Original Research Paper

The central vein sign in multiple sclerosis patients with vascular comorbidities

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Abstract

Background: The central vein sign (CVS) is an imaging biomarker able to differentiate multiple sclerosis (MS) from other conditions causing similar appearance lesions on magnetic resonance imaging (MRI), including cerebral small vessel disease (CSVD). However, the impact of vascular risk factors (VRFs) for CSVD on the percentage of CVS positive (CVS$^+$) lesions in MS has never been evaluated.

Objective: To investigate the association between different VRFs and the percentage of CVS$^+$ lesions in MS.

Methods: In 50 MS patients, 3T brain MRIs (including high-resolution 3-dimensional T2*-weighted images) were analyzed for the presence of the CVS and MRI markers of CSVD. A backward stepwise regression model was used to predict the combined predictive effect of VRF (i.e. age, hypertension, diabetes, obesity, ever-smoking, and hypercholesterolemia) and MRI markers of CSVD on the CVS.

Results: The median frequency of CVS$^+$ lesions was 71% (range: 35%–100%). In univariate analysis, age ($p < 0.0001$), hypertension ($p < 0.001$), diabetes ($p < 0.01$), obesity ($p < 0.01$), smoking ($p < 0.05$), and the presence of enlarged-perivascular-spaces on MRI ($p < 0.005$) were all associated with a lower percentage of CVS$^+$ lesions. The stepwise regression model showed that age and arterial hypertension were both associated with the percentage of CVS$^+$ lesions in MS (adjusted $R^2 = 0.46$; $p < 0.0001$ and $p = 0.01$, respectively).

Conclusion: The proportion of CVS$^+$ lesions significantly decreases in older and hypertensive MS patients. Although this study was conducted in patients with an already established MS diagnosis, the diagnostic yield of the previously proposed 35% CVS proportion-based diagnostic threshold appears to be not affected. Overall these results suggest that the presence of VRF for CSVD should be taken into account during the CVS assessment.

Keywords: Central vein sign, multiple sclerosis, magnetic resonance imaging, cerebral small vessel disease, vascular risk factors

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Introduction

The presence of a vein at the center of brain white matter (WM) lesions is a prominent feature of MS pathology,[1] which can now be depicted in vivo using optimized susceptibility-based magnetic resonance imaging (MRI) sequences.[2] Several studies have shown that this "central vein sign" (CVS) can improve the differentiation between MS and other condition giving similar WM lesions on MRI, including cerebral small vessel disease (CSVD).[2–4]

CSVD is commonly associated with aging and other cardiovascular risk factors (vascular risk factors (VRFs)), such as arterial hypertension (HT), and causes brain WM lesions, which can mimic MS lesions on MRI.

From a pathogenetic point of view, in CSVD, vessel lumen restriction, chronic hypoperfusion, and WM lesion formation mostly occur at the arteriolar side of vascular microcirculation.[5,6] On the contrary, inflammatory demyelinating WM lesions in MS develop around small parenchymal veins.[7] Previous studies have shown that subjects with MS have a higher proportion of lesions with a central vein compared to CSVD patients.[2,8,9]

Vascular comorbidities are prevalent in MS and are associated with an increased MRI lesion burden and brain atrophy, as well as with clinical disability progression.[10,11] In this scenario, diagnostic uncertainty may arise in the diagnostic workup of patients

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with possible MS but with concomitant VRF for CSVD.[12] Moreover, the radiological follow-up of MS patients with VRF for CSVD can be challenging due to the difficulty to distinguish whether new individual MRI lesions in these patients are due to MS or to CSVD.[12] Advanced, highly specific MRI biomarkers like the CVS could be very helpful in the above-mentioned situations. However, data regarding the proportion of lesions with a central vein in MS patients with VRF for CSVD are lacking.[2] In this study we tested the association between the presence of VRF and MRI markers for CSVD, and the percentage of CVS positive (CVS$^+$) lesions in MS patients.

Methods

Study population

Patients with a diagnosis of relapsing–remitting MS (RRMS), primary progressive MS (PPMS), or secondary progressive MS (SPMS) according to the 2010 McDonald criteria[13] were recruited between September 2016 and September 2019 in three academic hospitals: the Erasme University Hospital (Brussels, Belgium), the Saint-Luc University Hospitals (Brussels, Belgium), and the Lausanne University Hospital (Lausanne, Switzerland). Exclusion criteria included suboptimal MRI image quality due to motion artifact and $\leqslant 3$ brain WM lesions eligible for CVS assessment on MRI. Lesion eligibility for CVS assessment was evaluated according to the North American Imaging in MS Cooperative (NAIMS) guidelines.[2] The study was approved by the local medical ethics committees of the different centers and informed consent was obtained for all subjects.

MRI acquisition protocol

All patients underwent brain MRI on a 3T Philips MRI Scanner (Ingenia, Best, The Netherlands) in Brussels and a 3T Magnetom Skyra or Prisma scanner (Siemens Healthcare, Erlangen, Germany) in Lausanne. A single MRI protocol was applied in all institutions including a high-resolution three-dimensional (3D) T2*-weighted echo-planar imaging (EPI), a 3D T2-fluid-attenuated inversion recovery (FLAIR), and a T2-weighted turbo spin echo (TSE). Isotropic resolution of the 3D T2*-EPI was 0.55 mm^3 in Brussels and 0.65 mm^3 in Lausanne (Supplementary Table 1).[14]

MRI post-processing and CVS assessment

The "CVS" assessment was performed on FLAIR* images generated by co-registration and voxel-wise multiplication of the high-resolution 3D T2* EPI and the 3D T2-FLAIR, as previously described.[15,16] For each subject brain WM matter lesions were manually segmented on FLAIR* images using Mipav (http://mipav.cit.nih.gov) and the presence/absence of the CVS (hereafter, CVS$^+$/CVS$^-$) was blindly and independently assessed by two investigators, one neurologist and one board certified neuroradiologist (F. G. and V. L.), according to the NAIMS guidelines.[2] In case of discrepancies between raters, lesions were reviewed to reach a consensus. Lesion volume and location (periventricular, juxtacortical/leucocortical, infratentorial and subcortical/deep WM, or infratentorial)[12,16] were recorded for each patient. In addition, patients were dichotomized in perivenular positive versus perivenular negative based on the previously proposed criteria: the 35%[4] and 40%[8,15] CVS proportion-based diagnostic thresholds, the "6-lesion rule,"[17] and the "3-lesion rule."[18]

Assessment of VRFs for CSVD

Demographic, clinical, and laboratory data were recorded for each patient. Demographic and clinical work-up included smoking and medications history, body mass index (BMI; measured as weight-to-height ratio), arterial blood pressure measurement, and Expanded Disability Status Scale (EDSS). Laboratory work-up included measurement of serum low-density lipoproteins (LDL) cholesterol (normal values <115 mg/dL),[19] random plasma glucose (normal values <200 mg/dL), and hemoglobin A1C level (normal values <6.5%).[20]

The presence/absence of the following VRF for CSVD were recorded for each patient:[21–23] (1) age $\geqslant 50$ years old; (2) HT, that is, established diagnosis and treatment with at least one antihypertensive drug; (3) type 1 or type 2 diabetes (diabetes), that is, established diagnosis or elevated diagnostic test on two repeated measurements; (4) smoking, current or former; (5) BMI $\geqslant 30$ kg/m^2; (6) hypercholesterolemia, that is, established diagnosis and treatment with statins or elevated LDL cholesterol serum levels.

Assessment of MRI markers of CSVD

Neuroimaging markers of CSVD severity were rated according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) consensus criteria.[24] Enlarged perivascular spaces (EPVS) were rated on axial T2-TSE images, in the basal ganglia (BG) and centrum semiovale (CSO), with a validated 4-point visual rating scale (0 = no EPVS, 1 = <10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = >40

EPVS), as previously described.[25] Lacunes were defined as small, ovoid, subcortical fluid-filled cavities of between 3 and 15 mm in diameters visible on T2-FLAIR and T1-weighted images.[24] Of note, when a central hypointensity was surrounded by a hyperintense rim on T2-FLAIR images, lacunes were differentiated from central veins (CVS) according to their apparent diameter (>3 mm for lacunes and <2 mm for the CVS).[2] Cerebral microbleeds were evaluated on T2*-EPI images, as previously described.[26] White matter hyperintensities (WMH) were evaluated on axial T2-FLAIR images using the Fazekas scale (range: 0–3).[27] Following the definition,[24] only symmetric signal hyperintensities were taken into account, to differentiate as much as possible CSVD-related WMH versus MS-related WMH.

Statistical analysis
All statistical analysis was computed using the statistical software JMP Pro 14.3.0®. The interrater agreement for CVS assessment was computed using the Cohen's κ. The association between the percentage of CVS+ lesions and the different VRF and MRI markers of CSVD as well as with lesion volume was first tested in a univariate analysis using simple linear regression analysis or Mann–Whitney test, when appropriate. Regional lesion distribution differences between CVS+ and CVS− lesions were assessed using chi-square test and two-sample test for equality of proportions. Backward stepwise regression was used to test the combined predictive effect of the candidate variables on the CVS.

Results

Demographic and clinical data
Of the 58 eligible consecutive MS patients, 50 were included in this study (three patients were excluded because of motion artifact and five because of ⩽3 lesions eligible for CVS assessment on brain MRI). Clinical and demographic characteristics as well as patients VRF are reported in Table 1.

Lesion counts, location, and CVS assessment
A total of 756 brain WM lesions were analyzed with a median of 12.5 (range: 4–43) lesions per patient. Among the 756 lesions, 535 (70.8%) were rated CVS+ after consensus agreement. The median frequency of CVS+ lesions per patient was 71% (range: 35%–100%). The inter-rater agreement for the percentage of CVS+ lesions was "substantial/good" with a Cohen's κ of 0.7 and agreement of 87%. No difference in

Table 1. Baseline characteristics and cardiovascular risk profiles.

Clinical and demographics	
Patients no.	50
Female, no. (%)	28 (56%)
Age, years, median (range)	44 (20−68)
EDSS score, median (range)	2.5 (1.0−6.5)
Clinical phenotype, no. (%)	
RRMS	31 (62%)
PPMS	12 (24%)
SPMS	7 (14%)
Cardiovascular risk factors	
Age ⩾50 years, no. (%)	18 (36%)
Arterial hypertension, no. (%)	11 (22%)
Diabetes, no. (%)	6 (12%)
Smoking, no. (%)	26 (52%)
BMI (kg/m²), no. (%)	
<25.0	23 (47%)
25–29	19 (39%)
⩾30.0	7 (14%)
Hypercholesterolemia, no. (%)	27 (54%)
Cumulative no. of VRF, median (range)	2 (0–6)

EDSS: Expanded Disability Status Scale; RRMS: relapsing–remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis; BMI: body mass index.

lesion volume was observed between the CVS+ and CVS− lesions (median = 50 mm³, range: 5–625 vs 52 mm³, range: 14–308, respectively). The topographical distribution significantly differed between CVS+ and CVS− lesions (χ² test, $p < 0.0001$). CVS+ lesions were more common in the periventricular (10% vs 4%, $p = 0.01$) and infratentorial (12% vs 5%, $p = 0.005$) locations (Table 2).

When applying the 35% and the 40% CVS proportion-based diagnostic thresholds,[4,8] all included patients and 49 of the 50 included patients were, respectively, perivenular positive.

When applying the simplified algorithms 6-lesion and 3-lesion rules,[17,18] 46 and 42 of the 50 included patients were, respectively, perivenular positive.

Association between VRF for CSVD and the CVS
Patients older than 50 years had a lower percentage of CVS+ lesions (median = 61.5%, range 35%–76%) compared to younger ones (median = 77.5%, range

Table 2. Dimension and topography of central vein sign positive (CVS$^+$) and central vein sign negative (CVS$^-$) lesions.

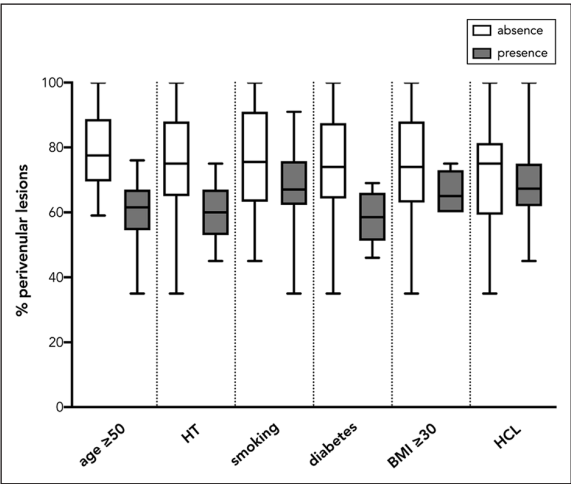|	CVS$^+$	CVS$^-$	Statistical analysis
Total lesions, no. (%)	535 (70.8%)	221 (29.2%)	NA
Lesion volume (mm³), median (range)	50 (5–625)	52 (14–308)	n.s.
Lesion location, no. (%)			
Subcortical/deep white matter	391 (73%)	174 (79%)	Prop. test $p = 0.1$, n.s.
Periventricular	53 (10%)	9 (4%)	Prop. test $p = 0.01$
Juxtacortical/Leukocortical	24 (4%)	27 (11%)	Prop. test $p = 0.0007$
Infratentorial	67 (12%)	11 (5%)	Prop. test $p = 0.005$

Figure 1. Association between different VRFs and the CVS. Comparative frequency (median and interquartile range) of perivenular lesions in MS patients with (gray box) or without (white box) the following VRF for CSVD: age ⩾50 years old, arterial hypertension (HT), ever-smoking (smoking), type 1 or type 2 diabetes (diabetes), body mass index (BMI) ⩾30 kg/m² and hypercholesterolemia (HCL).

59%–100%; $p < 0.0001$). Patients with HT had a lower percentage of CVS$^+$ lesions (median = 60%, range 45%–75%) compared with non-HT individuals (median = 75%, range 35%–100%; $p = 0.0005$). Smokers had a lower percentage of CVS$^+$ lesions (median = 67%, range 35%–91%) compared to non-smokers (median = 75.5%, range 45%–100%; $p < 0.05$). Patients with diabetes had a lower percentage of CVS$^+$ lesions (median = 58.5%, range 46%–69%) compared to non-diabetic (median = 74%, range 35%–100%; $p = 0.008$). Patients with BMI ⩾30 had a lower percentage of CVS$^+$ lesions (median = 65%, range 60%–75%) compared to patients with BMI < 30 (median = 74%, range 35%–100%; $p = 0.008$; Figure 1). The percentage of CVS$^+$ lesions did not significantly differ between patients with or without hypercholesterolemia (median = 67%, range 45%–100% vs

median = 75%, range 35%–100%, respectively; $p = 0.4$).

The percentage of CVS$^+$ lesions in MS patients negatively correlated with patient's age ($R^2 = 0.52$; $p < 0.0001$), systolic blood pressure ($R^2 = 0.14$; $p = 0.006$), BMI ($R^2 = 0.12$; $p = 0.015$) and with the patient's cumulative number of VRFs for CSVD ($R^2 = 0.33$; $p < 0.0001$). The association between patient's age and patient's cumulative number of VRF and the frequency of perivenular lesions is shown in Figure 2(a) and (b); representative cases are shown in Figure 2(c) and (d).

Association between MRI markers of CSVD and the CVS

The median EPVS CSO and BG scores were 2 (range: 4–1) and 1 (range: 3–1), respectively. The median WMH score was 1 (range: 0–3). Cerebral lacunes were observed in five patients (10%) and we did not find any cerebral microbleeds. Regarding the association between the imaging markers of CSVD and the CVS, the EPVS CSO score negatively correlated with the percentage of CVS$^+$ lesions per patient ($R^2 = 0.17$; $p < 0.004$). Representative cases are shown in Figure 3. The BG EPVS score did not show a significant association with the percentage of CVS$^+$ lesions ($R^2 = 0.03$, $p = 0.2$). Both the number of cerebral lacunes per patient and the WMH score did not show a significant correlation with the percentage of CVS$^+$ lesions ($R^2 = 0.016$, $p = 0.4$ and $R^2 = 0.02$, $p = 0.3$, respectively).

Combined association between clinical VRF and MRI markers of CSVD and the CVS

Among all the clinical and MRI markers of CSVD, the stepwise regression showed that age ⩾50 years (explained variance = 45%; $p < 0.0001$) and HT (explained variance = 16%; $p = 0.01$) were both
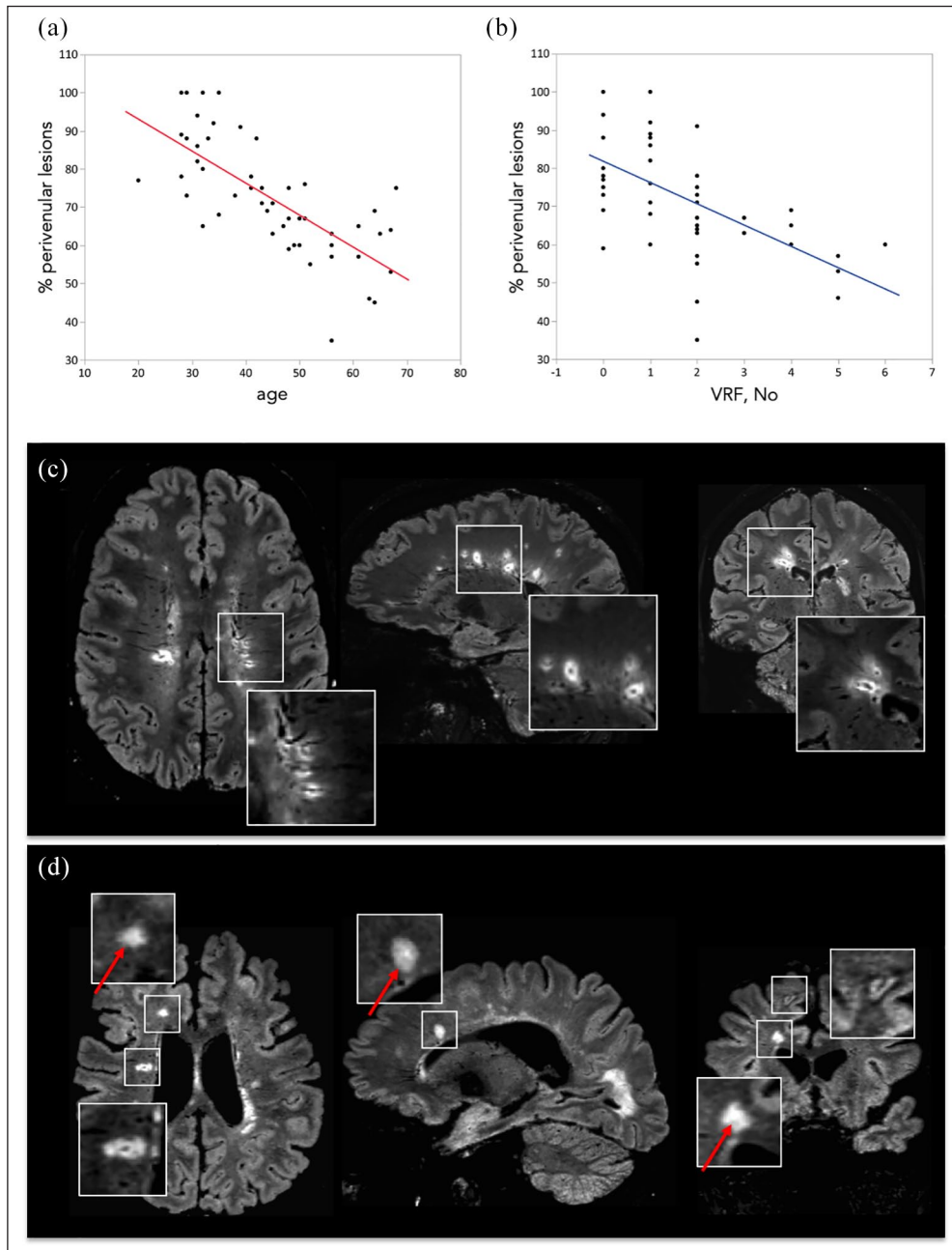
Figure 2. 3D FLAIR* images in MS patients with VRF for CSVD. Association between (a) patient's age and (b) patient's cumulative number of VRF (VRF, No) and the frequency of perivenular lesions $R^2 = 0.52$; $p < 0.0001$ and $R^2 = 0.33$; $p < 0.0001$, respectively. Representative 3-dimensional FLAIR* images of (c) a 28 year-old RRMS patient with only one VRF for CSVD (smoking) and (d) of a 61 year-old RRMS patient with five different VRFs for CSVD (age, HT, smoking, diabetes, and hypercholesterolemia). Although the majority of lesions in MS are perivenular, non-perivenular lesions are visible in the subject with several VRFs for CSVD (arrows).

associated with the percentage of CVS+ lesions (adjusted $R^2 = 0.46$).

Discussion

The major new finding of this multicentre study is that the percentage of lesions with a central vein in MS significantly decreases in the presence of VRF for CSVD. Specifically, we found that age ≥50 years and HT were the strongest inverse predictors of the percentage of MS-specific perivenular lesions. These results suggest that the CVS assessment in MS patients might help in differentiating new brain MRI lesions as either microangiopathic or demyelinating. Assessments
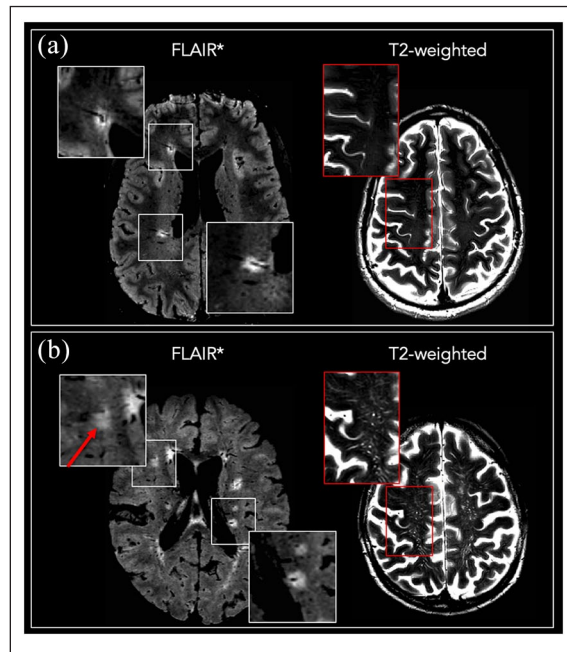
Figure 3. The central vein sign and enlarged perivascular spaces on MRI. Representative axial FLAIR* images of (a) a 29-year-old RRMS patient with a high frequency of perivenular lesions (% CVS+ lesions=100%) and (b) a 67-year-old SPMS patient with perivenular and non-perivenular (arrow) lesions (% CVS+ lesions=64%). Enlarged perivascular spaces (EPVS) on T2-weighted images (magnified boxes) are only barely visible in the subject with a high frequency of perivenular lesions ((a); EPVS rating score=1) but are prominent in the subject with a lower frequency of perivenular lesions ((b); EPVS rating score=4).

were performed on clinical 3T MRI scanners, using an optimized 3D T2*-weighted technique[28] able to efficiently detect a central vein in brain WM lesions.[4,16]

This is the first study specifically investigating the influence of vascular comorbidities on the proportion of CVS+ lesions in MS. Vascular comorbidities are prevalent in MS and are associated with worse clinical outcome and higher MRI brain lesion load.[10,11] The pathophysiology underlying brain WM lesion formation in CSVD is believed to reflect several mechanisms including brain hypoperfusion, reduced vascular reactivity, and tissue hypoxia, mostly occurring at the arteriolar side of the microcirculation.[5,6,10] Conversely, most focal inflammatory demyelinating lesions in MS develop around a central vein. Our results showing that the percentage of CVS+ lesions in MS decreases in the presence of vascular comorbidities are in line with previous studies, where CSVD patients had a lower percentage of CVS+ lesions compared to MS patients.[4,7–10]

A recent multicentre study investigating the effect of VRF on "MS-specific" WM lesions, that is, periventricular Dawson's fingers and juxtacortical lesions, has shown that smoking and dyslipidaemia increase the number of these topographically "MS-specific" lesions; presumably because of a pro-inflammatory effect of these VRF on MS-specific pathology.[29] In our MS cohort, although the univariate analysis showed that age, HT, smoking, diabetes, and BMI (but not hypercholesterolemia) were all associated with a lower percentage of CVS+ lesions, the stepwise regression analysis showed that only age and HT could significantly predict the percentage of CVS+ lesions. A possible explanation in line with the recent publication of Geraldes et al.[29] is that some VRF in MS (e.g. smoking and dyslipidaemia) could have an effect on both the CVS+ inflammatory and the CVS− microangiopathic MRI lesion burden. However, our results are in line with the consistent literature suggesting that age and HT are the most significant risk factors for CSVD.[6,30]

What is the value of adding the CVS assessment to the radiological follow-up of MS patients with vascular comorbidities? In clinical practice, it can be challenging for the treating neurologist/neuroradiologist to assess whether new individual lesions are due to the comorbid vascular disease or to inflammatory demyelination.[12] We showed that the percentage of CVS+ lesions in MS decreases in the presence of VRF for CSVD, and specifically older age and HT, suggesting that the CVS imaging biomarker could be used to monitor and to distinguish between new MS-inflammatory versus new CSVD-microangiopathic disease activity in these patients.

Moreover, diagnostic uncertainty may arise during the diagnostic work-up of patients with possible MS but with concomitant VRF for CSVD,[12] especially in patients with late onset MS.[31] Although given the cross-sectional nature of this study conducted in patients with an established MS diagnosis, we evaluated how the presence of vascular comorbidities might have changed a potential diagnosis for cases. Despite the presence of VRF for CSVD, we found that the previously proposed 35%[4] and 40%[8] CVS proportion-based thresholds remain valid diagnostic differentiators. The 35% CVS proportion-based threshold performed slightly better than the 40% one, being able to "indicate MS" in all included patients.

Among the neuroimaging markers of CSVD, we found that the presence of EPVS in the CSO was associated with a lower percentage of CVS+ lesions.

This finding aligns with the notion that T2-weighted MRI-visible perivascular spaces are a marker of CSVD severity and their visibility increases in subjects with vascular comorbidities.[32,33] On the contrary, perivascular inflammatory cuffing and thickening of the perivascular space is a prominent feature of MS lesion pathology.[7,34] Moreover, MRI-visible EPVS have been observed at the edges of MS plaques and have been associated to the presence of active inflammation in MS.[32,35] Of note, much of the available evidence suggests that MRI-visible EPVS are periarteriolar rather than perivenular.[33,36] Our data suggest that, in the specific context of MS patients with vascular comorbidities, the presence of EPVS in the CSO is associated with CVS⁻ microangiopathic lesions occurring at the arteriolar side of the microcirculation in CSVD. However, the significant association between CSO EPVS score and lower percentage of CVS⁺ lesions was lost in multivariable analyses. This is possibly due to the limited sample size. Future studies with larger cohorts are warranted to test whether the univariate association we are reporting it is not only explained by the presence of age and HT.

This study presents some limitations. Both lesion segmentation and CVS detection were done manually, limiting the applicability of this assessment in everyday clinical practice. Although automated methods for CVS detection are emerging,[14,37] future studies should test fully automated strategies for both lesion segmentation and CVS classification. Moreover, considering that CVS rating might have been biased based on whether lesions had an MS typical location, future work should compare the results of CVS rating with a purely topographical rating performed on non-CVS sensitive sequences. The number of MS patients featuring individual VRF was relatively low and this could potentially bias the results of our regression analysis. Future large multicentric studies using the same optimized MRI sequence for CVS detection (like 3D T2* EPI in this study) are needed to validate specific CVS cut-off values in MS patients with vascular comorbidities.

In conclusion, older age and arterial HT significantly decrease the percentage of brain WM lesions featuring a visible central vein in MS. Although results of the CVS assessment should be interpreted with caution in these patients, the diagnostic yield of the previously proposed thresholds,[4] appears to be not affected. Overall, our study provides novel findings that need to be considered as hypothesis generating and be replicated in larger cohorts.

Authors' Contribution

P. M. has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P. M., G. P., and V. vP. conceptualized and designed the study. Acquisition, analysis, or interpretation of data were performed by all authors. Drafting of the manuscript and/or preparation of the figures were done by F. G. and P. M. Critical revision of the manuscript for important intellectual content was done by all authors. Statistical analysis was performed by C. B. and P. M. Study supervision was carried by P. M.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Théaudin has no conflict of interest involving the work under consideration for publication and no relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing what is written in the submitted work. Outside the submitted work, she received speaker honoraria from Merck, BiogenIdec, Genzyme, Roche; fees for advisory boards from Merck, BiogenIdec, and Novartis; and travel grants from Merck, BiogenIdec, Genzyme, Roche, and Novartis. All the other authors declare no competing interests. V. vP. has received travel grants from Merck, Biogen, Sanofi, Celgene, Almirall, and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Celgene, Merck, and Novartis Pharma.

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Supplemental material
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