






# Central Vein Sign Differentiates Multiple Sclerosis from Central Nervous System Inflammatory Vasculopathies

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**Objectives:** In multiple sclerosis (MS), magnetic resonance imaging (MRI) is a sensitive tool for detecting white matter lesions, but its diagnostic specificity is still suboptimal; ambiguous cases are frequent in clinical practice. Detection of perivenular lesions in the brain (the “central vein sign”) improves the pathological specificity of MS diagnosis, but comprehensive evaluation of this MRI biomarker in MS-mimicking inflammatory and/or autoimmune diseases, such as central nervous system (CNS) inflammatory vasculopathies, is lacking. In a multicenter study, we assessed the frequency of perivenular lesions in MS versus systemic autoimmune diseases with CNS involvement and primary angiitis of the CNS (PACNS).

**Methods:** In 31 patients with inflammatory CNS vasculopathies and 52 with relapsing–remitting MS, 3-dimensional T2\*-weighted and T2–fluid-attenuated inversion recovery images were obtained during a single MRI acquisition after gadolinium injection. For each lesion, the central vein sign was evaluated according to consensus guidelines. For each patient, lesion count, volume, and brain location, as well as fulfillment of dissemination in space MRI criteria, were assessed.

**Results:** MS showed higher frequency of perivenular lesions (median = 88%) than did inflammatory CNS vasculopathies (14%), without overlap between groups or differences between 3T and 1.5T MRI. Among inflammatory vasculopathies, Behçet disease showed the highest median frequency of perivenular lesions (34%), followed by PACNS (14%), antiphospholipid syndromes (12%), Sjögren syndrome (11%), and systemic lupus erythematosus (0%). When a threshold of 50% perivenular lesions was applied, central vein sign discriminated MS from inflammatory vasculopathies with a diagnostic accuracy of 100%.

**Interpretation:** The central vein sign differentiates inflammatory CNS vasculopathies from MS at standard clinical magnetic field strengths.

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Multiple sclerosis (MS) is characterized by recurrent neurological symptoms beginning in young adulthood, associated with focal lesions scattered in the central nervous system (CNS).<sup>1</sup> Pathologically, white matter (WM) lesions correspond to inflammatory infiltrates that develop around venules.<sup>2,3</sup> These infiltrates (widely known as perivascular cuffs) mainly comprise mononuclear cells that dynamically accumulate, distribute, and evolve in the CNS following recurrent waves of invasion from peripheral blood.<sup>4</sup>

The CNS of young adults may also be targeted by chronic inflammatory vasculopathies. When these vasculopathies involve small vessels, they can result in a range of “MS-like” chronic neurological symptoms and syndromes, characterized by relapsing–remitting or progressive course.<sup>5,6</sup> The parenchymal WM lesions associated with these neurological phenotypes can be visualized by magnetic resonance imaging (MRI) and frequently meet the topographic MRI diagnostic criteria of MS,<sup>7</sup> which cannot distinguish the underlying pathology of the lesions.<sup>8,9</sup> When such cases occur in the context of systemic inflammatory or autoimmune diseases (SADs), MS is excluded on the basis of the diagnostic criterion of “better explanation.”<sup>7</sup> However, an acute neurological syndrome can be the first clinical presentation in SADs, and sometimes MS and SAD can coexist in the same patient.<sup>10</sup> In all these cases, differentiation from MS may be problematic, and a “better explanation” of the diagnosis cannot be invoked.<sup>11,12</sup> In addition, the current standard for diagnosis of inflammatory vasculopathies is brain/meningeal biopsy or angiography,<sup>11,12</sup> but these, unlike MRI, are substantially invasive procedures and are not always diagnostic.<sup>13</sup>

The physical relationship between WM lesions and venules can now be visualized by susceptibility-based MRI sequences, taking advantage of the T2\*-shortening effect of deoxyhemoglobin<sup>14,15</sup> in venous blood.<sup>16</sup> Several studies conducted with 3T and 7T MRI clearly showed that in MS, the association between brain WM venules and lesions (perivenular lesions), also named the “central vein sign,”<sup>17</sup> can be efficiently visualized; in MS, the proportion of lesions that have clear central veins is high.<sup>14,15</sup> These data suggest that high frequency of perivenular lesions is pathologically specific to MS, and therefore this marker is an important candidate for improving MRI diagnostic criteria<sup>14</sup> and for reducing the still too high rate of MS misdiagnosis, with its considerable clinical consequences.<sup>18,19</sup>

Thus far, the central vein sign has been compared primarily between MS and a limited set of other neurological diagnosis, such as migraine and ischemic small vessel disease of the elderly,<sup>20,21</sup> which do not involve

inflammation or autoimmunity similar to MS.<sup>11,12</sup> Proper validation of an MRI marker to improve differential diagnosis between MS and other MS-like neurological syndromes in young adults requires comparison with other inflammatory diseases with CNS involvement. Thus, in this study, the frequency of brain WM perivenular lesions visualized by MRI was compared between MS and SADs, encompassing Behçet disease, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), Sjögren syndrome, and primary angiitis of the CNS (PACNS).

## Patients and Methods

### Patients

Eighty-three consecutive patients diagnosed with either SADs and clinical/MRI evidence of brain involvement, or with PACNS (hereafter both termed “inflammatory vasculopathies”), or with relapsing–remitting MS according to the 2010 McDonald revised criteria,<sup>7</sup> were recruited between January 2015 and June 2017 at 4 academic research hospitals: the Careggi University Hospital (Florence, Italy), the Erasme University Hospital and Brugmann University Hospital (Brussels, Belgium), and the San Raffaele University Hospital (Milan, Italy). The study received approval from ethical standards committees on human experimentation at all centers. Written informed consent was obtained from all participants.

Patients were excluded if contraindicated for MRI or intravenous injection of gadolinium-based contrast material. To avoid problems related to assignment of central veins, patients with extremely high lesion loads (>100 lesions) as well as patients with diffuse leukoencephalopathy with no or few discrete lesions were excluded a priori based on previously available MRI.

Included patients with inflammatory vasculopathies encompassed: (1) SLE, diagnosed according to the Systemic Lupus International Collaborating Clinics classification criteria<sup>22</sup>; (2) APS, diagnosed according to the Miyakis criteria<sup>23</sup>; (3) Behçet disease, diagnosed according to the International Study Group for Behçet’s Disease<sup>24</sup>; (4) Sjögren disease, diagnosed according to the American College of Rheumatology/European League against Rheumatism criteria<sup>25</sup>; and (5) PACNS (imaging or biopsy proven), diagnosed according to Schuster et al.<sup>13</sup>

### MRI Acquisition Protocol

All patients underwent a single brain MRI acquisition. MRI studies were performed on two 3T Philips (Best, the Netherlands) Intera MRI scanners (Brussels and Milan) and a 1.5T Philips Achieva MRI scanner (Florence). For all scans, 3-dimensional (3D) T2\*-weighted echo-planar imaging (EPI) and 3D T2–fluid-attenuated inversion recovery (FLAIR) images were acquired during or after intravenous injection of a single dose (0.1mmol/kg) of gadolinium-based contrast material, as previously described.<sup>26</sup> 3D T2\*-weighted EPI and 3D T2-FLAIR sequences were identical for the 3T scanners in Brussels

**TABLE 1. MRI Sequence Parameters of 1.5T and 3T MRI Scanners**

Sequence	3D T2*-EPI		3D T2-FLAIR	
Magnet strength, T	1.5	3	1.5	3
Manufacturer	Philips	Philips	Philips	Philips
Model	Achieva	Intera	Achieva	Intera
Receive channels	8	8	8	8
Imaging plane	Sagittal	Sagittal	Sagittal	Sagittal
Imaging resolution, mm	0.8	0.55	1	1
Slices, No.	200	336	180	180
Repetition time, ms	41	53	4,800	4,800
Echo time, ms	22	29	297	373
Inversion time, ms	—	—	1,660	1,600
Flip angle	10°	10°	90°	90°
Averages	2	2	1	1
Acquisition time, min:s	4:24	4:40	5:55	6:00

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

and Milan, but adapted and optimized for the 1.5T scanner in Florence, as previously described (Table 1).<sup>27</sup> Additional routine magnetic resonance images were acquired for clinical use, including T1-weighted sequences.

### MRI Postprocessing and Analysis

Four neurologists, with research training experience in MS imaging and training in central vein sign assessment according to the consensus criteria of the North American Imaging in Multiple Sclerosis (NAIMS) Cooperative,<sup>14</sup> analyzed the data blinded to the diagnosis. Two of them worked on 3T data (P.M., M.A.) and 2 on 1.5T data (L.V., M.G.). Data were collected as DICOM images and processed and visualized using Medical Image Processing, Analysis, and Visualization (MIPAV; NIH; <http://mipav.cit.nih.gov>). FLAIR\* images were generated with the following steps<sup>26</sup>: (1) coregistration between T2-FLAIR and T2\* images, (2) upsampling of the T2-FLAIR image to match the T2\* resolution, and (3) voxelwise multiplication.

For the central vein sign assessment, only discrete brain lesions with a diameter of  $\geq 3$ mm in at least 1 plane were included in the analysis. Small ( $< 3$ mm), confluent, and poorly visible lesions were excluded. On T2\* and FLAIR\* images, lesions were defined as “perivenular” by raters’ consensus agreement (2 reviewers for 3T and 2 reviewers for 1.5T MRI data), according to the NAIMS guidelines,<sup>14</sup> as follows: “(1) the lesion contains a thin hypointense line ( $< 2$  mm diameter) or small hypointense dot that is visible in at least two

perpendicular MRI planes; and (2) the vein, running partially or entirely through the lesion, appears as positioned approximately in the center of the lesion.” Lesions that did not meet these criteria were considered nonperivenular. The frequency of perivenular lesions per patient was expressed as a percentage of the total number of analyzed lesions.

For each patient, additional lesion morphological features were recorded: (1) brain location (periventricular, juxtacortical/leukocortical, subcortical/deep WM, or infratentorial), (2) lesion volume (manual segmentation using MIPAV), and (3) gadolinium enhancement.

Finally, for each patient, fulfillment of MS MRI criteria for dissemination in space was assessed, respectively, according to Polman et al<sup>7</sup> and Filippi et al.<sup>28</sup> We dichotomized patients as overall perivenular positive versus perivenular negative based on the highest frequency of perivenular lesions observed in the vasculopathy group. Similarly, we also dichotomized patients based on 3 previously published suggested criteria: (1) the “40% rule,” whereby a threshold of 40% perivenular lesions distinguishes MS from non-MS<sup>17</sup>; (2) the “6-lesion rule,” whereby 10 lesions are randomly assessed and MS is diagnosed if at least 6 lesions are perivenular<sup>20</sup>; and (3) the “3-lesion rule,” whereby 3 lesions are randomly assessed and MS is diagnosed if these 3 lesions are perivenular.<sup>29</sup>

### Statistical Analysis

Demographic, clinical, and MRI differences in patients with inflammatory vasculopathies versus MS were assessed with Mann–Whitney *U* test and Fisher exact test, when appropriate. Mean differences in lesion location proportion between groups were assessed with a 2-way repeated measures analysis of variance with interaction, where brain lesion location was the within-subject factor and group was the between-subject factor; probability values were adjusted for post hoc comparisons (Bonferroni).

## Results

### Clinical Data

Clinical and demographic characteristics of inflammatory vasculopathy ( $n = 31$ ) and relapsing–remitting MS ( $n = 52$ ) patients are reported in Table 2. The 2 groups were comparable for sex and disease duration. As expected, in patients with inflammatory vasculopathies, there was a higher frequency of seizures, systemic vascular events/stroke, and headache (Fisher exact test,  $p < 0.0001$ ). Cerebrospinal fluid data were available in 10 of the 31 inflammatory vasculopathy cases and in 47 of 52 MS cases; as expected, oligoclonal bands were more frequently detected in MS patients (see Table 2). None of the patients with inflammatory vasculopathies presented with spinal cord (or optic nerve) syndromes or with radiological signs typical of neuromyelitis optica (NMO) spectrum disorder (NMOSD). NMO IgG was tested in 1 of these patients (a case of Sjögren disease), resulting negative.

TABLE 2. Demographic and Clinical Features

Feature	Inflammatory Vasculopathies	MS	Statistical Comparison
Patients, No.	31	52	—
Median age (range)	45 (27–70)	41 (20–65)	Mann–Whitney $p = 0.02$
Sex, F/M	20/11	34/18	n.s.
Clinical data			
Clinical diagnosis	9 SLE, 10 Behçet, 2 Sjögren, 7 APS, 3 PACNS	52 RRMS	—
Median disease duration, yr (range)	10 (0.5–22)	7.7 (0.5–39)	n.s.
Median EDSS (range)	1 (0–3)	2 (0–4)	Mann–Whitney $p = 0.003$
Median mRS (range)	1 (0–2)	1 (0–2)	n.s.
MMSE < 24	0%	0%	n.s.
Focal neurological symptoms	39%	67%	Fisher $p = 0.0001$
History of seizures	29%	4%	Fisher $p < 0.0001$
History of systemic vascular events or stroke	39%	0%	Fisher $p < 0.0001$
History of headache	55%	12%	Fisher $p < 0.0001$
OCB presence, No. (%)	1/10 available (10%)	46/47 available (98%)	Fisher $p < 0.0001$

SLE= systemic lupus erythematosus; APS = antiphospholipid antibody syndrome; PACNS = primary angiitis of the central nervous system; RRMS = relapsing–remitting MS; EDSS = Expanded Disability Status Scale; F = female; M = male; MMSE = Mini-Mental State Examination; mRS = modified Rankin Scale; n.s. = not significant; OCB = oligoclonal band.

### Lesion Counts and Brain Location

The median number of brain WM lesions per patient did not differ between inflammatory vasculopathies and MS patients (median number = 15, range = 1–93 vs median number = 15, range = 2–66, respectively; Mann–Whitney  $U$  test,  $p = 0.6$ ), whereas the median lesion volume was 34% smaller in inflammatory vasculopathies than in MS ( $122\text{mm}^3$ , range = 15–734 vs  $186\text{mm}^3$ , range = 29–943; Mann–Whitney  $U$  test,  $p = 0.048$ ). Fewer patients with inflammatory vasculopathies (2 of 31 patients, 6%) had contrast-enhancing lesions than MS patients (11 of 52 patients, 21%).

The topographical distribution of brain lesions is shown in Figure 1. As expected, a significantly higher relative frequency of subcortical/deep WM lesions was observed in inflammatory vasculopathies than in MS ( $p < 0.0001$ ); conversely, periventricular lesions were more frequent in MS than in inflammatory vasculopathies ( $p < 0.0001$ ). However, there was a great deal of overlap between diagnostic groups. No differences in

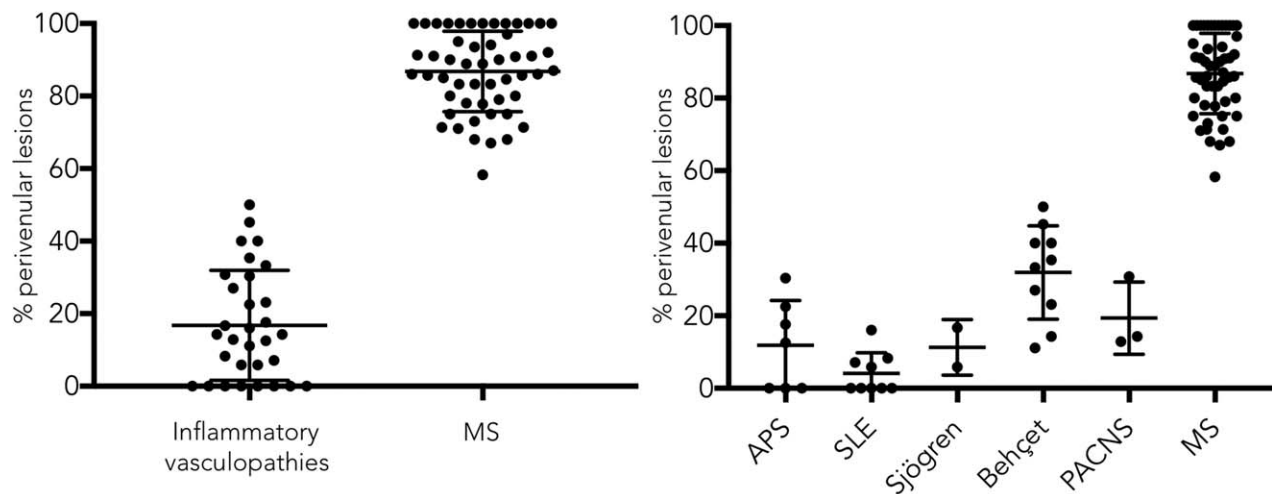
juxtacortical/leukocortical and infratentorial lesion frequency were observed between the 2 groups. The regional lesion distribution among patients with at least 1 lesion per brain location did not significantly differ between groups (chi-square test,  $p = 0.18$ ).

### Central Vein Sign Assessment

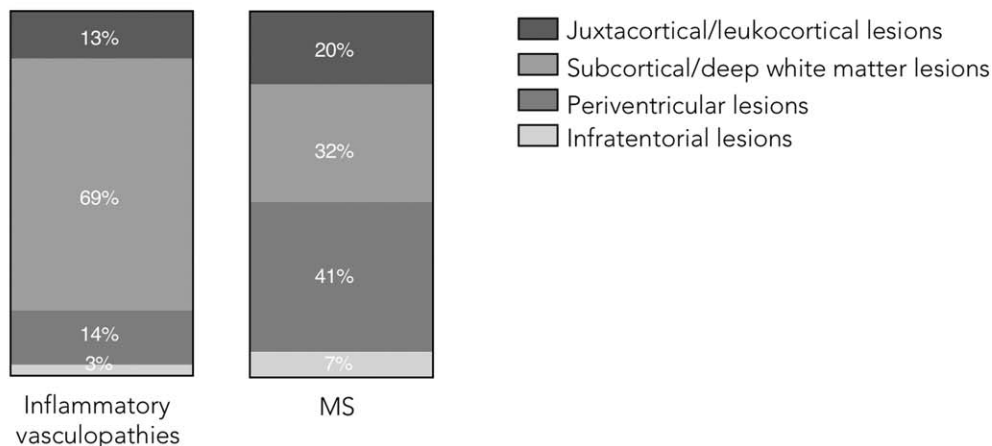
The frequency of perivenular lesions was remarkably higher in MS (median = 88%, range = 58–100%) versus inflammatory vasculopathies (14%, 0–50%; Mann–Whitney  $U$  test,  $p < 0.0001$ ; see Fig 1). The separation between the 2 groups based on perivenular lesion frequency was complete (>50% perivenular lesions threshold, hereafter referred as the “50% rule”).

The frequency of perivenular lesions within groups did not differ significantly between 1.5T and 3T MRI (median = 88%, range = 67–100% and median = 85%, range 58–100%, respectively, in MS; median = 18%, range = 0–50% and median = 14%, range 0–40%, respectively, in inflammatory vasculopathies).

## Central vein sign assessment



## Topographical distribution of brain lesion frequency



**FIGURE 1:** Frequency of perivenular lesions and topographical distribution of brain lesions in inflammatory vasculopathies and multiple sclerosis (MS). APS = antiphospholipid syndrome; PACNS = primary angiitis of the central nervous system; SLE = systemic lupus erythematosus.

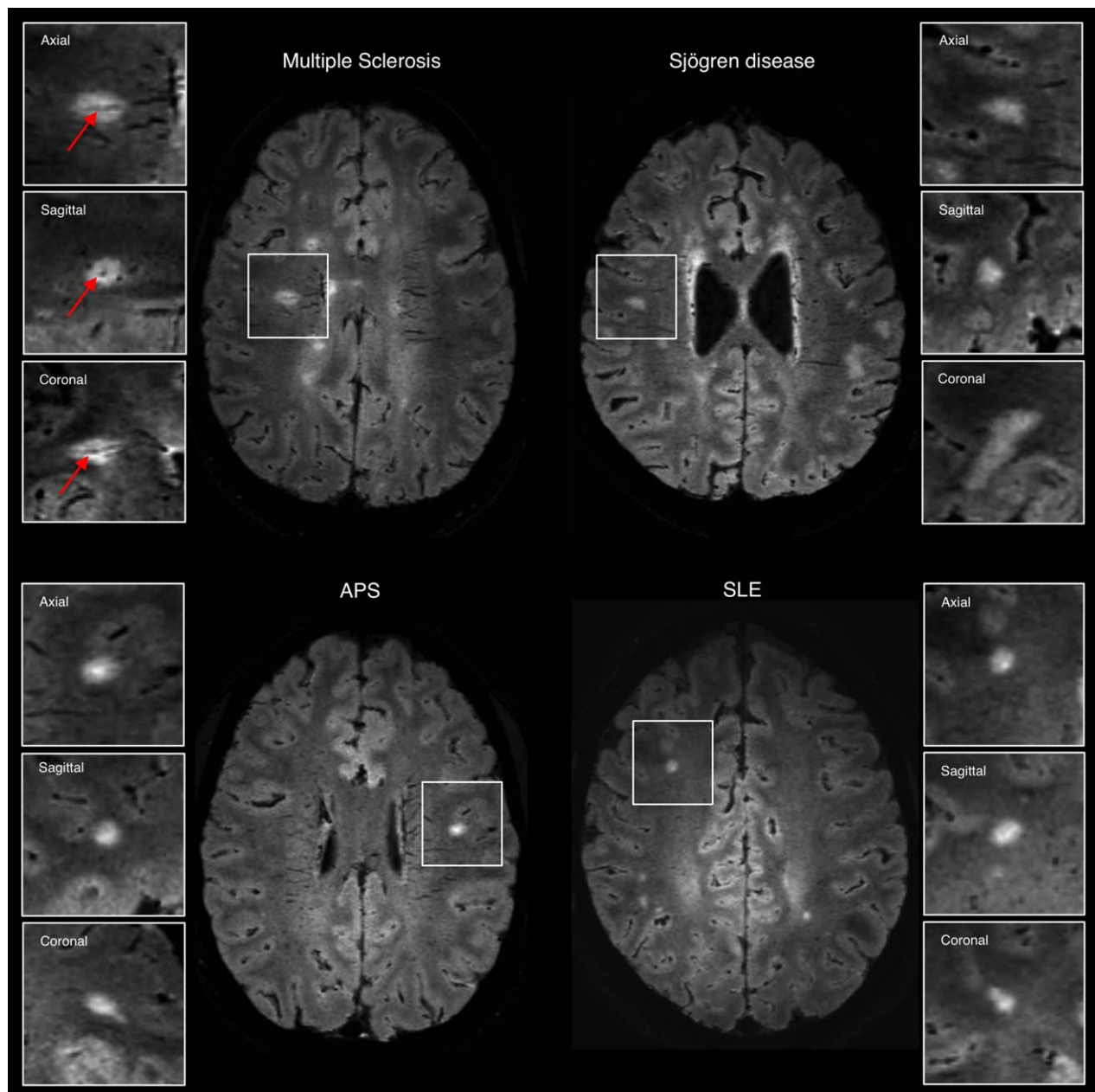
Among inflammatory vasculopathies, Behçet disease showed the highest frequency of perivenular lesions (median = 34%, range = 11–50%), followed by PACNS (median = 14%, range = 13–31%), APS (median = 12%, range = 0–30%), Sjögren (median = 11%, range = 6–17%), and SLE (median = 0%, range = 0–16%; Figs 1–5).

When patients were dichotomized based on the 40% rule (presence of  $\geq 40\%$  perivenular lesions),<sup>17</sup> all MS patients were perivenular-positive versus only 4 patients with vasculitis (all Behçet disease cases; Fisher exact test,  $p < 0.0001$ ; Table 3). The 50% rule and the 40% rule showed higher diagnostic accuracy in comparison to the 6-lesion rule<sup>20</sup> and the 3-lesion rule.<sup>29</sup> Diagnostic specificity, sensitivity, and accuracy are shown in Table 3.

### Fulfillment of MRI Dissemination in Space MS Diagnostic Criteria

Table 3 compares the fulfillment of MRI dissemination in space MS diagnostic criteria, according to Polman et al<sup>7</sup> and the more recent MAGNIMS criteria (Filippi et al).<sup>28</sup> As a caveat, the analysis focused only on brain lesions, neglecting the contribution of both spinal cord (cord MRI was not available for all patients) and optic nerve (relevant for the MAGNIMS criteria) lesions. The addition of the 40% rule to Polman and to Filippi criteria, respectively, increased the specificity, without decreasing the sensitivity, of current dissemination in space MRI criteria (see Table 3). Similarly, the addition of the 6-lesion rule or 3-lesion rule to Polman 2011 and to





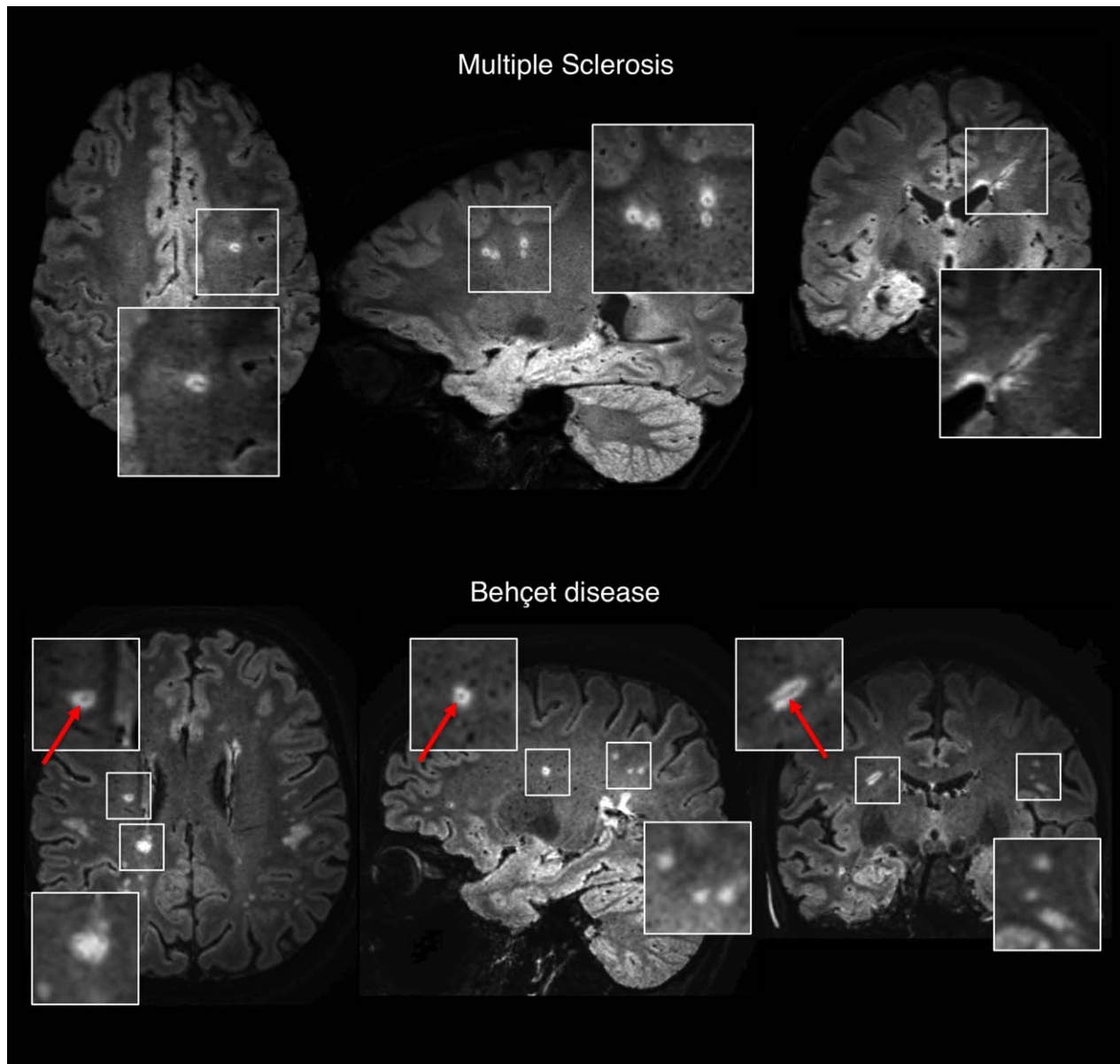
**FIGURE 2:** Representative axial 3T FLAIR\* images from individuals with relapsing–remitting multiple sclerosis (MS; 27-year-old woman), Sjögren disease (46-year-old woman), antiphospholipid antibody syndrome (APS; 37-year-old man), and systemic lupus erythematosus (SLE; 38-year-old woman). The central vein sign (arrows) is present in the majority of MS lesions but is not typical of white matter lesions in inflammatory vasculopathies. Boxes show magnified views of lesions in the 3 orthogonal planes for central vein assessment. [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

Filippi 2016 criteria, respectively, increased the specificity, but did not dramatically change the overall diagnostic accuracy, of current dissemination in space MRI criteria (see Table 3).

#### **Central Vein Sign Assessment in MS-Mimicking Inflammatory Vasculopathies**

Among the 31 patients with inflammatory vasculopathies, 15 satisfied the MRI dissemination in space MS

diagnostic criteria (Polman et al<sup>7</sup>) and had no history of previous stroke. When this MS-mimicking inflammatory vasculopathy population was compared to the MS group, the results were overall similar to those reported above. In particular, the frequency of perivenular lesions in the MS-mimicking inflammatory vasculopathy population remained significantly lower compared to MS, maintaining no distribution overlap between groups (median = 23%, range = 0–50%; Mann–Whitney *U* test,  $p < 0.0001$ ).

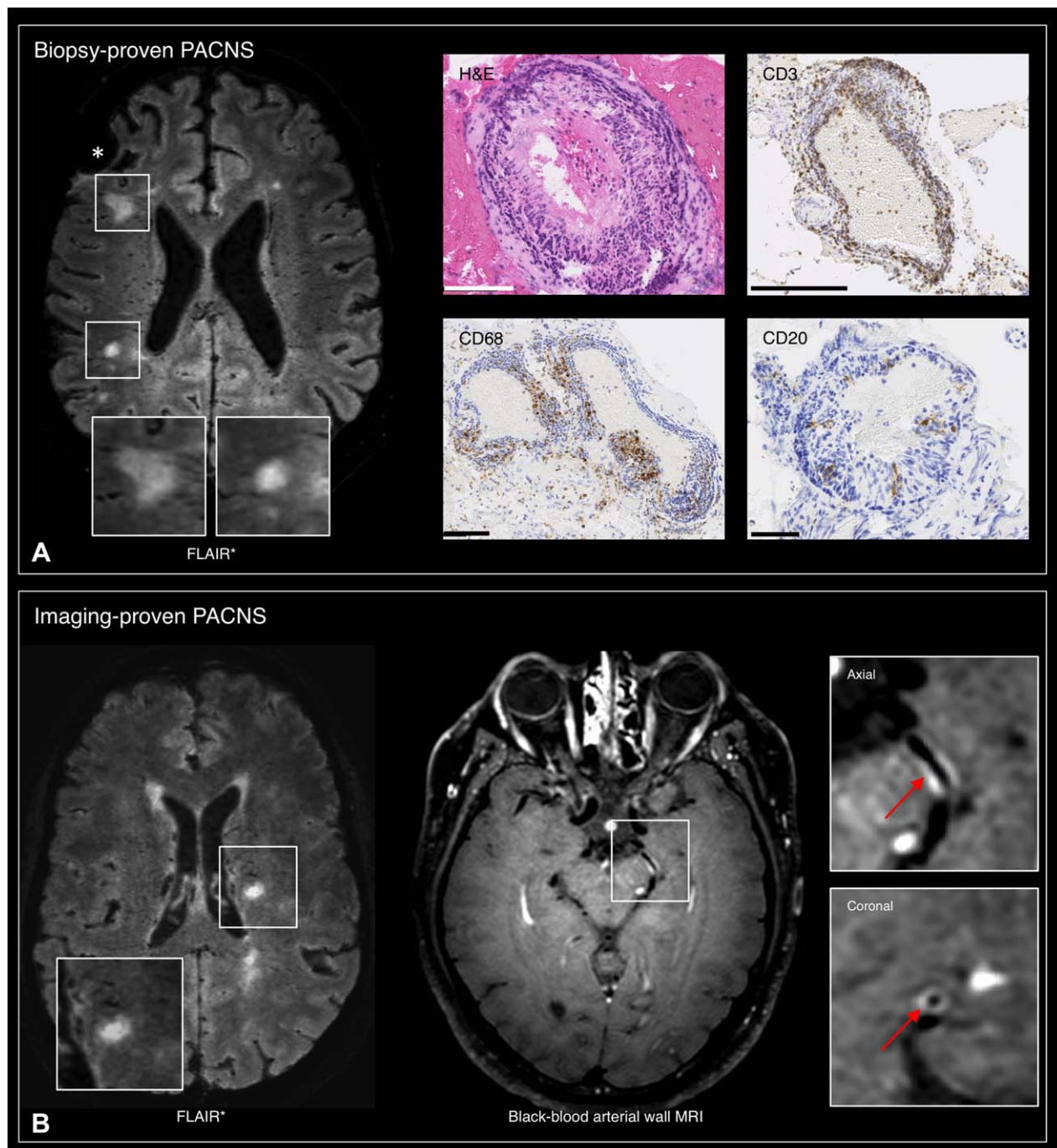


**FIGURE 3:** Axial, sagittal, and coronal 3T FLAIR\* images from individuals with relapsing–remitting multiple sclerosis (MS; 30-year-old woman; top) and Behçet disease (42-year-old woman; bottom), respectively. Perivenular MS-like lesions (arrows) can be seen in Behçet disease. Magnified views of representative lesions are displayed in the boxes. [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

## Discussion

The main finding of this multicenter study is that central vein assessment, provided by susceptibility-based MRI, significantly improves the differential diagnosis between MS and inflammatory vasculopathies involving the CNS. Specifically, the central vein sign alone or in combination with available MS diagnostic MRI criteria<sup>7,28</sup> improves the diagnostic accuracy and specificity, without lowering the sensitivity, of MS diagnosis. Assessments were performed on standard clinical magnetic field strength systems, and results at 3T and the more widely available 1.5T were indistinguishable.

Our findings are particularly relevant considering that CNS inflammatory vasculopathies can present with a chronic relapsing or progressive (MS-like) clinical course and often feature brain WM abnormalities indistinguishable from those observed in MS.<sup>10</sup> Moreover, the diagnosis of CNS inflammatory vasculopathies remains challenging due to the lack of well-defined diagnostic criteria and to the relatively high risk and limited accuracy of the available diagnostic techniques (biopsy and/or angiography), especially when involvement is limited to small vessels. Remarkably, despite some differences in brain lesion size (usually smaller) and location (mainly

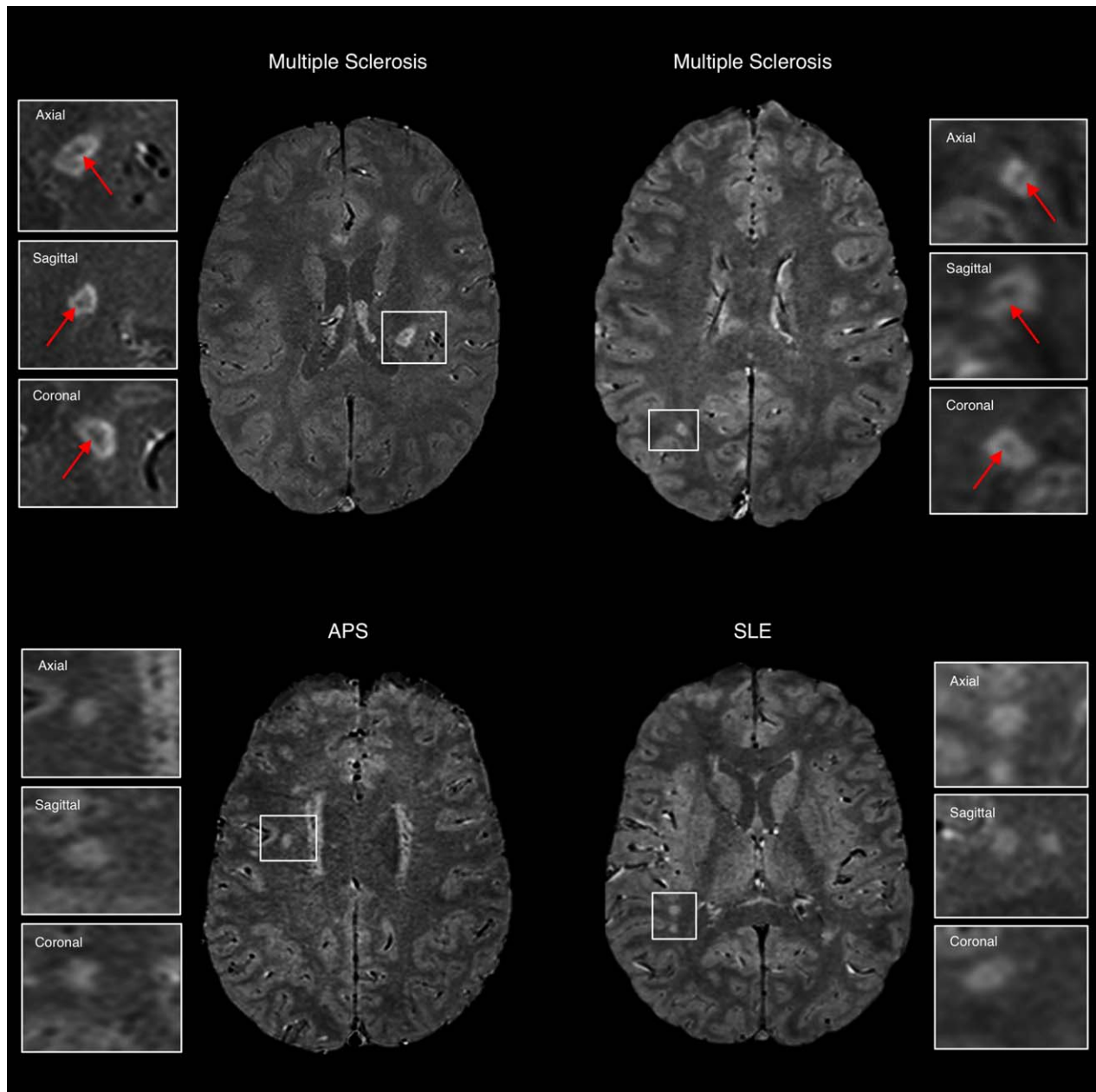


**FIGURE 4:** Axial 3T FLAIR\* images showing the presence of nonperivenular parenchymal lesions in 2 patients with primary angiitis of the central nervous system (PACNS). (A) Biopsy-proven PACNS (57-year-old man; biopsy of the right frontal lobe and overlying leptomeninges, asterisk). The histopathology shows the presence of a vasocentric, transmural, multilayer inflammatory infiltrate (predominantly T lymphocytes) involving both the leptomeningeal and parenchymal arterioles. Scale bars: hematoxylin & eosin (H&E), 100  $\mu\text{m}$ ; CD3 (T lymphocytes), 250  $\mu\text{m}$ ; CD68 (macrophages), 100  $\mu\text{m}$ ; CD20 (B lymphocytes), 50  $\mu\text{m}$ . (B) Imaging-proven PACNS (48-year-old man). Vessel-wall enhancement (arrows) of the left posterior and left middle cerebral artery is demonstrated using black-blood arterial wall magnetic resonance imaging (MRI).

subcortical), the two disease groups cannot be efficiently discriminated by these radiological markers. A large proportion of our inflammatory vasculopathy patients fulfilled the dissemination in space MRI criteria for MS (52% and 26% using Polman and Filippi 2016, MAGNIMS criteria, respectively<sup>7,28</sup>).

What is the value of adding the central vein assessment to the diagnostic workup? We found that the percentage of perivenular lesions was higher in every MS case than in any of the inflammatory vasculopathy cases, rendering the diagnostic accuracy of this marker outstanding. However, although the previously proposed





**FIGURE 5:** Representative axial 1.5T T2\* echo-planar images from individuals with relapsing–remitting multiple sclerosis (MS; 55-year-old and 24-year-old women), antiphospholipid antibody syndrome (APS; 51-year-old woman), and systemic lupus erythematosus (SLE; 40-year-old woman). The central vein sign (arrows) is present in the majority of MS lesions but is not typical of white matter lesions in inflammatory vasculopathies. Boxes show magnified views of lesions in the 3 orthogonal planes for central vein assessment. [Color figure can be viewed at [www.annalsofneurology.org](http://www.annalsofneurology.org)]

40% rule can differentiate MS from small vessel ischemic disease with high specificity and accuracy,<sup>17</sup> in our cohort 4 inflammatory vasculopathy patients (all with Behçet disease) had  $\geq 40\%$  perivenular lesions. Based on these results, we propose a new 50% rule for the workup of MS versus vasculitis. In this setting, the 50% rule performed better than other proposed criteria, namely the 6-lesion and 3-lesion rules,<sup>20,29</sup> which avoid the requirement for analysis of every single lesion. In our cohort, those criteria, relative to the Polman or Filippi 2016

MAGNIMS criteria for MS,<sup>7,28</sup> had better specificity but worse sensitivity for MS diagnosis.

Although the perivenular topography of MS lesions is well known and is considered a pathological hallmark of the disease, much less is known about the perivascular nature of parenchymal WM lesions in inflammatory vasculopathies. The immunopathogenesis of MS lesion formation is believed to follow a classical inflammatory cascade, where primed lymphocytes and monocytes crawl and extravasate at the venular side of the

TABLE 3. Fulfillment of Different MRI Criteria and Diagnostic Test Evaluation

Variables	Inflammatory Vasculopathies, No. (%) of Patients Fulfilling Criteria	Multiple Sclerosis, No. (%) of Patients Fulfilling Criteria	Diagnostic Test Evaluation		
			Sensitivity	Specificity	Accuracy
Perivenular lesion criteria					
50% perivenular rule	0/31 (0%)	52/52 (100%)	100%	100%	100%
40% perivenular rule	4/31 (13%)	52/52 (100%)	100%	94%	95%
6-lesion rule	9/31 (29%)	44/52 (85%)	85%	71%	79%
3-lesion rule	15/31 (48%)	51/52 (98%)	98%	52%	81%
Dissemination in space MRI criteria					
Polman 2011 <sup>7</sup>	16/31 (52%)	49/52 (94%)	94%	48%	77%
Filippi 2016 <sup>28</sup>	8/31 (26%)	47/52 (90%)	90%	74%	84%
Combined criteria					
Both Polman and 40% perivenular rule	3/31 (10%)	49/52 (94%)	94%	90%	93%
Both Filippi and 40% perivenular rule	0/31 (0%)	47/52 (90%)	90%	100%	94%
Both Polman and 6-lesion rule	7/31 (23%)	42/52 (81%)	81%	77%	76%
Both Polman and 3-lesion rule	11/31 (36%)	48/52 (92%)	92%	64%	82%
Both Filippi and 6-lesion rule	3/31 (10%)	41/52 (79%)	79%	90%	83%
Both Filippi and 3-lesion rule	6/31 (19%)	46/52 (88%)	88%	81%	85%

MRI = magnetic resonance imaging.

microcirculation, perhaps due in part to lower hemodynamic shear pressure on the venous side. As a consequence, inflammatory demyelination spreads in the parenchyma surrounding small parenchymal venules.<sup>30,31</sup> Conversely, in both CNS-isolated and systemic inflammatory vasculopathies, the pathogenic mechanism of the parenchymal WM lesions is different from MS. These inflammatory conditions affect medium and small vessels, usually arteries, and are pathologically characterized by inflammatory infiltrates of the vessel wall, fibrinoid necrosis, and thrombosis with ischemic damage of the CNS parenchyma.<sup>32</sup> Microthromboembolic events and accelerated small vessel disease have also been extensively described and are thought to contribute to chronic ischemic damage occurring at the arteriolar side of cerebral microcirculation.<sup>11,33,34</sup>

In our cohort, among all the inflammatory vasculopathies, patients with Behçet disease showed the highest frequency of perivenular brain lesions (range = 11–50%).

This is not surprising; previous pathological observations reported that inflammation, in Behçet disease, can involve both arteries and veins and that, similarly to MS, brain parenchymal damage can be associated with perivenular lymphocyte cuffing.<sup>35</sup> Based on the limited available data, a differential diagnosis based on the presence of perivenular lesions should be applied cautiously in Behçet disease.<sup>36</sup>

Of note, the perivenular lesion frequency observed in the subgroup of inflammatory vasculopathies fulfilling the McDonald MRI criteria for MS<sup>7</sup> and without any history of stroke events, was significantly lower compared to MS. Thus, even in this challenging clinical scenario, the separation between the two groups based on the perivenular imaging biomarker remained complete. This is particularly relevant because misdiagnosis is frequent in this subset of patients and becomes even more frequent when the vasculopathic process is confined to the CNS (PACNS).<sup>5,6,9</sup> Based on our results, we can speculate

that the central vein sign may help in the clinical workup of PACNS patients presenting with an MS-like clinical course.

This study presents some limitations. Our analysis was limited to the brain and did not consider the spinal cord in the assessment of dissemination in space MRI criteria for MS. Of note, in vivo imaging reports of the central vein sign in the spinal cord are lacking, due in part to the challenge of obtaining high-quality T2\*-weighted images of the cord.<sup>14</sup> Patients with primarily confluent lesions were excluded from the study, and therefore it may not be possible to generalize our results to such patients. In addition, in most of the inflammatory vasculopathy patients, possible co-occurrence of NMO-SD was excluded only by the absence of typical syndromes or MRI characteristics and not by NMO-Ig testing. Another limitation relies on the clinical applicability of the 50% rule proposed here. Although in our cohort the diagnostic accuracy was outstanding, applying this rule requires time-consuming lesion counting and frequency estimation, both of which are difficult to implement in a clinical setting. In addition, our results concern a specific clinical setting (ie, MS vs CNS inflammatory vasculopathies), and the 50% rule proposed here may apply differently in terms of diagnostic accuracy when dealing with other specific clinical situations (incidental WM lesions, small vessel disease, migraine).

In conclusion, the central vein assessment provided by susceptibility-based MRI is a useful tool when attempting to differentiate MS from inflammatory vasculopathies involving the CNS. These latter conditions are sometimes difficult to diagnose accurately, as they can have clinical and radiological presentations very similar to MS. Thus, when evaluating patients with chronic brain inflammatory conditions, the addition of the central vein sign assessment to the existing clinical and radiological workup can reduce the risk of misdiagnosis and aid therapeutic strategies. Moreover, considering the availability of this kind of assessment at clinical field strength (including 1.5T MRI scanners), future implementation of automated imaging postprocessing techniques (ie, automated FLAIR\* reconstruction and central vein sign detection) should allow direct translation of the central vein sign into the everyday clinical practice.

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## Author Contributions

Conception and design of the study: P.M., M.A., L.M. Acquisition and analysis of data: P.M., M.A., M.G., L.V., G.E., G.C., G.S., A.B., A.M.R., L.E., D.P., V.M., R.S., N.S., G.P., P.S., B.D. Drafting the text and/or preparing the figures: P.M., M.A., L.V., D.S.R., M.F., L.M.

## Potential Conflicts of Interest

Nothing to report.

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