Patterns of macular inner retinal layers involvement in eyes with optic nerve head drusen

Renata A. S. Modesto¹,², Elson C. Velanes Neto¹,², Rícia N. P. Moura¹,², Ana L. B. Scoralick¹,², Michele Ushida³, Carolina P. B. Gracitelli²,³, Syril Dorairaj⁴, Fábio N. Kanadani¹,⁴, Tiago S. Prata²,³,⁴, Diego T. Dias²,³

¹Department of Ophthalmology, Instituto de Olhos Ciências Médicas, Belo Horizonte, Brazil, ²Glaucoma Unit, Hospital Medicina dos Olhos, Osasco, Brazil, ³Glaucoma Service, Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil, ⁴Department of Ophthalmology, Mayo Clinic, Jacksonville, Florida, USA

Abstract

Purpose: The purpose of this study was to investigate the macular inner retinal layers involvement in eyes with optic nerve head drusen (ONHD) using spectral-domain optical coherence tomography (SD-OCT).

Methods: An observational case series was carried out. Consecutive patients with ONHD and age-matched healthy individuals were enrolled from a single center. Key exclusion criteria were significant media opacity, best-corrected visual acuity ≤20/40, and the presence of any ocular comorbidity. After inclusion, all patients underwent SD-OCT imaging, visual field (VF) testing (standard automated perimetry), and optic disc digital imaging. For SD-OCT, macular ganglion cell complex (GCC) and peripapillary retinal nerve fiber layer (pRNFL) protocols were obtained. SD-OCT examinations were classified as normal or abnormal (and subsequently as focal or diffuse loss pattern) based on previously described color-coded criteria.

Results: A total of 19 eyes with ONHD and 20 control eyes were included in the study. The VF mean deviation for ONHD eyes was −4.6 ± 3.9 dB. Regarding macular inner retinal layers (GCC protocol) analysis in ONHD eyes, nine eyes (47.4%) had significant macular GCC thinning, of which seven presented focal loss pattern and two diffuse loss pattern. Overall, both macular and pRNFL parameters were significantly thinner in eyes with ONHD when compared to healthy controls (P < 0.05). Analyzing the ability of the SD-OCTs normative database to detect abnormalities, 42.1% of the patients were presented abnormalities in both pRNFL and GCC parameters, while only one case presented an SD-OCT abnormality restricted to the macular GCC protocol.

Conclusions: Investigating macular inner retinal layers involvement in eyes with ONHD, we found detectable macular damage by SD-OCT in almost half of the cases. In most of these cases, macular damage had a focal loss pattern and was accompanied by concomitant pRNFL thinning.
neuro-ophthalmological pathologies such as papilledema, ischemic optic neuropathy, and others. In contrast, when the lesions are located closer to the lamina cribrosa, they can be difficult to detect and may require imaging techniques for confirmatory diagnosis, including low gain B-scan ultrasonography, autofluorescence, and, more recently, optical coherence tomography (OCT). An important feature of this condition is that ONHD may cause axonal damage through a compressive mechanism, leading to peripapillary retinal nerve fiber layer (pRNFL) thinning. Clinically, this can be associated or not with detectable pRNFL defects (as accessible by retinography) and visual field (VF) loss (as accessible by automated perimetry). In this context, OCT may have an important role in detecting structural damage. In the present case series, we sought to investigate patterns of macular inner retinal layers thinning as determined by spectral-domain OCT (SD-OCT) in patients with ONHD.

**Methods**

**Ethics statement**

This protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board.

**Participants**

In this observational case series, we enrolled consecutive patients with the diagnosis of ONHD attending to Hospital Medicina dos Olhos (Osasco, Brazil) between January 2017 and July 2018. In addition, healthy individuals were enrolled as controls for comparison of SD-OCT parameters with ONHD patients (respecting the age and sex distribution range of the latter group). All participants underwent a comprehensive ophthalmological evaluation, including best-corrected visual acuity, slit lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, dilated fundoscopy, VF testing (24-2 Swedish interactive threshold algorithm, Humphrey Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA), optic disc stereophotographs, color/red-free and autofluorescence fundus imaging, low gain setting B-scan ultrasonography, and SD-OCT imaging (RTVue-100 OCT, Optovue, Inc., Fremont, CA, USA).

The diagnosis of ONHD was based on the presence of at least one of the following criteria: (1) Hyperechogenic lesions on optic disc topography detected by low gain B-scan ultrasonography; (2) autofluorescent lesions on the optic disc topography; and (3) typical yellowish nodular images on the optic disc detected on fundus examination and digital disc photos. After inclusion, all eyes with ONHD were classified in single or multiple drusen based on fundus imaging. Cases that were detectable only by ultrasonography were classified as buried ONHD. Healthy participants needed to have intraocular pressure <21 mmHg (based on two different visits) and no signs of ONHD or glaucomatous optic neuropathy (defined as cup-to-disc ratio >0.6, asymmetry between eyes ≥0.2, presence of localized defects of the pRNFL, and/or neuroretinal rim in the absence of any other anomalies that could explain such findings).

Exclusion criteria were age <18 years, best-corrected visual acuity ≤20/40, previous ocular surgery (except for uneventful cataract surgery), media opacity, and systemic conditions that could affect the visual system, cognitive or physical inability to perform perimetry test, history of ocular trauma, or concomitant ocular diseases other than ONHD.

**Procedures**

The following demographic and ocular data were collected: Age, gender, race, central corneal thickness (based on ultrasound pachymetry), refractive error (spherical equivalent), and VF mean deviation index (VFMD) values. All participants underwent macular ganglion cell complex (GCC) and pRNFL thicknesses measurements with the RTVue SD-OCT. In brief, the GCC scan includes three layers: RNFL, ganglion cell layer, and inner plexiform layer. The GCC scan covered a 7 mm × 7 mm scan area centered on the fovea. Global, superior, and inferior average thicknesses of the two scan protocols as well as the GCC focal loss volume (FLV) and global loss volume (GLV) indices were obtained for analysis. We not only used the absolute values of each SD-OCT parameter but also considered the findings of the device normative database in depicting statistically abnormal results (considering these aforementioned parameters). Eyes were classified as abnormal if presenting at least one OCT parameter coded in yellow (0.01 < P < 0.05) or red (P < 0.01). Eyes with abnormal GCC results were then divided into two groups: Focal macular GCC loss (defined as a FLV index value below the 5th percentile of the normal distribution and a GLV index value equal or above the 5th percentile of the normal distribution) and generalized macular GCC loss (defined as a GLV index value below the 5th percentile of the normal distribution). Images with signal strength index <50 or not well centered (subjective assessment) and those with motion/capture artifacts were excluded from the analysis.

For the fundus analysis, color fundus imaging as well as red-free and autofluorescence imaging were evaluated by two experienced examiners to detect the presence of pRNFL defects. In cases of disagreement, the opinion of a third examiner was used to adjudicate. Regarding the classification of VF test results, a VF defect was defined as three or more points in clusters with a P < 5% (excluding those on the edge of the field or directly above and below the blind spot) on the pattern deviation plot, a pattern standard deviation index with a P < 5%, or a Glaucoma Hemifield Test with results outside the normal limits. For a VF to be considered reliable, fixation losses and false-positive errors were ≤15% and false-negative errors were ≤30%.

The main study outcome measurements were macular GCC thickness values and the pattern of macular GCC thinning as assessed by SD-OCT (focal loss or diffuse loss). Secondary outcomes were (1) analysis of pRNFL thickness values in ONHD patients as assessed by SD-OCT and (2) comparison...
of GCC and pRNFL SD-OCT parameters between ONHD patients and controls.

**Statistical analysis**

Descriptive analysis was used to present demographic and clinical data. D’Agostino–Pearson’s test was performed to determine whether the data had a normal distribution or not. Normally distributed data were presented as mean and standard deviation and those non-normally distributed were presented as median and interquartile intervals. Comparisons between groups were performed with an independent t-test or Mann–Whitney U-test, depending on the data distribution. Statistical analyses were performed using MedCalc software (MedCalc Inc., Mariakerke, Belgium) and the alpha level (Type I error) was set at 0.05.

**Results**

A total of 19 eyes from 10 patients with the diagnosis of ONHD and 20 control eyes were included in the study. Mean age and VFMD for ONHD patients were 46.8 ± 13.5 years and −4.6 ± 3.9 dB, respectively. Most patients were women (60%) and White (72.7%). Only one patient presented with unilateral ONHD. Table 1 provides additional clinical and ocular characteristics of ONHD patients.

Table 1: Demographic and clinical characteristics of patients with optic nerve head drusen

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.8 ±13.5</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Intraocular pressure</td>
<td>15.7 ±2.4</td>
</tr>
<tr>
<td>Central corneal thickness (µm)</td>
<td>571.9 ±43.5</td>
</tr>
<tr>
<td>Visual field mean deviation (dB)</td>
<td>−4.6 ±3.9</td>
</tr>
<tr>
<td>Visual field index (%)</td>
<td>92% ±8.7</td>
</tr>
<tr>
<td>Pattern standard deviation</td>
<td>1.14 ±1.41</td>
</tr>
</tbody>
</table>

*Data are given as mean ± standard deviation

Regarding macular inner retinal layers analyses in ONHD eyes, 9 eyes (47.4%) had significant macular GCC thinning, of which seven presented focal loss pattern and two diffuse loss pattern. Overall, both macular and pRNFL parameters were significantly thinner in eyes with ONHD when compared to healthy controls (P < 0.05). The only parameter that did not reach statistical significance was the inferior GCC thickness (P = 0.06). These data are presented in Table 2.

Finally, when it comes to the ability of the SD-OCT’s normative database to detect abnormalities, 42.1% of the patients presented abnormalities in both pRNFL and GCC parameters. In five cases, only the pRNFL thickness protocol had abnormal results, while only one case presented an SD-OCT abnormality.

**Discussion**

Ganglion cell loss and VF damage can occur in eyes with ONHD. In this context, SD-OCT presents as an important tool not only for morphological analysis of optic disc topography in ONHD eyes (specially EDI-OCT, which allows better imaging of deeper structures) but it could be also useful for quantifying the anatomical damage to the peripapillary retina and macula. In this case series, investigating structural damage in eyes with ONHD by SD-OCT, we not only found pRNFL loss in the majority of these cases (68.4%) but also significant macular damage in almost half of these eyes (47.3%), despite relative mild-to-moderate functional damage (mean VFMD of −4.6 dB). These findings suggest macular GCC thickness as an additional parameter for objective structural damage quantification and disease monitoring in cases of ONHD.

Even though several studies have reported on SD-OCT findings in eyes with ONHD, most of them focused on morphological analysis of the ONHD itself or pRNFL quantification. There are scant data when it comes to a segmented macular evaluation in these patients. In this context, Pilat et al. found RNFL and inner plexiform layer thinning in the inner annulus of macular OCT analysis in eyes with ONHD when compared to healthy eyes. Interestingly, the authors documented a thickening of the outer plexiform layer in the

Table 2: Results by color-coded classification of optic nerve head drusen eyes for each sector in ganglion cell-inner plexiform layer and RNFL analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Thickness (µm)*</th>
<th>Green** (%)</th>
<th>Yellow** (%)</th>
<th>Red** (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retinal nerve fiber layer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>87.5 (±21.7)</td>
<td>8 (42.1)</td>
<td>2 (10.5)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Superior RNFL</td>
<td>87.7 (±24.1)</td>
<td>7 (36.8)</td>
<td>1 (5.3)</td>
<td>11 (57.9)</td>
</tr>
<tr>
<td>Inferior RNFL</td>
<td>94.6 (±21.7)</td>
<td>11 (57.9)</td>
<td>1 (5.3)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td><strong>Ganglion cell complex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>85.5 (±12.8)</td>
<td>12 (63.2)</td>
<td>2 (10.5)</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Superior</td>
<td>85.1 (±12.9)</td>
<td>14 (73.7)</td>
<td>0</td>
<td>5 (26.3)</td>
</tr>
<tr>
<td>Inferior</td>
<td>81.7 (±13.1)</td>
<td>12 (63.2)</td>
<td>1 (5.3)</td>
<td>6 (31.5)</td>
</tr>
</tbody>
</table>

*Data are given as mean ± standard deviation. **Data are given in absolute numbers (and percentage values). RNFL: Retinal nerve fiber layer
nasal sector in these eyes, which could not be precisely explained by the authors.\cite{11} In another interesting study, Casado et al.\cite{12} reported that approximately one-quarter of the eyes with buried ONHD had abnormal macular parameters but normal pRNFL thickness values. In fact, a thicker pRNFL was observed in these patients. The authors proposed that a pseudoeudema in these cases could provide false-negative pRNFL results and that macular analysis could provide more accurate information or even that macular damage could precede the pRNFL thinning in some cases.\cite{12} The authors also found that structural damage to the macula (and to the pRNFL) was more significant in eyes with clinically visible ONHD when compared to those with buried drusen and controls. Finally, when considering the ability of the OCTs normative database to detect abnormalities in cases of ONHD, the authors documented a low-to-moderate agreement between pRNFL and ganglion cell-inner plexiform layer analyses.\cite{12} We believe that our results partially corroborate these previously reported data, as we also found significant macular inner retinal layer thinning in many eyes with ONHD using SD-OCT. Nonetheless, our results do not provide evidence to support the idea that the macular GCC protocol could provide a more accurate structural analysis than the conventional pRNFL scan in cases of ONHD, as in the majority of our cases, macular damage was accompanied by concomitant pRNFL thinning. In this scenario, the macular GCC thickness protocol would be better seen as an additional tool rather than a substitute for the conventional pRNFL analysis in these cases.

Regarding the pattern of macular inner retinal layers involvement in eyes with ONHD, we did not find any previous OCT study that classified macular damage in focal or diffuse loss. Our results suggest that, whenever macular thinning is documented in eyes with ONHD, it presents as focal damage in almost 80% of the cases. Notwithstanding, we believe that this finding should be interpreted taking into consideration the mild-to-moderate functional deficit (VF loss) of our study population. Finally, we believe that the main clinical implications of our findings rely on the pattern of structural damage, we have documented in these cases of ONHD. As many eyes had significant macular (focal) damage, we suggest that protocols for structure and functional assessment in these cases should include segmented macular SD-OCT and central VF (10-2) assessment.

It is important to stress some specific characteristics and limitations of our study. First, the results of this case series are based on 19 eyes of 10 patients. This relatively small sample size precluded any further subanalysis of our population (such as comparing eyes with buried ONHD vs. those with superficial drusen). Nonetheless, it should be noted that this is a prospective study that ONHD is not a very common pathology and that there are scant published data regarding the SD-OCT parameters reported herein. Second, even though aging can influence inner retinal layer thickness, patients’ age was not included as a covariate in our analysis. This fact should be considered while interpreting our findings. On the other hand, it should be noted that most study patients were relatively young, with a mean age of <50 years. Third, even though we documented structural damage to both macular and peripapillary regions, we could not investigate, whether one precedes the other as our data were collected cross-sectionally. For that purpose, a longitudinal protocol is warranted. Finally, it should be noted that our findings are not easily generalizable, as they are based on a specific (Brazilian) population. However, we believe our results provide data and knowledge for future studies, possibly including a larger sample and different populations.

Conclusions

Investigating macular inner retinal layers involvement in eyes with ONHD through SD-OCT imaging, we found detectable macular damage by SD-OCT in almost half of the cases. In most of these cases, macular damage had a focal loss pattern and was accompanied by pRNFL thinning. Our findings suggest macular GCC thickness as a useful objective metric for structural evaluation and disease monitoring in cases of ONHD.

References

Modesto, et al. Inner retinal layers thinning by optic disc drusen

Clinical and Experimental Vision and Eye Research

2014;252:1653-60.


How to cite this article: Modesto RAS, Neto ECV, Moura RNP, Scoralick ALB, Ushida M, Gracitelli CPB, Dorairaj S, Kanadani FN, Prata TS, Dias DT. Patterns of macular inner retinal layers involvement in eyes with optic nerve head drusen. Clin Exp Vis Eye Res J 2019;2(2):8-12.