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Paramagnetic Rim Lesions and Development of Clinical MS in Radiologically Isolated Syndrome

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IMPORTANCE Most people with radiologically isolated syndrome (RIS) have high proportions of white matter lesions (WMLs) demonstrating the central vein sign (ie, central vein sign–positive lesion [CVS+L]) and at least 1 paramagnetic rim lesion (PRL), representing perivenular lesion development and chronic active demyelination, respectively. Whether these imaging measures predict developing clinical multiple sclerosis (MS) in people with RIS is not yet known.

OBJECTIVE To determine the prognostic value of various magnetic resonance imaging (MRI) measures, particularly PRLs and CVS+L, in predicting clinical MS in people with RIS.

DESIGN, SETTING, AND PARTICIPANTS This was a multicenter prospective cohort study conducted from 2011 and 2024. Participants older than 18 years and fulfilling published RIS criteria were consecutively recruited from 3 large academic MS centers.

EXPOSURES Participants underwent 3-T MRI including brain and spinal cord (SC) sequences and longitudinal clinical assessments. MRIs were evaluated for the total WML, PRL, and SC lesion (SCL) counts as well as the proportion of CVS+L.

MAIN OUTCOMES AND MEASURES The primary outcome was the development of clinical symptoms of MS. Time-varying Cox regression assessed the association between PRLs and symptom onset. Elastic net regression identified key predictors, incorporating PRLs, age, sex, and SCL.

RESULTS A total of 79 eligible people with RIS were included (36 [46%] in the discovery cohort [DC], 43 [54%] in the validation cohort [VC]). Of the initial 46 DC participants, 10 withdrew or were lost to follow-up, whereas all VC participants completed follow-up. In the DC (median [IQR] age, 40 [31-51] years; 25 female [70%]; median [IQR] follow-up, 6.4 [5.0-9.1] years), 9 of 36 people with RIS (25%) developed MS (median [IQR] time, 5.2 [5.0-6.8] years). In the VC (median [IQR] age, 43 [36-51] years; 23 female [53%]; median [IQR] follow-up, 4.4 [2.5-7.9] years), 9 of 43 people with RIS (21%) developed MS (median [IQR] time, 4.4 [2.5-4.7] years). Higher PRL count was associated with earlier symptom onset between 5 and 30 years after initial RIS diagnosis (hazard ratio [HR], 1.15; 95% CI, 1.05-1.26; $P = .004$) in the DC, replicated in the VC (HR, 1.51; 95% CI, 1.00-2.27; $P = .04$). In the DC, having 4 or more PRLs (odds ratio [OR], 14.64; 95% CI, 2.00-207.23; $P = .02$) and higher PRL count (OR, 1.15; 95% CI, 1.03-1.32; $P = .02$) predicted clinical MS. In the VC, having any PRL was significantly associated with developing clinical MS (OR, 20.90; 95% CI, 2.35-533.30; $P = .02$).

CONCLUSIONS AND RELEVANCE Study findings suggest that accrual of nonresolving chronic inflammation in WML portends development of clinical MS in people with RIS, which may have clinical utility in guiding treatment decisions across the MS spectrum and strengthens the case for including asymptomatic MS in the diagnostic criteria. There is growing recognition that early detection of most chronic neurological diseases is critical to prevent or diminish future disability, and these findings are a specific example of how this principle might operate in practice.

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Supplemental content

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Radiologically isolated syndrome (RIS) refers to individuals with brain magnetic resonance imaging (MRI) lesions suggestive of multiple sclerosis (MS) without typical symptoms of demyelination. Although rarely detected,[1] people with RIS are a valuable population to evaluate as RIS is likely present in most MS cases before symptom onset, and growing evidence suggests that earlier disease identification and timely intervention may prevent disability in MS.[2] Furthermore, RIS is now considered part of the MS spectrum under the revised 2024 McDonald criteria.[3] Approximately one-half of people with RIS develop a first clinical event within 10 years of diagnosis.[4] Identified risk factors for developing overt clinical symptoms include younger age, male sex, the presence of spinal cord lesions (SCLs), cerebrospinal fluid-specific oligoclonal bands, and new T2- or gadolinium-enhancing lesions.[4-6]

Emerging MRI biomarkers using susceptibility-sensitive techniques have shown diagnostic and prognostic value in MS. Central vein sign–positive lesions (CVS+Ls) are white matter lesions (WMLs) with visible centrally located veins representing perivenular inflammation, a histopathologic hallmark of MS lesions.[7] A high proportion of CVS+Ls (typically ≥40%) is highly sensitive and specific for distinguishing MS from mimics.[7,8] Paramagnetic rim lesions (PRLs), WMLs exhibiting a paramagnetic rim on susceptibility-sensitive MRI, are another promising biomarker.[9] PRLs correspond to chronic active lesions with a rim of iron-laden microglia and macrophages on histopathology and are thought to drive central nervous system–compartmentalized disease processes in MS, resulting in clinical progression.[10] Although rarely observed in MS mimics, PRLs are frequent across the spectrum of MS, including RIS.[11,12] Additionally, prior studies have consistently shown a positive correlation of PRL burden with the degree of neurological disability in MS.[10,13]

We previously found that most people with RIS have greater than or equal to 40% CVS+Ls[14] and at least 1 PRL.[12] Furthermore, CVS+Ls and PRLs correlated with subclinical cognitive impairment in people with RIS,[15] supporting their potential prognostic utility. However, their predictive value in people with RIS has not yet been prospectively ascertained. Currently, the optimal management of people with RIS also remains unclear. With recent clinical trials showing efficacy of disease-modifying therapies (DMTs) in preventing a first clinical event in people with RIS,[16,17] identifying prognostic factors to discern which people with RIS may benefit from early DMT use becomes increasingly important. We, therefore, aimed to prospectively evaluate the association and predictive potential of PRLs and CVS+Ls for developing clinical MS in people with RIS.

Key Points

Question Are paramagnetic rim lesions (PRLs) and central vein sign–positive white matter lesions (CVS+L) associated with developing clinical symptoms of multiple sclerosis (MS) in people with radiologically isolated syndrome (RIS)?

Findings In this cohort of 36 people with RIS, a higher PRL count was associated with a shorter time to developing clinical symptoms of MS and was an independent predictor of symptom onset; these findings were validated in an independent cohort of 43 people with RIS.

Meaning Results show that PRLs may have prognostic utility for risk stratification and help guide treatment decisions in people with RIS, the earliest detectable stage of MS.

Methods

Study Design

This multicenter observational cohort study included participants recruited from 3 academic centers and prospectively followed up at each site according to local protocols. Participants were divided into 2 cohorts. The discovery cohort (DC) consisted of participants from St Michael's Hospital (Toronto, Ontario, Canada) followed up between July 2017 and January 2021. The validation cohort (VC) consisted of participants from the National Institutes of Health (NIH) Clinical Center in Bethesda, Maryland, from September 2011 to September 2023 and from the Fleni MS Clinic in Buenos Aires, Argentina, between June 2016 and January 2024. Data acquisition and analysis were approved by the institutional review boards of all 3 centers and adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. All participants provided written informed consent.

Clinical Assessment

Study participants underwent neurological examination within 30 days of the initial MRI. No participant experienced symptoms suggestive of MS before the first study visit.

Subsequently, participants in the DC underwent yearly follow-ups, whereas those in the VC were longitudinally followed up at periodic intervals (usually biannually at Fleni and at variable intervals at NIH) for symptoms typical of a demyelinating relapse or development of progressive neurological symptoms. A diagnosis of MS was made if there were clinical symptoms suggestive of MS and other paraclinical criteria aligned with the 2017 McDonald criteria.[18]

MRI Acquisition and Image Analysis

MRI of the brain and spinal cord were performed using 3-T MRI. Brain MRI sequences included 3D T2-weighted fluid-attenuated inversion recovery (FLAIR) and a susceptibility-sensitive sequence, either a 3D T2*-weighted segmented echo-planar imaging (T2*-segEPI) or a 3D SWAN-venule sequence providing magnitude and phase images, as previously described[19-21] (eTable 1 in Supplement 1). SC imaging was limited to the cervical SC in the DC, whereas the entire SC was imaged in the VC.

Image Analysis

The total number of WMLs, CVS+Ls, PRLs, and SCLs on the initial scans was documented. 3D T2-FLAIR and 3D T2*-segEPI/SWAN-venule sequences with multiplanar reconstructions were used to identify CVS+Ls and PRLs using previously published North American Imaging in Multiple Sclerosis (NAIMS) Cooperative consensus criteria.[7,9] WMLs were reviewed for

PRLs on phase images. All WMLs classified as PRLs were either nonenhancing (when gadolinium was administered) or present on a prior clinical scan (at least 3-6 months apart), indicating they were likely chronic PRLs. All raters completed training before assessment and were blinded to diagnosis.

For the DC, scans were assessed for the presence of CVS+Ls, PRLs, and SCLs by raters blinded to whether RIS participants had developed MS. Two independent raters evaluated the initial scans of 24 participants for the presence of PRLs (S.S., M.A.), and CVS+Ls (S.S., P.S.). The interrater reliability was substantial (Cohen κ = 0.77 and 0.65 for PRLs and CVS+Ls, respectively). Based on favorable interrater reliability analysis, additional scans from the DC were assessed by fellowship-trained neuroradiologists (S.S., T.R.L.) with substantial interrater reliability (Cohen κ = 0.72) for PRLs. Discrepancies were resolved through consensus.

For the VC, as initial results from the DC did not show significant differences between total WML and CVS+L counts and percentage of CVS+Ls, only the number of PRLs and SCLs were assessed and documented. Scans from NIH were evaluated by 2 independent raters (S.S., T.R.L.), whereas scans from Fleni were evaluated by an experienced neurologist (M.I.G.).

Statistical Analysis

All analyses were performed using the R statistical environment, version 4.4.2 (R Project for Statistical Computing). Fisher exact and Wilcoxon rank sum tests evaluated group comparisons. Our primary interest was how PRL count is associated with the development of clinical MS (difference between the date of first clinical symptoms and the date of MRI confirming RIS diagnosis). In separate Cox regressions for the DC and VC, we adjusted for the presence of any SCLs, age, sex, and site (only for the VC). We assessed the proportional hazards assumption for all Cox models using the R cox.zph function and visual inspection of complementary log-log plots. In both models, the proportional hazards assumption was not met for PRLs, meaning the effect of PRLs was not constant over the follow-up period. Thus, we used time-varying Cox regressions to account for changes in the effect of PRLs over time. With this approach, we used a step function to split the data into multiple time intervals. The effect of PRLs on MS conversion was then evaluated at each interval while controlling for the aforementioned covariates. Intervals were selected to reflect shorter-term (0-2 years), medium-term (2-5 years), and longer-term risk (5-30 years).

We then conducted an elastic net regression using the R glmnet package, version 4.1-8, to determine which subset of factors most strongly predicts conversion to MS. This regularization method for feature selection combines the L1 and L2 penalties of Lasso and Ridge regression, respectively, allowing coefficients to shrink in a way that reduces overfitting and addresses multicollinearity among predictors. Features included the presence of greater than or equal to 4 PRLs,[13] presence of any PRLs, number of PRLs, presence of any SCLs, as well as age, sex, and site (only for the VC). Age, sex, and site were included in the model without penalization. Given the collinearity between the presence of greater than or equal to 4 or any PRLs and the number of PRLs, the effect of each of these on MS conversion was tested in separate logistic regressions while adjusting for the remaining covariates. All *P* values were 2-sided, and $P < .05$ was considered statistically significant.

Results

A total of 79 eligible people with RIS were included (36 [46%] in the DC and 43 [54%] in the VC). Of the initial 46 DC participants, 10 withdrew or were lost to follow-up, whereas all VC participants completed follow-up. In the VC, 25 participants were from the NIH Clinical Center in Bethesda, Maryland, and 18 were from the Fleni MS Clinic in Buenos Aires, Argentina. All individuals met the 2023 revised RIS diagnostic criteria,[6] with 72 of 77 (93.5%) meeting the more stringent 2009 Okuda RIS diagnostic criteria.[22] Demographic, clinical and MRI characteristics are summarized in **Table 1**.

DC

Demographic, Clinical, and MRI Characteristics

The DC included 36 people (median [IQR] age, 40 [31-51] years; 25 female [70%]; 15 male [30%]; median [IQR] follow-up, 6.4 [5.0-9.1] years) with RIS. The most common reason for the index MRI leading to a RIS diagnosis was headaches (16 of 36 participants [44%]) (eTable 2 in Supplement 1). Only 3 individuals (8.3%) started MS DMT in the absence of any neurological symptoms consistent with MS.

Clinical MS developed in 9 people (25%) with RIS with a median (IQR) time to first clinical event of 5.2 (5.0-6.8) years from RIS diagnosis, of whom 6 of 9 (67%) were diagnosed with relapsing-remitting MS and 3 of 9 (33%) with primary progressive MS. The proportion of people with RIS who were male or 37 years old or younger was not different between those who developed MS and those who did not (Table 1).

On first MRI with a T2*-segEPI sequence, 34 of 36 individuals (95%) had greater than or equal to 40% CVS+L, and 25 of 36 (70%) had greater than or equal to 1 PRL. People with RIS who developed clinical MS had a higher median (IQR) number of PRLs (11 [4-20] vs 1 [0-4]; $P = .01$) (**Figure 1**). In contrast, the median (IQR) number of WMLs (57 [38-70] vs 32 [20-66]; $P = .33$) and SCLs (3 [2-4] vs 1 [0-3]; $P = .11$), proportion of CVS+Ls (89 [85-94] vs 80 [60-91]; $P = .09$), and proportion of participants with greater than or equal to 40% CVS+Ls (100% vs 93%; $P > .99$) were similar between groups.

PRLs as a Risk Factor for Developing Clinical MS

Cox regression revealed that PRLs had a significant effect on developing clinical MS from 5 to 30 years after initial RIS diagnosis (hazard ratio [HR], 1.15; 95% CI, 1.05-1.26; $P = .004$) (**Figure 2**), with more PRLs being associated with a shorter time to a first clinical event. This effect was not evident from 0 to 2 or 2 to 5 years of follow-up. Age, sex, and presence of SCLs were also not associated with developing clinical MS (**Table 2**). The median time to developing clinical MS was 5.8 years in those with PRLs vs 8 years in those without PRLs.

Elastic net regression was used to assess the relative importance of several factors including age, sex, total WML count,

Table 1. Demographic, Clinical, and Magnetic Resonance Imaging Characteristics of People With Radiologically Isolated Syndrome (RIS)

Demographics, clinical, and magnetic resonance imaging characteristics	Group			*P* value
	All people with RIS	RIS-MS	RIS-RIS	
Discovery cohort				
Sample, No. (%)	36 (100)	9 (25)	27 (75)	NA
Age at RIS diagnosis				
Median (IQR), y	40 (31-51)	36 (28-42)	43 (35-52)	.14
Age ≤37 y, No. (%)	12 (33)	5 (56)	8 (30)	.24
Sex, No. (%)				
Female	25 (70)	5 (56)	20 (74)	.41
Male	11 (31)	4 (44)	7 (26)	
Disease-modifying therapy, No. (%)[a]	3 (8.3)	0 (0)	3 (12)	.55
Follow-up time, median (IQR), y	6.4 (5.0-9.1)	6.2 (5.0-7.8)	6.7 (5.1-10.4)	.33
Time to development of clinical MS, median (IQR), y	NA	5.2 (5.0-6.8)	NA	NA
MRI parameters				
Time from RIS diagnosis to initial T2* MRI, median (IQR), y	3.3 (1.9-6.1)	3.3 (2.4-4.8)	3.2 (1.7-7)	.85
WML count, median (IQR)	40.5 (22-68)	57 (38-70)	32 (20-66)	.33
Proportion of CVS+L, median (IQR), %	85 (68-91)	89 (85-94)	80 (60-91)	.09
CVS+L ≥40%, No. (%)	34 (94)	9 (100)	25 (93)	>.99
PRL count, median (IQR)	2 (0-8.5)	11 (4-20)	1 (0-4)	.01[b]
PRL (+), No. (%)	25 (69)	8 (89)	17 (63)	.22
PRL ≥4, No. (%)	15 (42)	7 (78)	8 (30)	.02[b]
SCL (+), No. (%)	27 (75)	7 (78)	20 (74)	>.99
SCL count, median (IQR)	1.5 (0.5-3.5)	3 (2-4)	1 (0-3)	.11
Validation cohort				
Sample, No. (%)	43 (100)	9 (21)	34 (79)	NA
Age at RIS diagnosis				
Median (IQR), y	43 (36-51)	41 (28-54)	43 (38-49)	.62
Age ≤37 y, No. (%)	12 (28)	4 (44)	8 (24)	.24
Sex, No. (%)				
Female	23 (53)	5 (56)	18 (53)	>.99
Male	20 (47)	4 (44)	16 (47)	
Disease modifying therapy, No. (%)[b]	14 (33)	4 (44)	10 (29)	.44
Follow-up time, median (IQR), y	4.4 (2.5-7.9)	4.4 (2.5-7.3)	4.8 (2.7-8.8)	.98
Time to development of clinical MS, median (IQR), y	NA	4.4 (2.5-4.7)	NA	NA
MRI parameters				
Time from RIS diagnosis to initial T2* MRI, median (IQR), y	3.5 (2.1-6.2)	3.5 (2.1-4.7)	3.6 (2.2-7)	.44
PRL count, median (IQR)	1 (0-2)	2 (1-3)	0 (0-2)	.02
PRL (+), No. (%)	23 (53)	8 (89)	15 (44)	.02
PRL ≥4, No. (%)	5 (12)	2 (22)	3 (9)	.23
SCL (+), No. (%)	19 (45)	3 (33)	16 (48)	.48
SCL count, median (IQR)	0 (0-2)	0 (0-3)	0 (0-2)	.83

Abbreviations: CVS+L, central vein sign–positive white matter lesion; MS, multiple sclerosis; NA, not applicable; PRL, paramagnetic rim lesion; SCL, spinal cord lesion; WML, white matter lesion; +, positive.

[a] Disease-modifying therapy use before MS diagnosis.

[b] Statistically significant.

proportion of CVS+Ls, presence and number of PRLs, and presence of SCLs, in predicting the probability of developing a first clinical demyelinating event. Variables with nonzero coefficients were subsequently included in a logistic regression (ie, presence of ≥4 PRLs, number of PRLs, age, and sex). The presence of greater than or equal to 4 PRLs and number of PRLs were tested in separate models, given collinearity, while adjusting for age and sex. Both the presence of greater than or equal to 4 PRLs (odds ratio [OR], 14.64; 95% CI, 2.00-207.23; $P = .02$) and number of PRLs (OR, 1.15; 95% CI, 1.03-1.32; $P = .02$) were significantly associated with development of clinical MS, while age and sex were not (**Table 3**).

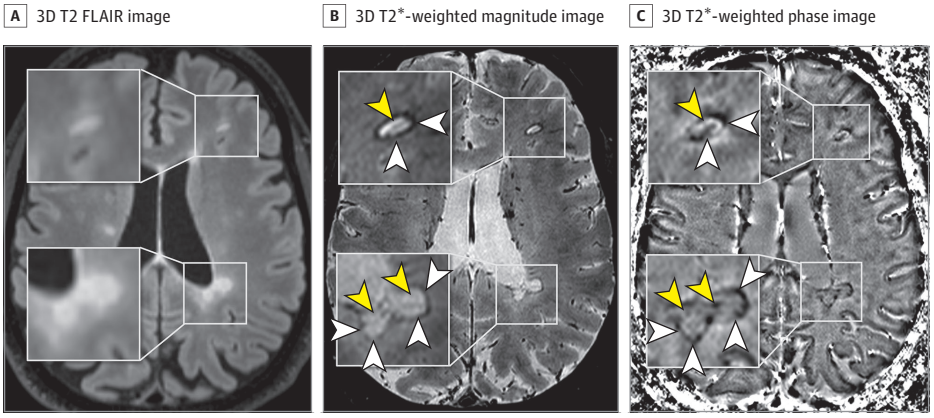
VC

Demographic, Clinical, and MRI Characteristics

The VC included 43 people (median [IQR] age, 43 [36-51] years; 23 female [53%]; 20 male [47%]; median [IQR] follow-up, 4.4 [2.5-7.9] years) with RIS. The most common reason for the index MRI leading to a RIS diagnosis was also headaches (14 of 43 participants [33%]) (eTable 2 in Supplement 1). A total of 14 individuals (33%) initiated MS DMT despite having no neurological symptoms consistent with MS.

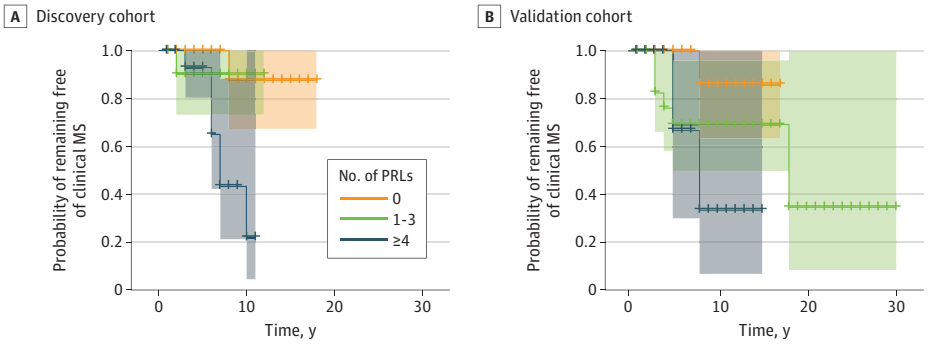
Clinical MS developed in 9 people (21%) with RIS with a median (IQR) time to first clinical event of 4.4 (2.5-4.7) years from RIS diagnosis, of whom 4 of 9 (44%) were diagnosed with

Figure 1. Participant With Radiologically Isolated Syndrome (RIS) in His Early 50s Who Eventually Developed Clinical Multiple Sclerosis (MS) Approximately 5 Years From Initial RIS Diagnosis



Representative axial reconstructed 3-dimensional (3D) T2-fluid-attenuated inversion recovery (FLAIR) (A), 3D T2*-weighted segmented echo-planar magnitude (B), and phase (C) images with magnified view (inset) of selected white matter lesions exhibiting the central vein sign (yellow arrowheads) and paramagnetic rims (white arrowheads), which were numerous in this individual.

Figure 2. Kaplan-Meier Curves of the Effect of the Number of Paramagnetic Rim Lesions (PRLs) on the Time to Developing Clinically Definite Multiple Sclerosis (MS) in Radiologically Isolated Syndrome (RIS)



No. at risk				
0 PRLs	11	4	0	0
1-3 PRLs	10	3	0	0
≥4 PRLs	15	2	0	0

No. at risk				
0 PRLs	19	4	0	0
1-3 PRLs	18	4	1	1
≥4 PRLs	5	1	0	0

A larger number of PRLs is significantly related to a shorter time to MS conversion in both the discovery and validation cohorts from 5 to 30 years after RIS diagnosis.

Table 2. Multivariable Time-Varying Cox Proportional Hazards Regression Model Adjusting for Age, Male Sex, Presence of Spinal Cord Lesions (SCLs) on Initial Magnetic Resonance Imaging, and Site in the Validation Cohort

	Discovery cohort		Validation cohort	
Features	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	0.93 (0.85-1.02)	.14	1.02 (0.95-1.10)	.55
Male sex	3.12 (0.707-12.63)	.11	0.77 (0.17-3.47)	.74
No. of PRLs (0-1.99 y)	0.86 (0.44-1.70)	.66	NA	NA
No. of PRLs (2-4.99 y)	1.08 (0.86-1.35)	.52	1.17 (0.91-1.49)	.22
No. of PRLs (5-30 y)	1.15 (1.05-1.26)	.004[a]	1.51 (1.00-2.27)	.04[a]
(+) SCL	0.57 (0.09-3.37)	.53	0.22 (0.03-1.48)	.12
Site (NIH vs Fleni)	NA	NA	1.23 (0.11-13.24)	.87

Abbreviations: Fleni, Fleni MS Clinic (Buenos Aires, Argentina); HR, hazard ratio; MS, multiple sclerosis; NA, not applicable; NIH, National Institutes of Health; PRL, paramagnetic rim lesion.

[a] Statistically significant.

relapsing-remitting MS and 5 of 9 (56%) with primary progressive MS. Similar to the DC, the proportion who were male or 37 years old or younger was not different between those who developed MS and those who did not.

On first MRI with susceptibility-sensitive sequences, 23 of 43 individuals (53%) had 1 or more PRLs. People with RIS who developed clinical MS had more PRLs (median [IQR], 2 [1-3] vs 0 [0-2]; $P = .02$), but SCL count was similar (0 [0-3] vs 0 [0-2]; $P = .83$). A greater proportion of people with RIS developing clinical MS had 1 or more PRLs (89% vs 44%; $P = .02$).

PRLs as a Risk Factor for Developing Clinical MS

The association between higher PRL count and shorter time to developing clinical MS 5 to 30 years after RIS diagnosis observed in the DC was replicated in the VC (HR, 1.51; 95% CI, 1.00-2.27; $P = .04$) (Figure 2). PRL count in 0- to 2-year and

Table 3. Elastic Net Regression Identifying Covariates Predictive of Progression to Clinically Definite Multiple Sclerosis (MS) in People With Radiologically Isolated Syndrome (RIS)

	Discovery cohort			Validation cohort		
Features	Coefficient[a]	Adjusted OR (95% CI)	*P* value	Coefficient[a]	Adjusted OR (95% CI)	*P* value
Age	−0.09	0.90 (0.79 to 0.99)	.06	−0.03	0.97 (0.89 to 1.06)	.44
Sex	0.77	1.72 (0.25 to 12.02)	.57	−0.81	0.29 (0.03 to 1.83)	.21
(+) PRL	0	NA	NA	1.49	20.9 (2.35 to 533.30)	.02[b]
≥4 PRLs	1.02	14.64 (2.00 to 207.23)	.02[b]	0	NA	NA
No. of PRLs	0.05	1.15 (1.03 to 1.32)	.02[b]	0.04	1.3 (1.01 to 1.81)	.06
No. of WMLs	0	NA	NA	NA	NA	NA
Proportion of CVS+Ls	0	NA	NA	NA	NA	NA
(+) SCL	0	NA	NA	−0.72	0.18 (0.02 to 1.13)	.09
Site (NIH vs Fleni)	NA	NA	NA	−1.16	0.33 (0.02 to 2.70)	.34

Abbreviations: CVS+L, central vein sign–positive white matter lesion; Fleni, Fleni MS Clinic (Buenos Aires, Argentina); NA, not applicable; NIH, National Institutes of Health; OR, odds ratio; PRL, paramagnetic rim lesion; SCL, spinal cord lesion; WML, white matter lesion.

[a] Coefficient reflects log odds in the full elastic net regression. OR and *P* value are obtained from subsequent logistic regressions.

[b] Statistically significant.

2- to 5-year follow-up intervals, age, sex, presence of SCLs, and site were not associated with developing clinical MS (Table 2). The median time to developing MS in those with PRLs was 5.1 vs 7.9 years in those without PRLs.

After performing elastic net regression, the presence of PRLs, PRL count, presence of SCLs, age, sex, and center were considered in a logistic regression (with presence of any PRL and PRL count tested separately). Here, the presence of any PRL had a significant effect on developing clinical MS (OR, 20.90; 95% CI, 2.35-533.30; *P* = .02), whereas the number of PRLs, age, sex, and presence of SCLs were not significantly related (Table 3).

Discussion

Although RIS is now considered part of the MS spectrum from a diagnostic viewpoint under the revised 2024 McDonald criteria,[3] management guidelines remain limited. Identifying biomarkers that predict subsequent development of clinical MS is crucial. Moreover, careful evaluation of people with RIS offers an opportunity to understand pathophysiological processes in the earliest stage of MS, and insights obtained have implications across the MS spectrum. In this prospective multicenter study, clinical MS developed in 25% of people with RIS in the DC (median follow-up: 6.4 years) and in 21% of the VC (median follow-up: 4.4 years). Among several clinical and MRI measures, a higher PRL count at baseline was associated with a shorter time to developing clinical MS (5.8 vs 8 years), and this was replicated in the VC (5.1 vs 7.9 years). When factors most associated with symptom onset were evaluated, it was evident that PRL lesion burden was relevant: clinical MS development was predicted by greater than or equal to 4 PRLs and higher PRL count in the DC and by having any PRL in the VC.

PRLs have gained attention as a specific MRI biomarker and imaging measure of progression-related biology in MS.[10,23] The presence of 1 or more PRL is highly specific for MS, particularly when combined with CVS+Ls.[11,24,25] Furthermore, the presence of greater than or equal to 4 PRLs was associated with earlier motor and cognitive impairment as well as long-term disability in people with MS.[11,13,26] In clinically isolated syndrome, 1 or more PRLs were seen in 53 of 94 patients (56%) who developed MS over a mean follow-up time of 4.6 years, whereas PRLs were absent in those who did not develop MS.[27] PRLs were also associated with cognitive impairment in people with RIS.[15] These findings highlight the relevance of PRLs as a marker of clinical disease progression across the MS spectrum, even at its earliest detectable stages.

In this study, higher PRL counts were associated with a shorter time to developing symptoms in both cohorts, although defining an optimal threshold remains challenging. Notably, the PRL burden and the proportion of individuals with greater than or equal to 4 PRLs differed between cohorts, potentially reflecting a combination of technical factors, biological heterogeneity, and potential enrolment bias. These differences, along with relatively small sample sizes and the fact that most people with RIS had not yet developed MS in both cohorts, may explain why different PRL measures predicted MS across cohorts. Nevertheless, we observed an incremental association between PRL count and time to clinical MS development, along with prior evidence linking PRL and SC lesion counts, that supports the relevance of this biomarker. Given recent clinical trials showing that early treatment with dimethyl fumarate or teriflunomide reduces the risk of developing MS in people with RIS,[16,17] reliable prognostic biomarkers such as PRLs will be of substantial clinical utility in guiding treatment decisions. However, PRL burden should be interpreted as 1 component within a broader risk profile alongside other established risk factors, rather than as a standalone marker.

To our knowledge, this was the first study to prospectively evaluate the association of PRLs with developing clinical MS in people with RIS. Compared with previously identified risk factors, this MRI biomarker has corresponding histopathological correlates directly linked to mechanisms of disease progression in MS. Consistent with findings in people with MS,[11,13] our findings suggest that PRL accrual in people with RIS may contribute to clinical progression as they reflect tissue destruction, chronic active inflammation, remyelination

failure, and compartmentalized central nervous system disease processes thought to drive clinical progression.[10,13,23] PRLs are also larger and structurally more damaged than non-PRL lesions[28] and have been associated with more frequent relapses in long-term studies.[29] Collectively, these findings suggest that PRL burden may be the most prognostically valuable MRI measure across the MS spectrum, relevant to both disease progression and more aggressive relapsing phenotypes, and even people without overt clinical symptoms. Due to the high specificity of PRLs for a diagnosis of MS, in the 2024 McDonald criteria, PRLs have been included to facilitate a diagnosis of MS in people presenting with typical clinical syndromes. Although PRLs are not currently incorporated as a diagnostic criterion for RIS being considered as MS in the 2024 McDonald criteria, our findings contribute new evidence supporting their predictive value for developing clinically definite MS. Taken together with their high specificity and strong biologic rationale, these data support PRLs as a candidate biomarker for inclusion in future diagnostic or classification frameworks, potentially extending to individuals with preclinical disease (people with RIS). If validated in larger cohorts, PRLs could inform diagnostic and treatment decisions in people with RIS and people with MS in clinical practice. Moreover, PRLs may also help enrich future clinical trial populations for individuals most likely to progress, as shown in a recent subgroup analysis of the phase 3 tolebrutinib clinical trials.[30]

PRLs can now be reliably detected at conventional field strengths (1.5 T and 3 T) using widely available susceptibility-sensitive sequences, making them an accessible MRI measure that can be derived from routine clinical scans. Studies show substantial concordance between the 2 field strengths,[31,32] and recent meta-analyses also show no significant difference in PRL detection between standard susceptibility-weighted imaging and T2*-weighted imaging, or between 2D and 3D acquisitions.[33,34] In keeping with the 2024 McDonald criteria revisions, the Magnetic Resonance Imaging Network in Multiple Sclerosis-Consortium of Multiple Sclerosis Centers-North America Imaging in Multiple Sclerosis (MAGNIMS-CMSC-NAIMS) consensus guidelines now advocate the routine inclusion of susceptibility-sensitive imaging—such as 3D T2* EPI or optimized susceptibility-weighted imaging with low flip angle and filtered-phase reconstruction—in the evaluation of patients with suspected MS or RIS.[35] Because these same sequences are used for assessing CVS, their inclusion also enables efficient identification of PRLs without added scan time or cost, making both CVS and PRLs accessible and useful measures in MS clinical practice.

Previously identified independent predictors such as younger age, male sex, and presence of SCLs[4,5,36] did not demonstrate an increased risk for earlier clinical MS development in people with RIS in this study, which aligns with findings from other similar or even larger-sized cohorts.[37-40] The inclusion of PRLs in multivariable models, which was highly predictive of developing clinical MS, likely made the relative contribution of other risk factors less significant. It is also possible that the clinical characteristics of contemporary people with RIS recruited in our study have evolved and more closely resemble clinical MS compared to historical RIS cohorts.

We observed a high proportion of people with RIS who developed primary progressive MS (33% in the DC, 56% in the VC) compared with prior retrospective cohorts (10%-12%).[5,41] This is not surprising considering that most people with RIS, who by definition should not have any evident symptoms or signs suggestive of MS, often have subtle clinical deficits when evaluated with sensitive tools. For instance, a substantial proportion of people with RIS have cognitive deficits when evaluated with appropriate cognitive batteries,[15,42] deficits in manual dexterity,[43] and fatigue[44] compared with healthy controls. It is, therefore, not unexpected that a good proportion of people classified as RIS are individuals with subtle, slowly progressive neurological deficits they may not even be aware of. When these deficits reach clinical detection thresholds on neurological examination, these individuals receive a primary progressive MS diagnosis.

Perivenular inflammation and demyelination are long-known pathologic hallmarks of MS. Several studies[45-49] have demonstrated the high specificity and sensitivity of CVS+Ls for MS. We have reported that people with RIS have a high proportion of CVS+Ls.[14] In this study, the proportion of CVS+Ls in the DC was 85%, comparable with the pooled incidence of 73% to 74% in people with MS in published meta-analyses.[8,50] The CVS+L proportions were similar in those who developed clinical MS and those who remained RIS (89% vs 80%), both far exceeding the greater than or equal to 40% threshold for distinguishing MS from other mimics.[7,8,50] This is consistent with a recent study showing no difference in the proportion of CVS+Ls between RIS and MS.[51] These findings support the diagnostic value of CVS and inclusion of RIS within the biologic MS spectrum in the updated 2024 McDonald criteria.[3] Combining CVS, PRLs, and cortical lesions improved diagnostic accuracy for MS, but only PRLs and cortical lesions correlated with greater disability and disease severity,[24] suggesting that baseline CVS+Ls proportion may have limited prognostic value for RIS developing MS.

Limitations

Our study has several limitations. Many participants had known RIS for several years when the susceptibility-sensitive MRI sequence was performed, potentially introducing a selection/survival bias in our cohort. MRI protocols varied across centers, and not all include gadolinium-enhanced imaging, limiting identification of new enhancing lesions, a known risk factor of developing clinical MS in people with RIS,[4,36] and definite differentiation of acute WMLs with transient rims from true chronic active lesions.[9] However, we confirmed that lesions exhibiting paramagnetic rims were present on a scan done 3 to 6 months prior. SC imaging coverage also varied across cohorts. High-resolution susceptibility-sensitive sequences proven to be reliable in detecting CVS+Ls and PRLs[19,21,52] were used in this study, which likely enabled the detection of a high number of CVS+L and PRLs, but whether alternate sequences would yield comparable results is unclear. In addition, interrater agreement of PRL detection was substantial, but not excellent, suggesting that further training and refinement of PRL detection guidelines may be necessary before widespread clinical application. Moreover, the study setting may limit generalizability,

given potential academic center bias, requirement for specialized MRI protocols and expert interpretation, and health care system differences that may preclude real-world implementation. Finally, cerebrospinal fluid studies were not routinely obtained. Cerebrospinal fluid-specific oligoclonal bands were therefore not included as a risk factor in our analyses.

Conclusions

In this prospective multicohort validation study, we found that a higher PRL count was most associated with development of clinical MS in people with RIS among other known relevant risk factors. As PRLs reflect a subset of chronic active lesions, our findings, together with prior data from people with MS, support their value as a prognostic biomarker for risk stratification and therapeutic decision-making in people with RIS and across the MS spectrum. Moreover, our findings shed light on the pathophysiology of MS at one of the earliest detectable stages, which has broad clinical and scientific implications. There is growing recognition that detecting chronic neurological diseases in their early stages is crucial for preventing future disability, and our findings in RIS exemplify how this principle can be put into practice. Confirmation in larger cohorts will be important to establish the clinical predictive value of PRL in people with RIS and people with MS.

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REFERENCES

1. Forslin Y, Granberg T, Jumah AA, et al. Incidence of radiologically isolated syndrome: a population-based study. *AJNR Am J Neuroradiol*. 2016;37(6):1017-1022. doi:10.3174/ajnr.A4660

2. Ontaneda D, Chitnis T, Rammohan K, Obeidat AZ. Identification and management of subclinical disease activity in early multiple sclerosis: a review. *J Neurol*. 2024;271(4):1497-1514. doi:10.1007/s00415-023-12021-5

3. Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. *Lancet Neurol*. 2025;24(10):850-865. doi:10.1016/S1474-4422(25)00270-4

4. Lebrun-Frenay C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda DT; 10-year RISC study group on behalf of SFSEP, OFSEP. Radiologically isolated syndrome: 10-year risk estimate of a clinical event. *Ann Neurol*. 2020;88(2):407-417. doi:10.1002/ana.25799

5. Okuda DT, Siva A, Kantarci O, et al; Radiologically Isolated Syndrome Consortium (RISC); Club Francophone de la Sclérose en Plaques (CFSEP). Radiologically isolated syndrome: 5-year risk for an initial clinical event. *PLoS One*. 2014;9(3):e90509. doi:10.1371/journal.pone.0090509

6. Lebrun-Frénay C, Okuda DT, Siva A, et al. The radiologically isolated syndrome: revised diagnostic criteria. *Brain*. 2023;146(8):3431-3443. doi:10.1093/brain/awad073

7. Sati P, Oh J, Constable RT, et al; NAIMS Cooperative. The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. *Nat Rev Neurol*. 2016;12(12):714-722. doi:10.1038/nrneurol.2016.166

8. Suh CH, Kim SJ, Jung SC, Choi CG, Kim HS. The "central vein sign" on T2*-weighted Images as a diagnostic tool in multiple sclerosis: a systematic review and meta-analysis using individual patient data. *Sci Rep*. 2019;9(1):18188. doi:10.1038/s41598-019-54583-3

9. Bagnato F, Sati P, Hemond CC, et al. Imaging chronic active lesions in multiple sclerosis: a consensus statement. *Brain*. 2024;147(9):2913-2933. doi:10.1093/brain/awae013

10. Absinta M, Sati P, Schindler M, et al. Persistent 7-tesla phase rim predicts poor outcome in new multiple sclerosis patient lesions. *J Clin Invest*. 2016;126(7):2597-2609. doi:10.1172/JCI86198

11. Maggi P, Sati P, Nair G, et al. Paramagnetic rim lesions are specific to multiple sclerosis: an international multicenter 3-T MRI study. *Ann Neurol*. 2020;88(5):1034-1042. doi:10.1002/ana.25877

12. Suthiphosuwan S, Sati P, Absinta M, et al. Paramagnetic rim sign in radiologically isolated syndrome. *JAMA Neurol*. 2020;77(5):653-655. doi:10.1001/jamaneurol.2020.0124

13. Absinta M, Sati P, Masuzzo F, et al. Association of chronic active multiple sclerosis lesions with disability in vivo. *JAMA Neurol*. 2019;76(12):1474-1483. doi:10.1001/jamaneurol.2019.2399

14. Suthiphosuwan S, Sati P, Guenette M, et al. The central vein sign in radiologically isolated syndrome. *AJNR Am J Neuroradiol*. 2019;40(5):776-783. doi:10.3174/ajnr.A6045

15. Oh J, Suthiphosuwan S, Sati P, et al. Cognitive impairment, the central vein sign, and paramagnetic rim lesions in RIS. *Mult Scler*. 2021;27(14):2199-2208. doi:10.1177/13524585211002097

16. Okuda DT, Kantarci O, Lebrun-Frénay C, et al. Dimethyl fumarate delays multiple sclerosis in radiologically isolated syndrome. *Ann Neurol*. 2023;93(3):604-614. doi:10.1002/ana.26555

17. Lebrun-Frénay C, Siva A, Sormani MP, et al; TERIS Study Group. Teriflunomide and time to clinical multiple sclerosis in patients with radiologically isolated syndrome: the TERIS randomized clinical trial. *JAMA Neurol*. 2023;80(10):1080-1088. doi:10.1001/jamaneurol.2023.2815

18. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2

19. Sati P, Thomasson DM, Li N, et al. Rapid, high-resolution, whole-brain, susceptibility-based MRI of multiple sclerosis. *Mult Scler*. 2014;20(11):1464-1470. doi:10.1177/1352458514525868

20. Li N, Wang WT, Sati P, Pham DL, Butman JA. Quantitative assessment of susceptibility-weighted imaging processing methods. *J Magn Reson Imaging*. 2014;40(6):1463-1473. doi:10.1002/jmri.24501

21. Gaitán MI, Yañez P, Paday Formenti ME, et al. SWAN-venule: an optimized MRI technique to detect the central vein sign in MS plaques. *AJNR Am J Neuroradiol*. 2020;41(3):456-460. doi:10.3174/ajnr.A6437

22. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology*. 2009;72(9):800-805. doi:10.1212/01.wnl.0000335764.14513.1a

23. Dal-Bianco A, Grabner G, Kronnerwetter C, et al. Slow expansion of multiple sclerosis iron rim lesions: pathology and 7-T magnetic resonance imaging. *Acta Neuropathol*. 2017;133(1):25-42. doi:10.1007/s00401-016-1636-z

24. Borrelli S, Martire MS, Stölting A, et al. Central vein sign, cortical lesions, and paramagnetic rim lesions for the diagnostic and prognostic workup of multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm*. 2024;11(4):e200253. doi:10.1212/NXI.0000000000200253

25. Meaton I, Altokhis A, Allen CM, et al. Paramagnetic rims are a promising diagnostic imaging biomarker in multiple sclerosis. *Mult Scler*. 2022;28(14):2212-2220. doi:10.1177/13524585221118677

26. Altokhis AI, Hibbert AM, Allen CM, et al. Longitudinal clinical study of patients with iron rim lesions in multiple sclerosis. *Mult Scler*. 2022;28(14):2202-2211. doi:10.1177/13524585221114750

27. Clarke MA, Pareto D, Pessini-Ferreira L, et al. Value of 3-T susceptibility-weighted imaging in the diagnosis of multiple sclerosis. *AJNR Am J Neuroradiol*. 2020;41(6):1001-1008. doi:10.3174/ajnr.A6547

28. Klistorner S, Usnich T, Clarke MA, et al. The presence of a paramagnetic phase rim is linked to lesion age in multiple sclerosis. Preprint posted online January 13, 2025. doi:10.1101/2025.01.12.25320426

29. Reeves JA, Mohebbi M, Wicks T, et al. Paramagnetic rim lesions predict greater long-term relapse rates and clinical progression over 10 years. *Mult Scler*. 2024;30(4-5):535-545. doi:10.1177/13524585241229956

30. Oh J, Fox RJ, Arnold DL, et al. Paramagnetic rim lesions as a prognostic and predictive biomarker in the tolebrutinib phase 3 trials for disability outcomes. Abstract presented at: ACTRIMS Forum 2025; March 1, 2025; West Palm Beach, FL.

31. Hemond CC, Reich DS, Dundamadappa SK. Paramagnetic rim lesions in multiple sclerosis: comparison of visualization at 1.5-T and 3-T MRI. *AJR Am J Roentgenol*. 2022;219(1):120-131. doi:10.2214/AJR.21.26777

32. Martire MS, Moiola L, Maggi P, et al. Reliability of paramagnetic rim lesion detection at 1.5-T MRI in multiple sclerosis patients. *Mult Scler*. 2025;31(8):955-963. doi:10.1177/13524585251314358

33. Toljan K, Amin M, Ontaneda D. Central vein sign and paramagnetic rim lesion abbreviated counting methods for diagnosis of multiple sclerosis: a systematic review and meta-analysis. *Clin Radiol*. 2025;88:106984. doi:10.1016/j.crad.2025.106984

34. Tranfa M, Cantoni V, Green R, et al. Prevalence and incidence of paramagnetic rim lesions in multiple sclerosis: a systematic review and meta-analysis. *Radiology*. 2025;316(3):e243718. doi:10.1148/radiol.243718

35. Barkhof F, Reich DS, Oh J, et al; Magnetic Resonance Imaging Network in Multiple Sclerosis; Consortium of Multiple Sclerosis Centers; North American Imaging in Multiple Sclerosis Cooperative MRI guidelines working group. 2024 MAGNIMS-CMSC-NAIMS consensus recommendations on the use of MRI for the diagnosis of multiple sclerosis. *Lancet Neurol*. 2025;24(10):866-879. doi:10.1016/S1474-4422(25)00304-7

36. Lebrun-Frénay C, Rollot F, Mondot L, et al; RISC, SFSEP, and OFSEP Investigators. Risk factors and time to clinical symptoms of multiple sclerosis among patients with radiologically isolated syndrome. *JAMA Netw Open*. 2021;4(10):e2128271. doi:10.1001/jamanetworkopen.2021.28271

37. Matute-Blanch C, Villar LM, Álvarez-Cermeño JC, et al. Neurofilament light chain and oligoclonal bands are prognostic biomarkers in radiologically isolated syndrome. *Brain*. 2018;141(4):1085-1093. doi:10.1093/brain/awy021

38. George IC, Rice DR, Chibnik LB, Mateen FJ. Radiologically isolated syndrome: a single-center, retrospective cohort study. *Mult Scler Relat Disord*. 2021;55:103183. doi:10.1016/j.msard.2021.103183

39. Landes-Château C, Ricigliano VA, Mondot L, et al. Choroid plexus enlargement correlates with periventricular pathology but not with disease activity in radiologically isolated syndrome. *Mult Scler*. 2024;30(10):1278-1289. doi:10.1177/13524585241272943

40. Fissolo N, Schaedelin S, Villar LM, et al; RIS Study Group. Prognostic factors for multiple sclerosis symptoms in radiologically isolated syndrome. *JAMA Neurol*. 2025;82(7):722-733. doi:10.1001/jamaneurol.2025.1481

41. Kantarci OH, Lebrun C, Siva A, et al. Primary progressive multiple sclerosis evolving from radiologically isolated syndrome. *Ann Neurol*. 2016;79(2):288-294. doi:10.1002/ana.24564

42. Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. *Mult Scler*. 2016;22(2):250-253. doi:10.1177/1352458515591072

43. Bonzano L, Bove M, Sormani MP, et al. Subclinical motor impairment assessed with an engineered glove correlates with magnetic resonance imaging tissue damage in radiologically isolated syndrome. *Eur J Neurol*. 2019;26(1):162-167. doi:10.1111/ene.13789

44. Labiano-Fontcuberta A, Aladro Y, Martínez-Ginés ML, et al. Psychiatric disturbances in radiologically isolated syndrome. *J Psychiatr Res*. 2015;68:309-315. doi:10.1016/j.jpsychires.2015.05.008

45. Sinnecker T, Dörr J, Pfueller CF, et al. Distinct lesion morphology at 7-T MRI differentiates neuromyelitis optica from multiple sclerosis. *Neurology*. 2012;79(7):708-714. doi:10.1212/WNL.0b013e3182648bc8

46. Mistry N, Abdel-Fahim R, Samaraweera A, et al. Imaging central veins in brain lesions with 3-T T2*-weighted magnetic resonance imaging differentiates multiple sclerosis from microangiopathic brain lesions. *Mult Scler*. 2016;22(10):1289-1296. doi:10.1177/1352458515616700

47. Maggi P, Absinta M, Grammatico M, et al. Central vein sign differentiates multiple sclerosis from central nervous system inflammatory vasculopathies. *Ann Neurol*. 2018;83(2):283-294. doi:10.1002/ana.25146

48. Solomon AJ, Schindler MK, Howard DB, et al. "Central vessel sign" on 3T FLAIR* MRI for the differentiation of multiple sclerosis from migraine. *Ann Clin Transl Neurol*. 2015;3(2):82-87. doi:10.1002/acn3.273

49. Sinnecker T, Clarke MA, Meier D, et al; MAGNIMS Study Group. Evaluation of the central vein sign as a diagnostic imaging biomarker in multiple sclerosis. *JAMA Neurol*. 2019;76(12):1446-1456. doi:10.1001/jamaneurol.2019.2478

50. Castellaro M, Tamanti A, Pisani AI, Pizzini FB, Crescenzo F, Calabrese M. The use of the central vein sign in the diagnosis of multiple sclerosis: a systematic review and meta-analysis. *Diagnostics (Basel)*. 2020;10(12):1025. doi:10.3390/diagnostics10121025

51. Landes-Chateau C, Levraut M, Okuda DT, et al; on behalf RISConsortium. The diagnostic value of the central vein sign in radiologically isolated syndrome. *Ann Clin Transl Neurol*. 2024;11(3):662-672. doi:10.1002/acn3.51986

52. Absinta M, Sati P, Fechner A, Schindler MK, Nair G, Reich DS. Identification of Chronic active multiple sclerosis lesions on 3-T MRI. *AJNR Am J Neuroradiol*. 2018;39(7):1233-1238. doi:10.3174/ajnr.A5660