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ORIGINAL COMMUNICATION

Criteria improving multiple sclerosis diagnosis at the first MRI

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Abstract The introduction of the McDonald criteria has enabled earlier diagnosis of multiple sclerosis (MS). However, even with the 2010 revised criteria, nearly 50 % of patients remain classified as "possible MS" following the first MRI. The present study aimed to demonstrate that time to MS diagnosis could be shorter than 2010 revised criteria, and established after a single early MRI in most patients with the association of the symptomatic lesion and at least one suggestive asymptomatic lesion. We also evaluated the short-term predictive capacity of an individual suggestive lesion on disease activity. We analyzed initial MRI results from 146 patients with MS from a multicenter retrospective study. Visualization of the symptomatic lesion was used as a primary criterion. Secondary criteria included one suggestive lesion (SL) aspect or topography on MRI, or one non-specific lesion associated with positive CSF. The proposed criteria led to a positive diagnosis of MS in 100 % of cases, from information available from the time of the first MRI for 145 patients (99.3 %). At least one SL was observed for 143 patients (97.9 %), and positive CSF for the 3 others. Compared to the McDonald criteria, the proposed criteria had 100 % sensitivity, with a significantly shorter mean time to reach a positive diagnosis. Furthermore, the simultaneous presence of corpus callosum, temporal horn, and ovoid lesions was associated with radiological or clinical activity after a year of follow-up. The proposed diagnostic criteria are easy to apply, have a good sensitivity, and allow an earlier diagnosis than the 2010 McDonald criteria. Nevertheless, prospective studies are needed to establish specificity and to confirm these findings.

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Introduction

Beyond the exclusion of other diagnoses, multiple sclerosis (MS) is diagnosed based on lesion location and number for demonstration of dissemination in space (DIS), and on lesions from different ages for dissemination in time (DIT). The emergence of MRI allows an earlier diagnosis, with a primary focus on clinical outcome. The McDonald criteria and their 2001, 2005, and 2010 revisions [1–3] simplify the diagnostic procedure by requiring fewer MRI examinations in patients with typical clinically isolated syndrome (CIS) [4]. Using the most recently revised criteria, MS can be diagnosed based on the first MRI if it provides evidence of DIS and DIT [3]. However, these criteria still leave almost half of CIS patients classified as "possible MS" after the first MRI [3, 5]. For these patients, the absence of a certain diagnosis is stressful and delays the announcement of diagnosis and development of a therapeutic strategy [6].

Using the revised 2010 criteria, DIT is demonstrated based on the presence of asymptomatic lesions from different ages on a single MRI, or on the detection of a new lesion on any follow-up MRI. DIS is currently identified based on lesion location, including periventricular, juxtacortical, infratentorial, and spinal cord [7]. Several other interesting features have also been considered to be highly sensitive or suggestive in MS, including ovoid lesions, and locations involving the corpus callosum, temporal horn, and U-fibers [8, 9], and their use may be relevant for diagnostic purposes. Identification of the symptomatic lesion explaining clinical presentation at the first MRI allows the determination that the initial presentation is related to a demyelinating lesion; however, it is not necessary for diagnosis. If other asymptomatic MS suggestive lesions are present, it may be unnecessary to determine DIT with active enhancing or new T_2-weighted (T_2-w) lesions. In cases with non-specific lesions (subcortical or deep white matter lesions), focal CNS inflammation as evidenced with CSF analysis may be helpful. In fact, including CSF analysis in the diagnostic procedure appears to be relevant because of the strong association between positive CSF and conversion to MS [10]. In the absence of complete MRI criteria, considering CSF analysis for the diagnosis seems relevant.

The present study aimed to demonstrate that MS diagnosis could be established as early as at the first event using a single early MRI without need of demonstrating DIT. We also evaluated the predictive value of lesion location or pattern on MRI or clinical activity during the first year.

Subjects and methods

Subjects and study design

We performed a retrospective analysis of data from patients with MS fulfilling the 2010 McDonald criteria [3] who were included in a French multicenter study with locations in Reims, Marseille, Rennes, and Paris. Inclusion criteria were as follows: age $\geq$18 years; no previous neurological history based on the PEDIAS questionnaire [11]; clinical presentation not attributable to other diseases; typical CIS signs and symptoms evaluated by a neurologist [4]; MRI acquired within 3 months after the first event; at least 1 year of clinical and MRI follow-up, with at least one asymptomatic lesion or one lesion appearing during an MRI follow-up within 1 year (whether symptomatic or not). The following exclusion criteria were used: radiological or biological abnormalities suggestive of Devic's neuromyelitis optica (DNMO), such as expanding spinal cord lesion over more than three vertebral segments, and NMO-IgG or aquaporin-4 antibody seropositive status [12]; MRI results compatible with stroke or bleeding; and bilateral and symmetrical periventricular lesions suggestive of neurometabolic disease. Clinical and biological assessments to exclude differential diagnosis (Lupus, Sjögren, sarcoidosis, Behçet, etc.) were performed at the time of the first clinical evaluation.

The clinical assessment included sex, age at clinical onset, modality (mono or multi-symptomatic) and clinical presentation of the first event, and relapse occurrence during the follow-up period. Positive CSF was determined by isoelectric focusing evidence of oligoclonal IgG bands, increased IgG index, or both [13]. Experienced neurologists (NC, MG, and RD) reviewed the available clinical and biological data, as well as the first MRI images, and ascertained the status in terms of the 2001 and 2005 McDonald's criteria. Time of conversion to MS was reported.

Early MRIs were reanalyzed for simultaneous evidence of a primary criterion: visualization of the symptomatic lesion, anatomically compatible with clinical presentation, regardless the enhancement status. The clinical symptom is defined by the appearance of neurological symptoms, for a period of 24 h or more—in the absence of a change in core body temperature or infection (determined by physical examination and blood sample tests). These MRIs were also analyzed for at least one secondary criterion. The first possible secondary criterion (2a) was the presence of at least one asymptomatic suggestive lesion defined by its aspect or location as follows: ovoid (O), juxtacortical (JC), involving the lower edge of the corpus callosum (LECC), unilateral or asymmetric temporal horn of lateral ventricle

(TH), or involving U-Fibers (UF) or spinal cord lesion (SC) seen on T_2-w sequences. A juxtacortical lesion was defined by a subcortical lesion that is in contact with the cortical ruban. LECC was defined by a lesion that is in contact with the inferior edge of corpus callosum in sagittal plane. A U-fiber lesion was identified as involving the cortical white matter that connects to adjacent gyrus. In the absence of 2a, and considering that CSF analysis for MS diagnosis may be relevant, the presence of at least one subcortical asymptomatic lesion associated with positive CSF could fulfill the secondary criterion (2b) (Figs. 1, 2). The same experienced neurologists (NC, MG, and RD) were trained to identify the proposed criteria.

Image acquisition

Brain MR Images were performed on 3 Tesla (T) commercially available MRI systems for 118 patients (Verio MR system Siemens, Erlangen Germany in Marseille and Rennes, Achieva MR system Philips, Amsterdam, Netherlands in Reims and Rennes) and Philips 1.5T gyroscan for 28 patients (Best MR system Philips, Amsterdam, Netherlands) in Paris.

The MRI protocol included axial fast/turbo spin echo proton density-weighted and T_2-weighted sequences (TR/TE_1/TE_2 = 2,269 to 6,530/8.2 to 8.8/88 to 100 ms; contiguous sections of 3- or 5-mm thickness; in-plane

Fig. 1 Proposed criteria for early MS diagnosis

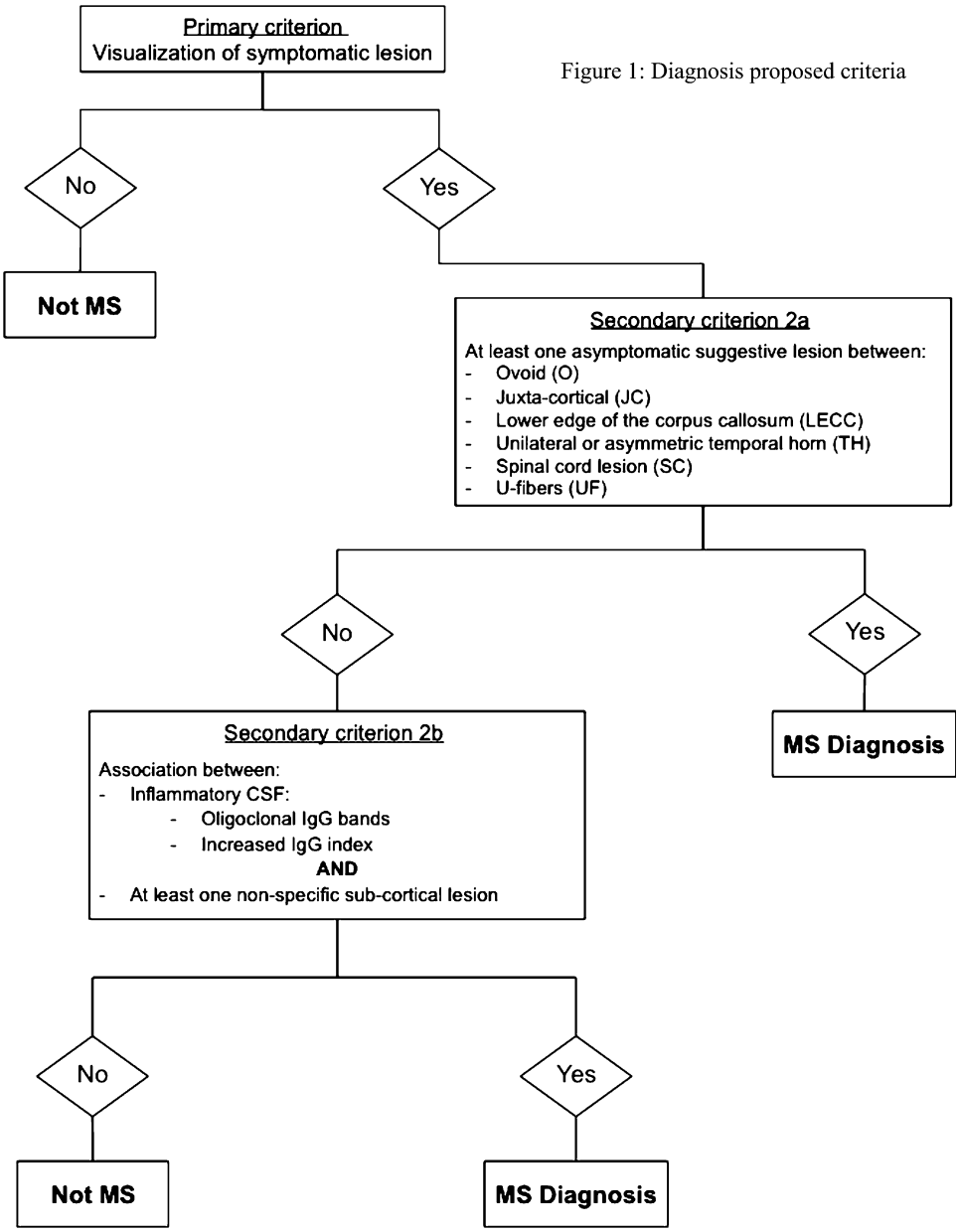

Figure 1: Diagnosis proposed criteria

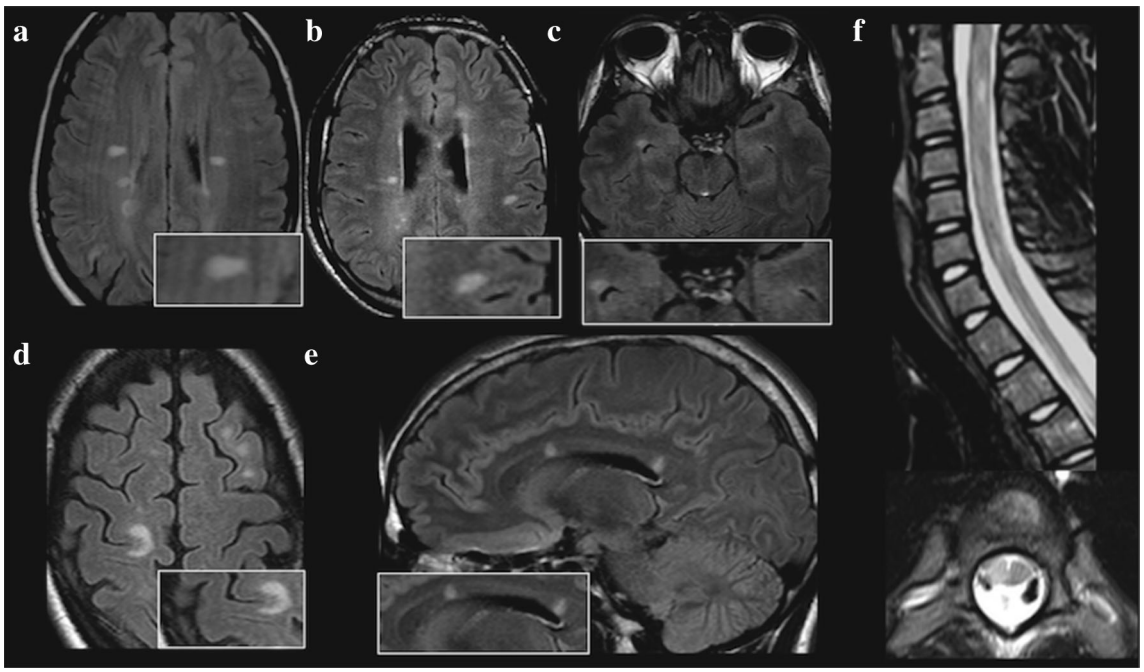

Fig. 2 Suggestive MS lesions visible on T_2 sequences, meeting secondary criterion 2a. Axial FLAIR brain images: **a** Ovoid, **b** juxtacortical, **c** asymmetric temporal horn of lateral ventricle. **d** U-Fibers. Sagittal FLAIR brain image, **e** lower edge of corpus callosum. Sagittal STIR and axial spin echo spinal cord images. **f** Spinal cord

resolution, 1 mm × 1 mm), sagittal fluid-attenuated inversion recovery (FLAIR) (TR/TE/TI: 11,000/125 to 140/2,800 ms; contiguous sections of 4.5-mm section thickness; in-plane resolution, 0.45 mm × 0.45 mm), transverse spin echo $T1_1$-weighted (T1-w) sequences (TR/TE = 500 to 600/8.4 to 9.3 ms; contiguous sections of 3- or 5-mm thickness; in-plane resolution, 1 mm × 1 mm) before and 5 min after intravenous infusion of 0.1 mmol/kg of gadolinium (Gd) chelate, 2D gradient-echo T2-weighted sequences (TR/TE = 50/27 ms; contiguous sections of 3- or 5-mm thickness; in-plane resolution, 1.3 mm × 1.3 mm). For patients with optic neuritis at onset, the MRI protocol included a sequence centered on anterior visual pathways with coronal fat saturation T_2-w sequences (short tau inversion recovery or spectral selection attenuated inversion recovery; TR/TE = 3,000/80 ms; 2.5-mm section thickness; in-plane resolution, 0.45 mm × 0.45 mm) and coronal T_1-w sequences with fat saturation (spectral presaturation with inversion recovery, TR/TE = 475/10 ms; 2.5-mm section thickness; in-plane resolution, 0.3 mm × 0.3 mm) before and after Gd infusion.

Whole spinal cord MRI was performed with 1.5-T scans at each center. The protocol included sagittal spin echo T_2-w, Short TI Inversion Recovery (STIR), and spin echoT_1-w before and after intravenous Gd. If a spinal cord lesion was detected, MR Images were completed by axial T_2-w and T_1-w before and after intravenous administration of Gd.

Patients were followed up clinically and with brain MRI. All patients underwent at least one follow-up MRI at 1 year after onset, read by the same experienced neurologists (NC, MG, and RD). Disease activity was defined by a relapse or an active lesion (T1-enhancing or new T2 lesion) observed on a follow-up MRI.

Statistical analysis

We assessed the sensitivity of the proposed diagnostic criteria in relation to the 2010 McDonald criteria. The time to positive diagnosis was compared between the proposed criteria and the 2010 McDonald criteria using *T* test for paired data. Specificity was not estimated, since all patients fulfilled the 2010 McDonald criteria. Fisher's exact tests were used to evaluate the prognostic value for the future MRI or clinical activity of isolated or associated lesions. We then used multivariate logistic regression models to assess the independent prognostic value of each lesion location on the future MRI or clinical activity. Active and inactive patients (defined according to their MRI and clinical activity within 1 year of follow-up) were compared with regard to age, sex, and monosymptomatic presentation; and the between-group differences were adjusted by multivariate regressions. Disease activity after 1 year was also compared in patients with 9 T2 lesions and more and those with less than 9 T2 lesions using Fisher exact test.

Table 1 Demographic, clinical, biological, and radiological characteristics of 146 patients

Sex	101 females/45 males sex ratio F:M = 2.24
Age in years	
Mean (±standard deviation)	31 (±9)
Monosymptomatic *N* (%)	129 (88.4 %)
Polysymptomatic *N* (%)	17 (11.6 %)
Optic Neuritis[a] *N* (%)	54 (36.9 %)
Myelitis[a] *N* (%)	36 (24.7 %)
Brainstem syndrome[a] *N* (%)	33 (22.7 %)
Other *N* (%)	23 (15.7 %)
Positive CSF *N* (%)	99 (91.7 % of the 108 patients tested)
≥9 T2 lesions *N* (%)	83 (56.8 %)
<9 T2 lesions *N* (%)	63 (43.2)
Relapses during the first year *N* (%)	71 (48.6 %)
Radiological activity during the first year	
T_1Gd+ lesion *N* (%)	76 (52.1 %)
New T_2 lesion *N* (%)	95 (65.1 %)

[a] as isolated presentation

Table 2 Distribution of each criterion

Criteria	*N* (%)
Primary criterion	146 (100 %)
Secondary criterion	
Criterion 2a	
Type of suggestive lesions (*N* = 146)	143 (97.9 %)
Ovoid lesion	123 (84.2 %)
Juxtacortical lesion	110 (75.3 %)
Lower edge of the corpus callosum lesion	103 (70.5 %)
Unilateral or asymmetric temporal horn lesion	66 (45.2 %)
Asymptomatic spinal cord lesion (*N* = 90)	49 (54.4 %)
U-fiber lesion	40 (27.4 %)
Criterion 2b	
Baseline or follow-up	3 (2.1 %)
Combination of different types of suggestive lesions within the same patient	
0	3 (2.1 %)
1	11 (7.5 %)
2	30 (20.5 %)
3	30 (20.5 %)
4	38 (26 %)
5	26 (17.8 %)
6	8 (5.5 %)

Differences were considered statistically significant if the p value was less than 0.05. Data were analyzed using Stata 11.0 software (StataCorp LP, Texas, USA).

Results

The study included 146 patients who fulfilled the 2010 McDonald criteria. These patients comprised 101 women and 45 men, with a median age at the first event of 31 years ± a standard deviation (SD) of 9 years. Table 1 shows the demographic, clinical, biological, and radiological characteristics of the included patients.

Comparison of proposed criteria to McDonald criteria for MS diagnosis

Table 2 shows the distribution of the fulfilled proposed primary and secondary criteria. All patients fulfilled the primary criterion at the first MRI. Secondary criterion 2a was met in 97.9 % of patients. Various types of suggestive lesions were found in 90.3 % of patients (Table 2). In two additional patients, MRI revealed a subcortical lesion and a positive CSF, fulfilling the 2b criterion. Based on these results, the proposed criteria enabled positive diagnosis of MS in 99.3 % patients after only the first clinical event (in all 28 cases for MRIs acquired at 1.5T and in 117/118 cases at 3T). For the single remaining patient, CSF analysis at baseline was not available. Lumbar puncture performed 5 months later showed positive CSF. A second MRI performed at the same time exhibited a new T2 lesion. Overall, using our criteria, the mean time from first event to positive diagnosis was 0.03 (±0.41) months (<1 day). There was no delay for 1.5T scans and a delay of 0.04 months at 3T (±46). Concerning lesion detection, a significant difference was observed for LECC ($p = 0.001$) and TH ($p = 0.02$) more often detected at 3T than at 1.5T. Compared to the 2010 McDonald criteria, our newly proposed criteria led to a positive diagnosis with a significantly shorter mean time (0.03 ± 0.41 versus 5.81 ± 15.24 months; $p < 0.00001$), and with the same level of sensitivity. Time to diagnosis using the new criteria was also shorter than that using the 2005 and 2001 McDonald criteria, with which 132 and 129 patients, respectively, were positively diagnosed after mean times of 9.1 (±15.4) months ($p < 0.00001$) and 9.2 (±15.5) months ($p < 0.00001$) after clinical onset (Fig. 3).

Predictive value of lesion location or MRI pattern on radiological or clinical activity at medium term

During the first year of follow-up, 71 patients (48.6 %) experienced clinical activity, 76 patients (52.1 %) had T_1 Gd-positive (T_1Gd+) lesions, and 95 patients (65.1 %) had

new T_2 lesions (Table 1). After 1 year of follow-up, clinically active and inactive patients were comparable regarding age and mode of presentation (mono or polysymptomatic), and high (≥9) or low (<9) number of T2 lesions on initial MRI. Women more frequently experienced relapses within the first year ($p = 0.048$; Table 3).

Univariate analysis (Table 4) showed that locations involving the LECC or TH were associated with the occurrence of T_1Gd+ lesions during the first year of follow-up ($p = 0.029$ for LECC; $p = 0.031$ for TH). But only LECC lesions remained a predictor of future Gd+ lesions in the multivariate logistic regression model, with a significant odds ratio of 2.35 (1.13–4.89) ($p = 0.022$). Suggestive lesions were not associated with occurrence of T_2 lesions or relapse during the first year, either in univariate (Table 4) or multivariate analysis.

Analysis of the 1-year predictive value of lesion combination (Table 5) demonstrated that a T_1Gd+ lesion occurred in 38/55 patients (69.1 %) with the simultaneous presence of LECC and TH (37.7 % total patients), versus in 38/91 patients (41.8 %) without this combination [$p = 0.002$; odds ratio OR = 3.12 (1.54–6.32)]. Furthermore, a new T_2 lesion occurred in 43/55 patients (78.2 %) with this combination (LECC and TH), verses in 52/91 patients (57.1 %) without this combination ($p = 0.012$; odds ratio OR = 2.69 [1.25–5.76]). We also found that the combination of LECC, TH, and O (found in 33.6 % of patients) was predictive of MRI activity [for T_1Gd + lesions, $p < 0.0001$ and OR = 3.94 (1.86–8.37); for new T_2 lesions, $p = 0.003$ and OR = 3.39 (1.48–7.76)]. When adjusted for sex and age (as age generally influences clinical activity in MS), both associations (LECC and TH with or without O) remained significantly predictive of clinical or MRI activity after 1 year, indicating that both associations are related to future disease activity, with an increased significance if all three lesion types are present (Table 5).

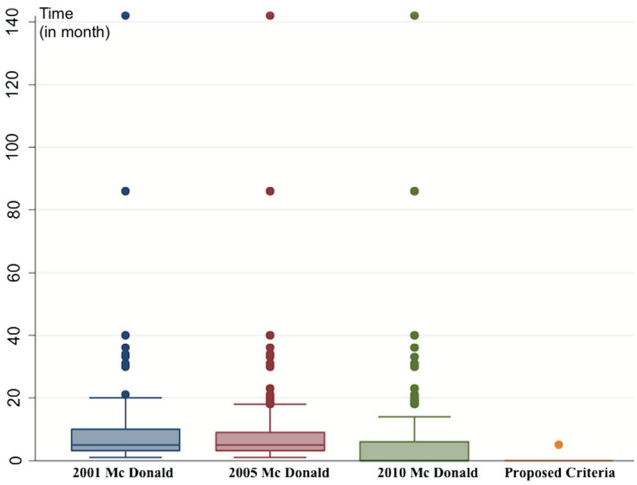

Fig. 3 The times between symptom presentation to MS diagnosis compared between using the proposed criteria and the McDonald criteria (2001, 2005, and 2010 revisions)

Discussion

This study demonstrated that the proposed criteria could be used to diagnose MS at the first MRI, leading to an earlier diagnosis than with the 2010 McDonald criteria (0.03 versus 5.81 months). Diagnosis was reached based on the assessment of a primary criterion in association with asymptomatic lesions, some of which had not been previously evaluated. We also found that MRI or clinical activity after a 1-year follow-up could be predicted by a combination of two or three lesion locations/aspects (LECC and TH, with or without O).

The proposed criteria are appropriate for a typical first demyelinating event in adulthood, after ruling out alternative diagnoses. Due to the choice of the primary criteria (visualization of the symptomatic lesion), it was not appropriate to evaluate them in parallel with a comparative group to test specificity. Instead, they were tested with cases of various typical clinical presentations, whereas previous studies have included a large percentage of optic neuritis [7, 8]. While not included in the assessment of previous criteria, the symptomatic lesion has a major role in this new assessment approach. At least one additional highly suggestive lesion was added as a secondary criterion. These novel criteria simplify the establishment of MS

Table 3 Comparisons between MRI and clinically active and inactive patients after 1 year for age, sex, and monosymptomatic mode of presentation

	MRI+ *N* (%)	MRI− *N* (%)	*p*	R+ *N* (%)	R− *N* (%)	*p*
Total	95 (65.1 %)	51 (34.9 %)		71 (49 %)	74 (51 %)	
Female	61/95 (64.2 %)	40/51 (78.4 %)	0.092	55/71 (77.5 %)	46/75 (61.3 %)	0.048*
Age (years)	30.8 ± 9.4	33.6 ± 8.2	0.075	31.0 ± 8.4	32.5 ± 9.7	0.337
Monosymptomatic presentation	87/95 (91.6 %)	42/51 (82.4 %)	0.111	65/71 (91.6 %)	64/75 (85.3 %)	0.306

The groups were comparable regarding age and monosymptomatic presentation. Women more frequently experienced relapses than men

MRI+ radiological activity, *MRI−* no radiological activity, *R+* clinical activity, *R−* no clinical activity

* Significant *p* value

Table 4 Univariate analysis of the prognosis value on disease radiological and clinical disease activity during the first year follow-up

Lesion	T_1 Gd+ *N* (%)	*p*	nT_2 *N* (%)	*p*	Relapse *N* (%)	*p*
O						
Present	65 (52.9 %)	0.821	81 (65.9 %)	0.641	60 (48.9 %)	1
Absent	11 (47.8 %)		14 (60.1 %)		11 (47.8 %)	
TH						
Present	41 (62.1 %)	0.031*	48 (72.7 %)	0.084	32 (48.5 %)	1
Absent	35 (43.8 %)		47 (58.9 %)		39 (48.8 %)	
LECC						
Present	60 (58.3)	0.029*	72 (69.9)	0.086	50 (48.5)	1
Absent	16 (37.2)		23 (53.5)		21 (48.8)	
JC						
Present	59 (53.6 %)	0.566	73 (66.4 %)	0.687	52 (47.3 %)	0.701
Absent	17 (47.2 %)		22 (61.1 %)		19 (52.8 %)	
SC						
Present ($N = 49$)	25 (51.0 %)	1	30 (61.2 %)	0.668	26 (53.1 %)	1
Absent ($N = 41$)	21 (51.2 %)		27 (65.9 %)		22 (53.7 %)	
UF						
Present	21 (52.5 %)	1	70 (66.0 %)	0.701	20 (50.0 %)	1
Absent	55 (51.9 %)		25 (62.5 %)		51 (48.1 %)	

The TH and LECC locations were significantly associated with the occurrence of a T_1Gd+ lesion after 1 year. nT_2, new T_2 lesion

* Significant *p* value

Table 5 Prognostic value of associated lesions for disease radiological and clinical activity during the first year of follow-up

	Gd+ *N* (%)	nT_2 *N* (%)	Relapse or MRI activity *N* (%)
Combination of LECC and TH lesions			
Present	38/55 (69.1 %)	43/55 (78.2 %)	49/55 (89.1 %)
Absent	38/91 (41.8 %)	52/91 (57.1 %)	70/91 (76.9 %)
p value	0.002	0.012	0.080
Crude OR (95 % CI)	3.12 (1.54–6.32)	2.69 (1.25–5.76)	2.00 (0.98–4.08)
After adjustment for sex and age			
p value	0.003	0.019	0.033
Adjusted OR (95 % CI)	2.98 (1.45–6.12)	2.53 (1.16–5.50)	2.22 (1.06–4.64)
Combination of LECC, TH, and O lesions			
Present	36/49 (73.5 %)	40/49 (81.6 %)	45/49 (91.8 %)
Absent	40/97 (41.2 %)	55/97 (56.7 %)	74/97 (76.3 %)
p value	0.0001	0.003	0.024
Crude OR (95 % CI)	3.94 (1.86–8.37)	3.39 (1.48–7.76)	2.05 (0.99–4.22)
After adjustment for sex and age			
p value	0.001	0.008	0.028
Adjusted OR (95 % CI)	3.73 (1.73–8.04)	3.14 (1.35–7.31)	2.34 (1.10–4.98)

The simultaneous presence of TH and LECC lesions predicted MRI activity. When adjusted for sex, the association was predictive of MRI or clinical activity, and results remained significant. Results were of greater significance if an O lesion was also present

diagnosis in daily practice using routine MRI sequences, avoiding a prolonged period of anxiety for patients. Both initial symptomatic and asymptomatic lesions are radiologically compatible with an inflammatory mechanism, leading to the high sensitivity of the proposed criteria, without the need to repeat MRI examination to demonstrate DIT.

MRI is currently the most specific tool available for visualizing MS lesions and demonstrating DIS [14]. DIS was initially based on evidence of more than four lesions regardless of their location or pattern, or of the presence of three lesions with at least one being periventricular. For differential diagnosis, three parameters were assessed, including two lesion locations (periventricular and infratentorial) [15]. Barkhof et al. [8] added assessment of juxtacortical location, and the revised 2005 McDonald criteria clarified the role of spinal cord lesions. In the present study, we analyzed other suggestive MS lesions that have been proposed to be sensitive but never previously included in MRI studies [8, 9]. An earlier study

assessed corpus callosum lesions with low-resolution axial MRI acquisition, and demonstrated these lesions to be very sensitive and specific, but not useful for diagnosis. The different results found in our present study may be due to our use of a high-resolution sagittal MRI sequence. Even if in this multicenter study, the resolution is higher than this previous study, a limitation is the lower magnetic field in a center, than can influence the diagnostic criteria classification [16]. Our present results also support previous findings that spinal cord lesion contribution assessment is important for MS diagnosis [17] and predictive of MS in CIS patient [18].

Infratentorial lesions seem to be more frequent in multiple sclerosis than other diseases. Although they have been described after CIS, silent infratentorial lesions are rare [19] and, to our knowledge, their diagnostic value has never been definitively established. This location seems more predictive of future disability [20–22] than of a higher risk of MS development, and the risk is more likely to be dependent on the number of supratentorial lesions [21].

Establishing MS diagnosis at the first MRI implies the need to also consider other diagnoses that may involve suggestive lesions. Juxtacortical lesions are reportedly highly specific to MS [1].The U-fiber location may also be involved in vascular diseases, but not with a "horseshoe" aspect (Fig. 2), which seems to be more specific to MS. Lesions located around the temporal horn have been described in metabolic, toxic, genetic, and vascular leukoencephalopathies, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), phenylketonuria, or autosomal dominant leukodystrophy [9]. In these cases, the temporal horn lesions are bilateral, usually symmetrical, and expand into the white matter temporal axis. Corpus callosum lesions are reportedly highly specific to MS [8], although they can be found in other diseases [23]. In Susac's syndrome, they involve central fibers with relative sparing of the periphery [24]. In Behcet's disease, lesions are nodular and associated with large pedunculo-thalamic lesions [25]. Corpus callosum lesions have also been observed in infectious diseases, such as HIV or progressive multifocal leukoencephalopathy, where they are described as large and confluent. Finally, metabolic or toxic disorders—such as adrenoleukodystrophy, metachromatic leukodystrophy or Marchiafava-Bignami—also involve the corpus callosum, typically showing large, symmetric, and confluent lesions. Acute demyelinated encephalomyelitis can involve all of the previously described lesions, including ovoid lesions [26], however, the clinical presentation is usually different. In other inflammatory or vascular diseases, such as lupus or DNMO, spinal cord lesions exhibit particular aspects, including the involvement of more than three vertebral segments with cord swelling (excluded in our criteria).

Up until the 2010 McDonald criteria, CSF inflammation has been considered a valuable parameter for the diagnosis of relapsing-remitting MS. In our study, CSF contributed to the diagnosis in three cases in association with a non-specific lesion, and delayed the diagnosis in a single case where it was obtained 5 months after clinical presentation.

The presently described criteria may be regarded as a new proposition to be included in discussions of further revised diagnostic criteria. Our present results show that these criteria allow early diagnosis announcement leading to an earlier progression into therapeutic planning, dissociate the diagnosis phase from therapeutic discussions. Thus, it is possible to reduce the period of "possible MS diagnosis" with a 100 % sensitivity using a single MRI in the majority of cases, and with additional testing for positive CSF if necessary. Further studies including clinically isolated patients are needed to evaluate the specificity of these criteria. This evaluation was conducted in relapsing-remitting MS, and future validation is necessary in primary progressive MS.

Up to now, the only MRI parameters that were considered as predictive of future disease activity are the presence of gadolinium-enhanced lesions and T2 lesion load. Recent studies show that lesion topography is correlated with physical or cognitive disability [27–29]. In line with this finding, our study demonstrates that initial lesion location (LECC or the TH) predicts disease activity after a 1-year follow-up.

Unlike previous studies that have focused on T_1Gd+ active or new T_2 lesions, our present study showed that combinations of lesion locations and patterns are predictive of short-term clinical or MRI activity. These results should be included in future studies concerning MRI predictive capacities. A prospective multicenter study is needed to evaluate their specificity and confirm their ability to predict long-term activity and disability.

Conflicts of interest On behalf of all the authors, the corresponding author states that there is no conflict of interest.

Ethical standard Data were collected from university hospital database, and all patients gave their informed consent for inclusion in the database before their admission. The study was performed in accordance with local ethical standards and French law.

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