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Diagnostic Performance of Adding the Optic Nerve Region Assessed by Optical Coherence Tomography to the Diagnostic Criteria for MS

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Abstract

Background: The optic nerve has been recommended as an additional region for demonstrating dissemination in space (DIS) in diagnostic criteria for multiple sclerosis (MS).

Objective: To investigate whether adding the optic nerve region as determined by optical coherence tomography (OCT) as part of the DIS criteria improves the 2017 diagnostic criteria.

Methods*:* From a prospective observational study, we included patients with a first demyelinating event who had complete information to assess DIS and a spectral-domain OCT scan obtained within 180 days. Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve to the current DIS regions based on validated thresholds for OCT inter-eye differences. Time to second clinical attack was the primary endpoint.

Results: We analyzed 267 MS patients (mean age 31.3 years [SD 8.1], 69% female) during a median observation period of 59 months (range: 13 - 98).

Adding the optic nerve as a fifth region improved the diagnostic performance by increasing accuracy (DIS+OCT 81.2% vs. DIS 65.6%,) and sensitivity (DIS+OCT 84.2% vs. DIS 77.9%) without lowering specificity (DIS+OCT 52.2% vs. DIS 52.2%).

Fulfilling DIS+OCT criteria (≥2 of 5 DIS+OCT regions involved) indicated a similar risk of a second clinical attack (HR 3.6, CI 1.4 – 14.5) compared to a 2.5-fold increased risk when fulfilling DIS criteria (HR 2.5, CI 1.2 – 11.8).

When the analysis was conducted according to topography of the first demyelinating event, DIS+OCT criteria performed similarly in both optic neuritis and non–optic neuritis.

Conclusions: Addition of the optic nerve, assessed by OCT, as a fifth region in the current DIS criteria improves diagnostic performance by increasing sensitivity without lowering specificity.

Classification of Evidence: This study provides Class II evidence that adding the optic nerve as determined by optical coherence tomography (OCT) as a fifth dissemination in space (DIS) criterion to the 2017 McDonald criteria improves diagnostic accuracy.

Introduction

Diagnosis of multiple sclerosis (MS) requires proof of dissemination in space (DIS) and time (DIT) [1]. While the presence of at least one clinical symptom typical of a central nervous system (CNS) demyelinating lesion remains a prerequisite, diagnostic criteria for MS have evolved by employing paraclinical investigations such as magnetic resonance imaging (MRI) and cerebrospinal fluid analysis to provide a faster and more accurate diagnosis and, thus, enable earlier initiation of disease-modifying treatments (DMT) [2–4]. Optic neuritis (ON) is a typical manifestation of MS, constituting the initial symptom in about a quarter of cases [5]. ON results in neuroaxonal damage to the optic nerve, measurable by optical coherence tomography (OCT) as reduced thickness of peripapillary retinal nerve fibre layer (pRNFL) and macular ganglion cell and inner plexiform layer (GCIPL) [6,7]. A further 10-30% of patients

with a clinically isolated syndrome (CIS) other than ON display signs of asymptomatic involvement of the optic nerve [5,8,9]. There is now mounting evidence that inter-ocular asymmetry in OCT provides highly sensitive, accurate and reproducible detection of retinal atrophy as a result of MS-associated ON [7,10–18]. Hence, OCT offers an intriguing method to objectify a history of clinical or subclinical optic nerve involvement in this context [19]. In 2016, the MAGNIMS group recommended the inclusion of the optic nerve as an additional region for demonstrating DIS in McDonald criteria, established either clinically or paraclinically by MRI, OCT, or visual evoked potentials (VEP) [5,8,9,20]. However, evidence was deemed insufficient and, thus, the optic nerve was not incorporated into the 2017 version of the McDonald criteria [4]. Since then, studies have evaluated the diagnostic performance of adding the optic nerve as a new region in DIS criteria using various combinations of clinical assessment, MRI, and VEP for determining optic nerve involvement [9,21,22]. However, studies using OCT are currently lacking.

Here, we aimed to investigate the primary research question whether adding the optic nerve as determined by OCT as a fifth DIS criterion to the 2017 McDonald criteria improves diagnostic accuracy in a well-characterized cohort of patients with a first demyelinating event.

Methods

For this study, patients were retrospectively identified from an ongoing prospective observational cohort study of patients with a first demyelinating event recruited between 2014 and 2022 at the Departments of Neurology of the Medical Universities of Vienna and Innsbruck. Briefly, baseline visit was conducted ≤180 days since occurrence of first clinical symptom and comprised complete clinical diagnostic work-up including cerebral and spinal cord MRI, OCT and diagnostic lumbar puncture.

MRI scans were done on 3T MR scanners. MRI protocols differed in some detail but included 3D fluid-attenuated inversion recovery sequences (FLAIR) and T2 sequences. Each MRI scan was assessed by experienced neuroradiologists under routine conditions. IgG oligoclonal

bands (OCB) were examined by standard isoelectric focusing with >2 bands considered OCB positive [23]. Follow-up visits were conducted at least biannually. Demographic data, neurological history and status including Expanded Disability Status Scale (EDSS), and treatment history including DMT were obtained from each participant at every visit [24]. Initiation of DMT was recommended to all patients. DMT status was classified as either initiation or no initiation of DMT after the first demyelinating event. Second clinical attack was defined as a second demyelinating event, occurring at least 30 days after the first demyelinating event [3].

Optical coherence tomography

OCT was performed at baseline visit on both eyes. If the first demyelinating event was classified as ON by consensus of the treating neurologist and neuroophthalmologist, OCT was delayed until ≥90 days after onset of ON symptoms. OCT imaging was done by experienced neuro-ophthalmologists using the same spectral-domain OCT (Heidelberg Engineering, Heidelberg, Germany; software Heidelberg eye explorer software version 6.9a) without pupil dilatation in a dark room on both eyes of each patient. Measurement of pRNFL was performed by a 3.4 mm (12°) custom ring scan head (1536 A-scans, automatic real-time tracking [ART]: 100 averaged frames) centered on the optic nerve. GCIPL thickness was measured by a macular volume scan (20°×20°, 512 A-scans, 25 B-scans, vertical alignment, ART: 16 averaged frames) centered on the macula. Mean GCIPL thickness of the four and outer quadrants of the circular grid around the foveola (corresponding to the 3mm and 6mm rings as defined by the Early Treatment Diabetic Retinopathy Study) was defined as GCIPL thickness [25]. Image processing was semiautomated using the built-in proprietary software for automated layer segmentation and manual correction of obvious errors. OSCAR-IB quality control criteria were applied for all examinations used and APOSTEL criteria for reporting results [26,27]. Patients with bilateral ON were excluded from the study. Other exclusion criteria

were presence of other neurological comorbidities potentially affecting disability and diagnoses of ophthalmological (i.e. myopia greater than -4 diopters, optic disc drusen, glaucoma), neurological, or drug-related causes of retinal damage not attributable to MS [26]. Involvement of the optic nerve was defined as abnormal interocular asymmetry in retinal thickness in either GCIPL (cut-off value ≥4µm) or pRNFL (cut-off value ≥5µm) [18,28]. The investigators performing the OCT were blinded to clinical parameters and vice versa.

Design and statistical analyses

For the purpose of this study, the database was locked on August 1st, 2022. To evaluate addition of the optic nerve as a fifth region to fulfill DIS, we included all patients with age ≥18 years and ≤180 days delay between onset of first clinical symptom and baseline visit who had complete information to assess the five DIS regions (MRI plus OCT) at baseline.

DIS and DIT were assessed at baseline according to 2017 McDonald criteria [4]. Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve region (as defined by abnormal interocular asymmetry in OCT) as a fifth criterion to the four current regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord) and using a cutoff value of ≥2 of 5. Occurrence of a second clinical attack was the primary endpoint.

Statistical analysis was performed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA). Categorical variables were expressed in frequencies and percentages. Continuous variables were tested for normal-distribution by Lilliefors test and, based on presence of normal-distribution, expressed as either mean and standard deviation or median and range.

Cox proportional hazards regression models regarding second clinical attack were performed using DIS and DIS+OCT as well as the number of DIS regions fulfilled as independent variables, adjusting for initiation of DMT after the first demyelinating event as a time-dependent variable.

Diagnostic performance of DIS+OCT in comparison to DIS, either alone or in combination with DIT, was analyzed by calculating area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for second clinical attack.

DIT was defined based on MRI (simultaneous presence of gadolinium-enhancing and non-enhancing lesions on initial MRI or new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI) and/or OCB positivity [4]. AUC was compared using variance estimates recovery on the basis of inverse hyperbolic sine transformations [29]. To mitigate distortion of results by late converters, these analyses were only conducted in a subgroup of the cohort with at least five years of follow-up.

Subgroup analyses for both Cox regression models and diagnostic performance analyses were conducted according to type of first demyelinating event (ON vs. non-ON) to test whether including the optic nerve by DIS+OCT would have different effects depending on the optic nerve involvement being symptomatic or asymptomatic.

Sensitivity analyses were conducted for effect of center as well by excluding patients with a) treatment initiation before presenting a second clinical attack, b) a follow-up of less than 2 years and c) a follow-up of less than 5 years. A two-sided p-value <0.05 was considered statistically significant.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the ethics committees of the Medical Universities of Vienna and Innsbruck (ethical approval number: 2323/2019 and AM3743-281/4.). Written informed consent was obtained from all study participants.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request by a qualified researcher and upon approval by the ethics committee of the Medical University Vienna.

Results

Of 763 patients screened, 267 MS patients were finally included with a median follow-up period of 59 months (range: 13 - 98). The detailed inclusion process is depicted in Figure 1. Characteristics of the study cohort are given in Table 1. Of note, the screened cohort did not significantly differ from the final study cohort in any of the variables analyzed.

After a median 82 days (range: 2 - 180) from first demyelinating event to OCT scan, interocular asymmetry indicating optic nerve involvement was found in 96 (36.0%). Of 186 patients without ON at baseline, 28 (15.1%) had an asymptomatic optic nerve involvement. A second clinical attack occurred in 100 patients (37.5%) after a mean 14.8 months (SD 18.5).

Placeholder Table 1. Baseline characteristics of the study cohort.

Placeholder Figure 1. Flow chart of study inclusion/exclusion process.

The risk of suffering a second clinical attack during follow-up increased with a growing number of DIS regions affected at baseline (Table 2). Referenced to patients with no region involved, the hazard ratio (HR) ranged from 5.9 (95% confidence interval [CI] 1.7 – 18.3) in the group with one involved DIS region to 16.5 (CI 5.7 – 54.5) if all five DIS+OCT regions were involved. Patients in whom there was only involvement of the optic nerve still had a nearly nine-fold increased risk (HR 8.9; CI 2.0 – 25.2) of a second clinical attack. Fulfilling

DIS criteria (≥2 of 4 DIS regions involved) translated to a 2.5-fold increased risk of a second clinical attack (HR 2.5, CI 1.2 – 11.8) as compared to not fulfilling DIS, whereas fulfilling the modified DIS+OCT criteria (≥2 of 5 DIS+OCT regions involved) indicated a 3.6-fold risk increase (HR 3.6, CI 1.4 – 14.5) with reference to not fulfilling DIS+OCT criteria.

Of note, the confidence intervals display considerable overlap, and this study was not designed to formally compare prediction of second relapse between modified DIS+OCT and DIS. However, these analyses were done to see whether the increase in sensitivity would have to be traded off against a lower risk of second relapse, which does not appear to be the case.

Placeholder Table 2. Risk for a second clinical attack according to dissemination in space.

Comparing the subgroups of patients with ON and non-ON as first demyelinating event (see Table 3), DIS provided very similar risk estimates after ON and non-ON (HR 2.4 vs. 2.6), while the modified DIS+OCT criteria seemed to indicate slightly higher risk in the ON than in non-ON group (HR 4.0 vs. 2.6).

Of note, all risk estimates were adjusted for initiation of DMT after the first demyelinating event as a time-dependent variable. Additionally conducted sensitivity analyses did not indicate a significant impact of follow-up duration (neither for <2 years nor for <5 years) or study center on risk estimates (data not shown).

Placeholder Table 3. Risk for a second clinical attack according to dissemination in space criteria in optic neuritis vs. non-optic neuritis

Diagnostic performance was assessed in the subgroup of patients with ≥5 years of follow-up (n=118). Apart from a longer median observation period (71 months vs. 59 months in the whole cohort) and a higher proportion of second clinical attacks (95/118 patients [80.5%] vs.

37.5% in the whole cohort), there were no significant differences in the diagnostic performance subgroup. OCT interocular asymmetry was abnormal in 46 (39.0%) with 15.5% (13/84) asymptomatic findings.

Diagnostic accuracy of modified DIS+OCT criteria for predicting a second clinical attack after the first demyelinating event was significantly higher than DIS criteria (AUC 81.2 vs. 65.6, p=0.021) by providing improved sensitivity (84.2% vs. 77.9%) and NPV (44.4% vs. 36.4%) without lowering specificity (52.2% vs. 52.2%) and PPV (87.1% vs. 87.9%) (Table 4). Taken together with DIT, modified DIS+OCT criteria still seemed slightly more accurate and more sensitive with equal specificity, although the differences were not statistically significant (Table 4).

Placeholder Table 4. Diagnostic Performance of dissemination in space with and without OCT for second clinical attack at 5 years follow-up

Comparing diagnostic performance in ON vs. non-ON as first demyelinating event, modified DIS+OCT criteria displayed improved overall accuracy as well as improved sensitivity and NPV without hampering specificity compared to DIS criteria in both groups (see Table 5). However, the improvement was more substantial in ON than in non-ON.

Again, there was no statistically significant difference between modified DIS+OCT criteria and DIS when adding fulfillment of DIT criteria, although DIS+OCT seemed slightly more accurate and more sensitive while maintaining specificity in both subgroups.

Sensitivity analyses did not show a significant impact of study center or DMT initiation before a second clinical attack on parameters of diagnostic accuracy (data not shown).

Placeholder Table 5. Diagnostic Performance in optic neuritis vs. non-optic neuritis of dissemination in space with and without OCT for second clinical attack at 5 years follow-up.

This study provides Class II evidence that adding the optic nerve as determined by OCT as a fifth DIS criterion to the 2017 McDonald criteria improves diagnostic accuracy.

Discussion

Investigating the effect of adding optic nerve involvement as determined by OCT as a fifth DIS criterion to current McDonald criteria in patients with a first demyelinating event, we found that the modified DIS+OCT criteria confer a similar risk of developing a second demyelinating event and slightly improve diagnostic accuracy (81% vs. 66%) by means of increasing sensitivity (84% vs. 78%) without compromising specificity (52% vs. 52%).

Our results are very much in line with a study using VEP instead of OCT to add the optic nerve to DIS criteria in an otherwise nearly identical setting, which reported similar risk increase for a second clinical attack and an improved diagnostic accuracy driven by increased sensitivity (82% vs. 79%) without impacting specificity (52% vs. 52%) [22]. An earlier study by Filippi et al also reported increased sensitivity compared to the 2010 version of McDonald criteria (90% vs. 87%) by adding the optic nerve by means of MRI and/or VEP, however, with the trade-off of decreased specificity (26% vs. 33%) resulting in similar diagnostic accuracy [21]. Brownlee and colleagues, using a definition of symptomatic optic nerve involvement by means of clinical and/or VEP, also found increased sensitivity (95% vs. 83%) at the expense of a decrease in specificity (57% vs. 68%) [9]. In our study as well as in the VEP study by Vidal-Jordana et al. overall accuracy and sensitivity for a second clinical attack increased without a decrease in specificity [22]. These differences could be explained by differences in baseline characteristics and/or varying follow-up periods influencing rates of second clinical attack and possibly by the different modalities/definitions used for establishing optic nerve involvement.

When adding DIT to DIS+OCT in our study, i.e. comparing current McDonald criteria to a version with optic nerve involvement defined by OCT inter-eye difference added as a fifth

region for DIS, the difference between DIS+OCT+DIT and DIS 2017+DIT was not statistically significant anymore, although DIS+OCT+DIT still seemed to display slightly better sensitivity and overall diagnostic accuracy for a second clinical attack than DIS 2017+DIT. This is in line with studies using clinical, MRI and VEP definitions of optic nerve involvement and is likely due to the available sample size as the improvement appears consistent through these studies in all subgroups [9,21,22].

Looking into the potential impact of whether optic nerve involvement was symptomatic or asymptomatic, subgroup analyses revealed very similar results for both diagnostic performance and risk prediction with a slightly higher improvement in symptomatic optic nerve involvement, i.e. patients with ON as first demyelinating event. This is also in line with reported results employing VEP [22].

First, this underlines that OCT is able to accurately detect optic nerve involvement in both ON and non-ON CIS patients [18,28,30]. In that context, it is important to point out that in symptomatic ON, OCT needs to be delayed ≥90 days after onset of ON symptoms to allow reliable detection of asymmetry by OCT [6]. Second, our results further underscore that no distinction should be made between symptomatic and asymptomatic lesions when determining dissemination in space [31,32]. While Brownlee et al. reported that inclusion of the optic nerve only improved diagnostic performance in patients with symptomatic ON, this is most likely due to the fact that this study defined optic nerve involvement only clinically, which is less sensitive to detecting asymptomatic lesions compared to MRI, OCT and VEP [9,30,33,34].

After the 2017 revision of the McDonald criteria did not include the optic nerve as a DIS region, we are convinced that the available overall body of evidence including our study is now sufficient to warrant that. Optic nerve involvement may be established either clinically, by imaging with MRI or OCT, or electrophysiologically by VEP [20]. Clinical assessment is based on detecting optic nerve atrophy or disc pallor, but is technically challenging, requires

availability of a trained neuroophthalmologist and is less sensitive than paraclinical investigations [33,34]. Thus, paraclinical investigations have been increasingly propagated in this context.

Retinal OCT provides a unique opportunity to depict the degree of clinical and even subclinical neuroaxonal damage in-vivo with low expenditure and excellent reproducibility by means of measuring pRNFL and GCIPL thickness [7,35]. Recent efforts by the scientific community have now yielded reliable and validated cut-offs for determining symptomatic and asymptomatic involvement of the optic nerve by OCT with high accuracy [18,28,36]. OCT shows very good concordance with MRI detection of optic nerve involvement, but has some considerable advantages over MRI as it is non-invasive, inexpensive, easy to perform and accessible, fast, and produces standardized, reliable quantitative measures [8,37]. Thus, OCT represents an attractive option for determining involvement of the optic nerve.

We acknowledge several limitations to this study. Although data were derived from a prospective observational cohort study, the study outcomes and inclusion criteria for the present study have been defined retrospectively, potentially introducing a selection bias compared to the full cohort. However, the full study cohort did not significantly differ from the final study cohort presented here in any of the variables analyzed. By only selecting patients who had complete information (MRI plus OCT) to assess the five DIS regions at baseline, our cohort might have potentially been enriched. Application and timing of DMT might have influenced the results of our study. However, risk estimates of Cox regression models were adjusted for DMT as a time-dependent variable, and sensitivity analyses did not show a significant impact of DMT on diagnostic accuracy. OCT scans were conducted at two different centers creating the potential of confounding inter-rater variability. However, both centers used the same type of OCT device (Heidelberg Engineering) with the same software configurations and sensitivity analyses for effect of center did not indicate a significant effect

of center. Our results are not directly applicable to other OCT devices, although previous findings suggest that retinal layer thickness thresholds might be robust independent of the OCT manufacturer. OCT scans were meticulously controlled for quality and confounding factors were ruled out rigorously (e.g. severe myopia, optic disc drusen, diagnoses of ophthalmological, neurological, systemic or drug-related causes of retinal damage not attributable to MS), which limits applicability to populations excluded from this study. In this context, we emphasize that the study cohort almost exclusively consists of patients of Caucasian origin, limiting applicability to other ethnicities.

Using abnormal interocular asymmetry on OCT for determining involvement of the optic nerve is not applicable in bilateral ON, which was therefore excluded from the study.

While concordance rate between GCIPL and pRNFL cut-off values was excellent (98.9%) in our cohort, likely due to the thorough quality control and ruling out of confounding influences, GCIPL is the more robust measure and should be preferred in clinical practice [17,28].

Generally, it needs to be stressed that abnormal interocular asymmetry on OCT is not specific for MS and may also occur due to other conditions such as ischemic or compressive optic neuropathy. Application of any version of McDonald criteria requires clinical presentation with a symptom typical of a demyelinating event and no better explanation for the clinical presentation, i.e. ruling out any relevant plausible alternative diagnosis.

Of note, patients who had only optic nerve involvement, i.e. with normal brain MRI, displayed a higher rate of second relapses than in other previously reported cohorts (36.4% vs. 15-20%) [38,39]. This is possibly due to the thorough definition of optic neuritis as well as a higher proportion of OCB positivity in our cohort, which might have led to a lower number of ON misdiagnoses and a higher rate of second relapses.

The constant evolution of diagnostic criteria for MS has yielded faster and more accurate diagnosis paving the way for earlier access to DMT for MS patients [2–4]. Still, there remains

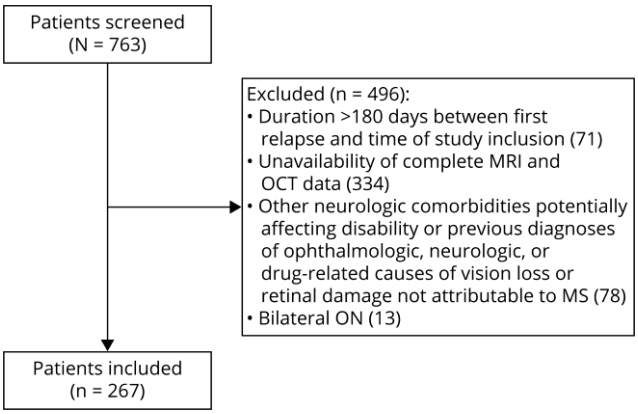
room for improvement. Clinically relevant, current McDonald criteria put patients with optic neuritis as initial manifestation at a disadvantage. Since the optic nerve is not considered a DIS region, a symptomatic lesion of the optic nerve, although a typical initial manifestation of MS concerning a quarter of all patients, is less likely to lead to an MS diagnosis than a symptomatic lesion of the brainstem or the spinal cord [40]. As an illustrative example, a patient with a symptomatic spinal cord lesion and one contrast-enhancing periventricular lesion in brain MRI can be diagnosed with MS, whereas a patient with optic neuritis displaying abnormal interocular asymmetry on OCT as well as an MRI lesion in the optic nerve cannot be diagnosed with MS if he or she displays the identical contrast-enhancing periventricular lesion in brain MRI.

In conclusion, we show that addition of the optic nerve, assessed by OCT, as a fifth region in the current DIS criteria moderately improves diagnostic performance by increasing sensitivity without compromising specificity. This provides additional evidence arguing in favor of inclusion of the optic nerve in the upcoming revision of the McDonald criteria and, thus, establishing OCT within the spectrum of routine MS diagnostics.

Figure legends

Figure 1. Flow chart of study inclusion/exclusion process.

MRI: magnetic resonance imaging. OCT: optical coherence tomography. ON: optic neuritis.



Appendix 1 author contributions

Gabriel Bsteh	Department of Neurology, Medical University of Vienna, Vienna, Austria	study concept and design, patient recruitment, acquisition of data, statistical analysis and interpretation of data, drafting of manuscript, study supervision.
Harald Hegen	Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria	patient recruitment, acquisition of data, assisted in statistical analysis, interpretation of data, critical revision of manuscript for intellectual content
Patrick Altmann	Department of Neurology, Medical University of Vienna, Vienna, Austria	patient recruitment, acquisition of data, critical revision of manuscript for intellectual content.
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Appendix 2 coinvestigators

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Rinner, Walter, Prof MD	Department of Neurology, Medical University of Vienna, Vienna, Austria	Site Investigator	Acquisition of data
Schmied, Christiane, Prof MD	Department of Neurology, Medical University of Vienna, Vienna, Austria	Site Investigator	Acquisition of data

References

1. Compston A, Coles A. Multiple sclerosis. Lancet. 2002;359:1221–1231.

2. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58:840–846.

3. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292–302.

4. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–173.

5. Toosy AT, Mason DF, Miller DH. Optic neuritis. Lancet Neurol. 2014;13:83–99.

6. Gabilondo I, Martínez-Lapiscina EH, Fraga-Pumar E, et al. Dynamics of retinal injury after acute optic neuritis. Ann Neurol. 2015;77:517–528.

7. Petzold A, Balcer LJ, Calabresi PA, et al. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol. 2017;16:797–812.

8. London F, Zéphir H, Drumez E, et al. Optical coherence tomography: a window to the optic nerve in clinically isolated syndrome. Brain. 2019;142:903–915.

9. 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–e1134.

10. Petzold A, Boer JF de, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol. 2010;9:921–932.

11. Behbehani R, Ali A, Al-Omairah H, Rousseff RT. Optimization of spectral domain optical coherence tomography and visual evoked potentials to identify unilateral optic neuritis. Mult Scler Relat Dis. 2020;41:101988.

12. Davion J-B, Lopes R, Drumez É, et al. Asymptomatic optic nerve lesions: An underestimated cause of silent retinal atrophy in MS. Neurology. 2020;94:10.1212/WNL.0000000000009504.

13. Outteryck O, Lopes R, Drumez É, et al. Optical coherence tomography for detection of asymptomatic optic nerve lesions in clinically isolated syndrome. Neurology. 2020;95:e733–e744.

14. Villoslada P, Sanchez-Dalmau B, Galetta S. Optical coherence tomography: A useful tool for identifying subclinical optic neuropathy in diagnosing multiple sclerosis. Neurology. 2020;95:239–240.

15. Coric D, Balk LJ, Uitdehaag BMJ, Petzold A. Diagnostic accuracy of optical coherence tomography Inter-Eye Percentage Difference (IEPD) for optic neuritis in multiple sclerosis. Eur J Neurol. 2017;24.

16. Nolan RC, Galetta SL, Frohman TC, et al. Optimal Intereye Difference Thresholds in Retinal Nerve Fiber Layer Thickness for Predicting a Unilateral Optic Nerve Lesion in Multiple Sclerosis. J Neuroophthalmol. 2018;38:451–458.

17. Bijvank JN, Uitdehaag BMJ, Petzold A. Retinal inter-eye difference and atrophy progression in multiple sclerosis diagnostics. J Neurology Neurosurg Psychiatry. Epub 2021.:jnnp-2021-327468.

18. Bsteh G, Hegen H, Altmann P, et al. Validation of inter-eye difference thresholds in optical coherence tomography for identification of optic neuritis in multiple sclerosis. Mult Scler Relat Dis. Epub 2020.:102403.

19. Costello F, Burton JM. Retinal imaging with optical coherence tomography: a biomarker in multiple sclerosis? Eye Brain. 2018;10:47–63.

20. Filippi M, Rocca MA, Ciccarelli O, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol. 2016;15:292–303.

21. Filippi M, Preziosa P, Meani 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;17:133–142.

22. Vidal-Jordana A, Rovira A, Arrambide G, et al. Optic Nerve Topography in Multiple Sclerosis Diagnosis: The Utility of Visual Evoked Potentials. Neurology. 2021;96:e482–e490.

23. Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended Standard of Cerebrospinal Fluid Analysis in the Diagnosis of Multiple Sclerosis: A Consensus Statement. Arch Neurol-chicago. 2005;62:865–870.

24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983;33:1444–1452.

25. Group ETDRSR. Photocoagulation for Diabetic Macular Edema. Early Treatment Diabetic Retinopathy Study Report Number 1. Arch Ophthalmol-chic. 1985;103:1796.

26. Schippling S, Balk L, Costello F, et al. Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria. Mult Scler J. 2014;21:163–170.

27. Cruz-Herranz A, Balk LJ, Oberwahrenbrock T, et al. The APOSTEL recommendations for reporting quantitative optical coherence tomography studies. Neurology. 2016;86:2303–2309.

28. Nolan- Kenney RC, Liu M, Akhand O, et al. Optimal intereye difference thresholds by optical coherence tomography in multiple sclerosis: An international study. Ann Neurol. 2019;85:618–629.

29. Zou GY, Yue L. Using confidence intervals to compare several correlated areas under the receiver operating characteristic curves. Stat Med. 2013;32:5077–5090.

30. Leocani L, Guerrieri S, Comi G. Visual Evoked Potentials as a Biomarker in Multiple Sclerosis and Associated Optic Neuritis. J Neuro-ophthalmol. 2018;38:350–357.

31. Tintore M, Otero-Romero S, Río J, et al. Contribution of the symptomatic lesion in establishing MS diagnosis and prognosis. Neurology. 2016;87:1368–1374.

32. Brownlee WJ, Swanton JK, Miszkiel KA, Miller DH, Ciccarelli O. Should the symptomatic region be included in dissemination in space in MRI criteria for MS? Neurology. 2016;87:680–683.

33. Sisto D, Trojano M, Vetrugno M, Trabucco T, Iliceto G, Sborgia C. Subclinical Visual Involvement in Multiple Sclerosis: A Study by MRI, VEPs, Frequency-Doubling Perimetry, Standard Perimetry, and Contrast Sensitivity. Invest Ophth Vis Sci. 2005;46:1264–1268.

34. Yuksel B, Dogan B, Koctekin B, et al. Color vision testing versus pattern visual evoked potentials and optical coherence tomography parameters in subclinical optic nerve involvement in multiple sclerosis. J Clin Neurosci. 2019;61:48–53.

35. Pemp B, Kardon RH, Kircher K, Pernicka E, Schmidt-Erfurth U, Reitner A. Effectiveness of averaging strategies to reduce variance in retinal nerve fibre layer thickness measurements using spectral-domain optical coherence tomography. Graefe's Arch Clin Exp Ophthalmol. 2013;251:1841–1848. Accessed at: message:%3C67c7e321b5bd1461b98add6151c6917d@meduniwien.ac.at%3E.

36. Xu SC, Kardon RH, Leavitt JA, Flanagan EP, Pittock SJ, Chen JJ. Optical coherence tomography is highly sensitive in detecting prior optic neuritis. Neurology. 2019;92:e527–e535.

37. Ontaneda D, Fox RJ. Imaging as an Outcome Measure in Multiple Sclerosis. Neurotherapeutics. 2017;14:1–11.

38. Tintore M, Rovira A, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain. 2015;138:1863–1874.

39. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain. 2008;131:808–817.

40. Galetta SL, Balcer LJ. The optic nerve should be included as one of the typical CNS regions for establishing dissemination in space when diagnosing MS – Yes. Mult Scler J. 2018;24:121–122.

Table 1. Baseline characteristics of the study cohort.

	(n=267)
Females[1]	184 (68.9)
Age at first demyelinating event[2] (years)	31.3 (8.1)
Type of first demyelinating event [1#]	
ON[1]	81 (30.3)
Non-ON[1]	186 (69.7)
Pyramidal[1]	34 (12.7)
Cerebellar[1]	24 (9.0)
Brainstem[1]	23 (8.6)
Sensory[1]	122 (45.7)
Other[1]	4 (1.5)
EDSS at baseline[3]	2 (1 – 4.5)
MRI[1]	
Abnormal[1]	218 (81.6)
Contrast-enhancing lesions[1]	56 (21.0)
Positive OCB[1]	184 (68.9)
Duration from first symptoms to OCT[2] (days)	82 (2 - 180)
ON[1]	112 (90 – 180)
Non-ON[1]	63 (2 - 180)
Abnormal OCT (interocular asymmetry)[1]	107 (40.1)
ON[1]	79/81 (97.5)
Non-ON[1]	28/186 (15.1)
Duration of follow-up[3] (months)	59 (13 - 98)

[1]number (percentage). [2]mean and standard deviation. [3]median and range. [#]percentage exceeds 100% due to polysymptomatic first demyelinating event

EDSS: Expanded Disability Status Scale. MRI: Magnetic resonance imaging. MS: multiple sclerosis. Non-ON: first demyelinating event other than ON. OCB: oligoclonal bands. OCT: optical coherence tomography. ON: optic neuritis.

Table 2. Risk for a second clinical attack according to dissemination in space.

	Absolute number (%)	Second clinical attack (n, %)	Adjusted Hazard ratio (95% CI)
Number of regions involved			
1	50 (18.7)	12/50 (24.0)	5.9 (1.7 – 18.3)
2	35 (13.1)	14/35 (40.0)	9.8 (2.4 – 33.1)
3	59 (22.1)	28/59 (47.5)	11.6 (3.8 – 35.3)
4	43 (16.1)	23/43 (53.5)	13.1 (4.0 – 38.2)
5	31 (11.6)	21/31 (67.7)	16.5 (5.7 – 54.5)
Only optic nerve involved	22 (8.2)	8/22 (36.4)	8.9 (2.0 – 25.2)
2017 DIS fulfilled (≥2/4)[1]	147 (55.1)	75/147 (51.0)	2.5 (1.2 – 11.8)[#]
2017 DIS+OCT fulfilled (≥2/5)[2]	168 (62.9)	86/168 (51.2)	3.6 (1.4 – 14.5)[##]

[1]DIS criteria as defined in McDonald criteria 2017: at least 1 lesion in at least 2 of 4 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord)
[2]Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve region (defined by abnormal interocular asymmetry in OCT): at least 1 lesion in at least 2 of 5 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord, optic nerve)
[#]with reference to not fulfilling 2017 DIS criteria
[##]with reference to not fulfilling 2017 DIS+OCT criteria

CI: confidence interval. DIS: dissemination in space. OCT: optical coherence tomography.

Table 3. Risk for a second clinical attack according to dissemination in space criteria in optic neuritis vs. non-optic neuritis

	Absolute number (%)	Second clinical attack (n, %)	Adjusted Hazard ratio (95% CI)
Optic neuritis (n=81)			
2017 DIS fulfilled (≥2/4)[1]	38 (46.9)	15/38 (39.5)	2.4 (1.1 – 11.5)[#]
2017 DIS+OCT fulfilled (≥2/5)[2]	45 (55.6)	18/45 (40.0)	4.0 (1.5 – 16.2)[##]
Non-optic neuritis (n=186)			
2017 DIS fulfilled (≥2/4) [1]	115 (61.8)	63/115 (54.8)	2.6 (1.3 – 12.3)[#]
2017 DIS+OCT fulfilled (≥2/5)[2]	130 (69.9)	723/130 (55.4)	3.3 (1.4 – 13.8)[##]

[1]DIS criteria as defined in McDonald criteria 2017: at least 1 lesion in at least 2 of 4 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord)
[2]Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve region (defined by abnormal interocular asymmetry in OCT): at least 1 lesion in at least 2 of 5 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord, optic nerve)
[#]with reference to not fulfilling 2017 DIS criteria
[##]with reference to not fulfilling 2017 DIS+OCT criteria

CI: confidence interval. DIS: dissemination in space. OCT: optical coherence tomography.

Table 4. Diagnostic Performance of dissemination in space with and without OCT for second clinical attack at 5 years follow-up

	Sensitivity	**Specificity**	**PPV**	**NPV**	**Accuracy (AUC)**
	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)
DIS 2017[1]	77.9 (68.6 – 85.1)	52.2 (33.0 – 70.8)	87.1 (78.3 – 92.6)	36.4 (22.2 – 53.4)	65.6 (52.3 – 78.8)
DIS+OCT[2]	84.2 (75.6 – 90.2)	52.2 (33.0 – 70.8)	87.9 (79.6 – 93.1)	44.4 (27.6 – 62.7)	81.2 (70.6 – 91.9)
DIS 2017 and DIT[1,3]	75.8 (66.3 – 83.3)	69.6 (49.1 – 84.4)	91.1 (82.8 – 95.6)	41.0 (27.1 – 56.6)	72.7 (60.7 – 84.7)
DIS+OCT and DIT[2,3]	76.8 (67.4 – 84.2)	69.6 (49.1 – 84.4)	91.3 (83.0 – 95.7)	42.1 (27.9 – 57.8)	73.2 (61.2 – 85.2)

[1]DIS criteria as defined in McDonald criteria 2017: at least 1 T2-hyperintense lesion in at least 2 of 4 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord)
[2]Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve region (defined by abnormal interocular asymmetry in OCT): at least 1 lesion in at least 2 of 5 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord, optic nerve).
[3]DIT criteria as defined in McDonald criteria 2017
AUC: area under the curve. CI: confidence interval. DIS: dissemination in space. DIT: dissemination in time. NPV: negative predictive value. OCT: optical coherence tomography. PPV: positive predictive value.

Table 5. Diagnostic Performance in optic neuritis vs. non-optic neuritis of dissemination in space with and without OCT for second clinical attack at 5 years follow-up

	Sensitivity	Specificity	PPV	NPV	Accuracy (AUC)
	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)	Percent (95% CI)
Optic neuritis					
DIS 2017[1]	67.7 (50.1 – 81.4)	62.5 (30.6 – 86.3)	87.5 (69.0 – 95.7)	33.3 (15.2 – 58.3)	65.1 (43.3 – 87.0)
DIS+OCT[2]	77.4 (60.2 – 88.6)	62.5 (30.6 – 86.3)	88.9 (71.9 – 96.2)	41.7 (19.3 – 68.1)	70.0 (48.3 – 91.6)
DIS 2017 and DIT[1,3]	64.5 (47.0 – 78.9)	87.5 (52.9 – 99.4)	95.2 (77.3 – 99.8)	38.9 (20.3 – 61.4)	76.0 (58.5 – 93.5)
DIS+OCT and DIT[2,3]	67.7 (50.1 – 81.4)	87.5 (52.9 – 99.4)	95.5 (78.2 – 99.8)	41.2 (21.6 – 64.0)	77.6 (60.5 – 94.8)
Non optic neuritis					
DIS 2017[1]	84.4 (73.6 – 91.3)	53.3 (30.1 – 75.2)	88.5 (78.2 – 94.3)	44.4 24.6 – 66.3)	68.9 (52.5 – 85.2)
DIS+OCT[2]	85.9 (75.4 – 92.4)	53.3 (30.1 – 75.2)	88.7 (78.5 – 94.4)	47.1 (26.2 – 69.0)	69.6 (53.3 – 86.0)
DIS 2017 and DIT[1,3]	76.6 (64.9 – 85.3)	60.0 (35.8 – 80.2)	89.1 (78.2 – 94.9)	37.5 (21.2 – 57.3)	68.3 (52.4 – 84.1)
DIS+OCT and DIT[2,3]	78.1 (66.6 – 86.5)	60.0 (35.8 – 80.2)	89.3 (78.5 – 0.95)	39.1 (22.2 – 0.59.2)	69.1 (53.2 – 84.9)

[1]DIS criteria as defined in McDonald criteria 2017: at least 1 T2-hyperintense lesion in at least 2 of 4 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord)
[2]Modified DIS criteria (DIS+OCT) were constructed by adding the optic nerve region (defined by abnormal interocular asymmetry in OCT): at least 1 lesion in at least 2 of 5 regions (periventricular, cortical or juxtacortical, infratentorial, spinal cord, optic nerve).
[3]DIT criteria as defined in McDonald criteria 2017
AUC: area under the curve CI: confidence interval. DIS: dissemination in space. DIT: dissemination in time. NPV: negative predictive value OCT: optical coherence tomography. PPV: positive predictive value.

Diagnostic Performance of Adding the Optic Nerve Region Assessed by Optical Coherence Tomography to the Diagnostic Criteria for MS

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