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Evaluation of the Central Vein Sign as a Diagnostic Imaging Biomarker in Multiple Sclerosis

Tim Sinnecker, MD; Margareta A. Clarke; Dominik Meier, PhD; Christian Enzinger, MD; Massimiliano Calabrese, MD; Nicola De Stefano, MD; Alain Pitiot, PhD; Antonio Giorgio, MD; Menno M. Schoonheim, MD, PhD; Friedemann Paul, MD; Mikolaj A. Pawlak, MD, PhD; Reinhold Schmidt, MD; Ludwig Kappos, MD; Xavier Montalban, MD, PhD; Àlex Rovira, MD; Nikos Evangelou, MD, PhD; Jens Wuerfel, MD; for the MAGNIMS Study Group

IMPORTANCE The central vein sign has been proposed as a specific imaging biomarker for distinguishing between multiple sclerosis (MS) and not MS, mainly based on findings from ultrahigh-field magnetic resonance imaging (MRI) studies. The diagnostic value of the central vein sign in a multicenter setting with a variety of clinical 3 tesla (T) MRI protocols, however, remains unknown.

OBJECTIVE To evaluate the sensitivity and specificity of various central vein sign lesion criteria for differentiating MS from non-MS conditions using 3T brain MRI with various commonly used pulse sequences.

DESIGN, SETTING, AND PARTICIPANTS This large multicenter, cross-sectional study enrolled participants (n = 648) of ongoing observational studies and patients included in neuroimaging research databases of 8 neuroimaging centers in Europe. Patient enrollment and MRI data collection were performed between January 1, 2010, and November 30, 2016. Data analysis was conducted between January 1, 2016, and April 30, 2018. Investigators were blinded to participant diagnosis by a novel blinding procedure.

MAIN OUTCOMES AND MEASURES Occurrence of central vein sign was detected on 3T T2*-weighted or susceptibility-weighted imaging. Sensitivity and specificity were assessed for these MRI sequences and for different central vein sign lesion criteria, which were defined by the proportion of lesions with central vein sign or by absolute numbers of lesions with central vein sign.

RESULTS A total of 606 participants were included in the study after exclusion of 42 participants. Among the 606 participants, 413 (68.2%) were women. Patients with clinically isolated syndrome and relapsing-remitting MS (RRMS) included 235 women (66.6%) and had a median (range) age of 37 (14.7-61.4) years, a median (range) disease duration of 2 (0-33) years, and a median (range) Expanded Disability Status Scale score of 1.5 (0-6.5). Patients without MS included 178 women (70.4%) and had a median (range) age of 54 (18-83) years. A total of 4447 lesions were analyzed in a total of 487 patients: 690 lesions in 98 participants with clinically isolated syndrome, 2815 lesions in 225 participants with RRMS, 54 lesions in 13 participants with neuromyelitis optica spectrum disorder, 54 lesions in 14 participants with systemic lupus erythematosus, 121 lesions in 29 participants with migraine or cluster headache, 240 lesions in 20 participants with diabetes, and 473 lesions in 88 participants with other types of small-vessel disease. The sensitivity was 68.1% and specificity was 82.9% for distinguishing MS from not MS using a 35% central vein sign proportion threshold. The 3 central vein sign lesion criteria had a sensitivity of 61.9% and specificity of 89.0%. Sensitivity was higher when an optimized T2*-weighted sequence was used.

CONCLUSIONS AND RELEVANCE In this study, use of the central vein sign at 3T MRI yielded a high specificity and a moderate sensitivity in differentiating MS from not MS; international, multicenter studies may be needed to ascertain whether the central vein sign–based criteria can accurately detect MS.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: Members of the MAGNIMS Study Group are listed at the end of the article.

Corresponding Author: Jens Wuerfel, MD, Medical Image Analysis Center, Marktgasse 8, 4051 Basel, Switzerland (jw@miac.ch).

The diagnosis of multiple sclerosis (MS) has remained challenging in current clinical routine given that alternative diagnoses such as migraine, vascular diseases, and other inflammatory disorders may mimic MS.[1,2] The McDonald MS diagnostic criteria were created to establish the MS diagnosis in patients with a clear demyelinating clinical event.[3] The inappropriate application of the McDonald diagnostic criteria in patients with atypical, nonspecific, or no clinical findings may be a factor in MS misdiagnosis, especially when magnetic resonance imaging (MRI) results show abnormalities of unknown significance.[1,4] Although the 2017 McDonald MS diagnostic criteria[3] shortened the time to diagnosis[5] and improved the sensitivity in diagnosing MS,[6] they seem to be less specific.[7-11] Furthermore, imaging findings in MS partially overlap with MS mimics[2] such as vascular (mostly small vessel disease–associated) signal abnormalities, migraine,[12] neuromyelitis optica spectrum disorder (NMOSD),[13] and systemic lupus erythematosus (SLE)–associated cerebral vasculitis.[14] Thus, recent diagnostic criteria[3] and consensus statements[2] emphasized the importance of a careful differential diagnosis to prevent disability and improve clinical outcomes.[15]

The central vein sign was proposed as a highly sensitive and specific biomarker for MS, mainly on the basis of results from ultrahigh-field MRI studies.[16-18] Indeed, studies that used advanced gradient-echo MRI techniques revealed that a small intralesional central vein was frequently detected in MS but less frequently in brain lesions of other origin, such as small vessel disease,[19,20] NMOSD,[21] and Susac syndrome.[22]

Ultrahigh-field MRI is not yet widely available for clinical routine, which motivated various research groups to apply optimized MRI protocols at 3 Tesla (T) for central vein sign detection in MS.[17,19,23,24] These studies confirmed that the central vein sign at 3T is a specific imaging finding for MS.[17,19,23,24] Nonetheless, these single-center studies had only small sample sizes, and little is known about the implication of different MRI hardware and protocols for central vein sign detection.

With this background, we conducted an international, multicenter cross-sectional study within the MAGNIMS (Magnetic Resonance Imaging in MS) Study Group framework. We aimed to investigate the sensitivity and specificity of various central vein sign–based criteria, using 3T MRI, in differentiating MS from other diseases that may mimic MS lesions, such as cerebral small vessel disease–associated brain lesions, migraine, NMOSD, and SLE. We also compared various MRI pulse sequences and sequence variables to identify an optimal MRI protocol for the clinical application of such central vein sign–based criteria.

Key Points

Question Is the central vein sign on clinical 3T magnetic resonance imaging a useful biomarker for the diagnosis of multiple sclerosis?

Findings In this multicenter cross-sectional study of 4447 lesions in 606 participants, use of a 35% central vein sign proportion threshold yielded a sensitivity of 68.1% and a specificity of 82.9% for distinguishing multiple sclerosis from non–multiple sclerosis. The criteria of 3 or more central vein sign lesions had a sensitivity of 61.9% and a specificity of 89.0%.

Meaning The 3T central vein sign–based criteria showed a high specificity in the differentiation between multiple sclerosis and non–multiple sclerosis; future studies may be needed to confirm the applicability of this finding to support the diagnosis of multiple sclerosis in clinical practice.

Methods

Participants

Participants (n = 648) were enrolled in this cross-sectional, multicenter study at 8 neuroimaging centers across Europe between January 1, 2010, and November 30, 2016. All enrollees were participants in ongoing observational studies or included in neuroimaging research databases. All of these studies were approved by the institutional review board at each center, and all patients provided written informed consent before the MRI examination.

We included patients who met the following criteria: (1) aged 18 to 85 years, with 2 exceptions (a 14.7-year-old boy with clinically isolated syndrome and a 17.8-year-old girl with MS) and (2) with a clinical diagnosis of 1 of the following: clinically isolated syndrome, as defined by 1 clinical attack consistent with a central nervous system inflammatory demyelinating disease not fulfilling the 2010 McDonald MS diagnostic criteria[25]; relapsing-remitting MS (RRMS), as defined by the 2010 McDonald MS diagnostic criteria[25]; NMOSD, as defined by the 2015 International Panel for NMO Diagnosis criteria[26]; SLE; cerebral vasculitis; episodic migraine; cluster headache; or small vessel disease, including patients with dementia. Patients were eligible for inclusion in this study if they had a 3T MRI scan, including a susceptibility-weighted imaging (SWI) sequence or T2*-weighted and 3-dimensional (3-D) fluid-attenuated inversion recovery (FLAIR) sequence. Exclusion criteria were insufficient SWI and/or FLAIR image quality and insufficient coregistration of SWI and FLAIR images.

Aquaporin 4 antibody status was assessed in patients with NMOSD using 1 of several published assays.[27] Antibodies against aquaporin 4 were present in all patients with NMOSD. Clinical disability was assessed using the Expanded Disability Status Scale (score range: 0-10, with the highest score indicating death from MS) in patients with MS and NMOSD. Patients with RRMS with a disease duration shorter than 5 years were considered to have early MS. We excluded 28 participants owing to missing clinical data.

MRI Data Acquisition

High-field MRI scans were acquired using various 3T MRI scanners and head coils. The imaging protocols included 3-D T2-FLAIR and a high-resolution gradient-echo sequence, which was either an SWI sequence or an optimized 3-D T2*-weighted sequence (**Table 1**). The T2*-weighted protocol covered only the supratentorial areas, brain stem, and upper part of the cerebellum.

Table 1. Overview of Participants and Analyzed Lesions

Variable	CIS	MS	NMOSD	SLE	Migraine and Cluster Headache	Diabetes and (Aging) Controls
Women, No./No. (%)	82/117 (70.1)	153/236 (64.8)	28/32 (87.5)	22/25 (88.0)	24/34 (70.6)	104/162 (64.2)
Age, mean (SD) [range], y	33 (8.6) [14.7-51.9]	38 (9.4) [17.8-61.4]	44.6 (14.6) [18.7-70.8]	32.1 (9.3) [18-56]	40.8 (9.8) [23-62]	60.2 (16.7) [21-83.3]
Disease duration, mean (SD) [range], y	0.6 (0.9) [0-7.7]	7 (6.3) [0-33.2]	3.3 (2.5) [0.5-9.7]	NA	NA	NA
EDSS score, median (range)	1.5 (0-4)	2 (0-6.5)	3 (0-6)	NA	NA	NA
Analyzed lesions						
No.	690	2815	54	54	121	713
Median (range)	5 (1-29)	10 (1-59)	2 (1-18)	2 (1-17)	3 (1-14)	3.5 (1-61)
Positive CVS lesions						
No. (%)	374 (54.2)	1335 (47.4)	9 (16.7)	11 (20.4)	21 (17.4)	107 (15.0)
Median (range)	3 (0-25)	4 (0-43)	0 (0-5)	1 (0-3)	1 (0-4)	0 (0-13)
Proportion of positive CVS lesions, median (range), %	0.6 (0-1)	0.5 (0-1)	0 (0-0.5)	0.16 (0-1)	0.09 (0-1)	0 (0-1)

Abbreviations: CIS, clinically isolated syndrome; CVS, central vein sign; EDSS, Expanded Disability Status Scale (score range: 0-10, with the highest score indicating death from MS); MS, multiple sclerosis; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorder; SLE, systemic lupus erythematosus.

Image Postprocessing

First, T2*-FLAIR images were coregistered to the SWI using the ITK registration library (Insight Software Consortium), which was implemented in 3D Slicer, version 4.6.2 (Slicer Community), with increasingly flexible transformations: rigid, then affine, and then low degree-of-freedom Bspline (7 × 7 × 7 grid). The latter makes it possible to correct for low-frequency spatial distortions between the 2 different sequences while only minimally altering the lesion shapes or sizes. The registered images were then split into 8 equal-sized 3-D blocks to restrict the field of view of the investigators (T.S., M.A.C., and non-coauthors) and hence blind them to the global information about the lesion load, the distribution pattern of lesions, and the presence or absence of central veins in other lesions in the same individual. This procedure was done to prevent an inference of the disease type on the central vein sign assessment. An automated randomization across centers, participants, and blocks was performed to assign an individual ID to each block.

Image Analysis

All images were analyzed by 5 trained investigators (T.S., M.A.C., and non-coauthors). These investigators were successively presented with overlays of a subset of SWI and FLAIR blocks using 3D Slicer, version 4.6.2 to decide on the presence of a central vein.

Each white matter lesion larger than 3 mm in its shortest diameter was marked by an investigator. Only those lesions clearly distinguishable from the normal-appearing white matter were considered. Confluent lesions and lesions that were poorly contrasted (eg, owing to motion artifacts, sequence-specific artifacts, or bad overall image quality) were excluded from this study. As a consequence, only a limited number of infratentorial lesions remained for the analysis.

Next, the existence of an intralesional and central intralesional vein was assessed. A vein was defined as a thin (<2 mm) hypointense line on T2*-weighted or SWI images. To be rated as intralesional, the vein had to cross the border of the lesion. Thus, the vein had to be clearly visible outside of the lesion also.

A central intralesional vein was defined in accordance with the North American Imaging in Multiple Sclerosis Cooperative criteria[23]: The vein had to cross the lesion border at 1 or 2 points and run through the lesion in equidistance to its edges. In ovoid lesions, the vein had to run along or follow the long lesion axis. In patients with a 3-D imaging data set, the central vein had to be visible in at least 2 perpendicular planes.

In addition, we measured lesion size along its shortest and longest axes. Lesions were also categorized as either juxtacortical (directly adjacent to the cortex), periventricular (adjacent to the ventricles), or other white matter lesions.

Sensitivity and Specificity of Different Lesion Criteria

A key point of this work was to identify the central vein sign criteria that most accurately differentiate between patients with MS and clinically isolated syndrome and patients without MS. For this purpose, we defined central vein sign lesion criteria according to the proportion of lesions with central vein sign. A threshold ranging from 20% to 50% was applied in 5% increments. For each increment, sensitivity and specificity for detecting MS were calculated.

Such a proportion-based approach, however, is time consuming given that all lesions, without any exception, need to be marked and analyzed. Thus, a proportion-based approach may be less applicable in daily clinical routine. Therefore, we decided to also test criteria by the absolute number of lesions, including the number of lesions, the lesion localization, and the existence of a central vein.

Quality Assessment and Interrater Reliability

A total of 14 scans were excluded owing to insufficient SWI quality. After the separation or randomization of lesions into blocks, the existence of a central vein was only assessed in lesions within an artifact-free volume and with a good to excel-

lent coregistration. Otherwise, blocks were marked and excluded from analysis (n = 80). Interrater reliability for the central vein sign detection was assessed in a randomly selected representative data set of 30 blocks with a total number of 76 MS and non-MS lesions. Interrater reliability was estimated by calculating intraclass correlation coefficients for absolute agreement. More specifically, a 2-way mixed model for single measures was applied.

Statistical Analysis

All analyses were performed in IBM SPSS Statistics, version 20 (IBM) between January 1, 2016, and April 30, 2018. Normal distribution was assessed visually and by using the Shapiro-Wilk test. Not all variables were normally distributed. To identify a potential association of gradient-echo sequence type, voxel volume, slice thickness, TR (repetition time), or TE (echo time) with the agreement between the clinical diagnosis and central vein sign criteria, we used least absolute shrinkage and selection operator (LASSO) regression, with agreement between the clinical diagnosis and the 35% central vein sign proportion threshold as the dependent variable. LASSO regression uses L1 regularization and is useful when variables need to be automatically selected from a larger sample. An importance value above 0 indicates a given variable's substantial contribution to the model. LASSO results were confirmed using a general linear model with bootstrapping (case resampling rate n = 1000). In addition, differences between SWI and T2*-weighted or lesion localization were assessed using the nonparametric Mann-Whitney test. Receiver operating characteristic curves were created for proportion-based and lesion-based central vein sign criteria. Two-sided $P < .05$ was considered statistically significant.

Results

Cohort Description

The existence of a central vein was analyzed in 606 participants, of whom 413 (68.2%) were women. The cohort included 117 patients (19.3%) with clinically isolated syndrome, 236 (38.9%) with RRMS (of whom 108 had early MS with a disease duration shorter than 5 years), 32 (5.3%) with aquaporin-4 antibody–positive NMOSD, 25 (4.1%) with SLE, 29 (4.8%) with migraine, 5 (0.8%) with cluster headaches, 20 (3.3%) with diabetes mellitus, and 142 (23.4%) with cerebral small vessel disease. Among the 353 patients with clinically isolated syndrome and RRMS, 235 (66.6%) were women, median (range) age was 37 (14.7-61.4) years, and median (range) disease duration was 2 (0-33) years. The RRMS and clinically isolated syndrome groups were characterized by a predominantly mild to moderate clinical disability (median [range] Expanded Disability Status Scale score, 1.5 [0-6.5]). Patients without (n = 253) included 178 women (70.4%) and had a median (range) age of 54 (18-83) years. eTable 1 in the Supplement summarizes the contribution of the individual imaging centers, and more demographic details are presented in Table 1.

Lesion Count and Distribution

A total of 4447 lesions (Table 1) were analyzed in a total of 487 patients: 690 lesions in 98 participants with clinically isolated syndrome, 2815 lesions in 225 participants with RRMS, 54 lesions in 13 participants with NMOSD, 54 lesions in 14 participants with SLE, 121 lesions in 29 participants with migraine or cluster headache, 240 lesions in 20 participants with diabetes, and 473 lesions in 88 participants with other types of small vessel disease. No analyzable lesions were present in the other 119 participants (Table 1). Of these, 109 participants had no or only small brain lesions with a diameter less than 3 mm, and 8 participants presented with confluent lesions only. In the remaining 2 participants, all candidate lesions were incidentally split and separated among different blocks during the blinding procedure.

Multiple sclerosis lesions were more often located in the periventricular white matter compared with non-MS lesions (1160 of 3505 lesions [33.1%] vs 119 on 942 lesions [12.6%]; $P < .001$). Juxtacortical lesions were generally less frequent in both MS and non-MS cases (527 [15.0%] vs 151 [16.0%]; $P = .08$). The most frequent lesion localization in MS and not MS was the remaining other white matter, which included 42 infratentorial lesions in 27 participants (1818 [51.9%] vs 672 [71.3%]; $P < .001$). The intraclass correlation coefficient for the number of central veins per block was 0.924.

Central Vein Sign in Patients With MS and Clinically Isolated Syndrome

A central intralesional vein (positive central vein sign) was found in 1335 (47.4%) of 2815 RRMS lesions and in 374 (54.2%) of 690 clinically isolated syndrome lesions (**Figure**). In RRMS, the median (range) proportion of a positive central vein sign per patient was 50% (0%-100%). The median (range) percentage of a positive central vein sign per patient with clinically isolated syndrome was 60% (0%-100%) (Table 1).

A total of 295 (91.3%) of 323 patients with MS and clinically isolated syndrome had at least 1 lesion with a central vein. Two or more lesions with a central vein were found in 246 (76.2%) of these patients, and 200 (61.9%) showed at least 3 lesions with a central vein.

Central Vein Sign in Patients With Non-MS

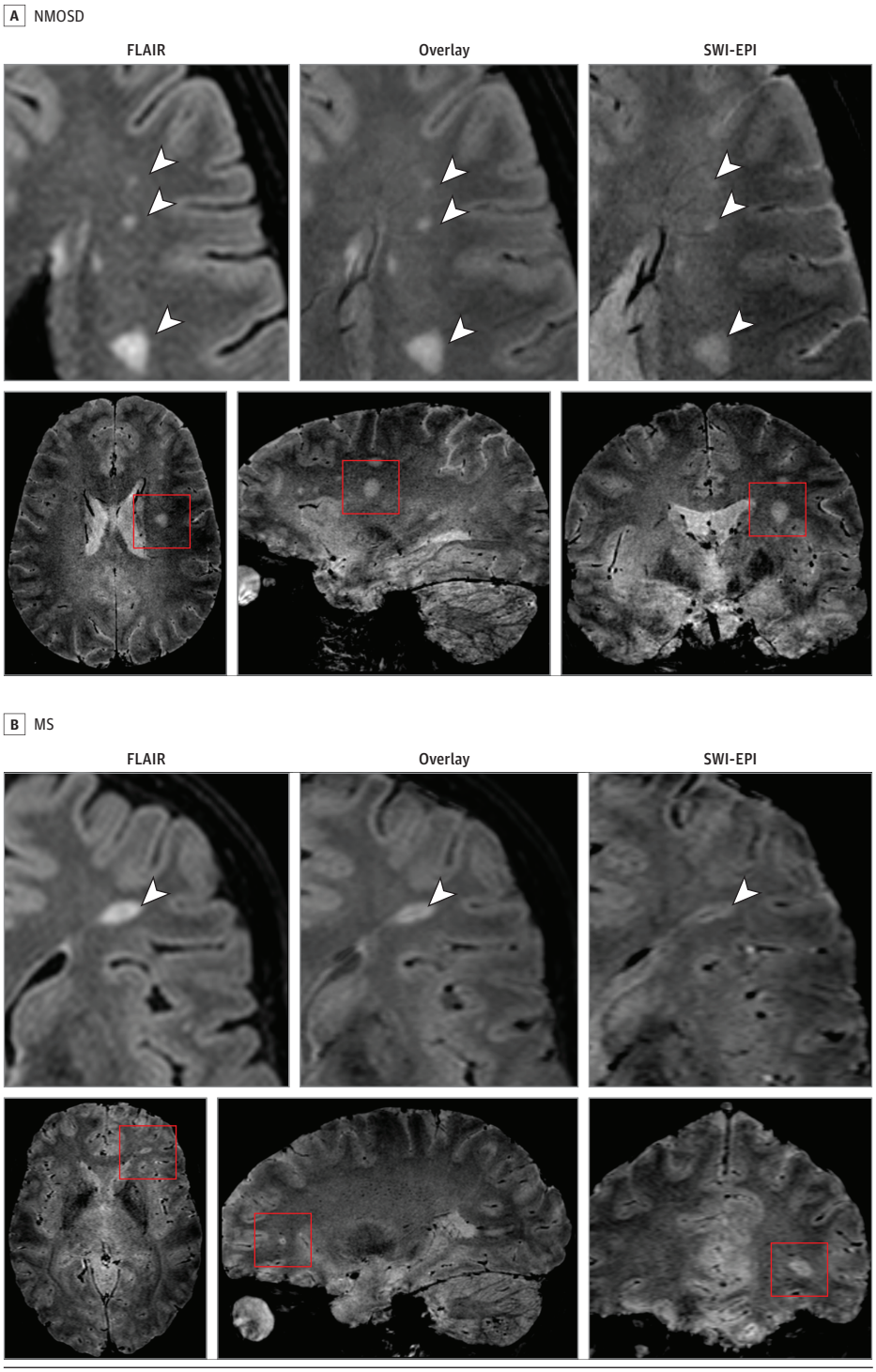
A central intralesional vein (positive central vein sign) was found in 148 of 942 non-MS lesions (15.7%), and the median (range) proportion of a positive central vein sign per patient was 0% (0%-100%). This finding was consistent among all studied non-MS subgroups (Table 1 and eFigure 1 in the Supplement).

Of 164 participants without MS who had lesions, 90 (54.9%) did not have a single lesion with a central vein. One or more lesions with a central vein were observed in 74 participants without MS (45.1%). Thirty-four (20.7%) had 2 or more central vein lesions, and 18 (11.0%) presented with 3 or more central vein lesions.

Central Vein Sign and Lesion Localization

Lesion localization may be a factor in the detection of a central vein. In patients with MS and clinically isolated syndrome, a central vein was more often detectable within periventricular lesions (615 of 1160 lesions [53.0%]; $P < .001$) and other white matter lesions (897 of 1818 lesions [49.3%];

Figure. Exemplary Lesions With and Without a Central Vein



Lesions of a patient with exemplary neuromyelitis optica spectrum disorder (NMOSD) are shown in the top 6 images (A), whereas the lesion of a patient with multiple sclerosis (MS) is shown in the bottom 6 images (B), using Verona imaging protocol (original magnification ×3.5 [3-D view]). Fluid-attenuated inversion recovery (FLAIR) images (left) were coregistered to susceptibility-weighted imaging (SWI) with echo-planar SWI–echo-planar imaging (EPI) (right). The existence of a central vein was evaluated using the overlay (middle) of FLAIR and SWI. Although no central vein is visible in the NMOSD lesions (white arrowheads in A), a distinct central vein is displayed within the MS lesion (white arrowheads in B). The 3-dimensional view (red boxes) confirms the presence or absence of a central vein.

$P < .001$) compared with juxtacortical lesions (197 of 527 lesions [37.4%]).

In participants without MS, a central vein was also most frequently visible in periventricular lesions (29 of 119 lesions [24.4%]) compared with juxtacortical (23 of 151 lesions [15.2%]; $P = .052$) or other white matter lesions (96 of 672 lesions [14.3%]; $P = .047$), which may be explained by the high density of SWI/T2*-weighted hypointense veins in the periventricular white matter.

Accordingly, the ratio of the percentage of MS and clinically isolated syndrome compared with non-MS lesions with a central vein was highest for other white matter lesions (ratio, 3.5; juxtacortical lesions ratio, 2.5; and periventricular lesions ratio, 2.2).

Table 2. Sensitivity, Specificity, and Positive and Negative Likelihood Ratio of the Central Vein Sign

Marker	%		LR		Youden J Index
	Specificity	Sensitivity	Positive	Negative	
Threshold, %					
20	72.6	84.5	3.08	0.21	0.57
25	78.0	80.2	3.65	0.25	0.58
30	79.3	76.2	3.67	0.30	0.56
35	82.9	68.1	3.99	0.38	0.51
40	84.1	61.3	3.87	0.46	0.45
45	86.0	58.8	4.19	0.48	0.45
50	89.6	46.4	4.48	0.60	0.36
Positive CVS lesion, No.					
1	54.9	91.3	2.02	0.16	0.46
2	79.3	76.2	3.67	0.30	0.56
3	89.0	61.9	5.64	0.43	0.51
4	94.5	50.2	9.14	0.53	0.45
5	98.2	40.9	22.34	0.60	0.39
JC positive CVS lesion, No.					
1	87.8	32.5	2.67	0.77	0.20
2	98.2	14.6	7.95	0.87	0.13
3	100	5.3	NA	0.95	0.05
4	100	3.1	NA	0.97	0.03
PV positive CVS lesion, No.					
1	84.8	71.8	4.71	0.33	0.57
2	97.6	47.7	19.55	0.54	0.45
3	100	29.4	NA	0.71	0.29
4	100	14.9	NA	0.85	0.15
2 PV or JC positive CVS lesions	71.3	79.6	2.78	0.29	0.51
2 PV or JC positive CVS lesions or 35% threshold	57.9	92.3	2.19	0.13	0.50
2 Positive CVS lesions or 35% threshold	62.8	87.0	2.34	0.21	0.50
3 Positive CVS lesions or 35% threshold	68.3	83.0	2.62	0.25	0.51

Abbreviations: CVS, central vein sign; JC, juxtacortical; LR, likelihood ratio; NA, not applicable; PV, periventricular.

Sensitivity and Specificity of the Central Vein Sign

Sensitivity and specificity values for differentiation between patients with MS and clinically isolated syndrome and patients without MS of all tested criteria and combinations are summarized in **Table 2**. For the 35% central vein sign proportion threshold, the specificity was 82.9% and the sensitivity was 68.1% (Table 2). The presence of 3 or more central vein sign lesions had a sensitivity of 61.9% and specificity of 89.0% in differentiating MS and clinically isolated syndrome from not MS (Table 2). The combination of the 3 lesion criteria and the 35% central vein sign proportion threshold was associated with a higher sensitivity (83.0%) but lower specificity (68.3%) (Table 2). These findings were consistent across all included MS differential diagnoses as well as for the differentiation between early MS and clinically isolated syndrome and not MS. **Table 3** lists sensitivity and specificity values among different disease subgroups.

Twenty-eight patients with MS had a central vein sign proportion of 0%, and 12 patients with non-MS had a central vein sign proportion of 100%, reducing the specificity of the central vein sign in differentiating between the disease groups. Only 1 or 2 lesions were analyzed per participant in 28 of 40 participants (70.0%). The minimum number of analyzable lesions was associated with the specificity of the central vein sign. Receiver operating characteristic curves (eFigure 2 in the Supplement) highlighted that the specificity for MS for proportion-based central vein sign criteria was higher when only patients with at least 3 to 6 analyzable lesions were included in the analysis. Such an association was not clearly observable for lesion-based central vein sign criteria (eFigures 2 and 3 in the Supplement).

Furthermore, we asked whether any characteristic features were shared among these 40 participants. We observed 1 larger pontine lesion and 1 tumefactive lesion (the tumefactive lesion was not analyzed for central vein sign) in patients with MS. Three patients with clinically isolated syndrome had nonspecific brain lesions. Other morphologic abnormalities were not found.

Central Vein Sign and Imaging Sequence

We used a set of different high-resolution 3T gradient-echo sequences that enabled us to estimate the association between different imaging variables and the detectability of a central vein. eTable 1 in the Supplement gives an overview of the different MRI protocols. All 8 centers in this study had provided either an SWI sequence or a highly optimized T2*-weighted sequence for the detection of central veins.

Table 3. Sensitivity and Specificity of the Central Vein Sign in Differentiating Between MS/CIS or Early MS/CIS and Other Diseases

	%							
	CIS/MS vs NMOSD		CIS/MS vs SLE		CIS/MS vs SVD		CIS/Early MS vs Not MS[a]	
Marker	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity
Threshold, %								
20	69.2	84.5	57.1	84.5	74.5	84.5	72.6	83.3
25	69.2	80.2	64.3	80.2	80.3	80.2	78.0	80.9
30	76.9	76.2	64.3	76.2	81.0	76.2	79.3	77.5
35	84.6	68.1	64.3	68.1	84.7	68.1	82.9	69.6
40	92.3	61.3	64.3	61.3	85.4	61.3	84.1	64.2
45	92.3	58.8	71.4	58.8	86.9	58.8	86.0	62.3
50	100	46.4	85.7	46.4	89.1	46.4	89.6	48.0
Positive CVS lesion, No.								
1	69.2	91.3	42.9	91.3	54.7	91.3	54.9	89.7
2	84.6	76.2	85.7	76.2	78.1	76.2	79.3	71.6
3	92.3	61.9	92.9	61.9	88.3	61.9	89.0	55.9
4	92.3	50.2	100	50.2	94.2	50.2	94.5	43.6
5	92.3	40.9	100	40.9	98.5	40.9	98.2	34.3
JC positive CVS lesion, No.								
1	92.3	32.5	71.4	32.5	89.1	32.5	87.8	27.9
2	100	14.6	100	14.6	97.8	14.6	98.2	11.3
3	100	5.3	100	5.3	100	5.3	100	2.9
4	100	3.1	100	3.1	100	3.1	100	2.0
PV positive CVS lesion, No.								
1	84.6	71.8	92.9	71.8	83.9	71.8	84.8	67.2
2	100	47.7	100	47.7	97.1	47.7	97.6	42.2
3	100	29.4	100	29.4	100	29.4	100	26.5
4	100	14.9	100	14.9	100	14.9	100	13.2
2 PV or JC positive CVS lesions	92.3	79.6	85.7	79.6	67.9	79.6	71.3	72.1
2 PV or JC positive CVS lesions or 35% threshold	76.9	92.3	50.0	92.3	56.9	92.3	57.9	90.7
2 Positive CVS lesions or 35% threshold	84.6	87.0	78.6	87.0	59.1	87.0	62.8	82.4
3 Positive CVS lesions or 35% threshold	92.3	83.0	78.6	83.0	65.0	83.0	68.3	77.0

Abbreviations: CIS, clinically isolated syndrome; CVS, central vein sign; JC, juxtacortical; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; PV, periventricular; SLE, systemic lupus erythematosus; SVD, small vessel disease.

[a] Including NMOSD, SLE, diabetes, (aging) healthy control participants, and migraine and cluster headache.

Overall, LASSO regression identified only a minor association of sequence variables for the agreement between the clinical diagnosis and 35% central vein sign proportion threshold. The type of the gradient-echo sequence, SWI voxel volume, SWI slice thickness, and FLAIR voxel volume added substantial information to the statistical model and together explained approximately 12% of the variance, with the type of the gradient-echo sequence being the strongest input. More details on the LASSO regression analysis are presented in eFigure 4 in the Supplement. The LASSO results were confirmed by a general linear model that also showed the minor implication of sequence variables for agreement between the clinical diagnosis and 35% central vein sign proportion threshold (R^2 = 0.058; P = .003).

With this background, we further analyzed the association of optimized 3-D T2*-weighted imaging with the detectability of a central vein. In the small subgroup of 30 patients scanned with optimized 3-D T2*-weighted imaging, we observed a higher sensitivity in detecting a central vein: The median (range) proportion of a positive central vein sign in MS and clinically isolated syndrome lesions was 50% (0%-100%) on SWI images and 67% (50%-100%; P = .008) on T2*-weighted images. Moreover, optimized T2*-weighted imaging was most suitable for differentiating MS and clinically isolated syndrome from not MS, with a sensitivity of 100% and specificity of 86.7% for the 35% central vein sign proportion threshold. For the same threshold, the sensitivity was 66.6% and specificity was 82.6% of the central vein sign on SWI imaging (eTable 2 in the Supplement).

Discussion

In this large, multicenter cross-sectional study, we evaluated the applicability and diagnostic value of the so-called central vein sign on clinical 3T MRI in differentiating clinically iso-

lated syndrome and RRMS from MS mimics using a novel parcellation algorithm that ensured optimal blinding of the raters. We observed a high proportion of central veins in the lesions of patients with clinically isolated syndrome and RRMS but not in patients with MS mimics such as cerebral small vessel disease–associated brain lesions, migraine, NMOSD, or SLE (as an example of a small vessel vasculitis). Moreover, the 3-central vein sign lesion criteria and a 35% central vein sign proportion threshold showed high specificity in differentiating MS from non-MS. The sensitivity of central vein sign–based criteria in differentiating between MS and non-MS was higher when using optimized T2*-weighted sequences. These findings appear to be encouraging given that this study was based on data derived from academic clinical routine and thus represents current clinical settings.

The existence of a central vein within MS lesions has been known for more than a century. Driven by advances in gradient-echo MRI techniques, a number of studies analyzed the existence of a central vein in vivo by using high- and ultrahigh-field MRI.[16,17,19-22] It was shown that 7T MRI is able to visualize in great detail a central vein within MS lesions,[18] and it was demonstrated that the central vein sign on advanced 7T MRI scans in small studies allows for a near-perfect differentiation between MS and unspecific white matter lesions,[20] NMOSD,[21] or Susac syndrome.[22] Moreover, the central vein sign was observed in equal frequency in patients with RRMS and primary-progressive MS.[16]

Stimulated by these promising 7T MRI findings, several authors aimed at facilitating the practical application of the central vein sign by using optimized 3T MRI for central vein sign detection.[17,19,24,28-35] Most of these 3T MRI studies used a proportion-based threshold for the differentiation of MS from inflammatory vasculopathies (50% threshold),[31] small vessel disease–associated lesions (45% threshold),[19,28] NMOSD (54% threshold),[29] and migraine (no specific threshold described).[24] Choosing an optimal proportion-based threshold is challenging given that such a threshold is likely to be dependent on the used MRI sequence. Maggi et al[31] reported achieving 100% sensitivity and specificity for the differentiation between MS and non-MS by using a 50% central vein sign proportion-based threshold and an optimized 3-D T2*-weighted imaging sequence. The findings reported by Maggi et al[31] are well in line with our own observations in the subgroup of patients with optimized 3-D T2*-weighted images. The 50% central vein sign proportion-based threshold was also specific for MS (specificity of 89.9%) when using the SWI and FLAIR approach; however, the threshold had a low sensitivity of 44.5% in this setting. Thus, it seems that the more sensitive an imaging sequence is for the detection of small veins, the higher a proportion-based threshold can be set to increase the specificity without losing too much sensitivity for detecting MS.

Generally, a proportion-based threshold is labor intensive and thus less applicable to nonacademic purposes. Moreover, some studies reported a lower proportion of central vein sign–positive MS lesions at 3T[30,36] compared with highly resolving 7T MRI.[17] Indeed, a 3T SWI study observed a low mean proportion of 41% central vein sign–positive lesions in MS.[35]

Alternatively, a central vein sign threshold defined by the absolute number of lesions with central vein sign would be more convenient to use in distinguishing MS from non-MS compared with a proportion-based central vein sign threshold. Thus far, 3 studies have evaluated a threshold-based approach on the absolute number of central vein sign lesions.[34] In an initial study, Mistry et al[19] reported achieving differentiation between MS and non-MS by applying a diagnostic rule that encompassed a category of 6 or more central vein sign lesions with an MS-specific lesion morphologic structure. Solomon et al[34] found that a 3-central vein sign lesion threshold is suitable for differentiating MS from other diseases, which is consistent with our findings. Moreover, 2 central vein sign–positive lesions yielded a high specificity in differentiating MS from non-MS in this large cohort. The specificity further increased when these 2 lesions were located in the periventricular or juxtacortical white matter. On the other hand, a recent study by Maggi et al[31] reported a lower specificity for the differentiation between MS and non-MS for the 3 central vein sign lesions or 6 central vein sign lesions criteria compared with a proportion-based threshold. In comparison to our study, the study by Maggi et al[31] had a higher median number of analyzed lesions per patient because our cohort included a high number of patients with clinically isolated syndrome and early MS. This finding suggests that a proportion-based threshold may be more suitable in patients with higher lesion counts. However, we did not observe such an association in the present cohort.

A lesion-based approach that uses central vein sign is simple, time saving, and easy to apply as an additional diagnostic criterion for current clinical practice. Moreover, our results indicate that it is possible to use a combination of lesion-based and proportion-based thresholds for the differentiation of MS and non-MS.

Positive central vein sign–based criteria have a high specificity for MS. Thus, positive central vein sign–based criteria may be applied to support the diagnosis of MS. The sensitivity of central vein sign–based criteria is still moderate when using SWI at 3T. Hence, negative central vein sign–based criteria are not yet suitable to rule out the diagnosis of MS.

One additional scientific question is whether central vein sign–based criteria can improve MS diagnosis according to the 2017 International Panel on Diagnosis of Multiple Sclerosis.[3,6] Two potential scenarios exist in which central vein sign–based criteria may add valuable information to the diagnostic process. First, the International Panel criteria aim to differentiate patients who had a clear demyelinating clinical event.[3] The criteria do not apply to other clinical or radiologic presentations, such as cases of radiologically isolated syndrome or cases in which the clinical presentation is less specific (eg, mild cognitive impairment or fatigue as the presenting symptom). As a consequence, it was shown that the criteria overlap with those for migraine,[12] NMOSD,[13] and SLE.[14] Furthermore, recent studies reported a lower specificity of the 2017 International Panel criteria compared with the 2010 McDonald MS diagnostic criteria.[7-11] Central vein sign–based criteria may fill the gap in specificity, particularly because results of the present study indicate that they are characterized by a high specificity.

Second, the International Panel criteria require proof of dissemination in time by visualizing at least 1 new or contrast-enhancing lesion over time. Although the inclusion of positive oligoclonal bands in the diagnostic criteria seems to allow for an earlier diagnosis,[6] central vein sign–based criteria can be applied on MRI at a single time point. Furthermore, considering the inconvenience, morbidity, and cost associated with lumbar punctures, it would be interesting to test whether the central vein sign could replace oligoclonal bands in future criteria. Our findings suggest that the central vein sign may be an early diagnostic MS biomarker, as we observed it as frequently in clinically isolated syndrome and early MS as in RRMS.

Limitations

This study has several limitations, and the application of diagnostic rules based on the central vein sign is not free of restraints. We observed a reduced specificity in detecting MS for proportion-based but not for lesion-based central vein sign criteria in patients with only a few brain lesions. This finding is further complicated given that not all brain lesions can be reliably analyzed for the existence of the central vein sign. Small lesions with a diameter less than 3 mm were excluded from the study. This 3-mm threshold is, however, primarily dependent on spatial resolution, and future optimized 3-D T2*-weighted sequences may enable the reliable delineation of veins within smaller lesions.

A central vein on clinical 3T MRI, in comparison to that on ultrahigh-field MRI at 7T, is challenging to visualize.[17] Various optimized sequence protocols for the detection of a central vein at 3T have been proposed. In general, 2 different approaches exist: either optimized T2*-weighted sequences[37] or a combination of T2*-weighted or SWI and FLAIR.[28,30,33] In the present study, we observed that the sensitivity and specificity in detecting veins were highest on optimized T2*-weighted images. The sensitivity and specificity were lower when a combined SWI and FLAIR approach was applied. Nonetheless, the T2*-weighted imaging was applied only in a small subgroup of 30 participants, and hence the comparison between FLAIR or SWI and T2*-weighted sequences is not generalizable.

We included different imaging protocols to evaluate optimal MRI sequence variables for central vein sign detection, and participants were not equally distributed among the different imaging protocols. Because 3-D SWI and 3-D FLAIR sequences were not available from all of the 8 neuroimaging centers, the existence of a central vein could not always be confirmed in 2 perpendicular planes, which may be associated with a decreased specificity in detecting the central vein sign. As mentioned, lesions smaller than 3 mm were excluded in this study for quality reasons, reducing the number of analyzable lesions and patients. In addition, the number of analyzed infratentorial lesions in the cohort was low. Thus, the results need to be confirmed in a large-scale, international, multicenter prospective study.

Conclusions

In this cross-sectional study, the 3T central vein sign–based criteria showed a high specificity in differentiating MS from non-MS. Sufficient differentiation was achieved by applying a 3 lesion-based threshold or a 35% central vein sign proportion threshold. The application of T2*-weighted imaging may further increase the sensitivity of the central vein sign. We propose the conduct of a large prospective study of the central vein sign in patients with symptoms suggestive of MS to confirm this study's cross-sectional findings and to identify whether central vein sign–based criteria can be used in clinical practice to support the diagnosis of MS.

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Author Affiliations: Neurologic Clinic and Policlinic, Departments of Medicine, Clinical Research and Biomedical Engineering, University Hospital, University of Basel, Basel, Switzerland (Sinnecker, Kappos); Medical Image Analysis Center, Basel, Switzerland (Sinnecker, Meier, Wuerfel); Neurocure Clinical Research Center, Charité—Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany (Sinnecker, Paul, Wuerfel); qbig, Department of Biomedical Engineering, University of Basel, Basel, Switzerland (Sinnecker, Meier, Wuerfel); School of Psychology, University of Nottingham, Nottingham, United Kingdom (Clarke); Clinical Neurology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom (Clarke); Division of Neuroradiology, Vascular and Interventional Radiology, Departments of Neurology and Radiology, Medical University of Graz, Graz, Austria (Enzinger); Neurology Unit, Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Verona, Italy (Calabrese); Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy (De Stefano, Giorgio); Laboratory of Image and Data Analysis, Ilixa Ltd, London, United Kingdom (Pitiot); Department of Anatomy and Neurosciences, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands (Schoonheim); Experimental and Clinical Research Center, Charité—Universitätsmedizin Berlin Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health and Max Delbrück Center for Molecular Medicine, Berlin, Germany (Paul, Wuerfel); Department of Neurology and Cerebrovascular Disorders, Poznan University of Medical Sciences, Poznan, Poland (Pawlak); Department of Neurology, Medical University of Graz, Graz, Austria (Schmidt); Section of Neuroradiology, Department of Radiology (IDI), VHIR, Barcelona, Spain (Montalban, Rovira); Division of Neurology, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Montalban); Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom (Evangelou).

Author Contributions: Dr Sinnecker, Ms Clarke, Dr Evangelou, and Dr Wuerfel are equally contributing authors. Dr Wuerfel had 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.
Concept and design: Sinnecker, Pitiot, Schoonheim, Pawlak, Kappos, Rovira, Evangelou, Wuerfel.
Acquisition, analysis, or interpretation of data: Sinnecker, Clarke, Meier, Enzinger, Calabrese, De Stefano Nicola, Pitiot, Giorgio, Schoonheim, Paul, Pawlak, Schmidt, Montalban, Rovira, Evangelou, Wuerfel.
Drafting of the manuscript: Sinnecker, Calabrese, Pawlak, Evangelou, Wuerfel.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Sinnecker, Clarke, Meier, Pitiot, Pawlak.
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Supervision: Rovira, Evangelou, Wuerfel.

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Group Information: The MAGNIMS (Magnetic Resonance Imaging in MS) Study Group members are Frederik Barkhof, MD, MS Centre Amsterdam, VU University Medical Center; Olga Ciccarelli, MD, Queen Square MS Centre, UCL Institute of Neurology; Nicola De Stefano, MD, University of Siena; Christian Enzinger, MD, Department of Neurology, Medical University of Graz; Massimo Filippi, MD, and Mara A Rocca, MD, San Raffaele Scientific Institute, Vita-Salute San Raffaele University; Jette L Frederiksen, MD, Rigshospitalet Glostrup Hospital and University of Copenhagen; Claudio Gasperini, MD, San Camillo-Forlanini Hospital; Ludwig Kappos, MD, University of Basel; Jacqueline Palace, MD, University of Oxford Hospitals Trust; Alex Rovira, MD, and Jaume Sastre-Garriga, MD, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona; Tarek Yousry, MD, Queen Square MS Centre, UCL Institute of Neurology; Hugo Vrenken, PhD, MS Centre Amsterdam, VU University Medical Center.

Additional Information: This study was run under the auspices of the MAGNIMS Study Group, which explicitly supports the idea of data sharing to facilitate research in the field of multiple sclerosis. Deidentified magnetic resonance imaging data included in this study will be shared with researchers by the corresponding author in consultation with the MAGNIMS Study Group.

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