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Short report

MRI activity in pre-symptomatic multiple sclerosis: the role of paramagnetic rim lesions beyond the 2024 McDonald diagnostic criteria

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ABSTRACT

Background The 2024 McDonald criteria allow multiple sclerosis (MS) diagnosis in pre-symptomatic individuals but their association with MRI activity remains uncertain. We assessed whether paramagnetic rim lesions (PRL) predict future MRI activity beyond the 2024 McDonald criteria.

Methods We retrospectively included individuals with incidental MRI findings suggestive of MS, ≥6 months of radiological follow-up, 3D T2*-weighted echo-planar-imaging MRI. Clinico-radiological data included PRL, central vein sign (CVS) Select-6, cerebrospinal fluid positivity, optic nerve, spinal cord involvement and disease-modifying treatment. Time to first MRI activity and annualised lesion rate (ALR) were analysed using multivariable-penalised Cox and mixed-effects Poisson models.

Results Among 68 patients (mean age 38 years; 79.4% female; mean follow-up 55.7 months), 21 showed MRI activity. PRL were associated with shorter time to first MRI activity (HR 5.66, 95% CI 1.33 to 28.39, p=0.019). PRL (RR 3.45, 95% CI 1.40 to 8.47, p=0.007) and CVS positivity (RR 4.09, 95% CI 1.17 to 14.27, p=0.027) predicted higher ALR. Fulfilment of the 2024 McDonald criteria associated with increased risk of future MRI activity (HR=11.95, 95% CI 2.77 to 51.51, p=0.001; Cox regression). Adding PRL presence to the criteria changed classification performance (χ^2=18, p<0.001; McNemar's test), improving specificity and accuracy while reducing sensitivity.

Conclusions PRL are associated with subsequent radiological activity in pre-symptomatic MS, featuring complementary predictive value beyond biomarkers currently included in the 2024 McDonald criteria.

INTRODUCTION

The 2024 revision of the McDonald criteria allows multiple sclerosis (MS) diagnosis in individuals with incidental MRI findings suggestive of inflammatory demyelination, even in the absence of clinical symptoms.[1] Although these criteria were developed for diagnosis rather than prognosis, it remains unclear whether individuals who fulfil the 2024 diagnostic criteria are more likely to experience subsequent MRI activity during the pre-symptomatic phase of MS.

Paramagnetic rim lesions (PRL) have been incorporated as a paraclinical feature supporting MS diagnosis, although their use is currently limited to patients with a typical clinical presentation.[1 2] Emerging evidence, nevertheless, suggests that PRL may also serve as a predictive biomarker of clinical conversion in pre-symptomatic patients.[3 4]

The present study aimed to evaluate: (a) whether PRL predict MRI activity in pre-symptomatic individuals with incidental imaging findings suggestive of MS; (b) the ability of the 2024 McDonald criteria to identify individuals at risk of future MRI activity; and (c) whether the incorporation of PRL improves the predictive performance of these criteria.

METHODS

Study population and clinico-radiological assessments

We retrospectively evaluated pre-symptomatic individuals with incidental MRI findings suggestive of MS[2 5] followed up at Cliniques Universitaires Saint-Luc, Brussels.

Inclusion criteria were: (a) index brain MRI (first MRI) showing ≥1 FLAIR hyperintense lesion ≥3 mm in periventricular, juxtacortical/cortical or infratentorial regions[2]; (b) ≥6 months of radiological follow-up; (c) availability of ≥1 3T sub-millimetric three-dimensional segmented T2*-weighted echo-planar-imaging (T2*-EPI) brain MRI (MRI protocol: online supplemental table 1). Individuals with a history of neurological symptoms at the time of index MRI, MRI mimics or patients with alternative diagnoses were excluded after a careful clinical and radiological review.

At study entry we collected age at index MRI, sex, MS family history, reason for index MRI (headache vs others), index MRI characteristics (according to recommendations[2 5]: ≥9 T2 and/or gadolinium-enhancing, ≥3 periventricular, juxtacortical/cortical, infratentorial, corpus callosum or ovoid-shaped periventricular lesions), brain MRI frequency per year, spinal cord lesions presence and optic nerve involvement (either abnormal orbital MRI, visual evoked potentials or optical coherence tomography).[6] PRL (presence of ≥1 PRL) and central vein sign (CVS, Select-6 algorithm) positivity were assessed on the first MRI with a T2*-EPI sequence (figure 1A).[2] A PRL was considered to be

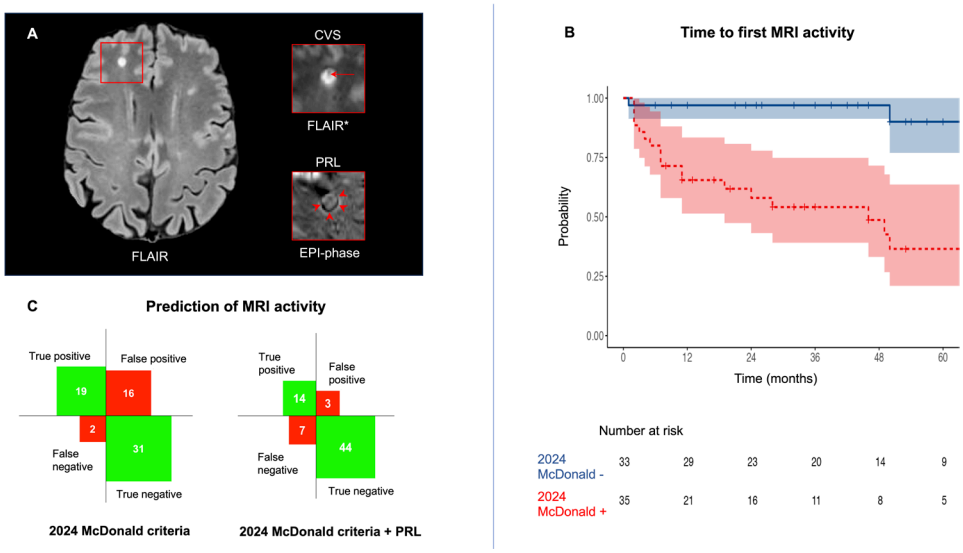

Figure 1 (A) Representative T2-FLAIR hyperintense lesion in a pre-symptomatic patient who underwent MRI activity. This lesion featured the multiple sclerosis (MS)-typical susceptibility-based MRI biomarkers (magnified boxes): the central vein sign (CVS) on FLAIR* images (arrow) and the paramagnetic rim lesion (PRL) sign on 3D T2*-weighted EPI unwrapped phase images (arrowheads). This individual fulfilled the 2024 McDonald criteria for MS. (B) Survival curves based on Kaplan-Meier estimates for time to first MRI activity according to the 2024 McDonald criteria classification. (C) Confusion matrix testing the performance of the 2024 McDonald criteria alone versus 2024 McDonald criteria in combination with PRL (as an additional feature) to predict MRI activity in patients with incidental MRI findings suggestive of MS. EPI, echo-planar imaging; FLAIR, fluid-attenuated inversion recovery.

already present at the time of the index MRI if it corresponded to a visible T2 lesion on the index scan; otherwise, it was considered absent (online supplemental methods). Cerebrospinal fluid (CSF) positivity was defined as oligoclonal bands detection and/or kappa free light chain index positivity.[1] Disease-modifying treatments (DMTs) exposure was categorised as a binary variable.

Clinical conversion was defined as the development of any neurological symptoms suggestive of MS, MRI activity as ≥1 new T2 lesion or gadolinium-enhancing lesion at follow-up MRI. Annualised lesion rate (ALR) was calculated as the number of new T2 lesions detected at follow-up MRIs divided by the radiological follow-up duration.

Patients were classified according to the fulfilment of the 2024 revised McDonald criteria in positive (2024McDonald+) or negative (2024McDonald−).[1] Fulfilment of the 2024 McDonald criteria together with the presence of PRL as an additional feature was considered as an exploratory model ('2024 McDonald+PRL'), as PRL are not currently included in the diagnostic criteria for pre-symptomatic MS. Patients were subsequently classified as either positive (2024McDonaldPRL+) or negative (2024McDonaldPRL−).

Statistical analysis

Group comparisons used t-test/Mann-Whitney and χ^2/Fisher tests. Time to first MRI activity was analysed using a multivariable Cox model with Firth correction, including significant univariable predictors and DMT exposure as a time-varying covariate. ALR was analysed using a mixed-effects Poisson model, including significant predictors, radiological follow-up as an offset, DMT exposure and PRL as time-varying covariates.

The predictive performance of the 2024 McDonald criteria for MRI activity was assessed using penalised Cox regression. Logistic regression and receiver operating characteristic analyses evaluated the predictive value of the 2024 McDonald criteria versus 2024 McDonald+PRL for MRI activity; McNemar's test compared binary classifications. Sensitivity analyses and statistical details are described in online supplemental methods.

RESULTS

Baseline characteristics and risk stratification

We recruited 68 participants with a mean (SD) radiological follow-up of 56(50) months. Demographic, clinical and MRI features in individuals who did (n=21) and did not (n=47) show MRI activity are summarised in online supplemental table 2. Mean (SD) time to MRI activity was 20 (23) months. Two of the 21 patients undergoing MRI activity also underwent clinical conversion.

Univariable Cox regression analyses identified MS family history, infratentorial lesions, PRL presence, CVS Select-6 and CSF positivity as associated with a shorter time to first MRI activity (table 1).

In the multivariable model, PRL presence was the only feature independently associated with an approximately sixfold higher risk of MRI activity (HR 5.66, 95% CI 1.33 to 28.39, p=0.019).

In univariable Poisson models, younger age at index MRI, infratentorial, ovoid-shaped periventricular lesions and PRL presence, CVS Select-6 and CSF positivity were all associated with a higher ALR (online supplemental table 3). In the multivariable model, only PRL presence (rate ratio (RR) 3.45, 95% CI 1.40 to 8.47, p=0.007) and CVS Select-6 positivity (RR 4.09, 95% CI 1.17 to 14.27, p=0.027) remained independently associated with lesion accrual.

Sensitivity analyses confirmed these findings (a) in the subgroup of patients with at least 18 months of radiological follow-up (n=51), (b) in the larger cohort (irrespective of available CSF results) (n=67), (c) in patients with less than 2 years between index MRI and susceptibility-based MRI (n=42) and in patients fulfilling dissemination in space (DIS) criteria (n=56) (online supplemental results).

Adding PRL to the 2024 McDonald criteria

In our cohort, 35 patients were 2024McDonald+ and 33 2024McDonald−. All 2024McDonald+ patients fulfilled DIS (in ≥2 of 5 CNS locations: cortical/juxtacortical, periventricular, infratentorial, spinal cord, optic nerve)[1]: 32 were CVS Select-6 and 23 CSF positive. All patients were diagnosed according to

Table 1 Univariable and multivariable Cox regression analyses for time to first MRI activity

Variable	Patient (n)	Univariable analyses HR (95% CI, p value)	Multivariable analysis* HR (95% CI, p value)
Age at index MRI	68	0.98 (0.94 to 1.03, p=0.43)	–
Sex, female	68	0.59 (0.23 to 1.53, p=0.28)	–
MS family history	68	**4.79 (1.59 to 14.49, p=0.006)**	1.38 (0.27 to 5.93, p=0.67)
Reason for index MRI, headache	68	0.78 (0.32 to 1.95, p=0.6)	–
≥9 T2 lesions or gadolinium-enhancing lesion presence	68	1.47 (0.61 to 3.56 p=0.4)	–
≥3 periventricular lesion presence	68	1.87 (0.75 to 4.66, p=0.18)	–
Juxtacortical/cortical lesion presence	68	1.54 (0.52 to 4.57, p=0.44)	–
Infratentorial lesion presence	68	**6.28 (2.34 to 16.84, p<0.001)**	1.27 (0.34 to 4.94, p=0.72)
Corpus callosum lesion presence	68	1.85 (0.67 to 5.10, p=0.23)	–
Ovoid periventricular lesion presence	68	1.79 (0.69 to 4.69, p=0.23)	–
Spinal cord lesion presence	58	2.15 (0.85 to 5.43, p=0.11)	–
PRL presence	68	**21.95 (6.15 to 78.4, p<0.001)**	**5.66 (1.33 to 28.39, p=0.02)**
CVS Select-6 positivity	67	**11.64 (2.69 to 50.32, p=0.001)**	1.84 (0.47 to 10.53, p=0.41)
CSF positivity (oligoclonal bands or kFLC)	41	**7.57 (1.71 to 33.5, p=0.008)**	2.69 (0.68 to 15.55, p=0.17)
Optic nerve involvement (OCT, VEP and/or MRI)	34	1.98 (0.6 to 6.56, p=0.26)	–
DMT exposure before the event/censoring†	68	NA‡	3.77 (0.03 to 49.91, p=0.47)

Bold values indicate statistical significance (p < 0.05).
*Multivariable analysis was performed on the long-format complete-case dataset (n=41 subjects, n=45 observations) as lumbar puncture was performed only in patients who provided consent for the procedure (n=41). Patients with CSF assessment did not differ in terms of age and sex from the full cohort (mean (SD) age 37.6 (10.7) vs 37.9 (10.4), p=0.83; n (%) females 33 (80.5) vs 54 (79.4), p=0.89).
†DMT was fitted into the penalised Cox regression model as a binary time-varying covariate.
‡This result was not estimable as no MRI activity events were observed in patients under DMT (n=5).
CI, confidence interval; CSF, cerebrospinal fluid; CVS, central vein sign; DMT, disease-modifying treatment; HR, hazard ratio; kFLC, kappa free light chain; MS, multiple sclerosis; n, number; NA, not assessed; OCT, optical coherence tomography; PRL, paramagnetic rim lesions; VEP, visual evoked potentials.

the DIS fulfilment and either CVS Select-6 or CSF positivity, while the inclusion of dissemination in time did not change patient classification. Fulfilment of the 2024 McDonald criteria increased the risk of future MRI activity (HR=11.95, 95% CI 2.77 to 51.51, p=0.001) (figure 1B).

Adding the presence of any PRL to the 2024 McDonald criteria changed the classification performance for MRI activity prediction (2024 McDonald: R^2=0.25, OR=18.41, area under the curve (AUC)=0.78; accuracy 0.74, specificity 0.66, sensitivity 0.91, positive predictive value (PPV) 0.54 vs 2024 McDonald+PRL: R^2=0.33, OR=29.33, AUC=0.8, accuracy 0.85, specificity 0.94, sensitivity 0.67, PPV 0.82). McNemar's test showed a significant difference in binary classification between the two approaches (χ^2=18, p<0.001) (figure 1C).

DISCUSSION

In this study, PRL emerged as the most robust predictor of radiological activity in pre-symptomatic MS, being independently associated with both time to first MRI activity and ALR, outperforming traditional clinical/laboratory/MRI biomarkers. Moreover, among individuals fulfilling the 2024 McDonald diagnostic criteria, the addition of PRL provided further information for risk stratification for subsequent MRI activity.

Previous studies identified younger age, infratentorial or spinal cord lesions, and CSF positivity as predictors of clinical conversion in radiologically isolated syndrome (RIS).[5 7–9] In our cohort, many of these features showed similar associations with MRI activity and ALR in univariable analyses, confirming their role as early markers of disease activity. Interestingly, none of these associations remained significant in multivariable models once the advanced susceptibility-based MRI biomarkers were included. Specifically, PRL emerged as the most consistent predictor across different analyses, highlighting their potential to predict future radiological activity in pre-symptomatic individuals.

The CVS was incorporated into the 2024 McDonald criteria because of its high diagnostic accuracy and prevalence in RIS.[10–12] In our study, CVS Select-6 positivity was associated with higher ALR but less consistently with time to first MRI activity, supporting evidence of no clear association with clinical conversion in RIS.[3]

PRL reflect chronic active inflammation at the lesion edge, with ongoing microglial activation and iron accumulation, leading to both focal and diffuse tissue damage and remyelination failure.[13 14] This pathological substrate likely explains their stronger association with radiological activity. Consistently, higher PRL burden in RIS has been associated with a shorter time to symptom onset, outperforming white matter and spinal cord lesions.[3] Our data extend these previous findings by showing that, in a pre-symptomatic MS cohort systematically assessed with susceptibility-based MRI, PRL retain an independent predictive value for lesion accrual even after adjusting for clinical variables, index MRI characteristics, CSF assessment and CVS Select-6.

The 2024 McDonald criteria allow MS diagnosis in selected pre-symptomatic individuals, enabling earlier DMT initiation to potentially reduce the risk of future disease progression.[15] We found that incorporating PRL as an additional requirement in the 2024 McDonald criteria increased specificity, PPV, and accuracy (although decreasing sensitivity) for predicting MRI activity. In a context where early identification of high-risk individuals could inform closer monitoring or earlier therapeutic intervention,[16] PRL assessment may provide clinically relevant information to support risk stratification.

This study has some limitations, including its retrospective design, relatively small sample size and single-centre MRI protocol, which may limit generalisability. In addition, the limited number of events relative to the number of candidate predictors resulted in wide CIs for some estimates, limiting the precision of the estimated effect sizes. However, to reduce the risk of model instability associated with small samples, we used penalised Cox regression with Firth's

correction, an approach specifically designed to provide robust and less biased estimates in this setting.

Although main analyses included patients with at least one≥3 mm FLAIR hyperintense lesion in a typical MS location, our results remained unchanged when analyses were restricted to patients fulfilling DIS criteria, thereby minimising potential risk of misdiagnosis.

PRL were assessed on susceptibility-based MRI acquired after the index MRI (median interval ~12 months). Given the gradual fading of paramagnetic rims, this approach may have underestimated PRL prevalence and, consequently, the observed associations. Nevertheless, sensitivity analyses restricted to patients with less than 2 years between the two MRIs confirmed and further supported our findings, identifying PRL as the main predictor of radiological activity.

In our cohort, 9 out of 14 treated patients initiated DMT after the first MRI activity event, reflecting the clinical practice of treating individuals with higher radiological disease activity earlier. Although DMT exposure was included as a time-varying covariate in our models, the limited number of treated patients restricted the ability to reliably assess treatment effects; therefore, these analyses should be considered exploratory.

Finally, we focused on complementary radiological outcomes rather than clinical conversion, as these measures capture both the timing (time to first MRI activity) and extent (ALR) of subclinical disease activity. This approach enables the detection of earlier disease activity preceding overt clinical manifestations and aligns with a biology-driven clinical decision framework for MS.

In conclusion, PRL identify pre-symptomatic MS individuals at higher risk of radiological activity and may complement current diagnostic criteria for risk stratification.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. The study received approval from the local ethical committee of Cliniques Universitaires Saint-Luc (IRB: B4032020000104). Participants gave informed consent to participate in the study before taking part.

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