

# diagnosis

## A reappraisal

OPEN

Georgina Arrambide, MD, PhD\*  
 Mar Tintore, MD, PhD\*  
 Cristina Auger, MD  
 Jordi Río, MD, PhD  
 Joaquín Castelló, MD, PhD  
 Angela Vidal-Jordana, MD, PhD  
 Ingrid Galán, MD  
 Carlos Nos, MD  
 Manuel Comabella, MD, PhD  
 Raquel Mitjana, MD  
 Patricia Mulero, MD  
 Andrea de Barros, MD  
 Breogán Rodríguez-Acevedo, MD  
 Luciana Midaglia, MD  
 Jaume Sastre-Garriga, MD, PhD  
 Alex Rovira, MD†  
 Xavier Montalban, MD, PhD†

Correspondence to Dr. Montalban: [xavier.montalban@cem-cat.org](mailto:xavier.montalban@cem-cat.org)

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### ABSTRACT

**Objectives:** To assess the contributions of cortico-juxtacortical and corpus callosum lesions to multiple sclerosis diagnosis and to compare the value of  $\geq 1$  vs  $\geq 3$  periventricular lesions in clinically isolated syndromes (CIS).

**Methods:** Step 1: We evaluated lesion topography classifications in 657 patients with CIS with stepwise Cox proportional hazards regression models considering second attack as the outcome. Step 2: We established 2 dissemination in space (DIS) versions according to the periventricular lesion cutoffs of  $\geq 1$  and  $\geq 3$  and assessed their performance at 10 years with second attack as the outcome, first individually and then combined with dissemination in time (DIT) in all cases ( $n = 326$ ), by age, and by CIS topography.

**Results:** Step 1: The models (hazard ratios [95% confidence interval]) favored  $\geq 1$  over  $\geq 3$  periventricular lesions (2.5 [1.7–3.6]) and cortico-juxtacortical over juxtacortical lesions (1.4 [1.0–1.8]). Callosal lesions were not selected. Step 2: DIS specificity with  $\geq 1$  periventricular lesions was slightly lower than with  $\geq 3$  (59.1 vs 61.4) and the same after adding DIT (88.6). Regarding age,  $\geq 3$  periventricular lesions improved DIS specificity over  $\geq 1$  lesions in the 40–49 years of age bracket (66.7 vs 58.3). This difference disappeared when adding DIT (83.3). Optic neuritis had a similar pattern when evaluating CIS topographies.

**Conclusions:** Our results comply with the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) consensus recommendation of combining cortical and juxtacortical lesions into a single term when possible. Concerning periventricular lesions, maintaining the current  $\geq 1$  cutoff in the McDonald criteria does not compromise specificity in typical CIS cases, but attention should be paid to older patients or optic neuritis cases. *Neurology*® 2017;89:2351–2356

### GLOSSARY

**CC** = corpus callosum; **CIS** = clinically isolated syndrome; **CJC** = cortical and juxtacortical; **DIR** = double inversion recovery; **DIS** = dissemination in space; **DIT** = dissemination in time; **EDSS** = Expanded Disability Status Scale; **FLAIR** = fluid-attenuated inversion recovery; **Gd** = gadolinium; **JC** = juxtacortical; **MAGNIMS** = Magnetic Resonance Imaging in Multiple Sclerosis; **MS** = multiple sclerosis; **PV** = periventricular; **SC** = spinal cord.

Recently, an expert opinion consensus on proposed modifications to the multiple sclerosis (MS) diagnostic criteria suggested the increase of periventricular (PV) lesions from  $\geq 1$  to  $\geq 3$  and the inclusion of cortical, optic nerve, and symptomatic lesions for determining dissemination in space (DIS).<sup>1</sup> Previous publications showed the relevance of lesion topographies for MS diagnosis<sup>2,3</sup> or reassessed the role of PV lesion number.<sup>4</sup> Regarding cortical lesions, they can be identified using nonconventional MRI and were proposed as part of the DIS criteria before,<sup>5</sup> but interobserver variability is high.<sup>6</sup> In this sense, the expert opinion consensus proposed

\*These authors contributed equally to this work.

†These authors contributed equally as principal investigators.

From Servei de Neurologia–Neuroimmunologia, Centre d'Esclerosi Múltiple de Catalunya (CEM-CAT) (G.A., M.T., J.R., J.C., A.V.-J., I.G., C.N., M.C., P.M., B.R.-A., L.M., J.S.-G., X.M.), and Magnetic Resonance Unit, Department of Radiology (IDI) (C.A., R.M., A.d.B., A.R.), Vall d'Hebron Institut de Recerca, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Spain; and Division of Neurology (X.M.), St. Michael's Hospital, University of Toronto, Canada.

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combining cortical and juxtacortical (JC) lesions into a single term (CJC). Finally, corpus callosum (CC) lesions are common in MS but do not appear to contribute to the diagnosis.<sup>7</sup>

Therefore, the objective of this study was to assess the contributions of CJC and CC lesions to MS diagnosis and to compare the value of  $\geq 1$  vs  $\geq 3$  PV lesions, additionally stratified by age or clinically isolated syndrome (CIS) topography, in CIS.

**METHODS Study cohort.** This study was based on a longitudinal, open CIS cohort at the MS Centre, Vall d'Hebron University Hospital, Barcelona, Spain, following a protocol described elsewhere.<sup>3,8</sup> Briefly, we included patients <50 years of age first seen within 3 months of the CIS. We recorded demographic data, CIS topography, presence of oligoclonal bands, and disability according to the Expanded Disability Status Scale (EDSS) at baseline, and performed follow-up visits every 3–6 months assessing for relapses and disability according to the EDSS measured during stability periods. Concerning additional MRI acquisition and analysis for this study, transverse or sagittal 3D double inversion recovery (DIR) sequences were performed since 2010. One of two experienced neuroradiologists (C.A., A.R.) blinded to clinical follow-up assessed the MRI scans during the daily clinical practice. In doubtful cases, the final analysis was based on their consensus opinion. They scored the number and location of lesions on T2-weighted images and the number of gadolinium (Gd)-enhancing lesions on brain MRI. From 2006, we recorded the presence of CC lesions on T2–fluid-attenuated inversion recovery (FLAIR) sagittal sequences prospectively in the CIS database. We constructed the CJC variable by combining supratentorial JC and intracortical lesions and assessed it on DIR and T2-FLAIR images. Importantly, we defined PV lesions as

those in contact with the lateral or third ventricles, but not when in contact with the fourth ventricle. CC lesions were not considered PV unless they extended outside the CC, and we only considered a lesion to be callosal when identified in 3–5 mid-sagittal images (with a 3-mm slice thickness), therefore excluding those that were paracallosal and thus considered PV. Finally, from 2007, we scored lesion number and presence of Gd enhancement on spinal cord (SC) MRI systematically.

**Experimental design. Step 1.** To evaluate the effect of individual lesion topographies, we selected patients with sufficient information on baseline brain MRI to assess DIS and dissemination in time (DIT) according to the 2010 McDonald criteria ( $n = 657$ ). Next, we established the following lesion topography classifications:  $\geq 1$  PV,  $\geq 3$  PV,  $\geq 1$  JC,  $\geq 1$  CJC,  $\geq 1$  CC,  $\geq 1$  infratentorial, and  $\geq 1$  SC. We then ran univariable and multivariable Cox proportional hazards regression models using a forward and backward stepwise analysis with likelihood ratio statistics ( $p$  value for entry of 0.05 and  $p$  value for removal of 0.1) considering second attack as the outcome during the total follow-up time. We added a “missing” category for patients with no recorded SC or CC lesions. We used bootstrap resampling to cope with overfitting.

**Step 2.** To evaluate performance, we selected cases from step 1 with a minimum follow-up of 10 years or a second attack within 10 years of the CIS<sup>9</sup> ( $n = 326$ ). We constructed the 2010 DIS criteria<sup>10</sup> taking into account the symptomatic lesions<sup>11,12</sup> and using the CJC topography (according to the results from step 1). Next, we established 2 DIS versions according to the PV lesion cutoffs of  $\geq 1$  and  $\geq 3$ . We then assessed the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of both DIS versions, first individually and then combined with DIT, with second attack at 10 years as the outcome. Finally, we evaluated the performance of  $\geq 1$  and  $\geq 3$  PV lesions as part of DIS alone and DIS plus DIT according to age (40–49, 30–39, 20–29, and  $\leq 19$  years) and CIS topography (optic nerve, infratentorial, SC, and other, which can include multifocal or hemispheric syndromes).

Statistical tests were performed on the 0.05 level of significance using IBM SPSS Statistics (SPSS Inc., Chicago, IL), version 22.0.

**Standard protocol approvals, registrations, and patient consents.** This study received approval from the Clinical Research Ethics Committee at Vall d'Hebron University Hospital. All patients signed written informed consents.

**RESULTS** From January 1995 to January 2016, we included 1,214 patients in the CIS cohort. Of these, we excluded 71 (5.8%) during follow-up for having presented a previous demyelinating attack ( $n = 13$ ), exceeding the age limit ( $n = 4$ ), exceeding the entry window ( $n = 26$ ), or reaching an alternative diagnosis ( $n = 28$ ). Of the remaining 1,143 patients, 657 fulfilled the criteria for step 1 and 326 fulfilled the criteria for step 2.

**Step 1. Baseline characteristics.** Of the 657 patients, 66.5% were female, and they had a mean (SD) age of 32.2 (8.0) years. The baseline brain MRI was abnormal in 75.5%. During a mean follow-up of 6.5 (4.2) years, 282 (42.9%) presented a second attack (table 1).

**Effect of individual lesion topography classifications.** Table 2 shows the number of patients fulfilling each type of lesion topography classification, the

**Table 1** Baseline characteristics of the studied cohorts

	Step 1 (n = 657)	Step 2 (n = 326)
Female, n (%)	437 (66.5)	227 (69.6)
Mean (SD) age, y	32.2 (8.0)	31.5 (7.9)
CIS topography, n (%)		
Optic nerve	219 (33.3)	92 (28.2)
Brainstem	179 (27.2)	92 (28.2)
Spinal cord	180 (27.4)	101 (31.0)
Other	79 (12.0)	41 (12.6)
OB present, n (%) <sup>a</sup>	335 (59.3)	211 (72.5)
Abnormal baseline brain MRI, n (%)	496 (75.5)	293 (89.9)
Abnormal baseline SC MRI, n (%) <sup>b</sup>	172 (52.3)	76 (66.1)
Gd enhancement on brain MRI, n (%)	191 (29.1)	127 (39.0)
Gd enhancement on SC MRI, n (%) <sup>b</sup>	54 (16.4)	28 (24.3)
Mean (SD) follow-up, y	6.5 (4.2)	9.0 (3.8)
DMT before second attack, n (%)	184 (28.0)	101 (31.0)

Abbreviations: CIS = clinically isolated syndrome; DMT = disease-modifying treatment; Gd = gadolinium; OB = oligoclonal bands; SC = spinal cord.

<sup>a</sup>OB:  $n = 565$  in step 1,  $n = 291$  in step 2.

<sup>b</sup>SC MRI:  $n = 329$  in step 1,  $n = 115$  in step 2.

proportion presenting a second attack, and their corresponding hazard ratios (95% CI). Both stepwise models confirmed the significant contributions of  $\geq 1$  PV,  $\geq 1$  CJC, and  $\geq 1$  infratentorial lesions;  $\geq 1$  SC lesions remained in the second to last backward step (1.5 [1.0–2.2];  $p = 0.045$ ). Bootstrap showed no overfitting in our models (bias from  $-0.008$  to  $0.009$ ).

**Step 2. Baseline characteristics.** Of the 326 patients, 69.6% were female, and they had a mean (SD) age of 31.5 (7.9) years; the baseline brain MRI was abnormal in 89.9%. Gd enhancement was demonstrated in 39.0% of brain and 24.3% ( $n = 28/115$ ) of SC scans. During a mean follow-up of 9.0 (3.8) years, 86.5% presented a second demyelinating attack. Disease-modifying treatment was started before the second attack in 31.0% (table 1). The proportion of patients treated before the second attack fulfilling DIS with  $\geq 1$  PV lesions was similar to DIS with  $\geq 3$  PV lesions (40.3% and 42.5%, respectively), and between DIS plus DIT with  $\geq 1$  (51.6%) and  $\geq 3$  PV lesions (52.4%).

**Performance of DIS and DIS plus DIT according to the PV lesion number cutoffs.** Concerning the performance of the modified 2010 criteria, although the specificity of the criteria with  $\geq 1$  PV lesions was slightly lower than with  $\geq 3$  PV when assessing DIS (table 3), it was exactly the same after combining them with DIT (table 4).

When assessing age groups,  $\geq 3$  PV lesions conferred a higher specificity to DIS than  $\geq 1$  PV lesions in the 40–49 years of age bracket (table 3). This difference disappeared when evaluating DIS plus DIT (table 4). We observed a very similar pattern in optic neuritis when evaluating CIS topographies (tables e-1 and e-2 at Neurology.org).

**DISCUSSION** In step 1, the stepwise multivariable analyses selected CJC over JC lesions and thus we

used the former topography in our DIS model for step 2. If also considering the univariable analyses and the similar proportion of patients with JC and CJC lesions presenting a second attack, our findings support the notion that the sharp differentiation between JC and intracortical lesions is not necessary, complying with the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) consensus recommendation of combining them into a single term<sup>1</sup> in specialized institutions where this is possible, whereas in other centers the determination of JC lesions could suffice. Nevertheless, a limitation of our study is our recent implementation of DIR (2010), which could lead to missing patients with intracortical lesions; hence, further studies are needed to validate these results. Concerning CC lesions, our negative results coincide with a previous study,<sup>7</sup> even though in our case we did have sagittal images and T2-FLAIR sequences. Contrary to these findings, another study did show an effect of CC lesions but the individual contributions of each lesion topography were not taken into account,<sup>13</sup> an important issue since different lesion topographies can coexist. Nonetheless, our negative results could be influenced by the lower number of patients with prospectively recorded CC lesion data. Another possible explanation is that CC lesions are less frequently associated with Gd enhancement than deep white matter lesions and, therefore, may not be good predictors for the development of a second attack.<sup>14</sup> Another limitation in step 1 is the smaller sample size in the case of SC lesions.

Regarding PV lesions in step 1, the stepwise analyses favored  $\geq 1$  PV over  $\geq 3$  PV lesions. The MAGNIMS expert consensus proposed going back to the 3-lesion cutoff,<sup>7</sup> based on the detection of incidental PV lesions in healthy individuals and patients with other neurologic diseases, and on studies showing that this lesion threshold could help differentiate MS from other diseases.<sup>1</sup> Although incidental PV lesions could

**Table 2** Proportions and hazard ratios (HRs) of the different lesion topographies ( $n = 657$ )

	n (%)	Second attack, n (%)	Univariable HR (95% CI)	p	HR with forward and backward stepwise analyses (95% CI)	p
$\geq 1$ PV	414 (63.0)	232/414 (56.0)	3.7 (2.7–5.0)	<0.0001	2.5 (1.7–3.6)	<0.0001
$\geq 3$ PV	356 (54.2)	211/356 (59.3)	3.2 (2.4–4.2)	<0.0001	—	
$\geq 1$ JC	295 (44.9)	172/295 (58.3)	2.5 (2.0–3.2)	<0.0001	—	
$\geq 1$ CJC	298 (45.4)	174/298 (58.4)	2.5 (2.0–3.2)	<0.0001	1.4 (1.0–1.8)	0.025
$\geq 1$ CC	187/433 (43.2)	84/187 (44.9)	2.0 (1.4–2.7)	<0.0001	—	
$\geq 1$ IT	328 (49.9)	191/328 (58.2)	2.6 (2.0–3.3)	<0.0001	1.4 (1.1–1.9)	0.013
$\geq 1$ SC	172/329 (52.3)	76/172 (44.2)	2.2 (1.5–3.3)	<0.0001	—	

Abbreviations: CC = corpus callosum; CI = confidence interval; CJC = cortico-juxtacortical; IT = infratentorial; JC = juxtacortical; PV = periventricular; SC = spinal cord. Outcome: second attack.

**Table 3** DIS performance in all cases and by age groups, according to the PV lesion cutoffs ( $\geq 1$  vs  $\geq 3$ ) (total n = 326)

	DIS, n (%)	Second attack in patients with DIS, n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
<b>DIS <math>\geq 1</math> PV</b>							
All	236/326 (72.4)	218/236 (92.4)	77.3 (72.0–82.1)	59.1 (43.3–73.7)	74.8 (69.8–79.5)	92.4 (89.4–94.6)	28.9 (22.7–36.0)
40–49 y	45/57 (78.9)	40/45 (88.9)	88.9 (76.0–96.3)	58.3 (27.7–84.8)	82.5 (70.1–91.3)	88.9 (80.3–94.0)	58.3 (35.0–78.4)
30–39 y	84/122 (68.9)	78/84 (92.9)	73.6 (64.1–81.7)	62.5 (35.4–84.8)	72.1 (63.3–79.9)	92.9 (87.2–96.1)	26.3 (17.9–36.9)
20–29 y	97/130 (74.6)	90/97 (92.8)	78.3 (69.6–85.4)	53.3 (26.6–78.7)	75.4 (67.1–82.5)	92.8 (88.1–95.7)	24.2 (15.1–36.5)
$\leq 19$ y	10/17 (58.8)	10/10 (100.0)	62.5 (35.4–84.8)	100.0 (2.5–100.0)	64.7 (38.3–85.8)	100.0 (69.2–100.0)	14.3 (8.1–23.9)
<b>DIS <math>\geq 3</math> PV</b>							
All	221/326 (67.8)	204/221 (92.3)	72.3 (66.7–77.5)	61.4 (45.5–75.6)	70.9 (65.6–75.7)	92.3 (89.1–94.6)	25.7 (20.4–31.9)
40–49 y	41/57 (71.9)	37/41 (90.2)	82.2 (68.0–92.0)	66.7 (34.9–90.1)	78.9 (66.1–88.6)	90.2 (80.4–95.4)	50.0 (32.2–67.8)
30–39 y	77/122 (63.1)	71/77 (92.2)	67.0 (57.2–75.8)	62.5 (35.4–84.8)	66.4 (57.3–74.7)	92.2 (86.1–95.8)	22.2 (15.2–31.3)
20–29 y	93/130 (71.5)	86/93 (92.5)	74.8 (65.8–82.4)	53.3 (26.6–78.7)	72.3 (63.8–79.8)	92.5 (87.6–95.5)	21.6 (13.5–32.8)
$\leq 19$ y	10/17 (58.8)	10/10 (100.0)	62.5 (35.4–84.8)	100.0 (2.5–100.0)	64.7 (38.3–85.8)	100.0 (69.2–100.0)	14.3 (8.1–23.9)

Abbreviations: CI = confidence interval; DIS = dissemination in space; NPV = negative predictive value; PPV = positive predictive value; PV = periventricular.

Outcome: second attack at 10 years. Modifications to the criteria include symptomatic lesions and  $\geq 1$  cortical and juxtacortical lesions.

also suggest a radiologically isolated syndrome, it is important to emphasize the role of specificity to minimize the risk of overdiagnosing MS, especially in older patients. Therefore, in step 2 we compared their performance, observing that in DIS, the  $\geq 3$  cutoff was only 2.3% more specific than  $\geq 1$ . Furthermore, when evaluating DIS plus DIT, the diagnostic performance was practically the same for both. These results are in accordance with a more recent publication that studied the effect of a varying number of PV lesions in 151 patients with CIS.<sup>4</sup> In

addition, another study compared the performance of the 2010 McDonald criteria and the 2016 MAGNIMS proposal, observing an overall lower specificity for the latter, which includes  $\geq 3$  PV lesions for DIS (63.1% vs 46.4%, respectively).<sup>15</sup>

However, when assessing age brackets in our study, the specificity gap increased to 8.4% favoring DIS with  $\geq 3$  PV lesions in patients aged 40–49 years. But once again, when assessing DIS plus DIT, we found no differences in specificity. The same occurred with optic neuritis cases when we assessed

**Table 4** DIS plus DIT performance in all cases and by age groups, according to the PV lesion cutoffs ( $\geq 1$  vs  $\geq 3$ ) (total n = 326)

	DIS + DIT, n (%)	Second attack in patients with DIS + DIT, n (%)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	PPV (95% CI)	NPV (95% CI)
<b>DIS + DIT <math>\geq 1</math> PV</b>							
All	128/326 (39.3)	123/128 (96.1)	43.6 (37.8–49.6)	88.6 (75.4–96.2)	49.7 (44.1–55.3)	96.1 (91.4–98.3)	19.7 (17.5–22.1)
40–49 y	23/57 (40.4)	21/23 (91.3)	46.7 (31.7–62.1)	83.3 (51.6–97.9)	54.4 (40.7–67.6)	91.3 (74.0–97.5)	29.4 (22.3–37.7)
30–39 y	39/122 (32.0)	37/39 (94.9)	34.9 (25.9–44.8)	87.5 (61.7–98.5)	41.8 (32.9–51.1)	94.9 (83.1–98.6)	16.9 (13.9–20.4)
20–29 y	59/130 (45.4)	58/59 (98.3)	50.4 (41.0–59.9)	93.3 (61.7–98.5)	55.4 (46.4–64.1)	98.3 (89.6–99.7)	19.7 (16.4–23.6)
$\leq 19$ y	7/17 (41.2)	7/7 (100.0)	43.8 (19.8–70.1)	100.0 (2.5–100.0)	47.1 (23.0–72.2)	100.0 (59.0–100.0)	10.0 (6.7–14.6)
<b>DIS + DIT <math>\geq 3</math> PV</b>							
All	126/326 (38.7)	121/126 (96.0)	42.9 (37.1–48.9)	88.6 (75.4–96.2)	49.1 (43.5–54.6)	96.0 (91.3–98.2)	19.5 (17.3–21.9)
40–49 y	23/57 (40.4)	21/23 (91.3)	46.7 (31.7–62.1)	83.3 (51.6–97.9)	54.4 (40.7–67.6)	91.3 (74.0–97.5)	29.4 (22.3–37.7)
30–39 y	38/122 (31.1)	36/38 (94.7)	34.0 (25.0–43.8)	87.5 (61.7–98.5)	41.0 (32.2–50.3)	94.7 (82.7–98.5)	16.7 (13.7–20.1)
20–29 y	58/130 (44.6)	57/58 (98.3)	49.6 (40.1–59.0)	93.3 (68.1–99.8)	54.6 (45.7–63.4)	98.3 (89.5–99.7)	19.4 (16.1–23.2)
$\leq 19$ y	7/17 (41.2)	7/7 (100.0)	43.8 (19.8–70.1)	100.0 (2.5–100.0)	47.1 (23.0–72.2)	100.0 (59.0–100.0)	10.0 (6.7–14.6)

Abbreviations: CI = confidence interval; DIS = dissemination in space; DIT = dissemination in time; NPV = negative predictive value; PPV = positive predictive value; PV = periventricular.

Outcome: second attack at 10 years. Modifications to the criteria include symptomatic lesions and  $\geq 1$  cortical and juxtacortical lesions.

CIS topography. Altogether, these findings in patients with typical CIS suggest that, first, the presence of  $\geq 1$  PV lesions already indicates an increased risk of presenting a second attack; second, their diagnostic specificity is high when combined with at least another typical topography; third, this specificity is only slightly inferior to  $\geq 3$  PV lesions; and fourth, their specificity is the same if also considering DIT. The latter is particularly relevant when taking age into account, given that the difference in specificity favoring  $\geq 3$  PV lesions in older patients disappears after adding DIT. Furthermore, this increased specificity in older patients can be explained by the fact that the presence of small, focal high-intensity areas surrounding the regions around the anterior and posterior pole of the lateral ventricles, and thin linear hyperintensities along the body of the lateral ventricles on T2-weighted images, the so-called PV caps and bands, are a common finding in normal aging.<sup>16</sup> However, these incidental findings are usually symmetric and not oval-shaped, and should not be confused with the PV lesions seen in MS.

As for the increased specificity of DIS with  $\geq 3$  PV lesions in optic neuritis, previous studies demonstrated that the lower rate of second demyelinating attacks in this topography compared to others disappeared when selecting only the cases with abnormal brain MRIs<sup>17</sup> or when including other risk factors in the analyses.<sup>8</sup> Hence, the higher specificity observed in DIS with  $\geq 3$  PV lesions could probably be influenced by a higher T2 lesion number at baseline. That the difference disappears when adding DIT underscores the importance of Gd-enhancing lesions for establishing MS diagnosis.

Importantly, we do not consider it practical to produce a different set of criteria for older patients or cases presenting with optic neuritis. Preferably, we should underscore that the McDonald criteria were outlined to be applied in patients we suspect might have MS and that we should always ensure there is no better diagnostic explanation for the clinical presentation.

Therefore, maintaining the current threshold of  $\geq 1$  PV lesions in the McDonald criteria does not compromise specificity in typical CIS cases, but special attention should be paid to older patients and optic neuritis cases.

#### AUTHOR CONTRIBUTIONS

Georgina Arrambide contributed to the concept and design of the work; acquisition, analysis, and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. Mar Tintore contributed to the concept and design of the work; acquisition, analysis, and interpretation of data for the work; participated in the drafting of the work and revised it for important intellectual content; and gave final approval of the version to be published. Cristina Auger contributed to the acquisition and analysis of data for the work; participated in the revision of the manuscript

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#### DISCLOSURE

G. Arrambide has received compensation for consulting services from Biogen-Idec, research support from Novartis, and speaking honoraria from Sanofi-Aventis. M. Tintore has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma,

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