Journal of Stroke and Cerebrovascular Diseases 35 (2026) 108510

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Worse visibility of deep medullary veins is associated with larger lateral ventricles but not with cortical thickness

Sushruth Manchineella, BS [a], Henry Rusinek, PhD [b], Yuan Ma, PhD [c], Xiuyuan Hugh Wang, PhD [a], Surendra Maharjan, PhD [a], Liangdong Zhou, PhD [a], Tracy Butler, MD [a], Yi Li, MD [a], Alexus Jones, BS [a], Emily Tanzi, MA [a], Gloria C Chiang, MD [a], Silky Pahlajani, MD [a], Katarzyna Olejniczak-Gniadek, MD PhD [d], Seyed Hani Hojjati, PhD [a], Thomas Maloney, PhD [a], Mony J. de Leon, EdD [a], Lidia Glodzik, MD PhD [a,*]

[a] Brain Health Imaging Institute, Department of Radiology, Weill Cornell Medicine, New York, USA
[b] Department of Radiology, NYU School of Medicine, New York, USA
[c] Department of Epidemiology, Harvard TH Chen School of Public Health, Boston, Massachusetts, USA
[d] Neurorehabilitation Clinic, Military Institute of Medicine, Warsaw, Poland

ARTICLE INFO

Keywords:
deep medullary veins
ventricular enlargement
SWI
cortical atrophy

ABSTRACT

Background: Deep medullary veins (DMVs) play important roles within the cerebrovascular network related to brain drainage and clearance. Although they have been previously correlated with brain volume, it is unknown whether their count is specifically correlated with subcortical or cortical volume changes.
Purpose: This study aims to better understand the relationship between DMVs, subcortical (lateral ventricle to intracranial volume ratio (ICV)) and cortical atrophy (cortical thickness) to identify whether DMVs can be a predictor of volume changes in these regions.
Methods: We performed a retrospective analysis of 332 cognitively healthy subjects previously followed between 2010 and 2019. Imaging and patient charts were analyzed for baseline demographic and clinical characteristics. Patients underwent a standardized cognitive interview and received a magnetic resonance imaging scan to assess DMVs, cortical thickness, lateral ventricle and global gray matter (GM) volumes, white matter lesions (WMLs) and microbleeds.
Results: Among 332 patients (62% female, median age 70), lateral ventricle/ICV was significantly related to DMV count ($p<0.001$). Similarly, sex stratified analyses confirmed that a larger lateral ventricle/ICV ratio, but not cortical thickness or global GM volumes, was associated with fewer DMVs. In the entire group, subcortical atrophy remained a significant predictor of DMVs even after accounting for baseline characteristics, WMLs, microbleeds and total gray matter volume.
Conclusions: In a large cohort of cognitively unaffected people, subcortical, but not cortical, atrophy was significantly correlated with venous health as measured by DMVs. Reduced DMVs are a strong predictor of ventricular enlargement.

Introduction

Veins form an important component of the cerebrovascular network and are involved in clearing brain parenchyma,[1] cell migration, transendothelial transport,[2] and central nervous system (CNS) immune surveillance.[3] In a neuropathology study, individuals of 60 years and older

* Corresponding author at: Department of Radiology, Weill Cornell Medicine, School of Medicine, 407 East 61st Street, New York NY, 10021
E-mail addresses: sushruth.manchi@gmail.com (S. Manchineella), hr18@nyu.edu (H. Rusinek), yuanma@hsph.harvard.edu (Y. Ma), xiw4004@med.cornell.edu (X.H. Wang), sum4018@med.cornel.edu (S. Maharjan), liz2018@med.cornel.edu (L. Zhou), tab2006@med.cornel.edu (T. Butler), yil4008@med.cornel.edu (Y. Li), alj4006@med.cornel.edu (A. Jones), ebt4001@med.cornel.edu (E. Tanzi), gcc9004@med.cornel.edu (G.C. Chiang), sip9018@med.cornel.edu (S. Pahlajani), kgniadek-olejniczak@wim.mil.pl (K. Olejniczak-Gniadek), sh4006@med.cornel.edu (S.H. Hojjati), trm4001@med.cornel.edu (T. Maloney), mony.deleon@gmail.com (M.J. de Leon), lig4005@med.cornel.edu (L. Glodzik).

https://doi.org/10.1016/j.jstrokecerebrovasdis.2025.108510
Received 6 August 2025; Received in revised form 3 November 2025; Accepted 28 November 2025
Available online 29 November 2025

were found to have significant collagen deposits in the veins of the periventricular region, and these depositions were strongly correlated with leukoaraiosis.[4] Furthermore, venous collagenosis has also been related to the number of white matter hyperintensities (WMHs), the total volume of WMHs, myelin loss, and age.[5] All these suggest that changes in venular walls contribute to imaging manifestation of cerebral small vessel disease (CSVD).

Venous appearance can be assessed ante-mortem on susceptibility-weighted magnetic resonance (MR) imaging (SWI). Several reports examined relationships between visibility of deep medullary veins (DMVs) and CSVD (mostly white matter hyperintensities) with conflicting results.[6-15] The connection between brain volume and vein appearance was also examined, yielding more consistent associations between worse vein visibility and volume loss.[8,9,16-18] These studies examined gray matter volume[8,16,17] or total brain volume[9,18] as a ratio to the total intracranial volume (ICV). However, it is still unclear whether better venous conspicuity, putatively reflecting higher integrity of venous system, is related to subcortical or cortical atrophy. Studies reporting on gray matter utilized global indices likely including subcortical gray matter structures.[8,16,17] Moreover, it is not known whether DMVs are associated with measures of cortical structure other than volume. While cortical volume is highly interrelated with ICV,[19,20] the association between cortical thickness and ICV is much weaker.[20-22] Cortical gray matter volume depends more on cortical surface than thickness, and surface and thickness are uncorrelated.[22] Both measures predict independent fractions of variance in mean cognitive ability.[23] Moreover, thickness was slightly better correlated with Braak staging across the Alzheimer disease (AD) continuum than volume[19] and was suggested to be a better indicator of aging than gray matter volume.[24] Finally, if cortical or subcortical volume reduction correlate with venous integrity, then it is important to determine whether these relationships are independent of other factors commonly predicting brain atrophy.

We hypothesize that DMVs will be related to ventricular volume due to their anatomical proximity. In addition, we examined whether they are associated with cortical thickness (possibly the most sensitive index of pathology), and, for comparison, we included analyses of total gray matter volume. We accounted for common vascular risk factors and imaging manifestation of CSVD, known to be associated with vein visibility and atrophy. Lastly, since brain size may be a factor affecting visibility and vein count, we repeated analyses after stratification by sex, since it has been consistently reported than men have larger brains than do woman.[25]

Methods

Subjects

Our report is a cross-sectional, retrospective analysis of cognitively healthy subjects studied at the former Center for Brain Health (CBH) (NYU) from 2010 to 2019 (n=332). Subjects were recruited from the community, and all signed Institutional Review Board (IRB)-approved consent forms for imaging and biomarker studies of early AD, aging, and the contribution of vascular risk factors to neurodegeneration. Subjects diagnosed with large cortical stroke, normal pressure hydrocephalus, and active substance abuse were excluded. Supplemental Fig. 1 depicts participants' selection and flow. All subjects underwent physical and neurological exams, cognitive testing, laboratory testing, and magnetic resonance imaging that included SWI sequence.

Assessment of cognitive status

The staging of cognitive functioning was based on a physician-administered interview including the Brief Cognitive Rating Scale (BCRS),[26] the Global Deterioration Scale (GDS)[27] and the Clinical Dementia Rating (CDR) scale[28]. Cognitive status was defined as (1) "normal cognition" GDS=1 (no complaint)) or GDS=2 (subjective cognitive complaint only), or impaired" (GDS >2, and CDR $\geq$ 0.5). Only subjects diagnosed as cognitively healthy were included.

Laboratory testing, assessment of vascular risk factors

Blood samples were tested for complete blood count, liver function, metabolic, and lipid panels.

Medication: The use and type of antihypertensive medications was recorded. The categories included: angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors, beta-blockers, diuretics, and calcium channel blockers. We also recorded the use of statins and glucose-lowering drugs.

Body mass index (BMI) was calculated as weight/height^2 [kilograms]/[meters]^2.

Diabetes mellitus was established based on medical history, usage of glucose-lowering medication, or fasting glucose plasma level $\geq$126 mg/dL.[29]

Blood pressure (BP) was taken on the left upper arm using a sphygmomanometer in a sitting position.[30]

Smoking status was defined as positive if the subject was a current smoker or smoked within the last 10 years.

MR imaging

MR imaging was performed on the 3T Prisma system (Siemens, Erlangen, Germany). The imaging protocol consisted of sagittal T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE): repetition time [TR]=2250 ms, echo time [TE]=2.7 ms, inversion time [TI]=900 ms, flip angle [FA]=8°, slice thickness: 1.0 mm, isotropic resolution 1 mm^3, field of view [FOV]=200 mm, acquisition matrix=256 × 192 × 124, reconstructed as 256 × 256 × 124; susceptibility weighted imaging (SWI): TR=28 ms, TE=20 ms, FA=15°, slice thickness: 1.2 mm, in plane resolution 0.5 × 0.5 mm, FOV=230 mm, 352 × 448 matrix. Minimal intensity projection (MIP) images were created with slice thickness: 9.6 mm; and axial fluid attenuation inversion recovery (FLAIR): TR/TE/TI 9000/99/2500 ms; FA 130^O, voxel size = 0.7 × 0.7 × 5 mm, slice thickness: 3.3 mm, FOV 220 mm, matrix=256 × 192 reconstructed as 30 256 × 256 images.

MRI processing

Susceptibility weighted imaging

All SWI images were processed by applying minimum intensity projection (MIP) for better vein visualization. The MIP slab thickness was 9.6 mm. ***Deep medullary veins,*** traversing perpendicularly to the lateral ventricular, were counted on the axial slice placed at the level of the highest point of the inferior border of the corpus callosum (Fig. 1). The number of DMVs was defined as the sum of both hemispheres. Initially, twenty scans were read twice by the same rater and again by an independent rater. The intra-rater agreement was high: intraclass correlation coefficient (ICC) = 0.72, p=0.001. The inter-rater agreement was moderate: ICC =0.48, p=0.08 for the first rating, and ICC=0.65, p=0.01 for the second assessment. Given low inter-rater agreement we decided to rate each scan twice. Subsequently, ratings were compared and a final score for each case was agreed upon.

Microbleeds were assessed on SWI images and defined as hypointense lesions 2-10 mm in diameter.[31] They were coded in a binary manner as 'present' or 'absent'.

Magnetization prepared rapid acquisition gradient echo images

Gray matter (GM) and ***ICV*** were estimated using the Statistical Parametric Mapping segmentation procedure (SPM, version 8, with "New-Segment" extension).[32] Gray matter volumes were presented as ratios to the ICV. Lateral ventricle volumes and cortical thickness were obtained with Freesurfer version 7.1.0. Ventricular volume was the sum of the left and right ventricular volumes. It was also presented as a ratio

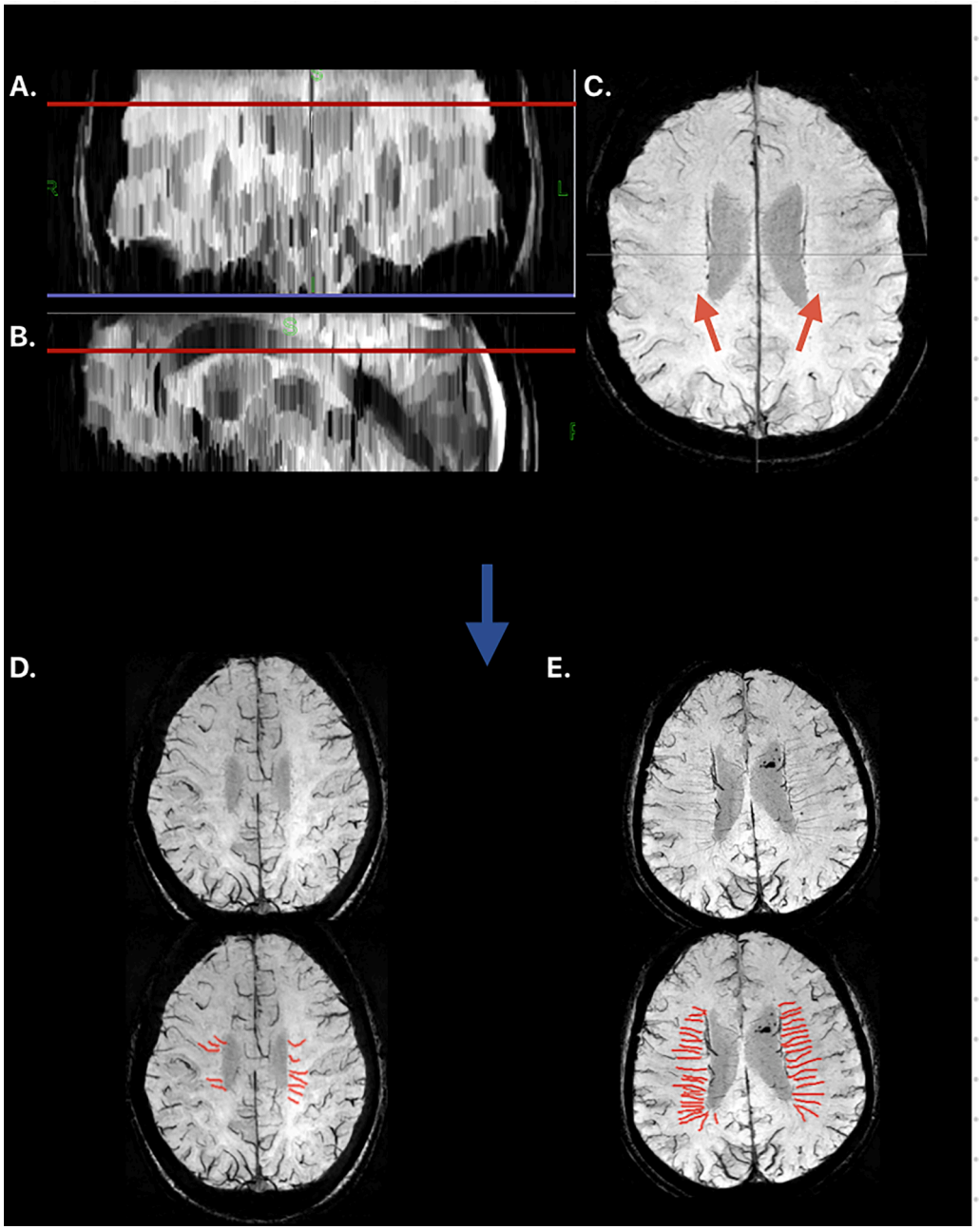

Fig. 1. Minimal intensity projection images (SWI) for veins traversing perpendicularly to the lateral ventricular. The number of DMVs was defined as the average count of both hemispheres. Panels A and B show coronal and sagittal projections, respectively, where the highest point of the inferior border of corpus callosum was determined. Veins were assessed at this level, on axial slice (C). Panel C highlights the visibility and prominence of deep medullary veins. Panels D and E present unannotated and annotated axial views for two individuals (different from subject presented in A-C) with significantly different amounts of visible deep medullary veins.

to ICV. Cortical thickness was the average of the left and right mean thickness.

Fluid attenuation inversion recovery images

The presence of ***white matter lesions (WML)*** was determined on FLAIR images. WMH were graded from 0-3 on the Fazekas scale.[33] Periventricular (PWML) and deep white matter lesions (DWML) were graded separately. The scores were added to create a final rating ranging from 0-6. For consistency the assessment of white matter hyperintensities was performed only by a single rater (LG).

Statistical analyses

Table presenting characteristics of subjects by sex was created using the *gtsummary* package in R. Variables were compared with the U Mann-Whitney test or Pearson's $\chi 2$ test. SPSS (version 28, SPSS, Inc., Chicago, IL) software was used for all other analyses.

Associations between DMV count and atrophy measures (gray matter to ICV ratio, ventricle to ICV ratio, cortical thickness) were initially examined in separate linear regression models. Atrophy measures were dependent variables and DMV count, age, sex, BMI, diabetes mellitus (yes/no), systolic blood pressure (BP), treatment with antihypertensive medication (yes/no), cholesterol, treatment with statins (yes/no), smoking status (yes/no), presence of microbleeds (yes/no), and WMH

on a scale ranging from 0-6 were independent predictors. Then, all the measures of atrophy, which were significantly associated with the DMV count, were included in one model together with all the covariates to predict DMVs. Since DMV count is not really a continuous variable, we repeated the last analysis using ordinal regression. We checked the linear models for violations of the models' assumptions. If necessary, analyses were confirmed with after log transformation of dependent variables. Collinearity was examined with the variance inflation factor. Finally, we repeated analyses after stratification by sex. Statistical significance was defined as a p-value <0.05. For all the models where DMV count was a predictor, we performed the Benjamini-Hochberg procedure to account for multiple testing. False discovery rate (FDR) was set at 5%.

Results

General characteristics of the study group

Characteristics of the study group by sex are presented in Table 1. The median age of all the participants was 70 years and 62% were women. The majority (88%) of participants were White. Hypertension was present in 42% and 22% were obese. Women were younger, had lower BMI and systolic BP, and higher cholesterol. They were less likely to have hypertension and diabetes. They had greater cortical thickness, higher GM/ICV, and smaller lateral ventricle/ICV ratio. All differences were at p<0.05, Table 1.

Table 1
Characteristics of the study group by sex.

Characteristic	Women N = 206[1]	Men N = 126[1]	p-value[2]
age (years)	69 (64, 74)	71 (67, 75)	0.04
education (years)	17.00 (16.00, 18.00)	18.00 (16.00, 19.00)	0.2
Race			0.10
Caucasian	175 (85%)	117 (93%)	
African American	22 (11%)	7 (5.6%)	
Other	9 (4.4%)	2 (1.6%)	
BMI	24.8 (22.5, 28.6)	26.6 (24.3, 30.0)	<0.001
Obesity	43 (21%)	31 (25%)	0.4
systolic BP (mmHg)	120 (110, 132)	122 (118, 135)	0.026
diastolic BP (mmHg)	72 (68, 80)	72 (68, 80)	0.9
hypertension	76 (37%)	65 (52%)	0.009
Smoking	11 (5.3%)	8 (6.3%)	0.7
diabetes mellitus	5 (2.4%)	12 (9.5%)	0.004
antihypertensive medications	58 (28%)	53 (42%)	0.009
ARBs	12 (5.8%)	22 (17%)	<0.001
ACE inhibitors	14 (6.8%)	15 (12%)	0.11
beta-blockers	18 (8.7%)	23 (18%)	0.011
CCBs	18 (8.7%)	7 (5.6%)	0.3
Diuretics	22 (11%)	11 (8.7%)	0.6
cholesterol (mg/dL)	203 (186, 225)	180 (155, 202)	<0.001
Statins	60 (29%)	47 (37%)	0.12
microbleeds	25 (12%)	20 (16%)	0.3
WMH[a]	2.0 (2.0, 4.0)	2.0 (1.0, 3.0)	0.58
ICV (dm^3)	1.41 (1.32, 1.49)	1.57 (1.52, 1.65)	<0.001
GM volume (dm^3)	0.58 (0.54, 0.61)	0.62 (0.58, 0.66)	<0.001
lateral ventricle (dm^3)	0.023 (0.013, 0.033)	0.031 (0.011, 0.051)	<0.001
GM/ICV	0.42 (0.39, 0.44)	0.39 (0.37, 0.42)	<0.001
lateral ventricle/ICV	0.017 (0.013, 0.023)	0.020 (0.015, 0.028)	<0.001
cortical thickness (mm)	2.39 (2.33, 2.45)	2.36 (2.31, 2.42)	0.002
DMV count	25 (19, 32)	29 (20, 35)	0.012

[1] n (%); Median (Q1, Q3)
[2] U Mann-Whitney test; Pearson's Chi-squared test; Fisher's exact test
[a] assessed with Fazekas scale. The final score (0-6) reflects the sum of periventricular and deep WMH scores

BMI: body mass index, BP: blood pressure, ARBs: angiotensin receptor blockers, ACE: angiotensin converting enzyme, CCBs: calcium channel blockers, WMH: white matter hyperintensities, ICV: intracranial volume, GM: gray matter, DMV: deep medullary veins

Association between atrophy measures and DMV count in the entire group

In the entire group, in models predicting atrophy measures, DMV count was positively associated with GM/ICV (p=0.008, Table 2) and negatively with lateral ventricle/ICV (p<0.001, Table 3). For lateral ventricle/ICV analysis was repeated with log transformed values, and results were unchanged. Both results were significant at 5% FDR (supplementary Table 8). Cortical thickness was not related to DMV count (supplementary Table 1).

When both GM/ICV and lateral ventricle/ICV were examined in the same model as predictors of DMV count in the entire group, only lateral ventricle/ICV remained significant. Table 4 presents the results of linear regression. No other variable, besides sex, was identified as a significant predictor of DMV count. Men had more veins than women. Neither WMH nor microbleeds were related to DMVs. Ordinal regression replicated the results: lateral ventricle/ICV and sex were significantly associated with DMV count (supplementary Table 9).

Association between atrophy measures and DMV count in men and women

In analyses stratified by sex DMV count was significantly negatively associated with lateral ventricle/ICV ratio both in women (supplementary Table 2) and in men (supplementary Table 5). Both results were significant at 5% FDR (supplementary Table 8). DMV count was not related to GM/ICV ratio or cortical thickness in men (supplementary 6-7). It was not related to cortical thickness in women (supplementary Table 4). Even though it showed an association with GM/ICV in women (supplementary Table 3), this relationship did not survive FDR correction (supplementary Table 8).

Discussion

There are a few major findings from our study. First, a lower DMV count was related to subcortical but not cortical atrophy. Second, men had more DMVs than women. Third, WMH burden or the presence of microbleeds, was not associated with DMV count. Finally, DMV count was related subcortical atrophy independent of other risk factors.

Current studies examined the connection between DMV count or visibility and global measures of brain atrophy, such as whole brain[9,18] or gray matter volume.[8,16,17] We have added measures reflecting cortical and subcortical atrophy. Lateral ventricle to ICV ratio was the variable showing the strongest association with DMV count. That was true both in the entire group and when analyses were stratified by sex. Lower visibility of deep medullary veins, and consequently lower count,

Table 2
Results of the linear regression predicting GM/ICV ratio.

predictor	unstandardized β (95% CI)	standardized β	significance
age	-0.002 (-0.003 – (-0.002))	-0.40	**<0.001**
sex (male)	-0.12 (-0.020 – (-0.004))	-0.14	**0.005**
BMI	-0.001 (-0.002- (-0.001))	-0.17	**<0.001**
systolic BP	0.000 (0.000-0.000)	-0.08	0.11
antihypertensive med	0.002 (-0.007 – 0.011)	0.02	0.65
cholesterol	-0.000 (-0.000 – 0.000)	-0.04	0.41
statin	0.002 (-0.007 – 0.011)	0.02	0.64
smoking	-0.02 (-0.036 – (-0.004))	-0.12	**0.012**
diabetes mellitus	-0.004 (-0.022 – 0.014)	-0.02	0.64
WMH	-0.004 (-0.006 – (-0.001))	-0.14	**0.004**
microbleeds	-0.004 (-0.015 – 0.007)	-0.03	0.50
DMVs count	0.001 (0.000 – 0.001)	0.12	**0.008**

GM: gray matter, ICV: intracranial volume, CI: confidence interval, BMI: body mass index, BP: blood pressure, WMH: white matter hyperintensities, DMVs: deep medullary veins

Table 3
Results of the linear regression predicting lateral ventricle/ICV ratio.

predictor	unstandardized β (95% CI)	standardized β	significance
age	0.000 (0.000 – 0.001)	0.28	**<0.001**
sex (male)	0.004 (0.002 – 0.006)	0.21	**<0.001**
BMI	0.000 (0.000- 0.000)	-0.09	0.10
systolic BP	0.000 (0.000-0.000)	0.04	0.44
antihypertensive med	0.001 (-0.001 – 0.003)	0.06	0.26
cholesterol	0.00004 (0.000 – 0.000)	0.16	**0.005**
statin	0.001 (-0.001 – 0.004)	0.08	0.17
smoking	0.000 (-0.004 – 0.004)	0.001	0.99
diabetes mellitus	0.000 (-0.005 – 0.004)	-0.01	0.89
WMH	0.001 (0.000 – 0.001)	0.10	0.08
microbleeds	-0.001 (-0.003 – 0.002)	-0.0	0.78
DMV count	0.000 (0.000 – 0.000)	-0.25	**<0.001**

GM: gray matter, ICV: intracranial volume, CI: confidence interval, BMI: body mass index, BP: blood pressure, WMH: white matter hyperintensities, DMVs: deep medullary veins

Table 4
Results of the linear regression predicting deep medullary veins count.

predictor	unstandardized β (95% CI)	standardized β	significance
age	-0.05 (-0.22 - 0.11)	-0.04	0.53
sex (male)	4.44 (2.30 -6.59)	0.24	**<0.001**
BMI	-0.19 (-0.39-0.01)	-0.11	0.06
systolic BP	-0.03 (-0.09-0.04)	-0.05	0.38
antihypertensive med	0.58 (-1.69 – 2.85)	0.03	0.62
cholesterol	0.01 (-0.02 – 0.04)	0.04	0.51
statin	1.97 (-0.31 – 4.25)	0.10	0.09
smoking	-2.50 (-6.68 – 1.67)	-0.06	0.24
diabetes mellitus	-3.05 (-7.66 – 1.56)	-0.07	0.19
WMH	0.56 (-0.12 – 1.24)	0.09	0.11
microbleeds	0.69 (-2.12 – 3.50)	0.03	0.63
GM/ICV	20.7 (-8.84 – 50.3)	0.09	0.17
lateral ventricle/ICV	-258.8 (-376 – (-141.6))	-0.26	**<0.001**

CI: confidence interval, BMI: body mass index, BP: blood pressure, WMH: white matter hyperintensities, GM: gray matter, ICV: intracranial volume

may reflect collagenosis. Thus, likely, it could be a potential, independent cause of subcortical atrophy. In line with vascular contributions to degeneration, other predictors of ventricular enlargement in the entire group included older age, male sex, and higher cholesterol. Men in our cohort had more vascular risk factors than women, supporting vascular origins of ventricular expansion. Although in the initial analysis, the GM/ICV ratio in the entire group showed an association with DMV count, it was not as strong a predictor as a lateral ventricle/ ICV. In addition, in sex-stratified models, GM/ICV no longer showed an association with DMV count. Cortical thickness was not related to DMVs, emphasizing the unique link between deep medullary veins and subcortical atrophy. If indeed, lesser count reflects stenotic and collapsed veins, it follows that there should be a connection between fewer visible veins and less tissue within the adjacent regions where venous system is putatively compromised, and much less so between DMVs and parenchyma in more distant regions.

Men had more veins than women, while at the same time, men had more brain atrophy. The association may be explained by a bigger intracranial cavity and brain size in men than women, which could result in more cerebral veins. Although both cortical volume and thickness are related to intracranial volume, this correlation is stronger for volume than for thickness.[20] We offer this could be a reason for observed positive correlations between veins and GM/ICV ratio, still reflecting brain size, and a lack of relationship between DMV count and cortical thickness.

White matter lesion load was not correlated with the number of visible DMVs. Previous studies have discovered multiple conflicting relationships, with some relating increased WMH volume to fewer DMVs,[10] while others showed correlations between WMH and more DMVs.[6] Similarly, in our group, there was no association between the presence of microbleeds and DMV count. As with WMH, earlier reports showed discrepant conclusions.[6,12]

Our findings suggest that the mechanism of venous contribution to subcortical cerebral volume loss is independent of arterial damage, manifesting as classical CSVD imaging markers. This is strengthened by analyses showing that DMVs predicted ventricular enlargement, even when WMH was included in the model (Table 3). Possibly, impaired venous caliber (fewer DMVs visible) leads to neurodegeneration through reduced perivenous (aka glymphatic) clearance, since perivenous spaces are an important part of the brain solute transport system.[1] Recent reports using diffusion tensor image analysis along the perivascular space (DTI-ALPS) MRI techniques centered on perivenous spaces of deep medullary veins showed that a lower index, thought to reflect reduced clearance, was related to age, amyloid accumulation, and brain atrophy.[34,35]

This study possesses a few potential limitations. Our study subjects were predominantly Caucasian, with higher-than-average educational attainment. Still, they represented the local population. We did not evaluate lacunar infarcts, enlarged periventricular spaces (PVS), and cerebral amyloid angiopathy (CAA). PVS and CAA have been proposed as markers of a small vessel disease in previous studies. However, quantification of PVS and CAA is very challenging, and its reproducibility is questionable.[36] DMVs were assessed only on one slice. Still, the slice under investigation was at a fixed anatomical location. Moreover, a recent neuropathology study found that the burden of collagen in the cerebral venules was distributed rather evenly, suggesting that assessment of one region would give a fair estimate of collagenosis in the entire brain.[37] Although intra-rater variability of our measure was acceptable, inter-rater variability was only moderate. If more than one rater is employed to qualitatively assess venous system in a given cohort, consensus meeting is recommended. Altogether further research is needed using an unbiased automatic vein segmentation in regions adjacent to the lateral ventricle, including subcortical gray matter structures. Moreover, to fully explore heterogeneity of the venous system, longitudinal studies of diverse populations are necessary. Finally, multimodal imaging including DTI-ALPS and/or parenchymal CSF mapping, will help to elucidate relationships between vein measures and estimates of glymphatic function.

Conclusion

We used a large cohort of cognitively unaffected older people and a detailed multivariable modeling. We found that subcortical, but not cortical, atrophy showed a significant association with lower number of DMVs visible via SWI. Most importantly, a reduced number of DMVs was related to ventricular enlargement independently of other factors which contribute to volume reduction, possibly indicating an additional independent pathomechanism.

Funding sources

Study funding comes from NIH grants HL111724, NS104364, AG022374, AG12101, AG057848, AG058913, AG057570.

CRediT authorship contribution statement

Sushruth Manchineella: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration. **Henry Rusinek:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Data curation. **Yuan Ma:** Writing – review & editing, Methodology. **Xiuyuan Hugh Wang:** Writing – review & editing, Software, Resources, Methodology, Data curation. **Surendra**

Maharjan: Writing – review & editing, Validation, Methodology. **Liangdong Zhou:** Writing – review & editing. **Tracy Butler:** Writing – review & editing, Resources, Project administration, Methodology, Investigation. **Yi Li:** Writing – review & editing, Methodology, Investigation. **Alexus Jones:** Writing – review & editing, Project administration, Investigation. **Emily Tanzi:** Writing – review & editing, Project administration, Investigation. **Gloria C Chiang:** Writing – review & editing, Resources, Project administration. **Silky Pahlajani:** Writing – review & editing. **Katarzyna Olejniczak-Gniadek:** Writing – review & editing. **Seyed Hani Hojjati:** Writing – review & editing, Methodology, Conceptualization. **Thomas Maloney:** Writing – review & editing, Data curation. **Mony J. de Leon:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition. **Lidia Glodzik:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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.

Acknowledgement

We thank Ms. Cynthia Fox for her careful review of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2025.108510.

References

1. M Iliff JJW, Liao Y, Plogg BA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4.
2. dela Paz NG, D'Amore PA. Arterial versus venous endothelial cells. *Cell Tissue Res*. 2009;335:5–16. https://doi.org/10.1007/s00441-008-0706-5.
3. Rustenhoven J, Drieu A, Mamuladze T, et al. Functional characterization of the dural sinuses as a neuroimmune interface. *Cell*. 2021;184:1000–1016.e1027. https://doi.org/10.1016/j.cell.2020.12.040.
4. Moody, D.M., Brown Wr Fau-Challa V.R., Challa Vr Fau-Anderson R.L. & Anderson, R.L. (1995). Periventricular venous collagenosis: association with leukoaraiosis.
5. Keith J, Gao F-q, Noor R, et al. Collagenosis of the deep medullary veins: an underrecognized pathologic correlate of white matter hyperintensities and periventricular infarction? *J Neuropathol Exper Neurol*. 2017;76:299–312. https://doi.org/10.1093/jnen/nlx009.
6. Yan S, Wan J, Zhang X, et al. Increased Visibility of Deep Medullary Veins in Leukoaraiosis: A 3-T MRI Study. *Front Aging Neurosci*. 2014;6. https://doi.org/10.3389/fnagi.2014.00144.
7. Houck AL, Gutierrez J, Gao F, et al. Increased diameters of the internal cerebral veins and the basal veins of rosenthal are associated with white matter hyperintensity volume. *Am J Neuroradiol*. 2019;40:1712–1718. https://doi.org/10.3174/ajnr.A6213.
8. Li C, Rusinek H, Chen J, et al. Reduced white matter venous density on MRI is associated with neurodegeneration and cognitive impairment in the elderly. *Front Aging Neurosci*. 2022;14, 972282. https://doi.org/10.3389/fnagi.2022.972282.
9. Brenlla C, Sozzi C, Girona A, et al. Deep medullary veins integrity and relationships with small vessel disease and interstitial diffusivity measures in patients with a recent small subcortical infarct. *AJNR Am J Neuroradiol*. 2024. https://doi.org/10.3174/ajnr.A8591.
10. Zhang R, Zhou Y, Yan S, et al. A brain region-based deep medullary veins visual score on susceptibility weighted imaging. *Front Aging Neurosci*. 2017;9. https://doi.org/10.3389/fnagi.2017.00269.
11. Zhang K, Zhou Y, Zhang W, Li Q, Sun J, Lou M. MRI-visible perivascular spaces in basal ganglia but not centrum semiovale or hippocampus were related to deep medullary veins changes. *J Cereb Blood Flow Metabol*. 2022;42:136–144. https://doi.org/10.1177/0271678x211038138.
12. Zhang R, Li Q, Zhou Y, Yan S, Zhang M, Lou M. The relationship between deep medullary veins score and the severity and distribution of intracranial microbleeds. *Neuroimage: Clin*. 2019;23, 101830. https://doi.org/10.1016/j.nicl.2019.101830.
13. Zhou Y, Li Q, Zhang R, Zhang W, et al. Role of deep medullary veins in pathogenesis of lacunes: Longitudinal observations from the CIRCLE study. *J Cereb Blood Flow Metabol*. 2020;40:1797–1805. https://doi.org/10.1177/0271678x19882918.
14. Wang H, Lei X, Lan H, et al. Impact of decreased visibility of deep medullary veins on white matter integrity in patients with cerebral small vessel disease. *JIN*. 2023;22. https://doi.org/10.31083/j.jin2206170.
15. Albani D, Marizzoni M, Ferrari C, et al. Plasma Aβ42 as a biomarker of prodromal Alzheimer's disease progression in patients with amnestic mild cognitive impairment: evidence from the PharmaCog/E-ADNI study. *J Alzheimer Dis: JAD*. 2019;69:37–48. https://doi.org/10.3233/JAD-180321.
16. Mao F, Xu Z, Shao M, Xiang X, Zhou X. Deep medullary veins score is associated with atrophy in patients with cerebral small vessel disease. *Front Neurol*. 2024;15, 1417805. https://doi.org/10.3389/fneur.2024.1417805.
17. Liu ZY, Zhai FF, Ao DH, et al. Deep medullary veins are associated with widespread brain structural abnormalities. *J Cereb Blood Flow Metabol: Off J Int Soc Cereb Blood Flow Metabol*. 2022;42:997–1006. https://doi.org/10.1177/0271678x211065210.
18. Ao DH, Zhang DD, Zhai FF, et al. Brain deep medullary veins on 3-T MRI in a population-based cohort. *J Cereb Blood Flow Metabol: Off J Int Soc Cereb Blood Flow Metabol*. 2021;41:561–568. https://doi.org/10.1177/0271678x20918467.
19. Schwarz CG, Gunter JL, Wiste HJ, et al. A large-scale comparison of cortical thickness and volume methods for measuring Alzheimer's disease severity. *Neuroimage Clin*. 2016;11:802–812. https://doi.org/10.1016/j.nicl.2016.05.017.
20. Im K, Lee JM, Lyttelton O, Kim SH, Evans AC, Kim SI. Brain size and cortical structure in the adult human brain. *Cereb Cortex*. 2008;18:2181–2191. https://doi.org/10.1093/cercor/bhm244.
21. Blumen HM, Schwartz E, Allali G, et al. Cortical thickness, volume, and surface area in the motoric cognitive risk syndrome. *J Alzheimer Dis*. 2021;81:651–665. https://doi.org/10.3233/jad-201576.
22. Winkler AM, Kochunov P, Blangero J, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *Neuroimage*. 2010;53:1135–1146. https://doi.org/10.1016/j.neuroimage.2009.12.028.
23. de Chastelaine M, Srokova S, Hou M, et al. Cortical thickness, gray matter volume, and cognitive performance: a crosssectional study of the moderating effects of age on their interrelationships. *Cereb Cortex*. 2023;33:6474–6485. https://doi.org/10.1093/cercor/bhac518.
24. Lemaitre H, Goldman AL, Sambataro F, et al. Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and gray matter volume? *Neurobiol Aging*. 2012;33:617.e611–617.e619. https://doi.org/10.1016/j.neurobiolaging.2010.07.013.
25. Giedd JN, Raznahan A, Mills KL, Lenroot RK. Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. *Biol Sex Differ*. 2012;3:19. https://doi.org/10.1186/2042-6410-3-19.
26. Reisberg B, Ferris SH. Brief Cognitive Rating Scale (BCRS). *Psychopharmacol Bull*. 1988;24:629–636.
27. S. S. Reisberg B, Franssen EH, de Leon MJ, et al. Clinical stages of normal aging and Alzheimer's disease: the GDS staging system *Neurosci Res Commun*. 1993;13(Suppl. 1):551–554
28. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412–2414. https://doi.org/10.1212/wnl.43.11.2412-a.
29. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabet Care*. 2020;43:S14–s31. https://doi.org/10.2337/dc20-S002.
30. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a scientific statement from the American Heart Association. *Hypertension*. 2019;73:e35–e66. https://doi.org/10.1161/hyp.0000000000000087.
31. Greenberg SM, Vernooij MW, Cordonnier C, et al. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009;8:165–174. https://doi.org/10.1016/s1474-4422(09)70013-4.
32. Ashburner J, Friston KJ. Voxel-based morphometry–the methods. *Neuroimage*. 2000;11:805–821.
33. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol*. 1987;149:351–356.
34. Zhou L, Butler TA, Wang XH, et al. Multimodal assessment of brain fluid clearance is associated with amyloid-beta deposition in humans. *J Neuroradiol*. 2024;51, 101164. https://doi.org/10.1016/j.neurad.2023.10.009.
35. Huang SY, Zhang YR, Guo Y, et al. Glymphatic system dysfunction predicts amyloid deposition, neurodegeneration, and clinical progression in Alzheimer's disease. Alzheimer's & dementia. *J Alzheimer Assoc*. 2024;20:3251–3269. https://doi.org/10.1002/alz.13789.
36. Downes MH, Kalagara R, Rossitto CP, et al. Validation of the boston criteria version 2.0 for cerebral amyloid angiopathy in patients presenting with intracerebral hemorrhage. *Neurology*. 2025;104, e213460. https://doi.org/10.1212/wnl.0000000000213460.
37. Cao Y, Huang MY, Mao CH, et al. Arteriolosclerosis differs from venular collagenosis in relation to cerebrovascular parenchymal damages: an autopsy-based study. *Stroke Vasc Neurol*. 2023;8:267–275. https://doi.org/10.1136/svn-2022-001924.