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Controversies in Multiple Sclerosis

The optic nerve should be included as one of the typical CNS regions for establishing dissemination in space when diagnosing MS – No

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The new 2017 McDonald criteria will not finally include the optic nerve as one of the typical central nervous system (CNS) regions for establishing dissemination in space when diagnosing multiple sclerosis (MS), as proposed by the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) group.[1] There is little doubt that the optic nerve is one of the most characteristic areas of involvement in MS and only as an example, in the Barcelona clinically isolated syndrome (CIS) cohort, approximately one-third of the patients presented with an optic neuritis as their first symptom.[2] Therefore, to incorporate a new MS characteristic topography seems clearly desirable. However, before incorporating this new topography to the diagnostic criteria, several considerations need to be examined. Although clinical features of optic neuritis such as visual impairment, scotoma, red–green desaturation and pain with ocular movement may seem easy to identify, in fact patients presenting with optic neuritis have a higher risk of having a normal brain magnetic resonance imaging (MRI) and a lower risk of developing MS compared to patients presenting with brainstem or spinal cord syndromes.[3] This different behaviour could be, at least partially, due to the fact that differential diagnosis in patients with subacute visual loss is vast and complex and other causes that mimic inflammatory-demyelinating optic neuritis may be difficult to identify. Clinical documentation alone is therefore not a reliable marker and confirmation of optic nerve involvement by MRI or by other techniques such as optical coherence tomography (OCT) or visual evoked potential (VEP) is recommended specially in atypical cases for ruling out an alternative diagnosis.[4] Unfortunately, to date, despite the optic nerve being a relevant and easy to assess area, there is insufficient published data regarding the performance of the different tests (MRI, VEP and OCT) to demonstrate optic nerve impairment in CIS patients or their utility to improve the current MS diagnostic criteria. Imaging the optic nerve is not yet performed routinely in clinical practice and presents some technical difficulties. The surrounding fat, bone and cerebrospinal fluid together with eye movements may result in artefacts that can compromise the quality of the images. In order to allow optic nerve lesions detection, several MRI sequences have been developed. The most sensitive MRI protocol for detecting acute inflammation of the optic nerve is a combination of coronal fat-saturated T2-weighted or STIR (short tau inversion recovery) and contrast-enhanced fat-saturated T1-weighted sequences, which typically show swelling and increased signal intensity of the optic nerve with enhancement of the nerve itself.[5,6] Optic nerve enhancement occurs in as many as 95% of cases with demyelinating optic neuritis, while very rarely occurs in nonarteritic ischaemic optic neuropathy,[7] therefore enabling differentiation between the two conditions. High signal intensity on T2-weighted images is detected in 84% of symptomatic and 20% of asymptomatic optic nerves. This increase in T2 signal may persist in the long term despite improvements in vision[8] and is commonly associated with nerve thinning.

In many settings, VEPs remain the standard means for detecting evidence of a prior optic neuritis and a unilateral delay in the P100 waveform is strongly suggestive of anterior visual pathway demyelination.[9] The accuracy of VEP test, however, is highly dependent on a cooperative patient, a reliable lab with adequate technical experience and a trained/experienced reader.[6] Moreover, with the increased reliance on MRI to inform the diagnosis of MS, nowadays VEP testing is less commonly used. The added value of VEPs as a possible sign of optic nerve involvement, and their contribution to the diagnostic criteria, is also lacking. OCT is an

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office-based imaging method that uses near-infrared light to generate high-resolution cross-sectional images of the retina. The most commonly assessed layer is the unmyelinated retinal nerve fibre layer (RNFL) in the optic nerve head, which originates from retinal ganglion cell bodies in the macula and continues through the optic nerve, chiasm and tract to synapse in the lateral geniculate bodies.[5] In the acute phase of an optic neuritis, there is usually a RNFL thickness increase due to optic nerve swelling that will be followed by a subsequent reduction in thickness (around 20% decrease) indicating axonal loss after acute optic neuritis. Silent optic nerve lesions and RNFL thinning may also occur in MS and can also be detected by OCT. Emerging interest is the thickness of the retinal ganglion cell layer and the total macular volume.[5] Although OCT and VEP can identify a demyelinated damaged optic nerve, cut-offs that would identify a symptomatic or asymptomatic optic nerve lesion in the individual patient need to be established (each separately and in different combinations of them). Due to their relevant prognostic and therapeutic implications, a special word of caution needs to be taken when distinguishing optic nerve involvement in neuromyelitis optica spectrum disorder (NMOSD) and MS. Although preliminary data suggest that NMOSD lesions in the optic nerve would be longitudinally extensive (as it occurs in the spinal cord), involve at least three optic nerve segments (measuring at least 17.6 mm in length), affect more posterior parts of the optic nerve (including chiasm) and more frequently have simultaneous bilateral disease,[10] the differential diagnosis is challenging. VEP and OCT may also contribute to the differential diagnosis, and in this sense, it is worth mentioning that optic neuritis in NMOSD would typically result in a more severe RNFL and ganglion cell layer thinning and the presence of microcystic macular oedema. Furthermore, silent optic nerve lesions and RNFL thinning may occur in MS but are rare in NMOSD.

In conclusion, there is insufficient published data regarding the ability of different tests (optic nerve MRI, VEP or OCT) to objectively demonstrate optic nerve involvement in CIS patients and how the demonstration of such involvement would actually improve the performance of the current MS diagnostic criteria. The burden in terms of cost for the patient and for our health care providers has not been evaluated. Other aspects such as the time spent by our patients in doing all these extra tests should also be taken into consideration and after all how many more patients are going to be diagnosed? At present, we simply don't know. So, 'The optic nerve should be included as one of the typical CNS regions for establishing dissemination in space when diagnosing MS': not yet!!

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