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Diagnostic Value of Inter-Eye Difference Metrics on OCT for Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis

Giulio Volpe, MD, MPhil, Neringa Jurkute, MD, PhD, Gabriela Girafa, MD, Hanna G. Zimmermann, PhD, Seyedamirhosein Motamedi, PhD, Charlotte Bereuter, BSc, Lekha Pandit, MD, DM, PhD, Anitha D'Cunha, PhD, Michael R. Yeaman, PhD, MSc, BS, Terry J. Smith, MD, PhD, Lawrence J. Cook, PhD, Alexander U. Brandt, MD, Friedemann Paul, MD, Axel Petzold, MD, PhD, FRCP, FRCOphth, FRCPath, and Frederike C. Oertel, MD/PhD

Correspondence
Dr. Petzold
a.petzold@ucl.ac.uk

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Abstract

Background and Objectives

The 2022 International Consortium for Optic Neuritis diagnostic criteria for optic neuritis (ON) include optical coherence tomography (OCT). The diagnostic value of intereye difference (IED) metrics is high for ON in patients with multiple sclerosis and aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders, but unknown in myelin oligodendrocyte glycoprotein antibody–associated ON (MOG-ON).

Methods

A multicenter validation study was conducted on the published IED cutoff values (>4% or >4 μm in the macular ganglion cell and inner plexiform layer [mGCIP] or >5% or >5 μm in the peripapillary retinal nerve fiber layer [pRNFL]) in individuals with MOG-ON and age-matched and sex-matched healthy controls (HCs). Structural data were acquired with Spectralis spectral-domain OCT >6 months after ON. We calculated sensitivity, specificity, and receiver operating characteristics for both intereye percentage (IEPD) and absolute difference (IEAD).

Results

A total of 66 individuals were included (MOG-ON N = 33; HCs N = 33). ON was unilateral in 20 and bilateral in 13 subjects. In the pooled analysis, the mGCIP IEPD was most sensitive (92%), followed by the mGCIP IEAD (88%) and pRNFL (84%). The same pattern was found for the specificity (mGCIP IEPD 82%, IEAD 82%; pRNFL IEPD 82%, IEAD 79%).
In subgroup analyses, the diagnostic sensitivity was higher in subjects with unilateral ON (>99% for all metrics) compared with bilateral ON (61%–78%).

Discussion

In individuals with MOG-ON, the diagnostic accuracy of OCT-based IED metrics for ON was high, especially of mGCIP IEPD.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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From the Moorfields Eye Hospital NHS Foundation Trust (G.V., N.J., G.G.), London, United Kingdom; Department of Ophthalmology (G.V.), Institute of Clinical Neurosciences of Southern Switzerland (INSI), Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland; Department of Neuro-ophthalmology (N.J.), The National Hospital for Neurology and Neurosurgery, UCL Queen Square Institute of Neurology, The National Hospital for Neurology and Neurosurgery; Institute of Ophthalmology (N.J.), University College London, United Kingdom; Federal University of the State of Rio de Janeiro (UNIRIO) (G.G.), Brazil; Einstein Center for Digital Future Berlin (H.G.Z.); Experimental and Clinical Research Center (ECRC) (H.G.Z., S.M., C.B., A.U.B., F.P., F.C.O.), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC) (H.G.Z., S.M., C.B., A.U.B., F.P., F.C.O.), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany; Centre for Advanced Neurological Research (L.P., A.D.C.), Nitte University, Mangalore, India; Department of Medicine (M.R.Y.), David Geffen School of Medicine at UCLA, Los Angeles; Divisions of Molecular Medicine and Infectious Diseases (M.R.Y.), Department of Medicine; Lundquist Institute for Biomedical Innovation at Harbor-University of California Los Angeles Medical Center (M.R.Y.), Torrance, CA; Departments of Ophthalmology and Visual Sciences (T.J.S.), Kellogg Eye Center; Division of Metabolism (T.J.S.), Endocrine and Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor; Department of Pediatrics (L.J.C.), University of Utah; Department of Neurology (F.P., F.C.O.), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany; National Hospital for Neurology and Neurosurgery (A.P.), University College London Hospitals NHS Foundation Trust, Moorfields Eye Hospital NHS Foundation Trust and Queen Square Dept. of Neuroinflammation, UCL, Queen Square Institute of Neurology, University College London, United Kingdom; and Neuro-ophthalmology Expert Centre (A.P.), Amsterdam University Medical Center, The Netherlands.

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Glossary

AUC = area under the curve; **HCs** = healthy controls; **ICON** = International Consortium for Optic Neuritis; **IEAD** = intereye absolute difference; **IED** = intereye difference; **IED** = intereye difference; **IEPD** = intereye percentage difference; **mGCIP** = macular ganglion cell and inner plexiform layer; **MOG-ON** = myelin oligodendrocyte glycoprotein antibody–associated ON; **NMOSD** = neuromyelitis optica spectrum disorders; **OCT** = optical coherence tomography; **ON** = optic neuritis; **pRNFL** = peripapillary retinal nerve fiber layer; **ROC** = receiver operating characteristic.

Classification of Evidence

This study provides Class III evidence that the intereye difference on OCT can distinguish between those with MOG and normal controls.

Introduction

The International Consortium for Optic Neuritis (ICON) has recommended inclusion of retinal optical coherence tomography (OCT) as a paraclinical test for the diagnosis of optic neuritis (ON).[1] The potential to identify clinical and even subclinical damage to the optic nerve through a noninvasive and cost-effective in vivo measurement of distinct retinal layers has been previously described in multiple sclerosis (MS)–associated ON (MS-ON).[2-4] Following ON, atrophy is observed in the peripapillary retinal nerve fiber layer (pRNFL) and the macular ganglion cell-inner plexiform layer (mGCIP) complex. In addition to absolute pRNFL and mGCIP values, intereye difference (IED) metrics proved valuable for identifying, especially unilateral, optic nerve damage. An intereye percentage difference (IEPD) of more than 5% for pRNFL or more than 4% for mGCIP is diagnostic for an episode of past unilateral ON, with a specificity up to 97% and sensitivity up to 100% in MS.[5-8] Recently, we validated these IED thresholds in people with aquaporin-4 antibody (AQP4-IgG) seropositive neuromyelitis optica spectrum disorders and unilateral ON (AQP4-IgG+ NMOSD).[9] Yet, no study has been performed evaluating the applicability of IED in people with a history of ON in myelin oligodendrocyte glycoprotein

Table 1 Cohort Data

Baseline (subjects)		
	HCs	**MOG-ON**
Subjects [N]	33	33
Subjects with unilateral ON [N (%)]		20 (61)
Subjects with bilateral ON [N (%)]		13 (39)
Eyes [N]	66	66
Age [y, mean (SD)]	34 (11)	39 (15)
Sex [m, N (%)]	16 (48.5)	16 (48.5)
Time since ON [y, mean (SD)]		3 (4)
pRNFL [µm, mean (SD)]	95.98 (7.91)	71.03 (24.35)
mGCIP [µm, mean (SD)]	86.48 (9.64)	67.32 (19.46)
IEAD pRNFL [µm, mean (SD)]	2.70 (2.49)	23.75 (17.50)
IEPD pRNFL [%, mean (SD)]	2.77 (2.61)	25.90 (16.85)
IEAD mGCIP [µm, mean (SD)]	2.61 (2.70)	20.60 (13.10)
IEPD mGCIP [%, mean (SD)]	2.92 (2.88)	24.94 (14.52)

Abbreviations: HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer.

Table 2 Intereye Percentage and Absolute Differences

	t	***p* Value**
MOG-ON (all subjects) vs HCs		
pRNFL IEAD [µm]	−6.739	<0.001
pRNFL IEPD [%]	−7.678	<0.001
mGCIP IEAD [µm]	−6.760	<0.001
mGCIP IEPD [%]	−7.473	<0.001
MOG-ON (unilateral) vs HC		
pRNFL IEAD [µm]	−7.796	<0.001
pRNFL IEPD [%]	−8.642	<0.001
mGCIP IEAD [µm]	−8.429	<0.001
mGCIP IEPD [%]	−8.213	<0.001
MOG-ON (bilateral) vs HC		
pRNFL IEAD [µm]	−2.499	0.028
pRNFL IEPD [%]	−3.118	0.009
mGCIP IEAD [µm]	−2.389	0.043
mGCIP IEPD [%]	−2.886	0.020

Abbreviations: HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer; *t* = *t* test statistics.

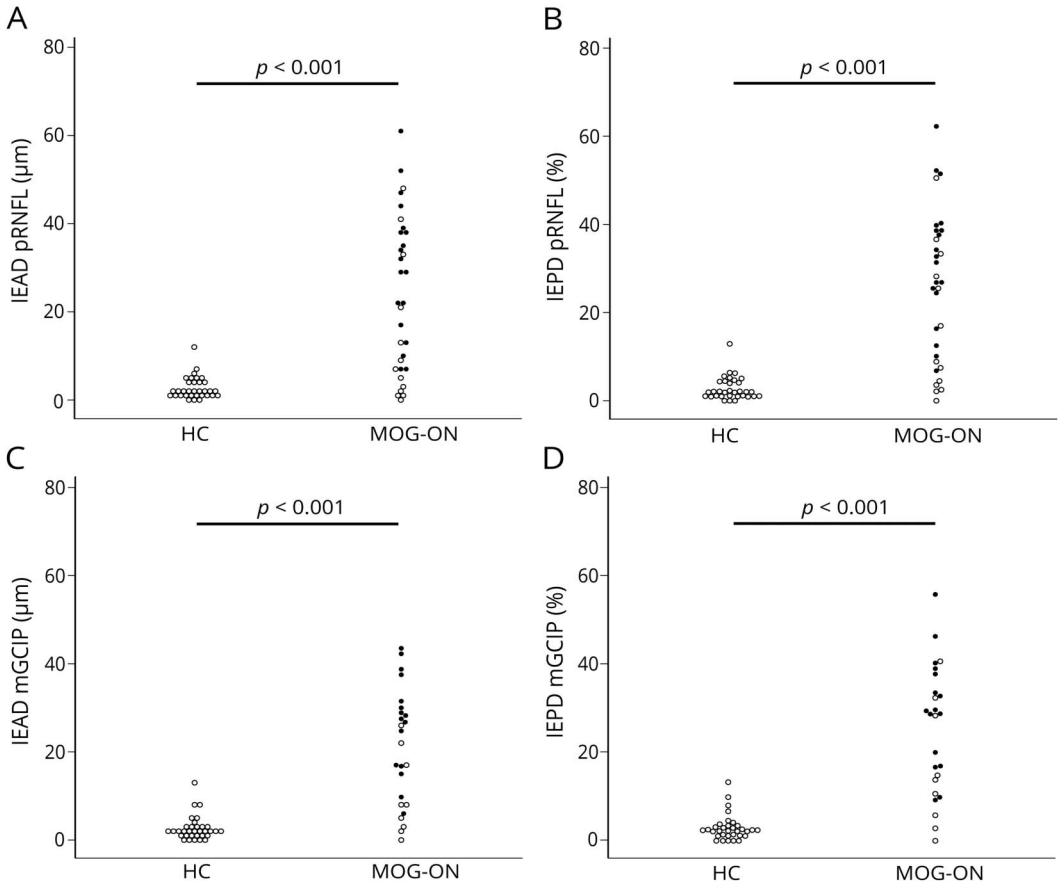
antibody–associated optic neuritis (MOG-ON) and in people with a history of bilateral ON.

Distinct from MS and AQP4-IgG seropositive neuromyelitis optica spectrum disorders (NMOSD), MOG-ON is characterized by serum antibodies directed against myelin oligodendrocyte glycoprotein (MOG-IgG). Patients with MOG-IgG may present with a range of neurologic manifestations, the most frequent presentation being ON. Characteristics of MOG-ON include, for example, severe edema[10] and a high frequency of bilateral MOG-ON.[11] While OCT has been used to quantify visual pathway damage and dysfunction in ON associated with MOG-IgG, no studies have yet evaluated the accuracy of previously established IED thresholds for diagnosing MOG-ON.[12,13] Owing to the high frequency of bilateral MOG-ON, it is particularly important to evaluate the diagnostic accuracy of current IED thresholds for bilateral presentation. Thus, this multicenter study aims to evaluate the diagnostic accuracy of reported IED values for people with unilateral and bilateral MOG-ON compared with healthy controls (HCs). The primary question being addressed is whether the intereye difference on OCT can effectively distinguish between individuals with MOG-ON and HCs.

Methods

This is an international, multicenter study. Data are cross-sectional and retrospective and curated by an adjudication committee to ensure that both quality and completeness of data sets were fulfilled. Data from patients with MOG-ON and HCs were collected at Moorfields Eye Hospital NHS Foundation Trusts and University College London Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery between February 2023 and May 2023 and at Charité-Universitätsmedizin Berlin, Germany, and Nitte University, Mangalore, India, as part of the international Collaborative Retrospective OCT in Neuromyelitis Optica (CROCTINO) study between September 2016 and September 2018.[14]

Figure 1 Intereye Percentage and Absolute Differences



IEPD and IEAD comparisons using a beeswarm plot for (A–B) pRNFL and (C–D) mGCIP. The IEPD and IEAD of pRNFL and mGCIP were significantly higher in MOG-ON compared with HCs ($p < 0.001$). HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer.

We included individuals diagnosed with MOG-ON according to published criteria,[11] who had experienced unilateral or bilateral ON at least 6 months before OCT measurements. An HC group was used for comparison. To be included in the study, the following criteria had to be met: (1) OCT data had to be acquired using Spectralis spectral-domain OCT (SD-OCT); (2) individuals must not have had any other eye conditions potentially affecting the OCT analysis (as defined in the OSCAR-IB criteria[15,16]); (3) individuals should not have experienced any additional episodes of ON within the 6 months leading up to the date of examination. Clinical information including age, sex, and the onset date of ON were collected at the discretion of each participating study center. MOG-IgG antibodies were detected in the serum samples using cell-based assays.[17] Our data have been reported in accordance with the guidelines outlined in the Enhancing the Quality and Transparency of Health Research reporting.[18]

Optical Coherence Tomography

All OCT imaging was acquired at each center using Spectralis SD-OCT devices (Heidelberg Engineering, Heidelberg, Germany).[9] The pRNFL thickness was measured using a 12° (or 3.5-mm diameter) peripapillary ring scan. The mGCIP thickness was determined by calculating a 3-mm diameter annulus around the fovea, excluding the central 1-mm diameter cylinder from a volume scan. The assessment of OCT data was conducted at Moorfields Eye Hospital NHS Foundation Trusts by 3 graders for the UK data set and the CROCTINO data set as previously described.[19] All OCT images met the OSCAR-IB criteria[15,16] and have been presented in compliance with the recommendations of Apostel V.2.0.[20,21]

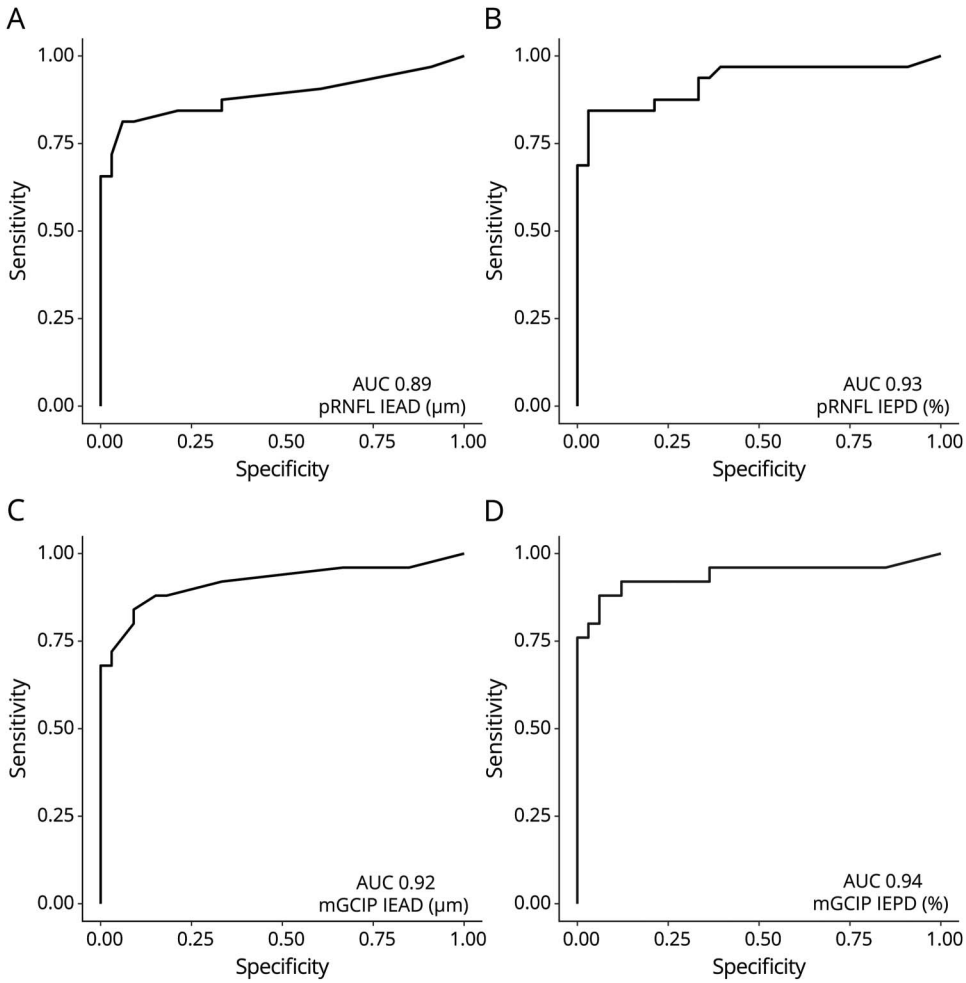
Standard Protocol Approvals, Registrations, and Patient Consents

This study was registered as an audit for publication (Study Number ROAD 17/01), and the institutional review board waived the need for approval and informed consent due to its noninterventional, retrospective design.

Statistical Analyses

We conducted statistical analyses using R (V.4.2.1) (RStudio, Boston, MA).[22] The data were stratified in cohorts based on diagnosis and history of unilateral or bilateral MOG-ON.

Figure 2 Diagnostic Sensitivity and Specificity of IED in MOG-ON



ROC curves for IED for pRNFL and mGCIP discriminating between MOG-ON vs HCs. ROC curves are plotted for all subjects with MOG-ON. All parameters exhibited a high discriminative power when comparing patients with MOG-ON with HCs, considering the entire subject pool (A–D). AUC = area under the curve; HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer; ROC = receiver operating characteristic.

Continuous data were described as the mean ± SD, unless specified otherwise. Intereye absolute difference (IEAD) was computed as the *absolute* difference between the measurements in the 2 eyes for both pRNFL and mGCIP. IEPD was calculated by dividing the IEAD by that of the eye with higher values and then multiplying the result by 100. Age, IEAD, and IEPD were compared between groups using unpaired t tests. Statistical significance was defined at $p < 0.05$. We assessed the diagnostic accuracy using receiver operating characteristic (ROC) curves. The area under the curve (AUC) was used to evaluate the discriminative power, categorized as low/no discriminative power (AUC <0.7), moderate discriminative power (AUC 0.7–0.9), or high discriminative power (AUC >0.9). The ROC curves were contrasted to evaluate statistically significant differences between the IEPD and IEAD. The optimal threshold values were determined using the Youden index.

Data Availability

Data are available on reasonable request.

Results

Cohort

There were a total of 54 patients with MOG-ON within the CROCTINO study, and 98 cases were identified at Moorfields Eye Hospital NHS Foundation Trusts and University College London Queen Square Institute of Neurology and The National Hospital for Neurology and Neurosurgery. Inclusion criteria were met by 11 patients in the CROCTINO study and 22 within the London cohort. In total, we included 33 patients with MOG-ON and a history of unilateral or bilateral ON and 33 age-matched ($p = 0.178$) and sex-matched ($p > 0.99$) healthy controls for comparison (Table 1).

Among the patients with MOG-ON, 20 individuals had a history of unilateral ON (age: 37.8 ± 15.5 years, 50% male, mean time since ON: 3.4 ± 4.0 years) and 13 patients had a history of bilateral ON (age: 40.1 ± 14.1 years, 46% male, mean time since ON: 3.3 ± 4.4 years).

IEPD and IEAD

As expected, the IEPD and IEAD of pRNFL and mGCIP were found to be higher in MOG-ON compared with HCs (Table 2 and Figure 1). This difference existed for both parameters in the entire cohort and in the subsets of patients with a history of unilateral ON ($p < 0.001$) and bilateral ON (IEPD pRNFL [$p = 0.009$], IEAD pRNFL [$p = 0.028$], IEPD mGCIP [$p = 0.020$], and IEAD mGCIP [$p < 0.044$]) (Table 2).

Diagnostic Sensitivity and Specificity of IED in MOG-ON

The discriminative power of IEPD and IEAD was found to be high (AUC >0.9) for HCs vs all patients with MOG-ON when considering the mGCIP. Similarly, the discriminative power of

Table 3 Diagnostic Sensitivity and Specificity of IED in MOG-ON

	AUC	95% CI	Specificity (%)	Sensitivity (%)	Positive predictive value	Negative predictive value
MOG-ON vs HCs						
pRNFL IEAD	0.89	0.80–0.98	79	84	0.80	0.83
pRNFL IEPD	0.93	0.86–1.0	82	84	0.82	0.84
mGCIP IEAD	0.92	0.83–1.0	82	88	0.83	0.87
mGCIP IEPD	0.94	0.86–1.0	82	92	0.84	0.91
MOG-ON (unilateral) vs HC						
pRNFL IEAD	0.99	0.98–1.0	79	≥99	0.74	0.99
pRNFL IEPD	>0.99	0.98–1.0	82	≥99	0.77	0.99
mGCIP IEAD	0.99	0.98–1.0	82	≥99	0.77	0.99
mGCIP IEPD	0.99	0.98–1.0	82	≥99	0.77	0.99
MOG-ON (bilateral) vs HC						
pRNFL IEAD	0.73	0.53–0.93	79	62	0.53	0.84
pRNFL IEPD	0.83	0.67–0.98	82	62	0.57	0.84
mGCIP IEAD	0.79	0.58–1.0	82	67	0.59	0.86
mGCIP IEPD	0.84	0.63–1.0	82	78	0.63	0.90

Abbreviations: HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer.

IEPD was excellent (AUC >0.9) and that of IEAD was moderate (AUC 0.8–0.9) for the pRNFL (Figure 2, A–D).

When assessing previously reported threshold values (IEAD: 5 μm, IEPD: 5% for pRNFL, and IEAD: 4 μm, IEPD: 4% for mGCIP), patients with MOG-ON could be distinguished from HCs with a strong discriminatory power using each metrics (Figure 2 and Table 3). Similarly, an excellent discriminative power was observed in subgroup analysis when considering unilateral or bilateral MOG-ON cases vs HCs (Figures 3 and 4). Remarkably, bilateral MOG-ON can be distinguished with moderate discriminative power from HCs using these metrics.

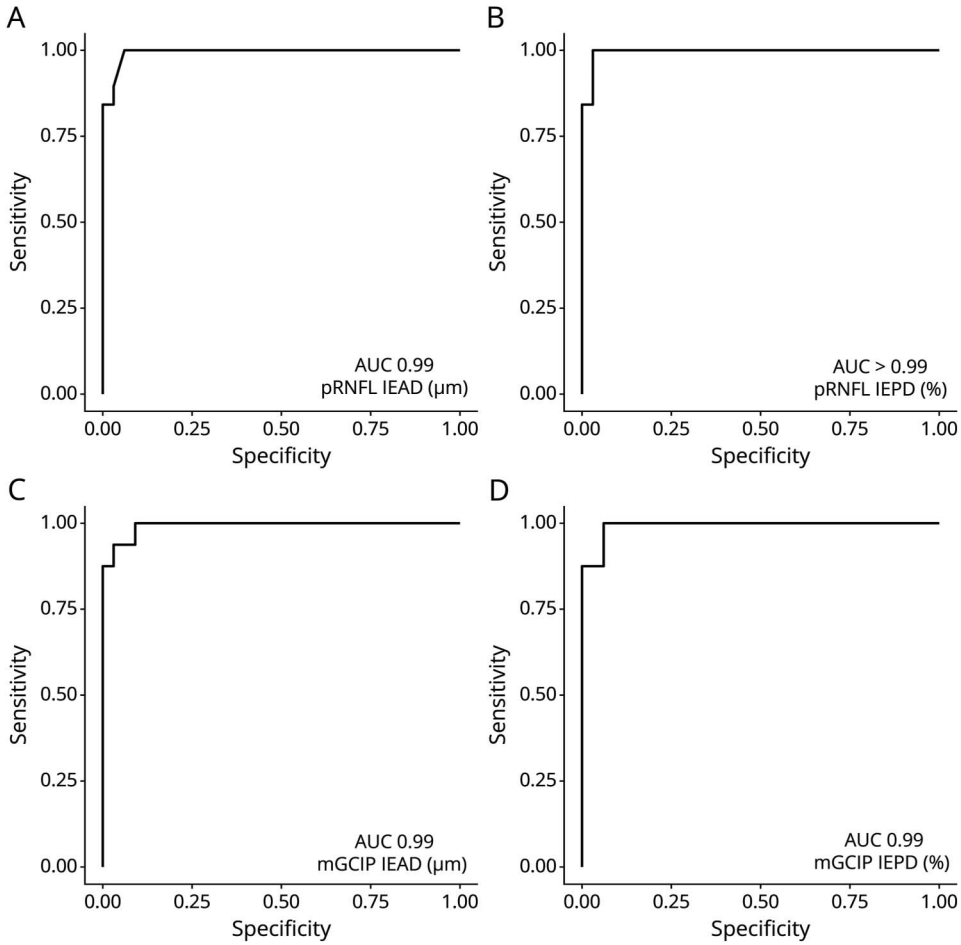
A statistically significant difference was observed when comparing the ROC curves for IEPD and IEAD in both pRNFL (p = 0.035) and mGCIP (p = 0.048) across the entire MOG-ON cohort. This difference was also evident in considering only bilateral cases, with pRNFL (p = 0.024) and mGCIP (p = 0.016).

When assessing the optimal combined sensitivity and specificity using the Youden index, the obtained thresholds were slightly higher than those published.[1] For the entire MOG-ON cohort, the thresholds for IEAD and IEPD in pRNFL were determined at 6.50 μm (specificity 94%; sensitivity 81%) and 6.58% (specificity 97%; sensitivity 84%), respectively. The optimal mGCIP thresholds were 5.50 μm for IEAD (specificity 91%; sensitivity 84%) and 8.62% for IEPD (specificity 94%; sensitivity 88%).

Similar thresholds were identified when restricting the analysis to subjects with unilateral MOG-ON for pRNFL (IEAD: 6.50 μm, specificity: 94%, sensitivity: ≥99%; IEPD: 6.58%, specificity: 97%, sensitivity: ≥99%) and for mGCIP (IEAD: 5.50 μm, specificity: 91%, sensitivity: ≥99%; IEPD: 8.62%, specificity: 94%, sensitivity: ≥99%). In the context of bilateral MOG-ON, the optimal pRNFL thresholds for IEAD were determined as 6.50 μm (specificity 94%; sensitivity 54%) and for IEPD as 6.91% (specificity 97%; sensitivity 61%). For mGCIP, the IEAD threshold was 4.50 μm (specificity 85%; sensitivity 67%) while the IEPD threshold was 5.16% (specificity 88%; sensitivity 78%).

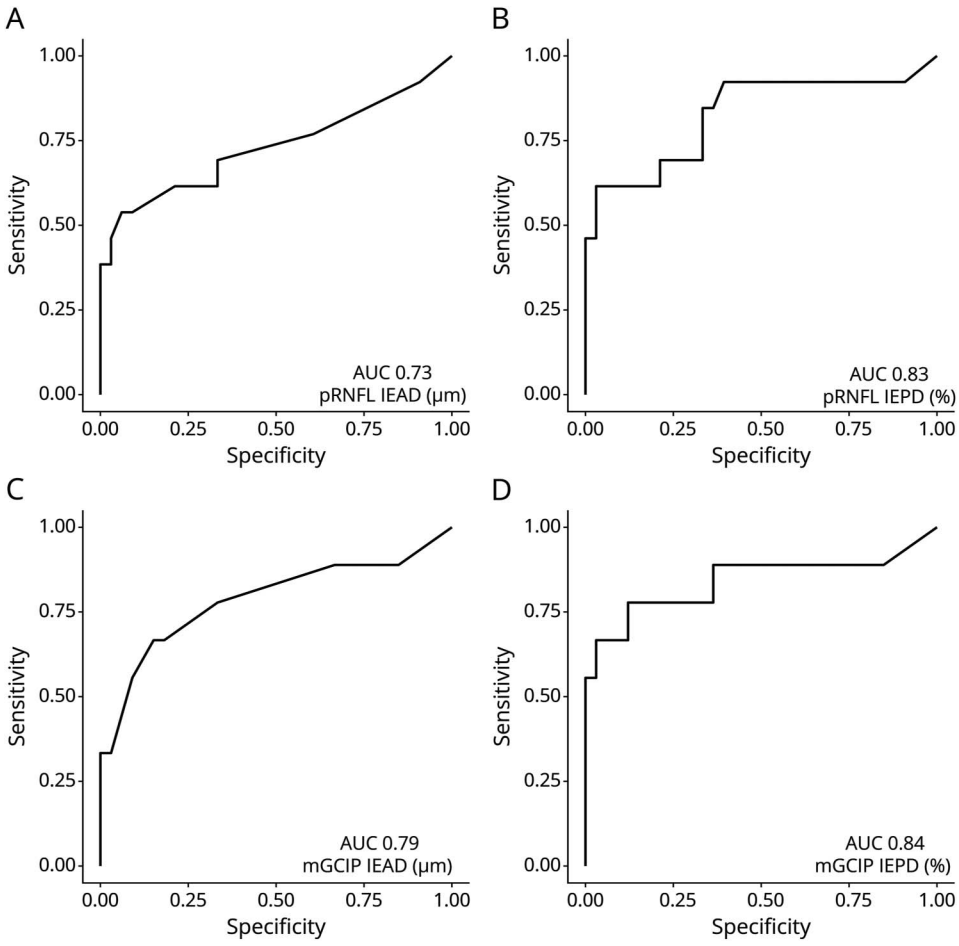
This study provides Class III evidence that the intereye difference on OCT can distinguish between those with MOG and controls.

Figure 3 Diagnostic Sensitivity and Specificity of IED in Unilateral MOG-ON



ROC curves for IED for pRNFL and mGCIP discriminating between unilateral MOG-ON vs HCs. ROC curves are plotted for unilateral MOG-ON. All parameters exhibited a high discriminative power when comparing patients with unilateral MOG-ON with HCs (A–D). AUC = area under the curve; HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer; ROC = receiver operating characteristic.

Figure 4 Diagnostic Sensitivity and Specificity of IED in Bilateral MOG-ON



ROC curves for IED for pRNFL and mGCIP discriminating between bilateral MOG-ON vs HCs. ROC curves are plotted for bilateral MOG-ON. In the context of bilateral MOG-ON presentations, measured parameters show a moderate discriminative power in distinguishing MOG-ON from the healthy control group (A–D). AUC = area under the curve; HCs = healthy controls; IEAD = intereye absolute difference; IEPD = intereye percentage difference; mGCIP = combined macular ganglion cell and inner plexiform layer; MOG-ON = myelin oligodendrocyte glycoprotein antibody–associated optic neuritis; pRNFL = peripapillary retina nerve fiber layer; ROC = receiver operating characteristic.

Discussion

This study provides evidence for the high performance of OCT as a paraclinical test for the diagnosis of past ON in individuals with unilateral and bilateral MOG-ON. Previous studies have validated the accuracy of IED metrics for identifying ON in MS[6,8,23] and AQP4-ON.[9] This study extends on the validation of the new diagnostic criteria regarding the IED to MOG-ON and suggests a clear benefit of applying IED metrics in people with a history of bilateral ON.[1]

Our data underscore the validity of IEAD (pRNFL 5 μm and mGCIP 4 μm) and IEPD (pRNFL 5% and mGCIP 4%) thresholds, as defined in the novel ON diagnostic criteria[1] and, in such, show excellent diagnostic sensitivity and specificity for MOG-ON.

Of interest, the established threshold showed a significant IED in bilateral MOG-ON cases as well. A similar unexpected result was previously observed in bilateral MS-ON, where asymmetric diffuse damage affecting the IEPD of the mGCIP was considered the likely underlying cause.[6] In the case of bilateral MOG-ON, it is plausible that a prompter corticosteroid treatment intervention at the onset of the inflammatory phase of ON might have contributed to a better retinal neuroaxonal salvage and maintenance in the second eye, leading to a high IEPD/IEAD in a significant proportion of our cases.[10,24] This speculation is based on the potential of corticosteroid administration at onset, which has been shown to lead to better visual outcomes,[25-27] yet it is important to note that there is currently no clear evidence regarding the effects of acute corticosteroid treatment in rescuing neuroaxonal retinal structures. Furthermore, a difference in the severity of the episodes among eyes might also have contributed to the conservation of a high IEPD/IEAD. Another factor to consider is the potential influence of asymmetric involvement in bilateral ON, where one side is primarily affected and milder damage occurs to the fellow nerve. This may occur as preferential impairment of axons compared with the actual cell bodies involved in the primarily affected side.

Consistent with studies assessing MS-ON, the IEPD seemed to have higher diagnostic accuracy compared with IEAD, with mGCIP being superior to the pRNFL in bilateral cases. The relatively more homogeneous configuration of the macula, compared with the higher anatomical variability of the optic disc,

likely explains why the mGCIP data are more consistent between eyes and patients than pRNFL in MS-ON[6,23] and our cohort.

When comparing the published thresholds established in MS with the optimal cutoff in the context of MOG-ON,[1] we observed that the optimal cutoffs were only marginally higher than the published thresholds. The higher cutoff values may be related to the fact that inner retinal layer atrophy is more severe in MOG than in MS or NMOSD.[9] This observation not only further validates the discriminative efficacy of the published cutoffs but also supports their value, even in the context of bilateral ON. Yet, cutoffs for differential diagnoses might be valuable to consider in the future.

In validating the IED criteria of the ICON 2022 in MOG-ON, we have confirmed the potential of IED as a diagnostic tool for objective assessment and monitoring in the most common entities of autoimmune ON. However, it is important to note that although these OCT criteria are useful in detecting previous ON episodes, they are not diagnostically specific for a subtype of ON.[6,11] Longitudinal studies are necessary to investigate potential OCT biomarkers that might help to differentiate ON subtypes. Specifically, MOG-ON is often associated with extreme optic disc and pRNFL edema in the acute phase, followed by marked retinal neurodegeneration.[12,13,27-30] The IED proves to be a useful parameter to detect the neuroaxonal degeneration subsequent to bilateral MOG-ON. Moreover, monitoring IED metrics over time could serve as a valuable additional tool to differentiate between monophasic and multiphasic MOG-ON, thereby supporting treatment recommendations and ensuring the correct enrollment of specific subgroup of patients in clinical trials.

Our study has several strengths, including the multicenter setting within the international CROCTINO cohort and the use of one OCT device type (Spectralis spectral domain) reducing the intermachine bias when considering absolute values of pRNFL and mGCIP. Yet, focusing on one paraclinical test alone is also a limitation of these findings. We are unable to comment on the potential added value of combining multiple paraclinical tests such as OCT and MRI[31] or OCT and visual evoked potentials.[32] In addition, we cannot estimate the influence of the acute treatment, or treatment delay, the patient underwent on the measured parameters. Another weakness is the retrospective design, and future work should consider including prospective and longitudinal data.

Overall, this study provides strong evidence of the diagnostic accuracy of IED metrics in MOG-ON, validating the recently published paraclinical OCT criteria in this subgroup of patients. Our findings emphasize the significance of incorporating IED parameters in future studies focusing on MOG-ON. By integrating these metrics, researchers and clinicians can use a noninvasive, cost-effective tool to diagnose MOG-ON, which has the additional advantage of providing easily comparable metrics.

Study Funding

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Disclosure

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Appendix Authors

Name	Location	Contribution
Giulio Volpe, MD, MPhil	Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom; Department of Ophthalmology, Institute of Clinical Neurosciences of Southern Switzerland (INSI), Ente Ospedaliero Cantonale (EOC), Lugano, Switzerland	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Neringa Jurkute, MD, PhD	Moorfields Eye Hospital NHS Foundation Trust; Department of Neuro-ophthalmology, The National Hospital for Neurology and Neurosurgery, UCL Queen Square Institute of Neurology, The National Hospital for Neurology and Neurosurgery; Institute of Ophthalmology, University College London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Gabriela Girafa, MD	Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom; Federal University of the State of Rio de Janeiro (UNIRIO), Brazil	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Hanna G. Zimmermann, PhD	Einstein Center for Digital Future Berlin; Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Seyedamirhosein Motamedi, PhD	Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Charlotte Bereuter, BSc	Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Lekha Pandit, MD, DM, PhD	Centre for Advanced Neurological Research, Nitte University, Mangalore, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Anitha D'Cunha, PhD	Centre for Advanced Neurological Research, Nitte University, Mangalore, India	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Michael R. Yeaman, PhD, MSc, BS	Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles; Department of Medicine, Divisions of Molecular Medicine and Infectious Diseases, Harbor-University of California at Los Angeles (UCLA) Medical Center; Lundquist Institute for Biomedical Innovation at Harbor-University of California Los Angeles Medical Center, Torrance	Drafting/revision of the manuscript for content, including medical writing for content
Terry J. Smith, MD, PhD	Departments of Ophthalmology and Visual Sciences, Kellogg Eye Center; Division of Metabolism, Endocrine and Diabetes, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor	Drafting/revision of the manuscript for content, including medical writing for content
Lawrence J. Cook, PhD	Department of Pediatrics, University of Utah	Drafting/revision of the manuscript for content, including medical writing for content
Alexander U. Brandt, MD	Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC), Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Friedemann Paul, MD	Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC); Department of Neurology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design

Continued

Appendix *(continued)*

Name	Location	Contribution
Axel Petzold, MD, PhD, FRCP, FRCOphth, FRCPath	National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, Moorfields Eye Hospital NHS Foundation Trust and Queen Square Dept. of Neuroinflammation, UCL, Queen Square Institute of Neurology, University College London, United Kingdom; Neuro-ophthalmology Expert Centre, Amsterdam University Medical Center, The Netherlands	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Frederike C. Oertel, MD/PhD	Experimental and Clinical Research Center (ECRC), Max-Delbrueck-Center Berlin & Charité - Universitätsmedizin Berlin; Neuroscience Clinical Research Center (NCRC); Department of Neurology, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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