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Optic nerve as a 5th location in the revised McDonald diagnostic criteria for multiple sclerosis: limitations of OCT in the acute phase

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ABSTRACT

Background The updated International Panel's diagnostic criteria for multiple sclerosis (2024 revision of McDonald criteria) have for the first time included the optic nerve as the fifth location for dissemination in space (DIS) criterion. The new requirement consists of evidence of significant retinal asymmetry. However, this can be challenging in the acute phase in absence of optic disc swelling. Here, we have investigated the sensitivity of retinal asymmetry over time, from the acute to the chronic phase of optic neuritis.

Methods This observational study analysed longitudinal optical coherence tomography (OCT) images of 25 patients with optic neuritis and 5 healthy controls. Spectral domain OCT scans were obtained from the macula and optic disc. The peripapillary retinal nerve fibre layer (pRNFL), macular ganglion cell (mGCL) and inner plexiform layers (mIPL) were measured in the acute (≤7 days), subacute (between 1 and 12 weeks) and chronic (>3 months) phase.

Results The OCT measurements showed progressive thinning in pRNFL and mGCIPL layers as the disease progressed. In the acute phase, the sensitivity of the pRNFL was 69% (due to optic disc swelling) and for the mGCPL 27%. In the chronic phase, sensitivity levels increased up to 76% (pRNFL) and 88% (mGCIPL) due to atrophy.

Conclusions A clear understanding of the temporal dynamics of diagnostic findings is important. For OCT, the highest diagnostic sensitivity is achieved for the mGCIPL in the chronic phase. This should be taken into account for timing the test in patients where the acquisition of optic nerve involvement is essential for DIS.

BACKGROUND

In 2024, the new International Panel diagnostic criteria for multiple sclerosis (MS) were presented at ECTRIMS, significantly enhancing diagnostic accuracy. For the first time, these updated criteria include optical coherence tomography (OCT) to identify optic nerve involvement as a fifth diagnostic location, offering an innovative approach to MS diagnosis.[1] This addition aims to improve sensitivity in detecting early signs of the disease, particularly in cases where optic nerve involvement might otherwise go undetected. The present report aims to provide a comparison of OCT metrics from the acute to the chronic phase of optic neuritis (ON), clarifying the variability seen with the disease progression. Both general OCT measures for clinicians and advanced OCT metrics in the MS criteria, available to select researchers, are reviewed to improve OCT interpretation in clinical practice, aiding in more accurate MS diagnoses.

METHODS

Subjects

We collected prospectively the OCT images of 25 patients diagnosed with ON according to the ICON diagnostic criteria[2] and 5 healthy controls (HCs) without any neurological or ophthalmological disease.

OCT: OCTs were obtained using Spectralis SD-OCT (Heidelberg Engineering, Germany) with eye-tracking on software V.6.7.13.0.[3] A macular volume scan (20°×20°, (ART)=25) centred on the fovea and a circular 12° peripapillary scan (ART=100) on the optic nerve head were obtained. All OCTs passed OSCAR-IB QC[4] and were reported according to APOSTEL-2.0 standards.[5] Automated B-scan segmentation was performed with Heidelberg Eye Explorer (V.6.15.7.0), followed by manual correction. The global average of the peripapillary retinal nerve fibre layer (pRNFL) was used from the ring scan. For the macular scan, mean layer thicknesses were measured within the 1–3.45 mm EDTRS grid, excluding the 1 mm central ring. Thickness (µm) and volume (mm^3) of the ganglion cell layer (mGCL), inner plexiform layer (mIPL) and their compound (mGCIPL) were reported. In addition, the inter-eye absolute and percentage differences (IEAD and IEPD,

respectively) were calculated for pRNFL (relevant when absolute value >5 µm or %) and macular (relevant when absolute value >4 µm or %)[6] (see online supplemental eFigure1).

Statistical analysis

All comparative analyses between patients (also subgroups) and controls were performed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variable. The Wilcoxon test was applied to test the difference between the acute and chronic phases in paired OCT. Statistical analysis was performed with Graphpad PRISM (V.10.5.0). Significance was accepted p values lower than 0.05.

RESULTS

Baseline characteristics of the study population

Among the 25 ON patients included, 10 were diagnosed with MS, 6 with MOG antibody-associated disease (MOGAD), and 9 with single isolated ON (SION). Demographic and clinical characteristics are reported in supplementary materials (see online supplemental eTable 1) . Briefly, binocular OCTs were performed for pRNFL (44 ON-OCTs, 9 HC-OCTs) and macula (42 ON-OCTs, 8 HC-OCTs). Optic disc and macular scans were divided into acute (≤7 days), subacute (between 1 and 12 weeks) and chronic (>3 months) phase based on the time point from symptoms onset[2] (see online supplemental eTable2).

In the acute phase, a frequent increase of pRNFL is observed

In the acute phase, retinal asymmetry was primarily driven by optic disc swelling in the affected eye. A pRNFL inter-eye difference >5% or >5 µm was found in 68.75% of ON–OCT cases. Macular asymmetry was less frequent: volume and inner retina (IR) thickness differences in mGCL, mIPL and mGCIPL were observed in <50% of cases. No significant differences were found between ON and HC groups (see figure 1, online supplemental eFigure2 and eTable3).

In the subacute phase, progressive inner retinal layer thinning begins

A reduction in pRNFL and macular thickness was observed in the affected eye, lowering IEPD and IEAD

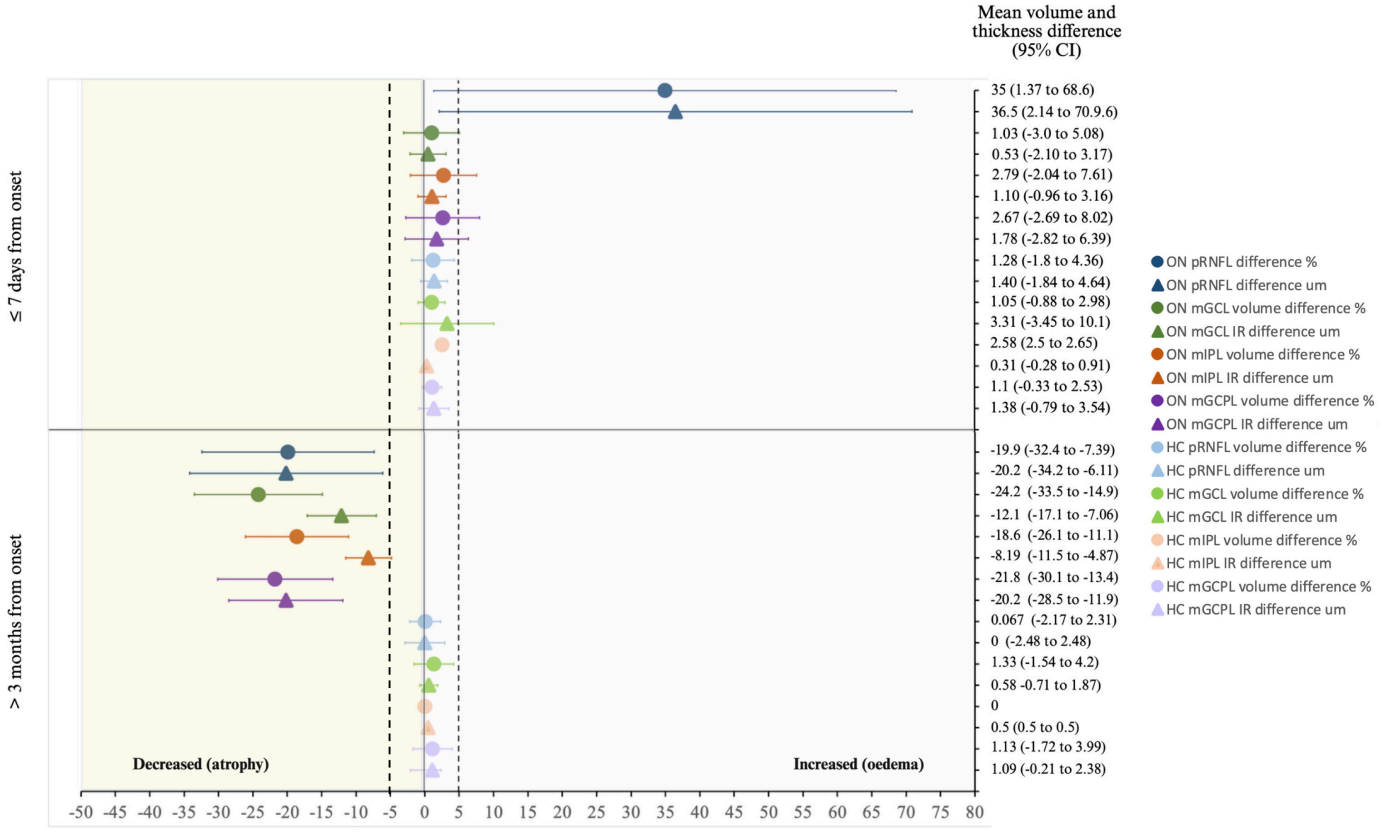

Figure 1 pRNFL, mGCL, mIPL and mGCIPL mean volume and thickness differences in different stage (acute and chronic phase). Within 7 days from onset (acute phase) in the ON group, retinal asymmetry above the cutoff is present mainly in pRNFL with increased thickness in the affected eye, due to optic disc swelling. After 3 months from onset (chronic phase), retinal asymmetry above the cutoff is seen in pRNFL, mGCL, mIPL and mGCIPL. In all cases in mGCL, mIPL and mGCIPL and most cases in pRNFL volume and thickness are decreased in the affected eye, confirming late optic nerve atrophy. No comparable differences are detected in the HC-OCT group. HC-OCT, healthy control-optical coherence tomography; mGCL, macular ganglion cell layer; mGCIPL, macular ganglion cell inner plexiform layer; mIPL, macular inner plexiform layer; pRNFL, peripapillary retinal nerve fibre layer.

values. In about half of the cases, pRNFL asymmetry was due to early thinning, while macular changes reflected progressive loss (see online supplemental eFigure2 and eTable3).

In the chronic phase, atrophy of the inner retinal layers is significant

A relevant difference was frequently observed in ON for both pRNFL (82.3%) and macular values (88%). The mean pRNFL difference was greater in the ON-OCT group compared with the HC-OCT both for IEPD (p=0.064) and for IEAD (p=0.056), showing a trend towards significance. Compared with HC-OCT, the ON group showed a significant reduction in terms of volume and thickness in mGCL (24.2%±18.1%, p<0.01; 12.1±9.8 µm, p<0.005), mIPL (18.6%±14.6% and 8.19±6.46 µm, both p<0.05) and mGCIPL (21.8%±16.2%, p<0.01; 20.2±16.1 µm, p<0.05) (see figure 1, online supplemental eFigure2 and eTable3).

Among patients with data from both acute to chronic phase, pRNFL and macular thicknesses and volumes significantly declined in the affected eye, increasing the asymmetry with the fellow eye (see online supplemental eFigure3).

OCT longitudinal modification among ON subgroups

When stratified by aetiology (MS, MOGAD, SION), all subgroups showed significant reductions in macular thicknesses and volumes from the acute to the chronic phase, while pRNFL thinning was significant in MS and MOGAD, but not in SION (see online supplemental eTable4 and eFigure4).

DISCUSSION

The integration of OCT into the 2024 revision of the McDonald criteria for MS marks a significant advancement, particularly including the optic nerve involvement as a 'new' typical location of inflammation in MS.[1] By providing high-resolution and quantitative metrics, OCT now allows clinicians to observe the optic nerve's structural changes with unprecedented specificity, making it a valuable diagnostic tool.[7] This development addresses long-standing challenges in early MS detection, offering enhanced accuracy in assessing optic nerve involvement, which has historically been difficult to confirm with conventional imaging.[8]

With OCT, early inflammatory damage and atrophic changes in the optic nerve can be visualised more directly, providing a reliable diagnostic pathway that previously relied heavily on patient symptoms and limited MRI markers. Notably, OCT offers clearer diagnostic value in the chronic stage, where optic nerve changes become more pronounced and stable over time.[9] In this later phase, structural changes, particularly the thinning of the mGCIPL, are more reliably detected, supporting the case for OCT's role as a critical tool in both diagnosis and disease monitoring.

In this short report, we underscore two key issues: (1) the temporal limitations of OCT in the acute phase of ON and (2) the importance of timing to weight OCT findings.

In the acute phase, ON presents a variable increase of pRNFL. Subgroup analysis revealed that the highest values of IEPD and IEAD were observed in MOG-ON. Indeed, all MOG-ON showed a pathological pRNFL increase at baseline, compared with the 67% of MS and 40% of SION. These findings are consistent with the known pathophysiology of MOGAD, which is characterised by a rapid, antibody-dependent myelin damage, also driven by the infiltration of inflammatory cells into the optic nerve, optic nerve head, which together induce a severe optic disc swelling in the acute stage.[10] Indeed, severe pRNFL thickening is well recognised as a hallmark in MOG-ON, and the IEPD performs significantly better than the IEAD.[11]

Despite the acute phase, our analysis demonstrates that OCT metrics such as pRNFL, mGCL, mIPL and mGCIPL thicknesses and volumes show significant changes in all disease subgroups (MS, MOGAD and SION) despite differences at baseline presentation, our data further support the observations that ON arising from different aetiologies (such as MS, MOGAD or SION forms) might follow distinct trajectories in terms of structural damage and recovery.[12–14] This aspect is particularly relevant when interpreting OCT-derived metrics or applying diagnostic thresholds. However, the inclusion of non-MS ON cases in this analysis allowed us to highlight the limitations of applying MS-centric OCT cut-offs during the acute phase, especially before a definitive aetiological diagnosis has been established.[15] These findings reinforce the need for careful timing and clinical context when integrating OCT results into diagnostic reasoning[16] .

Furthermore, this study emphasises the value of OCT metrics beyond those included in the current MS-specific criteria. Unlike advanced research-only parameters, these broader metrics are readily available on all commercial OCT systems, expanding diagnostic access to general neurology and even optometry settings.[3]

CONCLUSIONS

The greatest diagnostic utility of OCT in ON lies in its application during the subacute to chronic phases, where structural changes are more reliably detectable. During these stages, observable atrophic changes typically emerge, requiring at least three months to reach a size detectable by standard OCT measurements. In acute phases, however, the traditional adage 'the patient sees nothing, the doctor sees nothing' remains relevant for many patients, particularly those without optic disc swelling. Our subgroup analysis confirms that structural retinal changes between the acute and chronic phases occur consistently across different ON subgroups, although the pattern and magnitude of these changes vary. The incorporation of widely available OCT metrics, such as mGCL (ordepending on the OCT vendor, mGCIPL) volume,

provides a practical and inclusive diagnostic framework, applicable not only within MS-specific criteria but also in broader clinical settings[16], where ON often presents early, ambiguously and heterogeneously.

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