Published Ahead of Print on December 16, 2020 as 10.1212/WNL.0000000000011339

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000011339

Optic nerve region in multiple sclerosis diagnosis: the utility of visual evoked potentials

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The Article Processing Charge was funded by Fondo de Investigación en Salud (FIS: PI17/02162) from Instituto de Salud Carlos III, Ministry of Science, Innovation and Universities, Spain

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Word count: Title 95 characters with spaces; Abstract 232 words, Text (between 'Introduction' and end of 'Discussion'): 3210

References: 34; Tables: 5; Figures: 1

Key words: CIS, optic nerve, visual evoked potentials, MS diagnosis

Study funding: No targeted funding reported.

Disclosures

Angela Vidal-Jordana receives support for contracts Juan Rodes (JR16/00024) from Fondo de Investigaciones Sanitarias, Instituto de Salud Carlos III, Spain; and has engaged in consulting and/or participated as speaker in events organized by Novartis, Roche, Teva, Mylan, Biogen, Sanofi-Genzyme, and Merck.

Alex Rovira serves on scientific advisory boards for Novartis, Sanofi-Genzyme, Icometrix, Synthetic MR, Bayer, Merck, Biogen and OLEA Medical, and has received speaker honoraria from Bayer, Sanofi-Genzyme, Bracco, Merck-Serono, Teva Pharmaceutical Industries Ltd, Novartis, Roche and Biogen.

Georgina Arrambide has received compensation for consulting services or participation in advisory boards from Sanofi, Merck, and Roche; research support from Novartis; travel expenses for scientific meetings from Novartis and Roche; and speaking honoraria from Stendhal, Sanofi, and Merck.

Susana Otero-Romero has received speaking honoraria and consulting fees from Genzyme, Biogen-Idec, Novartis and MSD; and research support from Novartis.

Jordi Río has engaged in consulting and/or participated as speaker/chair in events organized by Merck, Novartis, Sanofi, Roche, Biogen and Excemed.

Manuel Comabella has received compensation for consulting services and speaking honoraria from Bayer Schering Pharma, Merk Serono, Biogen-Idec, Teva Pharmaceuticals, Sanofi-Aventis, Genzyme, and Novartis.

Breogan Rodríguez-Acevedo has received honoraria for consulting services from Wellspect

Jaume Sastre-Garriga has engaged in consulting and/or participated as speaker / chair in events organized by Merck, Novartis, Celgene, Sanofi, Biogen and Excemed.

Xavier Montalban has received speaking honoraria and travel expenses for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Actelion, Bayer, Biogen, Celgene, Genzyme, Merck, Novartis, Roche, Sanofi-Genzyme, Teva Pharmaceutical, Excemed, MSIF and NMSS.

Mar Tintoré has received compensation for consulting services and speaking honoraria from Almirall, Bayer Schering Pharma, Biogen-Idec, Genzyme, Merck-Serono, Novartis, Roche, Sanofi-Aventis and Teva Pharmaceuticals. MT is co-editor of Multiple Sclerosis Journal-ETC

Carlos Nos, Joaquin Castilló, Ingrid Galan, Sergio Cabello, Dulce Moncho, Kimia Rahnama, Vanessa Thonon, Ana Zabalza, Luciana Midaglia, and Cristina Auger report no disclosures

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 (DIT) 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 using univariable Cox proportional hazard regression analyses using 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 improve the diagnostic performance as it increases sensitivity without losing specificity.

Introduction

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 based on magnetic resonance imaging (MRI) findings, and since 2010 the diagnosis can be stablished shortly after presenting a typical clinically isolated syndrome (CIS) based on the results of a single baseline MRI[2,3]. More recently, oligoclonal bands (OB) have been reincorporated in 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 - 35% of CIS patients[5,6] and will occur during disease course in about 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 (VEP), 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 CIS patients, the optic nerve was finally not incorporated in the most recent revision of the McDonald diagnostic criteria[3].

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 two 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 *Brownlee et al*, found that the addition of optic nerve (evaluated mainly by clinical assessment) would improve the diagnostic performance of 2017 McDonald

criteria only in optic neuritis CIS patients[8], *Filippi et al.* concluded that there was no clear improvement of the 2010 Mc Donald criteria when adding the optic nerve region (assessed mainly by VEP) into the 2010 DIS criteria[9]. 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 impact 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 CIS patients[6]. We have also compared the added value of the fifth region according to optic nerve involvement (symptomatic vs asymptomatic CIS).

Material and Methods

Study cohort. Observational, retrospective study based on the Barcelona CIS cohort. Clinical, demographic, biological, and radiological data is collected prospectively following a pre-specified protocol described elsewhere[6,15]. Briefly, patients < 50 years of age first seen within 3 months of symptoms 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. Since 2007 spinal cord MRIs were done at baseline as part of the diagnostic process in all CIS patients. MRI scans were obtained at 3.0 T since 2010, and at 1.5 T 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%). VEP were performed with a mean time from CIS to VEP of 3.95 months (SD 3.82). Pre-existing eye conditions were taken into account when interpreting VEP results. 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 longer than 112 msec, there was an inter-eye latency asymmetry greater than 8 msec and / or there was an absence of the P100 wave.

Study design. To evaluate the effect of adding new regions to fulfil DIS, we performed a risk assessment analysis. We selected patients with complete information to assess the five 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 1). For both cohorts DIS and DIT were assessed at baseline. The modified DIS criteria (modDIS) were constructed by adding the optic nerve region to the current DIS topographies and using a cut-off value of 2 out of 5. The second attack was determined when new symptoms suggestive of a relapse occurred during the follow-up after an interval of at least one 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 using means

and standard deviations. Otherwise, continuous variables were summarized using medians and ranges, and categorical variables as percentages.

Cohort 1, risk assessment analysis: for the risk assessment analysis, the number of DIS regions fulfilled as well as the current and modified DIS criteria were evaluated using 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 Mc Donald MS criteria fulfilment as the secondary outcome. The results are expressed as the hazard ratios (HRs) with 95% confidence intervals (CI). The Schoenfeld residuals have been evaluated to test the proportional risk assumption. Finally, as initiating a disease modifying treatment before a second attack could have impacted 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 modified DIS criteria alone and in combination with either OB or MRI DIT, with second attack and 2017 Mc Donald 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.

In order to test if the fulfilment of the modDIS criteria would have a different impact in symptomatic (optic neuritis) and asymptomatic (non-optic neuritis) CIS patients, both risk assessment and diagnostic performance analyses were conducted based on CIS topography.

All the statistical tests were performed using the SPSS software version 22 and R version 3.6.0.

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, 1337 patients were included in the Barcelona CIS inception cohort; 99 patients were excluded due to different reasons (figure 1). Of the remaining 1238 patients, 388 fulfilled the criteria for the risk assessment analysis (cohort 1), and 151 for 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=1238) patients were younger, and there was a higher proportion of patients with positive OB and with abnormal VEPs.

VEPs were abnormal in 126 out 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. 130 patients (33.5%) presented a second attack, and all occurred within the first 10 years after CIS onset (mean time of 19.6 months, SD 22.3 months).

Risk assessment analysis (cohort 1).

After presenting 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 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 using 2017 Mc Donald MS as the outcome although with wider confidence intervals (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 also found: HR 4.6, 95% CI 2.9 – 7.2 for 2017 DIS and 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 both optic neuritis and non-optic neuritis CIS patients (table 3).

Diagnostic criteria performance analysis.

The addition of the optic nerve region to the DIS criteria improved the current DIS diagnostic performance by increasing the accuracy and the sensitivity, without decreasing the specificity (table 4). When the current and modDIS criteria were considered along with the presence of OB and / or DIT, the modified criteria remained more accurate, more sensitive, and with similar specificity as compared to the current 2017 McDonald MS criteria, although the improvement was less noticeable than when analyzing DIS alone (table 4). Similar results were found using

2017 Mc Donald MS as the outcome (2017 DIS vs modDIS: sensitivity 80.7% vs 83.6%; specificity 100% vs 100%; accuracy 82.1% vs 84.8%) as well as in the in the sensitivity analysis including only patients that were either never treated or that 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 both optic neuritis vs non-optic neuritis CIS patients, 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 and / or DIT, adding the optic nerve region into the DIS criteria also resulted in a more accurate, more sensitive diagnostic criteria, with a similar specificity to 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 evaluated the optic nerve involvement (mainly using VEPs) in 241 CIS patients, reporting a similar higher risk

for developing a second attack when patients fulfilled either the 2010 DIS criteria or the 2010 modified DIS criteria including the optic nerve (2010 DIS: 3.48, 95% CI 2.2-5.6 and 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 in order to test if the fulfilment of the modDIS criteria would have a different impact in symptomatic and asymptomatic CIS patients (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 as well as in symptomatic and asymptomatic CIS patients. These results are partially discordant with the results published in two 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.* found that the addition of the optic nerve region into the 2010 DIS criteria increased the sensitivity by lowering the specificity of the 2010 criteria using second attack five years after presenting the CIS 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, *Brownlee et al.* analyzed the diagnostic performance of the new modified criteria based on 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 partly explained by the longer follow-up of our cohort, as compared with *Filippi et al.*, that may have allowed us to detect late converters, or by the different methods used to evaluate optic nerve involvement in *Brownlee*'s work. Moreover, we have demonstrated that the addition of the optic nerve to the 2017 McDonald criteria increased the diagnostic performance both in optic neuritis (symptomatic) and non-optic neuritis (asymptomatic) CIS patients, although to a greater extent in the former group. These results are partially discordant with the results published by *Brownlee's et al*. and may be partly explained by a slight over-representation 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 either clinically (by detecting optic nerve atrophy or pallor), with neurophysiological tests (VEPs), or by imaging either using MRI to detect optic nerve lesions or optical coherence tomography (OCT) to detect peripapillary retinal nerve fibre layer (pRNFL) thinning[7]. Assessment of optic nerve involvement based only in 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 pursuing 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 as compared to clinical tools alone. Full field VEP have been classically 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 optic neuritis CIS patients (66.7%) which is a similar result to that reported in the literature (67.8% to 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 enormously evolved since the use of MRI, our work demonstrates the utility of VEP (in combination with brain and spinal cord MRI) in MS diagnosis, supporting the reintroduction of this test in the diagnostic work-up of CIS patients. It is important to bear in mind that VEP results may be influenced by several factors around test acquisition such as patient cooperation, luminescence and contrast patterns, and stimuli presentation rate[30,31]. In order to minimize these factors, VEP should be acquired following international guidelines[16], and a normative dataset obtained from normal subjects using the local equipment is commonly used to define the range of normal variation.

Some limitations should be taken into consideration when interpreting our results. VEPs were obtained as part of the routine diagnostic process of CIS patients, but information regarding the time elapsed since CIS to VEP was only available for three quarters of the patients. Because patients included in this analysis were slightly different from the full Barcelona CIS cohort (n=1238) 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 both in Cohort 1 and Cohort 2. We also acknowledge that by selecting only patients with complete information to analyze the modified DIS 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. Lastly, 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 presenting a typical CIS[2,3], lowering 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 as 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 one periventricular lesion and one enhancing brainstem lesion in brain MRI, while it won't 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 CIS patients 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 CIS patients.

Appendix 1: 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; 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
Carlos Nos, MD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data
Joaquin Castilló, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data
Ingrid Galan, MD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data
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Dulce Moncho, MD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data

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Cristina Auger, MD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; revised the manuscript for intellectual content
Jaume Sastre-Garriga, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Major role in the acquisition of data; revised the manuscript for intellectual content
Xavier Montalban, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Interpreted the data, revised the manuscript for intellectual content
Mar Tintoré, MD, PhD	Hospital Universitario Vall d'Hebron, Barcelona, Spain	Designed and conceptualized study, interpreted the data, revised the manuscript for intellectual content

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Figures and Tables

Figure 1. Patients disposition

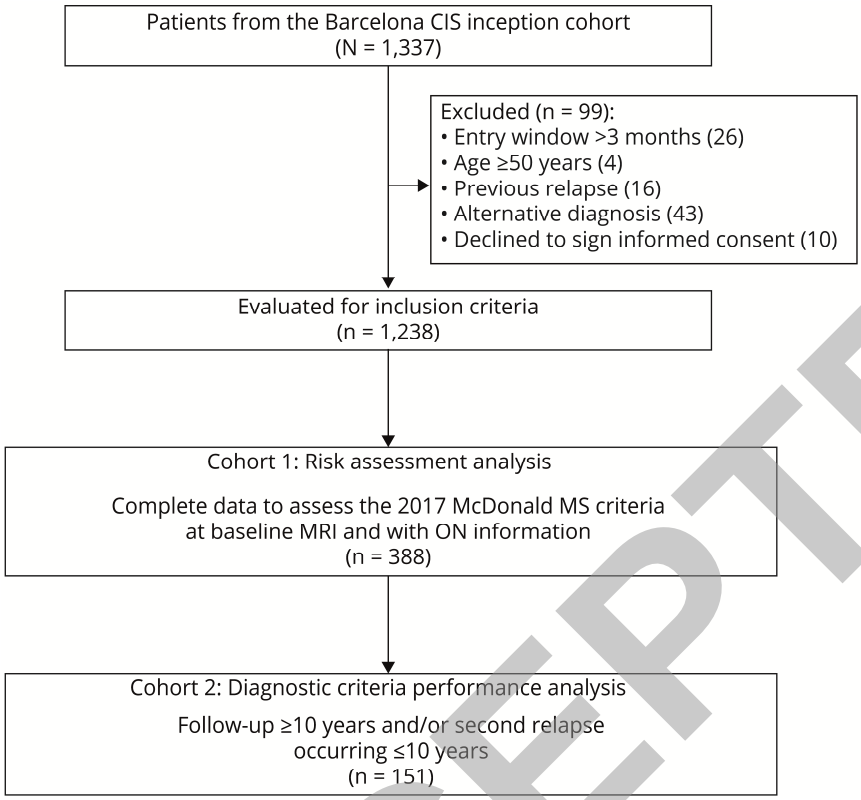

Table 1. Baseline characteristics

	Whole cohort n=1238	**Cohort 1 n=388**	**Cohort 2 n=151**
Age at CIS (years) (mean; SD)	31.6 (8.2)	33.5 (7.8)	32.4 (7.4)
Sex (female)	842 (68.0)	263 (67.8)	108 (71.5)
CIS topography			
Optic neuritis	446 (36.0)	138 (35.6)	40 (26.5)
Non-optic neuritis	787 (63.6)	250 (64.4)	111 (73.5)
Positive oligoclonal bands	582 / 990 (58.8)	182 / 335 (54.3)	100 / 136 (73.5)
Baseline EDSS (median, range)	1.0 (0 – 5.5)	1.0 (0 - 4.5)	1.5 (0 - 4.5)
Abnormal MRI	810 (71.2)	275 (71.1)	136 (90.1)
Gd-enhancing lesions	235 (29.3)	114 (29.4)	71 (47.0)
Number of patients with abnormal VEP	415 / 1098 (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 (months) (mean; SD)	107.9 (98.0)	62.7 (40.4)	88.9 (37.9)

All values are expressed as n (%) except if otherwise specified.

Abbreviations: CIS: clinically isolated syndrome, EDSS: expanded disability status scale, MRI: magnetic resonance imaging, SD: standard deviation, VEP: visual evoked potential.

Table 2. Risk assessment analysis for the whole cohort: hazard ratios for second attack as the outcome.

	n (%)	2nd attack n (%)	HR (95% CI)
Number 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 modified DIS			
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)

Table legend:

2017 DIS criteria as defined in *Thompson et al*[3]: at least 1 lesion in at least 2 out of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord).

modDIS, adding optic nerve assessed by VEP: at least 1 lesion in at least 2 out of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Abbreviations: CI: confidence interval; DIS: dissemination in space; HR: hazard ratio; modDIS: modified DIS.

Table 3. Risk assessment analysis according to optic nerve involvement: hazard ratios for second attack as the outcome.

	n (%)	2nd 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)

Table legend:

2017 DIS criteria as defined in *Thompson et al*[3]: at least 1 lesion in at least 2 out of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord).

modDIS, adding optic nerve assessed by VEP: at least 1 lesion in at least 2 out of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Abbreviations: CI: confidence interval; CIS: clinically isolated syndrome; DIS: dissemination in space; HR: hazard ratio; modDIS: modified DIS.

Table 4. Diagnostic performance analysis: diagnostic properties at 10 years with second attack as the outcome.

	Sensitivity	Specificity	Accuracy	PPV	NPV
	%, (95% CI)				
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)

Table legend:

2017 DIS criteria as defined in *Thompson et al*[3]: at least 1 lesion in at least 2 out of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord).

modDIS, adding optic nerve assessed by VEP: at least 1 lesion in at least 2 out of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Abbreviations: CI: confidence interval; CNS: central nervous system; DIS: dissemination in space; DIT: dissemination in time; modDIS: modified DIS; NPV: negative predictive value; OB: oligoclonal bands; PPV: positive predictive value.

Table 5. Diagnostic performance analysis according to optic nerve involvement: diagnostic properties at 10 years with second attack as the outcome.

	Sensitivity	Specificity	Accuracy	PPV	NPV
	%, (95% CI)				
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)

Table legend:

2017 DIS criteria as defined in *Thompson et al*[3]: at least 1 lesion in at least 2 out of 4 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord).

modDIS, adding optic nerve assessed by VEP: at least 1 lesion in at least 2 out of 5 areas of the CNS (periventricular, cortico-juxtacortical, infratentorial, spinal cord, optic nerve).

Abbreviations: CI: confidence interval; CIS: clinically isolated syndrome; CNS: central nervous system; DIS: dissemination in space; DIT: dissemination in time;

modDIS: modified DIS; NPV: negative predictive value; OB: oligoclonal bands; PPV: positive predictive value.

Optic nerve region in multiple sclerosis diagnosis: the utility of visual evoked potentials

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Neurology published online December 16, 2020
DOI 10.1212/WNL.0000000000011339