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Choroidal Vascular Changes in Arteritic and Non-arteritic Anterior Ischemic Optic Neuropathy

Marco Pellegrini, Giuseppe Giannaccare, Federico Bernabei, Fabiana Moscardelli, Costantino Schiavi, Emilio C. Campos

PII: S0002-9394(19)30139-4

DOI: https://doi.org/10.1016/j.ajo.2019.03.028

Reference: AJOPHT 10901

To appear in: *American Journal of Ophthalmology*

Received Date: 28 November 2018

Revised Date: 25 March 2019

Accepted Date: 27 March 2019

Please cite this article as: Pellegrini M, Giannaccare G, Bernabei F, Moscardelli F, Schiavi C, Campos EC, Choroidal Vascular Changes in Arteritic and Non-arteritic Anterior Ischemic Optic Neuropathy, *American Journal of Ophthalmology* (2019), doi: https://doi.org/10.1016/j.ajo.2019.03.028.

ABSTRACT

Purpose: To compare choroidal vascularity index (CVI) in patients with arteritic anterior ischemic optic neuropathy (A-AION), non-arteritic anterior ischemic optic neuropathy (NA-AION) and control subjects.

Design: Retrospective cross-sectional study.

Methods: This study was conducted at the Ophthalmology Unit of the S.Orsola-Malpighi University Hospital (Bologna, Italy). Macular and optic nerve head optical coherence tomography (OCT) scans of 20 patients with A-AION secondary to giant cell arteritis (biopsy-proven), 20 patients with NA-AION, and 20 control subjects were acquired with Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany). Images were binarized using the ImageJ software, and total choroid area (TCA), luminal area (LA) and stromal area (SA) were segmented. The main outcome measure was CVI, defined as the ratio of LA to TCA.

Results: Patients with A-AION showed a significantly lower macular and peripapillary CVI compared to both patients with NA-AION (respectively, 67.17±2.35 vs 69.66±4.18, P=0.048; 63.51±3.29 vs 67.67±3.07, P<0.001) and control subjects (respectively, 67.17±2.35 vs 70.00 ± 2.95, P=0.021; 63.51±3.29 vs 68.69 ± 3.19, P=0.002). Conversely, no significant difference in macular and peripapillary CVI was found between patients with NA-AION and controls (respectively, P=0.942 and P = 0.570). After adjustment for age, the difference of peripapillary CVI among groups remained statistically significant (P<0.001), while the difference in macular CVI did not (P=0.060).

Conclusions: Macular and peripapillary CVI are reduced in patients with A-AION. These parameters may be useful to evaluate quantitatively choroidal vascular dysfunction in A-AION, serving as a new additional diagnostic tool to distinguish A-AION from NA-AION.

Choroidal Vascular Changes in Arteritic and Non-arteritic Anterior Ischemic Optic Neuropathy

Short title: **Choroidal Changes in Anterior Ischemic Optic Neuropathy**

Marco Pellegrini, Giuseppe Giannaccare, Federico Bernabei, Fabiana Moscardelli, Costantino Schiavi, Emilio C Campos.

Ophthalmology Unit, S.Orsola-Malpighi University Hospital, University of Bologna, Bologna, Italy

Corresponding Author:

Marco Pellegrini, MD

Ophthalmology Unit, S.Orsola-Malpighi University Hospital, University of Bologna, Italy

Address: Via Palagi 9, 40138, Bologna, Italy

Tel: +39 051 2142845

Fax: +39 051 342821

E-mail: marco.pellegrini@hotmail.it

INTRODUCTION

Anterior ischemic optic neuropathy (AION) is characterized by acute, severe, and painless visual loss due to infarction of the optic nerve head.[1] This condition can be divided into two distinct entities: arteritic ischemic optic neuropathy (A-AION), and non-arteritic ischemic optic neuropathy (NA-AION), that are characterized by different clinical features and histopathological findings. Arteritic ischemic optic neuropathy is caused by giant cell arteritis (GCA), a vasculitis of medium and large-sized vessels affecting primarily the elderly.[2] Patients with GCA often present with systemic symptoms including fatigue, fever, weight loss, headaches, scalp tenderness and jaw claudication. It is considered an ophthalmic emergency because of its potential to cause acute irreversible vision loss due to inflammation and thrombotic occlusion of posterior ciliary arteries.[2,3]

Non-arteritic anterior ischemic optic neuropathy is presumed to result from transient non-perfusion or hypoperfusion of the optic nerve head. Several systemic and local factors may play a role in the complex pathogenesis, including nocturnal hypotension, rise of the intraocular pressure (IOP), venous insufficiency, location of the watershed zone of the posterior ciliary arteries in relation to the optic disc and the structural predisposition of a crowded optic disc with small or absent cup.[4-6]

Arteritic AION is often accompanied by choroidal ischemia, since posterior ciliary arteries provide blood flow to the optic disk as well as to the choroid.[7] Impaired choroidal perfusion on fluorescein angiography (FA) is considered a suggestive indicator of A-AION,[8,9] while is not a consistent feature of NA-AION.[9-11] However, FA is invasive, and the specificity of its findings for reaching the diagnosis of A-AION in patients with transient or permanent vision loss remains still unclear.[12] Therefore, new imaging modalities able to improve the detection of A-AION and reduce the rate of permanent vision loss are desirable.

In recent years, in vivo quantification of the choroidal vasculature based on image binarization of spectral-domain optical coherence tomography (SD-OCT) scans was introduced in various ocular diseases involving retina and choroid.[13-20] In particular, this analysis allows to calculate a new parameter named choroidal vascularity index (CVI), defined as the proportion of the luminal area (LA) to the total choroid area (TCA).[14]

The purpose of the present study was to determine the CVI by means of image binarization of SD-OCT images in patients with acute A-AION secondary to GCA, acute NA-AION and healthy controls.

MATERIALS AND METHODS

This retrospective cross-sectional study included patients with acute A-AION and NA-AION visited at the Neuro-ophthalmology Service of our Institution (S.Orsola-Malpighi University Hospital, Bologna, Italy) during the period between January 2015 and October 2018. Inclusion criteria for both groups were age older than 60 years, sudden onset of unpainful monocular vision loss associated with optic disc edema and altitudinal and/or central visual field defects, complete medical records including also SD-OCT scans of adequate quality. All patients belonging to the A-AION group had a diagnosis of GCA made by a rheumatologist, and confirmed by temporal artery biopsy. In 7 of them, the diagnosis of GCA was reached after the onset of AION, while 13 of them had already a diagnosis at the time of the ophthalmological disease. For these 13 patients, the time between the diagnosis of GCA and AION ranged between 1 and 18 months (mean 5.2 ± 4.7 months). None of the patients with NA-AION had signs of GCA, such as headache,

temporal artery tenderness to palpation, elevated erythrocyte sedimentation rate and C-reactive protein levels.[2] Healthy subjects with age older than 60 years, normal appearance of the optic disc and normal visual field were included as a control group. Exclusion criteria for all groups were presence or history of other ocular diseases (e.g. glaucoma or diabetic retinopathy) or systemic diseases (e.g. stroke or pituitary tumor) that could influence the study results, history of ocular surgery (except for uncomplicated cataract surgery), refractive error greater than ±5.0 D spherical equivalent. Each subject signed an informed consent before any study procedure. The study was performed in accordance with the principles of the Declaration of Helsinki, and was approved by the local Institutional Review Board of our Institution.

Patients with A-AION, NA-AION and control subjects underwent a complete ophthalmologic evaluation including best-corrected visual acuity (BCVA) testing, slit-lamp examination, applanation tonometry, fundus examination, automated perimetry, macular and optic nerve head SD-OCT. Data from BCVA were converted to logMAR equivalents of Snellen acuity for the statistical purposes. We used a value logMAR = 2.6 to represent vision of counting fingers, and used extrapolated values of 2.7, 2.8, and 2.9 logMAR to represent hand motion, light perception, and no light perception, respectively.[21] Perimetry was performed with the Swedish Interactive Thresholding Algorithm using the 24-2 pattern on the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, CA, USA). Only reliable examinations, defined as false positives, false negatives and fixation losses less than 33%, were included in the analysis. The SD-OCT acquisitions were obtained in all patients within one week from the onset of the AION with the Spectralis HRA-OCT (Heidelberg Engineering, Heidelberg, Germany). All the scans were obtained approximately at the same time of the day (9 am). Macular OCT images were acquired with enhanced depth imaging (EDI) mode using a volume scan of 30°x 20° containing 25 B-scans, and centered on the macular region. Individual B-scan was 8.5 mm in length, spaced 240 µm apart from each other, and was an average of 30 frames. The OCT scan centered across the central foveal region was chosen for the analysis. Optic nerve head OCT images were acquired using a 3.4 mm diameter 360° circle scan c entered on the optic nerve head with the standard protocol for retinal nerve fiber layer. Only data from the affected eyes of patients with AION, and right eyes of control subjects were included in the analysis.

To measure the CVI, the macular and optic nerve head SD-OCT scans were binarized and segmented using the public domain software ImageJ 1.51s (National Institutes of Health, Bethesda, MD, USA), with a semi-automated method previously described.[16] Briefly, the OCT image was opened in ImageJ, and the polygon tool was used to select the region of interest (ROI) across the entire length of the OCT scan. The upper boundary of the ROI was traced along the choroidal-RPE junction and the lower boundary along the choroidal-scleral junction in order to identify the TCA. After conversion to an 8-bit image, Niblack's auto-local threshold was applied to binarized the image and demarcate the LA. The image was converted back to a red, green, blue image, and the color threshold tool was used to select the dark pixels, representing the LA. The TCA and LA values were measured; the stromal area (SA) was calculated by subtracting LA from TCA; the CVI, defined as the LA divided by the TCA, was then computed (Figure 1). Optic nerve head scans were also segmented in four parts of the same width to evaluate the CVI in the temporal, superior, nasal and inferior sectors (Figure 2).[19] The CVI calculation was performed separately by 2 investigators (MP & FB) masked to patients' characteristics, in order to evaluate the interobserver reliability. The mean value for each parameter calculated was used for the statistical analysis.

Data analysis was conducted with SPSS statistical software (SPSS Inc, Chicago, Illinois, USA). Values are expressed as mean ± standard deviation (SD). The Shapiro-Wilk's test was used to determine normality of data, and the Levene's test was used to assess the homogeneity of variances. If the data was distributed normally, a one-way ANOVA test was used to compare continuous variables among patients with A-AION, NA-AION, and control subjects. Post hoc comparisons were performed using the Tukey's test. In the absence of normality, nonparametric statistical analysis (Mann-Whitney U test) was used to compare continuous variables among groups. The interobserver reliability of macular and peripapillary CVI calculation was evaluated using intraclass correlation coefficients (ICCs). The correlations of CVI with demographic and clinical parameters in patients with A-AION and NA-AION were examined using Pearson correlation analysis. An ANCOVA was run to determine the differences in macular and peripapillary CVI among patients with A-AION, NA-AION and controls after adjusting for age. A *P* value < 0.05 was considered statistically significant.

RESULTS

Overall, 20 patients with A-AION, 20 patients with NA-AION and 20 control subjects were included in the study. The demographical and clinical characteristics of patients and controls are reported in Table 1. There were no significant differences in sex distribution and IOP among the three groups (respectively, *P* = 0.410 and *P* = 0.492). Mean age was not significantly different in patients with A-AION and controls (*P* = 0.359), while patients with NA-AION were significantly younger than patients with A-AION (*P* < 0.001) and controls (*P* = 0.005). Mean BCVA was significantly lower in patients with A-AION compared to patients with NA-AION (*P* < 0.001), while visual field mean deviation did not significantly differ between the two groups (*P* = 0.359).

In macular OCT scans, the choroidal-scleral junction was visualized in all eyes. In optic nerve head OCT scans, the choroidal-scleral junction was not adequately visible in 5 patients with A-AION (25%) and in 3 patients with NA-AION (15%) because of optic disc edema. Therefore, these patients were excluded from peripapillary CVI calculation. Choroidal vascularity index results measured using the image binarization protocol of macular OCT (Figure 3, Top) and optic nerve head OCT scans (Figure 3, Bottom) in patients with A-AION, NA-AION controls are reported in Table 2. The CVI calculation showed an excellent interobserver reliability, with an ICC of 0.937 (95% CI: 0.894 to 0.963) for macular CVI and of 0.953 (95% CI: 0.919 to 0.973) for peripapillary CVI.

Macular CVI was significantly lower in patients with A-AION compared to patients with NA-AION (mean difference -2.5 [95% CI, -5.0 to -0.02], *P* = 0.048) and control subjects (mean difference -2.8 [95% CI, -5.3 to -0.4], *P* = 0.021). Conversely, no significant difference in macular CVI was found between patients with NA-AION and controls (mean difference -0.3 [95% CI, -2.8 to 2.1], *P* = 0.942). Peripapillary CVI was significantly lower in patients with A-AION compared to patients with NA-AION (mean difference -4.2 [95% CI, -6.9 to -1.4], *P* = 0.002) and control subjects (mean difference -5.2 [95% CI, -8.0 to -2.4], *P* < 0.001). Conversely, no significant difference in peripapillary CVI was found between patients with NA-AION and controls (mean difference -1.0 [95% CI, -3.4 to 1.4], *P* = 0.570).

In the sectorial sub-analysis of peripapillary CVI, patients with A-AION demonstrated a significantly lower peripapillary CVI compared to controls in the superior (mean difference of -4.1 [95% CI, -7.4 to -0.9], *P* = 0.010), nasal (mean difference -5.1 [95% CI, -8.7 to -1.6],

P = 0.003) and inferior sectors (mean difference -2.6 [95% CI, -6.6 to -1.4], *P* = 0.026), but not in the temporal sector (mean difference -3.2 [95% CI, -7.5 to 1.2] *P* = 0.134). Conversely, no significant difference in any of the sectors was found between patients with A-AION and NA-AION and patients with NA-AION and controls (all *P* > 0.05).

There was a significant correlation of macular and peripapillary CVI in patients with A-AION (R = 0.741, *P* = 0.006). Conversely, these two parameters were not correlated in patients with NA-AION (*P* = 0.357). In both patients with A-AION and NA-AION, no significant correlation of macular and peripapillary CVI with sex, age, IOP, BCVA and visual field mean deviation was found (all *P* > 0.05).

After adjustment for age, there was a statistically significant difference of peripapillary CVI among groups (*P* < 0.001). Post hoc analysis with a Bonferroni correction revealed that peripapillary CVI was significantly lower in patients with A-AION compared to patients with NA-AION (mean difference -4.4 [95% CI, -7.7 to -1.1], *P* = 0.006) and control subjects (mean difference -5.2 [95% CI, -8.1 to -2.3], *P* < 0.001). Conversely, no significant difference between patients with NA-AION and control subjects was found (mean difference -0.9 [95% CI, -0.2 to 0.4], *P* = 1.000). After adjustment for age, the difference of macular CVI among groups was no longer significant (*P* = 0.060).

DISCUSSION

The first crucial step in patients older than 60 years old presenting features of AION is to rule out GCA, given the potential for catastrophic bilateral loss of vision and systemic vasculitic sequelae. The immediate treatment of GCA with intensive high-dose corticosteroid may prevent visual loss but is not without risk. Therefore, the accuracy of the criteria used to establish or exclude the diagnosis is essential to minimize medication morbidities.[22] However, the specificity of the currently available ophthalmologic diagnostic testing, such as FA, remains unknown.[12]

In this study, we used a new image binarization technique applied on macular and optic nerve head SD-OCT scans to investigate the vascular status of the choroid in patients A-AION, NA-AION and control subjects. This semi-automated technique permits to calculate the CVI, which is an index of the proportion between the vascular and stromal components of the choroid. The CVI was validated as a useful diagnostic tool in various ocular diseases.[15-20]

To the best of our knowledge, this is the first study that applied this analysis in the setting of AION. We found that macular CVI and peripapillary CVI were reduced in patients with A-AION compared to those with NA-AION and control subjects. By contrast, no significant difference in macular and peripapillary CVI was found between patients with NA-AION and controls. In addition, we evaluated the peripapillary CVI in the temporal, superior, nasal and inferior sectors, as already done by Park et al in the setting of glaucoma.[19] In this sub-analysis, patients with A-AION showed a greater reduction of peripapillary CVI in the nasal sector, followed by the superior and inferior sectors, compared to controls. However, no significant differences between patients with A-AION and patients with NA-AION was found. Therefore, the clinical utility of segmenting peripapillary CVI in sectors for patients with AION remains unproven.

The decrease of the CVI in patients with A-AION may reflect the choroidal hypoperfusion secondary to vasculitis of posterior ciliary arteries. Indeed, A-AION is associated with thrombotic occlusion of posterior ciliary arteries proximal to their division into paraoptic and choroidal branches. This is well demonstrated by FA, which shows delayed choroidal filling

time as well as areas of choroidal ischemia in eyes with A-AION.[8,9,22] Furthermore, defects of the peripapillary choroidal perfusion were recently demonstrated in A-AION by using OCT angiography.[23,24] The results of this study are consistent with these observations, and suggest that CVI may be a useful tool to identify and measure quantitatively choroidal vascular dysfunction in A-AION.

It is recognized that A-AION and NA-AION have different pathogenesis, and show distinct patterns of choroidal vascular changes. In contrast to A-AION, the level of vascular occlusion in NA-AION seems to lie within the distribution of the paraoptic branches, distal to the branching of the choroidal vessels from the posterior ciliary arteries.[22] This is supported by previous FA studies, which showed delayed perfusion of the optic disc, but no choroidal perfusion defects in eyes with NA-AION.[9-11] In addition, histopathological studies of NA-AION revealed that the site of infarction is located predominantly in the retrolaminar optic nerve, with occasional extension into the laminar and prelaminar area.[25] In this study, macular and peripapillary CVI was not significantly different in patients with NA-AION compared to control subjects. This confirms that NA-AION does not seem to be associated with significant choroidal hypoperfusion.

Several previous studies investigated macular and peripapillary choroidal thickness (CT) in patients with NA-AION, showing inconsistent and conflicting results. Some of them reported an increased CT both in the macular[26] and peripapillary region,[27,28] while others showed a decreased macular[29] and peripapillary CT.[30] Finally, other studies reported no significant change of CT in eyes with NA-AION.[31,32] These disparities may arise from differences in population characteristics, stage of the disease, and techniques used to acquire and analyze OCT images. In addition, CT is influenced by several biological variables, including axial length, refractive error, intraocular pressure, systolic blood pressure and diurnal variation.[33,34] On the contrary, CVI shows lesser variability, being influenced by fewer physiologic factors. Thus, it appears a more robust marker to assess choroid vascular status.[14]

It has been hypothesized that choroidal alterations may be not a pathological consequence of NA-AION, but rather a contributing factor. This is supported by the observation of peripapillary choroidal changes not only in NA-AION eyes, but also in the unaffected fellow eyes.[27,28,30] Increased peripapillary CT combined with a crowded optic disc may produce a compartment-like syndrome with resultant ischemia.[27,28] On the other hand, a thinner peripapillary choroid may result in an optic nerve more vulnerable to choroidal circulation flow changes and more susceptible to hypoxia.[30] It is possible that such variability of CT predisposing to NA-AION occurs without a significant change of the proportion between the choroidal luminal and stromal components. This would explain the normal CVI observed in patients with NA-AION in this study. However, further research is needed to elucidate the choroidal contribution in the complex pathogenesis of the disease.

The main limitations of this study include its retrospective nature and the relatively small sample size. In addition, patients with A-AION and control subjects were slightly older compared to those with NA-AION. However, CVI is known to be less associated with age as opposed to CT.[14] After adjustment for age, peripapillary CVI was still significantly lower in patients with A-AION, while the difference in macular CVI was no longer significant. Lastly, optic disc edema precluded the clear visualization of choroidal-scleral junction in the optic nerve head OCT of 25% of patients with A-AION and 15% of patients with NA-AION. Hence, these eyes had to be excluded from the calculation of the peripapillary CVI, and this may limit the diagnostic efficacy of peripapillary CVI in eyes with significant disc edema.

In conclusion, macular and peripapillary CVI are reduced in patients with A-AION. This finding suggests that CVI calculation may serve as a useful adjunctive diagnostic tool to distinguish A-AION from NA-AION. Larger prospective studies are required to confirm our results, and define the clinical role of CVI in the diagnosis and management of AION.

Acknowledgement: none.

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FIGURE CAPTIONS

Figure 1. Choroidal vascularity index calculation with binarization of spectral-domain OCT images. Choroidal boundaries were traced to identify the total choroidal area (red lines, Top). The image was binarized using Niblack's auto-local threshold (Middle). The color threshold tool was used to select the dark pixels, representing the luminal area (yellow lines, Bottom). The CVI was computed dividing luminal area by total choroidal area.

Figure 2. Peripapillary choroidal vascularity index calculation in the four sectors of optic nerve head OCT scans. The luminal areas in the temporal (TMP), superior (SUP), nasal (NAS) and inferior (INF) sectors are represented respectively in red, green, blue and yellow lines.

Figure 3. Macular OCT with calculation of choroidal vascularity index in a representative patient with arteritic acute ischemic optic neuropathy (Top Left), and in a representative control subject (Top Right). Optic nerve head OCT with calculation of choroidal vascularity index in a representative patient with arteritic acute ischemic optic neuropathy (Bottom Left), and in a representative control subject (Bottom Right). Red lines represent the total choroidal area; yellow lines represent the luminal area.

Table 1. Demographic and clinical characteristics of patients with arteritic anterior ischemic optic neuropathy (A-AION), non-arteritic anterior ischemic optic neuropathy (NA-AION) and control subjects.

Characteristic	A-AION (n = 20)	NA-AION (n = 20)	Control subjects (n = 20)	*P*
Sex (m:f)	6:14	10:10	9:11	0.410
Age (years)	80.5 ± 7.9	69.4 ± 8.2	77.2 ± 6.6	**<0.001**
BCVA (LogMAR)	1.26 ± 1.18	0.46 ± 0.66	0.04 ± 0.05	**<0.001**
IOP (mmHg)	15.9 ± 2.9	14.9 ± 2.6	15.5 ± 3.0	0.492
Mean deviation (dB)	-18.8 ± 10.8	-14.8 ± 10.0	-0.1 ± 1.1	**<0.001**

BCVA: best-corrected visual acuity, IOP: Intraocular pressure.

Table 2. Choroidal parameters obtained with the image binarization protocol of macular and optic nerve head OCT scans in patients with arteritic anterior ischemic optic neuropathy (A-AION), non-arteritic anterior ischemic optic neuropathy (NA-AION) and control subjects.

Characteristic	A-AION (n = 20)	NA-AION (n = 20)	Control subjects (n = 20)	*P*
Macular CVI (%)	67.17 ± 2.35	69.66 ± 4.18	70.00 ± 2.95	**0.015**
Peripapillary CVI (%)	63.51 ± 3.29	67.67 ± 3.07	68.69 ± 3.19	**<0.001**
Temporal sector	65.16 ± 5.16	68.32 ± 5.75	68.67 ± 3.73	0.127
Superior sector	63.16 ± 4.05	64.89 ± 3.73	67.28 ± 3.39	**0.010**
Nasal sector	64.06 ± 3.20	66.90 ± 4.41	67.28 ± 4.06	**0.004**
Inferior sector	62.42 ± 6.35	65.01 ± 3.32	66.90 ± 4.38	**0.034**

CVI: choroidal vascularity index.