Multiple Sclerosis and Related Disorders 38 (2020) 101521

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

The accuracy of standard multiple sclerosis MRI brain sequences for the diagnosis of optic neuropathy

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ARTICLE INFO

Keywords:
Inflammatory disease
Multiple sclerosis
MRI
Orbit
Optic neuropathy
Optic neuritis

ABSTRACT

Background: Detection of optic neuropathy on MRI has potential implications for the diagnosis and management of Multiple Sclerosis (MS).
Objective: This study assessed the accuracy of T2 sagittal MRI brain for detection of optic neuropathy, compared to coronal STIR orbit.
Methods and materials: Retrospective single-center blinded diagnostic accuracy study of 100 consecutive patients who underwent both T2 sagittal brain and coronal STIR orbit MRI. All were performed on 1.5T scanners. T2 sagittal slice thickness was 4 mm for the first 50 patients (group1) and 3 mm for the second 50 (group2). The MRIs were reviewed in a blinded fashion to determine the presence of optic neuropathy. Coronal STIR orbit sequences were considered the diagnostic reference standard.
Results: The sensitivity of T2 sagittal brain imaging for ON was 44% in group 1 and 85% in group 2 ($p = 0.007$). The specificities were 98% and 97% respectively ($p = 0.9$). Sensitivity was poorest for evaluation of the intraorbital nerve segment (56% grp1, 69% grp2, $p = 0.4$).
Conclusion: T2 sagittal MRI brain has high specificity for the detection of optic neuropathy when compared to coronal STIR orbit. Sensitivity is increased when slice thickness is reduced, but remains poor for evaluation of the intraorbital segment.

1. Introduction

Optic neuritis (ON) is an inflammatory lesion of the optic nerve, which can be associated with a number of distinct entities, most commonly MS (Toosy et al., 2014; Wilhelm and Schabet, 2015). The incidence of ON ranges from 0.94–2.18/100,000 worldwide (Toosy et al., 2014) and it is normally a clinical diagnosis based upon the symptoms of reduced visual acuity, altered color perception and pain upon eye movement. This is often supported by testing visual evoked potentials (Toosy et al., 2014). ON can be easily demonstrated on dedicated MRI of the orbits (Kupersmith et al., 2002), however this is not a requirement to make the diagnosis. The role of MRI in symptomatic ON is primarily to assess for features suggestive of MS (Toosy et al., 2014). MRI also has an important role in the detection of new optic nerve lesions in patients with known MS, since the detection of new CNS lesions influences management (Rae-Grant, 2018).

When a non-contrast coronal T2 weighted MRI study of the orbits is performed, at least 80% of patients with acute ON will have high T2 weighted signal within the affected nerve and this signal abnormality has been shown to persist on follow up studies (Soelberg et al., 2017). Therefore, T2 hyperintensity within an optic nerve may represent an acute episode of ON or evidence of a past episode. The term optic neuropathy encompasses T2 signal abnormality due to either acute or prior ON. The coronal STIR orbit MRI sequence is a long established fat suppressed non-contrast T2-weighted study which has been validated for the diagnosis of optic nerve inflammation (Miller et al., 1988) and is recommended for the investigation of ON (Petzold et al., 2014). STIR has been shown to demonstrate an optic nerve lesion in 92.5% of acute ON cases and 85% of patients with a past episode of ON (Tartaro et al., 1996). In patients who undergo contrast enhanced MRI, the affected nerve segment will demonstrate enhancement in up to 94% of acute cases (Kupersmith et al., 2002) but this enhancement should resolve within three months, or else an alternative diagnosis would have to be considered (Wilhelm and Schabet, 2015). Contrast enhanced MRI

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https://doi.org/10.1016/j.msard.2019.101521
Received 26 August 2019; Received in revised form 9 November 2019; Accepted 11 November 2019
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imaging at many institutions is being used more sparingly due to emerging concerns regarding gadolinium accumulation within the brain with repeated examinations (Ramalho et al., 2016).

For patients with suspected or known MS, the standard MRI brain protocol in our institution includes a T2 sagittal FSE sequence of the brain, in order to assess the corpus callosum and pericallosal white matter. The optic nerves are visible on these sequences but, to our best knowledge, the diagnostic performance of T2 sagittal brain imaging for the detection of optic neuropathy has not previously been examined. This is a particularly relevant question in MS, since a standard MRI study of the brain takes approximately 20 min to acquire and the addition of dedicated orbital sequences adds approximately 10 min to the scan time (Petzold et al., 2014). Scan duration is an important determinate of workflow in radiology departments and it is particularly important in departments which have large cohorts of MS patients, as these patients now undergo frequent MRI imaging. If new optic nerve lesions can be confidently identified on the routine surveillance MRI in patients with MS, this would obviate the requirement for confirmatory coronal imaging. The aim of this study is therefore to determine the accuracy of T2 sagittal FSE MRI brain (both 3 mm and 4 mm slice thickness) in the detection of optic neuropathy, compared to coronal orbital STIR as the diagnostic reference standard.

2. Methods

2.1. Population

This was a retrospective single center blinded diagnostic accuracy study, carried out at a tertiary referral center for MS. The study was approved by our institution's research ethics committee and the Standards for Reporting of Diagnostic Accuracy (STARD) checklist was used (Bossuyt et al., 2003). The inclusion criteria were: patients aged over 18 years, who underwent both a T2 sagittal MRI brain and coronal STIR of the orbits during the same examination between February 2014 and October 2016. Patients were included regardless of the indication for the MRI. Cases were excluded if their MRI images were deemed inadequate due to artefact.

All patients were from specialist neurology, ophthalmology, endocrine or oncology clinics. Of the 100 patients included in the study, the indications for MRI were; suspected ON ($n = 59$), visual defect ($n = 10$), cranial nerve palsy ($n = 9$), suspected demyelination ($n = 2$) and other ($n = 17$, including retinal detachment, retinal artery occlusion, orbital swelling and suspected malignancy). No indication was available for three cases. Of the 59 patients who underwent MRI for suspected ON, 37 had documented clinical evidence of ON in their medical chart (clinical exam findings, visual evoked potential, optical coherence tomography), while two patients had clear documentation indicating no clinical evidence on ON. Population demographics are outlined in Table 1.

Five patients had a diagnosis of MS prior to this study (one patient from group 1, four from group 2) and 16 further patients were diagnosed with MS following this investigation (eight each from groups 1 and 2). At the time of publication, seven additional patients remain on surveillance for clinically isolated syndrome following their episode of ON (four in group 1, three in group 2), two patients from group 2 have been diagnosed with chronic relapsing inflammatory optic neuropathy and two patients have been diagnosed with Neuromyelitis Optica (one each from group1 and group 2). The remaining patients have been diagnosed with a variety of conditions including: cerebral vasculitis, retinal detachment, sarcoidosis, migraine and myasthenia gravis. There is no follow up data available for 21 patients because they transferred to other centers for ongoing care.

Table 1
Population demographics.

	Group 1 ($n = 50$)	Group 2 ($n = 50$)	P
Sex	24 male (48%)	20 male (40%)	0.5
Age (StDev)	39.2 (16.4)	41 (19.1)	0.6
Clinical evidence of optic neuritis*	14 (28%)	23 (46%)	0.06
MRI evidence of optic neuritis (by Coronal STIR)	18 (36%)	24 (48%)	0.3

* Considered positive only when clinical evidence of optic nerve lesion was documented in the patient's notes.

2.2. Image acquisition

All studies were performed using 1.5T magnets (one Siemens, Munich, Germany and one General Electric, Boston, USA) using standard head coils. A coronal STIR slice thickness of 3 mm was used for all patients. During the course of the study period, the standard MRI protocol was updated and the T2 sagittal imaging was changed from 4 mm slice thickness to 3 mm. The first 50 patients underwent a T2 sagittal brain sequence with 4 mm slice thickness (labeled group 1) and 3 mm was used for the second 50 patients (labeled group 2).

2.3. Image review

Each coronal STIR sequence was reviewed by a fellowship trained Neuroradiologist and a Radiology Fellow, in consensus. Both were blinded to the patient demographics and diagnosis. Each nerve segment was assigned as positive or negative for ON based on the presence of increased T2 signal in the nerve relative to frontal lobe white matter (Fig. 1) Fig. 2, a comparison which has been previously validated (Onodera et al., 2016). The location of the abnormality was documented as intraorbital, intracanalicular or intracranial. On a separate occasion, the T2 sagittal brain sequences were reviewed in a similar fashion. The location of abnormality along the course of the optic nerves was again recorded.

2.4. Statistical analysis

Data analysis was performed using SPSS v. 24 (IBM, New York, USA) and an alpha value of 0.05 was considered significant. The coronal STIR sequence was considered the diagnostic reference standard for the diagnosis of ON. Categorical data were analyzed using X^2 test and numerical data with T tests. Sensitivities and sensitivities were compared between the two study groups by constructing 2×2 tables, using only ON positive cases (according to the STIR sequence) for sensitivity and only ON negative cases for specificity. Then X^2 tests were applied.

3. Results

There was no significant difference in age or sex between the two study groups. Based upon the STIR sequence, 18 nerves were positive for ON in 18 patients from group 1, while 27 nerves were positive in 24 patients in group 2. There was no significant difference in the prevalence of ON between the two groups (Table 1).

The performance of the T2 Sagittal MRI sequence in the detection of optic neuropathy, compared between group1 (4 mm slice thickness) and group 2 (3 mm slice thickness), is presented in Table 2. Of the 18 optic nerves which were positive for ON on the STIR sequence in group 1, eight were correctly identified on the T2 Sagittal MRI. Of the 27 optic nerves positive for ON on the STIR sequence in group 2, 23 were correctly identified on the T2 sagittal MRI. This resulted in significantly higher sensitivity for T2 sagittal MRI brain in group 2 (0.85) compared to group 1 (0.44, $p = 0.007$). There was no significant difference in specificity between the two groups, (0.97 for group 2, 0.98 for group 1, $p = 0.9$).

The results for the individual nerve segments (intraorbital,

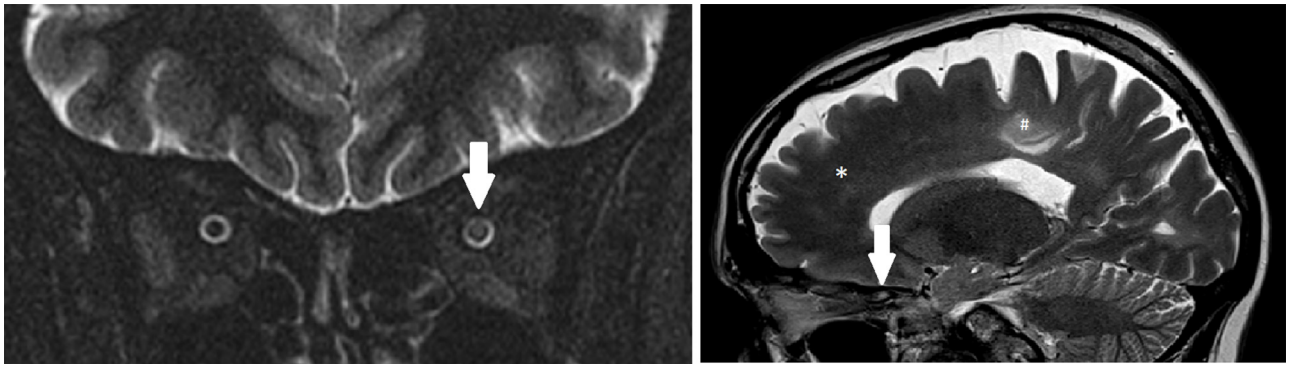

Fig. 1. True positive case. Left posterior intra-orbital and intracanalicular optic neuropathy demonstrated on coronal STIR of the orbits (arrow, left image) and T2 sagittal brain with 3 mm slice thickness (arrow, right image) MRI sequences. Neuropathy was defined as T2 signal higher than that in the frontal lobe white mater (*). Note also the pericallosal T2 hyperintensity (#), typical of MS.

intracanalicular and intracranial), are presented in Table 3. Optic neuropathy was identified on coronal STIR in the intraorbital segments of 34 nerves (18 in group1, 16 in group2), intracanalicular segments in 24 (6 in group1, 18 in group2) and intracranial segments in 6 (6 in group1, 0 in group2). The specificity of T2 Sagittal MRI was ≥96% for all segments in both groups. The sensitivity for intraorbital segment was 56% for group1 (4 mm slice thickness), which improved to 69% in group 2, but these was not a statistically significant difference ($p = 0.4$). Similarly, for the intracanalicular segment, the sensitivity improved from 83% to 100% but this was not statistically significant ($p = 0.08$). There were no cases of intracranial ON in group 1 (4 mm slice thickness) therefore it was not possible to calculate sensitivity for this segment.

The sensitivity for this segment in group 2 (3 mm slice thickness) was 83%.

Table 2
Results of the T2 Sagittal MRI sequence for detection of optic neuropathy compared to the diagnostic reference standard. Results are compared between group1 (4 mm slice thickness, 50 patients, 100 nerves) and group 2 (3 mm slice thickness, 50 patients, 100 nerves).CI = Confidence interval. PPV = Positive predictive value. NPV = Negative predictive value.

	Group 1	Group 2	
True positive	8	23	
False positive	2	2	
True negative	80	71	
False negative	10	4	
Sensitivity	0.44 (CI = 0.22–0.67)	0.85 (CI = 0.72 −0.99)	$p = 0.007$
Specificity	0.98 (CI = 0.94 −1.0)	0.97 (CI = 0.94–1.0)	$p = 0.9$
PPV	0.8	0.92	
NPV	0.89	0.95	

4. Discussion

We have shown that in an unselected population of patients, T2 sagittal MRI brain has high specificity for the identification of optic neuropathy (≥ 96% for all optic nerve segments). We have also shown that reducing the slice thickness from 4 mm to 3 mm significantly increased the sensitivity from 44% to 85% overall. The test has poor sensitivity in the intraorbital segment and while there is a trend towards improvement when the slice thickness is reduced, this is not statistically significant and it remains suboptimal at 69%.

The diagnosis of MS is supported radiologically by identification of T2 hyperintense CNS lesions disseminated in 'space and time'. The international consensus McDonald guidelines (revised in 2017) specify that in order to fulfill MRI criteria for dissemination in space, there must be typical T2 hyperintense lesions in at least two of four cardinal regions of the CNS (periventricular, cortical/juxtacortical, infratentorial and/or spinal cord white matter) (Thompson et al., 2018). The 2016 Magnetic Resonance Imaging in MS (MAGNIMS) network guidelines have proposed that the optic nerves be added as a fifth cardinal location (Filippi et al., 2016), since ON is commonly the first presentation of multiple sclerosis (approx. 23% of total MS cases (Marques et al., 2014)). This has since been shown to improve the sensitivity for MS diagnosis, without affecting specificity (Brownlee et al., 2018), however the 2017 McDonald consensus criteria did not follow suit, instead they have advised further research in this

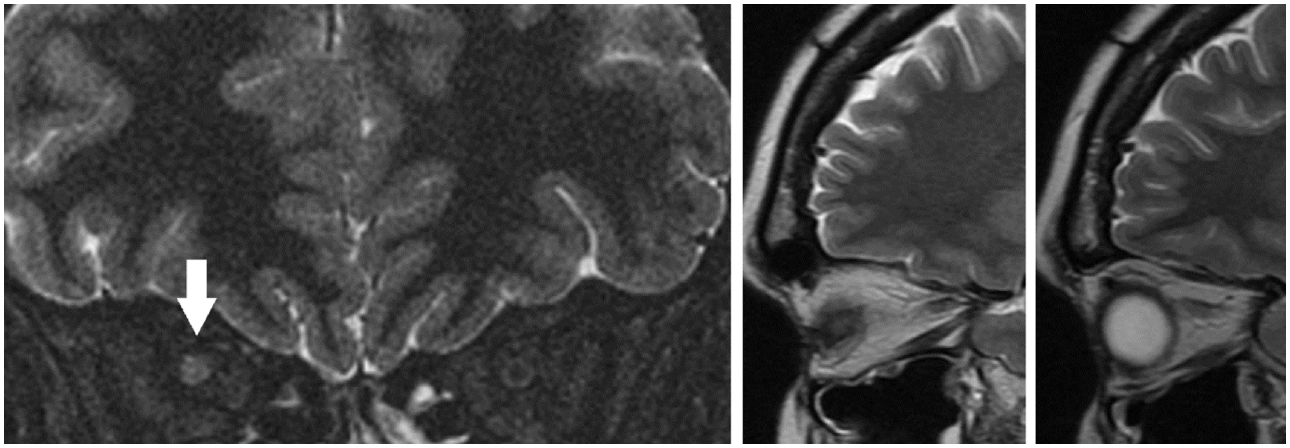

Fig. 2. False negative case. Right intra-orbital optic neuropathy demonstrated on coronal STIR orbits (arrow, left image) however there is normal signal within the visualized right optic nerve on the T2 sagittal brain sequence with 4 mm slice thickness (middle and right images).

Table 3
Results for the individual optic nerve segments compared between group1 (4 mm slice thickness, 50 patients, 100 nerves) and group 2 (3 mm slice thickness, 50 patients, 100 nerves), compared to coronal STIR as gold standard. CI = Confidence interval.

	Group 1	Group 2	
Intraorbital segment—sensitivity	0.56 (CI 0.33–0.79)	0.69 (CI 0.46–0.92)	$p = 0.4$
Intraorbital segment—specificity	0.99 (CI 0.96–1.0)	0.98 (CI 0.94–1.0)	$p = 0.6$
Intracanalicular segment—sensitivity	0.83 (CI 0.54–1.1)	1.0 (CI 1.0–1.0)	$p = 0.08$
Intracanalicular segment—specificity	0.99 (CI 0.97 - 1.0)	0.96 (CI 0.92 - 1.0)	$p = 0.2$
Intracranial segment—sensitivity	*	0.83 (CI 0.54–1.1)	*
Intracranial segment—specificity	1.0 (CI 1.0–1.0)	1.0 (CI 1.0–1.0)	*

* There were no cases of intracranial optic neuropathy in group 1.

area as a high priority (Thompson et al., 2018). Under the MAGNIMS guidelines, a patient with MRI confirmed ON would require only one additional characteristic MRI lesion in order to meet criteria and therefore potentially confirm the diagnosis at an earlier stage. Our present study indicates that identification of ON is possible on standard MS protocol MRI brain with high specificity. The sensitivity of 85% means that some cases will be missed on T2 sagittal brain imaging and therefore a coronal orbital MRI may still be warranted if there is clinical suspicion.

MRI plays an important role in surveillance of patients with known MS, since it has higher sensitivity for disease activity than clinical assessment alone (Giorgio and De Stefano, 2018). The aim of disease modifying therapy is to achieve a state of 'no evidence of disease activity' where there is no clinical or radiological evidence of disease progression. The identification of new lesions on interval surveillance MRI indicates a breakthrough inflammatory episode, potentially triggering a change in pharmacological treatment, even in the absence of clinical deterioration. It has been shown that MS patients may have subclinical episodes of optic neuritis (Sartoretti et al., 2017), which highlights the importance of MRI surveillance. The high positive predictive value of the T2 sagittal sequence (0.92 for the 3 mm slice thickness group) indicates that a new optic nerve lesion can be confidently diagnosed using this examination, without the need for additional confirmatory sequences. Given the findings of this study, we would recommend routine review of the optic nerves on T2 sagittal imaging of brain in cases of follow-up MRIs in MS, to exclude new optic nerve lesions that would indicate interval disease activity.

While the specificity of T2 sagittal sequences for ON is excellent in our study, the sensitivity varies for the different optic nerve segments and is poorest for the intraorbital segment, at 56% and 69% for 4 mm and 3 mm image slice thickness respectively. This is likely due to the relatively tortuous course of the intraorbital nerve segment compared to the intracanalicular or intraorbital segments, leading to the nerve moving in and out of individual sagittal image slices (Fig. 3). This segment is the longest individual component of the optic nerve, averaging 25 mm, compared to total nerve length of 50 mm (Gala, 2015) and isolated lesions of this segment constitute 48% of total ON cases (Soelberg et al., 2017). Three small studies have suggested that lesions of this segment are more associated with development of MS on follow up, compared to other locations (Soelberg et al., 2017; Khanna et al., 2012; Storoni et al., 2013). This is an important limitation of the utility of T2 sagittal MRI brain as a 'lesion finder' in excluding new optic nerve signal abnormalities. Conversely, neuromyelitis optica, which is one of the primary differential diagnoses in the setting of ON, is thought to have a predisposition for the posterior portions of the optic nerve (Khanna et al., 2012; Storoni et al., 2013) and therefore, detection of this condition will be less impacted by the poor sensitivity of T2 sagittal sequences for the intraorbital segment.

The decision to perform this study in an unselected population was made in order to robustly test the specificity and negative predictive value of the T2 sagittal sequence (Fig. 4). If we had only included patients with clinical evidence of optic neuritis or a history of MS, then the pre-test probability of ON would have been high. In such a population, the number of ON-negative cases would have been low and therefore the numbers would likely have been too small to calculate specificity. Therefore, we elected to include an unselected cohort of patients who underwent an MRI brain including both T2 sagittal and coronal STIR sequences, regardless of their indication. Based upon the results of our study, we believe that further study in a cohort of clinically and VER confirmed ON should now be undertaken, in order to validate our findings.

Our study has some limitations. Ireland has a high incidence and prevalence of multiple sclerosis (Gray et al., 2008). There is no literature available on the Irish prevalence of ON but it is closely related to MS and therefore the sensitivities achieved in our study may not be application to regions of the world where the prevalence of MS in low. This was a retrospective analysis, which has the potential for unmeasured cofounders. Clinical assessment for optic neuritis was not

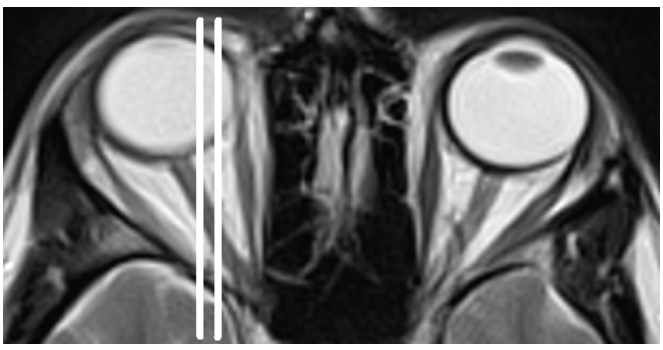

Fig. 3. Axial T2 MRI of the brain demonstrating the angulation of the optic nerves relative to the plain of the sagittal T2 sequence (represented by the white lines).

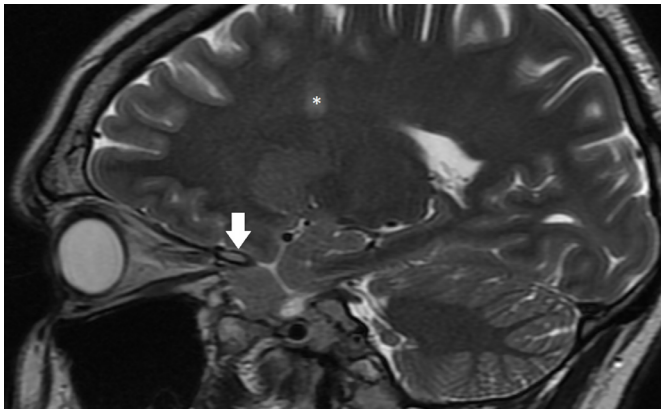

Fig. 4. Potential false positive on the T2 sagittal MRI brain sequence, due to the T2 bright bone marrow within the optic strut of the skull (arrow), located superior to the optic nerve canal. This can be recognized by the surrounding low T2 signal cortical bone. Note the ovoid periventricular T2 hypertensity (*) typical of demyelination.

explicitly documented in 20 cases, therefore it is not possible to determine the sensitivity of clinical assessment vs MRI or calculate the incidence of asymptomatic optic neuritis. Our center utilizes 1.5 T scanners, which adhere to the minimum advised in the recent MAGNIMS guidelines (Wattjes et al., 2015). The accuracy of T2 sagittal imaging on a 3T MRI has not been assessed.

5. Conclusion

In an unselected population of patients who underwent both T2 sagittal and coronal STIR imaging, high signal within the optic nerve can be clearly identified using the T2 sagittal sequence at 3 mm thickness.

The detection of these optic nerve signal abnormalities has implications for both the diagnosis and management of MS and we would recommend routine review of the optic nerves on standard MS brain imaging protocols. Further studies confirming our findings in a cohort of clinically and VER confirmed ON should be undertaken.

Funding

This work did not receive funding

Conflict of Competing Interest

The authors report no conflict of interest relating to this manuscript

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