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The "central vein sign" in patients with diagnostic "red flags" for multiple sclerosis: A prospective multicenter 3T study

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Abstract

Background: The central vein sign (CVS) has been shown to help in the differential diagnosis of multiple sclerosis (MS), but most prior studies are retrospective.

Objectives: To prospectively assess the diagnostic predictive value of the CVS in diagnostically difficult cases.

Methods: In this prospective multicenter study, 51 patients with suspected MS who had clinical, imaging, or laboratory "red flags" (i.e. features atypical for MS) underwent 3T fluid-attenuated inversion recovery (FLAIR*) magnetic resonance imaging (MRI) for CVS assessment. After the diagnostic work-up, expert clinicians blinded to the results of the CVS assessment came to a clinical diagnosis. The value of the CVS to prospectively predict an MS diagnosis was assessed.

Results: Of the 39 patients who received a clinical diagnosis by the end of the study, 27 had MS and 12 received a non-MS diagnosis that included systemic lupus erythematosus, sarcoidosis, migraine, Sjögren disease, SPG4-spastic-paraparesis, neuromyelitis optica, and Susac syndrome. The percentage of perivenular lesions was higher in MS (median = 86%) compared to non-MS (median = 21%; $p < 0.0001$) patients. A 40% perivenular lesion cutoff was associated with 97% accuracy and a 96% positive/100% negative predictive value.

Conclusion: The CVS detected on 3T FLAIR* images can accurately predict an MS diagnosis in patients suspected to have MS, but with atypical clinical, laboratory, and imaging features.

Keywords: Central vein sign, red flags, MS diagnosis

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Introduction

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) characterized by a relapsing or progressing clinical course and associated with characteristic hyperintensities on T2-weighted magnetic resonance imaging (MRI) of the brain and spinal cord.[1] There is no single diagnostic test for MS, and current diagnostic criteria rest upon the demonstration of disease dissemination in space (DIS) and dissemination in time (DIT) using clinical, laboratory, and MRI criteria.[2] Although highly useful, the specificity of the current diagnostic imaging criteria is limited, and the risk of diagnosing MS in individuals affected by other disorders is still substantial.[3,4]

Increasing scientific evidence suggests that novel imaging techniques could improve the specificity of the current diagnostic criteria.[2,5] The presence of a vein at the center of brain white matter (WM) lesions, the "central vein sign" (CVS), is a specific feature of MS and can now be depicted at clinical MRI field strength using specialized gradient-echo MRI sequences.[5–7] Several studies have shown how this promising imaging biomarker can differentiate MS from other disorders, including migraine,[8,9] cerebral

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small vessel disease,[10] neuromyelitis optica,[11] Susac syndrome,[12] and primary or secondary vasculitis of the CNS, showing similar WM lesions on MRI.[6] However, most prior studies are retrospective. Prospective, multicenter studies starting from the time of initial work-up are needed to assess the true diagnostic value of the CVS, especially in diagnostically difficult cases.

Cases presenting with syndromes typical for MS but with concurrent clinical, laboratory, or imaging features atypical for MS are particularly challenging for the treating neurologist in clinical practice. A number of important reviews have identified differentiating clinical, laboratory, or imaging features ("red flags") to guide clinicians during the diagnostic work-up of patients with suspected MS but with atypical features for the diagnosis.[2,4,13–18] Data regarding the prospective diagnostic value of the CVS in these challenging conditions are lacking. In this multicenter study, we prospectively tested the diagnostic value of the CVS at clinical 3T MRI in patients with possible MS but with atypical clinical, laboratory, or imaging features.

Methods

Patients

Between September 2016 and December 2018, patients with a clinical presentation suggestive of MS but who had clinical, imaging, or laboratory features atypical for MS[15,17,18] were prospectively enrolled in four academic research hospitals: the Lausanne University Hospital (Lausanne, Switzerland), the Erasme and Brugmann University Hospitals (Brussels, Belgium), and the San Raffaele University Hospital (Milan, Italy). Patients were excluded from the study if (1) they did not experience at least one clinical episode compatible with a focal or multifocal demyelinating event in the CNS, (2) they did not reach a clinical diagnosis at the end of the study period, (3) they had a contraindication for MRI or intravenous injection of gadolinium-based contrast material, and (4) MRI image quality was suboptimal because of motion artifact.

The study received approval from ethical standards committees on human experimentation at all centers. Written informed consent was obtained from all participants.

Diagnostic work-up

All enrolled patients received an extensive work-up, including clinical, laboratory, and radiological assessment. Laboratory testing included serological screening for autoimmune and infectious diseases and cerebrospinal fluid (CSF) examination with oligoclonal band (OCB) testing. Radiological assessment included 3T brain MRI with imaging sequences for central vein assessment (fluid-attenuated inversion recovery (FLAIR*) MRI, see below). Other paraclinical tests, including anti-aquaporin-4 IgG (AQP4 antibody), neuro-ophthalmological assessment, salivary gland biopsy, spinal cord MRI, chest and abdominal computed tomography (CT), and whole-body PET (positron emission tomography)–CT, were also performed when necessary.

MRI acquisition protocol

All patients underwent a single brain MRI on a 3T Magnetom Skyra or Prisma scanner (Siemens Healthcare, Erlangen, Germany) in Lausanne and two 3T Philips MRI scanners (Philips, Best, The Netherlands) in Brussels (Ingenia) and Milan (Intera). A single MRI protocol was adopted in all centers, including high-resolution three-dimensional (3D) T2*-weighted echo-planar imaging (EPI) and 3D T2-FLAIR images acquired, respectively, during or after intravenous injection of a single dose (0.1 mmol/kg) of gadolinium-based contrast material, as previously described.[6,19] Isotropic resolution of the 3D T2*-EPI was 0.55 mm^3 in Brussels/Milan and 0.65 mm^3 in Lausanne. Three-dimensional T2*-EPI and 3D T2 FLAIR sequence parameters were identical for the 3T Philips MRI scanners in Brussels and Milan and very similar for the 3T Siemens MRI scanners in Lausanne (Table 1).

MRI post-processing and analysis

For the "central vein sign" assessment, FLAIR* images were generated by coregistration (up-sampling of the T2-FLAIR to match the T2* resolution) and voxel-wise multiplication of the high-resolution 3D T2* EPI and the 3D T2-FLAIR, as previously described.[6,19] For each subject, WM lesions were manually segmented on 3D FLAIR* images using Medical Image Processing, Analysis, and Visualization (MIPAV; National Institutes of Health (NIH); http://mipav.cit.nih.gov), and, for each lesion, the presence/absence of the CVS was assessed according to the North American Imaging in Multiple Sclerosis (NAIMS) guidelines.[5] Cases were dichotomized as perivenular positive versus perivenular negative based on the four previously proposed criteria: (1) the "50% rule"[6] and (2) the "40% rule,"[10] whereby a 50% or 40% perivenular lesion cutoff distinguishes MS

Table 1. MRI sequence parameters in Brussels and Milan (Philips scanners) and Lausanne (Siemens scanners) healthcare systems.

Sequence	3D T2*-EPI		3D T2-FLAIR	
Magnet strength	3 T	3 T	3 T	3 T
Manufacturer	Siemens	Philips	Siemens	Philips
Model	Prisma/Skyra	Ingenia/Intera	Prisma/Skyra	Ingenia/Intera
Receive channels	64	8	64	8
Imaging plane	Sagittal	Sagittal	Sagittal	Sagittal
Imaging resolution (mm)	0.65	0.55	1	1
No. of slices	288	336	176	180
Repetition time (TR, ms)	64	53	5000	4800
Echo time (TE, ms)	35	29	391	373
Inversion time (TI, ms)	–	–	1800	1600
Flip angle (deg)	10	10	Variable	90
Averages	1	1	1	1
Acquisition time (minute:second)	6:20	4:40	4:47	6:00

MRI: magnetic resonance imaging; EPI: echo-planar imaging; FLAIR: fluid-attenuated inversion recovery; 3D: three-dimensional.

from its mimics; (3) the "3-lesion rule"[9] and (4) the "6-lesion rule,"[6,20] whereby 3 or 10 lesions are randomly selected and MS is diagnosed if at least 2 or 6 lesions are, respectively, perivenular. For each patient, two investigators (P.M. and M.A.) independently assessed the percentage of perivenular lesions for inter-rater reliability. Disagreements were adjudicated by an expert neuroradiologist (D.S.R.). For each patient, fulfillment of the MS MRI criteria for DIS and DIT according to the most recent criteria[2] was also recorded.

Clinical diagnosis and predictive value of the CVS

After the 3D FLAIR* MRI scan for perivenular assessment, patients were prospectively followed up to allow for a clinical diagnosis to be achieved. Patients received (1) an MS diagnosis if fulfilling MS diagnostic criteria and no better explanation for the clinical presentation was found, despite red flags and (2) a non-MS diagnosis if an alternative diagnosis better explained the clinical presentation. After follow-up, expert clinicians in each center, blinded to the results of the CVS assessment, came to an eventual clinical diagnosis. The value of the CVS to prospectively predict MS diagnosis was assessed.

Statistical analysis. Difference in perivenular frequency between MS and non-MS patients was tested using the Mann–Whitney *U* test. Inter-rater reliability for the perivenular assessment was computed using Cohen's κ.

Results

Patients

We prospectively included 51 patients. All patients underwent a single standardized 3T imaging research protocol including 3D FLAIR* MRI for CVS assessment. Of the 51 recruited patients, 1 had an uninterpretable scan due to motion artifact and 11 did not receive a clinical diagnosis by the end of the study (Figure 1). All 39 patients who received a clinical diagnosis by the end of the study (30 females and 9 males), median age 46 years (range 19–74 years), experienced at least one clinical episode compatible with a focal or multifocal demyelinating event in the CNS[2] and had at least one clinical, laboratory, or imaging feature atypical for MS, hereafter termed "red flags" (Table 2).[2,15,17,18] Of note, minor clinical red flags (denoted as "Minor" in Table 2) were features not specific of a disease involving the CNS but potentially associated with another systemic inflammatory/autoimmune disorder (SAD) involving the CNS. Patients carrying minor red flags needed at least another red flag to be included in this study.

Atypical MS diagnostic features for each patient are shown in Table 3.

Fulfillment of DIS and DIT 2017 McDonald revised criteria for MS

The most common clinical presentations were visual impairment (12 of 39 patients, 31%), followed by limb weakness (11 of 39 patients, 28%) or numbness

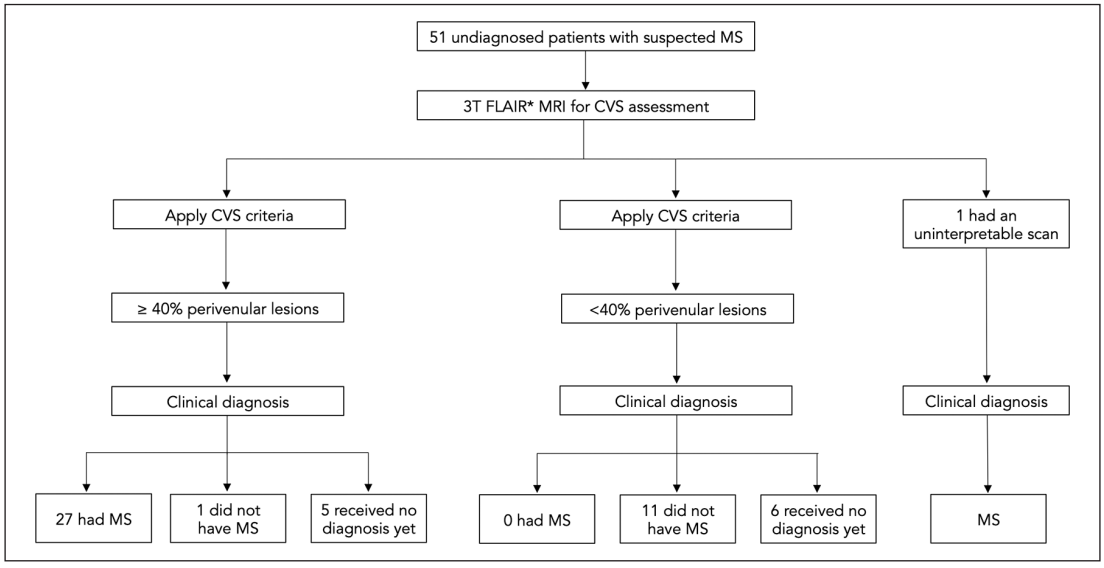

Figure 1. Patient flow diagram summarizing the study design and main results.
MS: multiple sclerosis; CVS: central vein sign.

Table 2. Atypical features for MS diagnosis, that is, "red flags.".

Red flags		Patients
Red flag type	Red flags (ID)	No. of patients (%)
Clinical		
Age at symptom onset >50 years	$C_{(1)}$	7 (18)
History of SAD	$C_{(2)}$	6 (15)
History of oral/genital aphthosis or VT	$C_{(3)}$	5 (13)
Poor recovery or bilateral ON	$C_{(4)}$	4 (10)
Uveitis and/or retinal vasculitis	$C_{(5)}$	4 (10)
Hearing loss and branch retinal artery occlusion	$C_{(6)}$	1 (3)
Cognitive decline at onset	$C_{(7)}$	1 (3)
Minor	$C_{(8)}$	6 (15)
Laboratory		
Absence of OCB	$L_{(1)}$	14 (36)
Abnormal biomarkers of SAD	$L_{(2)}$	12 (31)
Proteinorrachia >100 mg/dL	$L_{(3)}$	4 (10)
Positive IgM *Borrelia burgdorferi* serology	$L_{(4)}$	1 (3)
Imaging		
Atypical morphology[a]/distribution of WM lesions	$I_{(1)}$	12 (31)
Longitudinal extensive transverse myelitis	$I_{(2)}$	3 (8)
Diffuse meningeal contrast enhancement	$I_{(3)}$	3 (8)
Absence of ⩾2 spinal cord MRI lesions in OCB-negative suspected PPMS	$I_{(4)}$	3 (8)

MS: multiple sclerosis; SAD: systemic inflammatory/autoimmune disorder; VT: venous thrombosis; ON: optic neuritis; RRMS: relapsing–remitting multiple sclerosis; OCB: oligoclonal bands; WM: white matter; MRI: magnetic resonance imaging; PPMS: primary progressive multiple sclerosis.
Minor (i.e. "minor" red flags): spondyloarthritis, fibromyalgia, Raynaud's phenomenon, and history of joint inflammation with good response to corticosteroids.
[a]Large brainstem lesions.

Table 3. Red flags, fulfillment of MRI DIS and DIT MS diagnostic criteria, clinical diagnosis, and frequency of perivenular lesions.

Patient ID	Age	Red flags (ID)	Clinical onset	MRI DIS	MRI DIT	OCB	Diagnosis	Treatment	% Perivenular
1	28	$C_{(8)}$, $I_{(1)}$	Ataxia	Fulfilled	Fulfilled	Present	RRMS	Ocrelizumab	96
2	54	$C_{(1)}$, $L_{(2)}$	Limb weakness	Fulfilled	Fulfilled	Present	RRMS	Ocrelizumab	67
3	25	$C_{(5)}$, $L_{(2)}$	Visual impairment	Fulfilled	Not fulfilled	Present	Sjögren	Tocilizumab	33
4	52	$C_{(8)}$, $L_{(1)}$, $L_{(3)}$	Facial numbness	Fulfilled	Fulfilled	Absent	RRMS	Ocrelizumab	100
5	54	$L_{(1)}$, $I_{(1)}$	Facial numbness	Fulfilled	Fulfilled	Absent	RRMS	Glatiramer acetate	71
6	43	$C_{(2)}$, $L_{(2)}$	Limb weakness	Fulfilled	Fulfilled	Present	RRMS	Azathioprine	100
7	34	$C_{(2)}$, $C_{(3)}$, $L_{(2)}$	Limb weakness	Fulfilled	Not fulfilled	Present	RRMS	NA	83
8	68	$C_{(1)}$, $L_{(1)}$, $I_{(4)}$	Limb weakness	Fulfilled	Not fulfilled	Absent	SPG4 HSP	None[a]	13
9	29	$I_{(1)}$	Visual impairment	Fulfilled	Fulfilled	ND	RRMS	Rituximab	80
10	28	$C_{(2)}$, $C_{(3)}$, $C_{(5)}$	Visual impairment	Fulfilled	Fulfilled	Present	RRMS	Methotrexate	93
11	44	$C_{(5)}$, $C_{(8)}$	Visual impairment	Fulfilled	Fulfilled	Present	RRMS	Cyclophosphamide	98
12	20	$C_{(4)}$, $L_{(1)}$	Visual impairment	Fulfilled	Fulfilled	Absent	RRMS	Mitoxantrone	92
13	42	$C_{(4)}$, $L_{(1)}$	Visual impairment	Fulfilled	Fulfilled	Absent	RRMS	Interferon beta-1a	86
14	60	$C_{(1)}$, $L_{(1)}$	Limb weakness	Fulfilled	Fulfilled	Absent	RRMS	None	75
15	64	$C_{(1)}$, $I_{(1)}$	Vertigo	Fulfilled	Not fulfilled	ND	Migraine	None	6
16	54	$I_{(1)}$	Visual impairment	Fulfilled	Fulfilled	Present	SPMS	Rituximab	52
17	53	$L_{(1)}$, $L_{(2)}$, $I_{(2)}$	Limb numbness	Fulfilled	Fulfilled	Absent	SLE	Azathioprine	0
18	62	$C_{(1)}$, $C_{(8)}$, $L_{(1)}$	Limb weakness[b]	Fulfilled	Fulfilled	Absent	PPMS	Ocrelizumab	67
19	29	$C_{(3)}$, $C_{(8)}$	Visual impairment	Fulfilled	Fulfilled	Present	RRMS	Fingolimod	91
20	33	$C_{(8)}$, $L_{(1)}$	Visual impairment	Fulfilled	Fulfilled	Absent	RRMS	Teriflunomide	100
21	45	$C_{(4)}$, $L_{(1)}$, $I_{(2)}$	Limb weakness	Fulfilled	Fulfilled	Absent	NMO	Mycophenolate	29
22	44	$C_{(2)}$, $L_{(1)}$, $L_{(2)}$	Limb weakness[b]	Fulfilled	Fulfilled	Absent	PPMS	Ocrelizumab	88
23	51	$L_{(1)}$, $I_{(4)}$	Limb numbness[b]	Fulfilled	Not fulfilled	Absent	PPMS	None[a]	59
24	46	$I_{(1)}$	Visual impairment	Fulfilled	Fulfilled	Present	RRMS	Ocrelizumab	80
25	48	$C_{(2)}$, $L_{(2)}$	Limb numbness	Fulfilled	Fulfilled	Present	SLE	Mycophenolate	25
26	55	$C_{(6)}$, $L_{(2)}$, $I_{(1)}$, $I_{(3)}$	Limb weakness[b]	Fulfilled	Fulfilled	Present	Susac	Cyclophosphamide	20
27	53	$C_{(4)}$, $L_{(2)}$, $L_{(3)}$, $I_{(3)}$	Visual impairment	Fulfilled	Fulfilled	Present	Sarcoidosis	Azathioprine	57
28	47	$L_{(3)}$, $L_{(4)}$, $I_{(1)}$	Limb weakness	Fulfilled	Fulfilled	Present	RRMS	Ocrelizumab	40
29	51	$L_{(1)}$, $I_{(1)}$	Vertigo	Fulfilled	Fulfilled	Absent	Migraine	None[a]	25
30	74	$C_{(1)}$, $L_{(2)}$, $L_{(3)}$, $I_{(3)}$	Limb numbness	Fulfilled	Fulfilled	Present	Sarcoidosis	Methotrexate	12
31	61	$C_{(1)}$, $I_{(1)}$	Limb numbness	Fulfilled	Not fulfilled	ND	Migraine	None[a]	23
32	39	$C_{(3)}$	Limb numbness	Fulfilled	Fulfilled	Present	RRMS	Ocrelizumab	100
33	39	$C_{(2)}$, $L_{(2)}$	Limb numbness	Fulfilled	Fulfilled	Present	SLE	Azathioprine	0
34	46	$C_{(7)}$, $I_{(1)}$	Vertigo	Fulfilled	Fulfilled	Present	RRMS	Alemtuzumab	71
35	38	$C_{(3)}$	Limb numbness	Fulfilled	Fulfilled	Present	RRMS	Teriflunomide	100
36	19	$I_{(2)}$	Limb numbness	Fulfilled	Fulfilled	Present	RRMS	Fingolimod	83
37	23	$I_{(1)}$	Ataxia	Fulfilled	Fulfilled	Present	RRMS	Interferon beta-1a	100
38	44	$C_{(5)}$, $L_{(2)}$	Visual impairment	Fulfilled	Fulfilled	Present	RRMS	None	100
39	51	$L_{(1)}$, $I_{(4)}$	Limb weakness[b]	Fulfilled	Not fulfilled	Absent	PPMS	NA	78

Clinical onset: neurological symptoms at initial presentation; MRI: magnetic resonance imaging; DIS: dissemination in space; DIT: dissemination in time; OCB: oligoclonal bands; % Perivenular: frequency of perivenular lesions; Treatment: immunomodulatory/immunosuppressive treatment; RRMS: relapsing–remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; NA: not available; SPG4 HSP: hereditary spastic paraplegia; ND: not done; SLE: systemic lupus erythematosus; PPMS: primary progressive multiple sclerosis; NMO: neuromyelitis optica; Susac: Susac syndrome.
[a]Not immunomodulatory/immunosuppressive treatment.
[b]Progressive course at onset.

(9 of 39 patients, 23%; Table 2). All patients fulfilled the MRI criteria for DIS, and 32 of 39 (82%), the MRI criteria for DIT.[2] CSF-specific OCBs were detected in 22 of the 36 patients tested (Table 3). When taking into account the CSF results, 34 of 39 patients (87%) fulfilled the 2017 MS diagnostic criteria for both DIS and DIT in the context of a clinical presentation compatible with inflammatory demyelination (Table 3)[2]

Clinical diagnosis

The median follow-up period between the FLAIR* MRI scan and the eventual clinical diagnosis was 3 months (range 1–7 months). Clinical diagnosis did not change after a median post-diagnosis follow-up period of 13 months (range 7–31 months). MS was diagnosed in 27 patients, 2 of whom were strongly suspected of having primary progressive multiple sclerosis (PPMS) even if they did not fulfill the most recent criteria for PPMS,[2] (patient ID 23 and 39; Table 3). The remaining 12 patients received an alternative diagnosis: systemic lupus erythematosus (SLE)[21] ($n=3$), sarcoidosis[22] ($n=2$), migraine ($n=3$), Sjögren disease[23] ($n=1$), SPG4-spastic-paraparesis[24] ($n=1$), AQP4 antibody–positive neuromyelitis optica[25] ($n=1$), and Susac syndrome[26] ($n=1$). Nine of the 12 patients (75%), who eventually received an alternative diagnosis, still fulfilled the 2017 McDonald DIS and DIT criteria (Table 3).[2]

In four patients diagnosed with a systemic inflammatory disorder with involvement of the CNS (patient ID 3, 17, 27, 30), the neurological manifestation was the first manifestation of the disease. Four patients who received a diagnosis of MS had a concomitant systemic inflammatory disorder ("history of SAD" in Table 2) potentially affecting the CNS (patient ID 6, 7, 10, 22). Of note, none of these four patients harbored MS atypical clinical, laboratory, or imaging features at the level of the CNS.

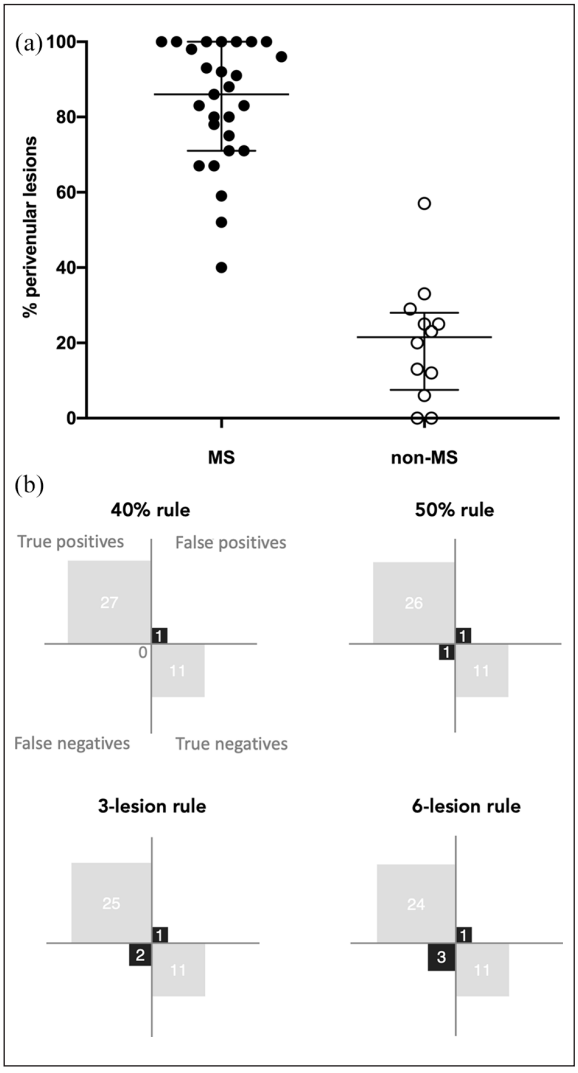

Figure 2. Frequency of perivenular lesions in MS and non-MS patients. (a) Frequency (median and interquartile range) of perivenular lesions in patients who did ("MS") and did not ("non-MS") receive an MS diagnosis and (b) confusion matrices for the differentiation between MS and non-MS based on the different CVS diagnostic tests.

CVS assessment and predictive value of the diagnosis

The percentage of perivenular lesions was significantly higher in the 27 patients who received a diagnosis of MS (median = 86%, range 40%–100%) as compared with the 12 non-MS patients (median = 21%, range 0%–57%; Mann–Whitney U test, $p < 0.0001$; Figure 2). Representative cases are shown in Figures 3 and 4. The inter-rater agreement for the percentage of perivenular lesions was "substantial/good" with a Cohen's κ of 0.7 and agreement of 85%.

When patients were dichotomized based on the 40% rule (presence of ⩾40% perivenular lesions), all MS patients were perivenular positive except for only one non-MS patient (patient ID 27). This patient fulfilled the McDonald 2017 DIS and DIT MRI criteria and had CSF-specific OCBs but presented a history of severe optic neuritis with poor visual recovery, despite steroids, elevated abnormal proteinorrachia, and leptomeningeal enhancement on brain MRI. The biopsy of a hilar adenopathy confirmed the diagnosis of systemic sarcoidosis with CNS involvement (of note, the neurological manifestation was the first manifestation of the SAD).

When the 50% perivenular rule was applied (presence of ⩾50% perivenular lesions), 26 of the 27 MS

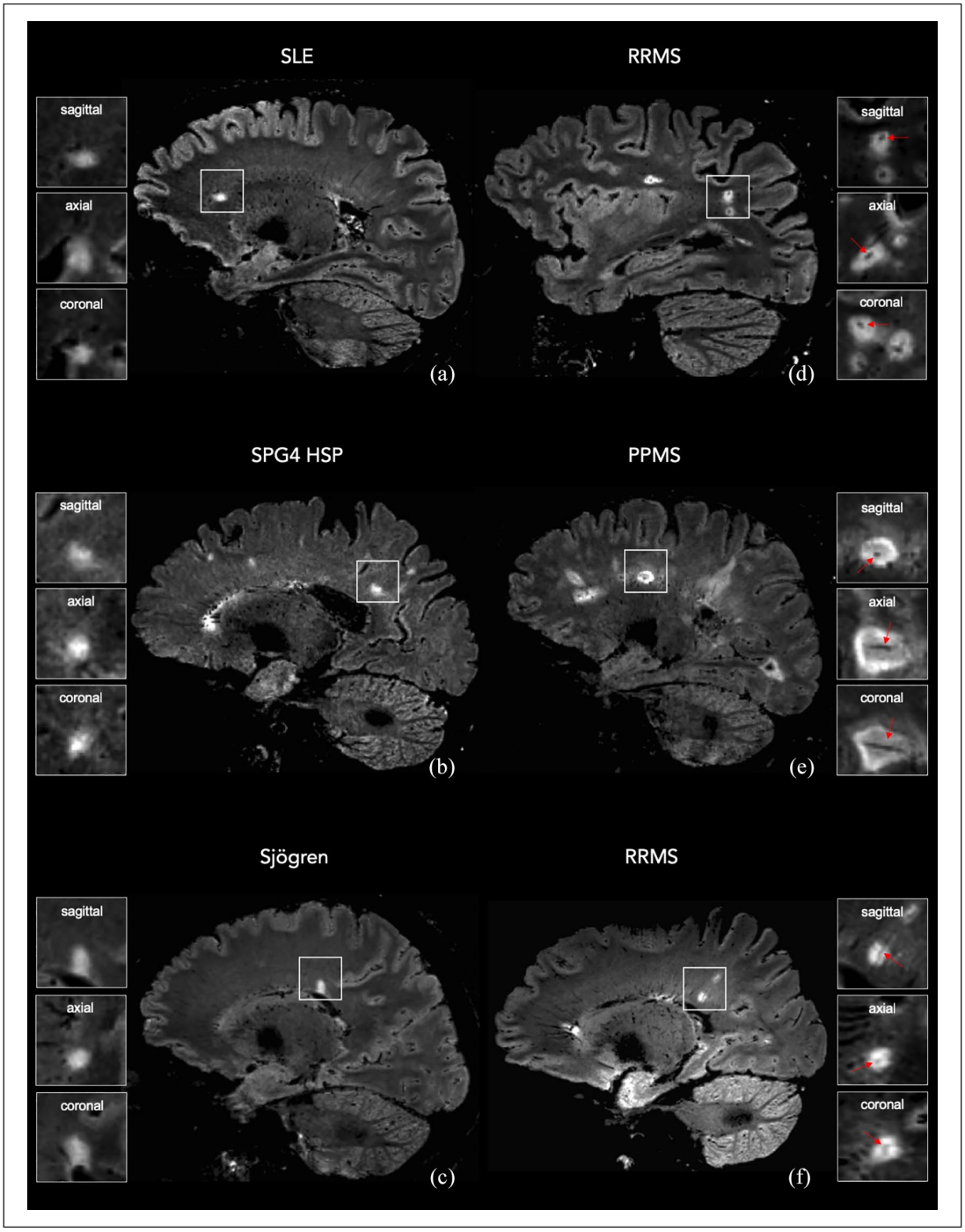

Figure 3. Three-dimensional FLAIR* MRI images in individuals who did and did not receive an MS diagnosis. Representative sagittal FLAIR* images of (a) a woman who received a diagnosis of systemic lupus erythematosus (SLE; patient ID 17), (b) a woman who received a diagnosis of SPG4-spastic-paraparesis (SPG4 HSP; patient ID 8), (c) a woman who received a diagnosis of Sjögren disease (Sjögren; patient ID 3), (d) a man who received a diagnosis of relapsing–remitting MS (RRMS; patient ID 19), (e) a woman who received a diagnosis of primary progressive MS (PPMS; patient ID 22), and (f) a man who received a diagnosis of RRMS (patient ID 6). A central vein running through the lesion (arrows) is visible in the majority of MS lesions but is not typical in non-MS lesions.

patients were perivenular positive except for one non-MS patient (patient ID 27, see above). The only MS patient who had less than 50% perivenular lesions (patient ID 28) fulfilled the diagnostic criteria for MS but had a history of IgM-positive *Borrelia burgdorferi* serology (on two repeated samples) and a

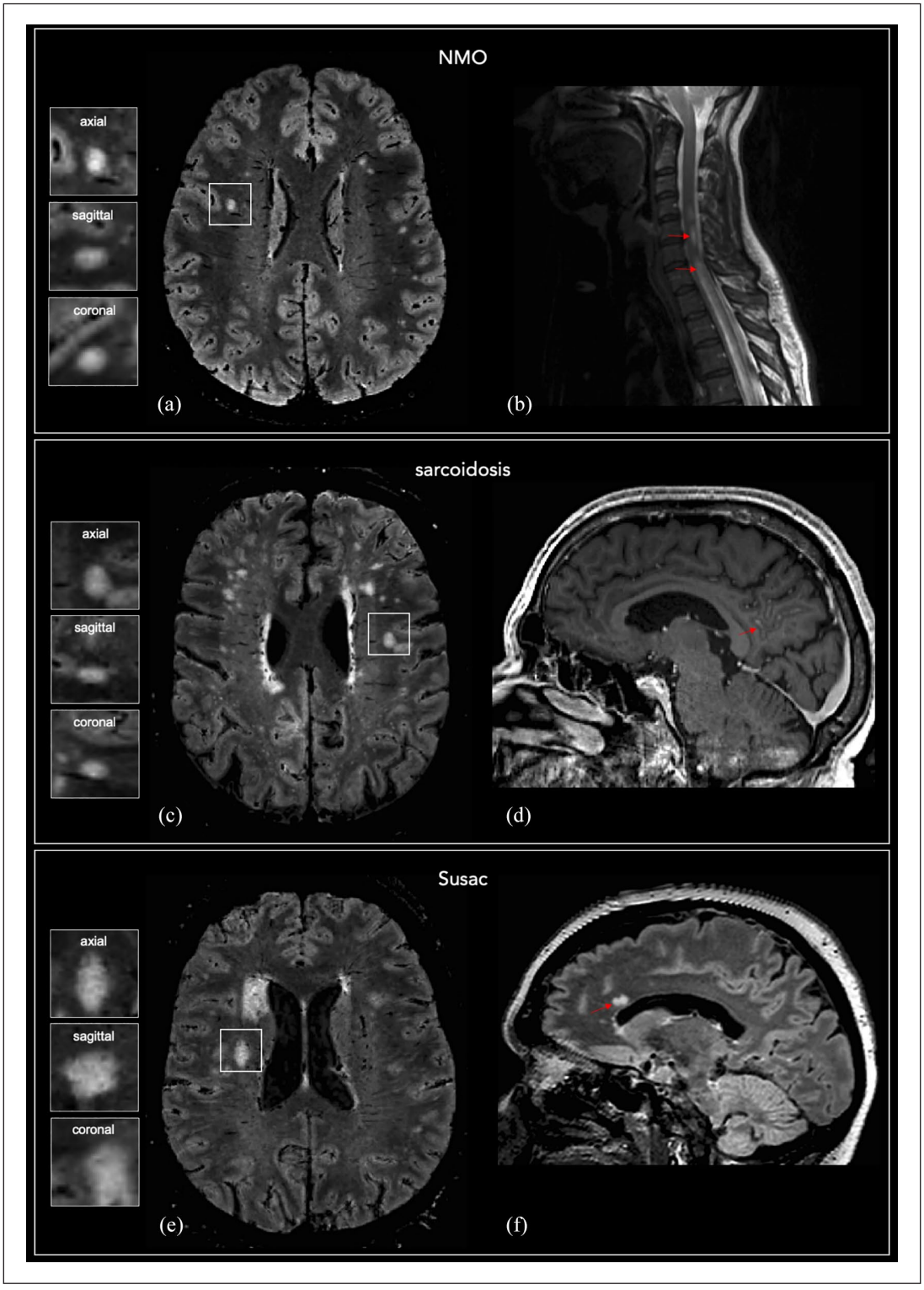

Figure 4. Central vein sign–negative lesions in patients who did not receive an MS diagnosis. Representative (a) axial brain 3D FLAIR* and (b) sagittal spinal cord T2-weighted images from a subject who received a diagnosis of AQP4 antibody–positive neuromyelitis optica (NMO; patient ID 21). Longitudinal extensive transverse myelitis can be seen in the spinal cord image (arrows). (c) Axial 3D FLAIR* and (d) sagittal post-gadolinium MPRAGE images from an individual who received a diagnosis of sarcoidosis (patient ID 30); the arrow shows leptomeningeal enhancement. (e) Axial 3D FLAIR* and (f) sagittal T2-FLAIR images in a subject who received a diagnosis of Susac syndrome (Susac; patient ID 26). Callosal "snowball-shaped" T2 hyperintense lesions (arrow). A central vein running through the lesion is not visible in the majority of white matter lesions in these cases (magnified boxes).

Balò-like WM lesion;[27] after an extensive work-up, he received a diagnosis of relapsing–remitting multiple sclerosis (RRMS). The 40% rule performed slightly better than the 50% rule, with a diagnostic sensitivity of 100%, specificity of 92%, accuracy of 97%, and positive and negative predictive value of 96% and 100%, respectively.

Among the simplified CVS lesion algorithms, the 3-lesion rule performed better than the 6-lesion rule, with a diagnostic sensitivity of 93%, specificity of 92%, accuracy of 92%, and positive and negative predictive value of 96% and 85%, respectively. Diagnostic test performance is shown in Figure 2. Of note, diagnostic test performance results did not change when patient IDs 23 and 39, suspected of PPMS but not fulfilling the McDonald 2017 criteria, were excluded from the analysis.

Discussion

The main finding of this prospective multicenter study is that the CVS detected on a single 3D FLAIR* MRI scan at clinical 3 T field strength can accurately predict a diagnosis of MS in patients with atypical clinical, laboratory, or imaging features for the disease. In particular, we found that using a 40% perivenular lesion threshold, the CVS could predict an MS diagnosis with 97% accuracy and a 96% positive/100% negative predictive value. Most existing studies focusing on the clinical value of the CVS for the differential diagnosis of MS included patients with an already known clinical diagnosis.[6,8–12] One prior study investigated the diagnostic predictive value of the CVS in patients with possible MS, showing promising results.[28] However, this pilot study was done on a research 7T MRI scanner, and not all included patients experienced a neurological syndrome suggestive of MS. Moreover, the presence of specific clinical, laboratory, or imaging features of MS was not an inclusion criterion, and patients who did not receive an MS diagnosis mostly had non-inflammatory diseases of the CNS, such as small vessel disease or migraine. Our prospective study was specifically designed to demonstrate the value of the CVS in the routine work-up of atypical cases and strongly suggests that the CVS could be an imaging biomarker for MS and could be used in routine practice to help neurologists in diagnostically challenging cases.

Our results are particularly relevant considering that the specificity of the current diagnostic imaging criteria for MS is limited[29] and that the prevalence of MS misdiagnosis is high in clinical practice.[3] The 2017 McDonald criteria were designed to facilitate an earlier diagnosis in patients presenting with typical clinical, laboratory or imaging features for MS.[2] Using these criteria to differentiate MS from other conditions or to diagnose MS in patients harboring red flags may lead to misdiagnosis.[15] In our series, 75% of the patients who did not receive an MS diagnosis still fulfilled the most recent DIS and DIT 2017 McDonald criteria, in the context of a clinical presentation compatible with inflammatory demyelination.[2] In those cases, additional MRI criteria, such as the frequency of perivenular lesions, are of great value. Indeed, the frequency of perivenular lesions was significantly lower in these patients compared with those who received an MS diagnosis, even though diagnosis was made blinded to the CVS. In a subgroup of our patients who did receive a diagnosis of SAD with secondary CNS involvement, the neurological manifestation was the first manifestation of the disease, making it hard to differentiate such conditions from MS. Even in this challenging clinical scenario, the CVS was able to correctly predict the non-MS diagnosis in most (three of the four) patients. The only one case where the CVS failed to predict the non-MS diagnosis presented clinical, imaging, and laboratory features compatible with CNS inflammatory demyelination and fulfilled the DIS and DIT diagnostic criteria for MS.[30] However, the patient harbored significant MS-atypical features at the level of the CNS and finally received a diagnosis of systemic sarcoidosis with secondary CNS involvement.

In the subgroup of patients with a progressive clinical course from onset suggestive of PPMS but who do not fulfill the McDonald 2017 criteria for PPMS,[2] appropriate diagnosis is also challenging. In this context, after exclusion of all other possible diagnosis, MS experts eventually considered a diagnosis of PPMS in two patients. Interestingly, in both cases, the CVS assessment was also suggestive of an MS diagnosis.

Regarding the available existing criteria for perivenular assessment, a 40% perivenular lesion cutoff[10] and a simplified 3-lesion algorithm[9] best differentiated MS from non-MS, and our prospective results are in line with those of a recent large retrospective multicenter study.[31]

This study presents some limitations. Despite the multicenter setting of our study, our cohort is rather small because challenging patients presenting with symptoms suggestive of MS and red flags for the diagnosis are rare. A definitive diagnosis is often hard to achieve, and in the absence of one highly specific biomarker for MS, it depends on MS experts' opinion. Even though we already reported a significant median

post-diagnosis follow-up of 13 months, further follow-up of this study cohort will be required to corroborate the eventual clinical diagnosis. Another limitation is the lack of a real objective gold standard for clinical diagnosis between centers, although an extensive work-up was carried out in each center and all centers are highly experienced in the area of neuroimmunological disorders. Four patients who received a diagnosis of MS also had a concomitant SAD potentially affecting the CNS. Although the CVS correctly predicted the clinical MS diagnosis in all cases, to assess whether the CNS disease results, at least in part, from the coexisting SAD remains impossible without biopsy.(Of note, none of these patients harbored MS-atypical clinical, laboratory, or imaging features at the level of the CNS.) Similarly, only biopsy could reveal whether an inflammatory demyelinating process (typical of MS) was responsible, at least in part, for the observed CNS disease in the single patient with a relatively high proportion of perivenular lesions who finally received a clinical non-MS diagnosis (sarcoidosis).[32] Finally, because our study was not designed to quantify the delay between initial clinical presentation, first MRI scan, and FLAIR* MRI scan for CVS assessment, we cannot demonstrate that the FLAIR* scan is able to shorten the delay of MS diagnosis in atypical presentations.

In conclusion, our prospective multicenter study shows that the CVS can accurately predict an MS diagnosis in diagnostically difficult cases using 3T clinical scanners. Multisite availability of an optimized MRI sequence,[33] such as FLAIR* imaging, is required to promote the larger multicenter clinical studies needed to confirm the value of introducing this promising imaging biomarker into everyday clinical practice.

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Authors' contribution

P.M. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. P.M., M.A., L.M., D.S.R., R.D.P., and M.T. helped in concept and design. All authors performed the acquisition, analysis, or interpretation of data. P.M., M.A., D.S.R., and M.T. helped in drafting the manuscript. P.M., M.A., D.S.R, R.D.P, and M.T. participated in the critical revision of the manuscript for important intellectual content. P.M. and M.A. helped in statistical analysis. R.D.P and M.T. helped in study supervision.

Declaration of Conflicting Interests

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