified, the remaining stroke and TIA groups had low sample sizes, which decreases the power of those analyses. We were also limited by low sample volumes, which limited our ability to explore other inflammatory markers that may be similarly elevated in patients with CVA. However, our work,[43] which is in agreement with others,[48] has shown VCAM-1 to be the most reliable marker when looking at cerebrovascular endothelial inflammation. Future studies are warranted to explore the associations between other inflammatory biomarkers and cerebrovascular events. Finally, we were limited to a self-reported history of stroke or TIA as our diagnoses of CVA, so different subtypes of CVA, as defined by the American Heart Association/American Stroke Association,[49] were unable to be distinguished from one another. Similarly, the timeline of when the CVAs occurred was unknown. Although our data provide support for a lasting effect on the BBB after CVA, future longitudinal studies in living participants are warranted to determine how serum PDGFRß concentrations change over time. The study is also limited (and exciting) because serum PDGFRß is not a proven marker of BBB injury, and we have no imaging or histology available in these patients to confirm this. However, PDGFRß is derived from pericytes, which are present in a 30× to 100× higher concentration in the central nervous system compared with other areas of the body, increasing the likelihood that this serum PDGFRß is associated with the BBB.[26] Future work could help confirm or refute this.

CONCLUSION

PDGFRß, a putative serum biomarker of BBB injury, was significantly elevated in subjects who had a history of stroke or TIA compared with subjects without CVA, indicating these clinical events are associated with lasting negative effects on the BBB. This was also associated with elevated VCAM-1, an established biomarker of endothelial inflammation. These data demonstrate the potential utility of a serum-based biomarker of BBB integrity, which could be a powerful tool in studying the role of the BBB in various neurodegenerative diseases and COVID-19 infection sequelae. Further longitudinal studies involving subjects particularly at risk for CVAs are currently underway to validate these findings.

AUTHOR CONTRIBUTIONS

Conception and design: CW
Analysis and interpretation: SF, JA, SZ, KK, EB, EM, CW
Data collection: SF, IB, GS, TB
Writing the article: SF, CW
Critical revision of the article: SF, JA, IB, SZ, KK, EB, GS, TB, EM, CW
Final approval of the article: SF, JA, IB, SZ, KK, EB, GS, TB, EM, CW
Statistical analysis: SF, SZ, KK, EB
Obtained funding: SF, GS, TB, CW
Overall responsibility: CW

DISCLOSURES

None.

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