Journal of Integrative Neuroscience

J. Integr. Neurosci. **2023**; 22(6): 170
https://doi.org/10.31083/j.jin2206170

Original Research

Impact of Decreased Visibility of Deep Medullary Veins on White Matter Integrity in Patients with Cerebral Small Vessel Disease

Huimei Wang[1,†], Xinjun Lei[2,†], Haiyuan Lan[2], Zhihua Xu[3,*], Hongxia Zhang[3], Zhenyu Cao[3], Yajie Wu[2]

[1]Department of Neurology, Lishui People's Hospital, 323000 Lishui, Zhejiang, China
[2]Department of Radiology, Lishui Hospital of Traditional Chinese Medicine Affiliated Zhejiang Chinese Medical University, 323020 Lishui, Zhejiang, China
[3]Department of Radiology, Tongde Hospital of Zhejiang Province, 310012 Hangzhou, Zhejiang, China
*Correspondence: xuzhihua001@yeah.net (Zhihua Xu)
[†]These authors contributed equally.

Academic Editor: Gernot Riedel
Submitted: 29 March 2023 Revised: 4 June 2023 Accepted: 25 June 2023 Published: 5 December 2023

Abstract

Background: Based on susceptibility-weighted imaging (SWI) visibility, deep medullary vein (DMV) scores are related to white matter damage (WMD) in patients with cerebral small vessel disease (CSVD). However, whether mechanisms are associated with DMV changes is unclear. We examined extracellular fluid (ECF) roles in white matter associations between DMV scores and white matter integrity (WMI) in patients with CSVD. **Methods**: We examined magnetic resonance imaging (MRI) and clinical data from 140 patients with CSVD. DMV scores (0–18) were assigned on SWI according to DMV anatomic regions and signal continuity/visibility. WMI and ECF volumes were evaluated using free water (FW) and fractional anisotropy (FA) values by diffusion tensor imaging (DTI). **Results**: DMV scores were independently associated with FA after adjusting for vascular risk factors, age, white matter hyperintensity (WMH) volume, and CSVD burden [β (95% confidence interval (CI)): –0.219 (–0.375, –0.061), $p = 0.006$]. We also observed a significant indirect effect of DMV scores on FA in white matter (mediated by FW in white matter) after controlling for age, vascular risk factors, WMH volume, and CSVD burden. **Conclusions**: DMV scores were independently related to WMI and mediated by ECF in the white matter of patients with CSVD.

Keywords: cerebral small vessel disease; deep medullary vein; diffusion tensor imaging; extracellular fluid; susceptibility-weighted imaging; white matter integrity

1. Introduction

In older adults, cerebral small vessel disease (CSVD) is often implicated in dementia and cognitive impairment [1]. Despite its prevalence and negative impact on cognitive function, underlying CSVD mechanisms and effective treatments are limited. Previous studies have indicated that white matter damage (WMD) is a major contributor to cognitive impairment in CSVD [2–4], but the causes of such damage are not fully understood, multifaceted, and may include: low cerebral blood flow [5], blood-brain barrier leakage [6], neuroinflammation [7], and venous abnormalities [8]. These mechanisms have garnered significant research traction in recent years.

The deep medullary vein (DMV) complex is of particular interest and is the main venous blood drain in periventricular white matter and the corona radiata. DMVs are perpendicular to the ventricle, have limited variation, and are often used to examine deep venous changes in cerebral vascular disease. Studies have reported that magnetic resonance imaging (MRI)-derived DMV scores, based on DMV visibility on susceptibility-weighted imaging (SWI), are associated with the presence and burden of CSVD [9]. Subsequently, studies also find that DMV scores are related to cognitive impairment or dementia in individuals with CSVD [10]. According to previous studies, a higher DMV score is associated with venous lumen stenosis and venous hypertension [11], which may obstruct venous drainage in white matter and cause extracellular fluid (ECF) accumulation [12]. Increased ECF may facilitate harmful substance accumulation (e.g., plasma protein and metabolic waste) and, critically, cause WMD [13]. Therefore, we hypothesized that decreased DMV visibility was associated with WMD when mediated by increased ECF.

To evaluate ECF volumes, diffusion tensor imaging (DTI) is widely used in nervous-system-disease research [12,14,15]. According to the free water (FW) elimination 2-compartmental model [16], FW reflects ECF volume corrected for partial volume effects in cerebrospinal fluid, while fractional anisotropy (FA) indicates white matter integrity (WMI) after removing FW signals.

Therefore, CSVD is a significant health challenge for older adults; thus, deeper mechanistic insights are warranted. This study focused on the DMV complex in CSVD-associated WMD and investigated relationships between

DMV scores, ECF volumes, and WMI using advanced multimodal magnetic resonance imaging (MRI) approaches.

2. Materials and Methods

2.1 Participants

The Institutional Review Board of our hospital approved the study, and patients provided written informed consent. Between January 2022 and August 2022, imaging and clinical data were prospectively collected from patients. Enrolled patients had MRI scans to assess for ischemic attack, lacunar infarct (LI), or dizziness. Inclusion criteria were: age >40 years, adherence of CSVD MRI markers to STRIVE guidelines [17], and ≥1 vascular risk factors. Exclusion criteria were: confirmed demyelinating diseases, severe occlusion/stenosis of a large intracranial or internal carotid artery, other brain abnormalities, and lung/heart/kidney insufficiency. Clinical baseline characteristics included age, sex, and vascular risk factor information.

2.2 MRI Protocol

In patients, a multimodal MRI protocol included 3D T1 weighted imaging (T1WI), T2 Flair, T2 weighted imaging (T2WI), SWI, and DTI sequences on a 1.5 Tesla scanner (MAGNETOM Aera, Syngo Platform VD13A, Siemens Healthcare, Erlangen, Germany). Sequence parameters were: (1) SWI: repetition time (TR) = 27 ms; echo time (TE) = 20 ms; flip angle = 10; slice thickness = 2 mm; intersection gap = 0 mm; field of view (FOV) = 24 × 24 cm^2; and matrix number = 512 × 512. (2) DTI: TR = 3600 ms; TE = 95 ms; slice thickness = 3 mm; FOV = 23 cm × 23 cm; matrix = 128 × 128; diffusion directions = 30 for every b value; b value = 0, 1000, and 2000 s/mm^2.

2.3 Image Analyses

Two blinded and experienced neuroradiologists independently reviewed images, and disagreements were resolved by consensus.

2.4 Total CSVD MRI Scores

From STRIVE guidelines [17], 4 CSVD MRI markers were identified: high-grade perivascular spaces (HPVS), high-grade white matter hyperintensities (HWMH), cerebral microbleeds (CMBs), and LIs. An LI finding indicated round or ovoid-shaped lesions (3–15 mm in diameter), which appeared as hypointensities on T1WI and hyperintensities on T2WI. HPVS were assessed as the maximum numbers of perivascular space (PVS) in unilateral basal ganglia and were represented by enlarged PVSs >10. When Fazekas scores in deep white matter and/or periventricular white matter were ≥2, HWMH were assigned. CMBs manifested as small, round, or ovoid hypointensities without surrounding edema. An average diameter = 3–5 mm (by SWI) was used to exclude abnormal iron deposits, such as cavernous hemangioma, calcification, and vascular cross-sections.

Total CSVD magnetic resonance (MR) scores were calculated and ranged from 0–4 accordingly, based on an absence (0)/presence (1) of each of the 4 CSVD markers. For example, a CSVD MR score of 4 was assigned when all the markers were identified on MR images. WMH volume was calculated on T2 Flair images using the WMH mask segmented by FSL BIANCA.

2.5 DMV Scores

SWI sequences were constructed (thickness = 10 mm) using minimum intensity projection, and DMV scores were assessed using constructed SWI images. To calculate scores, we selected 5 consecutive periventricular slices in patients which covered most DMVs, from the ventricle level above the basal ganglia to where ventricles disappeared.

Based on regional anatomy, the DMV complex was apportioned into 6 segments: frontal, parietal, and occipital regions bilaterally. In DMV scoring, we used a semi-quantitative approach [18] where each of the 6 segments were separately scored (0–3) based on observed continuity and visibility in SWI sequences (Fig. 1). Total DMV scores-individual scores summed from the 6 segments, ranged from 0–18. A DMV score = 0 indicated prominent DMV, while 18 suggested undetectable DMV.

2.6 ECF and FA in White Matter

Gibbs artifact removal, denoising, echo planar imaging (EPI) distortion, and eddy current correction preprocessing steps were conducted in Mrtrix3 software (https://mrtrix.org/). Pre-processed DTI images were analyzed for ECF and WMI in FW elimination 2-compartmental mode [19] (ECF and tissue compartment) in DIPY software (https://dipy.org/). FA and FW maps were generated, and 3D T1WI images co-registered with b = 0 s/mm^2 (b0) images. Finally, white matter mean FA and FW values were generated for patients using respective white matter masks segmented by FMRIB's automated segmentation tool (FSL FAST) with the default probability threshold recommended (Fig. 2). Calculated FA and FW values ranged from 0–1. The FW value represented the white matter ECF volume, with values closer to 1 indicating a marked increase in white matter ECF volume. FA values reflected WMI, with lower values indicating significant WMI loss.

2.7 Statistical Analyses

Categorical variables were represented as percentages and frequencies. Continuous, normal distribution data were represented as the mean ± standard deviation, while non-parametric data were reported as median and interquartile range (IQR) values. Relationships between DMV scores, FW, and FA values were processed using Spearman's or Pearson correlation coefficients and linear regression analyses. Mediation analyses (PROCESS for Statistical Package for Social Sciences (SPSS) (Model 4)) were performed

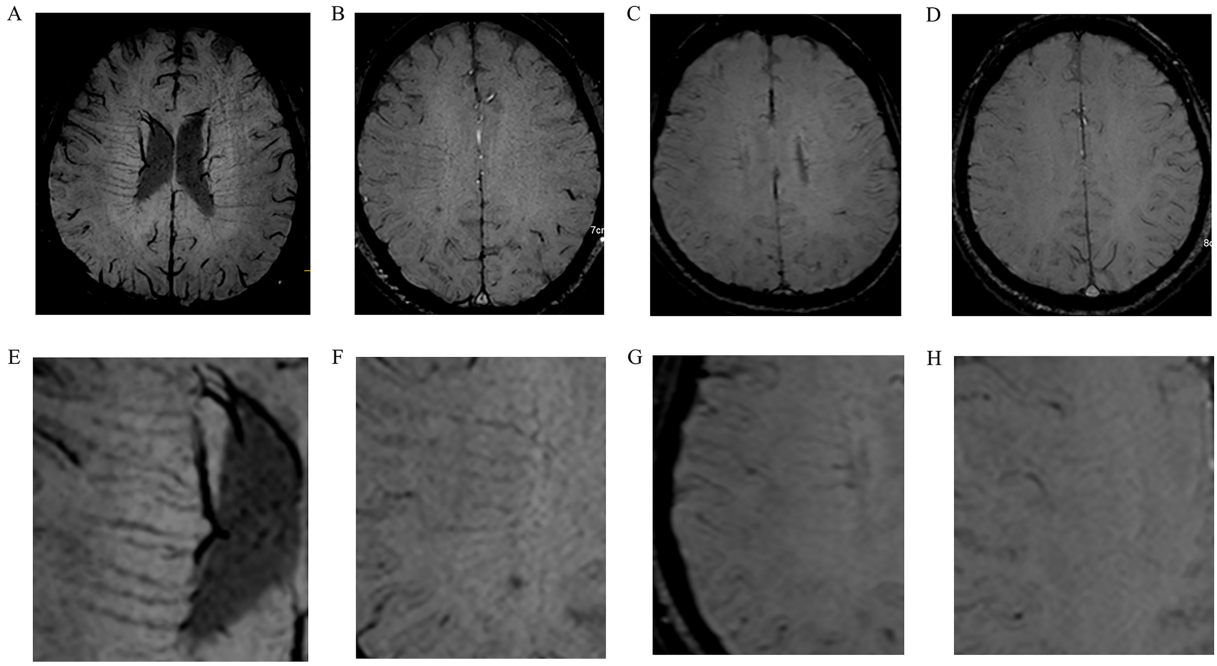

Fig. 1. Typical images showing deep medullary vein (DMV) scoring. (A,E) DMV score = 0. The DMV signal is continuous and visible on susceptibility-weighted imaging (SWI). (B,F) DMV score = 1. The DMV signal is continuous with unequivocal visibility but has a non-homogeneous signal in at least 1 vein. (C,G) DMV score = 2. At least 1 vein is not continuous, is faintly visible, and contains spot-like hypointensities. (D,H) DMV score = 3. The DMV is invisible.

with 95% confidence levels and 5000 bootstrap samples to examine FW mediating roles between DMV scores and FA values. DMV scores were predictors, FW values were mediators, and FA values were outcomes. Covariates were age, vascular risk factors, and CSVD burden. Statistical significance = $p < 0.05$. SPSS for Windows, V. 20 (IBM Corp., Armonk, NY, USA) was used for data analyses.

3. Results

We enrolled 140 patients (mean age = 60 $\pm$ 12 years, and 66 were men) with CSVD. Baseline clinical and imaging characteristics are shown (Table 1). Thirty-two (22.9%) patients showed HWMH, 53 (37.9%) showed CMBs, 20 (14.3%) showed HPVS and 56 (40%) showed LIs. The median (IQR) DMV score was 3 (0, 7), and mean FW and FA values in white matter were 0.25 $\pm$ 0.01 and 0.56 $\pm$ 0.03, respectively.

3.1 Relationship between DMV Scores and FA Values

As indicated (Fig. 3), Spearman's correlation coefficients identified a significant correlation between DMV scores and FA values in white matter (r = –0.251, $p < 0.05$). DMV scores were independently related to FA after adjusting for vascular risk factors, age, WMH volume, and CSVD burden [β (95% confidence interval (CI)): –0.219 (–0.375, –0.061), $p = 0.006$, Table 2].

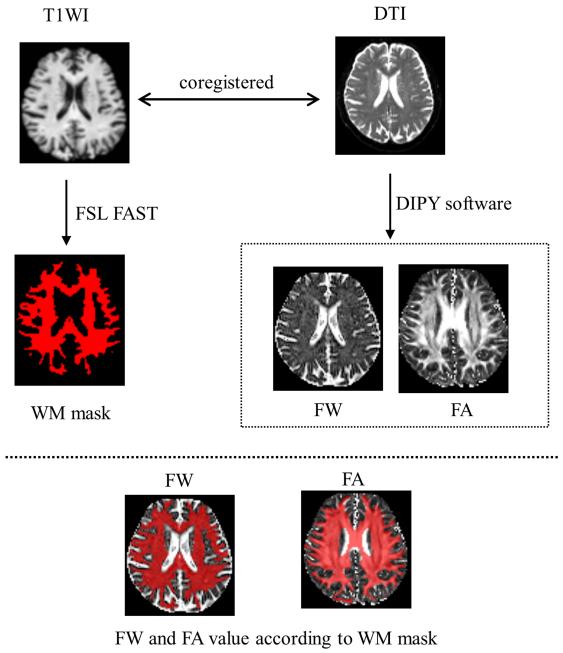

Fig. 2. The processing pipeline showing image registration, white matter (WM) mask generation, and the calculation of free water (FW) and fractional anisotropy (FA) values. DTI, diffusion tensor imaging; T1WI, T1 weighted imaging; FSL FAST, FMRIB's automated segmentation tool.

Table 1. Patient baseline clinical and imaging characteristics.

Variables	n = 140
Male, n (%)	66 (47.1)
Age, years	60 ± 12
Hypertension, yes, n (%)	76 (54.3)
Diabetes mellitus, yes, n (%)	25 (17.9)
Current smoking, yes, n (%)	33 (23.6)
Hyperlipidemia, yes, n (%)	36 (25.7)
LI, yes, n (%)	56 (40.0)
HPVS, yes, n (%)	20 (14.3)
HWMH, yes, n (%)	32 (22.9)
CMB, yes, n (%)	53 (37.9)
WMH volume, mL	12.29 ± 12.58
DMV score, median (IQR)	3 (0, 7)
FW	0.25 ± 0.01
FA	0.56 ± 0.03

LI, lacunar infarct; HPVS, high-grade perivascular spaces; HWMH, high-grade white matter hyperintensities; WMH, white matter hyperintensities; CMB, cerebral microbleed; DMV, deep medullary veins; FW, free water; FA, fractional anisotropy; IQR, interquartile range.

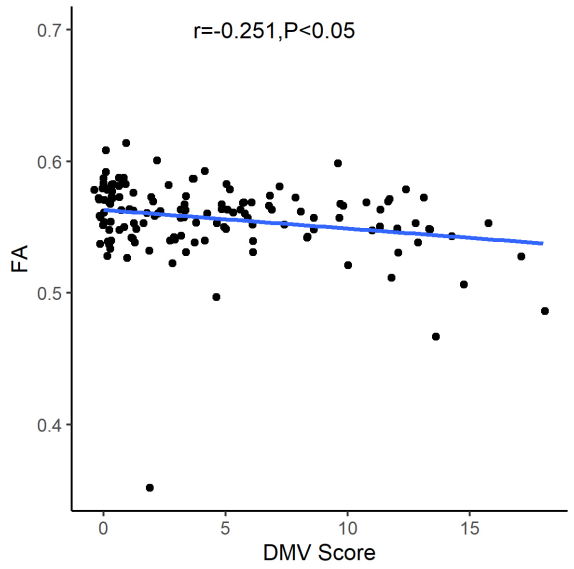

Fig. 3. Graph showing the relationship between deep medullary vein (DMV) scores and fractional anisotropy (FA) values.

3.2 Relationship between DMV Scores and FW Values

As indicated (Fig. 4A), Spearman's correlation coefficient analyses identified significant correlations between DMV scores and FW values in white matter (r = 0.425, $p < 0.001$). DMV scores were also independently associated with FW values after adjusting for age, vascular risk factors, CSVD burden, and WMH volume [β (95% CI): 0.145 (0.019, 0.571), $p = 0.037$, Fig. 5].

Table 2. Linear regression analysis of fractional anisotropy (FA) in patients with cerebral small vessel disease (CSVD).

Variables	β	β, 95% CI		p value
		Lowest	Highest	
Age	–0.046	–0.226	0.133	0.610
Hypertension	0.031	–0.116	0.179	0.677
Diabetes mellitus	–0.104	–0.245	0.036	0.143
Current smoking	0.110	–0.026	0.245	0.111
Hyperlipidemia	0.045	–0.092	0.183	0.515
Total CSVD MR score	–0.020	–0.200	0.159	0.825
WMH volume	–0.085	–0.257	0.087	0.331
DMV score	–0.219	–0.375	–0.063	0.006

CSVD, cerebral small vessel disease; CI, confidence interval; MR, magnetic resonance.

3.3 Relationship between FW and FA Values

As indicated (Fig. 4B), Spearman's correlation coefficient analyses identified significant correlations between FW and FA values in white matter (r = –0.323, $p < 0.001$). FW was also independently associated with FA after adjusting for age, vascular risk factors, CSVD burden, and WMH volume [β, 95% CI: –0.316 (–0.505, –0.128), $p = 0.001$, Fig. 5].

3.4 Mediation Analyses on DMV Scores, FW, and FA Values

Mediation analyses were controlled by age, vascular risk factors, WMH volume, and CSVD burden and identified significant indirect effects of DMV scores toward FA in the white matter when mediated by FW in white matter (Fig. 5).

4. Discussion

DMV scores were independently associated with FA values in white matter and mediated by FW values in patients with CSVD. Also, mediation effects were independent of vascular risk factors, age, WMH volume, and CSVD burden. Thus, relationships existed between DMV damage, increased ECF, and WMI loss in patients with CSVD.

With rapid improvements in MRI technology, SWI is widely used to investigate cerebral vascular and neurodegenerative diseases [20,21]. Many studies have reported that MRI-based DMV scores may be correlated with CSVD presence and severity [9,18,22]. Higher DMV scores are putatively correlated with a higher CSVD probability and severity. Previous autopsy and animal studies indicated that DMV damage may be caused by collagen type I and III deposition on vessel walls, leading to a stenotic or occluded lumen [11,23,24]. Higher DMV scores may reflect this DMV damage, and DMV abnormalities may be implicated in CSVD development.

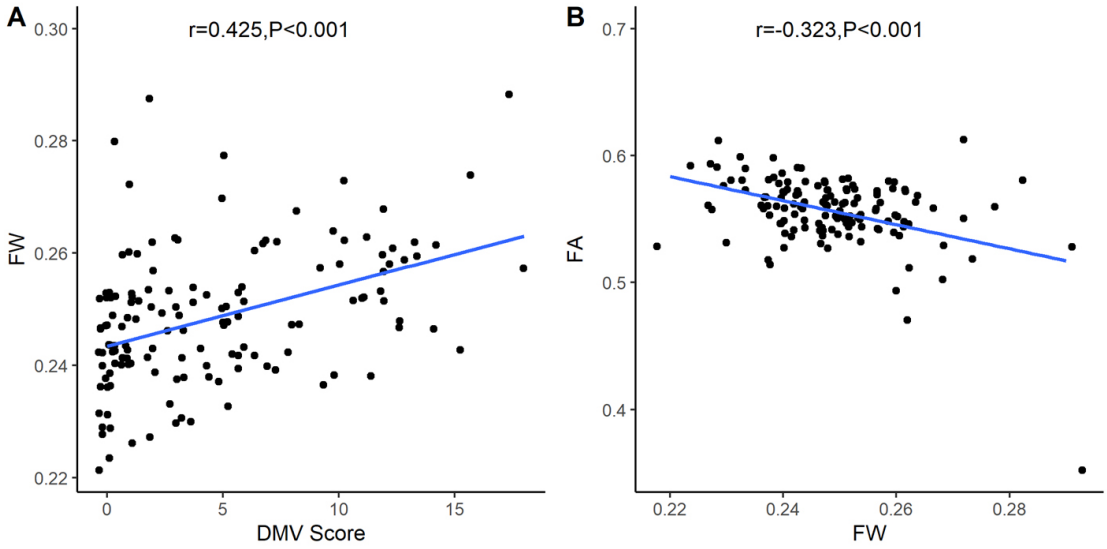

Fig. 4. Graphs showing relationships between deep medullary vein (DMV) scores, fractional anisotropy (FA), and free water (FW) values. A: There is a significant correlation between DMV scores and FW values in white matter (r = 0.425, $p < 0.001$). B: There is a significant correlation between FW and FA values in white matter (r = –0.323, $p < 0.001$).

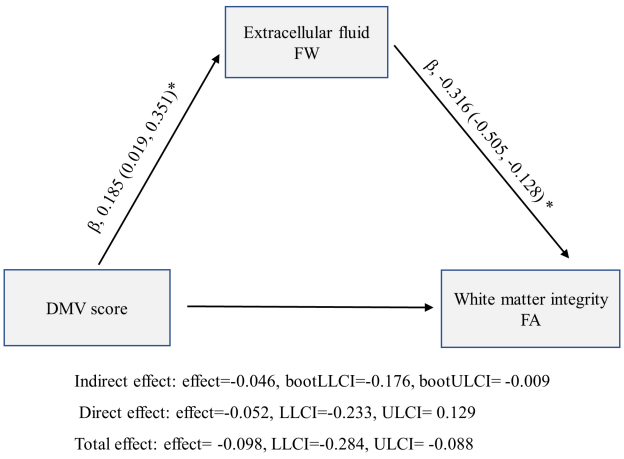

Fig. 5. Mediation model analyses exploring relationships between deep medullary vein (DMV) scores, fractional anisotropy (FA), and free water (FW) values (*$p < 0.05$).

DMV scores correlated with cognitive impairment in patients with CSVD [10], while associations between microstructure changes and WMI loss and cognitive impairment were reported in these patients [2]. However, the relationship between DMV damage and WMI loss and the precise influence of DMV scores on WMD remains unclear. Here, we identified links between DMV damage, increased ECF, and WMI loss in patients with CSVD. When a DMV abnormality was present, increased ECF initially occurred, followed by white matter demyelination and axonal damage.

Based on DMV structure and function, we suggest that DMV-associated white matter abnormalities occur when the DMV lumen narrows and venous pressure increases, causing obstructed venous drainage and increased vascular permeability [11], with increased PVS and ECF leakage volumes. It was previously believed that the index of diffusion tensor image along the PVS near the DMV was related to glymphatic system function [25]. Thus, a DMV abnormality may have caused glymphatic system dysfunction and increased ECF volume. However, venous hypertension may also have decreased cerebral blood flow and vascular edema, thereby increasing ECF. Either way, increased ECF volume may have facilitated harmful substance (e.g., plasma proteins and metabolic waste) accumulation, which elicited neuroinflammation, and further increased the ECF volume, thus ensuring a vicious circle. These substances can potentially damage white matter microstructures (e.g., myelin and axons), leading to WMI loss [13,26]. In considering WMI loss and cognitive impairment evidence, identifying DMV abnormality and cognitive impairment steps may uncover new CSVD venous-related prevention and control mechanisms.

CSVD is related to aging and associated with one or more vascular risk factors [27]. WMH volume and CSVD burden were often correlated with more severe WMD [28]. Therefore, in mediation analyses, we adjusted for age, vascular risk factors, WMH volume, and CSVD burden. This approach enhanced the practicality of our findings and suggested that cerebral venous abnormalities initially occurred with increased ECF volume, followed by WMD. Furtherly, this observation was consistent with other research [8], which confirmed links between DMV scores and FW and FA values in patients with CSVD. Although research has shown a correlation between WMH volume, CSVD burden, age, and cognitive decline [3,29], this study reveals that they are not independently associated with FA or WMI.

The possible explanation is that the underlying mechanism driving cognitive decline or WMI involves changes in the brain's microenvironment and microstructure, contributing to the development of WMH volume and CSVD burden.

Our study was limited. It was conducted at a single center and had a small sample. Secondly, no follow-up was conducted to examine relationships between DMV scores, FW and FA values, and cognitive impairment. Thirdly, low cerebral blood flow and inflammatory edema may also increase FW [28,30]; however, we did not include these factors or adjust for them in our models, thus introducing potential bias. Fourthly, although the DMV scores system has now been used in the serial study, the software automatically detecting and measuring DMV scores may be better to quantitatively assess DMV changes. We mainly focused on extracellular FW, while intracellular water content was not analyzed. Finally, capillary blood perfusion may have affected extracellular FW values. Thus a 3-compartment model may improve FW estimations. To address the limitations mentioned above, more multi-center investigations with more patients are required.

5. Conclusions

DMV scores were independently associated with WMI and mediated by ECF volume in white matter in patients with CSVD. This observation may underpin a venous element of WMD pathogenesis in CSVD.

Abbreviations

SWI, susceptibility-weighted imaging; DMV, deep medullary vein; CSVD, cerebral small vessel disease; DTI, diffusion tensor imaging; FW, free water; FA, fractional anisotropy; HWMH, high-grade white matter hyperintensities; CMB, cerebral microbleeds; HPVS, high-grade perivascular spaces; LI, lacunar infarcts; WMD, white matter damage; WMI, white matter integrity.

Availability of Data and Materials

Study datasets are available upon reasonable request from the corresponding author.

Author Contributions

HW, XL and ZX designed the research. HW, HZ, ZC, YW and HL performed the research. HL and HZ assisted with the research. HW and ZX analyzed data. HW, XL and ZX wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted according to the Declaration of Helsinki and approved by the Institutional Review Board of Tongde Hospital of Zhejiang Province (2022-042-JY). Written informed consent was provided prior to participation.

Acknowledgment

We thank our colleagues in the department of radiology for their support and assistance during data collection.

Funding

This research was funded by the Medical and Health Science and Technology Program of Zhejiang Provincial Health Commission of China, grant number 2022KY707.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. The Lancet Neurology. 2019; 18: 684–696.

[2] Huang L, Chen X, Sun W, Chen H, Ye Q, Yang D, *et al*. Early Segmental White Matter Fascicle Microstructural Damage Predicts the Corresponding Cognitive Domain Impairment in Cerebral Small Vessel Disease Patients by Automated Fiber Quantification. Frontiers in Aging Neuroscience. 2020; 12: 598242.

[3] Williams OA, Zeestraten EA, Benjamin P, Lambert C, Lawrence AJ, Mackinnon AD, *et al*. Predicting Dementia in Cerebral Small Vessel Disease Using an Automatic Diffusion Tensor Image Segmentation Technique. Stroke. 2019; 50: 2775–2782.

[4] Liu D, Li K, Ma X, Li Y, Bu Q, Pan Z, *et al*. Correlations Between the Microstructural Changes of the Medial Temporal Cortex and Mild Cognitive Impairment in Patients With Cerebral Small Vascular Disease (cSVD): A Diffusion Kurtosis Imaging Study. Frontiers in Neurology. 2020; 10: 1378.

[5] Kang P, Ying C, Chen Y, Ford AL, An H, Lee JM. Oxygen Metabolic Stress and White Matter Injury in Patients With Cerebral Small Vessel Disease. Stroke. 2022; 53: 1570–1579.

[6] Wong SM, Jansen JFA, Zhang CE, Hoff EI, Staals J, van Oostenbrugge RJ, *et al*. Blood-brain barrier impairment and hypoperfusion are linked in cerebral small vessel disease. Neurology. 2019; 92: e1669–e1677.

[7] Jiang L, Cai X, Yao D, Jing J, Mei L, Yang Y, *et al*. Association of inflammatory markers with cerebral small vessel disease in community-based population. Journal of Neuroinflammation. 2022; 19: 106.

[8] Zhang R, Huang P, Jiaerken Y, Wang S, Hong H, Luo X, *et al*. Venous disruption affects white matter integrity through increased interstitial fluid in cerebral small vessel disease. Journal of Cerebral Blood Flow and Metabolism. 2021; 41: 157–165.

[9] Chen X, Wei L, Wang J, Shan Y, Cai W, Men X, *et al*. Decreased visible deep medullary veins is a novel imaging marker for cerebral small vessel disease. Neurological Sciences. 2020; 41: 1497–1506.

[10] Xu Z, Li F, Xing D, Song H, Chen J, Duan Y, *et al*. A Novel Imaging Biomarker for Cerebral Small Vessel Disease Associated With Cognitive Impairment: The Deep-Medullary-Veins Score. Frontiers in Aging Neuroscience. 2021;13: 720481.

[11] Fulop GA, Tarantini S, Yabluchanskiy A, Molnar A, Prodan CI, Kiss T, *et al*. Role of age-related alterations of the cerebral venous circulation in the pathogenesis of vascular cognitive impairment. American Journal of Physiology-Heart and Circulatory Physiology. 2019; 316: H1124–H1140.

[12] Huang P, Zhang R, Jiaerken Y, Wang S, Hong H, Yu W, *et al*. White Matter Free Water is a Composite Marker of Cerebral Small Vessel Degeneration. Translational Stroke Research. 2022; 13: 56–64.
[13] Pintér P, Alpár A. The Role of Extracellular Matrix in Human Neurodegenerative Diseases. International Journal of Molecular Sciences. 2022; 23: 11085.
[14] Mayer C, Nägele FL, Petersen M, Frey BM, Hanning U, Pasternak O, *et al*. Free-water diffusion MRI detects structural alterations surrounding white matter hyperintensities in the early stage of cerebral small vessel disease. Journal of Cerebral Blood Flow and Metabolism. 2022; 42: 1707–1718.
[15] Zhao P, Gu Y, Feng W, Xia X, Tian X, Du Y,*et al*. Gait Disorders and Magnetic Resonance Imaging Characteristics in Older Adults with Cerebral Small Vessel Disease. Journal of Integrative Neuroscience. 2022; 21: 129.
[16] Hoy AR, Koay CG, Kecskemeti SR, Alexander AL. Optimization of a free water elimination two-compartment model for diffusion tensor imaging. Neuroimage. 2014; 103: 323–333.
[17] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurol. 2013; 12: 822–838.
[18] Ao DH, Zhang DD, Zhai FF, Zhang JT, Han F, Li ML, *et al*. Brain deep medullary veins on 3-T MRI in a population-based cohort. Journal of Cerebral Blood Flow and Metabolism. 2021; 41: 561–568.
[19] Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y. Free water elimination and mapping from diffusion MRI. Magnetic Resonance in Medicine. 2009; 62: 717–730.
[20] Xu Z, Tong Z, Duan Y, Xing D, Song H, Pei Y, *et al*. Diffusion- and Susceptibility Weighted Imaging Mismatch Correlates With Collateral Circulation and Prognosis After Middle Cerebral Artery M1-Segment Occlusion. Frontiers in Neurology. 2021; 12: 660529.
[21] You P, Li X, Wang Z, Wang H, Dong B, Li Q. Characterization of Brain Iron Deposition Pattern and Its Association With Genetic Risk Factor in Alzheimer's Disease Using Susceptibility-Weighted Imaging. Frontiers in Human Neuroscience. 2021; 15: 654381.
[22] Xu Z, Li F, Wang B, Xing D, Pei Y, Yang B, *et al*. New Insights in Addressing Cerebral Small Vessel Disease: Association With the Deep Medullary Veins. Frontiers in Aging Neuroscience. 2020; 12: 597799.
[23] Zhou Y, Li Q, Zhang R, Zhang W, Yan S, Xu J, *et al*. Role of deep medullary veins in pathogenesis of lacunes: Longitudinal observations from the CIRCLE study. Journal of Cerebral Blood Flow and Metabolism. 2020; 40: 1797–1805.
[24] Keith J, Gao FQ, Noor R, Kiss A, Balasubramaniam G, Au K, *et al*. Collagenosis of the Deep Medullary Veins: An Underrecognized Pathologic Correlate of White Matter Hyperintensities and Periventricular Infarction? Journal of Neuropathology and Experimental Neurology. 2017; 76: 299–312.
[25] Taoka T, Masutani Y, Kawai H, Nakane T, Matsuoka K, Yasuno F, *et al*. Evaluation of glymphatic system activity with the diffusion MR technique: diffusion tensor image analysis along the perivascular space (DTI-ALPS) in Alzheimer's disease cases. Japanese Journal of Clinical Radiology. 2017; 35: 172–178.
[26] Yu X, Yin X, Hong H, Wang S, Jiaerken Y, Zhang F, *et al*. Increased extracellular fluid is associated with white matter fiber degeneration in CADASIL: in vivo evidence from diffusion magnetic resonance imaging. Fluids and Barriers of the CNS. 2021; 18: 29.
[27] Zanon Zotin MC, Sveikata L, Viswanathan A, Yilmaz P. Cerebral small vessel disease and vascular cognitive impairment: from diagnosis to management. Current Opinion in Neurology. 2021; 34: 246–257.
[28] Kern KC, Wright CB, Leigh R. Global changes in diffusion tensor imaging during acute ischemic stroke and post-stroke cognitive performance. Journal of Cerebral Blood Flow and Metabolism. 2022; 42: 1854–1866.
[29] Li X, Yuan J, Qin W, Yang L, Yang S, Li Y, *et al*. Higher Total Cerebral Small Vessel Disease Burden Was Associated With Mild Cognitive Impairment and Overall Cognitive Dysfunction: A Propensity Score-Matched Case-Control Study. Frontiers in Aging Neuroscience. 2021; 13: 695732.
[30] Febo M, Perez PD, Ceballos-Diaz C, Colon-Perez LM, Zeng H, Ofori E, *et al*. Diffusion magnetic resonance imaging-derived free water detects neurodegenerative pattern induced by interferon-γ. Brain Structure and Function. 2020; 225: 427–439.