

Value of the central vein sign at 3T to differentiate MS from seropositive NMOSD

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Abstract

Objective

To assess the value of the central vein sign (CVS) on a clinical 3T scanner to distinguish between multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD).

Methods

Eighteen aquaporin-4-antibody-positive patients with NMOSD, 18 patients with relapsing-remitting MS, and 25 healthy controls underwent 3T MRI. The presence of a central vein in white matter lesions on susceptibility-weighted imaging, defined as a thin hypointense line or a small dot, was recorded.

Results

The proportion of lesions with the CVS was higher in MS than NMOSD (80% vs 32%, $p < 0.001$). A greater proportion of lesions with the CVS predicted the diagnosis of MS, rather than NMOSD (odds ratio 1.10, 95% confidence interval [CI] 1.04 to 1.16, $p = 0.001$), suggesting that each percent unit increase in the proportion of lesions with the CVS in an individual patient was associated with a 10% increase in the risk of the same patient having MS. If more than 54% of the lesions on any given scan show the CVS, then the patient can be given a diagnosis of MS with an accuracy of 94% (95% CIs 81.34, 99.32, $p < 0.001$, sensitivity/specificity 90%/100%).

Conclusion

The clinical value of the CVS in the context of the differential diagnosis between MS and NMOSD, previously suggested using 7T scanners, is now extended to clinical 3T scanners, thereby making a step towards the use of CVS in clinical practice.

Classification of evidence

This study provides Class III evidence that the CVS on 3T MRI accurately distinguishes patients with MS from those with seropositive NMOSD.

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Glossary

CI = confidence interval; CVS = central vein sign; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; OR = odds ratio; RRMS = relapsing-remitting multiple sclerosis; SWI = susceptibility-weighted imaging.

MRI has an important role in the diagnosis of neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS).¹ The differentiation between the 2 diseases is often challenging, since clinical manifestations may overlap, and up to 70% of patients with NMOSD have brain lesions on MRI.² An accurate differentiation between these 2 diseases is crucial, because some MS therapies cause disease worsening in NMOSD.³⁻⁵

Advanced MRI techniques may provide biomarkers that help the differential diagnosis.⁶ Recent studies at 7T have shown that the presence of the central vein sign (CVS) within white matter lesions is a hallmark of MS and differentiates MS from NMOSD.⁷⁻⁹ However, 7T scanners are not routinely available in the clinical setting. Further investigations that evaluate the clinical value of the CVS for the differential diagnosis of MS are needed.^{10,11}

The aim of this study was to investigate the predictive value of the CVS when using a clinical 3T scanner for differentiating seropositive NMOSD from MS.

Methods

Our primary question was whether the CVS on a clinical 3T scanner distinguishes between seropositive NMOSD and MS.

Study participants

We prospectively recruited patients from the NMO Clinical Service at the Walton Centre, Liverpool, and the National Hospital for Neurology and Neurosurgery, London, UK. The inclusion criteria were (1) diagnosis of AQP4-antibody-positive NMOSD according to 2015 Wingerchuk criteria¹ or diagnosis of relapsing-remitting MS (RRMS),^{12,13} which has a relapsing course as NMOSD; (2) absence of relapses within 6 months before the MRI scan; and (3) no major contraindications to MRI. We did not consider the presence of comorbidities as an exclusion criterion. Neurologic disability was assessed with the Expanded Disability Status Scale (EDSS)¹⁴ on the date of the MRI scan. Healthy controls were recruited to match the age and sex of patients.

Standard protocol approvals, registrations, and patient consents

Written informed consent was obtained from all participants; this study was approved by the NRES Committee London Bloomsbury.

MRI data acquisition

We acquired MRI scans using a 3T Philips Achieva MRI system with dual-transmit technology (Philips Healthcare,

Best, the Netherlands) and 32-channel head coil. The protocol included a dual-echo proton density/T2-weighted sequence and susceptibility-weighted imaging (SWI) (precontrast), using a 3D fast field echo sequence with shifted echo and no phase multiplication (acquisition measures: repetition time 16 ms, echo time 23 ms, flip angle 10°, field of view 240 × 180 mm², voxel size 1 × 1 × 1 mm³ [reconstructed to 0.5 × 0.5 × 0.5 mm³], number of averages 1, axial contiguous slices = 270, scanning time 7 minutes).

Image processing and analysis

A senior neuroradiologist (F.B.) and a trained rater (R.C.) identified the white matter lesions on the proton density/T2-weighted MRI, which were then contoured using a semiautomated edge finding tool (JIM v.6.0, Xinapse systems; xinapse.com). Only lesions with a diameter ≥3 mm in at least one plane were contoured; care was taken to exclude punctate round white matter lesions that may have represented age-related vascular abnormalities. Lesions were classified as infratentorial, periventricular (with one edge in contact with a ventricle), deep white matter, and juxtacortical (with one edge in contact with the cortex). The T2-weighted images were affine coregistered to the SWI using a symmetric and inverse-consistent approach.^{15,16} Afterwards, the T2 lesion masks were resampled to the corresponding SWI using the transformation measures obtained from the previous step. All registrations were done using the NiftyReg software package (niftyreg.sf.net) (figure e-1, links.lww.com/WNL/A310).

The identification of the CVS on SWI was based on the consensus between 2 readers (R.C., T.Y.). Depending on the slice angle, the CVS was either depicted as a centrally located, thin, hypointense line or a small dot, running partially or entirely through the lesion, visualized in at least 2 perpendicular planes. Veins that did not run through the center of the lesion, but were located somewhere in its periphery in all planes, were not counted. The inclusion and exclusion criteria for the radiologic definition of the CVS, as recently recommended by Sati and colleagues,¹¹ were followed. All readers worked independently and were blinded to clinical data.

To ensure that the scoring of the CVS was not influenced by the overall appearance of the scan, we performed an additional, fully blinded analysis using 165 lesions randomly selected from 4 patients with MS and 4 patients with NMOSD. These lesions were individually isolated and the SWI were then cropped in 3D around each individual

lesion, so that all the other white matter lesions, and the remainder of the brain, were not visible (figure e-2, links. [lww.com/WNL/A310](http://www.lww.com/WNL/A310)). The identification of the CVS was done as explained above.

Statistical analysis

MS, NMOSD, and healthy control groups were compared in terms of age, sex, disease duration, EDSS, and lesion characteristics using χ^2 test, linear regression, or Mann-Whitney *U* tests depending on the nature of the variable. The analysis for this study was divided into the following 2 parts.

Prediction of MS vs NMOSD based on the proportion of lesions with the CVS

Logistic regression models were fitted, where the type of disease was the dependent variable and the proportion of lesions with the CVS was the independent variable.

The median number of T2 white matter lesions was calculated considering all patients together (MS and NMOSD) and then used to divide patients in 2 groups: (1) patients with a small amount of lesions (below the median number of lesions); (2) patients with a large amount of lesions (above or at the median value). In each group, the proportion of lesions showing the CVS was calculated to identify the best cutoff (i.e., the value associated with the highest accuracy) that predicted the outcome (e.g., a diagnosis of MS rather than NMOSD) using receiver operating characteristic analysis. The same analysis was re-run using a cutoff of 40%, which was previously reported to be able to distinguish MS from non-MS disease.⁷

For all these models, age, sex, disease duration, total number of lesions, and (individual) mean lesion volumes were explored as covariates. EDSS score was also used as a covariate.

To further investigate the clinical feasibility of the CVS, we tested “pick 6” and “pick 3” algorithms,^{17,18} which were proposed as less time-consuming methods of counting lesions with the CVS to predict the diagnosis of MS. For

pick 6, we used 6 randomly selected lesions on SWI to allocate the scans into the disease category (presence/absence of inflammation). For pick 3, the CVS was evaluated in 3 lesions in the deep white matter randomly selected in each patient.

Predictors of the presence of the CVS in white matter lesions

Considering only patients with lesions, we first fitted univariate univariable generalized linear models for grouped binary data (clustered at the individual level). For these models, the probability of a lesion with the CVS was considered as the dependent variable, and the following variables were considered individually as the independent predictors: type of disease, age, mean lesion volume, disease duration. Second, univariate multivariable models were fitted, where the probability of a lesion with the CVS was again considered as the dependent variable, and all the covariates were included together as independent variables.

For both part I and part II, odds ratio (OR) and its corresponding 95% confidence interval (CI) are presented.

The Cohen kappa coefficient measured the agreement in the identification of the CVS between the fully blinded scoring (using the SWI cropped around each lesion) and the scoring of the CVS when using the whole images.

All tests were performed using STATA 14.2. Statistical significance was considered when *p* values were <0.05.

This work provides Class III evidence because of the case-control design and the risk of spectrum bias.

Results

Patients with NMOSD were older than patients with MS and healthy controls, and had higher disability than patients with MS; disease duration did not differ between the 2 patient

Table 1 Clinical and demographic characteristics of patients with neuromyelitis optica spectrum disorder (NMOSD) and relapsing-remitting multiple sclerosis (RRMS) and healthy controls

	NMOSD	RRMS	Healthy controls	<i>p</i> Value
No. of participants	18	18	25	—
Sex, male/female	4/14	4/14	7/18	0.868 ^a
Mean age, y (±SD)	52.5 (±2.8)	41.8 (±2.8)	37.1 (±2.4)	<0.001, ^b 0.009 ^c
Mean disease duration, y (±SD)	8.6 (± 7.3)	9 (± 6.4)	NA	0.870 ^d
Median EDSS (range)	5 (2–6.5)	2.5 (1–7.5)	NA	0.011 ^e

^a Obtained using the χ^2 test, to compare the 3 subject groups.

^b Obtained using a linear regression, to compare the 3 subject groups.

^c Obtained using a linear regression, to compare RRMS to NMOSD.

^d Obtained using a linear regression, to compare RRMS to NMOSD.

^e Obtained using Mann-Whitney *U* test, to compare RRMS to NMOSD.

Table 2 Lesion numbers and characteristics in multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and healthy controls

	NMOSD	MS	Healthy controls
Participants with white matter lesions, n (%)	16/18 (88)	18/18 (100)	4/25 (16)
Total number of lesions	186	783	11
Number of lesions per participant, mean (\pm SD)	10.3 (\pm 16.8)	43.5 (\pm 27.8) ^a	0.44 (\pm 1.3)
Number of lesions per participant, median (range)	5 (0–70)	36.5 (5–86)	0 (0–5)
Lesions with CVS/total number of lesions, n (%)	59/186 (32)	625/783 (80) ^a	0
Range of % of lesions with CVS	0%–100% ^b	53.85%–100%	0
Number of lesions with CVS per participant, mean (\pm SD)	3.3 (\pm 4.4)	34.7 (\pm 22.3)	0
Number of lesions with CVS per participant, median (range)	2 (0–13)	31.5 (4–67)	0
Lesion volume, mm ³ , mean (\pm SD)	1,991 (\pm 2,648.3)	8,861.8 (\pm 7,942.7) ^a	269.2 (\pm 183.4)
CVS lesion volume, mm ³ , mean (\pm SD)	1,437.8 (\pm 1,771.9)	8,325.4 (\pm 7,704.2)	0
Non-CVS lesion volume, mm ³ , mean (\pm SD)	738.4 (\pm 1,223.8)	596.5 (\pm 414.3)	269.2 (\pm 183.4)

Abbreviations: CVS = central vein sign; CVS lesion volume = volume of lesions with central vein sign; non-CVS lesion volume = volume of lesions without central vein sign.

^a $p < 0.001$, obtained using linear regression, to compare relapsing-remitting MS to NMOSD.

^b One patient had only one lesion and this lesion showed the CVS (resulting in 100%).

groups (table 1). A total of 18/18 (100%) patients with MS and 12/18 (66%) patients with NMOSD met the revised McDonald MRI criteria for dissemination in space.¹² A total of 3/18 (17%) patients with NMOSD had cardiovascular risk factors (diabetes mellitus or hypercholesterolemia), and 14/18 (78%) patients with NMOSD showed a lesion longer than 3 vertebral segments on MRI.

Lesions with the CVS: Count and location

A total of 783 white matter lesions were seen in 18 out of 18 (100%) patients with MS, 186 lesions were detected in 16/18 (88%) patients with NMOSD, and 11 lesions were seen in 4/25 (16%) healthy controls. The median number of white matter lesions in all patients together (MS and NMOSD) was 11. Table 2 shows the number and characteristics of lesions in the 3 groups of participants.

A typical example of a lesion with the CVS is shown in figure 1. The proportion of lesions with the CVS was higher in MS (80%) than NMOSD (32%) (table 2, figure 2). No lesions in healthy controls showed the CVS.

There was a very good agreement in the identification of the CVS between the fully blinded procedure and the original scoring method (Cohen kappa coefficient 0.95, standard error 0.0169, 95% CI 0.9183–0.9847).

In NMOSD, the highest proportion of lesions with the CVS, out of the total number of lesions with the CVS, was seen in the periventricular location (53%), while in MS the highest proportion of lesions with the CVS was detected in the deep white matter (56%). The proportion of lesions with the CVS

in the deep white matter, out of the total number of lesions in the same location, was higher in MS than NMOSD (87% vs 16%, respectively; $p < 0.001$); no differences in the proportion of lesions with the CVS in the periventricular region, out of the total number of lesions in the same location, were observed between the 2 conditions (table e-1, links.lww.com/WNL/A311).

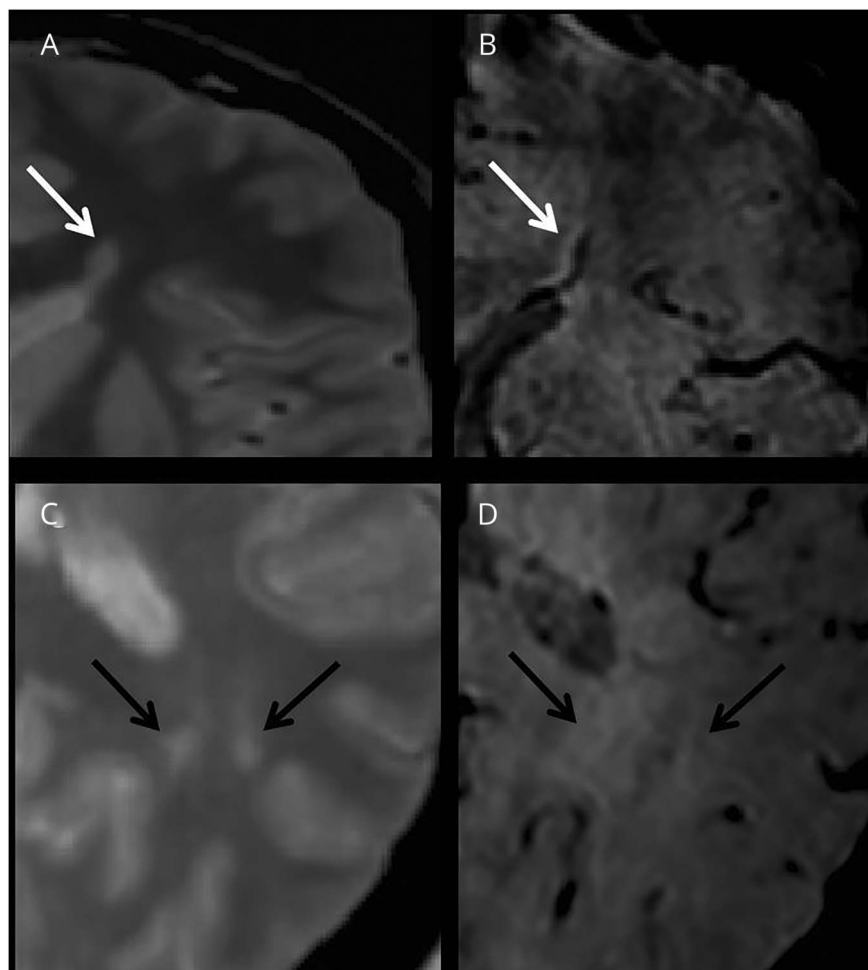
Prediction of MS vs NMOSD based on the proportion of lesions with the CVS

A greater proportion of lesions with CVS was predictive of MS (instead of NMOSD) (OR 1.10, 95% CI 1.04–1.16, $p = 0.001$): per each percent unit increase in the proportion of lesions with CVS in a given patient, this patient had a 10% higher risk of having MS instead of NMOSD. When this model was adjusted for age, sex, disease duration, and total number of lesions, similar results were obtained.

The best cutoff value in respect to the proportion of lesions with the CVS that predicted the diagnosis of MS, when all patients were included together, was 54% (table 3). Figure e-3 (links.lww.com/WNL/A310) shows the flow diagram of patients.¹⁹ This cutoff indicates that if more than 54% of the white matter lesions seen on any given scan show the CVS, then the patient can be given a diagnosis of MS. Similarly, when only patients with ≥ 11 lesions were considered, the best cutoff to diagnose MS remained 54%. When only patients with < 11 lesions were considered, the proportion of lesions with the CVS that best predicted the diagnosis of MS was 80%.

When 40% was used as a cutoff, sensitivity, specificity, and accuracy of the cutoff changed when all patients and patients

Figure 1 Example of lesions with the central vein sign (CVS) in multiple sclerosis (MS) and without CVS in neuromyelitis optica spectrum disorder (NMOSD)



Axial proton density (A, C) and corresponding susceptibility-weighted imaging (B, D) of periventricular lesions in MS (A, B) and NMOSD (C, D). The dark vein is located centrally in the majority of the lesion in MS (white arrow). On the other hand, a central vein is absent in most of the lesions of a patient with NMOSD (black arrows).

with <11 lesions were considered, but remained stable when only patients with ≥ 11 white matter lesions were included (table 3).

Results of the pick 6 and pick 3 algorithms showed that pick 6 was sensitive (100% [95% CI 81.47%–100.00%]) but not specific (88.89% [95% CI 65.29%–98.62%]), and pick 3 was specific (100.00% [95% CI 81.47%–100.00%]) but not sensitive (50.00% [95% CI 26.02%–73.98%]) for the diagnosis of MS.

Predictors of the presence of the CVS in white matter lesions

When using univariable models, only the variable “disease type” was associated with the probability of a lesion showing the CVS. In other words, the risk of finding the CVS in a lesion was greater if that lesion belonged to a patient with MS than NMOSD (OR 8.51 [95% CI 4.3–16.7], $p < 0.001$).

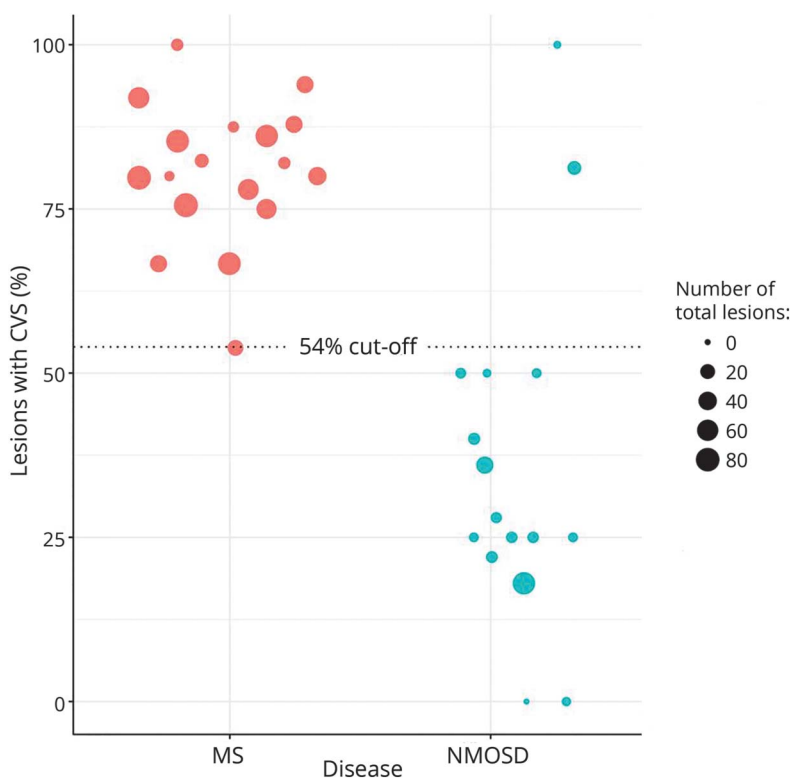
Age, sex, mean lesion volume, or disease duration were not associated with the probability of a lesion showing

the CVS. The multivariable models confirmed that only the disease type was associated with the presence of the CVS.

Discussion

We have validated the use of the CVS to support the differential diagnosis between MS and NMOSD by using a clinical 3T scanner, thereby extending early results obtained at 7T.^{8,9} We found that the presence of $\geq 54\%$ of white matter lesions with the CVS predicted a diagnosis of MS with a high accuracy, high sensitivity, and high specificity. This means that 90% of patients with MS were correctly identified as having MS and 100% of patients with NMOSD were correctly identified as not having MS. The 40% rule ($>40\%$ of white matter lesions with the CVS), which was proposed previously when using T2*-weighted imaging at 7T in all phenotypes of MS to distinguish it from non-MS,⁷ is not the best cutoff when studying patients with RRMS and NMOSD using a clinical 3T scanner and including all lesions. Only when patients with a large number

Figure 2 Proportion of lesions with the central vein sign (CVS) in patients with multiple sclerosis (MS) and AQP4-antibody-positive neuromyelitis optica spectrum disorder (NMOSD)



The scatterplot shows the proportion of lesions with CVS (out of the total number of lesions) in MS and NMOSD. Patients with NMOSD without brain lesions ($n = 2$) are not displayed. The dotted line indicates the 54% cutoff that distinguished between MS and NMOSD using receiver operating characteristic analysis.

of lesions were included, the accuracy of the 40% cutoff is high.

Interestingly, we found that the 54% cutoff worked equally well when all patients were considered together regardless of their total number of lesions, and when patients with at least 11 lesions (e.g., median number of lesions) were included. When patients with fewer than 11 lesions were analyzed, a much higher cutoff of 80% was identified, and this was associated with lower accuracy, lower sensitivity, and lower specificity, probably because patients with NMOSD tend to show a low number of white matter lesions.

Overall, the use of a cutoff has been criticized by the fact that counting all lesions in clinical practice may be unachievable, especially in patients with high lesion load.¹¹ In addition, varying cutoff values depending on lesion burden may be difficult to achieve with clinical scans, and applying the recommended inclusion/exclusion criteria¹¹ requires advanced radiologic expertise.

We used pick 6 and pick 3 algorithms for the diagnosis of MS,^{17,18} but we found that they were not superior to the 54% cutoff. Although the visual detection of the CVS can be influenced by the overall appearance of the MRI, the fully blinded analysis on a subgroup of randomly chosen lesions strongly suggests that this did not occur. Automatic

algorithms for lesion segmentation²⁰ are being optimized and validated, and they may facilitate the translation of the CVS to clinical practice, as lesion identification can be done automatically. An important step towards the use of CVS in clinical practice is to validate this cutoff value using large, multicenter studies, recruiting patients at disease onset and using standardized MRI protocols.

An interesting observation is that there is a higher percentage of the CVS in MS (80%) than NMOSD (32%) lesions. This finding highlights the different pathophysiologic mechanisms underlying lesion development in these 2 disorders. Pathologic studies²¹ and ultrahigh-field MRI studies²² have suggested that MS lesions grow outward from a central vein. The perivascular space is thought to be a privileged site for lymphomonocytic infiltrates, which can trigger an inflammation reaction and demyelination and lead to the centrifugal expansion of lesions around the veins.²¹ However, in long-standing MS, the widespread tissue damage may lead to decreased levels of oxygen extraction, which, in turn, reduces the visibility of the veins on MRI at ultrahigh field.^{23,24} One possible explanation is that younger lesions show the CVS, while more chronic lesions do not. Further imaging studies will test this hypothesis.

On the other hand, pathologic studies have demonstrated that in NMOSD the massive astrocytic damage is of primary

Table 3 Diagnostic accuracy of 3T susceptibility-weighted imaging for differentiating multiple sclerosis from neuromyelitis optica spectrum disorder lesions

	Cutoff for CVS, %	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Accuracy, % (95% CI)	AUC, (95% CI)
When all patients were included regardless of the number of white matter lesions	54	90 (68–99)	100 (79–100)	94 (81–99)	0.92 (0.80–1)
When patients with small number of white matter lesions were included (<11)	80	50 (1–99)	93 (68–100)	88 (64–99)	0.93 (0.80–1)
When patients with large number of white matter lesions were included (≥11)	54	94 (71–100)	100 (16–100)	94 (74–100)	0.83 (0.50–1)
When all patients were included regardless of the number of white matter lesions (cutoff predetermined)	40	75 (54–90)	100 (74–100)	83 (67–94)	0.92 (0.80–1)
When patients with small number of white matter lesions were included (<11) (cutoff predetermined)	40	29 (4–71)	100 (69–100)	71 (44–90)	0.93 (0.80–1)
When patients with large number of white matter lesions were included (≥11) (cutoff predetermined)	40	94 (71–100)	100 (16–100)	94 (74–100)	0.83 (0.50–1)

Abbreviations: AUC = area under the curve; CI = confidence interval; CVS = central vein sign.

importance in the development of lesions and that myelin damage may be a secondary phenomenon due to the underlying astrocyte pathology.²⁵ Therefore, the CVS found in a small number of NMOSD lesions may indicate that demyelination follows the primary astrocytic injury, while the absence of the CVS may indicate that the central vein has become occluded and therefore not visible on MRI.

In line with previous studies,^{7,18} when lesions were classified according to their location, MS lesions demonstrated the CVS more frequently in deep white matter than NMOSD lesions, which were more likely to show the CVS in the periventricular location. This is also in agreement with the previous report of reduced periventricular venous visibility in MS than NMOSD, as a consequence of more extensive brain parenchymal gliosis in MS.²⁶

From a clinical perspective, we hypothesize that the practical utility of the CVS is that its absence at the onset of optic neuritis or transverse myelitis would support a diagnosis of seropositive NMOSD, but this needs to be tested and validated in studies including patients with seropositive and seronegative NMOSD and patients at an early stage of their disease, when the number of lesions may be low, therefore reducing the discriminatory value of the CVS.

From a technical point of view, SWI is a technique used in clinical practice to aid the diagnosis of cerebral vascular diseases.²⁷ We used a high-resolution sequence with high sensitivity to susceptibility effects, which can be made available on 3T clinical scanners and is relatively quick to acquire, so that its translation to clinical practice may be achievable.^{28,29} Contrast-enhanced susceptibility images can further enhance the visualization of small parenchymal veins,³⁰ thus increasing the sensitivity of the technique in detecting the CVS.

However, the effect of gadolinium injection on the cutoff for the differential diagnosis between MS and NMOSD has to be evaluated.

This study is not without limitations. First, we only recruited patients with seropositive NMOSD. Also, in line with the known disease demographics, patients with NMOSD were older than patients with MS, and it is expected that age-related vascular lesions increase the lesion load in older patients. Moreover, all the statistical models were corrected for age and we did not find any association between age and risk of a lesion having the CVS.

The key questions that need to be addressed in future studies are whether the presence of the CVS at 3T early in clinically isolated syndrome is associated with a higher risk of developing MS, so that this sign can be included in the revised criteria for the diagnosis of MS, and what is the longitudinal evolution of the lesions with CVS. Moreover, no in vivo reports are available to assess the value of the CVS in MS spinal cord lesions and in pediatric MS brains.

The identification of the CVS on SWI at 3T MRI is of high clinical relevance as it may facilitate an accurate differentiation between MS and NMOSD. It also provides insights into the pathophysiologic processes underlying these 2 different diseases.

Author contributions

R.C. acquired data, analyzed data, interpreted the analysis, and wrote the manuscript. L.M., F.D., and M.C.Y. acquired data. C.T. analyzed data and contributed to interpret the analysis. K.A.-A. and A.J. contributed to patient recruitment. F.P., S.O., and T.Y. contributed to data analysis. F.B. contributed to research design and data analysis and revised the manuscript.

O.C. designed the project, supervised the project, and revised the manuscript.

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