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

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• PURPOSE: Optic disc drusen (ODD), present in 2% of the general population, have occasionally been reported in patients with nonarteritic 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 50 years old or younger, 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 ODDS Consortium guidelines. NA-AION eyes with ODD were termed "ODD-AION"; those without were termed "NODD-AION".

• RESULTS: A total of 65 patients (127 eyes) with NA-AION were included (mean 41 years old). Of the 74 eyes with NA-AION, 51% had ODD-AION, whereas 43% of fellow eyes without NA-AION had ODD ($P = .36$). No significant differences were found between ODD-AION and NODD-AION eyes in terms of Snellen best-corrected VA or perimetric mean deviation. According to EDI-OCT results, 28% of eyes with NODD-AION had peripapillary hyperreflective ovoid mass-like structures (PHOMS); 7% had hyperreflective lines, whereas 54% with ODD-AION had PHOMS; and 66% had hyperreflective lines ($P = .006$ and $P < .001$, respectively).

• CONCLUSIONS: Most of these 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. This study suggests ODD-AION be recognized as a novel diagnosis. (Am J Ophthalmol 2020;217:174–181. © 2020 Elsevier Inc. All rights reserved.)

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NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUropathy (NA-AION) is the most common acute-onset optic nerve disease in patients over the age of 50.[1] In this age group, the estimated annual incidence ranges between 2.3 and 10.2 cases per 100,000 persons.[2–6] In most 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 old, 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

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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 1.8-2.0% in the general population.[12–14] ODD are bilateral in most cases.[15] They are almost exclusively seen in crowded optic discs with a significantly smaller cup-to-disc ratio than that in healthy controls.[16,17] Although ODD classically are considered incidental findings, visual field defects have been found in up to 87% of affected eyes[12,18] and sudden, painless visual and visual field losses 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 rate of detecting ODD using ophthalmoscopy,[11,12] and the relatively low rate of detecting ODD using ultrasonography, fundus autofluorescence, or computed tomography of the orbits.[23–27] Recently, 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 (VA) and visual field defects in NA-AION patients with ODD (termed ODD-AION) differed from those in NA-AION patients without ODD (termed NODD-AION).

SUBJECTS AND 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, Health Insurance Portability and Accountability Act, and all federal and state laws in each participating center. In some centers, institutional review board approval of the study was required and obtained, whereas in other centers, the institutional review board 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.

A retrospective chart review of all patients seen was performed at the 11 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 evaluated 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 old or younger at the time of presentation and had acute NA-AION diagnosed in at least 1 eye. Furthermore, examination findings on presentation needed to include monocular acute VA, visual field loss, and ipsilateral optic disc edema and satisfy at least 1 of the following 2 criteria, either a diagnosis of ODD established by any means; or ODD excluded by EDI-OCT of the ONH obtained according to Optic Disc Drusen Studies (ODDS) Consortium acquisition protocol.[30] The first criterion ensured that any accepted imaging modality for ODD would suffice to diagnose ODD; and the second criterion 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 was 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), often associated with ODD, are nonspecific signs, presumably due to herniating retinal nerve fibers. PHOMS can also be associated with any type of disc edema or disc anomalies without ODD.[30] Figure 1 demonstrates the diagnosis of ODD on EDI-OCT.

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

• **DATA COLLECTION:** The following data were collected from each patient: age at onset of NA-AION, sex, eye(s) affected by NA-AION, presence or absence of ODD in each eye on ophthalmoscopy, EDI-OCT, ultrasonography, fundus autofluorescence, or computed tomography of the orbits; presence or absence of PHOMS and prelaminar hyperreflective lines in EDI-OCT imaging using ODDS Consortium guidelines; time from NA-AION diagnosis to EDI-OCT (if performed); best-corrected VA (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, and alcohol consumption; presence of absence of obstructive sleep apnea, and presence or absence of obesity (body mass index of ≥30).

Patterns of visual field defects were classified as central, concentric, altitudinal (upper or lower), nerve fiber layer,

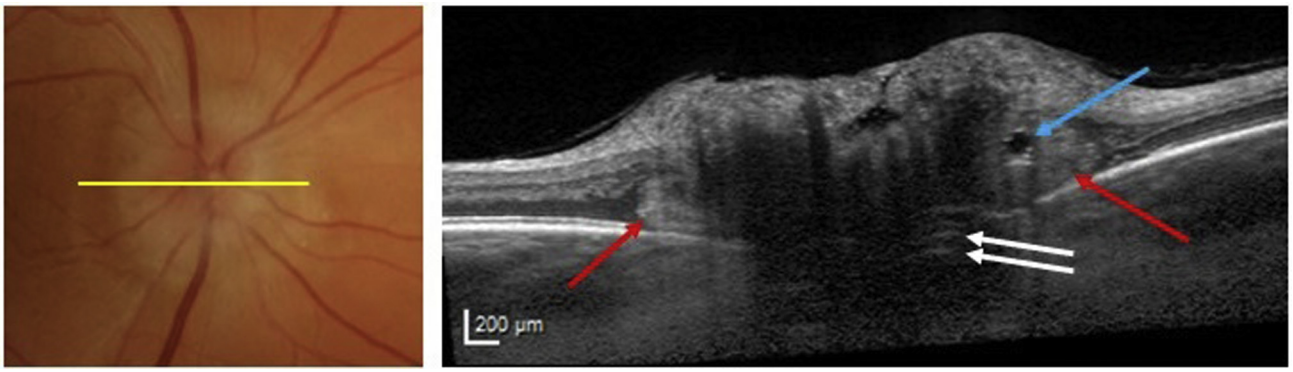

FIGURE 1. Diagnosis of ODD and ODD-AION. (Left) Fundus photograph of the right optic nerve head of a 44-year-old man with a few days' history of sudden visual loss due to NA-AION. The yellow line on the fundus photograph indicates the EDI-OCT scan position. Diffuse optic disc edema is seen but no ODD 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). EDI-OCT = enhanced depth imaging optical coherence tomography; NA-AION = nonarteritic anterior ischemic optic neuropathy; ODD = optic disc drusen; PHOMS = peripapillary hyperreflective ovoid mass-like structure.

diffuse, enlarged blind spot, or none. If more than 1 type of visual field defect for a specific eye was reported, the worse type was chosen by 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 version 9.4 software (SAS Institute, Cary, North Carolina). All included eyes were assigned to 1 of 4 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 nonparametric Wilcoxon signed-rank test was used to test for differences among 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 a P value of $<.05$.

RESULTS

A TOTAL OF 152 PATIENTS 50 YEARS OLD OR YOUNGER WERE identified with an ICD-10 code of "ischemic optic neuropathy" in the study period (Supplemental Table). Of these patients, 65 met study criteria (median age 41 years; range, 15-50 years old). Data from both eyes were available in 62 of these patients, but in 3 cases there were data for only 1 eye. Therefore, a total of 127 eyes were included, in which NA-AION was diagnosed in 74 eyes (Figure 2). In total, 38 eyes had ODD-AION, and 23 eyes had ODD without NA-AION.

• **VASCULAR RISK FACTORS:** A total of 54% of NODD-AION patients had 1 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 in a comparison between ODD-NAION and NODD-AION patients ($P = .16$).

• **VISIBILITY OF ODD:** In 46% of ODD eyes and 56% of ODD-AION eyes, the ODD were visible on ophthalmoscopy. No significant differences in visibility of ODD were found between eyes with ODD and those with ODD-AION ($P = .46$).

• **PREVALENCE OF ODD:** NA-AION was diagnosed in a total of 74 eyes. 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 ($P = .36$).

A total of 34 patients had ODD-AION in at least 1 eye. Three of these patients had no data from the fellow eye. 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 mean age of NA-AION onset between the patients with NODD-AION and the patients with ODD-AION (Table).

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 the ODD-

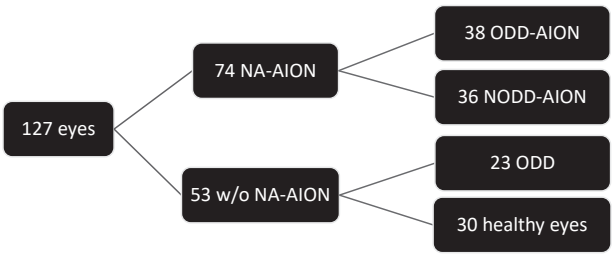

FIGURE 2. Flowchart demonstratescategorization of the 127 eyes included in the study. NA-AION = nonarteritic anterior ischemic optic neuropathy; NODD-AION = NA-AION not associated with ODD; ODD = optic disc drusen; ODD-AION = NA-AION associated with ODD; w/o = without.

AION, NODD-AION, ODD, and healthy eyes (Table), respectively. Significant differences in occurrence of hyperreflective lines were found among the 4 groups ($P < .001$). Post hoc analysis revealed that these significant differences were seen between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes). No significant differences were found between healthy eyes and eyes with NODD-AION and between ODD and ODD-AION eyes.

On EDI-OCT results, PHOMS were found in 54%, 28%, 63%, and 19% in the ODD-AION, NODD-AION, ODD, and healthy eyes, respectively. Significant differences in occurrence of PHOMS were found among the 4 groups ($P < .001$). Post hoc analysis revealed that these significant differences were seen between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes). No significant differences were found between healthy eyes and eyes with NODD-AION and between ODD and ODD-AION eyes.

Of the 127 study eyes, EDI-OCT was performed in 105 eyes. A total of 71 (67.6%) of these underwent OCT performed within 8 weeks, which can be considered 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 ODD-AION, NODD-AION, ODD, and healthy eyes, respectively (Table). Significant differences in Snellen BCVA were found among ODD-AION, NODD-AION, ODD, and healthy eyes ($P < .001$). Post hoc analysis revealed that these significant differences were seen between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes). No significant differences were found between eyes with ODD-AION and NODD-AION.

Median MDs were −7.8, −13.0, −3.2, and −2.0 dB for ODD-AION, NODD-AION, ODD, and healthy eyes, respectively. Significant differences in MD were found among ODD-AION, NODD-AION, ODD, and healthy eyes ($P < .001$). Post hoc analysis revealed that these significant differences were seen between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes). No significant differences were found between eyes with ODD-AION and NODD-AION, although a tendency toward more severe visual field defects was seen in the NODD-AION group.

Of the types of visual field defects noted (central, concentric, altitudinal [upper or lower], nerve fiber layer, diffuse, enlarged blind spot or none), 123 of 127 study eyes had 1 of the above-mentioned types of field defect. A total of 8 of 123 eyes had more than 1 type of field defect. In the presence of more than 1 type of field defect, the most severe type was chosen, as outlined in Methods. There were overall differences among the 4 study groups as to type of visual field defects ($P < .001$), with post hoc testing revealing significant differences in lower altitudinal defects between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes) (Figure 3).

DISCUSSION

THIS IS THE FIRST LARGE-SCALE STUDY TO SYSTEMATICALLY review a series of young patients (<50 years old) with NA-AION specifically for ODD. ODD were found more prevalent in this group than would be expected for the population (51% versus 2%, respectively). 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. Although 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 is not significantly different from that in control subjects.[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 may thicken prelaminar tissue. Hence, the question remains whether the ODD are contributing to the ischemia and compartment syndrome or whether they are coincidental due to shared risk factors.

Following previous studies of NA-AION, the diagnosis of ODD has become more reliable with OCT, particularly in EDI-OCT. In the present cohort, only approximately 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.

TABLE. Characteristics of the Study Patients[a]

	Healthy	ODD	NODD-AION	ODD-AION	*P* Value
Number of eyes	30 (24%)	23 (18%)	36 (28%)	38 (30%)	
Males/females	80/20	61/39	76/24	70/30	.44
Age, y (IQR)	45 (10)	43 (10)	45 (7)	41 (18)	.23
BCVA, Snellen (IQR)	1.0 (0)	1.0 (0.2)	0.5 (0.8)	0.8 (0.6)	<.001[b]
Perimetric MD, dB (IQR)	−2 (3.5)	−3.2 (4.9)	−13.0 (9.6)	−7.8 (7.5)	<.001[b]
PHOMS (no, percent)	5 (19%)	10 (63%)	8 (28%)	15 (54%)	.006[c]
Hyperreflective lines (no, percent)	1 (3.6%)	13 (76%)	2 (6.7%)	19 (66%)	<.001[c]
Tobacco use (no, percent)	7 (30%)	5 (28%)	9 (26%)	5 (18%)	.75
Obstructive sleep apnea	4 (27%)	4 (40%)	8 (31%)	4 (25%)	.86
Obesity	6 (30%)	2 (14%)	7 (23%)	6 (26%)	.75

Continuous variables are presented as median and interquartile range.

BCVA = best corrected visual acuity; IQR = interquartile range; MD = mean deviation; PHOMS = peripapillary hyperreflective ovoid mass-like structure.

[a]The cohort included healthy 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).

[b]Post hoc analysis with significant difference between NA-AION eyes (ODD-AION, NODD-AION) and eyes without NA-AION (ODD, healthy eyes)

[c]Post hoc analysis with significant difference between eyes with ODD (ODD-AION, ODD) and eyes without ODD (NODD-AION, healthy eyes).

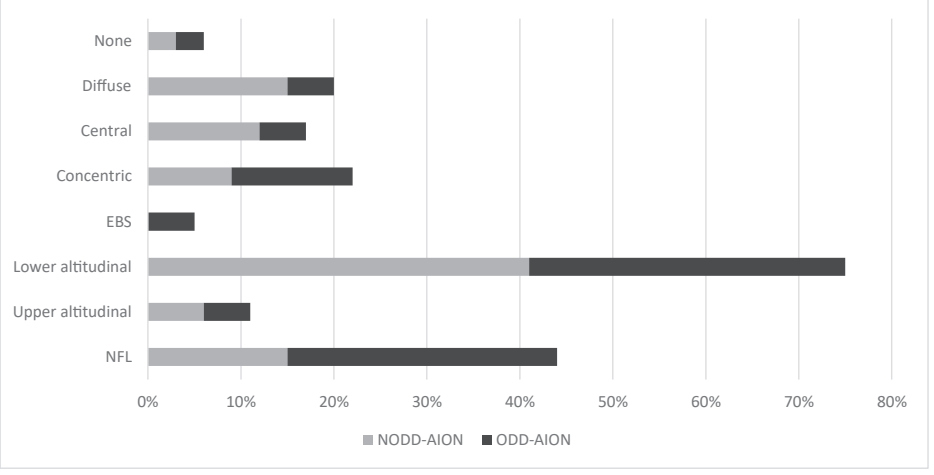

FIGURE 3. Percentage of eyes with different types of visual field defects in NODD-AION and ODD-AION. EBS = enlarged blind spot; NA-AION = nonarteritic anterior ischemic optic neuropathy; NFL = nerve fiber layer; NODD-AION = NA-AION not associated with ODD; ODD = optic disc drusen; ODD-AION = NA-AION associated with ODD.

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.[35] 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 fiber layers from elevated discs of any cause.[40] Therefore, the increased rate of PHOMS in NODD-AION is expected.

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 (Figure 1). If edema masked ODD in the present patients, then some cases of ODD might have been missed, and

the true prevalence of ODD might have been underestimated 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 the time of onset would not have affected the present results.

This study did not find any differences in VA 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 2 groups, with the most common defect being loss in the lower altitudinal field. 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.[41]

This study 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 such as vasculitis and hypercoagulability. Historically, NA-AION in the young has been linked with diabetes, hyperlipidemia, 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 2 groups.[7] In patients with unilateral NA-AION, age of <50 years reportedly increases the risk of second eye involvement, 42.6% versus 29.6%, respectively ($P = .047$), at 6 months.[7] Only diabetes was found to be linked with second eye involvement in the young. Interestingly, the study by Arnold et al.[7] 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 recent study of NA-AION with ODD included 16 patients with bilateral ODD and showed that 25% had bilateral sequential involvement.[19] Another recent paper reported that there was no increased risk to fellow eye NA-AION by age or sex, but the authors reported that ODD was a significant risk factor for second eye involvement after NA-AION (hazard ratio [HR], 2.78; $P = .02$).[42] However, in patients younger than 50 years old, the presence of bilateral ODD was the only significant risk factor for fellow eye involvement, increasing the risk by more than 8 times (HR = 8.31; range, 1.52-45.3; $P = .01$). For patients older than 50 years, the presence of ODD was not a significant risk (HR = 1.5; $P = .61$), suggesting that, although the presence of bilateral ODD was an overall risk for second eye involvement, this risk was overwhelmingly seen in those below 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 whether NA-AION patients with contralateral ODD have higher rates of second eye involvement than those without.

A limitation of this study was its 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.

A total of 87 young NA-AION patients seen in the study period were not included, primarily because EDI-OCT imaging 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 prevalence of ODD in young NA-AION eyes that was significantly higher than expected compared to the general population. Many cases of ODD were not detectable on ophthalmoscopy and required diagnosis by EDI-OCT imaging to confirm 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 younger than 50 years old. These authors propose that ODD-AION be recognized as an entity separate from NODD-AION and that ODD should be expressly looked for in all cases of young NA-AION.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

STEFFEN HAMANN: CONCEPTUALIZATION, METHODOLOGY, Validation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Lasse Malmqvist:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - review & editing, Visualization. **Marianne Wegener:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - review & editing, Visualization. **Masoud Aghsaei Fard:** Investigation, Writing - original draft, Writing - review & editing. **Valérie Biousse:** Investigation, Writing - original draft, Writing - review & editing. **Lulu Bursztyn:** Investigation, Writing - original draft, Writing - review & editing. **Gülsenay Citirak:** Investigation, Writing - original draft, Writing - review & editing. **Fiona Costello:** Investigation,

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