Young Adults with Anterior Ischemic Optic Neuropathy: A Multicenter Optic Disc Drusen Study

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ABSTRACT

PURPOSE: Optic disc drusen (ODD), present in 2% of the general population, have occasionally been reported in patients with non-arteritic anterior ischemic optic neuropathy (NA-AION). The purpose of this study was to examine the prevalence of ODD in young patients with NA-AION.

DESIGN: Retrospective, cross-sectional multicenter study.

METHODS: All patients with NA-AION age 50 years or less, seen in neuro-ophthalmology clinics of the international ODDS (Optic Disc Drusen Studies) Consortium between April 1, 2017, and March 31, 2019, were identified. Patients were included if ODD were diagnosed by any method, or if ODD were excluded by enhanced-depth imaging optical coherence tomography (EDI-OCT) using the ODDS Consortium guidelines. NA-AION eyes with ODD were termed “ODD-AION”; those without were termed “NODD-AION”.

RESULTS: Sixty-five patients (127 eyes) with NA-AION were included (mean age 41 years). Of the 74 eyes with NA-AION, 51% had ODD (ODD-AION), while 43% of (fellow) eyes without NA-AION had ODD (P=0.36). No significant difference was found between ODD-AION and NODD-AION eyes in terms of Snellen BCVA or perimetric mean deviation. On EDI-OCT, 28% of eyes with NODD-AION had peripapillary hyperreflective ovoid mass-like structures (PHOMS) and 7% had hyperreflective lines while 54% with ODD-AION had PHOMS and 66% had hyperreflective lines (P=0.006 and P<0.001, respectively).

CONCLUSIONS: The majority of our young NA-AION patients had ODD. This indicates that ODD may be an independent risk factor for the development of NA-AION, at least in younger patients. We suggest ODD-AION be recognized as a novel diagnosis.

Young Adults with Anterior Ischemic Optic Neuropathy: A Multicenter Optic Disc Drusen Study

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INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NA-AION) is the most common acute-onset optic nerve disease in patients over the age of 50 years.[1] In this age group, the estimated annual incidence ranges between 2.3 and 10.2 cases per 100,000 persons.[2-6] In the vast majority of cases, NA-AION occurs in a small, crowded optic nerve head (ONH) with a small physiological cup in the context of a local axonal compartment syndrome associated with disc edema.[7-9] The most common vascular risk factors for NA-AION are hypertension, diabetes, hypercholesterolemia, and obstructive sleep apnea.[1] Occasionally NA-AION also occurs in patients younger than 50 years, and approximately 25% of these cases have no vascular risk factors.[5] In young NA-AION patients, the association with optic disc crowding is more prominent and these patients are also more at risk for fellow eye involvement than older NA-AION patients.[7]

Optic disc drusen (ODD) are calcified deposits localized between the axons of the prelaminar ONH.[10] ODD are visible ophthalmoscopically in only 0.2-0.3% of the population,[11, 12] but histopathology studies have demonstrated that they are commonly buried in the ONH tissue giving an overall ODD prevalence of 1.8 to 2.0% in the general population.[12-14] ODD are bilateral in the vast majority of cases.[15] They are almost exclusively seen in crowded optic discs with a significantly smaller cup-to-disc ratio than healthy controls.[16, 17] Although ODD classically are considered as incidental findings, visual field defects have been found in up to 87% of affected eyes[12, 18] and sudden, painless visual and visual field loss have been described, usually manifesting as NA-AION.[12, 19-22]

Clinical *in vivo* ODD prevalence studies have until recently been limited by the low ODD detection rate using ophthalmoscopy,[11, 12] and the relatively low ODD detection rate using ultrasound (US), fundus autofluorescence (FAF), or computed tomography (CT) of the orbits.[23-27] In recent years, however, enhanced depth imaging optical coherence tomography (EDI-OCT) of the ONH has emerged as the most sensitive and precise tool to diagnose ODD[28-32] with an ODD detection rate on par with published histopathological prevalence. Consistent with earlier histological studies[33] EDI-OCT has illustrated that vessels are channeled through ODD.[34]

The purpose of this multicenter study was to examine the prevalence of ODD in young NA-AION patients from a large cohort of patients from different countries, and to investigate in depth whether demographic and functional parameters such as visual acuity and visual field defects differed between NA-AION patients with ODD (termed ODD-AION) and NA-AION patients without ODD (termed NODD-AION).

METHODS

Study participants:

This retrospective, cross-sectional, multicenter study included patients from 11 neuro-ophthalmology centers in 8 countries and 4 continents. The centers are all part of the Optic Disc Drusen Studies Consortium. The study adhered to the tenets of the Declaration of Helsinki and Health Insurance Portability and Accountability Act as well as all federal and state laws in each participating center. In some centers, IRB approval of the study was required and obtained, while in other centers, the IRB waived the need for approval of the study. Collection and handling of data took place in Denmark and was approved by the Danish Data Protection Agency.

We performed a retrospective chart review of all patients seen at the 15 participating centers between April 1, 2017, and March 31, 2019 with a diagnosis of "ischemic optic neuropathy" based on International Classification of Diseases (ICD) code 10: H47.01. Although the data collection was retrospective, all participating centers systematically evaluate NA-AION patients similarly with the same neuro-ophthalmic workup including fundus photographs, EDI-OCT of the ONH to look for ODD, and standard automated perimetry.

Patients were included in the study if they were 50 years or younger at time of presentation and were diagnosed with acute NA-AION in at least one eye. Further, exam findings on presentation needed to include monocular acute visual acuity and/or visual field loss and ipsilateral optic disc edema, and satisfy at least one of the following two criteria: (i) a diagnosis of ODD established by any means; or (ii) ODD excluded by EDI-OCT of the optic nerve head obtained as per the ODDS Consortium acquisition protocol.[30] Criterion (i) ensured that any accepted imaging modality for ODD would suffice to diagnose ODD, criterion (ii) ensured that only the most sensitive imaging modality for ODD, with 97 raster scans through the optic disc, could be used to safely rule out ODD.[24, 28, 30] Patients in whom the diagnosis of NA-AION was uncertain or associated with vasculitis were excluded, as were patients with optic nerve or retinal disease unrelated to NA-AION (other than ODD).

Diagnosis of ODD using EDI-OCT of the optic nerve head:

On EDI-OCT, ODD appear as rounded, hyporeflective structures, often surrounded by a hyperreflective margin, localized in the prelaminar region. Prelaminar hyperreflective lines are often seen in association with ODD and may represent ODD precursors.[35] Peripapillary hyperreflective ovoid mass-like structures (PHOMS), oftentimes associated with ODD, is a non-specific sign presumably due to herniating retinal nerve fibers. PHOMS can also be associated with any type of disc edema or disc anomalies without ODD.[30] Fig. 1 demonstrates the diagnosis of ODD on EDI-OCT.

In any cases of uncertainty about the OCT diagnosis, the Denmark group (SH) provided a second reading of the scans.

Data collection:

The following data were collected for each patient: age at onset of NA-AION, sex, eye(s) affected by NA-AION, presence/absence of ODD in each eye on: ophthalmoscopy, EDI-OCT, US, FAF, or CT orbits, presence/absence of PHOMS and prelaminar hyperreflective lines at EDI-OCT using ODDS Consortium guidelines, time from NA-AION diagnosis to EDI-OCT (if performed), BCVA at diagnosis, type of visual field defect at diagnosis (see below), perimetric mean deviation (MD) at diagnosis, known systemic or ocular disease at time of diagnosis, medications at time of diagnosis, tobacco use, alcohol consumption, presence/absence of obstructive sleep apnea, presence/absence of obesity (BMI of 30 or more).

The patterns of visual field defects were classified as follows: central, concentric, altitudinal (upper or lower), nerve fiber layer, diffuse, enlarged blind spot or none. If more than one type of visual field defect for a specific eye was reported, the worse type was chosen using the following order of severity: Central > concentric > upper/lower altitudinal > nerve fiber layer > diffuse > enlarged blind spot > none.

Statistical analysis:

Statistical analyses were performed using SAS statistical software (SAS 9.4; SAS Institute, Cary, NC, USA).

All included eyes were assigned to one of four groups: 1) eyes with ODD and NA-AION (ODD-AION); 2) eyes with NA-AION and no ODD (NODD-AION); 3) eyes with ODD but no previous NA-AION; and 4) eyes with no ODD, previous NA-AION or any other known eye disease (healthy eyes).

Because of the non-Gaussian distribution, the median and interquartile ranges were calculated. The non-parametric Wilcoxon signed-rank test was used to test for difference between the groups in continuous variables.

Normality of the distribution was assessed by review of relevant plots. The level of statistical significance for comparisons was set at $P<0.05$.

RESULTS

A total of 152 patients aged 50 years or less were identified with an *ICD-10* code of 'ischemic optic neuropathy' in the study period (Supplementary Table). Of these, 65 patients met study criteria (median age 41 years, range 15-50 years). Data from both eyes was available in 62 of these patients, while in three cases there was only data from one eye. Therefore, a total of 127 eyes were included, of which 74 eyes were diagnosed with NA-AION (Fig. 2). In total, 38 eyes had ODD-AION and 23 eyes had ODD without NA-AION.

Vascular risk factors:

54% of NODD-AION patients had one or more vascular risk factors compared to 35% in the ODD-AION patients. No significant differences were found in systemic vascular risk factors (diabetes, hypercholesterolemia, hypertension, and obesity) individually or grouped together when comparing ODD-NAION and NODD-AION patients (P=0.16).

Visibility of ODD:

In 46% of ODD eyes and 56% of ODD-AION eyes the ODD were visible on ophthalmoscopy. No significant difference in visibility of ODD was found between eyes with ODD and ODD-AION (P=0.46).

Prevalence of ODD:

Seventy-four eyes were diagnosed with NA-AION; of these 51% had ODD (ODD-AION) diagnosed by ophthalmoscopy or by one or more imaging modalities. Of the 53 fellow eyes, which did not have NA-AION, 43% had ODD (P=0.36).

Thirty-four patients had ODD-AION in at least one eye. Three of these had no data from the fellow eye. Out of the 31 ODD-AION patients with data from both eyes, 4 (12.9%) had bilateral ODD-AION, 2 (6.5%) had NODD-AION in the fellow eye, 20 (64.5%) had ODD (55% visible) without NA-AION in the fellow eye, and 5 (16.1%) had healthy fellow eyes. There were no statistically significant differences in sex or in the mean age of NA-AION onset between the patients with NODD-AION and the patients with ODD-AION (Table 1).

Out of all 62 patients with data from both eyes, ODD (with or without NA-AION) were present in 34 patients. Of these, 24 patients (71%) had bilateral ODD and 10 (29%) had unilateral ODD.

OCT findings:

On EDI-OCT, hyperreflective lines were found in 66%, 7%, 76%, and 4% in respectively the ODD-AION, NODD-AION, ODD, and healthy eyes (Table 1). A significant difference in occurrence of hyperreflective lines was found between the four groups (P<0.001). Post-hoc analysis revealed that this significant difference was seen between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes). No

significant difference was found between healthy eyes and eyes with NODD-AION and between ODD and ODD-AION eyes.

On EDI-OCT, PHOMS were found in 54%, 28%, 63%, and 19% respectively in the ODD-AION, NODD-AION, ODD, and healthy eyes. A significant difference in occurrence of PHOMS was found between the four groups (P<0.001). Post-hoc analysis revealed that this significant difference was seen between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes). No significant difference was found between healthy eyes and eyes with NODD-AION and between ODD and ODD-AION eyes.

Out of the 127 study eyes, EDI-OCT was performed on 105. Seventy-one (67.6%) of these had their OCT performed within eight weeks, which can be considered as the overall median time for optic disc edema resolution from the onset of visual loss.[36]

Correlation with visual acuity and visual field:

Median Snellen BCVAs were 0.8, 0.5, 1.0, and 1.0 for respectively ODD-AION, NODD-AION, ODD, and healthy eyes (Table 1). A significant difference in Snellen BCVA was found between ODD-AION, NODD-AION, ODD, and healthy eyes (P<0.001). Post-hoc analysis revealed that this significant difference was seen between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes). No significant difference was found between eyes with ODD-AION and NODD-AION.

Median MD, in dB, was -7.8, -13.0, -3.2, and -2.0 respectively for ODD-AION, NODD-AION, ODD, and healthy eyes. A significant difference in MD was found between ODD-AION, NODD-AION, ODD, and healthy eyes (P<0.001). Post-hoc analysis revealed that this significant difference was seen between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes). No significant difference was found between eyes with ODD-AION and NODD-AION, although a tendency towards more severe visual field defects in the NODD-AION group was seen.

Of the types of visual field defects noted (central, concentric, altitudinal (upper or lower), nerve fiber layer, diffuse, enlarged blind spot or none), 123/127 study eyes had one of the above types of field defect. 8/123 eyes had more than one type of field defect. In the presence of more than one type of field defect, the most severe type was chosen, as outlined in Methods. There was an overall difference between the four study groups in type of visual field defects (P<0.001), with post-hoc testing revealing significant difference in lower altitudinal defects between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes) (Fig. 3).

DISCUSSION

This is the first large scale study to systematically review a series of young (<50 years) patients with NA-AION specifically for ODD. We found that ODD was more prevalent in this group than would be expected for the population, 51% versus 2%. This discrepancy cannot be accounted for by differences in vascular risk factors and suggests that ODD may be a new risk factor for NA-AION, at least in young patients.

The pathophysiology of NA-AION involves crowding of the axons and microvasculature within an optic disc. While previously a narrow Bruch's membrane opening (BMO) was hypothesized to contribute to disc crowding, EDI-OCT studies have determined that the BMO "area" in NA-AION and control subjects is not significantly different.[37-39] It seems that thick prelaminar tissue resulting from thick peripapillary choroid contributes to the appearance of a "crowded" disc in NA-AION. On the other hand, the presence of ODD has been shown to be more common in patients with a smaller BMO,[38] and ODD might thicken prelaminar tissue. Hence the question remains as to whether the ODD are contributing to the ischemia and compartment syndrome or are coincidental due to shared risk factors.

Following the earlier publications on NA-AION, the diagnosis of ODD has become more reliable with OCT, in particular EDI-OCT. In our cohort, only about half of ODD were found on ophthalmoscopy (56% of those with NA-AION and 46% of those who were otherwise healthy). This implies that the rates of ODD may have been significantly underestimated in earlier studies.

The other OCT findings in this study reflected expected patterns, with hyperreflective lines being more common in eyes with ODD. This is in keeping with the hypothesis that hyperreflective lines are a precursor, or early OCT indicator of ODD.[40] PHOMS were also more common in patients with ODD. However, 26% of patients without ODD, but with disc edema from NODD-AION had PHOMS. These structures are thought to represent herniated retinal nerve fibre layers from elevated discs of any cause.[41] Therefore, the increased rate of PHOMS in NODD-AION is not unexpected.

Diagnosing ODD in the setting of disc edema from another cause can be difficult using an ophthalmoscope or autofluorescence, as the edema masks the typical features. EDI-OCT however, is still able to show the classic hyporeflective cores of ODD within a swollen nerve (see Fig. 1 as an example). If edema masked ODD in our patients, then some cases of ODD may have been missed and we may have underestimated the true prevalence of ODD in young NA-AION patients. There are no reports of large ODD caused by disc swelling in NA-AION, therefore a delay in EDI-OCT from time of onset would not have affected our results.

This study did not find any difference in the visual acuity or visual field MD between NA-AION associated with ODD or not. The insult to the optic nerve and its vasculature, whether from crowding due to ODD or other causes, therefore appears to have the same damaging effect on the axons. The pattern of the visual field changes appears evenly spread between the two groups, with the most common defect being a lower altitudinal field loss. This is in keeping with past studies, which found that a lower

altitudinal field defect was most common (34.9%), but a variety of defects can be present.[42]

In this study we found that 46% of NODD-AION patients versus 65% of ODD-AION patients had no vascular risk factors. Although this difference was not statistically significant, the absence of vascular risk factors in a patient with NA-AION should prompt a careful evaluation for buried ODD as well as systemic diseases like vasculitis and hypercoagulability. Historically, NA-AION in the young has been linked with diabetes, hyperlipidaemia, chronic renal failure and hypercoagulable states among others. In a 2013 study comparing old and young NA-AION patients, chronic renal failure and migraine were found to be more prevalent in the young, but other risk factors were similar between the two groups.[7] In patients with unilateral NA-AION, age <50 years reportedly increases the risk of second eye involvement, 42.6% versus 29.6% (p=0.047) at 6 months.[7] Only diabetes was found to be linked with second eye involvement in the young. Interestingly this study included fundus fluorescein angiography, but no mention was made of the presence of ODD, and via personal communication we know that ODD patients were excluded.

One study of NA-AION with ODD included 16 patients with bilateral ODD and showed that 25% had bilateral sequential involvement.[19] A recent paper reported that there was no increased risk to fellow eye NA-AION by age or sex, but they reported that ODD was a significant risk factor for second eye involvement after NA-AION, (HR 2.78, p=0.02).[43] However, in patients under the age of 50 years, the presence of bilateral ODD was the only significant risk factor for fellow eye involvement, increasing the risk by over 8 times (HR=8.31, range 1.52-45.3, p=0.01). For patients over 50 years, the presence of ODD was not a significant risk (HR 1.5, p=0.61), suggesting that while the presence of bilateral ODD was an overall risk for second eye involvement, this risk was overwhelmingly seen in those under the age of 50. This result is in keeping with the very high rates of ODD found in this study. Further studies are needed to see if NA-AION patients with contralateral ODD have higher rates of second eye involvement than those without.

A limitation of this study is the retrospective nature, which introduces the risk of bias – only those with clinical suspicion of ODD being examined properly, or young patients without visible ODD being excluded because the full EDI-OCT protocol had not been done. However, the study was conducted by centers that are all part of a consortium of optic disc drusen research specialists, who systematically evaluate all NA-AION patients similarly at time of initial evaluation. Therefore, although collected retrospectively, the data are not convenience samples but systematically collected and directly comparable data.

Eighty-seven young NA-AION patients seen in the study period were not included, primarily because an EDI-OCT using ODDS Consortium protocol was not performed or it was performed, but with too few raster scans. Even if none of these 87 excluded patients would have had ODD, an ODD prevalence of 25% among young NA-AION patients would have been calculated, which in itself is 12.5 times higher than the 2% prevalence in the general population.

This study identified a significantly higher than expected prevalence of ODD in young NA-AION eyes compared to the general population. Many cases of ODD were not detectable on ophthalmoscopy and required diagnosis via EDI-OCT confirming the superiority of EDI-OCT as the diagnostic test of choice for detecting and characterizing ODD. The presence of ODD has been shown to be a risk factor for bilateral NA-AION, particularly in patients less than 50 years. We propose that ODD-AION is recognized as an entity separate from NODD-AION, and that ODD should be expressly looked for in all cases of young NA-AION.

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REFERENCES

1. Biousse V, Newman NJ. Ischemic Optic Neuropathies. N Engl J Med 2015;372:2428-36.
2. Arnold AC. Pathogenesis of nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol 2003;23:157-63.
3. Hayreh SS. Ischemic optic neuropathies - where are we now? Graefes Arch Clin Exp Ophthalmol 2013;251:1873-84.
4. Characteristics of patients with nonarteritic anterior ischemic optic neuropathy eligible for the Ischemic Optic Neuropathy Decompression Trial. Arch Ophthalmol 1996;114:1366-74.
5. Preechawat P, Bruce BB, Newman NJ, Biousse V. Anterior ischemic optic neuropathy in patients younger than 50 years. Am J Ophthalmol 2007;144:953-60.
6. Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol 1997;123:103-7.
7. Arnold AC, Costa RM, Dumitrascu OM. The spectrum of optic disc ischemia in patients younger than 50 years (an Amercian Ophthalmological Society thesis). Trans Am Ophthalmol Soc 2013;111:93-118.
8. Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. Eye (Lond) 2015;29:65-79.
9. Knox DL, Kerrison JB, Green WR. Histopathologic studies of ischemic optic neuropathy. Trans Am Ophthalmol Soc 2000;98:203-20; discussion 221-2.
10. Hamann S, Malmqvist L, Costello F. Optic disc drusen: understanding an old problem from a new perspective. Acta Ophthalmol 2018. [Epub ahead of print].
11. You QS, Xu L, Wang YX, Jonas JB. Prevalence of optic disc drusen in an adult Chinese population: the Beijing Eye Study. Acta Ophthalmol 2009;87:227-8.
12. Lorentzen SE. Drusen of the optic disk. A clinical and genetic study. Acta Ophthalmol (Copenh) 1966:Suppl 90:1-180.
13. Friedman AH, Gartner S, Modi SS. Drusen of the optic disc. A retrospective study in cadaver eyes. Br J Ophthalmol 1975;59:413-21.
14. Skougaard M, Heegaard S, Malmqvist L, Hamann S. Prevalence and histopathological signatures of optic disc drusen based on microscopy of 1713 enucleated eyes. Acta Ophthalmol 2019.
15. Auw-Haedrich C, Staubach F, Witschel H. Optic disk drusen. Surv Ophthalmol 2002;47:515-32.
16. Wilkins JM, Pomeranz HD. Visual manifestations of visible and buried optic disc drusen. J Neuroophthalmol 2004;24:125-9.
17. Vahlgren J, Malmqvist L, Ruelokke LL, Karlesand I, Lindberg AW, Hamann S. The Angioarchitecture of the Optic Nerve Head in Patients with Optic Disc Drusen. Neuroophthalmology 2020;44:5-10.
18. Borruat FX, Sanders MD. [Vascular anomalies and complications of optic nerve drusen]. Klin Monbl Augenheilkd 1996;208:294-6.

19. Purvin V, King R, Kawasaki A, Yee R. Anterior ischemic optic neuropathy in eyes with optic disc drusen. Arch Ophthalmol 2004;122:48-53.
20. Nanji AA, Klein KS, Pelak VS, Repka MX. Nonarteritic anterior ischemic optic neuropathy in a child with optic disk drusen. J AAPOS 2012;16:207-9.
21. Newman WD, Dorrell ED. Anterior ischemic optic neuropathy associated with disc drusen. J Neuroophthalmol 1996;16:7-8.
22. Liew SC, Mitchell P. Anterior ischaemic optic neuropathy in a patient with optic disc drusen. Aust N Z J Ophthalmol 1999;27:157-60.
23. Pineles SL, Arnold AC. Fluorescein angiographic identification of optic disc drusen with and without optic disc edema. J Neuroophthalmol 2012;32:17-22.
24. Loft FC, Malmqvist L, Wessel Lindberg AS, Hamann S. The Influence of Volume and Anatomic Location of Optic Disc Drusen on the Sensitivity of Autofluorescence. J Neuroophthalmol 2018.
25. Kurz-Levin MM, Landau K. A comparison of imaging techniques for diagnosing drusen of the optic nerve head. Arch Ophthalmol 1999;117:1045-9.
26. Almog Y, Nemet A, Nemet AY. Optic disc drusen demonstrate a hyperechogenic artifact in B mode ultrasound. J Clin Neurosci 2016;23:111-119.
27. Lam BL, Morais CG, Jr., Pasol J. Drusen of the optic disc. Curr Neurol Neurosci Rep 2008;8:404-8.
28. Merchant KY, Su D, Park SC, et al. Enhanced depth imaging optical coherence tomography of optic nerve head drusen. Ophthalmology 2013;120:1409-14.
29. Sim PY, Soomro H, Karampelas M, Barampouti F. Enhanced Depth Imaging Optical Coherence Tomography of Optic Nerve Head Drusen in Children. J Neuroophthalmol 2019.
30. Malmqvist L, Bursztyn L, Costello F, et al. The Optic Disc Drusen Studies Consortium Recommendations for Diagnosis of Optic Disc Drusen Using Optical Coherence Tomography. J Neuroophthalmol 2018;38:299-307.
31. Costello F, Malmqvist L, Hamann S. The Role of Optical Coherence Tomography in Differentiating Optic Disc Drusen from Optic Disc Edema. Asia Pac J Ophthalmol (Phila) 2018;7:271-279.
32. Sato T, Mrejen S, Spaide RF. Multimodal imaging of optic disc drusen. Am J Ophthalmol 2013;156:275-282 e1.
33. Tso MO. Pathology and pathogenesis of drusen of the optic nervehead. Ophthalmology 1981;88:1066-80.
34. Maloca PM, Tufail A, Egan C, et al. Volume rendering of superficial optic disc drusen. Spektrum der Augenheilkunde 2017;31:288-293.
35. Malmqvist L, Li XQ, Hansen MH, et al. Progression Over 5 Years of Prelaminar Hyperreflective Lines to Optic Disc Drusen in the Copenhagen Child Cohort 2000 Eye Study. J Neuroophthalmol 2020.
36. Hayreh SS, Zimmerman MB. Optic disc edema in non-arteritic anterior ischemic optic neuropathy. Graefes Arch Clin Exp Ophthalmol 2007;245:1107-21.
37. Fard MA, Abdi P, Kasaei A, Soltani Mogaddam R, Afzali M, Moghimi S. Peripapillary choroidal thickness in nonarteritic anterior ischemic optic neuropathy. Invest Ophthalmol Vis Sci 2015.

38. Moghimi S, Afzali M, Akbari M, et al. Crowded optic nerve head evaluation with optical coherence tomography in anterior ischemic optic neuropathy. Eye (Lond) 2017;31:1191-1198.
39. Nagia L, Huisingh C, Johnstone J, et al. Peripapillary Pachychoroid in Nonarteritic Anterior Ischemic Optic Neuropathy. Invest Ophthalmol Vis Sci 2016;57:4679-85.
40. Malmqvist L, Li XQ, Hansen MH, et al. Progression over five years of prelaminar hyperreflective lines to optic disc drusen in the Copenhagen Child Cohort 2000 Eye Study. Journal of Neuro-Ophthalmology 2020 (in press).
41. Malmqvist L, Sibony PA, Fraser CL, et al. Peripapillary Ovoid Hyperreflectivity in Optic Disc Edema and Pseudopapilledema. Ophthalmology 2018;125:1662-1664.
42. Hayreh SS, Zimmerman B. Visual field abnormalities in nonarteritic anterior ischemic optic neuropathy: their pattern and prevalence at initial examination. Arch Ophthalmol 2005;123:1554-62.
43. Chang MY, Keltner JL. Risk Factors for Fellow Eye Involvement in Nonarteritic Anterior Ischemic Optic Neuropathy. J Neuroophthalmol 2019;39:147-152.

FIGURE LEGENDS

Figure 1. Diagnosis of ODD and ODD-AION.

(Left) Fundus photograph of the right optic nerve head of a 44-year-old man with a few days history of sudden visual loss due to NA-AION. The yellow line on the fundus photograph indicates the EDI-OCT scan position. Diffuse optic disc edema is seen, but no ODD are visible on the surface.

(Right) On EDI-OCT performed the same day, it is possible to visualize ODD (blue arrow), PHOMS (red arrow) and prelaminar, hyperreflective lines (white arrows).

Abbreviations: ODD = optic disc drusen; NA-AION = non-arteritic anterior ischemic optic neuropathy; EDI-OCT = Enhanced Depth Imaging Optical Coherence Tomography; PHOMS = peripapillary hyperreflective ovoid mass-like structure.

Figure 2. Flowchart demonstrating categorization of the 127 eyes included in the study.

Abbreviations: NA-AION = non-arteritic anterior ischemic optic neuropathy; w/o = without; ODD = optic disc drusen; ODD-AION = NA-AION associated with ODD; NODD-AION = NA-AION not associated with ODD.

Figure 3. Percentage of eyes with different types of visual field defects in NODD-AION and ODD-AION.

Abbreviations: ODD = optic disc drusen; NA-AION = non-arteritic anterior ischemic optic neuropathy; NODD-AION = NA-AION not associated with ODD; ODD-AION = NA-AION associated with ODD; EBS = enlarged blind spot; NFL = nerve fiber layer.

	Healthy	ODD	NODD-AION	ODD-AION	P-value
Number of eyes (%)	30 (24)	23 (18)	36 (28)	38 (30)	
Male/female (%)	80/20	61/39	76/24	70/30	0.44
Age (IQR), yrs	45 (10)	43 (10)	45 (7)	41 (18)	0.23
BCVA (IQR), Snellen	1.0 (0)	1.0 (0.2)	0.5 (0.8)	0.8 (0.6)	<0.001*
Perimetric MD (IQR), dB	-2 (3.5)	-3.2 (4.9)	-13.0 (9.6)	-7.8 (7.5)	<0.001*
PHOMS (no, percent)	5 (19%)	10 (63%)	8 (28%)	15 (54%)	0.006†
Hyperreflective lines (no, percent)	1 (3.6%)	13 (76%)	2 (6.7%)	19 (66%)	<0.001†
Tobacco use (no, percent)	7 (30%)	5 (28%)	9 (26%)	5 (18%)	0.75
Obstructive sleep apnea	4 (27%)	4 (40%)	8 (31%)	4 (25%)	0.86
Obesity	6 (30%)	2 (14%)	7 (23%)	6 (26%)	0.75

IQR=Interquartile range; BCVA=best corrected visual acuity; MD=mean deviation; PHOMS=Peripapillary hyperreflective ovoid mass-like structure. Continuous variables are presented as median and interquartile range. * *Post hoc analysis with significant difference between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes)*
† *Post hoc analysis with significant difference between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes).*

Table 1. Characteristics of healthy study participants, patients with optic disc drusen (ODD), patients with NODD-AION (non-arteritic anterior ischemic optic neuropathy not associated with ODD), and patients with ODD-AION (non-arteritic anterior ischemic optic neuropathy associated with ODD).