

# Letters

## RESEARCH LETTER

### Paramagnetic Rim Sign in Radiologically Isolated Syndrome

Individuals with radiologically isolated syndrome (RIS) have incidental magnetic resonance imaging (MRI) abnormalities suggestive of multiple sclerosis (MS).<sup>1</sup> Recent studies using susceptibility-based imaging have shown that a subgroup of chronic MS white matter lesions (WMLs) have a rim of paramagnetic susceptibility-associated signal loss at the lesion edge, the paramagnetic rim sign (PRS), that is associated with the presence of iron inside phagocytes, which indicates chronic, active demyelination.<sup>2,3</sup> The objective of this study was to determine whether patients with RIS have WMLs that are positive for PRS (PRS+).

**Methods** | This is a cross-sectional analysis of a prospective observational longitudinal cohort study of 28 individuals with RIS<sup>1</sup> recruited from July 2017 to August 2018. Institutional review board approval was granted and patients provided written informed consent. Three-dimensional (3-D) T1 magnetization-prepared rapid acquisition gradient echo, 3-D T2 fluid-attenuated inversion recovery, and 3-D T2-segmented echo-planar imaging results (with magnitude and phase images) of the brain and sagittal 2-dimensional T1-phase sensitive inversion recovery of the cervical spinal cord (SC) were acquired on a 3-T MRI scanner (Siemens-Skyra).<sup>4</sup> Three reviewers independently assessed for PRS+ WML, defined as a complete/incomplete rim of hypointense signal identified on phase images.<sup>3</sup> The presence of the central vein sign (CVS) was assessed according to published criteria.<sup>5</sup> The number, location, size, and presence of T1 black holes (T1 BHs) and the number of SC lesions were recorded. Brain and WML volume were extracted using automated software.<sup>4</sup> Statistics were performed using SPSS, version 24.0 (IBM). Pearson coefficients assessed correlations between PRS+ WMLs and MRI measures. Statistical significance was set at  $P < .05$ .

**Results** | Twenty-eight adults with RIS were included. Clinical and MRI characteristics are summarized in the **Table**. Cerebrospinal fluid studies were available for 8 of 28 patients (29%), and cerebrospinal fluid-specific oligoclonal bands were detected in 7 (87%). Of 1347 WMLs, 1068 (79%) were assessed for the PRS; 129 (12%) were PRS+. Seventeen patients with RIS (61%) had at least 1 PRS+ WML (**Figure**). The median number of PRS+ WMLs per patient was 1 (range, 0-23); 279 WMLs were excluded because of size (<3 mm) or poor visibility.

Six hundred thirty WMLs (47%) were included for CVS analysis in accordance with published criteria.<sup>5</sup> Of these, 480 (76%) were CVS+ WMLs. The median proportion of CVS+ WMLs per case was 84% (range, 29%-100%). When we applied the 40% rule, which distinguishes MS from other white matter disorders,<sup>6</sup> 26 patients with RIS (93%) had 40% or more CVS+

WMLs. There were significant univariable correlations of PRS+ WML counts with CVS+ WML count ( $r = 0.74$ ;  $P < .001$ ), T1 BH count ( $r = 0.81$ ;  $P < .001$ ), WML volume ( $r = 0.56$ ;  $P = .002$ ), brain volume ( $r = -0.38$ ;  $P = .046$ ), and SC lesion count ( $r = 0.5$ ;  $P = .01$ ).

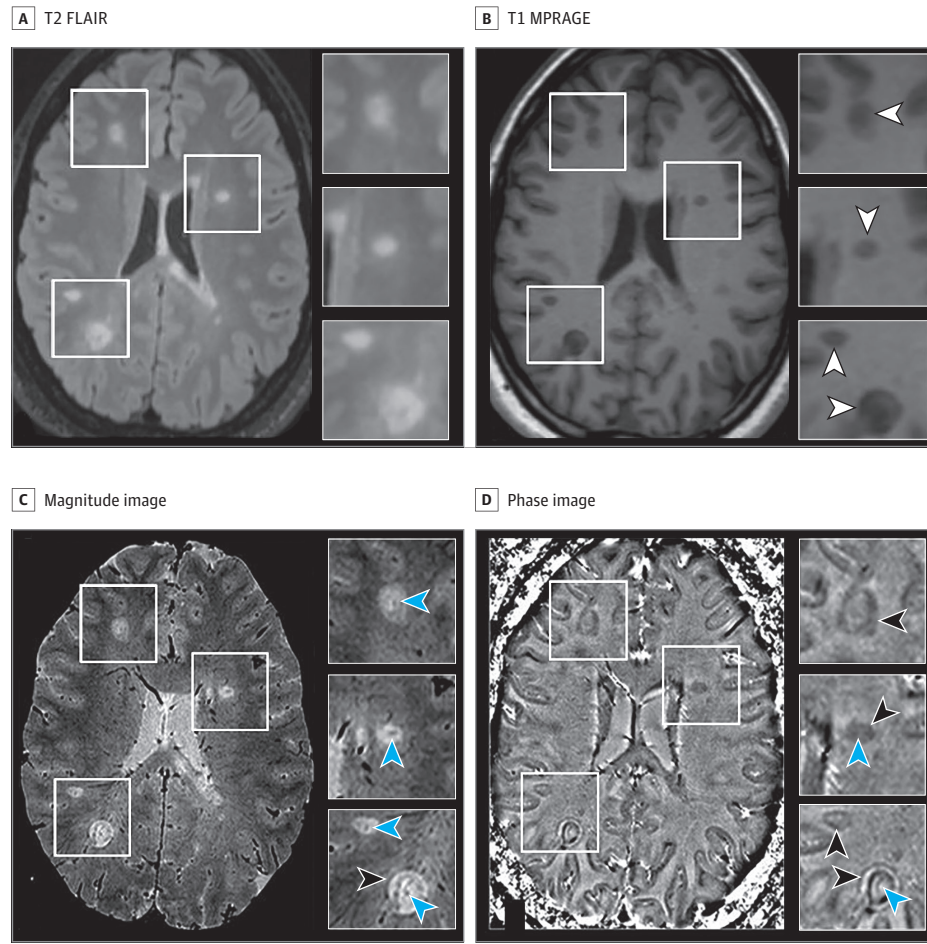
**Discussion** | We found that most patients with RIS (17 [61%]) in our cohort had at least 1 PRS+ WML. The number of PRS+ WMLs per patient varied substantially, ranging from 0 to 23. Prior work

**Table. Clinical and Magnetic Resonance Imaging Characteristics of Patients With Radiologically Isolated Syndrome**

Clinical Characteristics	No. (%)
Patients, No.	28
Age, mean (SD), y	46 (12)
Women	23 (82)
Patients with CSF analysis for oligoclonal band	8 (29)
Patients with oligoclonal bands (% of cases with CSF)	7 (87)
<b>MRI Characteristics</b>	
Brain WMLs, median (range)	
Total brain WML count, No.	1347
No. of total brain WMLs per patient	34 (9-165)
Brain WML volume, mL	3.2 (0.3-18)
Whole-brain volume, mL	1169 (970-1461)
T1-BHs	
Patients with T1-BHs	23 (82)
No. of T1-BH lesions	266 (20)
No. of T1-BHs per patient, median (range)	4 (0-43)
Proportion of T1-BHs per cases, median (range)	13 (0-68)
PRS+ WML	
No. of brain WMLs that were included in the PRS analysis	1068 (79)
No. of patients with PRS+ WML	17 (61)
No. of PRS+ WMLs	129 (12)
No. of PRS+ WMLs per patient, median (range)	1 (0-23)
Proportion of PRS+ WMLs per patient, median (range)	8 (0-44)
No. of PRS+ WMLs with T1-BHs	107 (83)
CVS+ WMLs	
No. of brain WMLs that were included in the CVS analysis	630 (47)
No. of CVS+ WMLs	480 (76)
No. of CVS+ WMLs per patient, median (range)	13 (4-63)
Proportion of CVS+ WMLs per case, median (range)	84 (29-100)
Patients for whom the proportion of CVS+ WMLs was $\geq 40\%$	26 (93)
Cervical spinal cord lesions	
No. of cases with spinal cord lesions	19 (68)
No. of spinal cord lesions	42
No. of spinal cord lesions per case, median (range)	1 (0-4)

Abbreviations: CSF, cerebrospinal fluid; CVS, central vein sign; MRI, magnetic resonance imaging; PRS, paramagnetic rim sign; T1-BHs, T1 black holes; WMLs, white matter lesions.

Figure. Paramagnetic Rim Sign (PRS) in a 29-Year-Old Woman With Radiologically Isolated Syndrome



A, Axial reconstructed T2 fluid-attenuated inversion recovery (FLAIR). B, Axial reconstructed T1 magnetization-prepared rapid acquisition gradient echo (MPRAGE). C and D, Axial reconstructed T2-segmented echo planar imaging with magnitude and phase image. Many of the lesions visible on T2 FLAIR (A) are also T1 black holes (white arrowheads) on T1 MPRAGE (B) and discrete lesions also demonstrate the central vein sign (arrowheads) best seen on the magnitude image (C) and the paramagnetic rim sign best seen on phase images (D). This individual also had a high proportion of central vein sign positive white matter lesions (92%) and evident infratentorial and spinal cord lesions.

in MS has shown that such lesions have chronic, active demyelination at the edge and are associated with greater disability.<sup>3</sup> Furthermore, most of the patients with RIS (26 [93%]) also had many CVS+ WMLs meeting the 40% rule (Figure), which has been proposed to distinguish MS-associated WMLs from other white matter disorders.<sup>4,6</sup> These findings collectively suggest that most WMLs observed in RIS develop from perivenous inflammation and demyelination, and, surprisingly, that most patients with RIS experience chronic, active inflammation.

We found that PRS+ WMLs are correlated with CVS+ WMLs, T1 BHs, WML volume, and brain volume, similar to what has been observed in established MS.<sup>3</sup> Moreover, there was a correlation between SC lesion counts and PRS+ WMLs. The presence of an SC lesion is one of the strongest predictors of developing clinical MS after RIS.<sup>1</sup> These findings collectively raise the possibility that the PRS may have useful clinical implications regarding prognostication and disease-monitoring in RIS.

Our study shows that many patients with RIS have at least 1 and often more WMLs demonstrating PRS, suggesting the presence of subclinical chronic active demyelination, as is often seen in patients with MS with more prominent disability. A prospective follow-up of this cohort is planned, which will be critical to better understand the diagnostic and predictive value of PRS in RIS.

Suradech Suthiphosuwat, MD, FRCR

Pascal Sati, PhD

Martina Absinta, MD, PhD

Melanie Guenette, MSc

Daniel S. Reich, MD, PhD

Aditya Bharatha, MD, FRCPC

Jiwon Oh, MD, FRCPC, PhD

**Author Affiliations:** Division of Neuroradiology, Department of Medical Imaging, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Suthiphosuwat, Bharatha); Division of Neurology, Department of Medicine, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Suthiphosuwat, Guenette, Oh); Translational Neuroradiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland (Sati, Absinta, Reich); Department of Neurology, Johns Hopkins University, Baltimore, Maryland (Reich, Oh); Division of Neurosurgery, Department of Surgery, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Bharatha).

**Corresponding Author:** Jiwon Oh, MD, FRCPC, PhD, Division of Neurology, Department of Medicine, St Michael's Hospital, University of Toronto 30 Bond St, Shuter 3-019, Toronto, ON M5B 1W8, Canada (ohjiw@smh.ca).

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**Concept and design:** Suthiphosuwat, Sati, Bharatha, Oh.

**Acquisition, analysis, or interpretation of data:** All authors.

*Drafting of the manuscript:* Suthiphosuwan, Sati, Oh.

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