Peripapillary Retinal Nerve Fiber Layer Thickness and Peripheral Microcirculation in Raynaud's Disease.

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Abstract

Purpose: Normal-tension glaucoma has been associated with systemic vascular diseases such as peripheral vasospasm. This study aims to evaluate the influence of peripheral vasospasm on the thickness of the retinal nerve fiber layer (RNFL) in Raynaud's disease (RD), and the correlation between global RNFL and peripheral microcirculation features in RD patients.

Methods: Observational cross-sectional study of 18 patients (35 eyes) with a diagnosis of RD followed in our clinic, and 20 healthy controls (39 eyes). RNFL parameters were obtained using spectral domain optical coherence tomography (SD-OCT Spectralis®, Heidelberg). Global and sectorial peripapillary RNFL thickness were registered. Age, gender, refractive error, best-corrected visual acuity and intraocular pressure were determined, and slit-lamp biomicroscopy and fundus examination were performed. Nailfold videocapillaroscopy (NC) was performed in the RD group to characterize capillary morphology and blood flow. Mann-Whitney and Fisher's exact tests were used for statistical analysis. Statistical significance level was set at $p<0.05$ (two-sided).

Results: There was no significant difference in the global RNFL between RD patients and the control group ($p=0.35$). The presence of avascular areas in NC was associated with a lower global RNFL thickness ($p=0.026$).

Conclusion: The association between avascular areas in NC and the lower global RNFL thickness in RD patients suggests that systemic vasospasm severity may be related to optic nerve damage propensity. Therefore, its presence in NC may identify RD patients at risk for optic nerve head damage. A larger sample with a long-term study is needed to support the clinical and therapeutic implications of our findings.

Keywords: vasospasm; primary Raynaud's disease; retinal nerve fiber layer thickness; normal-tension glaucoma.

Introduction

Chronic open angle glaucoma is a multifactorial and progressive disease, with elevated intraocular pressure (IOP) being the most commonly identified ocular risk factor for glaucomatous optic neuropathy development.[1] Nevertheless, approximately 25% of patients with glaucoma have IOP within the normal range.[2] Vascular deregulation and unstable ocular blood flow, with resulting oxidative stress, contribute to the pathogenesis of normal-tension glaucoma (NTG).[1,3] There is evidence that in NTG, abnormal neuro-endothelial mechanisms of vascular tone control, leading to ischemia of the optic nerve head, may assume a major pathological mechanism, although this is still unclear.[4,5] NTG has been related with systemic vascular diseases such as atherosclerosis, migraine, sleep apnea, immune-related diseases and vasospasm.[2,4,6]

Raynaud's phenomenon (RP), first characterized by Maurice Raynaud in 1962, is a vasospastic disorder of the microvasculature, usually affecting the extremities. A deregulated constriction of precapillary arterioles occurs most commonly when exposed to cold.[7,8] RP is defined clinically as a sudden triphasic colour change of the skin on affected areas (pallor, cyanosis, rubor), corresponding to ischemia, hypoxia and reperfusion, and it may be accompanied by numbness and swelling.[9] RP has been classified into primary and secondary; the former, named Raynaud's Disease (RD) refers to the idiopathic form of the disease, whereas the latter applies when RP is associated with an underlying systemic connective tissue disease.[9] Nailfold videocapillaroscopy (NC) consists of a non-invasive exam with great value for the diagnosis and differentiation of primary and secondary RP in rheumatic diseases, where the terminal microcirculation is optically observed *in vivo*.[10]

The present study hypothesized that, if there was a relationship between peripheral and ocular vasospasm, as described by some authors,[11-14] patients with RD could have consequent glaucomatous changes with damage in the

	RD Patients	Controls	N	P value
Eyes/Subjects (n/n)	35/18	39/20	74	
Gender (n)				
Females	13	10	23	
Males	5	10	15	0.097
Age (years)	42.00 (18.00–71.00)	39.00 (25.00–58.00)		0.267
BCVA (Snellen)	1.00 (0.80–1.00)	1.00 (0.80–1.00)		0.500
IOP (mmHg)	15.00 (9.00–21-00)	14.00 (8.00–20.00)		0.510
Spherical Equivalent	0.00 (-1.50–+3.50)	-0.50 (-3.25–+2.25)		0.047

Table 1 – Demographics and ophthalmological examination characteristics of patients with Raynaud's disease and normal control subjects.
RD=Raynaud's Disease; BCVA=best corrected visual acuity; IOP=intraocular pressure
Values represent median (minimum–maximum), respectively, unless otherwise specified.
There were no significant differences in median age, BCVA and IOP between the two groups.

peripapillary retinal nerve fiber layer (RNFL) thickness. Therefore, we analysed the peripapillary RNFL thickness in patients with RD, confirmed by NC, using spectral domain optical coherence tomography (SD-OCT Spectralis®, Heidelberg), and compared it to normal subjects. Also, we searched for a correlation between global RNFL thickness and peripheral microcirculation features in RD patients, using NC.

MATERIALS AND METHODS

Population sample

This cross-sectional study included 18 patients (35 eyes) with a RD diagnosis followed in the Systemic Immune-mediated Diseases Unit, and 20 healthy controls (39 eyes) recruited from the Ophthalmology Department of Hospital Prof. Doutor Fernando Fonseca, EPE. Inclusion criteria for RD patients were: 1) to have RD diagnosis, confirmed by NC, 2) best-corrected visual acuity > (BCVA)[3] 20/25, 3) spherical equivalent refraction within ±6.0 diopters and 4) IOP < 22 mmHg. Exclusion criteria for all participants were: 1) systemic diseases associated with secondary RP, 2) intraocular diseases, 3) optic nerve or neurologic diseases that could cause RNFL thickness changes, 4) intraocular surgery or intraocular opacities. This study was approved by the Ethics Committee of Hospital Prof. Doutor Fernando Fonseca, EPE, and complied with the tenets of the Declaration of Helsinki for research involving humans. Written informed consent was obtained from all participants.

Methods

Ophthalmological examination of participants included refractive error measured with an autorefractometer, best-corrected visual acuity measurement on the Snellen chart, slit-lamp biomicroscopy, IOP measured by Goldmann applanation tonometry, and fundus examination. A detailed history was taken to identify any retinal, neurological or optic disc disorder. Age and gender were registered and, in the primary RP group, duration of the disease was also recorded.

Mean peripapillary RNFL thickness was obtained as the global and sectorial nasal, superonasal, inferonasal, temporal, superotemporal and inferotemporal, with SD-OCT (Spectralis OCT, Heidelberg Engineering) software by the same technician, for all participants, on the same day of ophthalmological examination.

NC were all performed by the same physician, within two weeks from the ophthalmological examination, using an optical probe videocapillaroscope equipped with 100x and 200x contact lenses connected to an image analysis software (Videocap; DS MediGroup, Milan, Italy). Videocapillaroscopy studied capillary morphology and blood flow by the analysis of capillary density, the presence of avascular areas (absence of three consecutive capillary loops), dilated capillaries (diameter between 25-50µm), giant capillaries (over 50µm of diameter), haemorrhages, major and minor capillary abnormalities, oedema, reduced red blood cell velocity and presence of intermittent flux with sludge.

Statistical Analysis

After testing all variables with the Shapiro-Wilk test, Mann-Whitney and Fisher's exact tests were used for statistical analysis. Correlations between parameters were done using Spearman's ρ. Statistical significance level was set at $p<0.05$ (two-sided). Statistical analysis was performed using SPSSv21.

RESULTS

Demographic characteristics and ophthalmological examination

The study included 35 eyes of 18 patients (13 females, 5 males) with RD, and 39 eyes of 20 controls (10 females, 10 males). The median age of the RD and control groups was 42.00 years (range 18.00 to 71.00 years) and 39.00 (range 25.00 to 58.00 years), respectively. The mean duration of RD was 7.0 ± 8.2 years. There were no significant differences in median age (p=0.267), BCVA (p=0.500), and IOP (p=0.510) between the two groups. The median spherical equivalent was significantly higher (p=0.047) in the RD group (median 0.00D, range -1.50 to +3.50D) than in the control group (median -0.50D, range -3.25 to +2.25D).

Patient demographics and ophthalmological examination features are summarized in Table 1.

RNFL thickness in RD patients and control subjects

There was no significant difference (p=0.288) in the global RNFL median between RD patients (median 101.00 mm, range

	RNFL thickness (μm)		
	RD Patients (n=35)	Controls (n=39)	P value
Global	101.00 (75.00–129.00)	98.00 (88.00–123.00)	0.288
Nasal	82.00 (55.00-185.00)	71.00 (50.00-116.00)	0.037
Inferonasal	116.00 (94.00-240.00)	110.00 (90.00-159.00)	0.352
Superonasal	115.00 (85.00-159.00)	112.00 (83.00-162.00)	0.493
Temporal	67.00 (53.00-96.00)	69.00 (57.00-107.00)	0.845
Inferotemporal	145.00 (101.00-181.00)	142.00 (97.00-191.00)	1.000
Superotemporal	140.00 (100.00-174.00)	143.00 (112.00-170.00)	0.477

Table 2 – Global and sectorial RNFL thicknesses in RD patients and control subjects.

RNFL= Retinal Nerve Fiber Layer; RD=Raynaud's Disease.

Values represent median (minimum–maximum), respectively, unless otherwise specified.

There were no significant differences in global, inferonasal, superonasal, temporal, inferotemporal and superotemporal between the two groups.

75.00 to 129.00mm) and the control group (median 98.00 mm, range 88.00 to 123.00mm). The median thickness of nasal peripapillary RNFL was higher (p=0.037) in the RD group (median 82.00mm, range 55 to 185mm) than in the control group (median 71.00mm, range 50 to 116mm). The other quadrants of peripapillary RNFL thickness did not reveal any statistical significant difference between groups. There were no significant differences between the RNFL thicknesses according to RD duration (r=0.248, p=0.151). Detailed median RNFL thickness in RD patients and control subjects is summarized in Table 2.

Global RNFL thickness analysis of RD patients in association with NC features.

The global RNFL thickness was significantly lower (p=0.026) in the presence of avascular areas (median 83.00mm, range 75.00 to 91.005mm) in NC, when compared to absence of avascular areas (median 102.50mm, range 79.00 to 117mm). There was no significant correlation between the global RNFL thickness and the other capillary morphology and blood flow features analysed by NC. In addition, there were no significant differences between the NC features according to RD duration.

DISCUSSION

In 1988, Guthauser et al[11] found that the perimetric results correlated significantly with the capillaroscopic results, establishing a relationship between digital and ocular vasospasm. The clinical correlation between these two features was also confirmed by Broadway[12] and Delaney et al.[13] In addition, Pache et al[14] findings indicated that vasospasm and low blood pressure may be distinct risk factors for glaucomatous damage. Nicolela et al[15] assumed the abnormal increase in plasma endothelin-1 (ET-1) after the body cools in glaucoma patients as a possible explanation for this fact, confirming that systemic vasospastic stimuli may be involved in the pathogenesis of glaucomatous damage. In the presence of vasospasm, the autoregulation of the retinal and optic nerve head circulation may be impaired, leading to ET-1 and neuropetide Y potentiated vasoconstrictive reduction in blood flow, and ischemic damage, which seems to be a relevant component in the pathogenesis of glaucomatous optic neuropathy.[5,16] Nevertheless, Holló et al[17] did not confirm this correlation.

Although the perimetric changes showed correlation with systemic vasospasm, to the best of our knowledge, the RNFL thickness of patients with these peripheral manifestations has not been studied in comparing with normal subjects.[11]

Glaucomatous optic neuropathy characterized by progressive loss of retinal ganglion cells and associated morphological changes to the optic nerve and RNFL can be early and accurately detected by SD-OCT, mostly preceding visual field loss.[18,19] Furthermore, RNFL thickness parameters measured by SD-OCT have been shown to be significantly greater in normal subjects than in NTG.[20]

Our study showed that the global peripapillary RNFL thickness was not significantly different between patients with RD and normal subjects, although segmental analysis found a significantly higher RNFL thickness in the nasal quadrant, when compared to the same quadrant in the control group. Only patients with primary RP were included in this study because RP secondary to systemic diseases could have provided potential bias for the causes of possible optic nerve head abnormalities.

RD was, thus, associated with a RNFL thickness 9.8μm higher in the nasal quadrant. One possible explanation for this fact is that a risk factor for this type of open angle glaucoma is age, with the mean age of patients with NTG

reported being in the 6th decade of life.[4] Thus, the lower mean age of patients in our study may explain the lack of significant lower RFNL thickness in the primary RP group, even when comparing with normal subjects of the same mean age.

When analysing the sectorial RFNL thicknesses, the increase in the nasal sector of patients with peripheral vasospasm when compared with normal subjects, is unclear. It can be suggested that there is a correlation between the significant higher spherical equivalent in the RD group and a lower axial length, although this parameter hasn't been measured in our sample. If this is the case, considerably higher RNFL thickness of short eyes in comparison with medium and long eyes can explain this result.[21] The shorter axial length could also explain the lack of NGT or lower RFNL thickness in the primary RP group, since long axial length can be considered a risk factor of NTG and primary open-angle glaucoma.[22] The clinical implications of these results have to be further investigated, with axial length measurement in patients with such peripheral vasospasm as a necessary variable. In addition, the small sample size and the assumed independence between eyes are limitations of this study. A larger sample with a subsequent follow-up with a long-term study may be important to evaluate the RFNL changes in both groups, according to the refractive error and axial length.

The abnormalities in capillary morphology and blood flow found in NC have proven to be early indicators of progression into connective tissue diseases.[23] Therefore, this abnormalities such as capillary dilation, the presence of avascular areas, haemorrhages, giant capillaries, dilated or giant capillaries, haemorrhages, oedema, intermittent flux with sludge and reduced red blood cell velocity are associated with systemic microangiophathy and possible progression to a systemic disease with secondary Raynaud phenomenon.[24] The presence of avascular areas in the NC is, thus, a severity factor for a systemic disease.[24]

Our study showed that there was a correlation between this NC feature and the lower global RNFL thickness in RD patients, which can suggest that in these patients there is a propensity to optic nerve head damage. This damage may be associated with the systemic vasospasm but it would be necessary to confirm this hypothesis by enlarging the sample and by comparing it with a normal population.

In conclusion, this study showed an association between the presence of avascular areas in the NC, a vasospasm severity sign, and the lower global RNFL thickness in RD patients. It suggests that the systemic vasospasm severity may be related to optic nerve damage propensity. Therefore, its presence in NC may indicate the ophthalmological evaluation of RD patients, for the screening and early detection of optic nerve damage. Nevertheless, a larger sample with a long-term study is needed to support the clinical and therapeutic implications of our findings. ■

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