IS THE OPTIC NERVE OVERDUE AS A CRITERION TO SUPPORT THE DIAGNOSIS OF MULTIPLE SCLEROSIS?

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Currently, the diagnosis of multiple sclerosis (MS) relies upon the two foundational pillars of dissemination in space and time for inflammatory demyelinating lesions after an initial demyelinating clinical event. The last revisions of the MS McDonald diagnostic criteria, published in 2017, specified the requirement of at least one lesion in two out of four CNS regions (periventricular, juxtacortical/cortical, infratentorial, spinal) to satisfy dissemination in space (DIS).[1] Whilst an international panel had previously recommended the optic nerve as an additional region to support DIS,[2] given the lack of evidence at that time, it was not included in the 2017 McDonald criteria.[1] However, 25% of patients with MS present with optic neuritis (ON) and asymptomatic optic nerve demyelination is detectable in up to half of MS patients.[3,4,5] In addition, disease modifying treatments, initiated after optic neuritis as the initial manifestation of MS, delay long term disability progression.[6] Despite these considerations, infratentorial and spinal presentations effectively convey greater influence than optic nerve involvement in the MS diagnostic process.

Thus, there is mounting interest in evaluating the optic nerve as a fifth CNS region to support DIS. Recent studies have contributed to this knowledge gap. Brownlee et al[7] demonstrated improved sensitivity to predict clinically definite MS (CDMS – defined with a second relapse) up to 15 years after presenting with clinically isolated syndrome (CIS) when symptomatic optic nerve involvement was included in the DIS criteria based on clinical grounds or VEPs (visual evoked potentials). Vidal-Jordana et al[8] also reported that adding optic nerve region (using VEPs) as a fifth DIS location improved diagnostic accuracy in CIS after 10-year follow up by increasing the sensitivity of the 2017 McDonald criteria without compromising specificity.

In this issue of *Neurology*, Bsteh et al make significant contributions to this debate by publishing a study that utilizes, for the first time, optical coherence tomography (OCT) to distinguish optic nerve involvement.[9] The authors used data from 267 MS patients, enrolled at two centres (30% presenting with ON), and determined the effect on conversion to CDMS, of adding optic nerve as a fifth region to the current 2017 McDonald criteria. They defined optic nerve involvement as the presence of validated intereye asymmetry (IAE) thresholds from OCT parameters (macular ganglion cell-inner plexiform layer thickness $\geq 4\mu m$ and/or peripapillary retinal nerve fiber layer thickness $\geq 5\mu m$), which was present in 36% of patients.[10] The sensitivity of predicting conversion to CDMS significantly increased from 78% to 84% when optic nerve was added as a fifth region for DIS (defined as $\geq$ 2/5 CNS regions) compared with current 2017 DIS criteria ($\geq$ 2/4 locations). Importantly, specificity was not compromised (52% for both DIS definitions). Similar results for modified DIS criteria (including optic nerve evaluation) were found for both ON and non-ON presentations although, as expected, a greater effect was seen in ON CIS patients. Of note, when evaluating DIS together with dissemination in time (presence of gadolinium-enhancing lesions and/or new T2-hyperintensities and/or positive cerebrospinal oligoclonal bands) the addition of the optic nerve to DIS had minimal impact on diagnostic sensitivity (73%). The authors acknowledge some limitations of their study, including the retrospective analysis, different MRI protocols without centralized reading and heterogeneous follow up period (13 to 98 months).

Overall, this study reinforces the consensus to include optic nerve as the fifth region for DIS. Several issues, however, arising from this and other related studies should still be considered. First, the conventional philosophy of validating modified MS diagnostic criteria is to compare with existing criteria, their performance at predicting future CDMS.[1] This 'gold standard' may need revising in future. More patients are diagnosed with MS after their first episode and, by commencing high efficacy treatments, may not experience a second attack (i.e. convert to CDMS) for many years, making it harder to validate new criteria without extremely long follow up, yet they are still considered to have MS. Second, the reliable evaluation of optic nerve involvement needs deliberation. The three main paraclinical modalities to study the optic nerve (optic nerve magnetic resonance imaging (MRI), OCT, and VEPs) have advantages and disadvantages (see table) with variable concordance between them, which also depends on the thresholds applied for each technique, the time elapsed from acute optic nerve symptoms, and each center's experience with the modalities. In addition, there are technical limitations for these tests. For example, OCT has multiple exclusion criteria related to ocular co-morbidities or high refractive error, limiting its application to a broader population. Finally, as the authors of this study acknowledge, IED OCT asymmetry in isolation indicates an asymmetric or unilateral optic neuropathy, which may have a non-demyelinating cause.

As more evidence accumulates in favour of including the optic nerve as a new region to fulfil DIS, discussions should include how the current optic nerve diagnostic modalities can be implemented to achieve this.

Table: Comparisons of 3 Main Paraclinical Modalities Used to Identity Demyelinating Optic Nerve Lesions

ON-MRI = Optic Nerve MRI; OCT = optical coherence tomography; VEP = visual evoked potentials.

	ON – MRI	**OCT**	**VEP**
Accuracy	Very High	Moderate to good	Moderate
Differential diagnosis / MS diagnosis	Always needed	Non-specific findings. Validated mostly in MS vs healthy cohorts.	Might help to differentiate other ocular pathologies
Optic nerve lesion definition	Sensitivity of optic nerve lesion detection might differ between different MRI sequences	Validated asymmetry thresholds	Thresholds are center-specific
Lesion detection	Able to detect unilateral and bilateral involvement	Only able to detect unilateral/asymmetric involvement	Able to detect unilateral and bilateral involvement
Time elapsed since acute ON	Good for acute / subacute / chronic phase	Better results in the subacute / chronic phase	Better results in the acute phase
Convenience	Time consuming, especially coronal T2 sequences	Convenient / accessible	Center dependent – may vary
Other	Artefacts can cause non-diagnostic images	Unreliable in e.g. ocular co-morbidity, bilateral involvement, anomalous discs (for peripapillary retinal nerve fiber layer)	Potential influence of retro-geniculate lesions

REFERENCES

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

2. 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.

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

4. 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:e2468–e2478.

5. 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.

6. Kenney R, Liu M, Patil S, et al. Long-term outcomes in patients presenting with optic neuritis: Analyses of the MSBase registry. J Neurol Sci. 2021;430:118067.

7. 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.

8. 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.

9. Bsteh G, Hegen H, Altmann P, et al. Adding the optic nerve region assessed by optical coherence tomography to the diagnostic criteria for multiple sclerosis. Neurology 2023;XX:xx-xx.

10. 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.