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NEUROPHTHALMOLOGY

# Optical coherence tomography angiography in acute arteritic and non-arteritic anterior ischemic optic neuropathy

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**Abstract**
*Purpose* The purpose of our study was to describe the feature of acute non-arteritic or arteritic anterior ischemic optic neuropathy (NA-AION and A-AION) using optical coherence tomography angiography (OCT-A) and to compare it with fluorescein angiography (FA) and indocyanine green angiography (ICGA).
*Methods* In this retrospective, observational case-control study four NA-AION patients and one A-AION patient were examined by FA, ICGA and OCT-A within 2 weeks from disease presentation. The characteristics of the images were analyzed. Optic nerve head (ONH) and radial peripapillary capillaries (RPC) vessel densities (VDs) were compared between NA-AION and controls.
*Results* In two of four NA-AION cases and in the A-AION patient, OCT-A clearly identified the boundary of the ischemic area at the level of the optic nerve head, which was comparable to optic disc filling defects detected by FA. In the other two NA-AION cases, a generalized leakage from the disc was visible with FA, yet OCT-A still demonstrated sectorial peripapillary capillary network reduction. Both ONH and RPC VDs were reduced in NA-AION patients, when compared to controls.
*Conclusions* OCT-A was able to identify microvascular defects and VD reduction in cases of acute optic disc edema due to NA-AION and A-AION. OCT-A provides additional information in ischemic conditions of the optic nerve head.

**Keywords** A-AION · Arteritic anterior ischemic optic neuropathy · Fluorescein angiography · NA-AION · Non-arteritic anterior ischemic optic neuropathy · OCT-A;optical coherence tomography angiography · Vessel density

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## Introduction

Anterior ischemic optic neuropathy (AION) is characterized by acute, severe, painless visual loss due to ischemia of the anterior part of the optic nerve head, mainly supplied by the deep optic nerve plexus which derives from the short posterior ciliary arteries (PCAs) [1]. AION can be divided into two distinct entities: arteritic and non-arteritic, characterized and distinguished by different clinical features and histopathology [2]. The arteritic form (A-AION), otherwise known as Giant Cell Arteritis (GCA), is associated with the elderly; it is a constellation of constitutional symptoms and certain laboratory values including elevated level of erythrocyte sedimentation rate (ESR),C-reactive protein (CRP) and thrombocytosis. In A-AION the vasculopathy is located at the level of PCAs, proximal to their division into paraoptic and choroidal branches. The non-arteritic form of AION (NA-AION) is often related to arteriosclerosis, hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, relative nocturnal hypotension, sleep apnea and the structural predisposition of a crowded optic disc with small or absent optic cup ("disk at risk"). In NA-AION the vascular occlusion is distal to PCAs, affecting the paraoptic tributaries within the optic disc. This is

likely a watershed infarct, which is an ischemic lesion that involves the junction between two adjacent arterial territories and is typically caused by systemic or local hypoperfusion. Prompt diagnosis, individuation of risk factors and adequate therapy are important especially for A-AION to prevent or at least to reduce the risk of fellow eye involvement and further visual loss in the same eye [3].

Typical presentation signs are represented by: afferent pupillary defect and optic disc edema. However, other causes of isolated optic disc edema should be ruled out, since inflammatory or infectious optic neuropathies or increased intracranial pressure may present similarly to NA-AION.

Previous authors described the use of fluorescein angiography (FA) and indocyanine green angiography (ICGA) for the study of the optic nerve head and peripapillary vascularization in acute NA-AION [4–7] and A-AION [6]. Three different angiographic patterns were described: peripapillary choroid delay, leakage from the disc (focal or generalized) and/or disc filling defects [4]. The peripapillary choroidal filling delay is more typical in A-AION [6, 7], but it has been described also in NA-AION [4, 5]. However, FA and ICGA are invasive exams with possible side effects like nausea, vomiting and allergy.

Optical coherence tomography angiography (OCT-A) is a new, non-invasive technique, able to image retinal and optic nerve head vessels based on flow rather than simple reflectance intensity. OCT-A can visualize microvasculature by detecting motion contrast from flowing blood without dye injection [8, 9]. OCT-A is more sensitive than FA in visualizing macular capillaries and radial peripapillary capillaries (RPC) [10] that are derived from the retinal central artery (superficial plexus), and it can also visualize the deep optic nerve head microvasculature, derived from PCAs (deep plexus).

To date, few papers and case reports have described changes of the microvasculature in acute NA-AION [11–14] and A-AION [14, 15] using OCT-A, but a direct comparison of the optic disc and the peripapillar perfusion between OCT-A and FA-ICGA has never been performed.

The aim of our study was to assess the value of OCT-A in the evaluation and diagnosis of acute NA-AION and A-AION in comparison with FA and ICGA. Moreover, vessel density (VD) parameters were analyzed in order to quantify vascular changes.

## Materials and methods

A retrospective evaluation of the clinical charts and exams performed in patients affected by acute NA-AION or A-AION was made. The diagnosis were confirmed on the basis of the following criteria: acute, unilateral, painless visual loss, altitudinal and/or central visual field defects, unilateral characteristic acute optic nerve head features (diffused or segmental optic swelling variably associated with flame-shaped hemorrhages in the case of NA-AION and pallid disc edema in regards to A-AION) [16]. This was followed by the appearance of optic disc atrophy after a period of 6 to 11 weeks and no evidence of another neurological or ocular disorder that could be responsible for optic disc edema. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were assessed in the blood sample of the patients to help recognize the arteritic form.

All the patients and controls were evaluated at the Sant'Orsola-Malpighi Hospital of Bologna, Italy between January 2015 and June 2016. The research adhered to the tenets of the Declaration of Helsinki and informed consents were obtained from all the participants.

All the patients performed a complete ophthalmological examination followed by visual field (VF, Humphey 30–2 SITA standard 30–2, Humphrey VF analyzer, HFA II 750–4.1 2005; Carl Zeiss Meditec, Dublin, CA, USA), FA and ICGA (Spectralis, Heidelberg Engineering, Heidelberg, Germany) and OCT-A (AngioVue Imaging System; Optovue, Inc., software version 2015.100.0.33 Fremont, CA, USA) of the optic nerve head during the acute phase of the disease (within the first 2 weeks from symptoms presentation).

Inclusion criteria for the control group were the following: age greater or equal to 65 years-old, best corrected visual acuity (BCVA) of at least 0.8 (decimal fraction); spherical or cylindrical refractive errors of less than 4 and 2 diopters (D), respectively; intraocular pressure (IOP) < 21 mmHg; normal appearance of the optic disc; normal VF and absence of ocular or systemic disease that could interfere with OCT-A examination.

### OCT-A procedure

OCT-A scans were obtained by the spectral domain OCT system. This system has an A-scan rate of 70 kHz per second, using a light source centered on 840 nm and a bandwidth of 45 nm. The tissue resolution was 5 μm axially for OCT scans and 15 μm for OCT-A scans. Both eyes of each participant were examined and scanned at least twice within the same visit. Before imaging, each subject's pupils were dilated with a combination of 0.5% tropicamide and 10% phenylephrine. An internal fixation light was used to center the scanning area. The OCT signal position and signal quality were optimized by means of "Auto All" function, which performs in sequence the "Auto Z" to find the best position for obtaining the retina OCT image, the "Auto F" to find the best focus for the particular subject refraction, and the "Auto P" to find the best polarization match for the particular subject ocular polarization. Each image set comprised two raster volumetric patterns (one horizontal and one vertical) of 4.5 × 4.5 mm or 3 × 3 mm centered on the optic nerve head. An orthogonal registration

algorithm was used to produce merged 3- dimensional OCT angiograms. Each volume was composed of 304 B-scans at which two consecutive B-scans were obtained. Each B-scan contained 304 A-scans. The split-spectrum amplitude-decorrelation angiography (SSADA) algorithm compares the consecutive B-scans at the same location to detect flow using motion contrast [17, 18].

Scans with low quality (i.e., if the subject blinked or if there were motion artifacts in the data set) and signal strength index (SSI) <50 were excluded and repeated until at least two good quality scans were achieved. The best scan for quality was considered for analysis. All the images were evaluated by two different examiners and if an evaluation discrepancy emerged, a third examiner was asked to judge the images.

### Vessel density analysis

Peripapillary and optic nerve head vessel densities (VDs) were calculated as previously described [19]. VD is the percentage of area occupied by the large vessels and microvasculature in a particular region [20, 21]. Briefly, the software calculates VD in various layers of the retina and the optic nerve head (ONH). The ONH VDs were calculated from the "nerve head" segment of the optic nerve head angiogram (from 2000 μm above the internal limiting membrane (ILM) to 150 μm below the ILM). The software automatically fits an ellipse to the optic disc margin and calculates the average vessel density within the ONH. In the case where disc margin detection error was observed, manual correction of the disc margin was performed by the observers. The peripapillary vessels were analyzed in superficial retinal layers from the Radial Peripapillary Capillary (RPC) segment (from the ILM to the nerve fiber layer posterior boundary). The peripapillary region is represented by a 0.75 mm-wide elliptical annulus extending from the optic disc boundary (Fig. 1).

### Statistical analysis

Data were presented as median and range. Age and VD from A-AION and NA-AION patients and control group were compared using the non-parametric Mann-Whitney test. Categorical data was compared used the $X^2$ test. A $p$ value <0.05 was considered to be statistically significant. GraphPad Instat (V.3a) for Macintosh (GraphPad Software, San Diego, California, USA) was used for statistical analysis.

## Results

Six eyes of five patients were evaluated for optic disc edema due to acute A-AION and NA-AION. A single patient had second eye involvement 4 months after the first eye NA-AION (V.M.), but OCT-A images of the second eye were not analyzable due to severe motion artifacts. So, the images of five eyes were analyzed (female:male = 4:1, median age 73.4 years, range 65–81). Four patients had NA-AION and one A-AION (due to GCA). Clinical characteristics of the patients are summarized in Table 1.

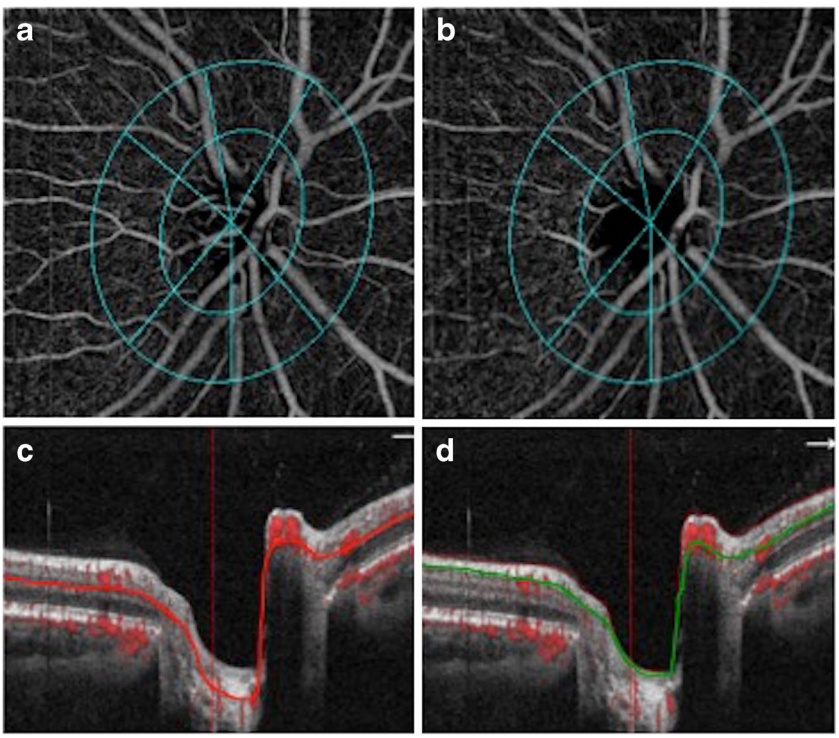


**Fig. 1** Optical coherence tomography-angiography (OCT-A, A and B) and optical coherence tomography (OCT, C and D) of a control's optic disc right eye. The images on the left (A and C) are referred to "optic nerve head" (ONH) segment of the optic nerve angiogram. The images on the right (B and D) are referred to "radial peripapillary capillary" (RPC) segment of the optic nerve angiogram. Note different vascular network visualization with OCT-A and the different layer segmentation with OCT-A: red line for ONH segmentation (C) and green line for RPC segmentation (D). Note the blue circles superimposed to the optic nerve head, representing the optic nerve boundary (inner circle) and the peripapillary sectors (outer circle), within which vessel density (VD) was calculated

**Table 1** Clinical characteristics of the patients

| Patient | Sex | Age | Eye | Diagnosis | OCT-A | FA-ICGA |
|---|---|---|---|---|---|---|
| #1 | M | 73 | RE | NA-AION | Non-perfusion areas in the nasal and inferior optic disc. | Focal leakage from the disc; disc filling defects. |
| #2 | F | 81 | RE | NA-AION | Superior peripapillary capillary network reduction, tortuous capillaries around the capillary network reduction. | Generalized leakage from the disc. |
| #3 | F | 73 | RE | NA-AION | Non-perfusion areas in the superior and temporal optic disc. | Focal leakage from the disc, disc filling defects. |
| #4 | F | 75 | LE | A-AION | Non-perfusion areas in the superior, inferior and temporal disc, inferotemporal peripapillary choroidal perfusion defect. | Inferotemporal peripapillary choroid filling delay; focal leakage from the disc; disc filling defects. |
| #5 | F | 65 | LE | NA-AION | Inferotemporal peripapillary capillary network reduction, tortuous capillaries around the capillary network reduction. | Generalized leakage from the disc. |

M: male; F: female; RE: right eye; LE:left eye; NA-AION: non-arteritic anterior ischemic optic neuropathy; A-AION: arteritic anterior ischemic optic neuropathy; OCT-A: optical coherence tomography angiography; FA-ICGA: fluorescein angriography and indocyanine green angiography

In patients affected by NA-AION, we found two different OCT-A patterns: in two cases, non-perfusion areas at the level of the optic nerve head were clearly detectable and were comparable to disc filling defects viewable with FA (Figs. 2) both in early and late phases. The extension and the boundary of the ischemic areas were not detectable with ICG images.

In the other two NA-AION cases, sectorial peripapillary capillary network reduction was detectable with OCT-A without a clear non-perfusion defect on the optic nerve head, associated with the presence of tortuous capillaries and telangiectasia around the region of microvascular network reduction (Fig. 3). These two cases presented generalized leakage from the disc in the late FA phases without optic disc filling defects. Specifically, the case presented in Fig. 3 showed optic disc filling delay in the very early FA in the inferotemporal sector (corresponding to the inferotemporal peripapillar capillary network reduction), but it is soon masked by generalize optic disc leakage.

In the single patient affected by A-AION, non-perfusion areas at the level of the optic nerve head were clearly detectable on OCT-A and were comparable to optic disc filling defects viewable with FA (Fig. 4) both in early and late phases.

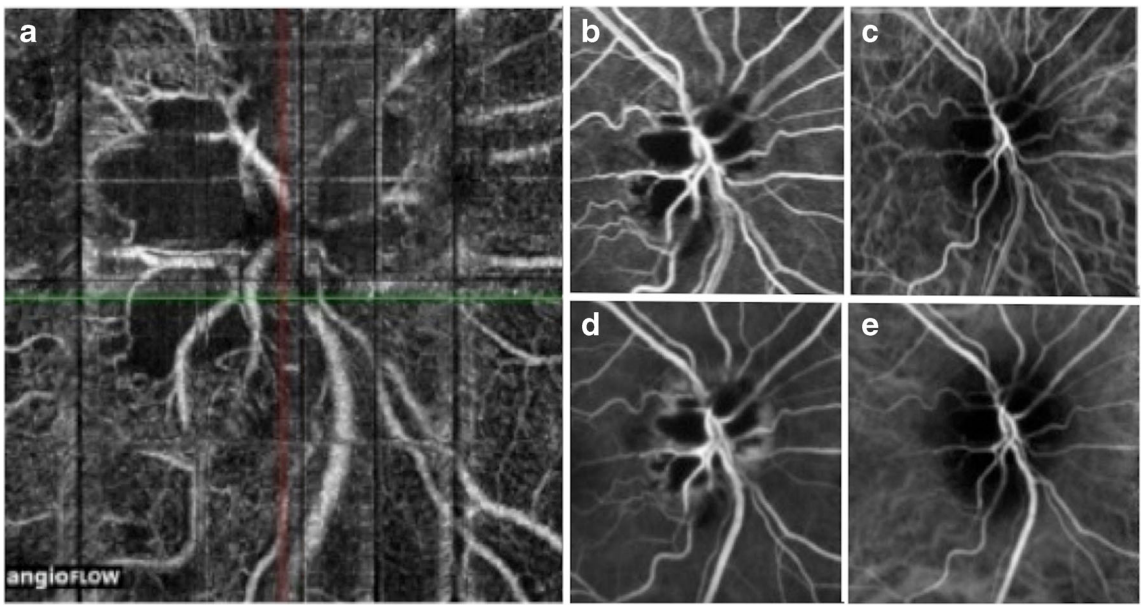


**Fig. 2** Female, 73 y.o. affected by acute non-arteritic anterior ischemic optic neuropathy (NA-AION). OCT-A (A) shows ischemic defects in the superior and temporal optic nerve head sectors. The extension and the border of the non-perfusion areas on OCT-A are comparable with that seen in early and late fluorescein angiography images (B and D, respectively). Peripapillary choroidal delay is better visible with indocyanine green angiography images (C:early phase; E:late phase)

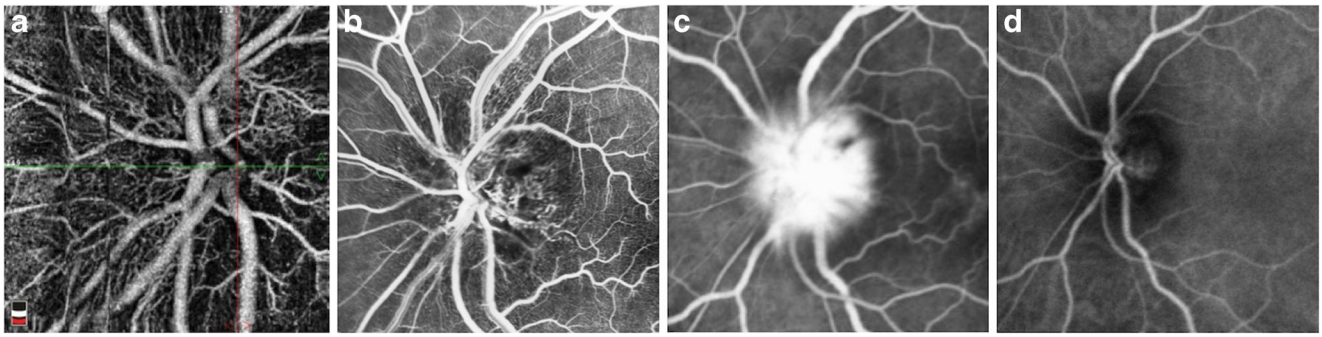


**Fig. 3** Female, 65 y.o. affected by bilateral NA-AION. In the figures are presented the images of the first eye involved (the left one). Optical coherence tomography angiography OCT-A (A) shows inferotemporal peripapillary capillary network reduction. Early fluorescein angiography (B) shows inferotemporal optic disc filling delay, which is soon masked by generalized optic disc leakage (C). No additional information was added by indocyanine green angiography (D)

In this case, the inferotemporal peripapillary watershed zone was more evident with ICGA, but both FA and OCT-A could detect it at the choriocapillary layer, although it was not possible to visualize the entire extension of the watershed zone using OCT-A, because of the smaller scan area.

## Vessel density analysis

Table 2 shows age, sex and VDs of NA-AION patients and the control group. Statistically significant ONH and RPC VDs reduction were detected in the NA-AION group when

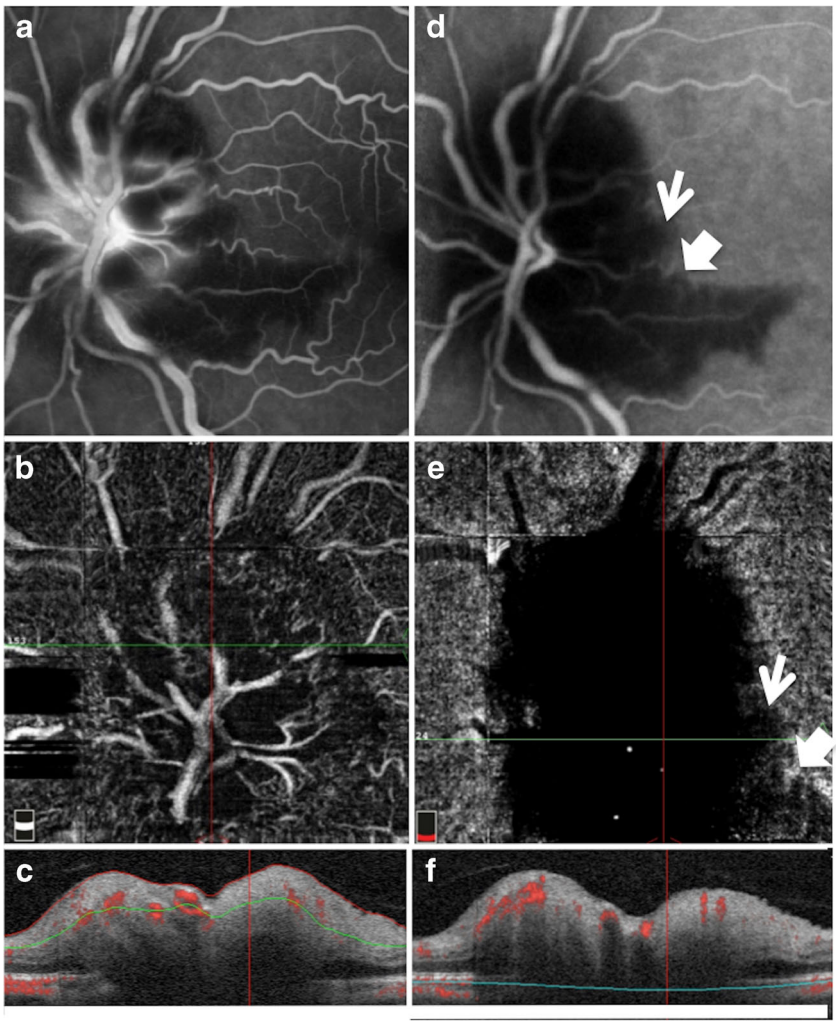


**Fig. 4** Female, 75 y.o. affected by A-AION. Late fluorescein angiography (A) shows optic disc filling defects in the superior, temporal and inferior sectors and an inferotemporal peripapillary watershed zone. The extension and the border of the ischemic areas at the level of the optic nerve head are comparable with that seen with OCTA (B). The OCT scan (C) shows the corresponding segmentation (between red and green lines) of the OCTA image. Late indocyanine green angiography (D) shows peripapillary choroidal perfusion defects and the watershed zone. OCTA at the level of the choriocapillaris layer (E) and corresponding OCT scan (light blue line, F). Note the correspondences of the border of the peripapillary choroidal perfusion defects and the watershed zone between OCT-A and ICG-A (white arrows)

**Table 2** Clinical data and vessel density of non-arteritic anterior ischemic optic neuropathy patients and controls

| | NA-AION ($n$ = 4) | Controls ($n$ = 8) | $P$ value* |
|---|---|---|---|
| Age (year) | 73 (65–81) | 71.9 (64–82) | n.s. |
| Sex (M:F) | 1:3 | 2:6 | n.s.** |
| ONH VD (%) | 44.55 (38.82–51.68) | 53.07 (50.1–55.05) | <0.01 |
| RPC VD (%) | 47.47 (43.13–49.62) | 60.38 (56.53–63.09) | <0.01 |

*Mann-Whitney test

**$X^2$ test

Age and vessel density (VD) are reported as median (range); NA-AION: non-arteritic anterior ischemic optic neuropathy; n = number of subjects; M: male; F: female; VD: vessel density; ONH: optic nerve head; RPC: radial peripapillar capillary

compared to controls (Table 2, Mann-Whitney test, $p < 0.01$ for all the variables). The VD of the single A-AION patient was not included in the statistical analysis, and it was not correct to include this case in the NA-AION group, due to the different etiology between the two forms.

## Discussion

The present study shows that OCT-A was able to detect microvascular perfusion defects in acute NA-AION and A-AION.

The arteritic form of AION is due to perfusion defects at the level of the short PCAs, proximal to their division into paraoptic and choroidal branches; on the other side, in the non-arteritic form, the location of the vasculopathy is distal to the PCAs, affecting the paraoptic branches or, more likely, their tributaries within the optic disc [2]. Until now, FA and ICG represented the gold standard for visualization of retinal, optic disc and choroidal vasculature and some studies were conducted to find different angiographic pattern in the two forms, but they were not conclusive [6, 7, 22].

Using OCT-A, two vascular patterns can be qualitatively recognized in NA-AION:

1) Optic nerve head non-perfusion area. OCT-A was able to visualize the boundary and the extensions of the optic nerve head non-perfusion areas, when present. These areas were perfectly comparable to optic disc filling defects detectable with FA images. In these cases we believe that OCT-A could be adequate to correctly diagnose acute NA-AION.
2) Sectorial peripapillary capillary network reduction. In cases where a diffuse leakage from the disc without a clear optic disc filling defect was visible with FA, no clear non-perfusion defects were detectable on OCT-A either. However, in these cases a sectorial peripapillary capillary network reduction was present in OCT-A images, as recently described [11]. Moreover, the presence of tortuous capillaries and telangiectasia is detectable around the region of microvascular network reduction, as previously reported [12]. In comparison to FA, a better visualization of the peripapillary microvasculature [10] associated with no masking due to vascular leakage allows better recognition of the sectorial peripapillary microvascular defect using OCT-A.

In the case of A-AION, we found optic nerve head non perfusion areas, which are not dissimilar to that detected in the first two cases of NA-AION described above. Moreover, evaluating the choriocapillar layer, OCT-A was able to visualize the peripapillary choroidal defect, although not entirely, as it scans only a small peripapillar area. FA and mostly ICG-A can better detect the entire watershed zone in this case (Fig. 4). Despite the different pathogenesis of A-AION and NA-AION, we did not find distinctly different vascular patterns between them using OCT-A, except for the detection of the peripapillary watershed zone. However, previous studies suggested that the detection of the watershed zone is not necessary for the diagnosis of NA-AION or A-AION, as it is present at the same rate also in the normal population [4, 6]. Larger scans and a better visualization of the choriocapillaris by OCT-A could improve future studies of choroidal microvasculature.

Moreover, OCT-A can provide quantitative information by vessel density analysis. Both optic nerve head and peripapillary VDs were reduced in NA-AION patients, when compared to controls, and these parameters could be useful to differentiate ischemic forms from other causes of acute optic disc edema. Further studies could recognize different OCT-A features and quantify possible VD modification (increase or reduction) in inflammatory, infectious and hypertensive acute optic disc edema.

In general, these OCT-A perfusion patterns suggest the hypothesis of a watershed infarct in NA-AION secondary to transient hypoperfusion or to venous infarct [23]. The microvascular network reduction associated with surrounding tortuous capillaries detected in some cases could be consistent with the hypothesis of venous insufficiency in NA-AION [12]. A-AION is more likely to represent stenosis or obstruction at the level of the more upstream arterioles (short PCAs), as suggested by the more diffuse ischemia involving both the optic nerve head and the peripapillar choroid.

This study has some limitations: first of all, the small sample size and the inclusion of only one A-AION case, but OCT-A is a new diagnostic tool and NA-AION and mostly A-AION are uncommon diseases. We believe that our cases are well documented, which can aid the ophthalmologists in their clinical practice. In the future, the collection of more cases could more extensively describe the diseases and shed light on the different pathophysiology of NA-AION and A-AION.

Secondly, OCT-A images from a patient were excluded due to motion artifacts. We expect that the recent software improvements with the introduction of a real time eye-tracker (DualTrac) will reduce this problem.

In conclusion, OCT-A is a safe, fast and non-invasive examination that should be performed as a primary test in all the patients with acute optic disc edema in order to find perfusion defects. Moreover, it gives information about retinal, choroidal and optic nerve head vasculature using a single scan. More invasive and slower examination methods (i.e., FA and ICGA) could be subsequently performed if OCT-A did not allow for definitive diagnosis.

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**Compliance with ethical standards**

**Conflict of interest** All authors certify that they have no affiliations with or involvement in any organization or entity with any financtial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Proprietary interest** None of the author has proprietary interest in the content of the manuscript.

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