Combining Paracentral Acute Middle Maculopathy and Peripapillary Fluid as Biomarkers in Anterior Ischemic Optic Neuropathy

Klefter, Oliver Niels; Hansen, Michael Stormly; Lykkebirk, Lea; Subhi, Yousif; Brittain, Jane Maestri; Jensen, Mads Radmer; Døhn, Uffe Møller; Fana, Viktoria; Wiencke, Anne Katrine; Heegaard, Steffen; Terslev, Lene; Hamann, Steffen

Published in:
American Journal of Ophthalmology

DOI:
10.1016/j.ajo.2024.12.001

Publication date:
2025

Document version:
Final published version

Combining Paracentral Acute Middle Maculopathy and Peripapillary Fluid as Biomarkers in Anterior Ischemic Optic Neuropathy

OLIVER NIELS KLEFTER, MICHAEL STORMLY HANSEN, LEA LYKKEBIRK, YOUSIF SUBHI, JANE MAESTRI BRITTAIN, MADS RADMER JENSEN, UFFE MØLLER DØHN, VIKTORIA FANA, ANNE KATRINE WIENCKE, STEFFEN HEEGAARD, LENE TERSLEV, AND STEFFEN HAMANN

• PURPOSE: To determine if paracentral acute middle maculopathy (PAMM) and peripapillary intraretinal and subretinal fluid (IRF/SRF) could help distinguish between arteritic anterior ischemic optic neuropathy (A-AION) and nonarteritic AION (NA-AION) at an early stage.

• DESIGN: Nested prospective cross-sectional diagnostic accuracy study.

• METHODS: This study used single-center optical coherence tomography (OCT) data from 8 patients with A-AION and 24 patients with NA-AION from two prospective cross-sectional studies with consecutive sampling (ClinicalTrials.gov: NCT05248906 and NCT05305079). The diagnosis of A-AION was based on expert interpretation of biochemical markers of inflammation, temporal artery biopsy and positron emission tomography/computed tomography. The diagnosis of NA-AION was made in cases without suspicion or clinical evidence of A-AION and with confirmed neuroophthalmological expert diagnosis. For this substudy patients were also required to have an OCT scan in relation to the diagnosis of AION. Macular OCT scans were graded by two independent, masked graders for the presence of PAMM and for IRF/SRF. The extension of IRF/SRF was assessed using an Early Treatment Diabetic Retinopathy Study (ETDRS) grid.

• RESULTS: PAMM was found in 50% of patients with A-AION and in 0% of patients with NA-AION ($P = .0019$). In the setting of AION, the sensitivity of PAMM for the diagnosis of A-AION was 50% (95% CI: 16%-84%) while the specificity was 100% (95% CI: 86%-100%). Conversely, peripapillary IRF/SRF with extension into the ETDRS grid was observed in 83% of patients with NA-AION but in 0% of patients with A-AION ($P = .000047$). The sensitivity of central macula-involving IRF/SRF for the diagnosis of NA-AION was 83% (95% CI: 63%-95%), while the specificity was 100% (95% CI: 63%-100%). Combining the two biomarkers, 75% of patients with AION could be classified based on OCT alone.

• CONCLUSION: PAMM appears to be a biomarker of A-AION while extensive peripapillary fluid appears to be a biomarker of NA-AION. Combining OCT biomarkers might allow for early classification of AION and warrants further prospective studies. (Am J Ophthalmol 2025;271: 329–336.

AJO.com Supplemental Material available at AJO.com.

Meeting Presentation: Presented at the North American Neuro-Ophthalmological Society, Honolulu, Hawaii, March 2024.
Accepted for publication December 3, 2024.

Department of Ophthalmology (O.N.K., M.S.H., L.L., Y.S., A.K.W., S.H., S.H.), Rigshospitalet, Copenhagen, Denmark; Department of Clinical Medicine (O.N.K., M.S.H., L.L., A.K.W., S.H., L.T., S.H.), University of Copenhagen, Copenhagen, Denmark; Department of Clinical Research (Y.S.), University of Southern Denmark, Odense, Denmark; Department of Clinical Physiology and Nuclear Medicine (J.M.B.), Rigshospitalet, Copenhagen, Denmark; Department of Clinical Physiology and Nuclear Medicine (M.R.J.), Bispebjerg Hospital, Copenhagen, Denmark; Department of Rheumatology and Spine Diseases (U.M.D., V.F., L.T.), Rigshospitalet, Copenhagen, Denmark; Department of Pathology, Eye Pathology Section, (S.H.), Rigshospitalet, Copenhagen, Denmark
Inquiries to Oliver Niels Klefter, Department of Ophthalmology, Rigshospitalet, Glostrup, Denmark.; e-mail: oliver.niels.klefter.01@regionh.dk

ONE OF THE MOST COMMON AND FEARED OCULAR complications of giant cell arteritis (GCA) is arteritic anterior ischemic optic neuropathy (A-AION). While it is less common than the nonarteritic variant (NA-AION), A-AION typically carries a poorer visual prognosis.[1-10] Distinguishing between A-AION and NA-AION is important because the management of the two conditions differs substantially. Still, making the correct distinction may be difficult at the initial clinical presentation. While the classical presentations are distinct, the appearance of the optic nerve head (ONH) in the two conditions can sometimes be similar and not all patients with GCA will have classical symptoms.[3,4,7,8,11] Even a small suspicion of GCA necessitates immediate, high-dose corticosteroid treatment and a work-up which typically includes blood tests for markers of systemic inflammation as well as

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2024.12.001

either a temporal artery biopsy, ultrasonography of the cranial arteries, 2-deoxy-2-[^{18}F]fluoro-D-glucose positron emission tomography / computed tomography (FDG PET/CT) or a combination.[8,12-15] In contrast, NA-AION is associated with local predispositions such as a crowded ONH ("disc at risk"), optic disc drusen, ONH edema of other causes, acute/subacute intraocular pressure increases, and sometimes eye surgery. It is also associated with systemic risk factors such as hypertension, diabetes, hypercholesterolemia, acute hypotension/hypovolemia, nocturnal hypotension, migraine, end-stage renal disease, obstructive sleep apnea, certain drugs and infections.[6,16,17] Because no effective treatments have been identified for NA-AION, the management is mainly directed at identifying and addressing modifiable risk factors.[6,18] Because of these differences, making an early, clinical distinction using noninvasive, widely available imaging techniques holds the potential to improve the diagnostic process and accelerate the relevant management.

One promising biomarker is paracentral acute middle maculopathy (PAMM), which has been defined by its appearance on macular optical coherence tomography (OCT).[19-21] The hyperreflective bands in the middle layers of the retina (primarily at the level of the inner nuclear layer and sometimes involving the adjacent inner and outer plexiform layer) presumably represent ischemia although the degree of ischemia appears to be variable. This is reflected in the prognosis with some cases resolving without noticeable structural damage while others progress to inner retinal atrophy. The visual prognosis is generally good although significant structural retinal damage may lead to visual loss.[19,21]

PAMM has been described in association with a variety of conditions, including retinal vascular disease, neurological conditions (idiopathic intracranial hypertension, meningitis, leptomeningeal infiltration, migraine, cerebral leukoencephalopathy), systemic vascular disease (carotid artery disease, following cardiac arrest and vascular surgery), pregnancy, antiphospholid antibody syndrome, Susac syndrome, juvenile dermatomyositis, livedo reticularis, GCA, following viral infections, following intra- and periocular surgery or as a side effect of certain medications and recreational drugs.[19,21] Recently, PAMM was reported in 17% of patients with GCA, thus making this OCT finding a potential ocular biomarker for GCA.[22] In addition, PAMM has shown promise in distinguishing between A-AION and NA-AION.[23]

Another potential OCT biomarker is peripapillary fluid accumulation which has been described in a variety of retinal and optic nerve conditions.[24] Macular intraretinal fluid (IRF) and subretinal fluid (SRF) may be present in eyes with ONH edema. This has recently been described in NA-AION.[25] Its prevalence in A-AION, however, remains to be investigated. Because the pathophysiology of NA-AION has been proposed to involve a local compartment syndrome,[6] it may be hypothesized that macular extension of peripapillary IRF/SRF would be observed in a larger proportion of eyes with NA-AION than A-AION.

Based on these observations we hypothesized that the combination of two presumably specific OCT biomarkers would allow for early classification of a larger proportion of AION patients than either biomarker alone.

In this study we compared macular OCTs of patients diagnosed with A-AION and NA-AION, respectively, to determine if the combination of PAMM and IRF/SRF would make the clinician able to differentiate between the two diagnoses at an early stage.

METHODS

• **STUDY DESIGN AND ETHICS:** This study analyzed OCT data from patients with A-AION and NA-AION from two prospective cross-sectional studies with consecutive sampling (ClinicalTrials.gov: NCT05248906 and NCT05305079). The study was conducted in a tertiary center in the Capital Region of Denmark, with 1.9 million inhabitants. Ethical approval was obtained from the Ethics Committee for the Capital Region of Denmark (H-20032069 and H-20073063). The study adhered to the ethical principles of the Declaration of Helsinki and to hospital guidelines for research conduct. Patients were recruited in a consecutive manner in the period March 2021 to June 2023 (A-AION) and August 2021 to August 2023 (NA-AION). All participants gave oral and written informed consent prior to study participation.

• **PATIENT ELIGIBILITY:** All participants underwent comprehensive neuroophthalmological examination. The diagnosis of A-AION was defined as AION in the setting of GCA. It was based on expert interpretation of the results of biochemical markers of inflammation (including platelet count, C-reactive protein, and erythrocyte sedimentation rate), temporal artery biopsy with presence of granulomatous inflammation with or without the presence of giant cells at the internal elastic lamina, and FDG PET/CT positive for the presence of vasculitis. Patients with active cancer or use of steroid for more than 1 week during the last 6 months were not included in the study according to the protocol. The diagnosis of NA-AION was made in cases without suspicion or clinical evidence of A-AION and with confirmed neuroophthalmological expert diagnosis. For this study, we did not consider the separate cohort of optic disc drusen associated NA-AION sampled for one of the studies (NCT05305079). For our analyses, we also employed a further participant eligibility criterion in that participants for this study had OCT scans obtained in relation to the diagnosis of either A-AION or NA-AION, and these scans had sufficiently high quality for making the diagnosis of PAMM as deemed by at least two independent evaluators. Patients

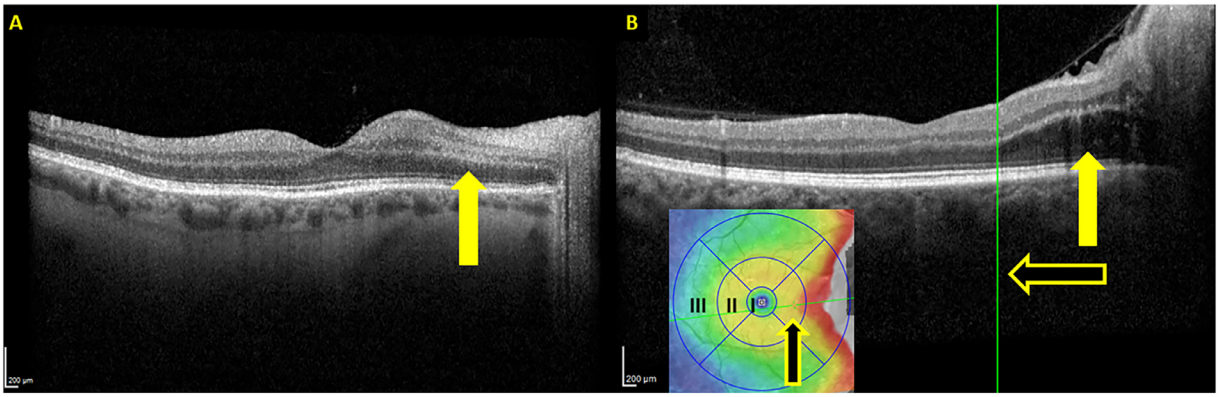

FIGURE. Macular optical coherence tomography (OCT) of the right eye in a patient with arteritic anterior ischemic optic neuropathy (A) and nonarteritic anterior ischemic optic neuropathy (B). The first OCT B-scan shows peripapillary paracentral acute middle maculopathy (A, yellow arrow). The second OCT B-scan shows peripapillary intraretinal fluid (B, yellow arrow) which extends into the second ring of the fovea-centered Early Treatment Diabetic Retinopathy Study grid (B, inset, black arrow). The vertical green bar (B, black arrow) delimits the leading edge of the intraretinal fluid. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

were excluded from the analysis if the final expert diagnosis could not support AION with certainty ($N = 2$) or if the evaluators identified another retinal condition that could contribute to the IRF/SRF ($N = 1$). To account for any effects of age, we also performed a subgroup analysis including all patients with A-AION and the subgroup of patients with NA-AION who were within the same age range.

• **MACULAR OCT:** For the assessment of PAMM, which was the primary outcome, macular OCT (Figure A) was performed using Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) spectral-domain OCT. The macular cube scan was obtained with 119 μm between each B-scan. Two independent investigators (M.S.H. and Y.S.) evaluated all scans for the presence of PAMM, defined as hyperreflectivity at the level of the inner nuclear layer.[19-21] Any discrepancies were discussed with a third author (O.N.K.), resulting in consensus for all scan results.

Because the Heidelberg OCT was performed at the first visit after initial presentation according to the study protocols, it was sometimes performed several weeks after the initial presentation. Therefore, we also analyzed OCT scans performed at the time of initial presentation. These scans were performed using the DRI-OCT Triton (TopCon Healthcare, Tokyo, Japan). The majority of scans included a 7 × 7 mm 3D macular scan, while a minority had a 12-line 6 mm radial macular scan and one had a 12 × 9 mm combined horizontal line scan with central radial scan performed. This analysis was done to determine if the presence or absence of PAMM could depend on the time since the initial diagnosis and, in the case of GCA, on the time from initiation of systemic corticosteroids.

In addition, we assessed the presence of macular IRF/SRF in association with AION in the OCT from the initial presentation (Figure B). As a proxy measure of peripapillary fluid extension, the most central extension towards the fovea was measured semi-quantitatively using a standardized Early Treatment Diabetic Retinopathy Study (ETDRS) grid[26] centered at the fovea (Figure B, inset). The three concentric rings have diameters of 1, 3 and 6 mm, respectively. IRF/SRF extending into eg, the second ring from the ONH would be located within 1.5 mm of the fovea. This would denote a larger extension of fluid than IRF/SRF located only adjacent to the ONH.

• **DATA ANALYSIS AND STATISTICS:** Demographics were used to describe the study population. As appropriate, unpaired *t*-test and unpaired Wilcoxon test were used to compare continuous variables between the groups. The prevalence of PAMM and IRF/SRF, respectively, were compared between patients with A-AION and NA-AION. Diagnostic test accuracy statistics were used to explore sensitivity, specificity, positive and negative predictive values of PAMM and IRF/SRF in the diagnosis of A-AION and NA-AION, respectively. Associations between categorical variables were analyzed by Chi-squared testing or Fisher's exact test as appropriate. We defined statistical significance in cases where *P* values were below .05. RStudio version 2023.03.01 (build 446, Posit Software PBC, Boston, MA, USA; R Statistical Software version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org) was used for the statistical analysis.

RESULTS

• **PARTICIPANT CHARACTERISTICS:** This study included 32 patients with AION, of which 8 had A-AION and 24 had NA-AION (Table 1). Patients with A-AION were

TABLE 1. Characteristics of Patients With A-AION and NA-AION

	A-AION	NA-AION	*P*-value
N	8	24	
Age (years), mean (SD)	74.5 (7.9)	61.8 (12.5)	.012
Sex (female/male), N	5/3	15/9	1.00
Bilateral AION, N	2	3	.58
PAMM presence, N	4	0	.0019
IRF/SRF presence, N			
Any, N	3	23	.0015
Within ETDRS grid, N	0	20	.000047
Within ring II, N	0	8	.081
Time to first OCT (days), median (range)	0 (0-8)	0 (0-21)	.47
Time to Heidelberg OCT (days), median (range)	7 (0-12)	20 (0-71)	.0083

A-AION = arteritic anterior ischemic optic neuropathy; ETDRS = Early Treatment Diabetic Retinopathy Study; IRF/SRF = intraretinal and/or subretinal fluid on macular optical coherence tomography; NA-AION = nonarteritic anterior ischemic optic neuropathy; OCT = optical coherence tomography; PAMM = paracentral acute middle maculopathy; within ring II = within the second ring of the ETDRS grid, ie, within 1.5 mm from the center of the fovea.

TABLE 2. Diagnostic Accuracy Statistics for Differentiating Anterior Ischemic Optic Neuropathy

Outcome	Predictor	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Arteritic AION	PAMM	0.50 (0.16-0.84)	1.00 (0.86-1.00)	1.00 (0.40-1.00)	0.86 (0.67-0.96)
Nonarteritic AION	Any fluid[a]	0.96 (0.79-1.00)	0.62 (0.24- 0.91)	0.88 (0.70-0.98)	0.83 (0.36-1.00)
	Fluid in ring III[b]	0.83 (0.63-0.95)	1.00 (0.63-1.00)	1.00 (0.83-1.00)	0.67 (0.35-0.90)
	Fluid in ring II[b]	0.33 (0.16-0.55)	1.00 (0.63-1.00)	1.00 (0.63-1.00)	0.33 (0.16-0.55)

Estimates are presented with 95% confidence intervals. AION = anterior ischemic optic neuropathy; PAMM = paracentral acute middle maculopathy.

[a] Any peripapillary fluid detectable on macular optical coherence tomography.

[b] Any peripapillary fluid extension into ring III and II, respectively of the fovea-centered Early Treatment Diabetic Retinopathy Study grid. Fluid within ring III is located within 3 mm from the center of the fovea. Fluid within ring II is located within 1.5 mm from the center of the fovea.

aged 74.5 years (SD: 7.9 years), on average more than a decade older than the patients with NA-AION aged 61.8 years (SD 12.5 years) ($P = .012$, independent samples *t*-test). The proportion of female patients was the same in both groups (62.5%; $P = 1.00$, Fisher's exact test). Of the 8 patients with A-AION, 2 were bilateral. Of these 10 eyes with A-AION, 3 had a retinal co-morbidity of non-neovascular age-related macular degeneration (AMD). Of the 24 patients with NA-AION, 3 were bilateral. Of these 27 eyes with NA-AION, 6 had retinal co-morbidities (2 with non-neovascular AMD and 4 epiretinal membranes, which the evaluators considered morphologically unrelated to the presence or absence of IRF/SRF).

• **PAMM IN A-AION VERSUS NA-AION:** PAMM was present in 50% of patients with A-AION, whereas it was not present in any patients with NA-AION ($P = .0019$, Fisher's exact test; Table 1). The sensitivity for detecting A-AION was 50% (95% CI: 16%-84%) and the specificity was 100% (95% CI: 86%-100%, Table 2).

PAMM was observed in both eyes of a patient with unilateral A-AION. No PAMM was observed in the other fellow eyes of patients with either A-AION or NA-AION.

• **INTRA- AND SUBRETINAL FLUID IN A-AION VERSUS NA-AION:** In A-AION, IRF/SRF was present in 37.5% of patients whereas in NA-AION, IRF/SRF was present in 96% of patients ($P = .0015$, Fisher's exact test). The sensitivity for detecting NA-AION was 96% (95% CI: 79%-100%) and the specificity 62% (95% CI: 24%-91%, Table 2).

As determined using the fovea-centered ETDRS grid, the IRF/SRF involvement of the macula was significantly more extensive in NA-AION than in A-AION. In A-AION, no patients had IRF/SRF within the ETDRS grid (3 mm radius from the fovea). In NA-AION, IRF/SRF was observed within the ETDRS grid in 83% of patients ($P = .000047$, Fisher's exact test). The sensitivity for detecting NA-AION was 83% (95% CI: 63%- 95%) and the specificity 100% (95% CI: 63%-100%). Using involvement of the 2 inner-

TABLE 3. Combining Optical Coherence Tomography Biomarkers in Anterior Ischemic Optic Neuropathy

	Arteritic AION	Nonarteritic AION
No PAMM, Fluid in ring III[a] (N)	0	20[b]
No PAMM, No fluid in ring III[a] (N)	4	4
PAMM, Fluid in ring III[a] (N)	0	0
PAMM, No fluid in ring III[a] (N)	4	0[b]

AION = anterior ischemic optic neuropathy; PAMM = paracentral acute middle maculopathy.

[a]peripapillary fluid extending into the Early Treatment Diabetic Retinopathy Study grid, within 3 mm of the center of the fovea.

[b]combinations of biomarker findings that resulted in correct classification into arteritic or nonarteritic AION. In total 24 of 32 patients (75%) could be correctly classified based on optical coherence tomography findings.

most rings of the ETDRS grid as the cut-off, the sensitivity was 33% (95% CI: 16%-55%) and the specificity 100% (95% CI: 63%-100%).

In eyes with AION, IRF/SRF was associated with the observation of a tight optic disc in the fellow eye (or in incidental previous images of the same eye; $P = .0030$, Fisher's exact test).

• **COMBINING PAMM AND IRF/SRF FOR CLASSIFICATION OF AION:** No eyes or patients demonstrated concomitant PAMM and IRF/SRF within the ETDRS grid (Table 3).

Using PAMM and IRF/SRF within the ETDRS grid in any eye as markers, 24 patients (75%) with AION could be classified based on the macular OCT alone. Using IRF/SRF involvement of the 2 inner-most rings of the ETDRS grid as the cut-off, 12 patients (37.5%) with AION could be classified based on the macular OCT alone. The patients who could not be classified based on OCT demonstrated a combination of absent PAMM and absent ETDRS grid involvement of IRF/SRF.

• **THE EFFECT OF AGE, SEX AND OCT PARAMETERS ON THE CLASSIFICATION OF AION:** Because of the significant age difference between patients with A-AION and NA-AION, the analyses were repeated in a subgroup of patients. This included the 8 patients with A-AION as well as 9 patients with NA-AION who were within the same age range, ie, older than 60 years. The results were unchanged (Supplementary Tables 1-3). PAMM remained associated with A-AION ($P = .029$), whereas IRF/SRF remained associated with NA-AION ($P = .0091$). The sensitivities and specificities for PAMM and any IRF/SRF were unchanged or higher. The sensitivity of IRF/SRF involvement of the ETDRS grid was 100% (95% CI: 66%-100%) whereas involvement of the 2 inner-most rings resulted in a sensitivity of 56% (95% CI: 21%-86%) with unchanged specificities of 100%. Because all patients in the older NA-AION subgroup had IRF/SRF within the ETDRS grid, all cases (100%) could be classified based on the OCT alone. Using involvement of the 2 inner-most rings of the ETDRS grid as the cut-off, 9 patients (53%) with AION could be classified based on the macular OCT alone in this subgroup analysis.

The prevalence of PAMM, IRF/SRF and its involvement of the ETDRS grid did not differ between male and female patients ($P = .29$ to 1.00, Fisher's exact test; Supplementary Table 4).

The Heidelberg OCT used for the primary evaluation of PAMM was performed at a median of 7 (range 0-12) days after initial presentation with commencement of corticosteroid treatment in patients with A-AION and 20 (0-71) days after initial presentation in patients with NA-AION ($P = .0083$, unpaired Wilcoxon test; Table 1). Macular OCT was available from the time of initial presentation in 7 patients with A-AION and 22 patients with NA-AION. PAMM findings were identical in these initial OCT scans.

The presence of IRF/SRF was evaluated in OCT scans performed at a median of 0 days (range 0-8 days) after initial presentation in patients with A-AION and at a median of 0 days (range 0-21 days) after initial presentation in patients with NA-AION ($P = .47$, unpaired Wilcoxon test; Table 1).

The detection of PAMM and IRF/SRF was not associated with the type of OCT used or with the specific scan protocol ($P = .36$ to 1.00, Fisher's exact test).

DISCUSSION

Our study demonstrated that in patients with AION, concomitant PAMM strongly suggests an arteritic etiology with a positive predictive value for GCA in our population of 100%. Conversely, the finding of peripapillary IRF/SRF extending into the macula within 3 mm of the fovea suggests a nonarteritic etiology with a positive predictive value for NA-AION in our population of 100%. Combining these highly specific OCT findings might allow for early classification of the majority of patients with AION.

Hypothetically, in the clinical setting these results would suggest that a patient with concomitant AION and PAMM can start treatment for GCA even before the first blood biochemistry results become available.[27] Conversely, a patient with AION, collateral IRF/SRF involving the central macula, no PAMM and no symptoms suggestive of GCA might avoid an extensive work-up and possibly the need for empirical treatment pending the results. These potential clinical applications, however, should await further prospective validation.

It should be noted that the negative predictive values of both PAMM and IRF/SRF were not 100%. There-

fore, if any aspect of the clinical presentation is suggestive of GCA, the patient should start high-dose corticosteroid therapy and undergo urgent evaluation with blood biochemistry and temporal artery biopsy and/or ultrasound and/or FDG PET/CT according to international and local guidelines.[8,12,13,15]

Our study confirms that PAMM is a consistent finding in GCA and particularly in A-AION. Recent studies found PAMM in 17% of all patients with GCA, 30% of patients with GCA and ocular involvement[22] and it appears to be a highly specific distinguishing feature in patients with A-AION.[23] Our results are also in line with previous findings suggesting that PAMM does not seem to occur in NA-AION.[22,23]

GCA involves medium and large elastic arteries and can lead to potential combinations of ophthalmic artery, posterior ciliary artery, central retinal or cilioretinal artery hypoperfusion.[4,8] Consequently, combinations of A-AION and PAMM are pathophysiologically possible in GCA. The presence of PAMM suggests that even in cases without obvious central retinal or ophthalmic artery occlusion, GCA may reduce retinal perfusion below the threshold that causes focal retinal capillary dysfunction and ischemia, sometimes bilaterally. The latter could explain the observation of bilateral PAMM in a patient with unilateral A-AION in the present study. Conversely, the absence of PAMM in NA-AION supports that NA-AION arises as an isolated ischemic insult of the ONH.[6,28,29] These hypotheses are in line with a recent case series of PAMM, which associated PAMM with retinal artery and vein occlusion and suggested a retinal ischemic etiology.[30]

The finding of a wide peripapillary zone of IRF/SRF at initial presentation might support the hypothesis that NA-AION is associated with a local compartment syndrome, accentuated by an anatomically predisposed tight optic disc.[6] Notably, IRF/SRF was associated with a tight optic disc either in the fellow eye or in incidental pre-AION images of the same eye in the present study.

Although it could be speculated that PAMM might help explain differences in visual prognosis, a previous study found no difference between GCA patients with and without PAMM.[22] The prognostic value of peripapillary fluid and its possible associations with the anatomy of the ONH warrants further studies.

Acute macular neuroretinopathy (AMN) may appear similar to PAMM on OCT but mainly affects the outer retinal layers, is thought to be caused by ischemia at the level of the deepest capillary plexus and has been reported less frequently in the literature.[21] Although our study cannot explain why GCA causes PAMM rather than AMN, it may suggest that the middle retinal layers are more vulnerable than those supplied by the deepest retinal capillaries and the choroid. In GCA, choroidal ischemia is considered a rare ocular manifestation.[8]

The main strength of the present study is the direct comparison of patients with A-AION and NA-AION regarding the prevalence of both PAMM and IRF/SRF. This reflects a common clinical situation where the etiological differential diagnosis is of paramount importance. Additionally, it seems that the combination of these two OCT markers might reflect the pathophysiological differences between A-AION and NA-AION. Limitations, which are discussed in detail below, include the sample size, the difference in age between the two groups and potential differences in eligibility criteria and examination time points in the two studies from which patients were included.

The patients with A-AION in this study represent the majority of patients seen during a 2-year recruitment period at the Department of Ophthalmology. Its uptake area covers a background population of approximately one-third of the total Danish population. Even larger, prospective multicenter studies with comprehensive recruitment of patients with recent-onset AION and other causes of ONH edema could further support our findings.

In general, NA-AION may occur at a younger age than A-AION[3,6] and it is therefore likely that the age difference in our study represents this difference in disease epidemiology. It may be speculated that the higher age of patients with A-AION could predispose to poorer autoregulation, a more vulnerable retinal capillary bed, a lower threshold for capillary compromise, and therefore a higher risk of ischemia and PAMM. However, in a subgroup analysis of age-matched patients with NA-AION in this study, the associations remained unchanged, suggesting they are independent of age and related to disease etiology *per se*. The associations also appeared to be independent of sex.

The primary outcome of PAMM prevalence was assessed in OCT scans that were performed on the Heidelberg Spectralis apparatus. This allowed for standardized comparisons between groups. To assess the potential effect of time from initial presentation in NA-AION and corticosteroid initiation in A-AION, we also assessed the OCT from the initial presentation. Although performed on different OCT equipment in the majority of cases, its results did not differ from those of the primary outcome assessment. This supports the validity of our findings and suggests that PAMM does not disappear within a timeframe of approximately 2 weeks from the initial presentation (and corticosteroid initiation) in A-AION. In NA-AION, subfoveal fluid has been reported to subside within 1 month in most cases.[25] Therefore, it is important to perform the first OCT at the time of initial presentation. Still, it may be speculated that variable symptom duration before seeking medical attention and potentially subclinical disease duration in GCA could influence the prevalence of OCT findings.

In this study, the ETDRS grid was used to standardize the assessment of IRF/SRF extension. This can be regarded as a semi-quantitative measure of peripapillary fluid volume and distribution. Linear measurements of IRF/SRF extension in multiple directions from eg, the centre of the ONH could

be considered more precise. However, the ETDRS grid allows for rapid and accessible evaluation of peripapillary fluid in the same macular OCT that is used for assessment of PAMM. This should be an advantage when used in an emergency eye care setting. The use of different types of OCT equipment could potentially lead to variation in the assessment of structural findings. This has especially been demonstrated for retinal thickness measurements.[31] In this study, however, the detection and observed extension of IRF/SRF appeared to be independent of the scanner type and scan protocol.

If these findings can be reproduced in a prospective study of an independent cohort, they could further optimize and accelerate the clinical management of AION. It requires that standardized OCT of the macula and optic disc is performed in all patients with suspected GCA and ocular symptoms as previously recommended[22,23] as well as in patients with recent-onset NA-AION and optic disc edema of other etiologies.

In conclusion, PAMM appears to be a biomarker for an arteritic etiology whereas central macular involvement of IRF/SRF appears to be a biomarker for a nonarteritic etiology in patients presenting with AION. Combining these disease-specific OCT observations could potentially classify the majority of patients at the first clinical presentation. Further studies are warranted to validate these findings with the purpose of providing the clinician with an important early diagnostic indicator.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Oliver Niels Klefter: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michael Stormly Hansen:** Writing – review & editing, Writing – original draft, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Lea Lykkebirk:** Writing – review & editing, Validation, Resources, Investigation, Data curation. **Yousif Subhi:** Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Jane Maestri Brittain:** Writing – review & editing, Investigation. **Mads Radmer Jensen:** Writing – review & editing, Investigation. **Uffe Møller Døhn:** Writing – review & editing, Investigation. **Viktoria Fana:** Writing – review & editing, Investigation. **Anne Katrine Wiencke:** Writing – review & editing, Supervision, Investigation. **Steffen Heegaard:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition. **Lene Terslev:** Writing – review & editing, Supervision, Investigation. **Steffen Hamann:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Funding/Support: This research was funded by the VELUX foundations, Gigtforeningen (The Danish Rheumatism Association), grant numbers R201-A7279 and R218-A7908, and Synoptik-fonden, application number 23090016.
Financial Disclosures: The authors indicate no financial support or conflicts of interest.

REFERENCES

1. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. *Ophthalmology*. 1993;100(4):550–555.
2. De Smit E, O'Sullivan E, Mackey DA, Hewitt AW. Giant cell arteritis: ophthalmic manifestations of a systemic disease. *Graefes Arch Clin Exp Ophthalmol*. 2016;254(12):2291–2306.
3. Hayreh SS. Ischemic optic neuropathy. *Prog Retin Eye Res*. 2009;28(1):34–62.
4. Hayreh SS. Giant cell arteritis: its ophthalmic manifestations. *Indian J Ophthalmol*. 2021;69(2):227–235.
5. Liu GT, Glaser JS, Schatz NJ, Smith JL. Visual morbidity in giant cell arteritis. Clinical characteristics and prognosis for vision. *Ophthalmology*. 1994;101(11):1779–1785.
6. Salvetat ML, Pellegrini F, Spadea L, Salati C, Zeppieri M. Non-arteritic anterior ischemic optic neuropathy (NA-AION): a comprehensive overview. *Vision (Basel)*. 2023;7(4):72.
7. Vodopivec I, Rizzo 3rd JF. Ophthalmic manifestations of giant cell arteritis. *Rheumatology (Oxford)*. 2018;57(suppl_2):ii63–ii72.
8. Bilton EJ, Mollan SP. Giant cell arteritis: reviewing the advancing diagnostics and management. *Eye (Lond)*. 2023;37(12):2365–2373.
9. Chen JJ, Leavitt JA, Fang C, Crowson CS, Matteson EL, Warrington KJ. Evaluating the incidence of arteritic ischemic optic neuropathy and other causes of vision loss from giant cell arteritis. *Ophthalmology*. 2016;123(9):1999–2003.
10. Donaldson L, Margolin E. Vision loss in giant cell arteritis. *Pract Neurol*. 2022;22(2):138–140.
11. Issa M, Donaldson L, Margolin E. Incidence of giant cell arteritis mimicking non-arteritic anterior optic neuropathy. *J Neurol Sci*. 2023;449:120661.
12. Dinkin M, Johnson E. One giant step for giant cell arteritis: updates in diagnosis and treatment. *Curr Treat Options Neurol*. 2021;23(2):6.
13. Hansen MS, Terslev L, Jensen MR, et al. Comparison of temporal artery ultrasound versus biopsy in the diagnosis of giant cell arteritis. *Eye (Lond)*. 2023;37(2):344–349.
14. Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis*. 2022;81(12):1647–1653.
15. Dejaco C, Ramiro S, Bond M, et al. EULAR recommenda-

tions for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. *Ann Rheum Dis*. 2024;83(6):741–751.
16. Chatziralli IP, Kazantzis D, Chatzirallis AP, et al. Cardiometabolic factors and risk of non-arteritic anterior ischemic optic neuropathy: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. 2022;260(5):1445–1456.
17. Hamann S, Malmqvist L, Wegener M, et al. Young adults with anterior ischemic optic neuropathy: a multicenter optic disc drusen study. *Am J Ophthalmol*. 2020;217:174–181.
18. Lantos K, Domotor ZR, Farkas N, et al. Efficacy of treatments in nonarteritic ischemic optic neuropathy: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2022;19(5):2718.
19. Moura-Coelho N, Gaspar T, Ferreira JT, Dutra-Medeiros M, Cunha JP. Paracentral acute middle maculopathy-review of the literature. *Graefes Arch Clin Exp Ophthalmol*. 2020;258(12):2583–2596.
20. Sarraf D, Rahimy E, Fawzi AA, et al. Paracentral acute middle maculopathy: a new variant of acute macular neuroretinopathy associated with retinal capillary ischemia. *JAMA Ophthalmol*. 2013;131(10):1275–1287.
21. Scharf J, Freund KB, Sadda S, Sarraf D. Paracentral acute middle maculopathy and the organization of the retinal capillary plexuses. *Prog Retin Eye Res*. 2021;81:100884.
22. Mairot K, Sene T, Lecler A, et al. Paracentral acute middle maculopathy in giant cell arteritis. *Retina*. 2022;42(3):476–484.
23. Mairot K, Gascon P, Stolowy N, et al. Paracentral acute middle maculopathy as a specific sign of arteritic anterior ischemic optic neuropathy. *Am J Ophthalmol*. 2023;248:1–7.
24. Arora S, Zur D, Iovino C, Chhablani J. Peripapillary fluid: obvious and not so obvious!. *Surv Ophthalmol*. 2024;69(3):311–329.
25. Chapelle AC, Rakic JM, Plant GT. The occurrence of intraretinal and subretinal fluid in anterior ischemic optic neuropathy: pathogenesis, prognosis, and treatment. *Ophthalmology*. 2023;130(11):1191–1200.
26. Early Treatment Diabetic Retinopathy Study Research GroupGrading diabetic retinopathy from stereoscopic color fundus photographs–an extension of the modified Airlie house classification. ETDRS report number 10. *Ophthalmology*. 1991;98(5 Suppl):786–806.
27. Hansen MS, Klefter ON, Terslev L, et al. Is erythrocyte sedimentation rate necessary for the initial diagnosis of giant cell arteritis? *Life (Basel)*. 2023;13(3):693.
28. Berry S, Lin WV, Sadaka A, Lee AG. Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. *Eye Brain*. 2017;9:23–28.
29. Miller NR, Arnold AC. Current concepts in the diagnosis, pathogenesis and management of nonarteritic anterior ischaemic optic neuropathy. *Eye (Lond)*. 2015;29(1):65–79.
30. Limoli C, Raja LD, Wagner SK, et al. Exploring patient demographics and presence of retinal vascular disease in paracentral acute middle maculopathy. *Am J Ophthalmol*. 2023;260:182–189.
31. Hanumunthadu D, Keane PA, Balaskas K, et al. Agreement between spectral-domain and swept-source optical coherence tomography retinal thickness measurements in macular and retinal disease. *Ophthalmol Ther*. 2021;10(4):913–922.