Optic Nerve Topography in Multiple Sclerosis Diagnosis

The Utility of Visual Evoked Potentials

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Abstract

Objective
To assess the added value of the optic nerve region (by using visual evoked potentials [VEPs]) to the current diagnostic criteria.

Methods
From the Barcelona clinically isolated syndrome (CIS) cohort, patients with complete information to assess dissemination in space (DIS), the optic nerve region, and dissemination in time at baseline (n = 388) were selected. Modified DIS (modDIS) criteria were constructed by adding the optic nerve to the current DIS regions. The DIS and modDIS criteria were evaluated with univariable Cox proportional hazard regression analyses with the time to the second attack as the outcome. A subset of these patients who had at least 10 years of follow-up or a second attack occurring within 10 years (n = 151) were selected to assess the diagnostic performance. The analyses were also performed according to CIS topography (optic neuritis vs non–optic neuritis).

Results
The addition of the optic nerve as a fifth region improved the diagnostic performance by slightly increasing the accuracy (2017 DIS 75.5%, modDIS 78.1%) and the sensitivity (2017 DIS 79.2%, modDIS 82.3%) without lowering the specificity (2017 DIS 52.4%, modDIS 52.4%). When the analysis was conducted according to CIS topography, the modDIS criteria performed similarly in both optic neuritis and non–optic neuritis CIS.

Conclusion
The addition of the optic nerve, assessed by VEP, as a fifth region in the current DIS criteria slightly improves the diagnostic performance because it increases sensitivity without losing specificity.

Glossary

CI = confidence interval; **CIS** = clinically isolated syndrome; **DIS** = dissemination in space; **DIT** = dissemination in time; **HR** = hazard ratio; **MAGNIMS** = Magnetic Resonance Imaging in Multiple Sclerosis; **modDIS** = modified DIS; **MS** = multiple sclerosis; **OB** = oligoclonal bands; **OCT** = optical coherence tomography; **VEP** = visual evoked potential.

The improvement in diagnosis is one of the main advances that have occurred in the multiple sclerosis (MS) field in the past decades. Since 2001,[1] dissemination in space (DIS) and in time (DIT) can be established from MRI findings, and since 2010, the diagnosis can be stablished shortly after presenting a typical clinically isolated syndrome (CIS) on the results of a single baseline MRI.[2,3] More recently, oligoclonal bands (OB) have been reincorporated into the 2017 diagnostic criteria as an alternative criterion for diagnosing MS in the absence of DIT.[3,4]

Optic neuritis represents the first manifestation of MS in 25% to 35% of patients with CIS[5,6] and will occur during disease course in ≈70% of patients.[5] The involvement of the optic nerve can be established either clinically or by the use of paraclinical tests such as visual evoked potentials (VEPs), MRI, and optical coherence tomography (OCT). In 2016, the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group proposed the inclusion of the optic nerve as an additional region to demonstrate DIS.[7] However, due to the lack of evidence regarding the diagnostic properties of the different tests to assess the optic nerve involvement in patients with CIS, the optic nerve was finally not incorporated into the most recent revision of the McDonald diagnostic criteria.[3]

A few studies have investigated the anterior visual pathway involvement in CIS cohorts using clinical features,[8] VEP,[8,9] OCT,[10–13] and MRI[9,12,14] alone or in combination, but only 2 of them have evaluated the diagnostic performance of adding the optic nerve as a new region in the diagnostic criteria,[8,9] yielding somewhat contradictory results. While the first study[8] found that the addition of optic nerve (evaluated mainly by clinical assessment) would improve the diagnostic performance of 2017 McDonald criteria only in patients with optic neuritis CIS, the study conducted by the MAGNIMS group[9] concluded that there was no clear improvement of the 2010 McDonald criteria when the optic nerve region (assessed mainly by VEP) was added to the 2010 DIS criteria. Moreover, the modified DIS criterion that included the optic nerve was the one with the lowest specificity.[9]

In this work, we have investigated the effect of adding the optic nerve region (evaluated by VEP) as part of the DIS criteria to improve the 2017 diagnostic criteria in a well-characterized cohort of patients with CIS.[6] We have also compared the added value of the fifth region according to optic nerve involvement (symptomatic vs asymptomatic CIS).

Methods

Study Cohort

This observational, retrospective study was based on the Barcelona CIS cohort. Clinical, demographic, biological, and radiologic data are collected prospectively following a pre-specified protocol described elsewhere.[6,15] Briefly, patients <50 years of age first seen within 3 months of symptom onset were included. Demographic data, CIS topography, and presence of OB at baseline were recorded, together with the occurrence of a second attack during follow-up. Brain MRI was obtained at baseline (within 5 months after CIS onset), at 1 year, and every 5 years thereafter. Beginning in 2007, spinal cord MRIs were done at baseline as part of the diagnostic process in all patients with CIS. MRI scans were obtained at 3.0T since 2010 and at 1.5T previously. Each MRI scan was assessed by experienced neuroradiologists under normal reporting conditions.

Pattern-reversal VEPs were performed during the diagnostic process in the same location by an expert neurophysiologist from the Neurophysiology Unit following international guidelines.[16] Although this is a prospective CIS cohort, the date of VEP was not part of the initially collected information. However, we have been able to retrieve this information from electronic clinical records for 288 patients (74.2%). VEPs were performed with a mean time from CIS to VEP of 3.95 months (SD 3.82 months). Preexisting eye conditions were taken into account when VEP results were interpreted. Patients presenting with any ocular pathology that may affect VEP were excluded. According to our normative data, VEPs were considered abnormal if the latency of the P100 wave was >112 milliseconds, there was an intereye latency asymmetry >8, milliseconds, or there was an absence of the P100 wave.

Study Design

To evaluate the effect of adding new regions to fulfill DIS, we performed a risk assessment analysis. We selected patients with complete information to assess the 5 DIS regions (brain and spinal cord MRI plus VEPs) and with gadolinium administration at baseline to assess DIT (cohort 1). From this cohort and to ensure that late converters were taken into account, patients who had at least 10 years of follow-up or who experienced a second attack within 10 years of the CIS were selected to test the diagnostic criteria performance (cohort 2) (figure). For both cohorts, DIS and DIT were assessed at baseline. The modified DIS (modDIS) criteria were constructed by adding the optic nerve region to the current DIS topographies and using a cutoff value of 2 of 5. The second attack was determined when new symptoms

Figure Patient Disposition

CIS = clinically isolated syndrome; MS = multiple sclerosis; ON = optic neuritis.
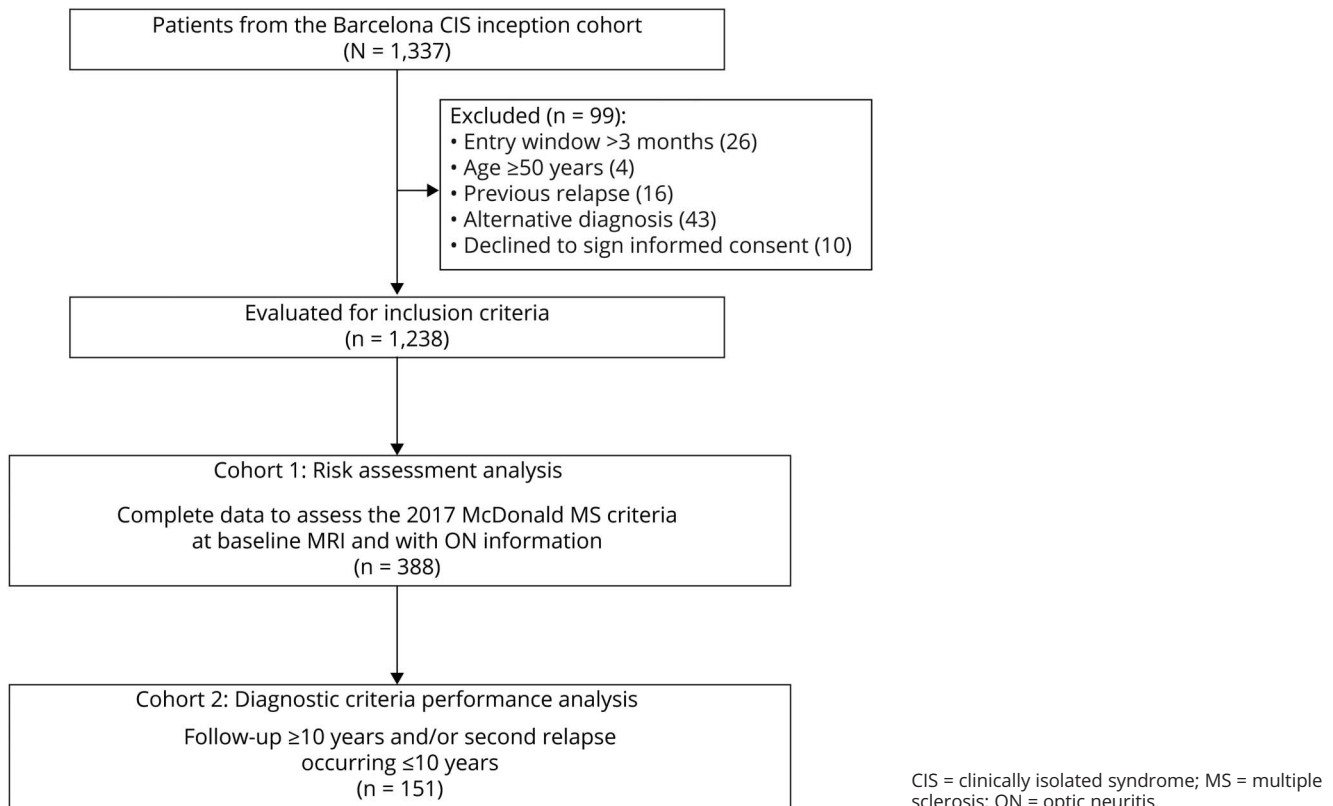
suggestive of a relapse occurred during the follow-up after an interval of at least 1 month since the CIS and in the absence of fever or concurrent diseases.[17]

Statistical Analysis

Descriptive statistics were performed on the baseline variables. Normally distributed continuous variables were summarized with means and SDs. Otherwise, continuous variables were summarized with medians and ranges; categorical variables were summarized as percentages.

Cohort 1, Risk Assessment Analysis

For the risk assessment analysis, the number of DIS regions fulfilled and the current and modDIS criteria were evaluated with univariable Cox proportional hazard regression analyses considering the time to the second attack during the follow-up as the primary outcome and the time to 2017 McDonald MS criteria fulfillment as the secondary outcome. The results are expressed as the hazard ratios (HRs) with 95% confidence intervals (CIs). The Schoenfeld residuals have been evaluated to test the proportional risk assumption. Finally, because initiating a disease-modifying treatment before a second attack could have affected the primary outcome, a sensitivity analysis with treatment exposure as a time-dependent variable was also conducted.

Cohort 2, Diagnostic Criteria Performance

We analyzed the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the current and modDIS criteria alone and in combination with either OB or MRI DIT, with second attack and 2017 McDonald MS at 10 years as the primary and secondary outcomes, respectively. A sensitivity analysis excluding patients with treatment onset before presenting a second attack was conducted.

To test whether the fulfillment of the modDIS criteria would have a different impact in symptomatic (optic neuritis) and asymptomatic (non–optic neuritis) patients with CIS, both risk assessment and diagnostic performance analyses were conducted according to CIS topography.

All statistical tests were performed with SPSS software version 22 (SPSS Inc, Chicago, IL) and R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Standard Protocol Approvals 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.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

From January 1995 to December 2017, 1,337 patients were included in the Barcelona CIS inception cohort; 99 patients were excluded for different reasons (figure). Of the remaining 1,238 patients, 388 fulfilled the criteria for the risk assessment analysis (cohort 1), and 151 were included in the diagnostic criteria performance analysis (cohort 2). Baseline characteristics of the whole cohort, cohort 1, and cohort 2 are detailed in table 1. Of note, in the whole cohort (n = 1,238), patients were younger, and there was a higher proportion of patients with positive OB and with abnormal VEPs.

VEPs were abnormal in 126 of 388 patients (32.5%), being asymptomatic in 13.6%. Mean time of follow-up was 62.7 months (SD 40.4 months) for cohort 1 and 88.9 months (SD 37.9 months) for cohort 2. Patients with the longest follow-up (cohort 2) had a greater proportion of abnormal baseline MRI and positive OB results. One hundred thirty patients (33.5%) presented a second attack, and all occurred within the first 10 years after CIS onset (mean time 19.6 months, SD 22.3 months).

Risk Assessment Analysis (Cohort 1)

After presentation of a CIS, the risk of developing a second attack during the follow-up increased as the number of regions fulfilled at baseline increased (from HR 5.6, 95% CI 1.9–16.5

for 1 criterion to HR 22.7, 95% CI 7.9–65.7 for 5 criteria affected) (table 2).

Both the 2017 DIS and modDIS criteria at baseline conferred a similar risk for developing a second attack during follow-up compared to patients not fulfilling these criteria (2017 DIS: HR 4.3, 95% CI 2.8–6.5; modDIS: HR 4.8, 95% CI 3.0–7.5) (table 2). Similar findings were obtained with the 2017 McDonald MS as the outcome although with wider CIs (2017 DIS: HR 20.4, 95% CI 13.6–30.6; modDIS: HR 21.8, 95% CI 14.1–33.9).

In the sensitivity analysis including treatment exposure as a time-dependent variable, similar results were found (HR 4.6, 95% CI 2.9–7.2 for 2017 DIS; HR 5.1, 95% CI 3.1–8.3 for modDIS).

When the risk assessment analysis was conducted according to CIS topography, fulfilling either the 2017 DIS or modDIS criteria (including the optic nerve region) conferred a similar higher risk for developing a second attack during the follow-up in patients with both optic neuritis and non–optic neuritis CIS (table 3).

Diagnostic Criteria Performance Analysis (Cohort 2)

The addition of the optic nerve region to the DIS criteria improved the current DIS diagnostic performance by increasing the accuracy and sensitivity without decreasing the specificity (table 4). When the current and modDIS criteria were considered along with the presence of OB or DIT, the modified criteria remained more accurate and more sensitive and had a specificity similar to that of the current 2017 McDonald MS criteria, although the improvement was less

Table 1 Baseline Characteristics

	Whole Cohort (n = 1,238)	Cohort 1 (n = 388)	Cohort 2 (n = 151)
Age at CIS, mean (SD), y	31.6 (8.2)	33.5 (7.8)	32.4 (7.4)
Female, n (%)	842 (68.0)	263 (67.8)	108 (71.5)
CIS topography, n (%)			
Optic neuritis	446 (36.0)	138 (35.6)	40 (26.5)
Non–optic neuritis	787 (63.6)	250 (64.4)	111 (73.5)
Positive OB, n (%)	582/990 (58.8)	182/335 (54.3)	100/136 (73.5)
Baseline EDSS score, median (range)	1.0 (0–5.5)	1.0 (0–4.5)	1.5 (0–4.5)
Abnormal MRI, n (%)	810 (71.2)	275 (71.1)	136 (90.1)
Gd-enhancing lesions, n (%)	235 (29.3)	114 (29.4)	71 (47.0)
Patients with abnormal VEPs, n (%)	415/1,098 (37.8)	126 (32.5)	53 (35.1)
Optic neuritis	297/416 (71.4)	92/138 (66.7)	28/40 (70.0)
Non–optic neuritis	118/682 (17.3)	34/250 (13.6)	25/111 (22.5)
Time of follow-up, mean (SD), mo	107.9 (98.0)	62.7 (40.4)	88.9 (37.9)

Abbreviations: CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; OB = oligoclonal bands; VEP = visual evoked potential.

Table 2 Risk Assessment Analysis for the Whole Cohort: HRs for Second Attack as the Outcome

	No. (%)	Second Attack, n (%)	HR (95% CI)
No. of regions affected			
1 criterion	78 (20.1)	19/78 (24.4)	5.6 (1.9–16.5)
2 criteria	49 (12.6)	21/49 (42.9)	11.7 (4.0–34.2)
3 criteria	71 (18.3)	38/71 (53.5)	15.8 (5.6–44.4)
4 criteria	57 (14.7)	24/57 (42.1)	12.5 (4.3–36.1)
5 criteria	39 (10.1)	24/39 (61.5)	22.7 (7.9–65.7)
2017 DIS vs modDIS			
2017 DIS	205 (52.8)	103/205 (50.2)	4.3 (2.8–6.5)
modDIS	216 (55.7)	107/216 (49.5)	4.8 (3.0–7.5)

Abbreviations: CI = confidence interval; DIS = dissemination in space; HR = hazard ratio; modDIS = modified DIS.
The 2017 DIS criteria as defined in Thompson et al.[3]: at least 1 lesion in at least 2 of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord). modDIS added optic nerve assessed by visual evoked potential: at least 1 lesion in at least 2 of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

noticeable than when DIS was analyzed alone (table 4). Similar results were obtained with 2017 McDonald MS as the outcome (2017 DIS vs modDIS: sensitivity 80.7% vs 83.6%, specificity 100% vs 100%, accuracy 82.1% vs 84.8%) and in the sensitivity analysis including only patients who either were never treated or started treatment after presenting a second attack (data not shown).

When the diagnostic performance analysis was conducted according to CIS topography, the addition of the optic nerve region improved the current DIS diagnostic performance in patients with both optic neuritis vs non–optic neuritis CIS, although this improvement was more noticeable in symptomatic (optic neuritis) patients (table 5). Again, when the different DIS criteria were considered in combination with presence of OB or DIT, adding the optic nerve region into the DIS criteria also resulted in more accurate, more sensitive diagnostic criteria, with a specificity similar to that of the 2017

McDonald MS criteria, although this improvement was less noticeable (table 5).

Discussion

In patients presenting a CIS, the addition of the optic nerve (both in symptomatic and asymptomatic patients) as a fifth region to the current DIS criteria confers a higher risk for developing a second attack during follow-up and slightly improves the diagnostic criteria performance by increasing sensitivity without losing specificity.

In our work, we have demonstrated that patients fulfilling the modDIS criteria at baseline were at a high risk of developing a second attack during follow-up, which was similar to the risk observed in patients fulfilling the 2017 DIS criteria. These findings are in line with the work by Filippi et al.[9] that

Table 3 Risk Assessment Analysis According to Optic Nerve Involvement: HRs for Second Attack as the Outcome

	No. (%)	Second Attack n (%)	HR (95% CI)
Optic neuritis CIS (n = 138)			
2017 DIS	61 (44.2)	23/61 (37.7)	3.8 (1.8–8.0)
modDIS	70 (50.7)	25/70 (35.7)	4.3 (1.9–9.6)
Non–optic neuritis CIS (n = 250)			
2017 DIS	144 (57.6)	80/144 (55.6)	4.1 (2.4–6.9)
modDIS	146 (58.4)	82/146 (56.2)	4.6 (2.7–8.0)

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; DIS = dissemination in space; HR = hazard ratio; modDIS = modified DIS.
The 2017 DIS criteria as defined in Thompson et al.[3]: at least 1 lesion in at least 2 of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord). modDIS added optic nerve assessed by visual evoked potential: at least 1 lesion in at least 2 of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Table 4 Diagnostic Performance Analysis: Diagnostic Properties at 10 years With Second Attack as the Outcome

	% (95% CI)				
	Sensitivity	Specificity	Accuracy	PPV	NPV
2017 DIS	79.2 (71.2–85.8)	52.4 (29.8–74.3)	75.5 (67.8–82.1)	91.1 (86.7–94.2)	28.9 (19.4–40.9)
modDIS	82.3 (74.6–88.4)	52.4 (29.8–74.3)	78.1 (70.7–84.5)	91.4 (87.1–94.4)	32.3 (21.6–45.4)
2017 DIS + DIT and/or OB	73.9 (65.4–81.2)	66.7 (43.0–85.4)	72.9 (62.0–79.8)	93.2 (88.1–96.2)	29.2 (21.3–38.5)
modDIS + DIT and/or OB	74.2 (65.9–81.5)	66.7 (43.0–85.4)	73.2 (65.5–80.0)	93.2 (88.4–96.3)	29.2 (21.3–38.5)

Abbreviations: CI = confidence interval; DIS = dissemination in space; DIT = dissemination in time; modDIS = modified DIS; NPV = negative predictive value; OB = oligoclonal bands; PPV = positive predictive value.
The 2017 DIS criteria as defined in Thompson et al.[3]: at least 1 lesion in at least 2 of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord). modDIS added optic nerve assessed by visual evoked potential: at least 1 lesion in at least 2 of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

evaluated the optic nerve involvement (mainly using VEPs) in 241 patients with CIS, reporting a similar higher risk for developing a second attack when patients fulfilled either the 2010 DIS criteria or the 2010 modDIS criteria including the optic nerve (2010 DIS: 3.48, 95% CI 2.2–5.6; 2010 DIS plus optic nerve: 3.34, 95% CI 1.9–5.6). In addition, we have conducted the risk assessment analysis based on CIS topography to test whether the fulfillment of the modDIS criteria would have a different impact in symptomatic and asymptomatic patients with CIS (optic neuritis vs non–optic neuritis CIS) and found similar results. This probably means that VEPs were able to capture optic nerve involvement in both symptomatic and asymptomatic eyes[18] and reinforces the fact that symptomatic lesions should be taken into account when considering the diagnosis of MS in patients with CIS.[19,20]

As for the diagnostic performance analysis, we have proved that the addition of the optic nerve to the current DIS criteria slightly increases the accuracy and sensitivity without lowering the specificity, both in the whole cohort and in symptomatic and asymptomatic patients with CIS. These results are partially discordant with the results published in 2 previous works showing that the addition of the optic nerve to the DIS criteria increased the sensitivity at the expense of decreasing the specificity.[8,9] In the first work, Filippi et al.[9] found that the addition of the optic nerve region to the 2010 DIS criteria increased the sensitivity by lowering the specificity of the 2010 criteria with second attack 5 years after presenting the CIS used as the outcome (sensitivity: 2010 DIS 0.87 vs 2010 DIS + optic nerve 0.90; specificity: 2010 DIS 0.33 vs 2010 DIS + optic nerve 0.26).[9] More recently,

Table 5 Diagnostic Performance Analysis According to Optic Nerve Involvement: Diagnostic Properties at 10 years With Second Attack as the Outcome

	% (95% CI)				
	Sensitivity	Specificity	Accuracy	PPV	NPV
Optic neuritis CIS (n = 40)					
2017 DIS	69.7 (51.3–84.4)	57.1 (18.4–90.1)	67.5 (51.0–81.4)	88.5 (76.0–94.9)	28.6 (14.9–47.7)
modDIS	75.8 (57.7–89.0)	57.1 (18.4–90.1)	72.5 (56.1–85.4)	89.3 (77.6–95.2)	33.3 (17.2–54.7)
2017 DIS + DIT and/or OB	63.6 (45.1–79.6)	85.7 (42.1–99.6)	67.5 (50.9–81.4)	95.5 (77.1–99.2)	33.3 (22.5–46.3)
modDIS + DIT and/or OB	66.7 (48.2–82.0)	85.7 (42.1–99.6)	70.0 (53.5–83.4)	95.7 (77.9–99.3)	35.3 (23.6–49.1)
Non–optic neuritis CIS (n = 111)					
2017 DIS	82.5 (73.4–89.5)	50.0 (23.0–77.0)	78.4 (69.6–85.6)	91.9 (87.0–95.1)	29.2 (17.3–44.8)
modDIS	84.5 (75.8–91.1)	50.0 (23.0–77.0)	80.2 (71.5–87.1)	92.1 (87.3–95.2)	31.8 (18.8–48.5)
2017 DIS + DIT and/or OB	77.3 (67.7–85.2)	57.1 (28.9–82.3)	74.8 (65.7–82.5)	92.6 (87.1–95.9)	26.7 (16.9-39-5)
modDIS + DIT and/or OB	78.4 (68.8–86.1)	57.1 (28.9–82.3)	75.7 (66.6–83.3)	92.7 (87.3–95.9)	27.6 (17.4–40.8)

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; DIS = dissemination in space; DIT = dissemination in time; modDIS = modified DIS; NPV = negative predictive value; OB = oligoclonal bands; PPV = positive predictive value.
The 2017 DIS criteria as defined in Thompson et al.[3]: at least 1 lesion in at least 2 of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord). modDIS added optic nerve assessed by visual evoked potential: at least 1 lesion in at least 2 of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Brownlee et al.[8] analyzed the diagnostic performance of the new modified criteria according to CIS topography (optic neuritis and non–optic neuritis CIS) using the presence of a second attack after a mean follow-up period of almost 15 years as the outcome. They reported that the inclusion of the symptomatic optic nerve involvement (assessed mainly clinically) increased the sensitivity and decreased the specificity of the 2017 DIS criteria (sensitivity: 2017 DIS 83% vs 2017 DIS + optic nerve 95%; specificity: 2017 DIS 68%, 2017 DIS + optic nerve 57%).[8] Both works reported that the decrease in specificity was no longer seen when the different DIS criteria were evaluated along with DIT criteria. The differences in the test specificity results between our work and the previous published works may be explained in part by the longer follow-up of our cohort compared with Filippi et al., which may have allowed us to detect late converters, or by the different methods used to evaluate optic nerve involvement in the Brownlee et al. work. Moreover, we have demonstrated that the addition of the optic nerve to the 2017 McDonald criteria increased the diagnostic performance in patients with both optic neuritis (symptomatic) and non–optic neuritis (asymptomatic) CIS, although to a greater extent in the former group. These results are partially discordant with the results published by Brownlee et al. and may be partly explained by a slight overrepresentation of optic neuritis in their work[8] or by the fact that VEPs are more capable of detecting subclinical optic nerve involvement than clinical assessment alone.[18,21–23]

The 2016 MAGNIMS proposal suggested that optic nerve involvement may be ascertained clinically (by detecting optic nerve atrophy or pallor), with neurophysiologic tests (VEPs), or by imaging with either MRI to detect optic nerve lesions or OCT to detect peripapillary retinal nerve fiber layer thinning.[7] Assessment of optic nerve involvement based only on clinical findings may be challenging if not assessed by a trained neuro-ophthalmologist,[24] and thus, the use of paraclinical tests to confirm optic nerve damage may be advisable. In addition, if we are trying to increase the sensitivity of a diagnostic test, we may want to use paraclinical tests that may allow us to detect a higher proportion of patients with asymptomatic optic nerve involvement compared to clinical tools alone. Full-field VEPs have classically been used to provide paraclinical evidence of demyelination to support the diagnosis of MS.[17] Very few studies have assessed VEPs in purely CIS cohorts,[25–29] reporting rates of abnormal VEP results that range from 15% to 49% and that are in line with the abnormal VEP rate of our study (32.5%). As expected, we have found VEPs to be more frequently affected in patients with optic neuritis CIS (66.7%), which is a result similar to that reported in the literature (67.8%–87%).[25,29] Most of the studies evaluating VEPs in CIS cohorts were published before the implementation of the McDonald criteria[25–27] to compare the diagnostic properties of VEP and MRI to detect patients at risk of developing MS during follow-up, concluding that the MRI was the most sensitive tool.[25–27] While the

diagnosis of MS has evolved tremendously since the use of MRI, our work demonstrates the utility of VEPs (in combination with brain and spinal cord MRI) in MS diagnosis, supporting the reintroduction of this test in the diagnostic workup of patients with CIS. It is important to bear in mind that VEP results may be influenced by several factors concerning test acquisition such as patient cooperation, luminescence and contrast patterns, and stimuli presentation rate.[30,31] To minimize these factors, VEPs should be acquired following international guidelines,[16] and a normative dataset obtained from normal controls using local equipment is commonly used to define the range of normal variation.

Some limitations should be taken into consideration in the interpretation of our results. VEPs were obtained as part of the routine diagnostic process of patients with CIS, but information on the time elapsed since CIS to VEP was available for only three-quarters of the patients. Because patients included in this analysis were slightly different from the full Barcelona CIS cohort (n = 1,238), we cannot exclude some minor selection bias. However, differences in VEP abnormalities were small (37.8 vs 32.5), and our results were still significant even with a lower proportion of abnormal VEPs in both cohorts 1 and 2. We also acknowledge that by selecting only patients with complete information to analyze the modDIS criteria (having brain and spinal cord MRI together with VEP information) and DIT criteria (administration of gadolinium at baseline MRI), we could have enriched our cohort. Last, we are aware that disease-modifying treatment started before second attack could have interfered with our results; however, no differences were found in our sensitivity analysis when this information was taken into account.

Since 2010, the McDonald diagnostic criteria have allowed the diagnosis of MS immediately after presentation of a typical CIS,[2,3] reducing patients' uncertainty and improving earlier treatment onset. However, with the exclusion of the optic nerve as one of the relevant DIS regions, this early diagnosis may not be applied to all patients equally because symptomatic spinal cord and brainstem syndromes are more meaningful in the diagnostic process than optic neuritis.[32–34] Thus, in a patient presenting a brainstem CIS, the diagnosis of MS can be established by showing 1 periventricular lesion and 1 enhancing brainstem lesion in brain MRI, while it will not be the case if the same patient had presented an optic neuritis with an abnormal VEP result and a brain MRI showing the same enhancing periventricular lesion.

Our results show that the addition of the optic nerve, assessed by VEP, as a fifth region in the current DIS criteria improves the diagnostic performance by slightly increasing sensitivity without losing specificity. Thus, our work provides additional evidence that argues in favor of including the optic nerve as a new region in the diagnostic criteria. Whether the optic nerve involvement in patients with CIS should be confirmed only by

means of VEPs, by the use of other structural tests (MRI or OCT), or by a combination of them requires further investigation in prospective studies with a systematic examination of the optic nerve in patients with CIS.

Study Funding

Disclosures

Publication History

Appendix Authors

Name	Location	Contribution
Angela Vidal-Jordana, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; designed and conceptualized study; analyzed the data; performed statistical analysis; drafted and revised the manuscript for intellectual content
Alex Rovira, MD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Georgina Arrambide, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Susana Otero-Romero, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Interpreted the data; revised the manuscript for intellectual content
Jordi Rio, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; revised the manuscript for intellectual content
Manuel Comabella, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; revised the manuscript for intellectual content
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