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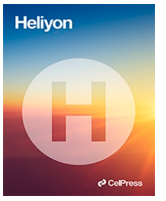

Research article

Association of ADAMTS13 activity with cerebral deep medullary vein: A community-based cross-sectional study

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ABSTRACT

Objectives: This study aims to investigate whether circulating ADAMTS13 activity can offer insights into the mechanism of pathophysiological changes in deep medullary veins (DMVs).
Methods: This study was conducted on a community cohort of elderly individuals in Shanghai. Plasma von Willebrand factor (VWF) levels and ADAMTS13 activity were measured. A validated DMV score described the overall burden of DMV on the brain. Through ordinal regression models, we investigated the correlation between VWF levels, ADAMTS13 activity, and increasing severity of DMV score while adjusting for demographics and cardiovascular risk factors.
Results: The study enrolled 262 subjects according to the inclusion criteria. The mean VWF level (1.35 ± 0.25) was higher in the DMV group than in the group without DMV (1.25 ± 0.30) ($p = 0.025$), and ADAMTS13 activity (83.76 ± 7.96) was relatively lower. After adjusting for age, sex, alcohol consumption, smoking, hypertension, and diabetes, reduced ADAMTS13 activity [$\beta = -7.78$; 95 % CI (-10.21, -5.35) $p < 0.01$] was associated with DMV. Moreover, correlation analysis indicated that ADAMTS13 activity was negatively correlated with the DMV score (Kendall's tau-b $= -0.53$, $p < 0.001$).
Discussion: In summary, there was an inverse correlation observed between ADAMTS13 activity and the DMV score, which may provide some clinical clues for exploring the potential pathogenesis of DMV.

1. Introduction

Deep medullary veins (DMVs) are tiny parenchymal vessels situated within the periventricular white matter, varying in diameter from tens to hundreds of microns. They play a crucial role in draining deeply and connecting to the deep venous system through the corresponding subependymal veins [1,2]. The significance of DMVs came to light with the description of periventricular venous collagen disease in 1995, highlighting non-inflammatory degenerative changes in periventricular and subependymal veins [1]. Since the advent of susceptibility-weighted imaging (SWI) as a non-invasive MRI technique, researchers have gained the ability to observe and evaluate DMVs in vivo, with minimal developmental variations in the paraventricular DMV [3].

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SWI technology has opened new avenues for studying DMVs, allowing for their visualization on 3-T magnetic resonance imaging (MRI) [4]. Notably, studies have revealed that alterations in DMV appearance on SWI, such as discontinuity or reduced numbers, may indicate venous collagenases in the absence of infection, inflammation, trauma, or tumor invasion [5,6]. In 2017, Zhang et al. established an SWI-based DMV score for visual scoring of deep medullary veins. They found that increased DMV scores were independently associated with higher white matter hyperintensity (WMH) volumes [7]. Consequently, Xu et al. concluded that the DMV score may be a novel imaging biomarker for cerebral small vessel disease (CSVD) associated with cognitive impairment [8].

Despite the potential utility of DMVs as an imaging marker, their assessment primarily relies on complex neuroimaging methods, with limited exploration of circulating biomarkers. Existing research has suggested that disruptions or reductions in DMVs may be attributed to various factors, including endothelial dysfunction, inflammatory reactions, chronic ischemia, or disturbances in cerebral blood flow circulation [9,10]. Among circulating biomarkers, A Disintegrin and Metalloproteinase with A Thrombospondin Motif Repeat 13 (ADAMTS13) has drawn interest for its involvement in cerebrovascular disease. The antithrombotic activity of ADAMTS13 arises from its role in breaking down von Willebrand factor (VWF) multimers. This enzymatic process is closely tied to the shear-dependent availability of its substrate, VWF [11,12] Moreover, ADAMTS13's function is significantly impacted by various factors, including genetic mutations, autoimmune diseases, pregnancy, infections, and immunosuppressants [13].

Our previous investigations have revealed a close correlation between ADAMTS13 activity and the severity of CSVD, underscoring its potential significance as a circulating biomarker [14]. Given the emerging role of DMVs as an imaging marker for CSVD, this study aims to explore the potential of circulating ADAMTS13 activity in shedding light on the pathophysiological changes in DMVs. By unraveling the link between ADAMTS13 and DMVs, valuable insights can be gained into the underlying mechanisms of DMV-related pathophysiology and its implications for CSVD.

2. Materials and methods

2.1. Study population

The subjects of this study were obtained from the "Investigation on the Status of Cerebrovascular Diseases and Establishing Cohort in Shang Hai Aging Population (ISCDECSHAP)", a population-based, prospective cohort study of the aging population in Shanghai. The protocol details were provided in previous studies [14,15]. Neurologists collected demographic and clinical data using standardized questionnaires, covering parameters such as gender, age, hypertension, diabetes mellitus, smoking and alcohol consumption, as well as other pertinent health conditions. All subjects underwent cerebral MRI and laboratory blood tests. Based on the study's objectives, our inclusion criteria were as follows: ≥60 years of community elderly; Without neurological symptoms and signs; Individuals with prior occurrences of non-specific neurological symptoms, such as headache, vertigo, dizziness and tinnitus that had completely resolved at the time of assessment were eligible for inclusion. Individuals who met the following criteria were excluded: history of stroke, cognitive dysfunction, heart disease, malignancies, hepatic or renal diseases, autoimmune diseases, or infection at enrollment. Participants or their legal guardians gave written informed consent, and the study received approval from the Ethics Committee for

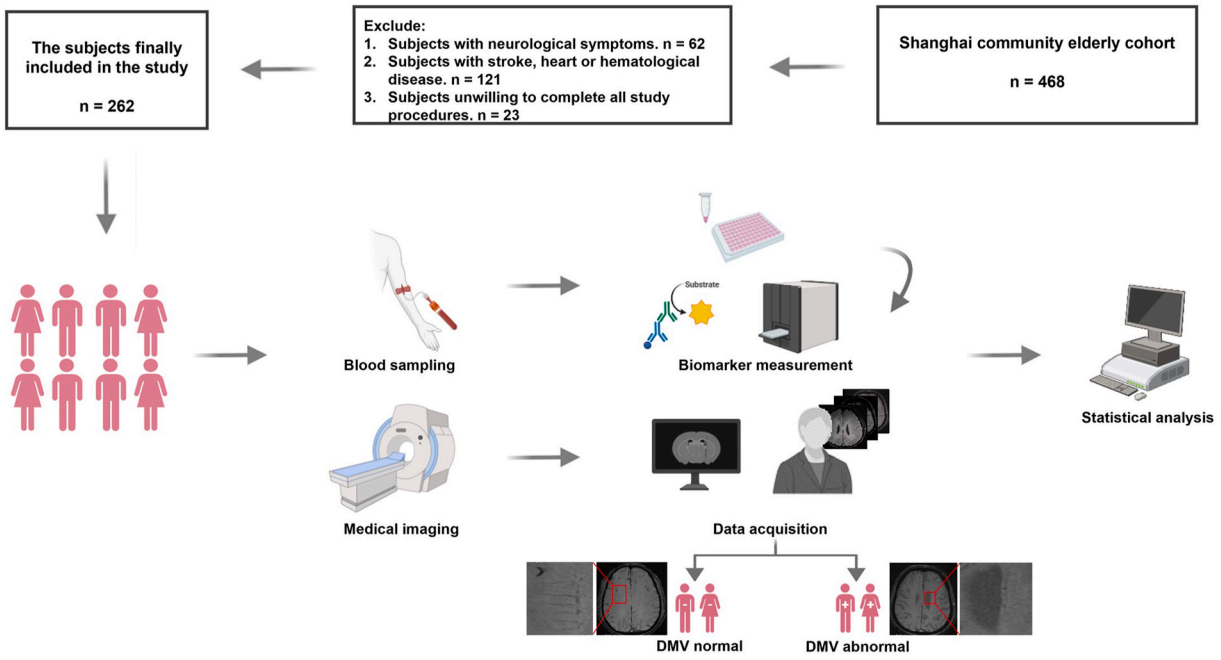

Fig. 1. Flow chart.

Human Experimentation at both Huashan Hospital of Shanghai and Fifth People's Hospital of Shanghai, China. The clinical trial was registered with the Chinese Clinical Trial Registry under Registration No.: ChiCTR1800019615. The details of the research design are illustrated in Fig. 1.

2.2. Brain MRI and DMV score

Brain MRI (3.0T, GE Medical System, USA), scanning 20 axial images, slice thickness 5 mm, interslice distance 2 mm, images including T2-weighted images, T1-weighted images, fluid-attenuated inversion-recovery (Flair), diffusion-weighted magnetic resonance imaging (DWI), and SWI sequences. SWI sequence parameters: echo time (TE) = 20 ms, repetition time (TR) = 27 ms, matrix size = 320 × 256, slice thickness = 2 mm, flip angle = 15°, intersection gap = 0 mm, field of view (FOV) = 240 mm × 240 mm. DMV scoring was performed on five consecutive periventricular slices (10 mm thick) in SWI images. According to regional brain anatomy, DMV was divided into six segments, frontal, parietal, and occipital (bilateral), and each segment was scored individually for a semi-quantitative assessment based on observed continuity and visibility, with scores ranging from 0 to 3 for each region [7]. The specific criteria for scoring were as follows: 1) score 0: when venules were not interrupted, and the segment was continuous and clearly visible; 2) score 1: venules were continuous and visible but had heterogeneous signals in at least one vein; 3) score 2: venules had at least one discontinuous, weak visibility, and punctate hypointensity; 4) score 3: venules were not visible; DMV scores ranged from 0 to 18 and was the sum of DMV scores for each of the six parts. A DMV score of 0 indicates a normal state, while a score of 18 suggests a significant DMV abnormality. Subjects with a DMV score >0 can be defined as having abnormal DMV. Two neurologists independently assessed brain MRI of all subjects at Shanghai Fifth People's Hospital in a blind method, and the interobserver agreement value for the presence of DMV was 0.83. Any disagreement regarding the DMV score was resolved by consensus with the third neuroimaging expert (Fig. 2).

2.3. Measurement of ADAMTS13 activity and VWF level

Three milliliters of fasting venous blood were drawn from all subjects and anticoagulated with sodium citrate. Within 20 min of collection, the samples were centrifuged (2000 g, 5 min) and the resulting plasma samples were stored at −80 °C. The concentration of VWF in plasma was measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) kit purchased from Abcam, following the manufacturer's guidelines. Fluorescence resonance energy transfer (FRET) was used to determine ADAMTS13 activity in participants' plasma [43]. FRETS-VWF73 (ADAMTS13 fluorescent substrate) was purchased from AnaSpec, USA. A standard plasma sample, a mixture of plasma from 20 healthy individuals provided by the Physical Examination Center of the Fifth People's Hospital of Shanghai, was used to set the ADAMTS13 activity level at 100 %. The percentage of ADAMTS13 enzyme activity was expressed in the assay.

2.4. Statistical analysis

Data analysis was conducted using SPSS 26.0 statistical software. For clinical and demographic data, continuous variables that followed a normal distribution were described as mean ± standard deviation and compared by independent samples *t*-test or one-way ANOVA. Non-normally distributed continuous variables were presented as medians (interquartile ranges) and compared using nonparametric tests. Categorical variables were presented as frequencies (percentages) and compared by $\chi 2$ or Fisher's exact test.

Circulating biomarkers (ADAMTS13 activity and VWF levels) were analyzed for association with DMV using logistic and linear regression analyses. Multivariate linear regression was performed to analyze the correlations between ADAMTS13 activity and clinical data changes in patients with varying DMV scores, adjusting for age, sex, history of hypertension and diabetes, smoking and drinking

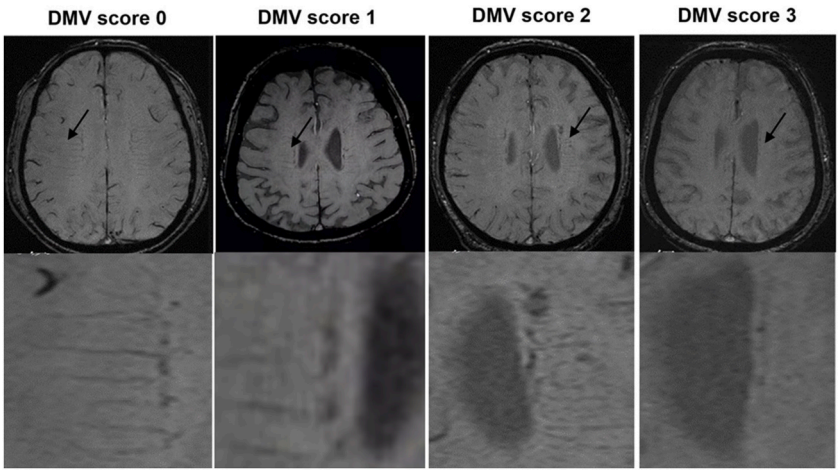

Fig. 2. Neuroimaging manifestations based on different DMW scores.

… Kendall's tau-b correlation analysis was utilized to evaluate the relationship between ADAMTS13 activity and DMV scores. Variables with $p < 0.1$ and significant clinical significance were included in the multiple regression model for all univariate analyses. *P*-value <0.05 was regarded as statistically significant.

3. Results

3.1. Associations between DMV and the ADAMTS13 activity

This study enrolled a total of 262 participants. Based on neuroimaging markers, subjects were divided into two groups: those with abnormal DMV and those with normal DMV. The data showed that abnormal DMV accounted for 49.6 % (n = 148) of the total sample. Subjects with abnormal DMV were older ($p < 0.001$) and had higher rates of hypertension ($p < 0.001$), diabetes ($p < 0.001$), smoking ($p < 0.001$), and alcohol consumption ($p < 0.001$) compared to the group with normal DMV. The mean VWF level in the abnormal DMV group (1.35 ± 0.25) was significantly higher than that in the group with normal DMV (1.25 ± 0.30) ($p = 0.025$), and ADAMTS13 activity (83.76 ± 7.96) was relatively lower in the abnormal DMV group with a statistically significant difference between the two groups ($p < 0.001$), as detailed in Table 1. In the regression model, reduced ADAMTS13 activity was associated with abnormal DMV after adjusting for age, sex, alcohol consumption, smoking, hypertension, diabetes, aspartate aminotransferase, alanine transaminase, c-reactive protein and VWF level ($\beta = -7.78$; 95 % CI (−10.21, −5.35), $p < 0.01$), as shown in Table 2. Additionally, we conducted calculations for the ADAMTS13:VWF ratio, and the findings revealed that when compared to ADAMTS13 alone, the ADAMTS13:VWF ratio exhibited a more pronounced association with DMV [$\beta = -8.71$; 95 % CI (−14.02, −3.39), $p < 0.01$] (Table 3).

3.2. Associations between DMV score and the ADAMTS13 activity

In this study, subjects were divided into three groups based on their DMV scores: 0, 1–6, 7–12, and 13–18. Participants were categorized into four groups based on quartiles of VWF level and ADAMTS13 activity respectively. According to different DMV scores, we observed significant differences in age ($p < 0.001$), smoking status ($p < 0.001$), alcohol consumption ($p < 0.001$), presence of diabetes mellitus ($p < 0.001$), hypertension ($p < 0.001$), ADAMTS13 activity ($p < 0.001$), and VWF level ($p < 0.001$). (Table 4). We conducted multiple linear regression analyses on four groups to explore the correlations between ADAMTS13 activity and clinical data changes in patients with varying DMV scores. However, no statistically significant differences were observed between ADAMTS13 activity and clinical data among the different DMV score groups (Supplementary Tables 1–4). More than half of the subjects had DMV scores of 0 (43.5 %) or 1–6 (15.6 %). ADAMTS13 activity was found to be present at levels <80.3 % in 66.1 % of patients with DMV scores of 13–18. Additionally, correlation analysis revealed that ADAMTS13 activity was negatively correlated with DMV score (Kendall's tau-b = −0.53, $p < 0.001$). Specific data can be found in Table 5. Increases in DMV scores were found to be inversely associated with ADAMTS13Q1$_{<80.3\ \%}$ [OR = 27.54, 95 % CI (12.63, 60.10) $p < 0.001$] and ADAMTS13Q2$_{80.3\ -\ 89.0\ \%}$ [OR = 7.40, 95 % CI (3.62, 15.12) $p < 0.001$], after adjusting for age, sex, alcohol consumption, current smoking, hypertension, and diabetes. Individuals with ADAMTS13 activity in Q1$_{<80.3\ \%}$ and Q2$_{80.3\ -\ 89.0\ \%}$ were 27.54 ($P < 0.01$) and 7.40 ($P < 0.01$) times more likely to have at least one grade higher DMV score than those with Q4 > 97.1 %. Furthermore, individuals with VWF levels in Q1$_{<1.14\ IU/mL}$, Q2$_{1.33\ -\ 1.14\ IU/mL}$, and Q3$_{1.33\ -\ 1.51\ IU/mL}$ groups were 0.04 ($P < 0.01$), 0.10, and 0.26 ($P < 0.05$) times more likely to have at least one grade higher DMV score than the Q4$_{>1.51\ IU/mL}$ population, respectively (Table 6).

Table 1
Baseline characteristics of the total study population.

	Normal DMV	Abnormal DMV	P
	n = 114	n = 148	value
Age, years	65 ± 4.9	72 ± 7.5	<0.001*
Male, n (%)	80 (46.8)	62 (49.6)	0.632
BMI, kg/m^2	24.7 ± 3.6	24.5 ± 3.6	0.754
Alcohol use, n (%)	22 (16.3)	60 (45.0)	<0.001*
Current smoking, n (%)	24 (17.9)	75 (55.1)	<0.001*
Hypertension, n (%)	51 (38.8)	101 (60.8)	<0.001*
Diabetes Mellitus, n (%)	22 (16.3)	58 (34.9)	<0.001*
Total cholesterol, mmol/L	4.26 ± 1.17	4.50 ± 1.20	0.560
HDL cholesterol, mmol/L	1.32 ± 0.61	1.37 ± 0.59	0.843
LDL cholesterol, mmol/L	3.38 ± 0.77	3.26 ± 0.81	0.564
AST, U/L	20.18 ± 6.9	21.80 ± 8.6	0.083
ALT, U/L	17.65 ± 6.7	19.65 ± 7.1	0.101
CRP. mg/L	1.77 ± 1.30	2.32 ± 1.35	0.128
FDP, ug/ml	2.94 ± 0.78	3.35 ± 0.97	<0.001
VWF:Ag, IU/mL	1.25 ± 0.30	1.35 ± 0.25	0.025*
ADAMTS13 activity (%)	93.48 ± 10.91	83.76 ± 7.96	<0.001*

Note: AST = aspartate aminotransferase; ALT = alanine transaminase; BMI = body mass index; CRP=C-reactive protein; FDP = fibrinogen-degradation products; LDL cholesterol = low density lipoprotein cholesterol; HDL cholesterol = high density lipoprotein cholesterol.

Table 2
Multiple linear regression analysis between ADAMTS13 and baseline characteristics.

	ADAMTS13 activity		
	Coefficient	95 % confidence interval	P valve
Male,	−0.18	[-2.35,1.98]	0.867
Age	−0.20	[-0.24,0.20]	0.860
Hypertension	−3.79	[-6.48,-1.10]	0.006
Diabetes Mellitu	−0.10	[-4.07,3.86]	0.960
Alcohol use	3.24	[-1.56, 8.04]	0.137
Current smoking	−4.34	[-8.12, −0.05]	0.025
AST, U/L	−0.06	[-0.21, 0.09]	0.434
ALT, U/L	0.05	[-0.06, 0.17]	0.375
CRP. mg/L	−0.22	[-0.56, 0.12]	0.202
VWF:Ag	−2.55	[-6.67, 1.58]	0.224
DMV	−7.78	[-10.21,-5.35]	< 0.001

Note：AST = Aspartate aminotransferase; ALT = Alanine transaminase; BMI = body mass index; CRP═C-reactive protein.

Table 3
Multiple linear regression analysis between ADAMTS13:VWF ratio and baseline characteristics.

	ADAMTS13:VWF ratio		
	Coefficient	95 % confidence interval	P valve
Male,	−3.05	[-7.78,1.68]	0.205
Age	−0.40	[-0.89,0.09]	0.105
Hypertension	−7.03	[-12.77,-1.30]	< 0.001
Diabetes Mellitu	1.68	[-6.99,10.35]	0.704
Alcohol use	3.95	[-0.17,10.46]	0.061
Current smoking	−4.04	[-10.22, −1.87]	0.001
AST, U/L	0.16	[-0.17, 0.50]	0.326
ALT, U/L	−0.87	[-0.34, 0.16]	0.495
CRP. mg/L	−0.29	[-1.03, 0.46]	0.202
DMV	−8.71	[-14.02,-3.39]	< 0.001

Note：AST = Aspartate aminotransferase; ALT = Alanine transaminase; BMI = body mass index; CRP═C-reactive protein.

Table 4
Baseline characteristics of patients with different DMV scores.

	DMV score 0	DMV score 1-6	DMV score 7-12	DMV score 13-18	P
	n = 114	n = 41	n = 45	n = 62	value
Age, years	65 ± 4.9	72 ± 7.7	70 ± 7.5	73 ± 7.2	< 0.001
Male, n (%)	80 (46.8)	20 (48.7)	20 (44.4)	30 (48.3)	0.907
BMI, kg/m^2	24.7 ± 3.6	23.9 ± 3.8	24.5 ± 3.8	24.9 ± 3.3	0.971
Alcohol use, n (%)	22 (16.3)	16 (39.0)	12 (26.7)	22 (35.5)	< 0.001
Current smoking, n (%)	24 (17.9)	17 (41.4)	17 (37.8)	32 (51.6)	< 0.001
Hypertension, n (%)	51 (38.8)	23 (56.1)	27 (60.0)	41 (66.1)	< 0.001
Diabetes Mellitus, n (%)	22 (16.3)	16 (39.0)	11 (24.4)	22 (35.5)	< 0.001
Total cholesterol, mmol/L	4.26 ± 1.17	4.56 ± 1.20	4.27 ± 1.21	4.65 ± 1.20	0.060
HDL cholesterol, mmol/L	1.32 ± 0.61	1.31 ± 0.70	1.35 ± 0.70	1.43 ± 0.54	0.196
LDL cholesterol, mmol/L	3.38 ± 0.77	3.39 ± 0.91	3.28 ± 0.75	3.17 ± 0.77	0.134
AST, U/L	20.18 ± 6.9	21.80 ± 8.6	20.00 ± 7.6	23.58 ± 10.20	0.210
ALT, U/L	17.65 ± 6.7	19.65 ± 7.1	19.10 ± 12.4	20.10 ± 11.86	0.125
CRP. mg/L	1.77 ± 1.30	2.32 ± 1.35	2.15 ± 1.92	2.68 ± 1.35	< 0.001
FDP, ug/ml	2.94 ± 0.78	3.23 ± 0.89	2.99 ± 0.94	3.70 ± 1.10	< 0.001
VWF:Ag, IU/mL	1.25 ± 0.30	1.30 ± 0.22	1.36 ± 0.24	1.38 ± 0.27	0.001
ADAMTS13 activity (%)	93.48 ± 10.91	90.81 ± 7.04	83.36 ± 6.59	79.14 ± 5.75	< 0.001

Note: AST = aAspartate aminotransferase; ALT = aAlanine transaminase; BMI = body mass index; CRP═C-reactive protein; FDP = fibrinogen-degradation products;: LDL cholesterol = low density lipoprotein cholesterol; HDL cholesterol = high density lipoprotein cholesterol; Values are expressed as frequency (percentage) or mean ± standard deviation.

4. Discussion

The assessment of performance of DMV on SWI is a quick and easily measured parameter that can predict the extent of neurological deficits in patients with acute cerebral infarction and serve as a predictive imaging marker of stroke risk in Transient Ischemic Attack patients [16,17]. However, the mechanism of DMV pathogenesis and progression is, unclear and no circulating biomarkers can assist in

Table 5
Distribution of patients with different DMV scores in the 4th quartile of ADAMTS13 activity.

	Total DMV Score				
	n = 262	0 (n = 114)	1-6 (n = 41)	7-12 (n = 45)	13-18 (n = 62)
ADAMTS13 activity,n(%)					
$Q1_{<80.3\ \%}$		11 (9.6)	3 (7.3)	10 (22.2)	41 (66.1)
$Q2_{80.3–89.0\ \%}$		17 (15.0)	9 (22.1)	24 (53.3)	14 (22.5)
$Q3_{89.0–97.1\ \%}$		41 (36.0)	16 (39.6)	9 (20.0)	3 (4.8)
$Q4_{>97.1\ \%}$		46 (40.3)	12 (39.0)	2 (4.4)	2 (3.2)

Note: Kendall's tau-b = 0.46, p < 0.001.

Table 6
Multiple ordinal regression analysis of total DMV score with ADAMTS13.

	OR 95 % confidence interval	p-value	
VWF:Ag (IU/mL)			
$Q1_{<1.14\ IU/mL}$	0.04	[0.02,0.08]	< 0.001
$Q2_{1.33\text{-}1.14\ IU/mL}$	0.10	[0.03,0.12]	< 0.001
$Q3_{1.33–1.51\ IU/mL}$	0.26	[0.14,0.50]	< 0.001
$Q4_{>1.51\ IU/mL}$		Reference	
ADAMTS13 activity(%)			
$Q1_{<80.3\ \%}$	27.54	[12.63,60.10]	< 0.001
$Q2_{80.3–89.0\ \%}$	7.40	[3.62,15.12]	< 0.001
$Q3_{89.0–97.1\ \%}$	1.65	[0.79,3.48]	0.18
$Q4_{>97.1\ \%}$		Reference	

Note: Adjusted for age, sex, alcohol use, current smoking, hypertension, diabetes mellitus.

the evaluation. In this study, we investigated the association between plasma VWF levels, ADAMTS13 activity, and cerebral DMV. After adjusting for DMV-related risk factors, we confirmed that ADAMTS13 activity was independently and inversely associated with DMV defects. Additionally, the lower ADAMTS13 activity group was more likely to have a higher DMV score than the higher VWF level group. Thus, ADAMTS13 may play an essential role in the progression of DMV.

The visibility of cerebral venular vessels on SWI sequence images mainly depends on the deoxygenation of blood, so the decrease in the number of DMV observations on imaging may be the result of changes in venous hemodynamics or venous obstruction [18]. Thickening and obstructing the periventricular veins may lead to increased venous pressure, distention, or disruption of the venous blood-brain barrier (BBB) [1]. In animal models, Wu et al. discovered that VWF released during acute traumatic brain injury (TBI) was activated and became microvesicle-bound, thereby promoting vascular leakage and leading to coagulopathy in mice. Experiments have demonstrated that recombinant ADAMTS13 can protect endothelial cell barrier integrity and prevent the development of coagulopathy by enhancing the cleavage of VWF without compromising basal hemostasis [19]. Thus, it can be speculated that the effect of ADAMTS13 on DMVs may be mediated by endothelial cell barrier disruption. In addition, venous outflow obstruction due to coagulation disorders may also contribute to the development of DMVs. In this study, we found that subjects with DMV had higher mean VWF levels and lower ADAMTS13 activity, but the causal relationship between the two remains to be verified by further studies.

Lymphoid clearance disorders caused by venous collagen disease and decreased autoregulated cerebral blood flow (CBF) in the neurovascular unit (NVU) may also explain the reduced visibility of DMV on SWI. On the one hand, the continuous convection of cerebrospinal fluid into the para-arterial space versus interstitial fluid into the para-venous space maintains the homeostasis of cerebral metabolism. Reduced distribution or stenosis of the DMV may impede lymph outflow and lead to under drainage of lymph from the perivascular space. Impaired lymphoid clearance may, in turn, lead to the accumulation of toxic metabolic byproducts (β-amyloid and tau) and further trigger inflammatory responses to myelin [20,21]. Yongliang Cao et al. found that ADAMTS13 can increase the clearance rate of Aβ from the brain to the plasma by improving the blood-brain barrier (BBB) function in mouse model, which may partially explain the potential connection between ADAMTS13 and DMV [22]. On the other hand, non-inflammatory periventricular vascular diseases, including atherosclerotic stenosis and concentric collagen deposition, wall thickening, stenosis, and venous occlusion, cause cerebrovascular remodeling [23], which ultimately leads to increased vascular resistance to cerebral perfusion. Ultimately, chronic hypoperfusion and hypometabolic state of small cerebral vessels can cause insufficient blood supply to the brain, resulting in the narrowing of the DMV and relatively low oxygen carrying capacity in the NVU, as indicated by a decrease in DMV seen on SWI. In addition to the aforementioned studies in ADAMTS13 activity and CSVD that lack of ADMTS13 promotes BBB disruption and leads to reduced cerebral blood flow, Land et al. also conducted a clinical study and found that lower ADAMTS13 activity was associated with lower CBF in white matter [24].

The innovation of this study lies in reporting the correlation between plasma VWF levels, ADAMTS13 activity, and neuroimaging of DMV for the first time. However, there are some limitations that should be acknowledged. First, the study was a single-center cross-sectional study with a relatively small sample size, and the measures of biological markers were not comprehensive enough. Second, ADAMTS13 activity showed a threshold effect, and the increased risk was observed only in the lower range of ADAMTS13. However,

the lower range of ADAMTS13 activity in the average population is typically sufficient to maintain the balance of VWF multimer formation and degradation. Therefore, our results do not prove that ADAMTS13 activity synergizes with VWF levels on DMV. Finally, VWF levels are highly variable among individuals and may be influenced by physiological factors, the disease process, or treatment, while ADAMTS13 activity is also affected by race. Consequently, our findings need to be validated through a more comprehensive prospective study.

In summary, our study found a negative correlation between ADAMTS13 activity and DMV score, providing some clinical insights into exploring the potential pathogenesis of DMV.

Ethics declarations

Participants or their legal guardians gave written informed consent, and the study received approval from the Ethics Committee for Human Experimentation at both Huashan Hospital of Shanghai and Fifth People's Hospital of Shanghai, China. The clinical trial was registered with the Chinese Clinical Trial Registry under Registration No.: ChiCTR1800019615.

Data availability statement

The relevant research data has not been deposited in a publicly available repository, as some of the data pertains to unpublished papers. The data supporting the findings of this study are accessible through the corresponding author.

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CRediT authorship contribution statement

Wenbo Sun: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Shengwen Huang:** Writing – review & editing, Data curation. **Xiaoli Yang:** Writing – review & editing, Validation, Project administration. **Yufan Luo:** Data curation. **Luqiong Liu:** Formal analysis, Data curation. **Danhong Wu:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29534.

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