Title page:

Authors:

Julio González Martín-Moro[1,2] (M.D.; Ph.D.) ORCID: 0000-0002-8056-2630

Inés Contreras [3] (M.D.; Ph.D.)

Consuelo Gutierrez-Ortiz[4] (M.D.; Ph.D.)

Fernando Gómez-Sanz[1,5] (Optometrist)

Maria Castro-Rebollo[1] (M.D)

Ana Fernández-Hortelano[1](M.D.; Ph.D.)

Belén Pilo-de-la-Fuente[6] (M.D.; Ph.D.)

(1) Department of Ophthalmology. University Hospital of Henares. Coslada. Madrid. Spain.
(2) University Francisco de Vitoria. Madrid. Spain.
(3) Department of Ophthalmology. Ramón y Cajal University Hospital. Madrid. Spain. Clínica Rementería. Madrid. Spain.
(4) Department of Ophthalmology. Príncipe de Asturias University Hospital. Madrid. Spain.
(5) School of Optometry. Complutense University. Madrid. Spain.
(6) Department of Neurology. Getafe University Hospital. Madrid. Spain.

Corresponding author:

Julio González Martín-Moro

Américo Castro 102 6ºA

28050 Madrid España

juliogmm@yahoo.es

c) Meeting Presentation: a previous version was presented as a poster at the European Neuro-Ophtalmological Society Meeting (Ljubljana, 2015).

d) Financial Support: None

e) Conflict of Interest: The authors have no financial or proprietary interest in a product, method, or material described herein.

f) Address for reprints:

Julio González Martín-Moro

Américo Castro 102 6ºA

28050 Madrid España

Tel: +34 659 91 25 78

Fax: + 34 91 191 22 84

juliogmm@yahoo.es

juliogazpeitia@gmail.com

Keywords: non-arteritic anterior ischemic optic neuropathy; NAION; disc at risk; optic disc diameter; compartment syndrome

Disc configuration as a risk and prognostic factor in NAION: the impact of cup to disc ratio, disc diameter, and crowding index.

Abstract

PURPOSE: The presence of the so called disc at risk (a small disc with no cupping) has been considered the main risk factor for the development of non-arteritic anterior ischemic optic neuropathy (NAION). However its role as a prognostic factor has not been studied. Our aim was to determine the weight of disc configuration as a risk and a prognostic factor for NAION.

METHODS: Case control study. Forty eyes of 40 patients who were diagnosed with NAION between 2008 and 2017, and 120 controls (3 controls for each patient) were included in the study. Disc diameter (DD), cup to disc ratio (CDR), and peripapillar retinal nerve fiber layer thickness (RNFLT) of the non-affected eye were measured using optic coherence tomography (3D OCT 2000, Topcon). Crowding index (CI) was defined as the quotient of average RNFLT and disc area. Mean deviation (MD) at the time of diagnosis and at least three months later was determined using a Humphrey Visual Field Analyzer (SITA standard 24-2 strategy). VA was measured using Snellen charts and transformed into LogMAR values.

RESULTS: Only CDR was found to be a risk factor for NAION. No correlationship was found between CI and visual loss.

CONCLUSIONS: DD and CI did not show value as either prognostic or risk factors. Glial tissue may be a part of the content of the optic disc as important as axons. Our results are

in line with the latest studies about NAION pathophysiology. Contrary to classic thinking, these papers have not found smaller disc diameters, but smaller values of lamina cribosa depth in NAION patients.

INTRODUCTION

Non-arteritic anterior ischemic optic neuropathy (NAION) is the most common acute optic neuropathy among over 50-year old patients.[1] Although its clinical course is well known, NAION seems to be an atypical and poorly understood infarct in which cerebrovascular risk factors seem to play a secondary role. Indeed NAION is not clearly linked to a higher cerebrovascular or cardiovascular risk and antiaggregation and anticoagulation have not been shown to be useful to prevent second-eye involvement.[2] Several additional risk factors like obstructive sleep apnea,[3,4] or the use of phosphodiesterase type 5 inhibitors[5] have been associated with the development of this condition. Nevertheless the anatomic configuration of the optic disc, the so called *disc at risk*, seems to be the most significant risk factor.[1]

Our aim was to determine the impact of disc configuration both as a risk and as a prognostic factor. We hypothesized that patients who had suffered NAION would have a higher degree of crowding (smaller discs, smaller cup/disc ratios and higher peripapillary retinal never fiber layer thickness) than controls and that a higher degree of crowding would be associated with worse visual prognosis (more severe visual field damage and

worse visual acuity). In order to test both hypothesis, we developed the concept of crowding index. This index was obtained dividing peripapillary retinal never fiber layer thickness by disc area.

MATERIALS AND METHODS

Patients diagnosed with NAION during the last ten years (2008-2017) were evaluated for inclusion. Patients were considered eligible, if they met the following criteria: had experienced abrupt visual loss in one eye; diffuse or sectorial optic disc edema was present at initial evaluation (with or without hemorrhages); visual field defect was compatible with NAION; there was an afferent pupillary defect in the affected eye; had no pain consistent with arteritic neuropathy or with optic neuritis; had no significant elevation of erythrocyte sedimentation rate; no other cause could explain the acute visual loss; had no previous history of optic neuropathy or optic neuritis in either eye. Only patients with at least 3 months follow-up were included. For every patient included, we included 3 control subjects. Controls were considered eligible if they were referred to the primary care eye clinic and did not have any neuro-ophthalmologic condition. One eye of each control was randomly selected. The study was approved by the institutional ethics committee and adhered to the tenets of the Declaration of Helsinki.

This study is based on inter-eye correlation because measurements of the cases were taken in the unaffected eye. We assumed that the optic disc of the unaffected eye was similar to the disc of the affected eye prior to the development of NAION. All participants underwent a comprehensive neuro-ophthalmic examination. Visual acuity (VA) was measured using Snellen charts. The mean deviation on visual field of the affected eye at diagnosis

(determined using a Humphrey Visual Field Analyzer,SITA FAST 24-2 strategy) was considered the main variable to determine visual loss. To be considered reliable a visual field should have less than 20% false positive responses or false negative responses. If unreliable, visual fields were repeated. Disc diameter (DD), cup to disc ratio (CDR), and peripapillary retinal nerve fiber layer thickness (RNFLT) were measured using the automatic algorithm implemented in our optic coherence tomography device (3D OCT 2000, Topcon). The Optic Disc Cube scanning protocol was chosen; this strategy registers 1024 dots in each of the128 vertical scans, covering an area of 6 x 6 mm around the optic disc. Optic disc diameter was calculated as the average between horizontal and vertical measures. Subjects underwent ocular imaging with dilated pupils. Only centered, high quality scans (image quality>75), with focused images were included in the analysis. Other recorded variables were age, gender, laterality, high blood pressure (HBP), diabetes mellitus (DM), migraine and previous ocular surgery.

The degree of crowding is the result of the relationship between continent and content at the optic disc. For expressing this concept we developed a new parameter. This parameter was named crowding index (CI), and was defined as the quotient of RNFL and disc area. To avoid observer bias, automated Bruch`s opening area was used as an estimation of optic disc area. RNFL is supposed to be proportional to the volume of fibers that go through the lamina cribosa.

$$Crowding\ index = \frac{RNFL\ thickness\ (\mu)}{BOA\ (mm^2)}$$

To assess the role of disc morphology as a risk factor, optic disc biometric measurements of NAION patients were compared with control subjects. To quantify the impact of optic disc morphology as a prognostic factor, the correlation between these variables and visual acuity and visual field mean defect was studied in the NAION group. Before comparing cases and controls the normality of the quantitative variables was tested using the Kolmogorov-Smirnov test. Many of the studied variables did not meet this assumption, so non parametric tests were chosen to compare them.

Due to the non-normal distribution of many of the studied variables, descriptive statistics were expressed as median values and interquartile range for quantitative variables. Qualitative variables were described as proportions. The Mann-Whitney U test was chosen to test the impact of biometric parameters as risk factors (to test the differences between NAION cases and controls). The level of signification was corrected using Bonferroni method. Seven contrasts were chosen (cup to disc ratio, disc diameter, global crowding index, and crowding index in each quadrant), so contrasts were considered significant when $p<0.0071$.

Spearman`s correlation coefficient (two-tailed) was used to identify potential prognostic factors, to evaluate the relationship between potential prognostic factors (CDR, DD, CI, HBP, DM and age) and outcome variables (MD and VA at the time of diagnosis). Ten variables were studied, so applying Bonferroni correction, values of 0.005 were considered statistically significant. A secondary analysis was performed to determine the prognostic

value of these variables at the last follow up visit. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Forty consecutive patients diagnosed with NAION met the inclusion criteria. One hundred and twenty control eyes (3 controls for each NAION eye), were included. Demographical and clinical data are recorded in table 1. Cases and controls were similar in age, male-female ratio, and prevalence of diabetes mellitus, but high blood pressure was more frequent among NAION patients than among controls.

Most cases of NAION were idiopathic. However, two cases occurred after cataract surgery, and two cases as a complication of a migraine attack. In one patient who suffered migraine (although visual loss didn't develop in association with a migraine attack), an antiphospholipid syndrome was diagnosed. One patient suffered advanced non-proliferative diabetic retinopathy. None of the cases was considered related to phosphodiesterase type 5 inhibitors intake (one patient had taken tadalafil (Cialis®), however he reported having taken it two months before suffering visual loss). None of the patients reported amiodarone intake.

The impact of biometric measurements as risk factor was studied comparing the NAION group with a group of 120 controls using the Mann-Whitney test. (Table 2) Only cup to disc ratio was different between both groups.

Correlation of potential prognostic factors with visual field damage and visual acuity was studied using Spearman´s correlation coefficient (Table 3). Correlation was studied at two times, at the time of diagnosis (short term prognosis), and at the last follow-up visit (long term prognosis). Median follow up was 33.1 months for visual acuity (interquartile range: 16-72.4 months) and 27.9 months for visual field (interquartile range: 15.7-73.2 months). No correlation was found between visual acuity and visual field mean deviation and any of the studied biometric parameters.

DISCUSSION

The pathogenesis of NAION is not fully understood; however, it is believed that NAION is caused by vascular insufficiency resulting from disturbed small vessel autoregulation of the posterior ciliary circulation that leads to optic nerve head ischaemia.[6] Indeed when the morphology of the infarct is studied, the infarct does not correspond to the territory of a particular artery.[7]

Although disc morphology is not considered a diagnostic criterion, most neuro-ophthalmologists believe that the presence of a disc at risk in the contralateral eye supports the diagnosis. For at least three decades, disc configuration has been considered the main risk factor.[8] In Palombi´s series, vertical disc diameter was 1.8 mm (SD 0.17 mm) and the average CDR was 0.21(SD=0.09).[9] These values are similar in our study, however they did not differ from controls in our sample.

Most of the research concerning this disease has been focused on risk factors [2-5,9-11] and potential treatments.[12-17] In our sample, diabetes mellitus did not seem to be a risk factor but NAION was clearly linked to high blood pressure (50% of NAION patients had HBP, while this risk factor was present in only 24% of controls). These figures are slightly lower than those previously reported in the literature.[9,10].

Disc morphology was poorly related to NAION as a risk factor. Disc diameter and crowding index were similar in NAION patients and controls. Only CDR proved to be a risk factor. However cognitive bias could be in part responsible for this association as ophthalmologists are more prone to diagnose NAION when a small CDR is present in the contralateral eye.

The term optic disc encloses a gross simplification. The dictionary defines disc as a circular thin object and the papilla is a three dimensional body with no geometrical shape and high inter-individual variation. The optic disc head is neither a disc nor a cylinder. It is clear that the clinical disc border and the neural canal opening may not be the same.[18] To avoid observer bias, automated Bruch opening area was used as an estimation of optic disc area.

Few publications have focused on prognostic factors.[19,20] However, a better understanding of the involved prognostic factors could improve our knowledge of this disease and help to design new treatment strategies. Even more, it could also help to make comparable groups when potential treatments are studied. For example, when evaluating the potential utility of corticosteroids in NAION, some authors considered that in the original article that suggested a beneficial effect of corticosteroids, the study groups were not comparable because in the treatment group there was a lower percentage of diabetics. Nevertheless in our study DM did not behave as a risk factor and was not linked to worse prognosis.[21-23]

As the origin of the compartment syndrome is the disproportion between the compartment and the content, we have created a new parameter that brings together both factors. We have named this parameter crowding index (CI). In it, the compartment (denominator) is represented by optic disc area, measured at the level of the pigment epithelium while the content (numerator) is represented by retinal nerve fiber layer thickness. This parameter was studied globally. Surprisingly this parameter did not show any value as a prognostic or risk factor.

We have tried to express the degree of crowding in a single parameter. Nevertheless we have found only a significant association with CDR. In contrast to what we expected, crowding index did not show any value as a risk or prognostic factor. Our study suggests that either the content or continent of the optic disc are not correctly expressed in this equation. The optic disc head comprises retinal ganglion cell axons, blood vessels, glia and connective tissue.[18] Glial tissue may represent a part of the content of the optic disc as important as axonal tissue, and RNFL measures were taken 1.7 mm from the center of the optic disc (the RNFL protocol measures the RNFL in a circle with a t **3.4 mm diameter centered on the optic disc).** Maybe closer measurements would have shown greater correlation. Optic nerve glial and connective tissue may have greater weight than axonal tissue as a determinant of compartment syndrome**.**[24]

On the other hand disc area may not correctly express the continent. These results are in line with the latest studies about NAION pathophysiology. Contrary to classical thinking, these papers have not found smaller disc diameters, but smaller values of lamina cribosa surface depth in NAION patients than in normal tension glaucoma and healthy controls.[25-27] We recognize several shortcomings in our study. The study was performed at only one site.

The number of patients is small. The fact that this study is based on interocular correlation also constitutes a limitation. A good study on prognostic risk factors should also include the risk of bilateralization. This variable could not be included because this is a retrospective study and patients that had suffered bilateralization didn`t have a healthy eye to study disc configuration prior to the occurrence of NAION.

Reference List

1. 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.
2. Hasanreisoglu M, Robenshtok E, Ezrahi D, Stiebel-Kalish H. Do patients with non-arteritic ischemic optic neuritis have increased risk for cardiovascular and cerebrovascular events? *Neuroepidemiology.* 2013;40(3):220-224.
3. Archer EL, Pepin S. Obstructive sleep apnea and nonarteritic anterior ischemic optic neuropathy: evidence for an association. *J Clin Sleep Med.* 2013;9(6):613-618.
4. Stein JD, Kim DS, Mundy KM, et al. The association between glaucomatous and other causes of optic neuropathy and sleep apnea. *Am J Ophthalmol.* 2011;152(6):989-998 e983.
5. Campbell UB, Walker AM, Gaffney M, et al. Acute Nonarteritic Anterior Ischemic Optic Neuropathy and Exposure to Phosphodiesterase Type 5 Inhibitors. *J Sex Med.* 2014.
6. Hayreh SS. Ischemic optic neuropathy. *Prog Retin Eye Res.* 2009;28(1):34-62.
7. Tesser RA, Niendorf ER, Levin LA. The morphology of an infarct in nonarteritic anterior ischemic optic neuropathy. *Ophthalmology.* 2003;110(10):2031-2035.
8. Beck RW, Savino PJ, Repka MX, Schatz NJ, Sergott RC. Optic disc structure in anterior ischemic optic neuropathy. *Ophthalmology.* 1984;91(11):1334-1337.
9. Palombi K, Renard E, Levy P, et al. Non-arteritic anterior ischaemic optic neuropathy is nearly systematically associated with obstructive sleep apnoea. *Br J Ophthalmol.* 2006;90(7):879-882.
10. Li J, McGwin G, Jr., Vaphiades MS, Owsley C. Non-arteritic anterior ischaemic optic neuropathy and presumed sleep apnoea syndrome screened by the Sleep Apnea scale of the Sleep Disorders Questionnaire (SA-SDQ). *Br J Ophthalmol.* 2007;91(11):1524-1527.
11. Kerr NM, Chew SS, Danesh-Meyer HV. Non-arteritic anterior ischaemic optic neuropathy: a review and update. *J Clin Neurosci.* 2009;16(8):994-1000.
12. Pece A, Querques G, Quinto A, Isola V. Intravitreal ranibizumab injection for nonarteritic ischemic optic neuropathy. *J Ocul Pharmacol Ther.* 2010;26(5):523-527.
13. Jonas JB, Spandau UH, Harder B, Sauder G. Intravitreal triamcinolone acetonide for treatment of acute nonarteritic anterior ischemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol.* 2007;245(5):749-750.
14. Modarres M, Sanjari MS, Falavarjani KG. Vitrectomy and release of presumed epipapillary vitreous traction for treatment of nonarteritic anterior ischemic optic neuropathy

associated with partial posterior vitreous detachment. *Ophthalmology.* 2007;114(2):340-344.
15. Simsek T, Eryilmaz T, Acaroglu G. Efficacy of levodopa and carbidopa on visual function in patients with non-arteritic anterior ischaemic optic neuropathy. *International journal of clinical practice.* 2005;59(3):287-290.
16. Wilhelm B, Ludtke H, Wilhelm H, Group BS. Efficacy and tolerability of 0.2% brimonidine tartrate for the treatment of acute non-arteritic anterior ischemic optic neuropathy (NAION): a 3-month, double-masked, randomised, placebo-controlled trial. *Graefes Arch Clin Exp Ophthalmol.* 2006;244(5):551-558.
17. Atkins EJ, Bruce BB, Newman NJ, Biousse V. Treatment of nonarteritic anterior ischemic optic neuropathy. *Surv Ophthalmol.* 2010;55(1):47-63.
18. Reis AS, Sharpe GP, Yang H, Nicolela MT, Burgoyne CF, Chauhan BC. Optic disc margin anatomy in patients with glaucoma and normal controls with spectral domain optical coherence tomography. *Ophthalmology.* 2012;119(4):738-747.
19. Larrea BA, Iztueta MG, Indart LM, Alday NM. Early axonal damage detection by ganglion cell complex analysis with optical coherence tomography in nonarteritic anterior ischaemic optic neuropathy. *Graefes Arch Clin Exp Ophthalmol.* 2014;252(11):1839-1846.
20. Papchenko T, Grainger BT, Savino PJ, Gamble GD, Danesh-Meyer HV. Macular thickness predictive of visual field sensitivity in ischaemic optic neuropathy. *Acta Ophthalmol.* 2012;90(6):e463-469.
21. Hayreh SS, Zimmerman MB. Non-arteritic anterior ischemic optic neuropathy: role of systemic corticosteroid therapy. *Graefes Arch Clin Exp Ophthalmol.* 2008;246(7):1029-1046.
22. Rebolleda G, Perez-Lopez M, Casas LP, Contreras I, Munoz-Negrete FJ. Visual and anatomical outcomes of non-arteritic anterior ischemic optic neuropathy with high-dose systemic corticosteroids. *Graefes Arch Clin Exp Ophthalmol.* 2013;251(1):255-260.
23. Hayreh SS. Role of steroid therapy in nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol.* 2010;30(4):388-389.
24. Moghimi S, Afzali M, Akbari M, et al. Crowded optic nerve head evaluation with optical coherence tomography in anterior ischemic optic neuropathy. *Eye (Lond).* 2017;31(8):1191-1198.
25. Lee EJ, Choi YJ, Kim TW, Hwang JM. Comparison of the Deep Optic Nerve Head Structure between Normal-Tension Glaucoma and Nonarteritic Anterior Ischemic Optic Neuropathy. *PLoS One.* 2016;11(4):e0150242.
26. Rebolleda G, Perez-Sarriegui A, Diez-Alvarez L, De Juan V, Munoz-Negrete FJ. Lamina cribrosa position and Bruch's membrane opening differences between anterior ischemic optic neuropathy and open-angle glaucoma. *Eur J Ophthalmol.* 2018:1120672118782101.
27. Rebolleda G, Garcia-Montesinos J, De Dompablo E, Oblanca N, Munoz-Negrete FJ, Gonzalez-Lopez JJ. Bruch's membrane opening changes and lamina cribrosa displacement in non-arteritic anterior ischaemic optic neuropathy. *Br J Ophthalmol.* 2017;101(2):143-149.