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ORIGINAL ARTICLE

Choroidal Thickness in Nonarteritic Anterior Ischaemic Optic Neuropathy: A Study with Optical Coherence Tomography

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ABSTRACT

Nonarteritic anterior ischemic optic neuropathy (NA-AION) is the most common nonglaucomatous optic neuropathy in adults over 50 years of age. It is usually related to cardiovascular risk factors. The primary objective of this study was to evaluate choroidal thickness in patients with chronic NA-AION, and the secondary objective was to evaluate macular thickness in these patients. This cross-sectional study compared two groups: group 1 included 20 eyes of 20 patients with chronic NA-AION, and group 2 included 31 eyes of 31 healthy controls. In both groups, the choroidal thickness was measured using the enhanced depth imaging program of Heidelberg Spectralis® optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany). The macular thickness was also measured using the automatic software of the same device. The mean follow-up time after NA-AION in group 1 was 57.17 ± 26.92 months. The mean choroidal thickness of the posterior pole was 244.38 ± 61.03 μm in group 1 and 214.18 ± 65.97 μm in group 2 ($p = 0.004$). The mean macular thickness was higher in group 2. Macular thickness is reduced in eyes that had an episode of NA-AION, whereas choroidal thickness is generally higher in these eyes when compared with normal eyes. The increase in choroidal thickness may be due to a local dysfunction in vascular autoregulatory mechanisms, which may predispose to ischemic phenomena.

Keywords: Choroidal thickness, enhanced depth imaging, macular thickness, nonarteritic anterior ischemic optic neuropathy, optical coherence tomography

INTRODUCTION

Nonarteritic anterior ischaemic optic neuropathy (NA-AION) is the second most common optic neuropathy in adults older than 50 years of age, after glaucoma.[1] The reported incidence is 2 to 10 cases per 100,000, affecting more commonly Caucasian Europeans.[2] Classically the patient presents with acute, unilateral, painless visual loss that evolves over several hours to days. The examination reveals optic disc oedema, relative afferent pupillary defect, dyschromatopsia, diminished light brightness and contrast sensitivity, and inferior altitudinal visual field defect (however, any region of the visual field can be affected). Symptomless optic disc oedema may precede visual loss in NA-AION and could constitute the earliest sign of the disease.[3] Ischaemia or hypoperfusion of the optic nerve head at the level of lamina cribrosa is the most widely accepted pathophysiology of NA-AION, but the location of the associated vasculopathy and mechanism of ischaemia remain uncertain. The optic disc in these patients has,

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characteristically, a small or nonexistent physiological cup and retinal nerve fibre crowding—disc at risk.[4] A few weeks after the ischaemic event, optic disc pallor supervenes as a result of ganglion cell apoptosis.[5,6]

The choroid is part of the uveal tract and, histologically, it is arranged in three layers of vessels from the outer to the inner part of the choroid: the Haller layer (large choroidal vessels), the Sattler layer (medium-sized vessels), and the choriocapillaris.[7,8] Its main function is to provide oxygen and nourishment to the outer retina, retinal pigment epithelium (RPE) and the prelaminar portion of the optic nerve.[9] Therefore, choroidal vascular changes may be implicated in retinal, pigment epithelium, or optic nerve diseases.

Until recently, choroidal imaging was limited to fluorescein angiography, indocyanine green angiography, laser Doppler flowmetry, and high-resolution ultrasonography, with marked restrictions in terms of resolution and ability to differentiate structures. In 2008, Spaide and colleagues described a new method called enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) that enables *in vivo* cross-sectional imaging of the choroid.[11,12] Since then, several studies evaluated choroidal thickness (CT) in eye diseases such as central serous chorioretinopathy (CSCR),[10] myopic retinopathy,[13] age-related macular degeneration (AMD),[14] among others.

The primary objective of this study is to evaluate CT in patients with chronic NA-AION, and the secondary objective is to evaluate macular thickness in these patients, comparing both parameters with a demographically similar control group.

MATERIALS AND METHODS

This cross-sectional case-control study was conducted at Central Lisbon Hospital Center, a university-based tertiary centre. Two groups of patients were enrolled in the study: group 1: 20 eyes of 20 patients with NA-AION; group 2: 31 eyes of 31 age-matched controls with a best-corrected visual acuity higher than or equal to 20/25, using a Snellen chart. All the participants had a refractive error lower than ±6 dioptres of spherical equivalent. In phakic patients with no prior refractive surgery, the most recent manifest refraction was recorded. The preoperative manifest refraction was used in patients who had prior cataract or refractive surgery. Participants were excluded if they had ocular hypertension, glaucoma, diabetes mellitus, significant cataract (Lens Opacities Classification System III grade 4 or more for any criteria[15]), retinal disease, previous retinal laser photocoagulation or vitreoretinal surgery, and other optic neuropathies except for NA-AION. Written, informed consent was obtained from all subjects, and this investigation adhered to the tenets of the Declaration of Helsinki. Ethics Committee approval was obtained.

The diagnosis of NA-AION was based on the following criteria: (1) history of sudden onset of visual loss with absence of other ocular and neurological diseases that might influence or explain the patient's visual symptoms; (2) optic nerve head oedema at the onset and spontaneous resolution within 2 to 3 months; (3) absence of systemic symptoms of giant cell arteritis, absence of a high erythrocyte sedimentation rate (>50 mm/hour) or a high C reactive protein; (4) visual field defect consistent with NA-AION; and (5) no clinical evidence of inflammatory, demyelinating, or compressive causes of optic neuropathy.[16,17] Every patient was submitted to a complete ophthalmological evaluation that included visual acuity assessment, biomicroscopy, fundoscopy, Goldmann applanation tonometry, and macular and choroidal thickness measurement using OCT Heidelberg Spectralis® (Heidelberg Engineering, Heidelberg, Germany). Macular thickness parameters were automatically calculated by existing Heidelberg OCT software (version 5.3.2). Choroidal imaging was made using EDI-OCT. Twenty-five sections, each comprising 100 averaged scans, were obtained in a $20^\circ \times 20^\circ$ (5.8 mm × 5.8 mm) square centred on the fovea. The horizontal section going through the centre of the fovea and the horizontal section located 1250 μm superior and inferior to the fovea were used for CT measurements. The choroid was measured using the caliper function from the outer border of the hyperreflective line corresponding to the RPE to the inner scleral border. CT measurements were made centrally (in the foveal meridian) and at 1500 μm in the nasal and temporal directions. A total of nine CT points were thus obtained in each eye (Figure 1). All the measurements were made between 2 PM and 4 PM by two ophthalmologists experienced in analysing OCT images. Only one eye was included per subject. In case of patients with bilateral disease, the eye with the better image quality was selected.

The data were statistically analysed using SPSS for Windows, version 20.0 (IBM SPSS, Armonk, NY, USA). Student's *t* test was performed to compare the mean differences between continuous variables. Correlations between tissue thickness (both macular and choroidal) and follow-up time were determined using Spearman's correlation test. A p value of less than 0.05 was deemed statistically significant. All the results were expressed as mean ± standard deviation.

RESULTS

Of the 20 patients initially recruited with a diagnosis of NA-AION, 2 were excluded due to the concomitant diagnosis of diabetes mellitus. Thus, in group 1 we

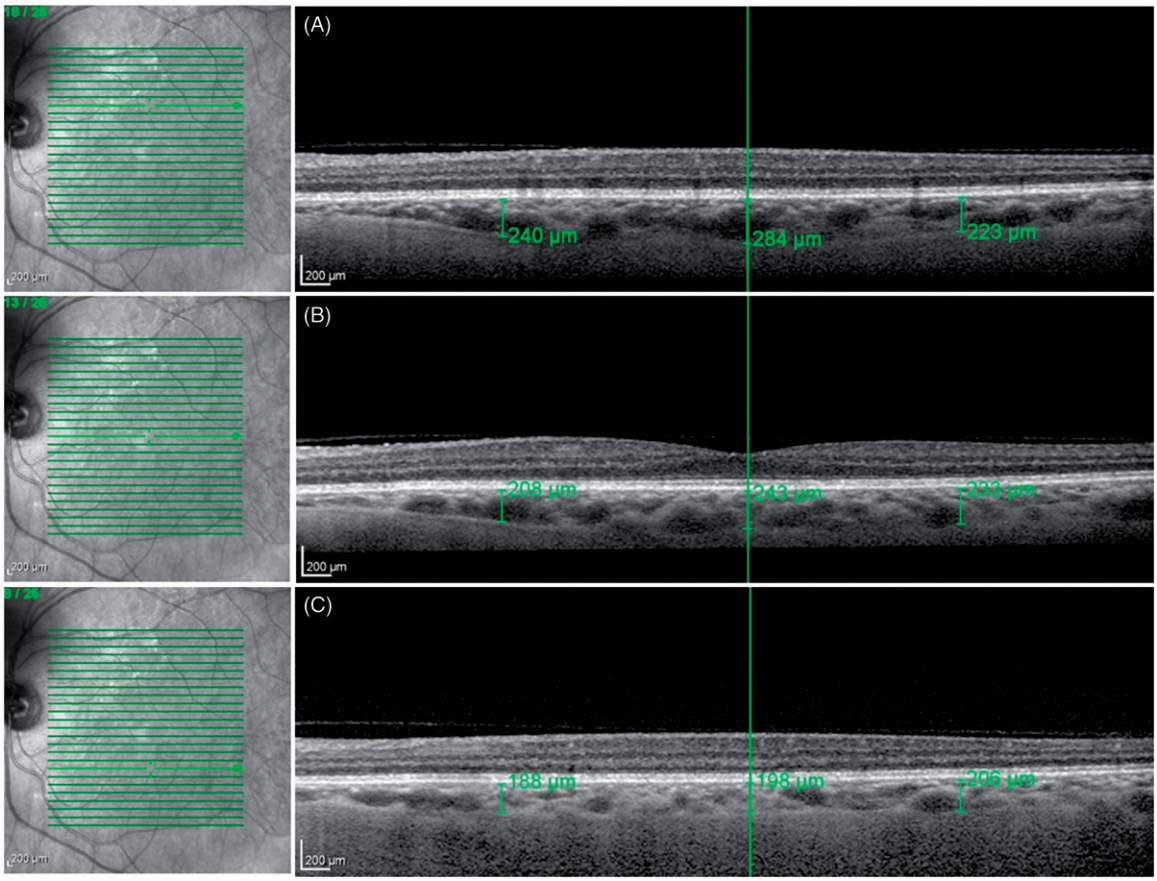

FIGURE 1 EDI-OCT imaging in three horizontal sections of the posterior pole. The choroid was measured vertically from the outer border of the hyperreflective line corresponding to the RPE to the inner scleral border. Choroidal thickness measurements were made centrally (in the foveal meridian) and at 1500 µm in the nasal and temporal directions.

studied 18 eyes of 18 patients, 3 of them with bilateral disease (where we included only 1 eye). Twelve patients were female and six were male. The mean age in this group was 65.25 ± 12.76 years, and the mean spherical equivalent was 0.75 ± 1.62 dioptres. In group 2 (control), 3 eyes were excluded due to the diagnosis of subclinical epiretinal membrane after OCT examination, with 28 eyes qualifying for the study. Twenty-three patients were female and five were male. The mean age in this group was 69.95 ± 10.28 years and the mean spherical equivalent was 0.76 ± 1.98 dioptres. The mean age ($p = 0.051$) and spherical equivalent ($p = 0.49$) were not significantly different between the two groups. Mean best-corrected visual acuity was 0.36 ± 0.35 in group 1 and 0.95 ± 0.84 in group 2 ($p < 0.001$). One patient in group 1 and two patients in group 2 were former smokers, but there were no current smokers in any of the study groups. The mean follow-up time after the NA-AION in group 1 was 57.17 ± 26.92 months.

Mean central retinal thickness was 264.61 ± 32.92 µm in group 1 and 279.25 ± 26.62 µm in group 2 ($p = 0.052$); in the upper macular quadrants, the mean thickness was 287.22 ± 47.24 µm in group 1 and 345.00 ± 37.08 µm in group 2 ($p < 0.001$); in the lower quadrants, the average thickness was 281.61 ± 49.17 µm in group 1 and 328.11 ± 38.02 µm in group 2 ($p < 0.001$). Retinal thickness was higher in group 2 (control) in all the locations studied, and these differences were significantly different in the upper and lower quadrants.

The average posterior pole CT was 244.38 ± 61.03 µm in group 1 and 214.18 ± 65.97 µm in group 2 ($p = 0.004$). The mean CT in the horizontal foveal section was 239.11 ± 50.84 µm in group 1 and 215.39 ± 62.23 µm in group 2 ($p = 0.092$); the mean thickness of the choroid in the upper quadrants was 253.99 ± 65.42 µm in group 1 and 223.38 ± 65.64 µm in group 2 ($p = 0.065$), the mean thickness of the choroid in the inferior quadrants was 240.04 ± 67.84 µm in group 1 and 203.75 ± 70.69 µm in group 2 ($p = 0.046$). There were statistically significant differences in the average CT of the posterior pole and in the CT of the lower quadrants, with higher values in group 1 (Figure 2).

A statistical association was found between choroidal thickness and the time elapsed since the onset of NA-AION ($r = 0.456$, $p = 0.047$) in group 1 (Figure 3). However, no such association was detected between

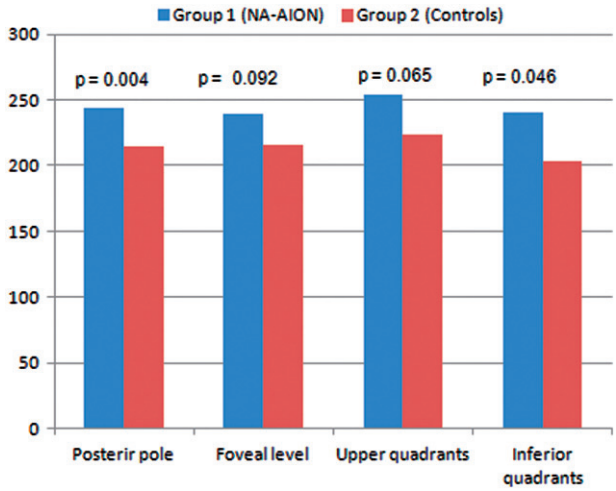

FIGURE 2 Mean choroidal thickness (in μm) in both groups.

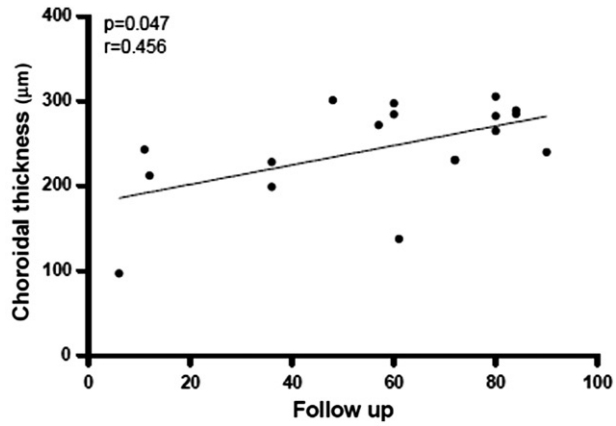

FIGURE 3 Correlation between choroidal thickness (in μm) and the time (in months) since the onset of NA-AION.

the follow-up time and macular thickness in this group ($p = 0.53$).

DISCUSSION

This study demonstrates that there are changes in the CT of patients with chronic NA-AION. In these patients, the mean CT at the posterior pole is significantly higher compared with demographically similar controls. Macular thickness in turn is lower in patients with chronic NA-AION, as has been demonstrated in previous studies.[18,19] The decrease in macular thickness is the result of a reduction in the thickness of the ganglion cell complex, which encompasses the retinal nerve fibre layer, the ganglion cell layer, and the inner plexiform layer. A recent study by Gonul et al. demonstrated that macular ganglion cell complex thickness was comparable to peripapillary nerve fibre layer thickness for accessing ganglion cell loss in patients with chronic NA-AION.[20]

The choroid has the highest blood flow per unit weight of any tissue in the body.[21] It has a key role in the nutrition and homeostasis of the outer layers of the retina and prelaminar portion of the optic nerve.[9] Although it is not consensual, several studies suggest the existence of autoregulation in choroidal blood flow, intended to offset fluctuations in blood pressure and intraocular pressure.[22–24] Some of the proposed vasoregulatory mechanisms are the nitric oxide, endothelins, and the autonomic nervous system.[25–27] However, such mechanisms appear to be incomplete and labile. The choriocapillaris oxygen partial pressure is so high that it seems likely that the choroidal circulation is regulated by additional factors different from those acting in other vascular beds.[28] For example, Houssier et al. showed that CD-36 is a scavenger receptor expressed in the basal RPE. CD-36–deficient mice failed to induce cyclooxygenase-2 (COX-2) and subsequent vascular endothelial growth factor (VEGF) synthesis at the level of the RPE and developed progressive degeneration of the choriocapillaris.[29] The change in CT could thus be an indirect sign of various retinal diseases, intrinsic pathologies of the choroid, optic neuropathies, or systemic microangiopathy. Since the advent of EDI-OCT, it has been possible to measure CT with very good interobserver,[11] intervisit,[30] and intersystem[31] reproducibility, despite the lack of automated software.

A study with normal subjects with a mean age of 47.5 years has shown an average subfoveal thickness of 280.23 μm.[32] Besides, CT decreases towards the periphery asymmetrically, being thinner nasally than temporally, and thinner inferiorly than superiorly.[33] Increasing age correlates significantly with decreasing CT; in one study it was found to decrease 14 μm for each decade of life.[34] It also correlates inversely with myopic spherical equivalent and axial length. Subfoveal choroidal thickness was shown to decrease 15 μm for each dioptre increase in myopic spherical equivalent and to decrease 22 μm per mm increase in axial lengh.[35] Moreover, subfoveal CT is, on average, 62 μm higher in men than women[35] and has a circadian variation, being slightly thicker at the end of the day.[36,37] Existing studies did not find a clear relationship between CT and systemic arterial blood pressure.[37,38]

Recently, we have witnessed a growing interest for the study of the choroid in various retinal, choroidal, or optic nerve pathologies. In the case of high myopia, it was demonstrated that the choroid is thinner, with higher refractive errors and lower visual acuity.[13,39] In CSCR, the choroid is thicker compared with normal eyes and does not show the expected age-dependent thinning.[10] Kim et al. reported an increase in CT associated with polypoidal choroidal vasculopathy (PCV).[40] AMD is another disease associated with changes in choroidal circulation.[41,42] However, studies

with EDI-OCT failed to demonstrate a consistent change in CT relative to normal eyes or a relationship between CT and the severity or type of AMD.[14,43] The study of CT can also be useful in the follow-up of posterior uveitis. In the case of Voght-Koyanagi-Harada disease, for example, there is a significant increase in subfoveal CT during the acute phase, which gradually decreases in response to corticosteroids.[44] In glaucomatous optic neuropathy, although there is no absolute consensus, most studies found no changes in CT in comparison with normal eyes.[45] Likewise, the studies in diabetes mellitus present contradictory results, but the study with the largest sample ($N = 3468$) showed an increase of subfoveal CT in patients with diabetes mellitus compared with healthy controls. However, CT was not higher in the presence of diabetic retinopathy compared with diabetic patients without retinopathy, nor did it correlate significantly with the severity of the retinopathy.[46]

Similarly to what happens in diabetes mellitus, PCV, and CSCR, this study demonstrated that in chronic-phase NA-AION there is also an increase in choroidal thickeness, compared with a control group with similar demographic characteristics and spherical equivalent. In the case of PCV and CSCR, choroidal thickening is a primary manifestation of the disease and may secondarily lead to clinical manifestations such as subretinal oedema and macular detachment in the case of CSCR and subfoveal choroidal neovascularization in the case of PCV.[46] In NA-AION and diabetes mellitus–related choroidal thickening, the clinic and pathological significance is not so straightforward. In the particular case of NA-AION, the primary pathophysiological phenomenon leading to ischaemia of the optic nerve head is not completely understood.[47] The optic nerve head is supplied by an anastomotic arterial circle derived from the short posterior ciliary arteries. Fluorescein angiography studies provide indirect evidence that circulatory insufficiency in the paraoptic branches of the short posterior ciliary arteries is the primary cause of the ischaemic event.[47] However, no adequate systematic histopathological study of these vessels was able to demonstrate if it results from an atherosclerotic, thrombotic, or embolic phenomena.[48] Levin and Danesh-Meyer recently proposed that NA-AION may be primarily a venous disease.[49] Hayreh et al., on the other hand, consider defective vascular autoregulation as the primary pathophysiological event. This abnormality would render some individuals more susceptible to flow-reducing events, such as nocturnal hypotension.[50] This theory is supported by the fact that nearly 75% of NA-AION occur during sleep.[51] In our opinion, the increase in CT in patients with chronic NA-AION is a marker of the local dysfunction of the vascular autoregulation mechanisms, further supporting this theory. The positive correlation between CT and the time elapsed since the ischaemic event suggests either two hypotheses. The first hypothesis is that defective vascular autoregulation could be a slowly progressive and cumulative process. At some moment, the autoregulation mechanisms could become insufficient to compensate for a hypotensive event, leading to NA-AION. Considering these microvascular changes act as a continuum, we hypothesise that a slight increase in CT could be present for some time before the ischaemic event. Another hypothesis is that the macular tissue, which is decreased in these patients, could be relevant to the underlying choroid. The decrease in metabolic activity in that overlying retinal area could interfere with the choroidal vascular regulation, by promoting an imbalance in the vasoactive mediators. In fact, a number of papers suggest an important cross-talk between the metabolic activity of these two compartments.[52–54] These two hypotheses could even be complementary. Future prospective and multicentric studies should evaluate CT in subjects at risk for NA-AION as well as the CT in the contralateral eye of individuals who have had an episode of NA-AION, in order to test a hypothetical relationship between this parameter and the future occurrence of NA-AION.

There are important limitations to this study. The small sample size may have limited the identification of statistically significant differences in CT and macular thickness in all the quadrants analysed. The spherical equivalent was determined in all participants but not axial length, which, as mentioned before, has a greater influence in CT than the refractive error. Systemic arterial hypertension and the use of antihypertensive medication were not considered exclusion criteria in this study. However, as stated before, published studies did not find a clear relationship between choroidal thickness and systemic arterial blood pressure.[37,38] Moreover, the mean age is slightly higher in the control group, although this difference was not statistically significant. Taking into account the highly significant difference in the mean CT of the posterior pole between the two groups ($p < 0.01$), we believe that this fact does not compromise the major conclusions of this study. Given the irregularity of the chorioscleral border, measuring CT at isolated points is not the most accurate method to investigate the choroid, as the measurements may be affected by focal irregularities of this boundary. The methodology adopted in this work—measurement of CT at 9 points per eye—aims to reduce this error. However, the measurement of choroidal volume[55] or the development of automatic software would certainly be better ways to study its anatomy.

In conclusion, this study was the first to demonstrate an increase in CT in eyes with chronic NA-AION. This finding may contribute to a better understanding of the pathophysiology of a disease that can have devastating consequences for visual function. Future studies are needed to test the

potential of this characteristic in the identification of patients at risk and in the follow-up of patients with NA-AION.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

***Note*:** Figures 1 and 2 of this article are available in colour online at www.informahealthcare.com/oph.

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