Title

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Journal

Neuro-Ophthalmology, 46(6)

ISSN

0165-8107

Authors

Sguigna, Peter
Tardo, Lauren
Blackburn, Kyle
et al.

Publication Date

2022

DOI

10.1080/01658107.2022.2109687

Peer reviewed

NEURO-OPHTHALMOLOGY
2022, VOL. 46, NO. 6, 375–382
https://doi.org/10.1080/01658107.2022.2109687

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ORIGINAL ARTICLE

Application of the International Interocular Difference Thresholds into Practice: Localising the Patient Experience

Peter V. Sguigna[a], Lauren M. Tardo[a], Kyle M. Blackburn[a], Lindsay A. Horton[a], Darrel L. Conger[a], R. Nick Hogan[a,b,c,d], Morgan C. McCreary[a], and Benjamin M. Greenberg[a]

[a]Multiple Sclerosis & Neuroimmunology Division, Department of Neurology, University of Texas Southwestern, Dallas, Texas, USA; [b]Department of Ophthalmology, University of Texas Southwestern, Dallas, Texas, USA; [c]Department of Pathology, University of Texas Southwestern, Dallas, Texas, USA; [d]Department of Neurosurgery, University of Texas Southwestern, Dallas, Texas, USA

ABSTRACT

Demyelinating diseases of the central nervous system (CNS) often have neuro-ophthalmological manifestations, and retinal examination can be helpful in making the diagnosis. The latest iteration of optical coherence tomography (OCT)-based criteria for optic neuritis in multiple sclerosis has been developed in the research realm, but its application to clinical practice, and to the more uncommon demyelinating diseases requires further study. The ability to use OCT data to distinguish between various CNS demyelinating disorders could provide additional paraclinical tools to accurately diagnose patients. Furthermore, neuro-ophthalmological testing can define the extent of inflammatory damage in the CNS, independent of patient-reported history. New referrals for OCT at a tertiary multiple sclerosis and neuro-immunology referral centre ($n = 167$) were analysed retrospectively for the self-reporting of optic neuritis, serological test results, and diagnosis. Only approximately 30% of patients with a clinical history of unilateral optic neuritis solely had a unilateral optic neuropathy, nearly 40% of those subjects actually having evidence of bilateral optic neuropathies. Roughly 30% of patients reporting a history of bilateral optic neuritis did not have any evidence of structural disease, with 20% of these patients having a separate, intervenable diagnosis noted on macular scans. OCT is a useful adjunct diagnostic tool in the evaluation of demyelinating disease and has the ability to aid in a more accurate diagnosis for patients. Application of the international interocular difference thresholds to a clinical patient population generally reproduces the original results, emphasising their appropriateness. The analysis distinguishing the demyelinating diseases needs to be replicated in a blinded, multi-centre setting.

ARTICLE HISTORY
Received 27 August 2021
Revised 30 June 2022
Accepted 28 July 2022

KEYWORDS
Multiple sclerosis; optical coherence tomography; MOG; AQP4; NMOSD; MOGAD

Introduction

Multiple sclerosis (MS) is the most common non-traumatic cause of disability in young people, and visual symptoms can be the initial manifestation in up to 20% of cases.[1,2] Over the last two decades, many patients previously characterised as MS have subsequently been reclassified as neuromyelitis optica spectrum disorder (NMOSD) or, more recently, myelin-associated glycoprotein antibody disease (MOGAD). These diseases have been split into separate entities based on distinct neuro-immunological mechanisms and respective therapeutic interventions. All of these conditions have common neuro-ophthalmological manifestations, with optic neuritis (ON),[3] macular oedema,[4,5] and accelerated retinal volume loss[6–10] all being described. These multifaceted neuro-ophthalmological manifestations all adversely affect visual function, and can become the second-largest contributor to the patient's disability as measured by the expanded disability status scale.[11]

ON is a common manifestation of MS, occurring in over 50% of patients,[2] with nearly all patients displaying optic nerve disease at autopsy.[12] There are less data regarding the prevalence of ON in NMOSD as well as MOGAD. For NMOSD, there are conflicting data regarding the presence of accelerated retinal atrophy,[13] and the presence of asymptomatic optic neuropathy.[14] There are even less data available for adult MOGAD, both in terms of pathology[15,16] and optical coherence tomography (OCT) testing.[5,17]

OCT provides a quick, quantitative, and non-invasive evaluation for diagnostic pursuits.[18] In MS, OCT-derived metrics have strong correlations

CONTACT Peter V. Sguigna Peter.Sguigna@UTSouthwestern.edu Multiple Sclerosis & Neuroimmunology Division, Department of Neurology, University of Texas Southwestern, 5323 Harry Hines Blvd, Dallas, TX

with visual function,[19,20] as well as an association with the accumulation of disability.[21] The most common clinical use of OCT in MS and neuroimmunology clinical practice is to identify the presence of an optic neuropathy, with various structural thresholds developed to optimise the sensitivity and specificity of detection. More recently, an international study incorporating data from various OCT devices was proposed to define ON in an MS research cohort without binocular optic neuritis or ocular comorbidities other than correctable refractive errors.[22] The authors presented data that suggested that using an interocular retinal nerve fibre layer (RNFL) thickness difference of 5 µm yields a sensitivity and specificity of 76% and 75%, respectively, for the detection of unilateral ON in the lesser eye. Similarly, an interocular ganglion cell layer and inner plexiform layer (GCL+IPL) thickness difference of 4 µm has approximately a 68% and 77% sensitivity and specificity, respectively, for the detection of ON. While there were slight differences between the thresholds, the specificity and positive predictive value were higher using the GCL+IPL threshold. The authors made the argument that such thresholds could be used for further investigation to validate the fulfilment of asymptomatic optic nerve lesions as a dissemination in space criterion to diagnose MS.

As OCT is becoming an increasingly used technology to assist in the evaluation of MS, the clinical application of these criteria, and their utility in distinguishing between the various demyelinating diseases, is less reported. To this end, we sought to evaluate the application of the international interocular difference thresholds by OCT testing on new referrals to our tertiary care centre while simultaneously applying these thresholds to determine the prevalence of ON in the different demyelinating disease subtypes, NMOSD and MOGAD.

Methods

The study was approved by the UTSW Institutional Review Board in accordance with the International Conference on Harmonisation. A retrospective analysis was performed on all new referrals for OCT testing of patients as part of their clinical evaluation at the UTSW Multiple Sclerosis and Neuroimmunology Clinic from March 2019 to March 2020. OCT was performed on a Spectralis OCT-2 (Heidelberg Engineering, Heidelberg, Germany) machine operated by a single user acquiring both macular and optic nerve head scans with included eye tracking software. Images were acquired in a dark, quiet room without mydriasis. The vast majority of scans utilised Nsite, with the exception of three where Glaucoma Module Premium Edition was used, given the difficulty in determining the location of the centre of the optic nerve head in these subjects. OCT scans that did not fulfil at least five of the seven OSCAR-IB criteria were excluded,[23] and retinal segmentation was performed with a semi-automated algorithm. Manual correction of segmentation was performed as required following review of acquisition while blinded to clinical data. The RNFL was taken as a 3.4 mm ring scan centred on the optic disc. The GCL+IPL was taken as an average thickness across the standard 6 mm Early Treatment of Diabetic Retinopathy Study grid. Interpretation was performed by a single reader. Each patient's clinical diagnosis, laboratory results, and OCT results were reviewed. Separately, the patient's reported history of ON, independent of a clinical diagnosis of ON, was taken from the patient at the time of OCT testing. Optic neuropathy by OCT was defined as either (1) interocular difference in RNFL of greater than 5 µm if there was congruous GCL+IPL asymmetry of 4 µm, or (2) monocular general RNFL thickness ≤5% expected of an age- and sex-matched control subject, as suggested in the literature.[24,25] The results are reported in accordance with Advised Protocol for OCT Study Terminology and Elements recommendations with additional information available upon reasonable request.[26]

Clinical diagnoses used in categorical analyses, such as MS, were obtained from the chart and verified by an independent reviewer. The diagnosis of MS was verified by the 2017 Revised McDonald Criteria,[27] the diagnosis of NMOSD was verified by the 2015 International Consensus Criteria,[28] and the diagnosis of MOGAD was verified by criteria as suggested in the literature.[29] Specifically, MOG antibody was considered positive regardless of the titre. Both anti-aquaporin 4 (AQP4) and anti-MOG serological assessments were performed with commercially available assays. The diagnosis of

neurosarcoidosis was similarly verified as recommended by the Neurosarcoidosis Consortium Consensus Group.[30]

Statistical analysis was performed using R (The R Foundation for Statistical Computing, Institute for Statistics and Mathematics, Vienna, Austria) with Matlab (MathWorks, Natick, MA, USA) being used for generalised estimating equations accounting for within-patient intereye correlations as well as linear regression models as appropriate. Generalised estimating equations were created assuming a robust covariate matrix and a normal distribution controlling for age, which were centred and scaled for ease of interpretation. Similarly, linear regression models were estimated controlling for age, which were also centred and scaled. Correlation values are reported in reference to the MS population. The significance level was defined to be 5%. Given the exploratory nature of the proposal, no adjustment was performed for multiple analyses.

Results

The demographics of the cohort are shown in Table 1. The majority of the cohort was female, and the mean age was 47.6 years. Clinical diagnoses identified were quite heterogeneous, with MS and NMOSD constituting the majority. Both MOGAD and NMOSD had relatively high prevalences in our cohort, with seronegative ON contributing a smaller but notable proportion. In total, a history of ON was reported in 37% of the patients.

OCT was captured in 167 patients, with four scans discarded for not fulfilling pre-specified criteria (total $n = 326$ eyes). In our cohort, 23 out of the 61 patients with a reported history of ON did not fit the structural criteria (37%), as demonstrated in Table 2. Of the patients with a reported history of only unilateral ON, 40% revealed evidence of bilateral optic neuropathy. For 18% of the patients reporting no history of ON, there was evidence of bilateral optic neuropathy based on structural criteria. In those patients reporting a history of bilateral ON, 38% displayed another retinopathy without evidence of an optic neuropathy. Of all patients without structural evidence of optic nerve disease, 20% of the OCT derived data was consistent with a different diagnosis, with nearly 20% of these patients having a separate, treatable diagnosis.

The listing of these OCT findings independent of central nervous system (CNS) demyelinating disease, shown in Table 3, reveals that macular drusen were the most common finding. Epiretinal membranes were next, followed by a constellation of findings that were suspicious of glaucomatous changes. Other findings not included on the table were amelanotic choroidal naevus, paracentral acute middle maculopathy, geographic atrophy with drusenoid deposits, and macular hole (in a patient with contralateral AQP4 ON) (Figure 1).

Table 1. Demographics of the cohort.

Patient number	167
Mean age in years (standard deviation)	47.6 (13.3)
Percentage female	69
Clinical diagnosis	
Percentage with MS	40
Percentage with NMOSD	13
Percentage with MOGAD	9
Percentage with idiopathic ON (%)	5
Percentage with transverse myelitis (%)	7
Percentage with other disorders	26

MOGAD = myelin associated glycoprotein antibody disease; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

Table 2. Reported history of optic neuritis relative to the optical coherence tomography findings.

	OCT evidence of optic neuropathy in OS only ($N = 13$)	OCT evidence of optic neuropathy in OD only ($N = 8$)	OCT evidence of optic neuropathy in OU ($N = 42$)	No OCT evidence of optic neuropathy ($N = 104$)	OCT evidence of other retinopathy ($N = 38$)
History of ON in OS only ($N = 21$)	8	0	4	9	3
History of ON in OD only ($N = 19$)	0	5	7	7	4
History of ON in OU ($N = 21$)	1	1	12	7	8
No history of ON ($N = 106$)	4	2	19	81	23

OCT = optical coherence tomography; OD = right eye; ON = optic neuritis; OS = left eye; OU = both eyes.

Table 3. Retinopathy findings.

Retinopathy	Number
Dry drusen	14
Epiretinal membrane*	7
Glaucomatous changes*	3
Ischaemic retinopathy	2
Central serous chorioretinopathy	2
Macular hole*	2
Macular star*	2
Retinal haemorrhage	2
Other	4
Total	38

*Indicates potentially treatable finding.

The patients with CNS demyelinating disease were then grouped by serological autoantibody results. Of the cohort of 94 subjects, results were available for 184 peripapillary and macular scans. During the 12 months of data reviewed, nine patients tested positive for anti-MOG antibodies and 13 patients tested positive for anti-AQP4 antibodies. Mimicking the entire cohort, both groups showed an under-diagnosis of optic neuropathy, with nearly 50% of the patients showing evidence of bilateral structural deficits. Unlike the cohort as a whole, all patients who tested positive for anti-AQP4 antibodies or anti-MOG antibodies and reported a history ON, had structural evidence of disease. While both anti-AQP4-antibody and anti-MOG-antibody positive patients shared similar ON history prevalence, qualitatively both absolute values of RNFL and GCL+IPL were lower relative to patients with MS. Despite this, there was no statistically significant difference between categorical groups when accounting for known covariates, with the exception of comparing those with anti-AQP4 antibodies to those with MS, shown in Table 4.

Discussion

OCT is considered a highly sensitive test for ON,[31] with certain structural criteria providing up to 96% sensitivity.[32] It is predominantly used to localise the patient's complaints of a unilateral visual disturbance to the optic nerve, although data it produces have numerous other uses.[21,33,34] If obtained, macular scans can increase the specificity of structural findings suspicious of ON while simultaneously providing useful clinical data regarding vision as well as risk of disability progression.[24,35]

A translational hurdle of the international criteria defining the presence of ON by interocular asymmetry is (1) that this study excluded subjects with ophthalmological co-morbidities, including the need for refraction ≥5 dioptres; (2) this definition has not been applied to a more diverse demyelinating disease population; and (3) interocular visual differences often have limited correlation with these OCT-based metrics in the population as a whole. While addressing these limitations, in addition to concerns with equating an abnormal OCT to the clinical diagnosis of optic neuropathy, we found that our results closely resemble those of the international criteria.

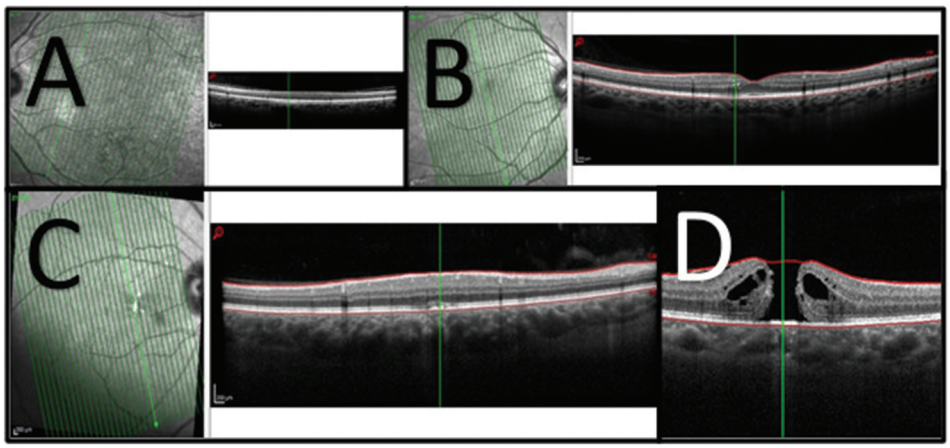

Figure 1. Graphics of retinopathies detected by macular optical coherence tomography scans. (a) Amelanotic choroidal naevus. (b) Paracentral acute middle maculopathy. (c) Geographic atrophy with drusenoid deposits. (d) Macular hole in a patient with contralateral anti-aquaporin 4 associated optic neuritis.

Table 4. Demyelinating disease subtype patient characteristics.

	MOG antibody positive	AQP4 antibody positive	MS	MOG compared with MS	AQP4 compared with MS
Subjects	9	13	72		
Median age (Std)	44 (11.4)	49 (11.9)	47 (14)		
Number of females (%)	7 (78)	11 (85)	61 (84)		
ON by history, eyes (%)	5 (28)	9 (35)	31 (22)		
Optic neuropathy by criteria, eyes (%)	8 (44)	14 (54)	52 (36)		
Mean RNFL thickness (Std) µm	77.3 (16.3)	86.6 (22.9)	91.0 (15.3)	†Δ = 1.42	†Δ = −3.39
N = 184 eyes				***p*=0.68**	***p*=0.23**
IOD RNFL thickness (Std) µm	5.9 (5.3)	16.6 (21.7)	7.5 (8.8)	*Δ = −1.5 [2.71]	*Δ = 8.94 [2.29]
N = 92 subjects				***p*=0.58**	***p*<0.05**
Mean GCL+IPL thickness (Std) µm	31.1 (6.1)	30.7 (7.6)	33.75 (9.9)	†Δ = −2.2	†Δ = −2.8
N = 184 eyes				***p*=0.37**	***p*=0.15**
IOD GCL+IPL thickness (Std) µm	3.75 (3.9)	3.4 (3.3)	3.9 (4.4)	*Δ = −0.78 [1.59]	*Δ = −0.81 [0.31]
N = 92 subjets				***p*=0.63**	***p*=0.54**

AQP4 = aquaporin 4; GCL+IPL = ganglion cell layer and inner plexiform layer; IOD = interocular difference; MOG = myelin associated glycoprotein; MS = multiple sclerosis; ON = optic neuritis; RNFL = retinal nerve fibre layer; Std = standard deviation.

*Correlation coefficient [standard error] for antibody status by linear regression model with age (centred and scaled), antibody status, and objective evidence of optic neuropathy (any), as covariates.

†Calculated by generalised estimating equations incorporating binocular retinal nerve fibre layer thickness results with age (centred and scaled), antibody status, objective evidence of optic neuropathy, and sex as covariates.

Applying the international definition of optic neuropathy into practice, regardless of ophthalmological co-morbidities, shows that 40% of the patients reporting ON are without any structural evidence of disease. This is consistent with similar reports of patient populations, ranging from 1% to 60%.[24,36–38] None of the patients incorrectly lateralised a visual disturbance, whereas a substantial population of patients with a unilateral ON history had structural evidence of bilateral disease. An even greater fraction of patients reporting bilateral ON had no structural evidence of disease. This was much greater than would be expected for the false-negative rate for OCT, even when accounting for timing relative to onset and available longitudinal data. OCT can be "normal" if there is robust RNFL thickening in acute ON with images captured as the swelling decreases into the normal range (before it reaches a lower, abnormally lower steady state level). Importantly, in this patient population, only a fraction had visualised retinopathies, with macular oedema conspicuously absent from the cohort. Despite the concerns with the specificity of the international criteria, this emphasises the use of the technology in practically ruling out optic nerve disease, allowing the clinical team to localise the visual disturbance elsewhere in the pathway.

The 11% prevalence of retinopathies is nearly identical to other academic literature,[39] with the exception that macular oedema was not noted in our cohort. Drusen and epiretinal membranes were the most common findings, which is consistent with the historical literature[40] from representative patient populations. These retinopathies were noted in a significant proportion of patients with a history of ON who did not fit structural criteria for ON, suggesting that they may be associated with their subjective complaint of a unilateral visual disturbance. In a substantial fraction of these patients, the identification of these retinopathies did offer a new therapeutic path, further emphasising the ability of this technology to provide actionable information.

In the patient population who reported no history of ON, 23% had structural criteria for optic neuropathy, which is less than the 45% in a pure MS population,[25] underlining the specificity of interocular differences when applied into practice. This is despite the older median age of our patient population, where non-ON optic neuropathy is likely more common. Incorporating macular scan data into the analysis identified alternative retinopathies in roughly 20% of the population, with most of these findings having little to no impact on subjective visual disturbances.

In the demyelinating disease subgroup consisting of MS, NMOSD, and MOGAD, the presence of optic neuropathy as defined by OCT is largely congruous with other reported data, with a higher prevalence of ON by structural criteria compared with patients' reports. While there are numerous descriptions of severe asymmetrical ON in the antibody-associated demyelinating diseases, generalised estimating equations incorporating age, sex, and history of ON into interocular differences were only able to separate MS from NMOSD.

Accordingly, an "upper bound" to interocular differences could be considered as part of diagnostic criteria incorporating OCT-based metrics for demyelinating diseases.

Those patients with a history of bilateral ON often fit structural criteria for bilateral optic neuropathies but also had an increased prevalence of retinopathy. As bilateral ON is more common in antibody associated CNS demyelinating disease, and concomitant retinopathies are well documented in NMOSD and MOGAD, this finding is consistent with the literature. Most of the patients who reported ON, but had no structural evidence of disease on peripapillary scans, did have objective evidence of disease elsewhere in the visual pathway. A significant amount of this pathology was visualised within the retina itself as demonstrated on macular scans and in Table 3. These results underscore that unilateral visual disturbance, a complaint often ascribed to ON in this patient population, cannot readily be localised to optic nerve pathology by history alone. The attempt to validate the patient experience, namely the localisation of optic nerve disease from elsewhere in visual pathway, has significant implications for the fulfilment of various diagnostic criteria for the demyelinating diseases.[27,41]

Ultimately, these data emphasise that while interocular thresholds purely using peri-papillary scan results are sensitive, they do lack specificity for optic nerve disease in a practical setting. This is reflected in the 18% of the patients with no history of ON, even when accounting for those with the more specific macular scan threshold findings. Despite the theoretical obstacle of translating these thresholds to patients with ocular comorbidities, the results from our cohort study are relatively similar to those of the literature with regard to the presence of asymptomatic optic neuropathy. There is generally a twofold increase in asymptomatic optic neuropathy relative to those who report a history of ON in a large cohort of MS patients.[24] In other words, in the demyelinating disease population, including patients with ocular comorbidities did not significantly detract from determining ON by interocular differences.

While our study was conducted with a large number of participants, the relatively low number of those patients with antibody associations cautions against making steadfast conclusions in comparing NMOSD, MOGAD, and MS. In addition, not all subjects had serological testing for CNS demyelinating disease-associated antibodies. Our prevalence data likely overestimate neuro-ophthalmological findings given the inherent bias of sampling patients who had OCT testing. This may be counterbalanced by the bias that the majority of patients sent for OCT testing were newly referred to the clinic, and generally had shorter disease durations. Prospective studies, including follow-up of patients with disability metrics such as disease duration, are ongoing to validate these findings.

Disclosure statement

Peter Sguigna has no disclosures related tothis publication. He has received grant support from the NMSS, CTM, PSTP, andthe PRC. He has received consulting fees from Medical Logix LLC, Genentech, andBristol Myers Squibb. Research reported in this publication was supported inpart by the National Center for Advancing Translational Sciences of the NationalInstitutes of Health under award number UL1TR001105. The content is solely theresponsibility of the authors and does not necessarily represent the officialviews of the NIH.

Lauren Tardo has nothing to declare.

Kyle Blackburn has nothing to declare.

Lindsay Horton has nothing to declare.

Darrel Conger has nothing to declare.

Robert "Nick" Hogan has nothing to declare.

Morgan McCreary has nothing to declare.

Benjamin Greenberg has received grant supportfrom the NIH, NMSS, Transverse Myelitis Association, PCORI, Guthy JacksonCharitable Foundation, Chugai, MedImmune, Medday, and Genentech. He hasreceived consulting fees from Alexion, Novartis, EMD Serono, Genentech, andCelgene; he is an unpaid board member of the Transverse Myelitis Association.

Funding

The authors reported that there is no funding associated with the work featured in this article.

ORCID

Peter V. Sguigna http://orcid.org/0000-0003-1825-575X
Lauren M. Tardo http://orcid.org/0000-0003-0214-633X
Kyle M. Blackburn http://orcid.org/0000-0001-5227-153X
Lindsay A. Horton http://orcid.org/0000-0001-6040-1947
R. Nick Hogan http://orcid.org/0000-0001-7482-7746

Morgan C. McCreary http://orcid.org/0000-0002-8378-460X
Benjamin M. Greenberg http://orcid.org/0000-0002-2091-8201

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