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Characteristics, Prevalence, and Clinical Relevance of Juxtacortical Paramagnetic Rims in Patients With Multiple Sclerosis

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Abstract

Background and Objectives

A subgroup of patients with multiple sclerosis (MS) presents focal paramagnetic rims at the border between cortex and white matter (juxtacortical paramagnetic rims [JPRs]). We investigated the presence of this finding in our in vivo MS cohort and explored its potential clinical relevance. Moreover, we exploited postmortem MRI of fixed whole MS brains to (1) detect those rims and (2) investigate their histologic correlation.

Methods

Quantitative susceptibility mapping (QSM) and magnetization-prepared 2 rapid acquisition gradient-echo (MP2RAGE) images at 3T-MRI of 165 patients with MS from the in vivo cohort were screened for JPRs and the presence of cortical lesions. Five postmortem brains from patients with MS were imaged with 3T-MRI to obtain QSM and MP2RAGE sequences. Tissue blocks containing JPRs were excised and paraffin-embedded slices stained by immunohistochemistry for myelin basic protein (for myelin) and anti-CR3/43 (for major histocompatibility complex II–positive microglia/macrophages). DAB-Turnbull stain was performed to detect iron.

Results

JPRs are present in approximately 10% of in vivo patients and are associated with increased cortical lesion load. One of the 5 postmortem brains showed JPRs. Histologically, JPRs correspond to an accumulation of activated iron-laden phagocytes and are associated with demyelination of the whole overlying cortical ribbon.

Discussion

JPRs are a novel potential MRI biomarker of focal cortical demyelination, which seems related to global cortical pathology and might be useful for diagnostic and stratification purposes in a clinical setting.

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Glossary

BMI = body mass index; **CL** = cortical lesion; **CLV** = CL volume; **EDSS** = Expanded Disability Status Scale; **EPI** = echo planar imaging; **FLAIR** = fluid-attenuated inversion recovery; **JPR** = juxtacortical paramagnetic rim; **MP2RAGE** = magnetization-prepared 2 rapid acquisition gradient-echo; **MS** = multiple sclerosis; **PRL** = paramagnetic rim lesion; **QSM** = quantitative susceptibility mapping; **RRMS** = relapsing remitting MS; **SMSC** = Swiss Multiple Sclerosis Cohort study; **sNfL** = serum neurofilament light chain; **WML** = white matter lesion.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated and degenerative disease of the CNS, which affects both white and grey matter.[1] In the past few decades, histologic[2] and neuroimaging studies[3] showed extensive focal and diffuse cortical involvement in MS. The most frequent form of focal cortical damage is represented by subpial cortical demyelination, which is specific to MS,[4] and is predominant in the progressive phase of the disease. The overall volume of cortical lesions (CLs) represents 1 contributor of clinical disability and cognitive impairment.[5] As such, detecting cortical involvement more accurately might be useful for disease prognostication.[6]

The detection of CLs in clinical practice is challenging because of (1) the lack of contrast sensitivity and a relatively low signal-to-noise ratio for CLs in conventional MRI protocols, (2) the paucity of gadolinium enhancement in the cortex due to the relatively low frequency of blood-brain barrier disruption, and (3) the small size of CL.[7]

Nonconventional MRI protocols might improve the evaluation of cortical alterations. Susceptibility-based MRI has already been proven useful in detecting MS-specific tissue changes.[8] In the white matter, paramagnetic rim lesions (PRLs) have been extensively investigated: PRLs are detectable in susceptibility-based imaging because they harbor an edge of iron-laden activated microglia/macrophages, they are highly specific to MS, and they represent the imaging correlate of the histologically defined chronic active lesions.[9] A subgroup of patients with MS presents peculiar paramagnetic rims extending along the border between white matter and cortex on susceptibility-sensitive MRI, which we will hereafter refer to as juxtacortical paramagnetic rims (JPRs). In contrast to the classic juxtacortical PRLs, JPRs are adjacent to the cortex and do not surround white matter lesions (WMLs).

After having observed the presence of these rims in quantitative susceptibility mapping (QSM) images in 1 postmortem brain, we undertook an investigation to understand their nature and implications. The aim of this study was (1) to assess the frequency of JPRs, (2) to explore their clinical relevance in patients with MS in vivo, and (3) to characterize them histologically.

Methods

Clinical Study

To assess the prevalence and clinical significance of JPRs, we selected 165 MS patients with availability of susceptibility-based MRI from an ongoing monocentric cohort study that enrolled patients with active relapsing remitting MS (RRMS) and nonactive progressive MS. We screened QSM maps (obtained from segmented 3D-echo planar imaging [3D-EPI]), magnetization-prepared 2 rapid acquisition gradient-echo (MP2RAGE), and 3D-fluid–attenuated inversion recovery (FLAIR) to assess for the presence of JPRs (QSM), PRLs (QSM), WMLs (FLAIR), and CL count/CL volume (CLV) (MP2RAGE). All scans were performed on a 3T-MRI clinical scanner.

JPRs were identified independently by 2 experienced neurologists (R.G. and A.C.), followed by a consensus review. Serum samples for measurement of serum neurofilament light chain (sNfL) were collected at the time of the MRI (±3 months) in 123 of 165 patients. sNfL Z scores were calculated as previously described by other authors.[10] Since body mass index (BMI) values were missing in our data, a BMI of 25 was used. One hundred eight of the patients had a longitudinal standardized Expanded Disability Status Scale (EDSS) assessment in the context of the Swiss Multiple Sclerosis Cohort study (SMSC) (98 without JPRs and 10 with JPRs). These patients with MS were comparable with the whole original cohort (the data are listed in eTable 1, links.lww.com/WNL/D308).

We tested the following H0-hypothesis: MS patients with JPRs do not differ from patients without JPRs in demographics (age and sex); disease duration; clinical phenotype; EDSS at time of the MRI and EDSS evolution over time; sNfL Z scores; number of PRLs, WMLs, and CLs; and total CLV.

To test this hypothesis, we used a χ^2 test for categorical data and a t test for normally distributed continuous data. For nonnormal data, a Wilcoxon rank-sum test was used (Table 1). To evaluate the disease progression rate in the 2 groups, we performed a Kaplan-Meier estimator for time to first worsening (defined by the EDSS score) by using the above-mentioned data from the SMSC. We also studied the association between the presence of JPRs and total CLV (independent variable) in a logistic regression model, which was adjusted for age, disease duration, and EDSS.

Table 1 Univariate Analyses Investigating Differences Between the 2 Groups of Patients With MS In Vivo (Without and With JPRs)

	Without JPR (n = 149)	With JPR (n = 16)	*p* Value
Age, y, median (IQR)	47.0 (35.0–58.0)	45.0 (32.0–53.2)	0.251
Sex, male, n (%)	60.0 (40.3)	5.0 (31.2)	0.665
Diagnosis, PMS, n (%)	61.0 (40.9)	3.0 (18.8)	0.144
EDSS score, median (IQR)	3.0 (1.5–4.5)	2.3 (1.5–4.5)	0.670
MSSS, median, (IQR)	4.3 (2.6–5.9)	4.8 (3.0–5.7)	0.992
Disease duration, median (IQR)	5.6 (0.8–16.7)	4.5 (0.7–8.7)	0.553
Medication, n (%)			0.568
Interferon	5.0 (3.7)	0.0 (0.0)	
Copaxone	2.0 (1.5)	0.0 (0.0)	
Dimethyl fumarate	14.0 (10.4)	2.0 (15.4)	
Siponimod	2.0 (1.5)	0.0 (0.0)	
Teriflunomide	5.0 (3.7)	0.0 (0.0)	
Fingolimod	13.0 (9.6)	4.0 (30.8)	
Ocrelizumab	62.0 (45.9)	6.0 (46.2)	
Rituximab	15.0 (11.1)	1.0 (7.7)	
Natalizumab	4.0 (3.0)	0.0 (0.0)	
No therapy at the time of imaging	13.0 (9.6)	0.0 (0.0)	
sNfL, pg/mL, median (IQR)	8.6 (6.2–12.6)	9.4 (6.7–16.3)	0.647
sNfL *Z* score BMI, median (IQR)	0.4 (−0.4, 1.1), 66th percentile	1.0 (0.2–1.5), 83rd percentile	0.108
No. of WML, median (IQR)	40.0 (21.0–71.0)	36.5 (10.7–63.0)	0.509
Total WML volume, mm^3, median (IQR)	6,211.0 (2,158.0–15,101.0)	5,611.0 (1,974.0–11,341.7)	0.498
No. of periventricular lesions, median (IQR)	8.0 (4.7–13.0)	9.0 (2.0–10.2)	0.484
Periventricular lesion volume, mm^3, median (IQR)	575.0 (186.7–1,467.0)	355.0 (66.7–1,301.7)	0.300
No. of juxtacortical lesions, median (IQR)	31.0 (14.7,56.0)	26.0 (8.7–49.5)	0.485
Juxtacortical lesion volume, mm^3, median (IQR)	2,340.0 (744.2–5,560.7)	2,336.0 (820.7–4,241.2)	0.672
No. of cortical lesions, median (IQR)	2.0 (0.0–8.2)	4.0 (1.5–12.0)	0.158
Cortical lesion volume, mm^3, median (IQR)	28.5 (0.0–146.0)	128.0 (15.0–352.0)	0.040
No. of leukocortical lesions, median (IQR)	2.0 (0.0–7.0)	3.0 (1.0–10.5)	0.219
Leukocortical lesion volume, mm^3, median (IQR)	25.0 (0.0–124.0)	72.0 (13.0–196.0)	0.150
No. of rim-positive WMLs, median (IQR)	2.0 (0.0–6.0)	1.5 (1.0–7.5)	0.086

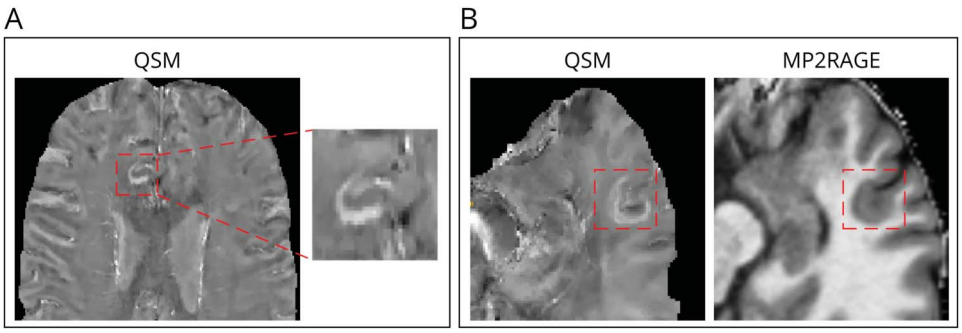
Abbreviations: EDSS = Expanded Disability Status Scale; IQR = interquartile range; JPR = juxtacortical paramagnetic rim; MSSS = Multiple Sclerosis Severity Score; NfL = neurofilament light chain; PMS = progressive multiple sclerosis; WML = white matter lesion.

Postmortem Imaging and Histology

Five whole postmortem brains were obtained from the German MS Brain Bank and imaged on a clinical 3T-MRI (patients' characteristics are listed in eTable 2, links.lww.com/WNL/D308). The following sequences were acquired, adapted to ex vivo conditions: (1) segmented 3D-EPI to enable QSM[11] and (2) MP2RAGE.[12]

After imaging, brains were cut by using the state-of-the-art approach described in detail elsewhere.[13] Under MRI guidance, we selected and excised tissue blocks containing JPRs from the brain slabs. Slices of 4 μm thickness were stained immunohistochemically for myelin and activated microglia/macrophages; moreover, we performed iron staining (Turnbull).

Figure 1 Examples of JPRs in Patients With MS In Vivo



In vivo QSM of a patient with multiple sclerosis included in our cohort showing a JPR (A) and in vivo QSM of another patient showing a JPR and the corresponding MP2RAGE revealing an underlying focal cortical/juxtacortical hypointensity (B). JPR = juxtacortical paramagnetic rim; MP2RAGE = magnetization-prepared 2 rapid acquisition gradient-echo; MS = multiple sclerosis; QSM = quantitative susceptibility mapping.

Standard Protocol Approvals, Registrations, and Patient Consents

The postmortem study was approved by the ethical review committee of the University Medical Center Göttingen. The in vivo study was approved by the local ethics committee (Institutional Review Board of Northwest Switzerland), and all participants gave written consent before enrollment.

Data Availability

The data sets generated and analyzed in this study are available from the corresponding author on a reasonable request.

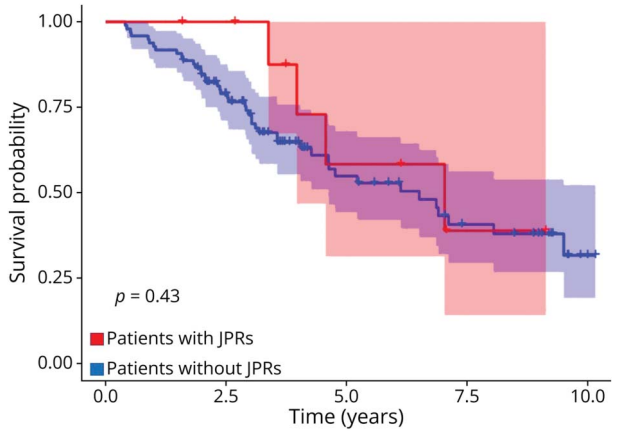
More details regarding methods are available in the eMethods (links.lww.com/WNL/D308).

Results

In the in vivo cohort, 16 of 165 (10%) patients with MS presented at least 1 JPR (range 1–4) (total = 26 JPRs); 15 JPRs showed an underlying focal cortical/juxtacortical hypointensity on MP2RAGE (Figure 1). The group of patients with JPRs did not differ significantly regarding demographics, disease duration, clinical phenotype, EDSS, and sNfL Z scores from those without JPRs. In total, 80% of patients with JPRs and 60% of patients without JPRs had RRMS. In the univariate analysis, total CLV was higher in the patients with JPRs ($p = 0.040$). In a logistic regression model, JPRs and CLV were associated, after adjusting for age ($p = 0.029$). Surprisingly, we did not find any association between the presence of JPRs and the number of PRLs (Table 1). Moreover, patients with JPRs did not show a different grade or evolution of clinical disability level (Figure 2). We also did not find any significant difference in cortical thickness change over a follow-up period of 2 years (±3 months) between the 2 groups (the data are given in eTable 3, links.lww.com/WNL/D308); however, we only had data available for 97 patients (89 without JPRs and 8 with JPRs).

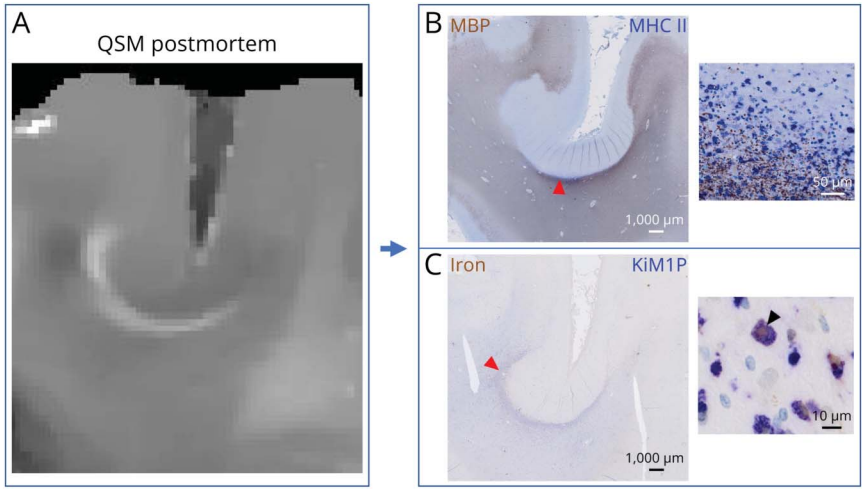
Only 1 of the 5 postmortem brains showed JPRs (patient 3, see eTable 2, links.lww.com/WNL/D308). In this brain, we observed 20 JPRs (Figure 3A) and we obtained the histologic profile of 6 of them. JPRs were associated with an infiltrate of major histocompatibility complex II–expressing amoeboid microglia, many of which were iron-laden (Figure 3, B and C). The edges of iron-laden microglia were positioned at the immediate subcortical white matter, only rarely in the cortex itself. Remarkably, those microglia rims (JPRs) were always underlying areas of demyelination extending through all cortical layers and were often located in the sulci (Figure 3B). In our postmortem patient cohort, no CLs with intracortical microglia rim were observed. The brain with JPRs was characterized by extended and confluent regions of cortical demyelination frequently involving the entire width of the cortical ribbon. In the other brains, the regions of cortical demyelination were fewer and less extensive. 3D-EPI magnetic resonance images showed 15 ± 8 whole cortical band lesions in the brains without JPR (range 6–25) and 126 whole cortical band lesions in the brain with JPRs. In contrast to the

Figure 2 Estimation of the Disease Progression Rate of Patients With and Without JPRs



Kaplan-Meier estimate for time to first clinical worsening (EDSS progression). Number of patients with JPRs = 10, number of patients without JPRs = 98. This is a retrospective analysis, and the group (JPR) was not defined at the beginning of the observation time. EDSS = Expanded Disability Status Scale; JPR = juxtacortical paramagnetic rim; MS = multiple sclerosis.

Figure 3 Histologic Characterization of JPRs



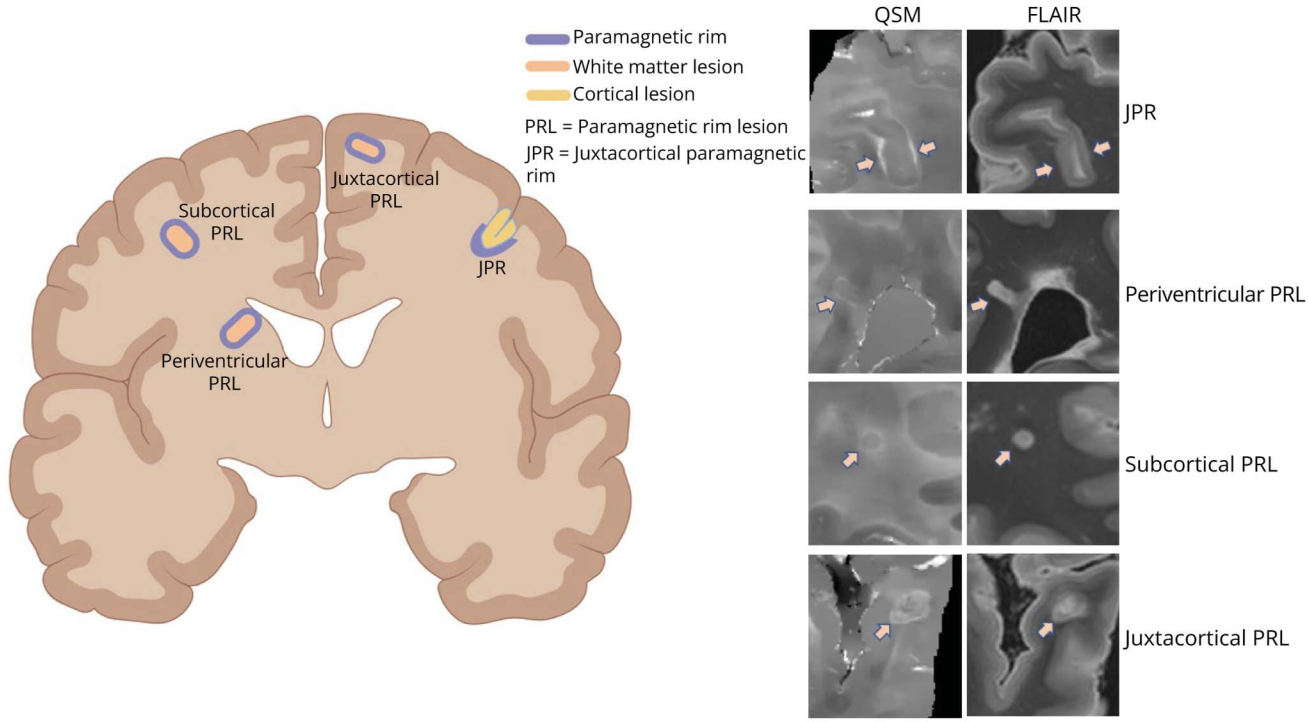
Postmortem QSM showing a juxtacortical rim (A) and its histologic correlate showing accumulation of activated phagocytes (B) and iron-laden macrophages (C). Cortical demyelination is reaching the cortical layer VI. JPR = juxtacortical paramagnetic rim; QSM = quantitative susceptibility mapping.

classical PRL, JPRs do not surround white matter lesions (Figure 4). By immunohistochemistry, the demyelinated cortex adjacent to JPRs did not contain relevant inflammatory infiltrates; also, we did not observe an increased presence of lymphoid aggregates in the meninges nearby. Classical PRLs were found in 3 of the 5 postmortem brains.

Discussion

A subgroup of patients with MS shows rims of increased susceptibility right underneath the cortex (JPRs). This imaging feature was found in approximately 10% in our in vivo cohort of patients with MS. Histopathologically, those areas

Figure 4 Different Types and Locations of Paramagnetic Rims in MS



PRLs are lesions located in the periventricular, subcortical, and juxtacortical white matter, which are surrounded by a rim of increased susceptibility. They represent the imaging correlation of chronic active white matter lesions. JPRs are areas of local increase in susceptibility that are located in the juxtacortical white matter and that surround a cortical lesion involving the whole cortical ribbon (not a white matter lesion). FLAIR = fluid-attenuated inversion recovery; JPR = juxtacortical paramagnetic rim; MS = multiple sclerosis; PRL = paramagnetic rim lesion; QSM = quantitative susceptibility mapping.

corresponded to a dense infiltrate of activated, in part, iron-laden phagocytes and were associated with demyelination involving the whole thickness of the cortical ribbon. Accordingly, the role of these rims in MS differential diagnosis should be explored because such areas of extended cortical demyelination are specific to MS[4] and are difficult to detect in conventional MR images.

Since in all of our 6 specimens, the cortical demyelination adjacent to the rims also involved cortical layer VI (Figure 3B), we hypothesize that this rim of activated phagocytes represents a reaction of the immediate subcortical white matter to a pathologic process extending from the cortex.[14] As such, JPRs might indicate a temporal stage of cortical demyelination. Histopathologically, no CLs with an intracortical microglia rim were observed in our postmortem patient cohort. In QSM images, we could not detect (at least with the resolution and sensitivity of our susceptibility MRIs) intracortical rims comparable with JPRs. This supports the hypothesis that JPRs originate in the subcortical white matter and that expansion of demyelination within the cortex occurs in the absence of relevant microglia/macrophage activation. Future work in samples that are acquired at higher spatial resolution should corroborate or refute this hypothesis. Furthermore, longitudinal MRI studies should aim at demonstrating whether the pathologic changes leading to JPR formation are originating from the subpial surface and hence proceed with a "surface-in" mechanism.

It is of interest that innate immunity activation in JPRs colocalized with WM demyelination but was not associated with WML. Therefore, JPRs represent a phenomenon distinct from that described in a previous study, where rims of increased susceptibility were reported close to the WM interface in leukocortical type I lesions.[15]

In our work, JPRs were associated with an increase in CL load in univariate analysis and in a logistic regression model. Our data suggest therefore that—when JPRs are present—demyelination of the whole overlying cortical ribbon is also present. Since this type of demyelination is specific to MS,[4] JPRs might thus be useful for MS diagnosis; in addition, they may also be considered as an indirect sign of cortical pathology, which has been shown to be prognostic for increased disability and development of cognitive deficits.[3] Consequently, the role of JPRs in MS differential diagnosis should be further explored because they underlie areas of extended cortical demyelination that are specific to MS[4] and we normally cannot easily identify in conventional MRI. In addition, since CLs are a prognostic factor of conversion to progressive MS,[6] JPRs might help us to identify patients deserving more aggressive treatment regimens in a first place. The identification of JPRs in clinical practice is feasible because it may be achieved using high-resolution susceptibility-based sequences such as the ones that are currently used to detect the central vein sign and PRLs.[16]

Remarkably, the number of JPRs was not associated with the number of PRLs in our MS cohort. This aspect might indicate that these pathologic processes are independent from each other and deserve ad hoc investigations in future studies.

A limitation of our work is that we could detect JPRs in only 1 postmortem brain. On the other hand, this reflects the frequency of this finding observed in vivo in a large cohort of patients with MS (10%). Another limitation was that we could not assess the association between the presence of JPRs and long-term disability, which is intrinsically due to the timing of the introduction of a susceptibility-based sequence in our MS protocol. New studies should aim at establishing this relationship for a better understanding of the prognostic value of this new imaging biomarker. Furthermore, since we did not administer gadolinium-based contrast agents within this study, we cannot determine with certitude whether an acute lesion was present in the JPR area at the time of the study scan. However, this scenario seems rather improbable to us. In fact, early rims have so far only been described in white matter, but not CLs by Absinta et al.,[17] and they were reported after gadolinium administration. Thus, gadolinium deposits in microglia/macrophages might have contributed to it, although the nature of this early rim remains unclear to date. Moreover, in our study, JPRs were also found in patients with nonactive progressive MS, and our patients with active RRMS were all on disease-modifying treatment for at least 3 months, rendering the formation of new lesions unlikely. In addition, no patient enrolled in our study had active lesions in the location of JPR on the last conventional MRI before study inclusion.

In summary, we describe here a novel MRI feature in a subgroup of patients with MS, which has the potential to be used as a diagnostic and prognostic biomarker. Future longitudinal studies are warranted to corroborate the diagnostic and prognostic value of JPRs in patients with MS.

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Disclosure

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Continued

Appendix *(continued)*

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