ARTIGO ORIGINAL/ORIGINAL ARTICLE

Inclusion of Optic Nerve Assessed by Visual Evoked Potentials in Dissemination in Space Criteria for the Diagnosis of Multiple Sclerosis

Inclusão do Nervo Ótico Avaliado por Potenciais Evocados Visuais nos Critérios de Disseminação no Espaço para o Diagnóstico de Esclerose Múltipla

Sofia Delgado [1,*], Ângela Timóteo [2], Joana Moniz Dionísio [1], Ana Rodrigues [2], Ana Arraiolos [2], Pedro Lopes das Neves [1], André Rêgo [1], José Vale [2], Vasco Salgado [1], Lia Leitão [1], Mariana Santos [1]

1-Serviço de Neurologia / Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal
2-Serviço de Neurologia / Hospital Beatriz Ângelo, Loures, Portugal

DOI: https://doi.org/10.46531/sinapse/AO/240003/2024

Informações/Informations:
Artigo Original, publicado em Sinapse, Volume 24, Número 3, julho-setembro 2024. Versão eletrónica em www.sinapse.pt;
Original Article, published in Sinapse, Volume 24, Number 3, July-September 2024. Electronic version in www.sinapse.pt

Keywords:
Demyelinating Diseases;
Evoked Potentials, Visual;
Magnetic Resonance Imaging;
Multiple Sclerosis/diagnosis;
Multiple Sclerosis/diagnostic imaging;
Optic Nerve/diagnostic imaging.

Palavras-chave:
Doenças Desmielinizantes;
Potenciais Evocados Visuais;
Esclerose Múltipla/diagnóstico;
Esclerose Múltipla/diagnóstico por imagem;
Nervo Ótico/diagnóstico por imagem;
Ressonância Magnética.

***Autor Correspondente / Corresponding Author:**
Sofia Delgado
IC19 276
2720-276 Amadora, Portugal
sofiacdelgado20@gmail.com

Recebido / Received: *2024-01-12*
Aceite / Accepted: *2024-08-20*
Ahead of Print: *2024-09-30*
Publicado / Published: *2024-11-07*

Abstract

Introduction: Optic nerve (ON) inclusion as the fifth location in dissemination in space (DIS) for the diagnosis of multiple sclerosis (MS) was proposed in 2016 by the Magnetic Resonance Imaging in Multiple Sclerosis Group. However, there was insufficient evidence to include this recommendation in the 2017 revision of McDonald criteria.

Our objective was to investigate the effect of including ON involvement assessed by visual evoked potentials (VEP) as the fifth location in DIS criteria for MS diagnosis, in patients with a typical clinically isolated syndrome (CIS).

Methods: We studied consecutive patients presenting with typical CIS between 2012 and 2019 from two Portuguese hospitals with complete initial evaluation, including brain and spine magnetic resonance imaging (MRI) and VEP. McDonald 2017 criteria and a set of modified criteria that included ON involvement in DIS assessed by VEP were applied retrospectively. Performance of the two sets of criteria to predict development of clinically definite multiple sclerosis (CDMS) and/or MRI activity during follow-up was evaluated.

Results: Seventy-six patients were included, 25% of which had an ON CIS. Asymptomatic ON involvement on VEP was found in 12.3% of non-ON CIS. Twenty-seven (35.5%) patients converted to CDMS and 37 (48.7%) had MRI activity during follow-up (median = 3.12 years, 1.04 - 8.36). Fifty-nine percent of patients begun disease-modifying treatment before conversion to CDMS. Modified DIS criteria in combination with dissemination in time were more sensitive (77.8% *vs* 74.1%), but less specific (57.1% *vs* 61.2%) to predict CDMS, and were more sensitive (73.2% *vs* 65.9%) with equal specificity (65.7% *vs* 65.7%) to predict CDMS or MRI activity, but these differences were not statistically significant. Modified criteria allowed for the correct diagnosis of 3 additional patients at baseline (42/76 *vs* 39/76), in average 9 months before fulfilment of McDonald 2017 criteria.

Conclusion: Although inclusion of ON involvement assessed by VEP in DIS criteria led to the accurate identification of more MS patients, in our sample it did not allow for statistically significant increase in sensitivity for MS diagnosis. Even so, our work supports the need for discussion of the inclusion of ON in DIS criteria in the future revision of MS diagnostic criteria.

Resumo

Introdução: A inclusão do nervo óptico (NO) nos critérios de disseminação no espaço (DIS) para o diagnóstico de esclerose múltipla (EM) foi proposta em 2016

pelo grupo *Magnetic Ressonance Imaging in Multiple Sclerosis*. Contudo, existia evidência insuficiente para incluir esta recomendação na revisão de 2017 dos critérios de McDonald.

O nosso objetivo foi investigar o efeito de incluir o NO avaliado por potenciais evocados visuais (PEV) como quinta localização nos critérios de DIS para o diagnóstico de EM, em doentes com síndrome clínico isolado (CIS) típico.

Métodos: Estudámos doentes que se apresentaram com CIS entre 2012 e 2019 em dois hospitais portugueses, com avaliação inicial completa, incluindo ressonância magnética crânio-encefálica e medular, e PEV. Aplicámos retrospetivamente os critérios de McDonald 2017 e um conjunto de critérios modificados que incluíam o NO avaliado por PEV na DIS. Avaliámos a performance dos dois conjuntos de critérios para predizer conversão em esclerose múltipla clinicamente definida (EMCD) e/ou atividade imagiológica.

Resultados: Incluímos 76 doentes, 25% com nevrite ótica como CIS. Os PEV identificaram envolvimento assintomático do NO em 12,3% dos CIS-não nevrite ótica. Vinte e sete (35.5%) doentes converteram em EMCD e 37 (48,7%) apresentaram atividade imagiológica durante o *follow-up* (mediana = 3,12 anos, 1,04 – 8,36). Cinquenta e nove por cento iniciaram terapêutica modificadora da doença antes da conversão em EMCD. Os critérios de DIS modificados em combinação com disseminação no tempo foram mais sensíveis (77,8% *vs* 74,1%), mas menos específicos (57,1% *vs* 61,2%) para predizer EMCD, e mais sensíveis (73,2% *vs* 65,9%) e igualmente específicos (65,7% *vs* 65,7%) para predizer EMCD ou actividade imagiológica, mas estas diferenças não foram estatisticamente significativas. Os critérios modificados permitiram o diagnóstico de 3 doentes adicionais no *baseline* (42/76 *vs* 39/76), em média 9 meses antes do cumprimento dos critérios de McDonald 2017.

Conclusão: Embora a inclusão do NO avaliado por PEV nos critérios de DIS tenha levado à correta identificação de mais doentes com EM, na nossa amostra não permitiu um aumento estaticamente significativo da sensibilidade de diagnóstico. Ainda assim, o nosso trabalho apoia a necessidade de discussão da inclusão do NO nos critérios de DIS na futura revisão dos critérios de diagnóstico de EM.

Introduction

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease of the central nervous system (CNS). The existence of great clinical and imaging heterogeneity, and the absence of a diagnostic biomarker with absolute sensitivity and specificity, constitutes a diagnostic challenge.[1] Its diagnosis is thus based (1) on the identification of a typical demyelination syndrome, (2) on the existence of objective evidence of CNS involvement, (3) on the demonstration of a disease with dissemination in time (DIT) and (4) dissemination in space (DIS), and (5) in the exclusion of other entities that can simulate MS due to its clinical and laboratory profile.[2] There is robust evidence of the importance of early initiation of disease-modifying treatment (DMT) in MS, since it reduces the risk of conversion to clinically definite multiple sclerosis (CDMS) and the risk of disability accumulation.[3,4] The existence of increasingly effective therapies makes the benefit of early treatment even more relevant.[5,6] Thus, the criteria for the diagnosis of MS have evolved over time, allowing an earlier diagnosis (along with the start of DMT), while trying to preserve its specificity to avoid incorrect diagnoses.[7]

Optic neuritis is a common presentation of MS, representing 25%-30% of clinical isolated syndromes (CIS).[8] Approximately 70% of MS patients have an optic neuritis during the course of the disease[8] and the involvement of the optic nerve (ON) in the autopsy is almost universal.[9] ON involvement can be symptomatic (optic neuritis) or asymptomatic, and can be determined clinically or through paraclinical data.[9] Clinically, the involvement

of ON can present with decreased visual acuity, presence of scotomas, dyschromatopsia or pain with eye movements, and can be objectively demonstrated by a relative afferent pupillary defect and optic disc oedema or pallor.[8,9] In diagnostic workup (paraclinical data), the involvement of ON can be detected by: T2 hyperintensity, enhancement after gadolinium or ON oedema in magnetic resonance imaging (MRI); asymmetric conduction delay in visual evoked potentials (VEP) and evidence of rarefaction of the retinal nerve fiber layer on optical coherence tomography (OCT) assessment.[10]

Despite its clear clinical relevance, this topography is not considered in the paraclinical criteria of DIS for the diagnosis of MS. The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group proposed in 2016 the inclusion of ON involvement, documented by objective clinical signs, by VEP, MRI or OCT, in the DIS criteria for the diagnosis of MS.[10] However, in the 2017 revision of the McDonald criteria (current criteria), the Panel considered that there was insufficient evidence to support the inclusion of ON as the 5th anatomical location for the demonstration of DIS.[7] For this reason, it has been given a high priority to studies that evaluate the use of MRI, VEP or OCT to determine the involvement of ON as a possible component of DIS.[7]

The objective of this study was, then, to investigate the effect of including ON involvement assessed by VEP as the 5th location in DIS criteria for MS diagnosis, in patients with a typical CIS.

Material and Methods

Study design and patients:

We revised the databases of the demyelinating diseases consultations and the records of the Neurophysiology Laboratories (list of patients who underwent VEP), of two Portuguese hospitals and retrospectively studied consecutive patients presenting with CIS between 2012 and 2019, through clinical file consultation. Central field pattern reversal VEPs were done as part of routine clinical care at diagnosis. ON involvement was defined as the presence of an unilateral prolongation of P100 wave latency (≥ 116 ms), absence of the P100 wave, or significant intereye P100 wave latency asymmetry (≥ 10 ms) when the prolongation of latency was bilateral.[11,12]

Inclusion criteria for the study were: (1) Patients with typical CIS (as defined by Miller DH *et al*),[2] (2) with brain MRI within 6 months of CIS, (3) cervical spine MRI within 6 months of CIS, if McDonald2017 criteria for MS diagnosis were not met with brain MRI, (4) dorsal spine MRI within 6 months of CIS, if McDonald2017 criteria for MS diagnosis were not met with brain MRI, (5) VEP within 6 months of CIS, (6) follow-up brain MRI within 3-24 months of CIS, and (7) follow-up of at least 1 year. Exclusion criteria were atypical CIS, with clinical or paraclinical red flags (as defined by Miller DH *et al*)[2] and insufficient data on clinical file.

Procedures:

We retrospectively applied, at the time of CIS:

- The McDonald 2017 DIS criteria alone,
- the McDonald 2017 criteria (DIS + DIT),
- a set of modified DIS criteria including ON assessed by VEP as the 5th location (**Table 1**),
- and the modified DIS criteria (**Table 1**) + McDonald 2017 DIT criteria.

On follow-up we assessed: (1) the conversion to CDMS, defined as the development of clinical activity (relapse or clinical progression),[13] (2) the presence of MRI activity (new lesion or enlarged hyperintense T2 lesion or any gadolinium enhancing lesion), (3) initiation of DMT.

Statistical analysis:

We calculated the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the McDonald 2017 DIS criteria and the modified DIS criteria, alone, and in combination with McDonald 2017 DIT criteria, to predict conversion to

Table 1. Modified Dissemination in Space (DIS) criteria.

Involvement of ≥ 2 of 5 anatomical locations, including:
≥ 1 periventricular lesion on brain MRI
≥ 1 cortical/juxtacortical lesion on brain MRI
≥ 1 infratentorial lesion on brain MRI
≥ 1 spinal-cord lesion on cervical or dorsal spine MRI
Involvement of ON assessed by VEP (unilateral or asymmetrical prolongation of P100 latency)

MRI, magnetic resonance imaging; ON, optic nerve; VEP, visual evoked potentials.

CDMS, development of MRI activity, and occurrence of CDMS or MRI activity, during follow-up.

A McNemar test was performed to compare the performance of the two sets of criteria, with significance reported at $p<0.05$.

Results

Patient demographic and clinical characteristics:

We included 76 patients, 60 (78%) women, with a mean age at CIS of 34 years (range 11 - 64), and a median follow-up of 3.12 years (range 1.04 – 8.36). Nineteen patients (25%) had an optic neuritis as their CIS. Asymptomatic ON involvement on VEP was found in 12.3% of non-ON CIS.

During follow-up, 27 (35.5%) patients converted to CDMS, 37 (48.7%) had MRI activity, and 41 (53.9%) had one or the other. However, it is important to denote that 59.2% of the patients begun DMT before conversion to CDMS, and of these only 37.8% had a second clinical event on follow-up.

Modified criteria allowed for the diagnosis of 3 additional patients at baseline, when compared with McDonald 2017 criteria (42 of 76 *vs* 39 of 76, respectively), two with an ON-CIS and one with a myelitis, in average 9 months before fulfilment of McDonald 2017 criteria and subsequent initiation of DMT.

Demographic, clinical, and paraclinical findings of the 76 patients are resumed in **Table 2**, and demographic and clinical characteristics of the 3 additional patients identified with the modified criteria are resumed in **Table 3**.

Performance of the criteria:

The performance of the different combined diagnostic criteria (Modified DIS criteria, Modified DIS criteria + McDonald 2017 DIT criteria, McDonald 2017 DIS criteria, McDonald 2017 DIS + DIT criteria) is shown in **Table 4**.

Modified DIS criteria, alone and in combination with DIT, were slightly more sensitive than McDonald 2017 (DIS and DIS + DIT) criteria to predict conversion to CDMS (92.6% *vs* 88.9% and 77.8% *vs* 74.1%, respectively), but less specific (42.9% *vs* 46.9% and 57.1% *vs* 61.2%, respectively).

When the outcome was MRI activity, modified DIS criteria alone and in combination with DIT, were more sensitive than McDonald 2017 (DIS and DIS + DIT) criteria (83.8% *vs* 75.7% and 70.3% *vs* 62.2%, respectively) with equal specificity (43.6% *vs* 43.6% and 59.0% *vs* 59.0%, respectively).

When the outcome was either conversion to CDMS or MRI activity during follow-up, modified DIS criteria alone and in combination with DIT were, once more, more sensitive than McDonald 2017 (DIS and DIS + DIT) criteria (85.4% *vs* 78.0% and 73.2% *vs* 65.9%, respectively) with equal specificity (48.6% *vs* 46.6% and 65.7% *vs* 65.7%, respectively). They had also better PPV, NPV, and accuracy.

However, when compared using the McNemar test there were no statistically significant differences between the performance of the two sets of criteria to predict

Table 2. Patient demographic and clinical characteristics.

Characteristics	
Age at onset, years, mean (range)	34 (11 – 64)
Sex, n (%)	
Female	60 (78)
Male	16 (22)
CIS topography, n (%)	
Optic neuritis	19 (25)
Brainstem syndrome	15 (19.7)
Spinal-cord syndrome	26 (34.2)
Cerebral syndrome	9 (11.8)
Polyfocal	3 (3.9)
Undetermined	4 (5.3)
Follow-up time, years, median (range)	3.12 (1.04 – 8.36)
ON involvement on VEP, n (%)	
Optic neuritis (n=19)	12 (63.2)
Non-ON CIS (n=57)	7 (12.3)
Criteria fulfilment at CIS, n (%)	
McDonald 2017 DIS	50 (55.8)
Modified DIS	53 (69.7)
McDonald 2017 (DIS + DIT)	39 (51.3)
Modified DIS + DIT	42 (55.3)
Outcomes on follow-up, n (%)	
Conversion to CDMS	27 (35.5)
MRI activity	37 (48.7)
CMDS or MRI activity	41 (53.9)
Initiation of DMT	53 (69.7)
Initiation of DMT before conversion to CDMS	45 (59.2)
Time to reach outcomes on follow-up, years, median (range)	
Time to conversion to CDMS	1.11 (0.18 – 5.63)
Time to MRI activity	1.20 (0.25 – 6.34)
Time to CDMS or MRI activity	1.04 (0.18 – 5.63)
Time to initiation of DMT	0.33 (0.07 – 3.46)

CIS, clinically isolated syndrome; ON, optic nerve; VEP, visual evoked potentials; DIS, dissemination in space; DIT, dissemination in time; CDMS, clinically definite multiple sclerosis; MRI, magnetic resonance imaging; DMT, disease modifying therapy.

Table 3. Characteristics of the 3 additional patients identified by modified DIS criteria.

	CIS topography	Follow up (years)	At follow up:			
			McDonald17? (when)	MRI activity? (when)	CDMS? (when)	DMT? (when)
♂ 45y	Myelitis	5.21	Yes (0.40y)	Yes (0.40y)	Yes (0.40y)	Yes (0.53y)
♀ 51y	Optic neuritis	1	Yes (0.99y)	Yes (0.99y)	No	Yes (0.99y)
♀ 47y	Optic neuritis	2.84	Yes (0.87y)	Yes (0.87y)	No	Yes (0.96y)

CIS, clinically isolated syndrome; MRI, magnetic resonance imaging; CDMS, clinically definite multiple sclerosis; DMT, disease modifying therapy; y, years.

Table 4. Performance of the McDonald 2017 criteria and the set with modified DIS criteria.

	Sensitivity % (CI 95%)	Specificity % (CI 95%)	PPV % (CI 95%)	NPV % (CI 95%)	Accuracy % (CI 95%)
Prediction of conversion to CDMS					
McDonald17 DIS	88.9 (70.8 - 97.7)	46.9 (32.5 - 61.7)	48.0 (40.7 - 55.4)	88.5 (71.7 - 95.9)	61.8 (50.0 - 72.8)
Modified DIS	92.6 (75.7 - 99.1)	42.9 (28.8 - 57.8)	47.2 (40.7 - 53.8)	91.3 (72.7 - 97.6)	60.5 (48.7 - 71.6)
McDonald17 DIS + DIT	74.1 (53.7 - 88.9)	61.2 (46.2 - 74.8)	51.3 (41.0 - 61.5)	81.1 (68.6 - 89.4)	65.8 (54.0 - 76.3)
Modified DIS + DIT	77.8 (57.7 - 91.4)	57.1 (42.2 - 71.2)	50.0 (40.6 - 59.4)	82.4 (68.9 - 90.8)	64.5 (52.7 - 75.1)
Prediction of MRI activity					
McDonald17 DIS	75.7 (58.8 - 88.2)	43.6 (27.8 - 60.4)	56.0 (47.8 - 63.9)	65.4 (49.1 - 78.7)	59.2 (47.3 - 70.4)
Modified DIS	83.8 (68.0 - 93.8)	43.6 (27.8 - 60.4)	58.5 (50.8 - 65.8)	73.9 (55.6 - 86.5)	63.2 (51.3 - 73.9)
McDonald17 DIS + DIT	62.2 (44.8 - 77.5)	59.0 (42.1 - 74.4)	59.0 (47.8 - 69.3)	62.2 (50.2 - 72.8)	60.5 (48.7 - 71.6)
Modified DIS + DIT	70.3 (53.0 - 84.1)	59.0 (42.1 - 74.4)	61.9 (51.4 - 71.4)	67.7 (54.4 - 78.6)	64.5 (52.7 - 75.1)
Prediction of conversion to CDMS or MRI activity					
McDonald17 DIS	78.0 (62.4 - 89.4)	48.6 (31.4 - 66.0)	64.0 (55.4 - 71.8)	65.4 (49.1 - 78.7)	64.5 (52.7 - 75.1)
Modified DIS	85.4 (70.8 - 94.4)	48.6 (31.4 - 66.0)	66.0 (57.9 - 73.3)	73.9 (55.7 - 86.5)	68.4 (56.8 - 78.6)
McDonald17 DIS + DIT	65.9 (49.4 - 79.9)	65.7 (47.8 - 80.9)	69.2 (57.5 - 78.9)	62.2 (50.2 - 72.8)	65.8 (54.0 - 76.3)
Modified DIS + DIT	73.2 (57.1 - 85.8)	65.7 (47.8 - 80.9)	71.4 (60.4 - 80.4)	67.6 (54.5 - 78.5)	69.7 (58.1 - 79.8)

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval; CDMS, clinically definite multiple sclerosis, DIS, dissemination in space; DIT, dissemination in time; MRI, magnetic resonance imaging; DMT, disease modifying therapy.

conversion to CDMS ($p=1$), MRI activity ($p=0.250$) and conversion to CDMS or MRI activity ($p=0.250$).

Discussion

Inclusion of ON involvement assessed by VEP on DIS criteria in our sample, led to accurate identification of 3 more MS patients sooner than McDonald 2017 criteria, but it did not allow for statistically significant increase in sensitivity for MS diagnosis. The small sample size, short mean follow-up time and the high percentage of patients that begun DMT before conversion to CDMS might have influenced these results.

In the 2017 revision of the McDonald criteria the Panel considered that there was insufficient evidence to support the inclusion of ON as the 5th location of DIS. In fact, at the time there was scant and contradictory evidence in this field. A multicenter study carried out by MAGNIMS (N=241),[14] had demonstrated that the inclusion of ON involvement (determined by MRI or VEP) in DIS, led to a very slight improvement in the sensitivity of prediction of CDMS (92% *vs* 91% at 36 months; 90% *vs* 87% at 60 months), but to a decrease in specificity (26% *vs*

33% at 36 and 60 months), when compared with McDonald 2010 DIS criteria. On the other hand, a study by Brownlee *et al* (N=160)[15] with a 15-year follow-up, had demonstrated that the inclusion of symptomatic ON involvement (determined by clinical evaluation or VEP) in DIS criteria in patients with optic neuritis improved the overall performance of MS diagnostic criteria (sensitivity modified DIS + DIT 83% *vs* McDonald 2017 74%; specificity modified DIS + DIT 77% *vs* McDonald 2017 77%); but that the inclusion of asymptomatic ON involvement did not bring additional value.

Since then, two more recent studies were consistent with a better performance of diagnostic criteria including ON as a 5th location of DIS. Vidal-Jordana *et al*[16] demonstrated that the addition of ON (assessed by VEP) in DIS, both in symptomatic and asymptomatic patients, conferred a higher risk for developing a second attack during follow-up and slightly improved the diagnostic criteria performance by increasing sensitivity (82.3% *vs* 79.2%) without losing specificity (52.4% *vs* 52.4%), when compared with McDonald 2017 DIS criteria, in a subset of patients (N=151) with at least 10 years of follow-up. Finally, Bsteh *et al*[17] showed that the diagnostic accuracy of a set of modified DIS criteria including ON (accessed by OCT) was significantly higher (AUC 81.2 *vs* 65.6, p=0.021) than McDonald 2017 DIS criteria, for prediction of a second clinical attack. They provided improved sensitivity (84.2% *vs* 77.9%) without lowering specificity (52.2% *vs* 52.2%), in a group of patients (N=118) with a follow-up of at least 5 years.

Our study supports the potential utility of VEP in the evaluation of ON involvement in CIS. In fact, in our sample, 25% of patients presented with an optic neuritis, but asymptomatic ON involvement on VEP was found in 12.3% of non-ON CIS. In line with this, some studies[18-20] found a higher sensitivity of VEP in identifying clinical and/or subclinical ON involvement, when compared with OCT. Besides the potential use in detecting clinical and subclinical ON involvement and its utility for diagnosis, both multimodal evoked potentials (including VEP) and OCT might have a role in the assessment of risk of disability progression in MS patients at onset and over time.[21-25] Indeed, a recently proposed tool for individual prognostication of MS patients included both OCT and VEP data in the model.[26] On the other hand, when compared to VEP, OCT and MRI can provide more information in the acute phase of symptomatic ON involvement in relation to the classification of optic neuritis and related etiological diagnosis.[27] The determination of the ideal method of evaluation of ON involvement in patients with CIS (VEP, MRI, OCT, or a conjunction of all methods), requires further investigation in larger prospective multicentre studies with complete evaluation of ON at CIS onset.

Conclusion

To conclude, despite its limitations and in line with other recent studies, our work supports the need for discussion of the inclusion of ON involvement at CIS onset in DIS criteria, in the expected near future revision of MS diagnostic criteria, since it can improve the sensitivity of diagnosis without compromising specificity, thus contributing to an earlier diagnosis and treatment of MS patients. ■

Contributorship Statement / Declaração de Contribuição

SD: Writing, edition and revision of the article; study design; data collection and validation; statistical treatment and data analysis.

AT: Study coordination and implementation in her hospital; data collection and validation; writing, edition and revision of the last versions of the article prior to publication.

JMD, AR, AA PLN, AR: Writing, edition and revision of the last versions of the article prior to publication; data collection and validation in their hospital.

JV, VS, LL: Clinical validation of included patients in their hospital; supervision, edition and revision of the last versions of the article prior to publication.

MS: Global coordination, article conceptualization and study design; writing, edition and revision of the article; data collection and validation.

All authors discussed and reviewed the final manuscript and agreed with it before submission.

SD: Redação, edição e revisão do artigo; desenho do estudo; recolha e validação de dados; tratamento estatístico e análise de dados.

AT: Coordenação e implementação do estudo no seu hospital; recolha e validação de dados; redação, edição e revisão das últimas versões do artigo anteriores à publicação.

JMD, AR, AA PLN, AR: Redação, edição e revisão das últimas versões do artigo antes da publicação; recolha de dados recolha e validação de dados no seu hospital.

JV, VS, LL: Validação clínica dos doentes incluídos no seu hospital; supervisão, edição e revisão das últimas versões do artigo antes da publicação.

MS: Coordenação global, concetualização do artigo e desenho do estudo conceção do estudo; redação, edição e revisão do artigo; recolha de dados e validação dos dados.

Todos os autores aprovaram a versão final a ser publicada.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos

dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

References / Referências

1. Solomon AJ, Arrambide G, Brownlee WJ, Flanagan EP, Amato MP, Amezcua L, et al. Differential diagnosis of suspected multiple sclerosis: an updated consensus approach. Lancet Neurol. 2023;22:750-68. doi: 10.1016/S1474-4422(23)00148-5.
2. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler. 2008;14:1157–74. doi: 10.1177/1352458508096878.
3. Kappos L, Edan G, Freedman MS, Montalbán X, Hartung HP, Hemmer B, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology. 2016;87:978-87. doi: 10.1212/WNL.0000000000003078.
4. Tintore M, Rovira À, Río J, Otero-Romero S, Arrambide G, Tur C, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain. 2015;138:1863-74. doi: 10.1093/brain/awv105.
5. He A, Merkel B, Brown JWL, Zhovits Ryerson L, Kister I, Malpas CB, et al. Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study. Lancet Neurol. 2020;19:307-16. doi: 10.1016/S1474-4422(20)30067-3.
6. Spelman T, Magyari M, Piehl F, Svenningsson A, Rasmussen PV, Kant M, et al. Treatment Escalation vs Immediate Initiation of Highly Effective Treatment for Patients With Relapsing-Remitting Multiple Sclerosis: Data From 2 Different National Strategies. JAMA Neurol. 2021;78:1197-204. doi: 10.1001/jamaneurol.2021.2738.
7. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162-73. doi: 10.1016/S1474-4422(17)30470-2.
8. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol. 2014;13:83–99. doi: 10.1016/S1474-4422(13)70259-X.
9. Kolappan M, Henderson AP, Jenkins TM, Wheeler-Kingshott CA, Plant GT, Thompson AJ, et al. Assessing structure and function of the afferent visual pathway in multiple sclerosis and associated optic neuritis. J Neurol. 2009;256:305-19. doi: 10.1007/s00415-009-0123-z.
10. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016;15:292-303. doi: 10.1016/S1474-4422(15)00393-2.
11. Drislane FW. Visual Evoked Potentials. In: Blum AS, Rutkove SB, editors. The Clinical Neurophysiology Primer. Totowa: Humana Press; 2007. p.461-73.
12. Ekayanti MS, Mahama CN, Ngantung DJ. Normative values of visual evoked potential in adults. Indian J Ophthalmol. 2021;69:2328-32. doi: 10.4103/ijo.IJO_2480_20.
13. Kappos L, Edan G, Freedman MS, Montalbán X, Hartung HP, Hemmer B, et al. The 11-year long-term follow-up study from the randomized BENEFIT CIS trial. Neurology. 2016;87:978-87. doi: 10.1212/WNL.0000000000003078.
14. Filippi M, Preziosa P, Meani A, Ciccarelli O, Mesaros S, Rovira A, et al. Prediction of a multiple sclerosis diagnosis in patients with clinically isolated syndrome using the 2016 MAGNIMS and 2010 McDonald criteria: a retrospective study. Lancet Neurol. 2018;2: 133–42. doi: 10.1016/S1474-4422(17)30469-6.
15. Brownlee WJ Miszkiel KA, Tur C, Barkhof F, Miller DH, Ciccarelli O. Inclusion of optic nerve involvement in dissemination in space criteria for multiple sclerosis. Neurology. 2018; 91: e1130–4. doi: 10.1212/WNL.0000000000006207.
16. Vidal-Jordana A, Rovira A, Arrambide G, Otero-Romero S, Río J, Comabella M, et al. Optic nerve topography in multiple sclerosis diagnosis: the utility of visual evoked potentials. Neurology. 2021;96:e482-e490. doi: 10.1212/WNL.0000000000011339.
17. Bsteh G, Hegen H, Altmann P, Auer M, Berek K, Di Pauli F, et al. Diagnostic Performance of Adding the Optic Nerve Region Assessed by Optical Coherence Tomography to the Diagnostic Criteria for Multiple Sclerosis. Neurology. 2023;101:e784-93. doi: 10.1212/WNL.0000000000207507.
18. Naismith RT, Tutlam NT, Xu J, Shepherd JB, Klawiter EC, Song SK, et al. Optical coherence tomography is less sensitive than visual evoked potentials in optic neuritis. Neurology. 2009;73:46-52. doi: 10.1212/WNL.0b013e3181aaea32.
19. Behbehani R, Ahmed S, Al-Hashel J, Rousseff RT, Alroughani R. Sensitivity of visual evoked potentials and spectral domain optical coherence tomography in early relapsing remitting multiple sclerosis. Mult Scler Relat Disord. 2017;12:15-9. doi: 10.1016/j.msard.2016.12.005.
20. Di Maggio G, Santangelo R, Guerrieri S, Bianco M, Ferrari L, Medaglini S, et al. Optical coherence tomography and visual evoked potentials: which is more sensitive in multiple sclerosis? Mult Scler. 2014;20:1342-7. doi: 21.1177/1352458514524293.
21. Swinnen S, De Wit D, Van Cleemput L, Cassiman C, Dubois B. Optical coherence tomography as a prognostic tool for disability progression in MS: a systematic review. J Neurol. 2023;270:1178-86. doi: 10.1007/s00415-022-11474-4.
22. Martinez-Lapiscina EH, Arnow S, Wilson JA, Saidha S, Preiningerova JL, Oberwahrenbrock T, et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurol. 2016;15:574-84. doi: 10.1016/S1474-4422(16)00068-5.
23. Hardmeier M, Leocani L, Fuhr P. A new role for evoked potentials in MS? Repurposing evoked potentials as biomarkers for clinical trials in MS. Mult Scler. 2017;23:1309-19. doi: 10.1177/1352458517707265.
24. Giffroy X, Maes N, Albert A, Maquet P, Crielaard JM, Dive D. Multimodal evoked potentials for functional quantification and prognosis in multiple sclerosis. BMC Neurol. 2016;16:83. doi: 10.1186/s12883-016-0608-1.
25. Vecchio D, Barbero P, Galli G, Virgilio E, Naldi P, Comi C, et al. Prognostic Role of Visual Evoked Potentials in Non-Neuritic Eyes at Multiple Sclerosis Diagnosis. J Clin Med. 2023;12:2382. doi: 10.3390/jcm12062382.
26. Van Wijmeersch B, Hartung HP, Vermersch P, Pugliatti M, Pozzilli C, Grigoriadis N, et al. Using personalized prognosis in the treatment of relapsing multiple sclerosis: A practical guide. Front Immunol. 2022;13:991291. doi: 10.3389/fimmu.2022.991291.
27. Petzold A, Fraser CL, Abegg M, Alroughani R, Alshowaeir D, Alvarenga R, et al. Diagnosis and classification of optic neuritis. Lancet Neurol. 2022;21:1120-34. doi: 10.1016/S1474-4422(22)00200-9.