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Prevalence of the Central Vein Sign on Susceptibility-Weighted Imaging in People With Pediatric-Onset Multiple Sclerosis

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Abstract

Background and Objectives

Given the high sensitivity but only moderate specificity of current diagnostic criteria for multiple sclerosis (MS), novel diagnostic biomarkers for pediatric-onset MS (POMS) are highly warranted. The central vein sign (CVS) is a such promising MRI biomarker candidate that has been shown to distinguish MS from other neuroimmunologic diseases with high specificity. The aim of this study was to assess the prevalence of the CVS in POMS under real-world conditions by analyzing T2-hyperintense lesions using 1.5T susceptibility-weighted imaging (SWI).

Methods

We retrospectively reviewed clinical MRI scans acquired at 1.5T in patients with POMS based on International Paediatric Multiple Sclerosis Study Group criteria and 2017 McDonald criteria at first clinical presentation. Each examination included (1) fluid-attenuated inversion recovery in sagittal, axial, or coronal plane and (2) SWI sequences obtained in the axial plane. Lesions with diameters >3 mm were assessed for CVS according to the North American Imaging in Multiple Sclerosis Cooperative criteria, and Select6* criteria were applied in every patient by 2 experienced raters.

Results

We assessed 31 POMS patients (mean age 13.8 ± 2.6 years; 81% female) with 4 children initially diagnosed as patients with radiologically isolated syndrome (RIS). In total, 535 of 605 T2-hyperintense cerebral lesions were assessable for CVS evaluation, corresponding to a median number of 14 (IQR: 6–21], range 2–57) lesions per patient adequate for CVS assessment. Most lesions were characterized as periventricular (n = 201 [37.6%]), while 20 cortical lesions (3.7%) were detected. The median individual CVS percentage per patient was 75% (IQR: 70%–82%). All POMS patients exhibited a CVS percentage above 40% and fulfilled Select6* criteria, including those investigated at the time of RIS.

Discussion

CVS was frequently observed in T2-hyperintense lesions of patients with POMS, consistent with the proposed MS-specific Select6* criteria and above the 40% cutoff, despite the use of heterogeneous MRI protocols at 1.5T under real-world clinical conditions. SWI at 1.5T may therefore hold the potential to increase the specificity of MS diagnostic criteria also in pediatric patients.

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Supplementary Material

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Glossary

CVS = central vein sign; **FLAIR** = fluid-attenuated inversion recovery; **IPMSSG** = international paediatric multiple sclerosis study group; **mIP** = minimum intensity projection; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG antibody-associated disease; **MS** = multiple sclerosis; **NAIMS** = North American Imaging in Multiple Sclerosis Cooperative; **OCB** = oligoclonal band; **POMS** = pediatric-onset MS; **RIS** = radiologically isolated syndrome; **SWI** = susceptibility-weighted imaging; **TE** = echo time.

Introduction

Despite the application of modern neuroimaging techniques and CSF investigations, the diagnosis of pediatric-onset multiple sclerosis (POMS) remains challenging.[1] The 2017 McDonald criteria for MS[2] are characterized by a high sensitivity but only moderate specificity at the time of incident demyelinating attack when applied to real-life pediatric cohorts.[3] Therefore, novel diagnostic imaging markers for the early and accurate identification of POMS are highly warranted.

The central vein sign (CVS) is a promising MRI diagnostic marker that has been shown to reliably distinguish MS from other neuroimmunologic diseases with high specificity.[4,5] The CVS directly reflects MS pathophysiology, which is characterized by inflammation surrounding small cerebral veins.[6] Previous investigations using immunohistochemistry and pathology have consistently shown that MS lesions develop around small veins,[7] leading to the formation of the CVS on MRI.[4] The North American Imaging in MS North American Imaging in Multiple Sclerosis Cooperative (NAIMS) criteria have standardized the evaluation of the CVS in MS diagnosis, emphasizing its importance in clinical practice.[4] Indeed, the currently proposed revision of the McDonald criteria for adults includes the CVS as an optional parameter to increase the specificity of MS diagnosis.[8]

Imaging studies at 7T and 3T have reported a high CVS prevalence differentiating MS from important differential diagnoses, including neuromyelitis optica spectrum disorder,[9,10] myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease (MOGAD),[11] cerebral vasculitis,[12,13] Susac syndrome,[14] and small vessel disease.[15,16] A "40% cutoff value" has frequently been proposed, suggesting patients with MS to exhibit CVS positivity in ≥40% of lesions.[4,15] The Select6* criteria represent an alternative approach defined by the presence of 6 or more lesions demonstrating the CVS, or when fewer than 6 total lesions are present, most lesions exhibiting a central vein.[15] Recent applications of these criteria have demonstrated excellent diagnostic performance, with high sensitivity and specificity for MS.[13,17]

Using susceptibility-weighted imaging (SWI) sequences, CVS identification is now also feasible at lower field strengths (i.e., 1.5T MRI), which is more commonly available in routine clinical practice. However, data on CVS frequency in MS at 1.5T MRI are still scarce with only a few studies conducted in exclusively adult MS populations reporting CVS frequencies ranging from 40.9% to 65.6%.[18-20] Furthermore, only few studies investigated the frequency of the CVS in white matter lesions of children with POMS under real-world clinical conditions at 1.5T. Here, we retrospectively assessed CVS frequency and distribution in a pediatric MS patient cohort using SWI MRI at 1.5T.

Methods

Participants

Patients were retrospectively recruited from the neuroimaging database of Children's Hospital Datteln, Witten/Herdecke University, Datteln, Germany. Inclusion criteria were (1) established diagnosis of POMS according to the criteria of the International Paediatric Multiple Sclerosis Study Group (IPMSSG)[21] and the revised 2017 McDonald criteria for MS,[2] (2) cerebral MRI at 1.5T including fluid-attenuated inversion recovery (FLAIR) and SWI sequences at first clinical presentation before administration of methylprednisolone therapy, and (3) clinical data on the POMS diagnosis. All patients (31/31) underwent testing for MOG antibodies as part of the diagnostic workup to exclude MOG-associated disease. In addition, aquaporin-4 (AQP4) antibody testing was performed in a clinically indicated subset of patients (7); in all cases, the results were negative. CSF oligoclonal bands (OCBs) testing results were available in 30 of 31 patients and were positive in 29 of 30 (96.7%). We used the Standards for Reporting of Diagnostic Accuracy Studies (STARD) reporting guidelines as reporting checklist for the diagnostic test study.[22]

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethics Committee of the University Witten/Herdecke, Germany, and was performed in accordance with The Code of Ethics of the World Medical Association (1964 Declaration of Helsinki) in its currently applicable version. All caregivers gave written informed consent.

MRI Acquisition

MRI studies were performed at first clinical presentation before methylprednisolone treatment in clinical settings at different 1.5T MRI scanners using various sequence protocols. In all cases, MRI was performed within 7 days of symptom onset. Each examination included (1) a FLAIR sequence in at least one (sagittal, axial, or coronal) plane and (2) an SWI

sequence in the axial plane. Owing to the retrospective, real-world nature of the study, SWI at 1.5T was performed using in-house protocols with varying acquisition parameters. Previous studies have suggested that longer TEs (>25 ms) may enhance the visualization of susceptibility effects from venous structures at 1.5T, thereby improving CVS detection. It was suggested that maximum visibility of veins might occur with a TE of around 46 msec at 1.5T (while being 23 ms at 3.0T and 9.8 msec at 7.0T).[23] TE applied in the protocols used in our study ranged from 35 ms (n = 9 patients) to 40 ms (n = 22 patients), that is, they were close to the proposed optimal TE. Detailed sequence parameters for every acquisition are listed in eTable 1. SWI images were postprocessed with the minimum intensity projection (mIP) algorithm in the axial plane with a slice thickness of 3–10 mm to improve visualization of the "signal void" of the vessel structures.

Image Analysis and Lesion Assessment

Retrospective image analysis was performed using Horos medical image viewer (version 4.0.0) by 2 experienced raters (J.K., C.F.) in consensus. Both raters were agnostic to the patients' clinical presentation, disability, and demographic characteristics at the time of image evaluation. Lesions were assessed for the presence of CVS according to the standard radiologic definition established in the NAIMS guidelines.[4] In detail, all T2-hyperintense lesions with diameter >3 mm were electronically flagged and were reviewed and compared together with the corresponding lesions seen on the axial SWI sequence. The SWI images were then evaluated for the presence or absence of a venous structure within the lesions. The criteria for identification of a central vein in a lesion included (1) a thin hypointense line or small hypointense dot on SWI; (2) visualization in at least 2 perpendicular MRI planes, appearing as a thin line in at least 1 plane; (3) a small apparent diameter (<2 mm); and (4) central positioning within the lesion. In controversial cases, mIP was used to assess the continuity of the hypointense linear structure with the rest of the veins, as previously reported.[19] Lesions were excluded from CVS classification (1) when they were less than 3 mm in diameter in any plane and (2) when they appeared as confluent lesions (merged with at least one other lesion). Select6* criteria were applied to all MRI scans, as previously published.[15,24] For Select6*, experts rated a scan as CVS-positive if there were ≥6 morphologically characteristic lesions with central veins, or if there were <6 morphologically characteristic lesions, but CVS-positive lesions outnumbered CVS-negative lesions. If neither condition was met, the scan was rated as Select6* negative. In addition to CVS rating, lesions were classified based on their localization as (1) periventricular, (2) juxtacortical, (3) subcortical, (4) deep white matter, (5) deep gray matter, (6) cerebellar, (7) brainstem, and (8) cortical lesions.

Statistical Analysis

Statistical analysis was performed using *R* (version 4.2.1). The proportion of CVS-positive lesions was calculated for each patient and averaged across the cohort. In addition, CVS frequency was calculated for each lesion localization subset. To explore potential predictors of CVS positivity, a series of univariate and linear regression analyses and multivariate analyses were performed using variables grouped into 3 main categories: demographic, lesional, and clinical factors (eAppendix 1). Data are presented as percentages and mean ± SD.

Data Availability

The individual deidentified participant data underlying this study will not be made publicly available due to ethical and legal restrictions in accordance with the terms of the ethics committee approval and participant consent. No additional study documents (e.g., protocol, statistical analysis plan) will be shared. Only the aggregated, anonymized data results—as presented in the main article and Supplementary Material—are available for public access.

Results

Demographic and Clinical Characteristics

We retrospectively assessed clinical MRI scans from 31 patients obtained as part of the diagnostic procedures during the first clinical event (mean age 13.8 ± 2.6 years; 81% female; Table 1). Among these, 4 children were initially diagnosed with radiologically isolated syndrome (RIS) at the time of image acquisition and all 4 children were later developing POMS based on IPMSSG criteria and 2017 McDonald criteria for MS.

CVS Frequency Analysis

A total of 70 of 605 brain T2-hyperintense lesions (11.6%) were excluded from CVS classification based on the NAIMS exclusion criteria.[4] Consequently, 535 lesions (88.4%) were assessable for CVS classification across the cohort (eTable 2). On a patient level, the median number of excluded lesions was 1 (IQR: [0; 3], range: 0–16), resulting in a median of 14 lesions (IQR: [6; 21], range: 2–57) per patient available for CVS assessment (Table 1). The median individual CVS percentage per patient was 75% (IQR: 70%–82%; range: 60%–100%) (Table 2). All POMS patients exhibited a CVS percentage above 40% (Figure 1), and fulfilled Select6* criteria, including those investigated at the time of RIS (Figure 2 and Figure 3). Regression analyses revealed no significant demographic, lesional, or clinical predictors of individual CVS positivity (eAppendix 1 and eTable 3).

Lesion Distribution Analysis

Most lesions were characterized as periventricular (overall n = 201 [37.6%]; periventricular lesions per patient: median 50%; mean ± SD: 46.4% ± 22.7%), deep white matter lesions (overall n = 100 [18.70%]; deep white matter lesions per patient: median: 14%; mean ± SD: 13.7% ± 11.1%), and juxtacortical lesions (overall n = 100 [18.7%]; juxtacortical lesions per patient: median: 14%; mean ± SD: 14.1% ± 12.5%). In addition, 20 cortical lesions were detected (overall 3.74%; cortical lesions per patient: median: 0%; mean ± SD: 3.3% ± 6.8%; Table 2 and eTable 2). Patient-level analysis revealed that CVS frequency was highest in deep white matter (median: 100%; mean ± SD: 80.4% ± 30.2%), cerebellar

Table 1 Clinical Cohort Description

	POMS Patients
Patient Demographics	
Number (n)	31
Age (y; mean ± SD)	14 (6–17)
Sex (f; %)	25 (80.6)
Diagnostic Characteristics, (%)	
POMS diagnosis at the time of acquisition	27/31 (87.1)
RIS diagnosis at the time of acquisition	4/31 (12.9)
MOG-antibody positivity	0/31 (0)
AQP4-antibody positivity[a]	0/7 (0)
CSF OCB[b]	29/30 (96.7)
Disease Course, (%)	
Monophasic disease course at the time of scan[c]	19/30 (63.3)
Polyphasic disease course at the time of scan[c]	7/30 (23.3)
Asymptomatic (RIS) at the time of scan[c]	4/30 (13.3)
Clinical Presentation, (%)[d]	
Brainstem syndrome	5/26 (19.2)
Cerebral deficits[e]	9/26 (34.6)
ON	7/26 (26.9)
Cerebral deficits[e] + Brainstem syndrome	5/26 (19.2)
Brain Lesion Characteristics	
Total Lesion Count per patient (TLC; median [IQR], range)	16 (6–25), 3–73
Number of lesions adequate for CVS assessment per patient (median [IQR], range)	14 (6–21), 2–57
Number of lesions excluded for CVS assessment per patient (median [IQR], range)	1 (0–3), 0–16

Abbreviations: AQP4 = aquaporin-4; CSF = CSF; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; OCB = oligoclonal bands; ON = optic neuritis; POMS = pediatric-onset multiple sclerosis; RIS = radiologically isolated syndrome; TM = transverse myelitis.
[a] Includes only participants with known/tested OCB status (7 of 31 patients).
[b] Includes only participants with known/tested OCB status (30 of 31 patients).
[c] Includes only participants with available data on clinical symptoms (30 of 31 patients).
[d] Includes only participants with clinical symptoms at onset—excludes RIS patients (26 of 31 patients).
[e] Includes focal neurologic symptoms attributable to supratentorial brain lesions, such as hemiparesis, hemisensory loss, and visual field defects.

(median: 100%; mean ± SD: 77.5% ± 32.8%), and periventricular (median: 79%; mean ± SD: 77.1% ± 21.2%) lesions, while the frequency was lowest in cortical lesions (median: 50%; mean ± SD: 33.3% ± 35.0%; Table 2).

Discussion

In this study, we retrospectively assessed the presence of CVS in T2-hyperintense POMS lesions using SWI at 1.5T MRI. Our findings demonstrate that CVS is frequently detectable in POMS, consistent with the previously established "40% cutoff rule" and Select6* criteria in adult MS. We found CVS frequency to be highest in lesions with deep white matter (80%), cerebellar (77%), and periventricular (77%) localization, compared with a slightly lower CVS frequency in subcortical (72%) and juxtacortical (72%) lesions, and lowest frequency in cortical (33%) POMS lesions. Taken together, our results show that the CVS holds great potential for inclusion also in pediatric MS diagnostic criteria.

Our findings complement previous studies conducted at 1.5T in adult patients with MS who likewise reported a high prevalence of CVS in MS lesions. A recent 1.5T MRI investigation retrospectively assessed combined information of FLAIR and SWI sequences to compare CVS frequency in 21 patients with MS and 18 patients with a clinical diagnosis of dementia.[18] This study observed CVS in both periventricular lesions (75%) and subcortical lesions (52%) in adult patients with MS, in contrast to a much lower frequency in patients with dementia (14%).[18] Another recent study focused on the detection of CVS at 1.5T SWI in exclusively non–ovoid-shaped atypical lesions with perpendicular extensions to the ventricle in 95 patients with MS and found 65.6% of these atypical lesions to contain venous structures.[19]

By contrast, another report on 19 adult patients with MS showed CVS only in a relatively low proportion of MS lesions (40.9%) at 1.5T SWI MRI, and this frequency was only slightly higher when compared with 19 patients with cerebral small vessel disease (29.3%).[20] Importantly, this frequency (40.9%) was considerably lower compared with the CVS frequency in our current analysis (77.7%) and to other adult MS studies (63%,[18] 66%[19]) at 1.5T. This marked disparity might be related to differences in SWI sequence protocols: Our POMS study and the 2 adult MS studies with high CVS detection rates used longer TE (TEs) of 35–40 ms in contrast to the study with the low CVS rate that used an SWI sequence with a shorter TE of 24 ms.[20] Indeed, it has been shown that SWI sequences with longer TEs compared with shorter TEs of 20–25 ms improve the visualization of susceptibility effects originating from venous structures at 1.5T and it was suggested that maximum visibility of veins might occur with a TE of around 46 msec at 1.5T (while being 23 ms at 3.0T and 9.8 msec at 7.0T).[23] Hence, the longer TE close to the proposed optimal value at 1.5T used in our SWI sequence protocols might account for better visibility and subsequent higher CVS frequency in the MS lesions in our study compared with the previous report.[20] Another factor that might contribute to the differing CVS frequencies between our study and other adult MS studies is the higher prevalence of nonspecific or microangiopathic white matter lesions in adults, which tend to increase with age.[25] These nonspecific white matter lesions are less likely to exhibit a central vein,[26] potentially leading to a lower proportion of CVS-positive lesions in adult MS populations. By contrast, children are naturally less affected by

Table 2 Patient-Level Analysis of Central Vein Sign and Lesion Distribution

	Number of assessable lesions		Percentage of assessable lesions		Percentage of CVS + lesions	
	Median (IQR), min-max	n; mean ± SD	Median (IQR), min-max, (%)	%; mean ± SD	Median (IQR), min-max, (%)	%; mean ± SD
Total assessable lesion count (TLC)	14 (6–21) 2–57	17.26 ± 14.89	100	100	75 (70–82) 60–100	77.65 ± 11.23
Periventricular	6 (3–9) 0–20	6.48 ± 4.61	50 (29–62) 0–100	46.39 ± 22.65	79 (75–90) 0–100	77.06 ± 21.16
Juxtacortical	1 (1–4) 0–20	3.23 ± 4.66	14 (3–21) 0–40	14.14 ± 12.53	83 (58–100) 0–100	71.68 ± 33.53
Subcortical	1 (0–3) 0–10	2.13 ± 2.66	13 (0–17) 0–43	11.91 ± 11.97	93 (58–100) 0–100	71.95 ± 36.20
Deep white matter	2 (0–4) 0–16	3.23 ± 4.24	14 (0–22) 0–40	13.73 ± 11.09	100 (73–100) 0–100	80.41 ± 30.21
Deep gray matter	0 (0–1) 0–2	0.35 ± 0.55	0 (0–4) 0–50	4.40 ± 10.80	100 (63–100) 0–100	75.00 ± 42.49
Cerebellum	0 (0–1) 0–7	0.68 ± 1.40	0 (0–5) 0–20	3.26 ± 5.39	100 (58–100) 0–100	77.49 ± 32.77
Brainstem	0 (0–1) 0–4	0.52 ± 1.03	0 (0–1) 0–33	2.81 ± 6.79	83 (50–100) 0–100	70.83 ± 36.46
Cortical	0 (0–1) 0–4	0.65 ± 1.05	0 (0–5) 0–33	3.37 ± 6.83	50 (0–50) 0–100	33.33 ± 34.96

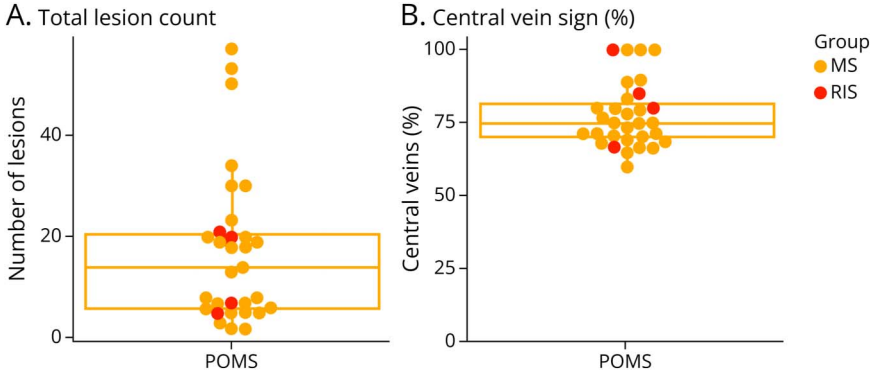
Results are presented as median (interquartile range and minimum/maximum range) and as mean ± SD for the number of lesions, the percentage of assessable total lesion count (TLC), and the percentage of CVS + lesions relative to the lesions adequate for CVS assessment per patient and with regards to different lesion localizations (excluding patients with no lesions in the respective localization).

these age-related vascular changes,[27] which may explain the higher CVS frequency in our pediatric patients. Future prospective SWI studies are warranted to further explore the optimal sequence parameters for CVS detection at 1.5T.

Based on 7T and 3T MRI findings, a "40% cutoff value" has been proposed that discriminates patients with MS (with CVS positivity in ≥40% of lesions) from other diseases with frequencies below 40%.[4,26] However, this rule has certain limitations, as counting lesions can be time consuming in patients with high lesion burden, and the mitigated reliability of the "40% cutoff" in cases with low total lesion count.[4] The Select6* criteria present an alternative diagnostic approach defined by the identification of 6 or more lesions exhibiting the CVS. In cases with fewer than 6 lesions, most lesions must demonstrate a central vein to meet the criteria.[15] Recent applications of these criteria have demonstrated excellent diagnostic performance by maintaining real-world practicability, with high sensitivity and specificity for MS at 3T MRI.[13,17] In our study, all patients met both the "40% cutoff rule" and the Select6* criteria, thus confirming that both criteria are applicable in patients with POMS, even at 1.5T.

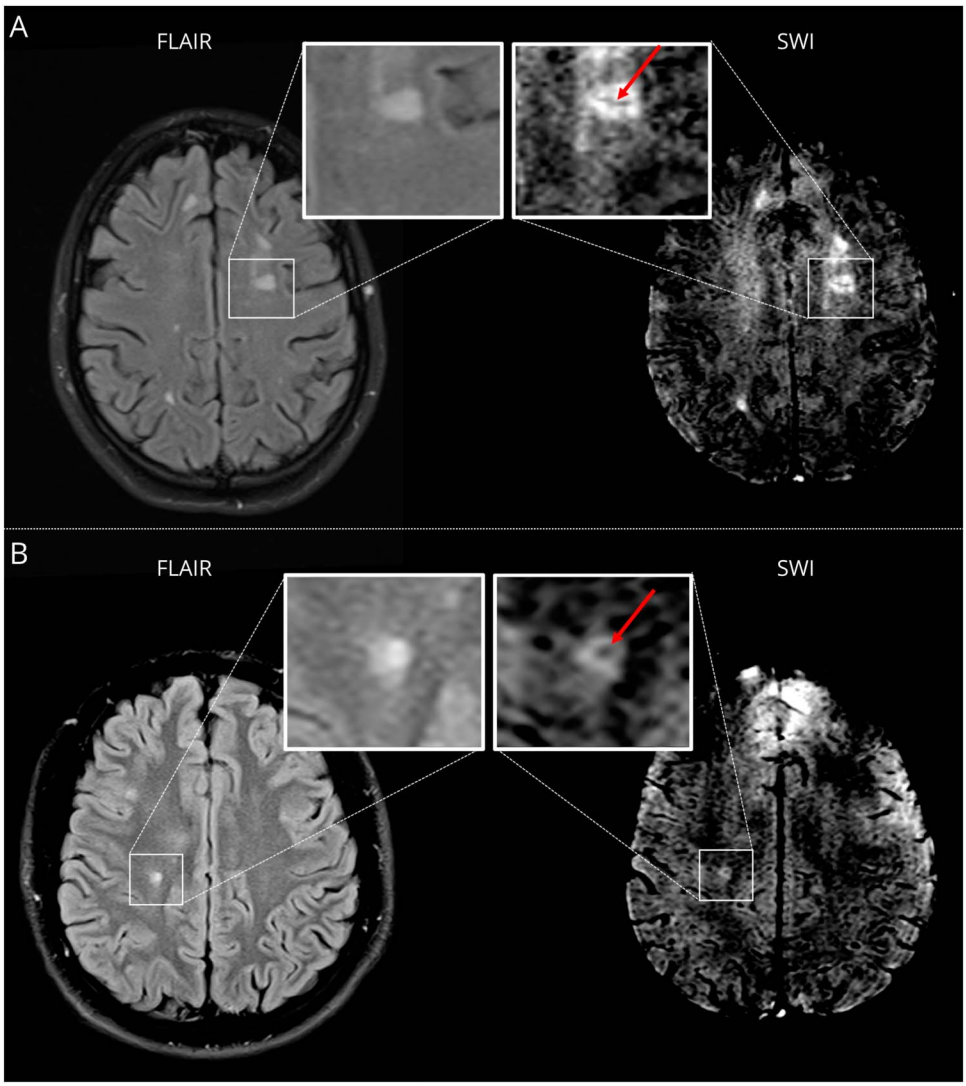
This observation is particularly important given the high sensitivity, but relatively moderate specificity of current 2017 McDonald criteria for MS at the time of incident demyelinating attack when applied to real-world pediatric[3] and adult MS cohorts.[28] While MRI already plays a pivotal role in the current pediatric and adult MS diagnostic criteria,[2,21] there is a need for more specific biomarkers to improve diagnostic accuracy. This need was addressed by the recently proposed 2023 McDonald criteria,[8] which will incorporate the CVS Select6* criteria as an optional component into the diagnostic algorithm. This McDonald criteria revision aims to

Figure 1 Distribution of T2-Hyperintense Lesions



(A) Distribution of total lesion count per patient, with orange dots representing confirmed pediatric-onset multiple sclerosis (POMS) patients, and red dots representing patients initially diagnosed with radiologically-isolated syndrome (RIS) at the time of acquisition. (B) Percentage of central vein sign (CVS) frequency per patient (same color coding as in plot A). Notably, all patients exceeded the 40% CVS frequency threshold.

Figure 2 Exemplary Images of POMS Patients With T2-FLAIR and SWI Central Vein Sign

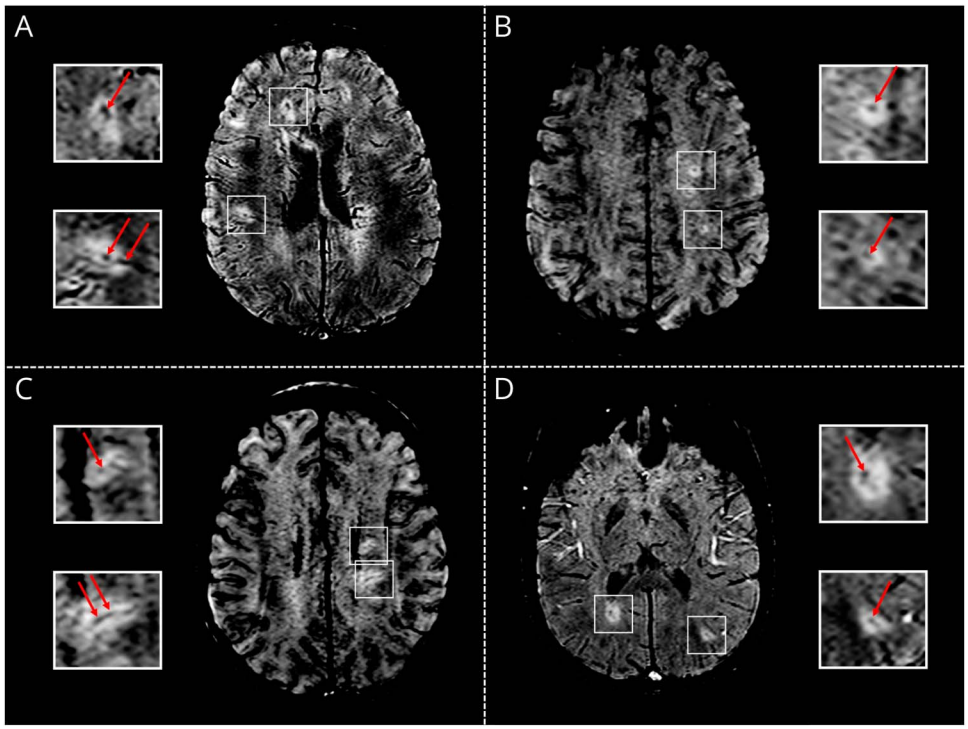


(A and B) present imaging data from 2 patients with pediatric-onset multiple sclerosis (POMS). Each panel displays a T2-weighted fluid-attenuated inversion recovery (FLAIR) image on the left and the corresponding susceptibility-weighted imaging (SWI) on the right. Insets show a zoomed-in view of an exemplary lesion in both FLAIR and SWI sequences, highlighting the presence of the central vein sign (CVS; red arrow) in SWI.

improve the confirmation of MS diagnosis, particularly in cases where the previous criteria led to diagnostic uncertainty. In light of these updates, our findings suggest that the Select6* criteria could be likewise integrated into the diagnostic workup for POMS, potentially improving diagnostic accuracy without the need for higher-field MRI.

In a recent study, 3-dimensional echoplanar imaging (3D-EPI)/SWI-based CVS frequency distinguished 26 patients with POMS from 14 patients with MOGAD.[11] In particular, the application of an individual CVS-cutoff of 41% yielded an area under the receiver operating characteristic (ROC) curve of 1.0 indicating excellent diagnostic performance. While a small subset of POMS patients (n = 7) underwent 1.5T SWI, most POMS patients (n = 19) were scanned at 3T and no distinct 1.5T subgroup analyses were reported, therefore limiting direct comparability with our study, which exclusively focuses on 1.5T acquisitions. A more recent study in POMS found that the presence of CVS was associated with a worse disease progression as reflected in a higher Expanded Disability Status Scale (EDSS) at the 5-year follow-up and annual relapse rate and higher percentage of new T2 lesions.[29] In addition, a recent report on 22 POMS patients that were investigated at 3T showed that 68% of patients exhibited at least 6 CVS-positive lesions.[30] However, only half of the patients with POMS who were investigated met the 40% cutoff threshold with a relatively low median proportion of 39% CVS-positive white matter lesions per patient.[30] Notably, the authors applied a FLAIR* approach, which multiplies a transformed FLAIR image with a T2* image acquired at the longest echo time from a multiecho sequence to enhance lesion contrast.[31] While effective for improving lesion visualization, this FLAIR* technique may not achieve the same level of sensitivity for detecting venous structures within lesions compared with SWI. Indeed, SWI is

Figure 3 Exemplary Images of POMS Patients With SWI and Central Vein Sign



(A–C) Exemplary susceptibility-weighted imaging (SWI) MRI scans of the brain from 3 patients with pediatric-onset multiple sclerosis (POMS), with enlarged insets highlighting lesions that exhibit the central vein sign (CVS; red arrows). (D) SWI from a patient diagnosed with a radiologically isolated syndrome (RIS) at the time of imaging, who was diagnosed with POMS during follow-up 8 months after first MRI acquisition.

suggested to yield a higher sensitivity in detecting veins, compared with T2* sequences.[32] Here, we used SWI for CVS detection and found all POMS patients to fulfill the "40% cutoff rule". Hence, our study is the first to assess CVS in a pediatric MS cohort using real-world clinical routine 1.5T MRI data with combined use of SWI and FLAIR sequences. The retrospective use of real-world data performed in our study additionally suggests that this marker can be reliably used in typical clinical settings, without the need for higher field strengths or specialized sequences. However, further research is needed to confirm these findings across larger pediatric MS populations.

Our study has some limitations that should be considered when interpreting the results. The use of heterogeneous T2-FLAIR and SWI sequences based on real-world clinical data may introduce variability in imaging quality, potentially affecting the detection of CVS. However, despite this data heterogeneity, we achieved a very high detection rate of the CVS, demonstrating the robustness and clinical applicability of our findings. In addition, the lack of a healthy control group or a comparative disease cohort limits the ability to assess the specificity of CVS in this population. In particular, comparing our results with a control group with patients with acute disseminated encephalomyelitis (ADEM) would be relevant given that ADEM is an important differential diagnosis for POMS and is considered to be a perivenous encephalomyelitis.[33] Hence, future comparative studies investigating CVS in both POMS and ADEM are warranted to better delineate the diagnostic specificity of SWI at 1.5T. Moreover, a comprehensive analysis of demographic and clinical data was beyond the scope of this study, warranting further investigation to explore potential correlations with CVS prevalence in a larger data set.

Our study demonstrates that CVS can be reliably detected in T2-hyperintense lesions of patients with POMS using real-world data from clinical routine SWI at 1.5T MRI. The CVS detection rate was consistently above the 40% cutoff value, and every POMS patient fulfilled the Select6* criteria established for adult patients with MS. Our results thus suggest that the implementation of CVS detection as part of routine MRI protocols could improve the diagnostic accuracy also in POMS and lead to earlier treatment initiation in pediatric patients. Future research should focus on validating these findings in larger, multicenter studies[24] at different magnetic field strengths to explore the diagnostic capacity of CVS detection in POMS at the time of incident demyelinating attack.

Author Contributions

J. Kuchling: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. G. Koukou: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. F. Bartels: drafting/revision of the manuscript for content, including medical writing for content. R. Cleaveland: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A. Wegener-Panzer: drafting/revision of the manuscript for content, including

medical writing for content; major role in the acquisition of data. T. Gowert: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I. El Naggar: drafting/revision of the manuscript for content, including medical writing for content. A. Bertolini: drafting/revision of the manuscript for content, including medical writing for content. F. Paul: drafting/revision of the manuscript for content, including medical writing for content. K. Rostasy: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. C. Finke: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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Disclosure

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