Enhanced Depth Imaging Optical Coherence Tomography of Optic Nerve Head Drusen: a Comparison of Cases with and without Visual Field Loss

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Financial Support: None
The authors have no proprietary or commercial interest in any materials discussed in this article. Dr. Keane reports personal fees from Allergan, personal fees from Bayer, personal fees from Novartis, personal fees from Heidelberg, personal fees from Topcon, personal fees from Haag-Streit, grants from National Institute for Health Research, UK, grants from Fight For Sight, UK, outside the submitted work. The other authors have nothing to disclose.

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Abbreviations

AF	Autofluorescence
EDI	Enhanced Depth Imaging
MD	Mean Deviation
ONHD	Optic Nerve Head Drusen
PSD	Pattern Stardard Deviation
RNFL	Retinal Nerve Fiber Layer
SD-OCT	Spectral-Domain Optical Coherence Tomography
VF	Visual Field

Abstract

Purpose: Enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT) has been recognized as the most sensitive tool to diagnose optic nerve head drusen (ONHD). The relationship between OCT characteristics and visual loss has not been well documented. This study compares EDI SD-OCT determined morphological characteristics of drusen in eyes with or without visual field (VF) defects.

Design: Descriptive study of patients attending the neuro-ophthalmology service of Moorfields Eye Hospital between January 2013 and October 2014.

Subjects: Patients with diagnosed ONHD and EDI SD-OCT imaging of the optic nerve head.

Methods: Eyes with and without VF defects were compared with regard to retinal nerve fiber layer (RNFL) thickness, drusen morphology, size, extent, visibility on funduscopy, ultrasound and fundus autofluorescence.

Main Outcome Measure: Difference in OCT characteristics of ONHD between patients with or without visual field defects

Results: Of 38 patients, 69 eyes with ONHD were included. 33 eyes had a normal VF with average mean deviation (MD) –0.96dB (±1.2), pattern standard deviation (PSD) 1.6dB (±0.3) (group I), and 36 eyes had VF defects with MD -13.7dB (±10.4), PSD 7.2dB (±3.6) (group II). Mean global RNFL thickness was 62µm (±20.9) in the latter group, and 99.0µm (±12.9) in group I. In group I, the predominant drusen type were peripapillary drusen, of variable size. In group II, most eyes had confluent ($p < 0.02$) and large (>500µm; $p < 0.003$) drusen, and drusen were more commonly visible on funduscopy ($p = 0.001$), ultrasound ($p= 0.013$) and autofluorescence ($p =$

66 0.002). Differences between the two groups reached statistical significance in a
67 clustered analysis. RNFL thinning and autofluorescence showed relative sparing of
68 the temporal sector. 64% of patients with a VF defect in one eye also had a VF
69 defect in their fellow eye.
70 **Conclusions:** Drusen size and drusen type as classified by OCT morphological
71 characteristics are significantly different in patients with or without VF defects.
72 Confluent, large and autofluorescent drusen were more commonly found in patients
73 with VF defects. These findings may assist in clarifying how drusen give rise to visual
74 loss which is currently not known.
75
76

Introduction

Drusen of the optic disc were first described by Liebrich in 1868[1, 2]. Although the clinical picture and associated complications of optic nerve head drusen (ONHD) have been well described since the last century[3-5], the pathogenesis of ONHD and the mechanism of resultant visual field loss remain poorly understood. Based on findings on electron microscopy, Tso[6] concluded that drusen are related to axonal degeneration in the optic nerve head. He suggested that intracellular mitochondrial calcification with rupture of axons and subsequent progessive deposition of calcium on the surface of these nidi form calcified microbodies in the extracellular space. ONHD are known to consist of calcium phospate ($Ca_3[PO_4]_2$), mucoproteins, acid mucopolysaccharides, amino and nucleic acids, and occasionally iron[2, 7]. Tso[6] found drusen size to vary between 5 and 1000µm.

Until recently, imaging of ONHD was limited to fundus autofluorescence, computed tomographic (CT) scanning and ultrasound, with ultrasound being most sensitive[8]. Today, spectral domain optical coherence tomography (SD-OCT), particularly with the application of enhanced depth imaging (EDI) algorithms, allows visualization of ONHD of hitherto unknown resolution[9].

Generally, EDI SD-OCT is known to improve image quality of deeper structures of the posterior pole[9-11]. In particular, it allows imaging of the posterior margin of buried ONHD. EDI SD-OCT is now the most sensitive method of detecting ONHD[9]. Using OCT, a number of different morphologic types of ONHD have recently been described.

Johnson et al.[12] identified a druse as a peripapillary „subretinal hyporeflective space“ on Stratus OCT, an older „time-domain“ OCT system. This possibly corresponds to the peripapillary „subretinal mass“ with a reflectance similar to that of the inner and

outer plexiform layers as described by Lee et al.[13]. Other published morphologic features of ONHD are small isolated or clustered hyperreflective bands[9], and hyporeflectant areas with fine hyperreflective borders within the optic nerve[9, 14]. Based on the published literature and on our own EDI SD-OCT findings, we suggest that ONHD can be differentiated into three morphological categories. 1) Peripapillary subretinal hyperreflective drusen, 2) granular hyperreflective drusen, and 3) confluent hyporeflective drusen. These three morphological categories will hence be referred to peripapillary, granular and confluent drusen for ease of reference.

Disc drusen are often associated with visual field loss[5, 15, 16]. Nerve fiber bundle defects, a nasal step, enlargement of the blind spot as well as concentric visual field constriction have all been described. There is usually preservation of central vision. Retinal nerve fiber layer (RNFL) thinning of patients with ONHD is also well described in the more recent literature[17-19]. Peripapillary RNFL thickness changes are believed to be an indicator of anatomic location (superficial versus buried) of ONHD and to be associated with visual field defects. In a large retrospective cross sectional study, Malmqvist et al.[20] reported more RNFL loss as well as higher frequency and extent of VF defects in patients with superficial ONHD. However, to our knowledge, the relationship between OCT-determined morphological characteristics of ONHD and visual field loss has not been investigated, see Silverman et al. for review [21].

This study compares EDI SD-OCT characteristics of ONHD in patients with or without visual field (VF) defects.

Methods

This retrospective descriptive study was approved by the institutional review board of Moorfields Eye Hospital and adhered to the tenets of Declaration of Helsinki. 38

patients attending the neuro-ophthalmology clinics of Moorfields Eye Hospital between 1/2013 and 10/2014 were included. Patients with diagnosed optic disc drusen, with available EDI SD-OCT imaging of the optic nerve head, were included. Diagnosis of ONHD was based on OCT, as this has been shown to be the most sensitive diagnostic tool[9]. However, ultrasound, autofluorescence imaging, or both were obtained in some patients as well. All patients had full ophthalmologic examinations including slit lamp biomicroscopy, applanation tonometry, dilated fundus examination, color disc photography, and automated perimetry (Humphrey field analyzer, strategy SITA-standard, 24-2 threshold). Eyes with other ophthalmic pathologies known to affect the optic nerve head structure or VF were excluded, as well as fellow eyes without evidence of ONHD. Eyes with and without visual field defects were compared with regard to best-corrected visual acuity (Snellen chart), color vision (Ishihara plates), RNFL thickness, ONHD type, ONHD layer, ONHD size, ONHD extent, and visibility on funduscopy, on ultrasound and autofluorescence.

The definition of visual field defects was based on the criteria published by the IIHTT (Idiopathic Intracranial Hypertension Treatment Trial) group[22]. An abnormal visual field test was defined as having a Glaucoma Hemifield Test (GHT) outside normal limits and/or a pattern standard deviation (PSD) $p<5\%$.

Patients included in this study had serial horizontal or vertical volume scans of the optic nerve head with enhanced depth imaging using the Spectralis SD-OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany; Eye Explorer Version 1.9.3.0, Acquisition Software Version 5.7.5.0, Viewing Module Version 6.0.7.0). Mean B-scan distance was 87.9 μm (± 61 μm standard deviation), mean scan quality 23.6 dB (± 5.7), and mean ART (automatic real-time function) 42.7 (± 10.4).

The average peripapillary RNFL thickness was automatically obtained using a 12° (3.5 mm) diameter circle centred on the optic disc. All scans were reviewed. Absence of motion artefacts and good centering on the optic disc was checked. Scans also were evaluated in terms of the adequacy of the algorithm for detecting the RNFL. Scans with gross algorithm failure in detecting the retinal layers were excluded, whereas scans with minor algorithm failures over an angle of less than two clock hours were manually corrected and included in the present study. Mean RNFL scan quality was 27.4 dB (± 4.8 standard deviation), and mean ART (automatic real-time function) 57.1 (± 37.1).

Most patients had autofluorescence images that were obtained on the Heidelberg Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany). The area of autofluorescence was measured using the integrated caliper tool. Instead of comparing absolute area values, the area was analysed in relation to the whole disc area (autofluorescence area / disc area = autofluorescence ratio) to avoid measurement inaccuracies related to possible differences in refraction.

ONHD size was categorized as small (< 300 μm), medium (300 - 500 μm) and large (> 500 μm) as described elsewhere[23].

ONHD extent is a qualitative estimate of the ONHD volume in relation to the total optic nerve head volume. A quantitative ONHD volume measurement was not considered appropriate as this was a retrospective study with some variability in OCT acquisition and quality. An experienced observer categorised the ONHD volume into the following groups: minimal (<10% ONHD volume compared to total optic nerve head volume), small (<50%), moderate (>50%), large (>75%), and extensive (>90%).

Statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX, USA). We used logistic regression with cluster-robust standard error with

176 ‚visual field defect' as dependent variable. The alpha level (type I error) was set at
177 0.05.
178
179 **Results**
180 Sixty-nine eyes of 38 patients (26 women and 12 men) were included in this study.
181 For seven patients, only one eye was included. Four of these patients had no
182 detectable ONHD in the fellow eye, and three had other ophthalmic diseases in their
183 fellow eye (previous retinal detachment, herpetic corneal scar, segmental inferior
184 hypoplasia of the disc). Thus, both eyes were included in 31 patients. Among these,
185 28 patients either had a visual field defect in both eyes or in neither eye; only three
186 patients had a field defect in one eye but not in the other.
187 Of the 69 eyes in 38 patients, 33 had a normal VF (**group I**) with average MD -
188 0.96dB ±1.2, PSD 1.6dB ±0.3, and 36 had VF defects (**group II**) with MD -13.7dB
189 ±10.4, PSD 7.2dB ±3.6 (**Table 1**). VF defects in the latter group were non-specific in
190 6/36 eyes, either a nasal step or nerve fiber bundle defect in 16/36 eyes and a
191 concentric defect in 14/36 eyes. 64% of patients with a VF defect in one eye also had
192 a VF defect in their fellow eye.
193 Best-corrected visual acuity was slightly better in group I at 1.1 ± 0.2 compared with
194 0.9 ± 0.3 (p = 0.003). Differences in color vision did not reach statistical significance
195 (**Table 1**). *Global* RNFL thickness was 99.0µm ±12.9 in group I with none of the
196 individual patients having an abnormal global RNFL thickness compared with the
197 normative database of Heidelberg Spectralis. In patients with VF defects (group II),
198 global RNFL thickness was 62µm ±20.9 (p<0.001) and 25/36 eyes (69%) had an
199 abnormal global RNFL (p=0.004) (**Fig. 1 A and B**). Quantitative RNFL *sector*
200 analysis with measurement of absolute RNFL thicknesses showed thinner RNFL in

all sectors for group II, which reached statistical significance for all sectors (**Fig. 1 A**). Qualitative RNFL sector analysis (**Fig. 1 B**) showed few eyes with abnormal sectors in group I, whereas in group II, a majority of the eyes had atrophic sectors except for the temporal sector. Differences in sector atrophy between group I and II reached statistical significance except for the temporal sector. There seemed to be relative sparing of the temporal sector in both groups.

We identified all three morphologic types of ONHD in our series: peripapillary ONHD (hyperreflective), granular ONHD (hyperreflective) and confluent ONHD (hyporeflective) (**Fig. 2**). One single optic nerve head often showed more than one type of ONHD. In that case, the predominant ONHD type was chosen for statistical analysis. In group I, the predominant drusen type were peripapillary subretinal masses, and drusen were of variable size. In group II, most eyes had large (>500um) and confluent drusen. In line with these findings, ONHD extent was small in a majority of group I patients and extensive in a majority of group II patients (**Table 1**). Differences in ONHD type (p=0.02), size (p=0.003), and extent (p=0.001) reached statistical significance. **Figure 3 A-C** plots mean deviation (MD) on 24-2 Humphrey fields against different ONHD characteristics grouped for eyes without or with VF defects. In eyes with VF defects, confluent drusen clearly show worst MD values and there is a trend for worsening MD with increasing size and extent of the ONHD.

ONHD were visible in 11/33 eyes in group I compared with 30/36 in group II (p=0.001). ONHD were detectable on ultrasound in 15/31 eyes and autofluorescent in 11/31 eyes in group I compared to 30/36 (p=0.013) and 29/34 (p=0.002) in group II, respectively (**Table 1, Fig. 3 D-F**). None of the eyes with only peripapillary ONHD showed autofluorescence. There were three eyes with granular ONHD only, two of those had positive autofluorescence. No eyes had exclusively confluent ONHD.

Figure 4 shows an overlay of autofluorescence (AF)-positive images. AF images of the left eye were laterally inverted in order to allow overlay of right and left optic discs. **Figure 4 A** starts with those five optic discs each right and left with least autofluorescence, stepwise adding another five right and five left AF images with increasing AF areas. **Figure 4 D** finally shows a summation of all available AF-positive images of our cohort. The sequence **A-D** corroborates the fact that there is relative sparing of the temporal sector at least in an ealier stage of ONHD formation.

Discussion

Visual field (VF) defects are generally thought to be caused by impaired axonal transport in an eye with a small scleral canal leading to gradual attrition of optic nerve fibers, by direct compression by ONHD and/or ischemia within the optic nerve head[5, 6, 24]. Patients with ONHD-associated VF defects usually show a very slowly progressive course of the disease. However, sudden VF loss even without disc swelling has been described[25]. In our study population, 64% of patients with a VF defect in one eye also had a VF defect in their fellow eye.

Visual acuity, color vision and the central visual field as well as the temporal RNFL are known to be least affected by ONHD[17, 18] which was also true for our study. Although the centro-caecal projection (papillomacular bundle)[26] is particularly vulnerable in most optic neuropathies, there is relative sparing of the latter with ONHD. The same is true for glaucoma and papilloedema. Not surprisingly, all three conditions also share the same pattern of RNFL loss. **Figure 4 A-D** illustrates that in the case of ONHD this is not only a matter of relative susceptibility of nerve fibers in different sectors of the optic nerve head. Overlay of the autofluorescence pictures demonstrates that ONHD do not tend to form in the temporal sector of the optic nerve

head unless there is extensive involvement. In the context of glaucoma, regional differences of the lamina cribrosa structure are believed to affect the susceptibility of axons to glaucomatous damage. Larger pores and thinner connective tissue were found in the superior and inferior parts of the lamina cribrosa and might offer less structural support for optic nerve axons as compared to the temporal and nasal part.[27, 28] Interestingly, Ogden et al. also found a naso-temporal difference with smaller pores in the temporal part[29]. In a similar way, the axoplasmatic transport which is involved in the pathophysiology of both ONHD and papilloedema might be differently affected by the lamina cribrosa structure. More structural support in the temporal sector might protect the temporal sector from axoplasmatic stasis and might thus protect central vision.

Visual field loss is more often associated with visible ONHD[5, 15, 30, 31]. Sato et al.[32] published a case series of 15 patients showing a negative correlation between drusen diameter and autofluorescence area with RNFL thickness. Our study corroborates this finding. The data presented here not only provide structure-structure correlation but also structure-function correlation in that visible, autofluorescent and ultrasound-positive ONHD were significantly more common in eyes with VF defects. Moreover, ONHD size and type were relevant with regard to VF function meaning that most eyes had large (>500um) and/or confluent drusen in group II which we conclude reflects the severity of the disease.

Sixteen eyes had evidence only of peripapillary ONHD. These eyes were both autofluorescence- and ultrasound-negative. Peripapillary drusen also were the predominant drusen type in patients with normal VF. Thus the question arises whether or not these OCT structures truely are ONHD? On histologic sections similar sturctures have been described as peripapillary retinal scarring by Friedman et al.[33]

(**Fig. 5**). However, the fact that we found confluent drusen within peripapillary drusen in our patients seems to corroborate the assumption that peripapillary drusen are possibly an early or parallel form of ONHD. We hypothesize that the different OCT morphologies of ONHD correspond to the pathogenesis cascade with peripapillary ONHD indicating axonal stasis as an initial step of ONHD formation. Calcified mitochondria released into the extracellular space then become apparent as granular hyperreflective structures on OCT[34] until further deposition of calcium on the surface of these nidi leads to formation large confluent drusen. Of note, a great majority of the eyes had evidence of peripapillary ONHD on OCT (group I 29/33, group II 29/36; **Table 1**), however, in group II this was not the predominant drusen type. It seems counterintuitive that large calcified drusen become *hypo*reflective on OCT. However, Yi et al.[35] were able to correlate hyporeflective drusen on OCT with histology in the same patient who sadly underwent exenteration for a melanoma. Slotnik and Sherman[14] suggested that a lack of change in the index of refraction leads to this hyporeflective appearance.

To conclude, we have identified three morphogical types of ONHD on EDI SD-OCT. 1) Peripapillary subretinal hyperreflective drusen, 2) granular hyperreflective drusen, and 3) confluent hyporeflective drusen. ONHD that are larger and of the confluent hyporeflective type are more commonly found in patients with field defects, whereas field defects are rare in patients with peripapillary subretinal drusen. Thus, other causes must be ruled out if field defects are detected in patients with peripapillary subretinal ONHD only. In patients with field defects, ONHD are also more frequently visible on funduscopy, autofluorescence and ultrasound. 64% of patients with a VF defect in one eye had a VF defect in their fellow eye. Our data show relative temporal sparing of both RNFL and autofluorescence which possibly explains how drusen

301 produce visual field and not acuity loss. For future research, EDI SD-OCT may assist
302 in clarifying how drusen give rise to visual field loss which is currently not known.
303

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392 **Legends**

393 Table 1

394 Clinical and EDI SD-OCT features of eyes without (group I) or with (group II) visual
395 field defects. In group I, both ultrasound and autofluorescence were not available for
396 two eyes each. In group II, autofluorescence was not available for five eyes.
397 n: number of eyes, MD: mean deviation, PSD: pattern standard deviation, BCVA:
398 best corrected visual acuity, Ishihara: color vision, RNFL: global retinal nerve fiber
399 layer thickness, abnormal RNFL: eyes with abnormal global RNFL, ONHD: optic
400 nerve head drusen, +Funduscopy: ratio of eyes with visible ONHD, remaining
401 patients had burried ONHD, +Ultrasound: ratio of eyes with gross ONHD on
402 ultrasound, +Autoflurescence: ratio of eyes with autofluorescent ONHD.
403

404 Figure 1

405 **A**: Comparison of group I and II with regard to RNFL thickness [µm] of the global
406 RNFL and the different RNFL sectors. Both the global RNFL and all RNFL sectors
407 were statistically significantly thinner in group II.
408 **B**: Relative number of eyes in both groups with abnormally thin RNFL sectors
409 compared to the normative database of Heidelberg Spectralis (Heidelberg
410 Engineering GmbH, Heidelberg, Germany). In group I, RNFL sector analysis showed
411 few eyes with atrophy of the nasal, inferonasal, inferotemporal, superotemporal and
412 superonasal sectors, whereas in group II more than half of the eyes had abnormal
413 sectors nasally and more than two third of the eyes had abnormal sectors
414 inferotemporally, superotemporally, superonasally as well as globally. Differences in
415 abnormal sector thickness between group I and II reached statistical significance
416 except for the temporal sector.

417 G: global RNFL; N: nasal, NI: inferonasal, TI: inferotemporal, T: temporal, TS:
418 superotemporal, NS: superonasal sector
419
420 Figure 2
421 Three different types of ONHD were identified on EDI SD-OCT. **A)** peripapillary
422 subretinal hyperreflective drusen (box: scanning laser ophthalmoscopy (SLO) image
423 of the optic disc; the horizontal green line shows the peripapillary location of the OCT
424 B-scan) **B)** granular hyperreflective drusen, **C)** confluent hyporeflective drusen. Often
425 more than one type of ONHD was detected in one eye. **D-F** shows the corresponding
426 histologic sections of the different ONHD types. However, there is a doubt whether
427 section **D** really represents drusen tissue. In the original publication it has been
428 described as peripapillary scarring.
429 **D** and **E** reproduced from Friedman et al.[33] with permission from BMJ Publishing
430 Group Ltd. (Licence has to be obtained once the article is accepted and ready for
431 publication.), and **F** reprinted from Tso[6] with permission from Elsevier.
432
433 Figure 3
434 All graphs (**A-F**) show the 24-2 Humphrey visual field index mean deviation (MD) on
435 the y-axis plotted against different drusen characteristics grouped for eyes without
436 (group I, circle) or with (group II, square) visual field defects. Whiskers indicate the
437 95% confidence interval. **A)** Group II patients with the confluent drusen type had the
438 highest MD indicating the most severely impaired visual fields. Interestingly, group I
439 patients could also have confluent drusen despite having normal visual fields. This is
440 likely explained by differences in drusen size between group I and II. Peripapillary
441 and granular drusen had a similar MD in group II. **B)** After Lee et al.[23], drusen size

was categorized as small (< 300µm), medium (300-500µm), large (> 500µm) based on the maximum drusen diameter on OCT. Large ONHD are associated with worse MD in group II. **C)** Drusen extent is an approximation of drusen volume. An experienced ophthalmologist rated the ratio [drusen volume / optic nerve head volume] as minimal [<10%], small [<50%], moderate [>50%], large [>75%], extensive [>90%] based on the EDI optic nerve head volume scan. In group II patients, MD gets progressively worse as a function of increasing drusen volume. **D-F)** In group II, visible drusen **(D)**, ultrasound positive drusen **(E)**, and autofluorescent drusen **(F)** are associated with worse MD.

Figure 4

Overlay of autofluorecence (AF)-positive images. AF-positive images of the right and left eye respectively were put into an order of increasing AF area and then overlayed in groups of five. AF images of the left eye were laterally inverted in order to allow overlay of right and left optic discs. **Figure 4 A** starts with those five optic discs each right and left with least autofluorescence. In **figure 4 B** another five right and five left AF images were superimposed, which was repeated in **figure 4 C** with further AF images of increasing AF area. **Figure 4 D** finally shows a summation of all available AF-positive images of our cohort. The sequence **A-D** corroborates the fact that there is relative sparing of the temporal sector at least in an ealier stage of ONHD formation.

Figure 5

EDI SD-OCT image with evidence of confluent ONHD (arrow head) within a peripapillary subretinal ONHD (arrow).