Optic Disc Structural, Vascular and Functional Assessment in Patients with Primary Raynaud's Phenomenon

Avaliação Estrutural, Vascular e Funcional do Disco Ótico em Doentes com Fenómeno de Raynaud Primário

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ABSTRACT

INTRODUCTION: Our aim was to assess optic disc structural, vascular and functional parameters in patients with primary Raynaud's phenomenon (PRP).

METHODS: This study enrolled patients with PRP and healthy age-matched controls.

Subjects underwent evaluation of intraocular pressure (IOP), anterior chamber angle, optic disc structural and vascular parameters (measured by optical coherence tomography) and visual field.

RESULTS: Twenty-four eyes were included in the control group, with a mean age of 44.20 ± 4.67 years, and 20 eyes in the PRP group, with a mean age of 43.00 ± 6.08 years (p=0.20). Inferior and nasal retinal nerve fiber layer (RNFL) thickness was lower in PRP group (104.05 ± 17.64 *vs* 118.67 ± 12.60µm, p=0.01; 70.05 ± 12.21 *vs* 79.50 ± 12.70 µm, p=0.04, respectively). Vascular density was lower in PRP group, mostly in the inner ring (15.90 ± 2.10 *vs* 14.20 ± 0.43 mm^{-1}, p=0.02). No difference was found in functional parameters (p>0.05). No correlation was found between optic disc vascular density and RNFL thickness on multivariate regression analysis (p>0.05).

CONCLUSION: Our findings suggest that PRP may possibly negatively affect the optic nerve, with a reduced vascular density and RNFL thickness.

KEYWORDS: Low Tension Glaucoma; Optic Disk; Raynaud Disease; Tomography, Optical Coherence.

RESUMO

INTRODUÇÃO: O nosso objetivo foi avaliar os parâmetros estruturais, vasculares e funcionais do disco ótico em doentes com fenómeno de Raynaud primário (FRP).

MÉTODOS: Este estudo incluiu pacientes com FRP e controlos saudáveis de idade equivalente. Avaliou-se a pressão intraocular (PIO), ângulo iridocorneano, parâmetros estruturais e vasculares do disco ótico (determinados por tomografia de coerência ótica) e os campos visuais.

RESULTADOS: Foram incluídos 24 olhos no grupo de Controlo, com uma idade média de 44,20 ± 4,67 anos, e 20 olhos no grupo de FRP, com uma média de idade de 43,00 ± 6,08 anos (p=0,20). A espessura nasal e inferior da camada de fibras nervosas (CFN) foi inferior no grupo de FRP (104,05 ± 17,64 *vs* 118,67 ± 12,60 µm, p=0,01; 7,.05 ± 12,21 *vs* 79,50 ± 12,70 µm, p=0,04, respetivamente). A densidade vascular foi igualmente inferior no grupo de FRP group, particularmente no anel interno (15,90 ± 2,10 *vs* 14,20 ± 0,43 mm-1, p=0,02). Não foram encontradas diferenças nos parâmetros funcionais (p0,05). Não se verificou uma correlação entre a densidade vascular do disco óticos e a espessura da CFN na análise de regressão multivariada (p0,05).

CONCLUSÃO: Os nossos achados sugerem que a FRP pode afetar negativamente o nervo ótico, com uma menor densidade vascular e espessura da CFN face a uma população normal.

PALAVRAS-CHAVE: Disco Óptico; Doença de Raynaud; Glaucoma de Baixa Tensão; Tomografia de Coerência Óptica.

INTRODUCTION

Raynaud's phenomenon (RP) is a vasospastic disorder affecting 5%-10% of the world's population.[1] It classically consists of a triphasic color change of the digits with initial white (ischemic phase), followed by blue (deoxygenation phase) and finally red (reperfusion phase).[1,2] The disease is attributed to recurrent vasospasm triggered by exposure to cold temperatures or emotional stress, and may be categorized as primary RP (PRP) or secondary RP (SRP), the latter usually occurring in association with connective tissue diseases.[1,2] PRP tends to affect young females between 15 and 30 years of age, and is generally considered a benign condition, with possible remission over time.[2] Features suggesting PRP include symmetric attacks, absence of tissue necrosis/ulceration, absence of a secondary cause, negative tests for antinuclear antibodies (ANAs) and normal inflammatory markers, such as erythrocyte sedimentation rate (ESR).[1,2] Additionally, a normal nailfold capillaroscopy, namely without hemorrhages, giant loops, large avascular areas and neoangiogenesis, is also suggestive of PRP. [1-3]

Glaucoma is the second leading cause of visual loss worldwide.[4] Normal tension glaucoma (NTG), a type of glaucomatous optic neuropathy, is associated with progressive retinal nerve fiber layer (RNFL) thinning, visual field defects, open iridocorneal angle and intraocular pressure (IOP) below 22 mmHg, suggesting an IOP-independent etiology.[4] Although NTG pathophysiology is not yet fully understood, its main contributing factors seem to be of mechanical or vascular origin, the latter mainly due to abnormal vasoregulation (such as in diseases like RP and migraine).[4,5] Prior studies evaluating optic disc structural and vascular parameters in vasospastic conditions, have concluded that they might constitute a risk factor for NTG development.[6-8] Our aim was to assess optic disc structural, vascular and functional parameters in adult patients with PRP.

MATERIAL AND METHODS

This prospective observational study enrolled patients with PRP that were not under treatment with calcium channel blockers for at least 6 months prior to examination and healthy age-matched controls. Exclusion criteria for both groups included diabetes mellitus, systemic hypertension/hypotension and nocturnal hypotension (based on medical records within 6 months of enrollment), cardiac arrhythmias, chronic obstructive arterial disorder, acute ischemic events, sleep apnea syndrome, chronic obstructive lung disease, connective tissue disorders (including scleroderma), endothelial diseases, migraine, smoking habits, glaucoma or other optic neuropathy, retinal diseases, pathologic myopia (spherical equivalent> -6,00 D or axial length> 26 mm), central corneal thickness<500 µm assessed by anterior segment optical coherence tomography (OCT), ocular trauma, keratorefractive/cataract surgery in the 3 months period prior to enrollment, patients on current treatment with ocular hypotensive agents or systemic/local drugs with optic nerve toxicity or possibly associated with reduced blood flow/ocular perfusion pressure, media opacities and lack of collaboration. This study was undertaken at Garcia de Orta Hospital, Portugal, according to the tenets of Helsinki Declaration and was approved by the hospital's ethic committee. Informed consent was obtained from all patients after they were fully informed of the purpose of the study.

All PRP patients were already under follow-up at the Rheumatology Department of Garcia de Orta Hospital, Portugal, prior to enrollment. Diagnosis was made according to history of digital symmetric vasospastic attacks precipitated by exposure to cold temperatures or emotional stress, absence of tissue necrosis or gangrene, absence of physical findings/prior history of a suggestive secondary cause, normal ESR and ANAs levels and a nailfold capillaroscopy without hemorrhages, giant loops, large avascular areas and neoangiogenesis.[9] Duration of PRP diagnosis and annual frequency of vasospastic attacks were documented on clinical records of previous consultations.

Patients were divided in 2 groups: Control group and

PRP group. All subjects underwent an evaluation of IOP, anterior chamber angle (ACA) and optic disc structural, vascular and functional parameters.

IOP was assessed in the morning in all patients by Goldmann applanation tonometry. The mean of 3 consecutive measurements was considered in the analysis. ACA was evaluated manually by anterior segment OCT (AS-OCT) by using Zeiss Cirrus HD-OCT 5000®, Carl Zeiss Meditec device and was performed under similar dark room conditions for all participants. Optic nerve structural parameters were assessed by OCT (Zeiss Cirrus HD-OCT 5000®, Carl Zeiss Meditec). Measurements included mean, superior, inferior, temporal and nasal RNFL thickness, mean ganglion cell layer complex (GCLC) thickness, rim area, disc area, mean cup/disc (C/D) ratio and vertical C/D ratio. Optic disc vascular density (VD) was assessed by OCT-A (Zeiss Cirrus HD-OCT 5000® with Angioplex 6x6 mm, Carl Zeiss Meditec). A 6x6 mm scan centered on the optic disc was used for data analysis, with all scans being analyzed by OCT-A software. Superficial VD was automatically measured by the OCT-A software.[10,11] The diameter of the concentric circles was 1, 3 and 6 mm. Measurements included VD of the center, inner and outer rings and full area. Images with insufficient scan quality were excluded. Optic nerve functional parameters were assessed by standard automated perimetry (SAP) by using the 24-2 glaucoma programme (Octopus 900®, Haag-Streit USA). Mean sensibility (MS), mean deviation (MD), false positive (FP) and false negative (FN) response rates measurements and presence or absence of visual field defects were included in the analysis.

Data were analyzed by using IBM SPSS Statistics V.25.0. The normal distribution of the parameters was verified by using the Kolmogorov-Smirnov test. t-Student test was used to compare measurements between groups. A multiple linear regression analysis with stepwise variable selection was conducted to assess the correlations between duration of PRP diagnosis, annual frequency of vasospastic attacks, IOP and peripapillary VD and optic nerve structural and functional parameters (RNFL thickness, mean GCLC thickness, MS and MD). For evaluating the potential risk factors for optic disc damage and NTG development, multivariate linear regression analysis was conducted, and only variables with a *p*-value of less than 0.10 were selected as independent variables in multivariate linear regression model. The level of statistical significance was set at $p<0.05$.

RESULTS

This study enrolled 44 eyes of 44 patients. Twenty-four eyes were included in the control group (75% female), with a mean age of 44.20 ± 4.67 years, and 20 in the PRP group (100% female), with a mean age of 43.00 ± 6.08 years ($p=0.20$). Among patients in the PRP group, mean duration of diagnosis was 26.13 ± 3.45 years, with an average of 8.56 ± 2.41 vasospastic attacks per year. Best corrected visual acuity was 0.12 ± 0.01 logMAR in the control group and 0.11 ± 0.02 logMAR in the PRP group ($p=0.24$).

Regarding IOP measurement, all subjects of control group and PRP group had IOP values below 22 mmHg. No significant difference was found (controls *versus* PRP group: 15.33 ± 2.18 *vs* 15.90 ± 1.55 mmHg, $p=0.25$).

Mean ACA width in the control group was 40.25º ± 3.40º and in PRP group was 38.84 ± 2.63º ($p=0.16$), both corresponding to an open iridocorneal angle.

Optic nerve structural assessment is described in Table 2.1. Inferior and nasal RNFL values were significantly lower in the PRP group (controls *versus* PRP group: 118.67 ± 12.60 *vs* 104.05 ± 17.64 μm, $p=0.01$; 79.50 ± 12.70 *vs* 70.05 ± 12.21 μm, $p=0.04$, respectively). No difference was found in the remaining parameters. ($p>0.05$) (Table 1.1). Optic disc superficial VD evaluation is described in Table 2.1. VD in the center and inner ring areas was lower in PRP group (controls *versus* PRP group: 2.42 ± 0.90 *vs* 2.13 ± 0.60 mm^{-1}, $p=0.04$; 15.90 ± 2.10 *vs* 14.20 ± 0.43 mm^{-1}, $p=0.02$, respectively). No difference was found between groups in VD of the outer ring or the full area ($p>0.05$) (Table 2.1).

Regarding optic nerve functional assessment, no significant differences were found between groups ($p>0.05$) (Table 3.1). No visual field defects were observed in both groups.

Multiple linear regression analysis revealed that there is no correlation between RNFL thickness and the covariates duration of PRP diagnosis, annual frequency of vasospastic attacks, IOP or peripapillary VD ($p>0.05$), nor between GCLC thickness, MS or MD measurements and the same covariates ($p>0.05$).

Table 1.1. Clinical and demographic features.

	Control Group, n=24 eyes	PRP Group, n=20 eyes	*p*
Age, years (Mean ± SD)	44.20 ± 4.67	43.00 ± 6.08	0.20
Sex (n; %)			
Female	18; 75	20; 100	0.06
Duration of PRP, years (Mean ± SD)	-	26.13 ± 3.45	-
Frequency of VEs per year (Mean ± SD)	-	8.56 ± 2.41	-
BCVA, logMAR (Mean ± SD)	0.12 ± 0.01	0.11 ± 0.02	0.24

BCVA: best corrected visual acuity, PRP: primary Raynaud's phenomenon, SD: standard deviation, VE: vasospastic event.

Table 2.1. Comparison of Optic Nerve Structural Parameters between Groups.			
Parameter (Mean ± SD)	**Control Group**	**PRP Group**	***p***
RNFL, µm			
Mean	94.90 ± 5.56	86.18 ± 6.65	0.15
Superior	115.05 ± 20.70	109.91 ± 18.30	0.09
Inferior	118.67 ± 12.60	104.05 ± 17.64	0.01
Temporal	66.38 ± 9.50	60.70 ± 10.80	0.08
Nasal	79.50 ± 12.70	70.05 ± 12.21	0.04
GCLC, µm	83.17 ± 6.98	78.40 ± 5.84	0.06
Rim area, mm²	1.28 ± 0.61	1.31 ± 0.29	0.10
Disc area, mm²	2.03 ± 0.21	1.99 ± 0.30	0.09
Mean C/D ratio	0.47 ± 0.17	0.52 ± 0.13	0.07
Vertical C/D ratio	0.45 ± 0.16	0.49 ± 0.08	0.10

C/D: cup/disc, GCLC: ganglion cell layer complex, PRP: primary Raynaud's phenomenon, RNFL: retinal nerve fiber layer, SD: standard deviation.

Table 2.2. Comparison of Peripapillary Superficial Vascular Density between Groups.			
Parameter (Mean ± SD)	**Control Group**	**PRP Group**	***p***
Average VD, mm^{-1}			
Central	2.42 ± 0.90	2.13 ± 0.60	0.04
Inner ring	15.90 ± 2.10	14.20 ± 0.43	0.02
Outer ring	17.00 ± 1.55	16.76 ± 2.31	0.07
Full area	16.45 ± 4.87	15.39 ± 3.79	0.06

PRP: primary Raynaud's phenomenon, SD: standard deviation, VD: vascular density.

Table 3.1. Comparison of Visual Field Parameters between Groups.			
Parameter (Mean ± SD)	**Control Group**	**PRP Group**	***p***
MS, dB	29.43 ± 2.73	27.01 ± 4.56	0.10
MD, dB	0.99 ± 2.70	1.01 ± 1.64	0.30
FP, %	7.63 ± 4.68	6.00 ± 1.43	0.15
FN, %	1.96 ± 6.65	1.33 ± 7.87	0.22

FP: false positive error, FN: false negative error, MD: mean defect, MS: mean sensibility, PRP: primary Raynaud's phenomenon, SD: standard deviation.

DISCUSSION

RP is a relatively common, although frequently unrecognized, vascular dysregulation disorder that is characterized by recurrent vasospastic events affecting the digits.[2,4] According to the etiology, it may be classified as PRP or SRP, the latter generally occurring in association with connective tissue diseases.[2] Although NTG pathophysiology remains challenging, it seems that one of its key components is reduction in ocular perfusion due to vascular dysregulation, a term used to describe diseases, such as RP, in which there is a lack of ability to maintain adequate blood flow despite alterations in perfusion pressure, resulting in irregular vasospastic/vasodilating events that may lead to retinal ganglion cell loss and axonal damage.[5] To our knowledge, there are very few publications on optic disc parameters in PRP, which is why it is not yet clarified the impact of the disease on optic disc characteristics regardless of the effect of associated disorders, as scleroderma. As such, our aim was to assess optic disc structural, vascular and functional parameters in patients with PRP.

Although to a lesser degree than in SRP, patients with PRP seem to have vascular, intravascular and neural abnormalities that predispose to abnormal vascular constriction and subsequent reduced capillary blood flow.[2] Vascular abnormalities are associated with an imbalance between vasoconstrictive (endothelin-1) and vasodilator (nitrous oxide) agents, favoring vasoconstriction.[2] Intravascular abnormalities lead to an abnormal increased platelet activation with elevation of thromboxane levels, defective fibrinolysis, increased activation of white blood cells and oxidative stress.[2] Neural abnormalities include increased activation of

the sympathetic system, which also contributes to disruption of capillary blood flow.[2] Together, these changes impair vasoregulation and reduce blood flow, which in turn may progressively decrease ocular perfusion pressure and ocular blood flow and possibly lead to optic nerve damage.[5]

In our study, PRP patients had an open ACA (mean 38.84º ± 2.63º), as measured by AS-OCT.

Although MS measurement was lower and MD measurement was higher in PRP group (27.01 ± 4.56 *vs* 29.43 ± 2.73dB, p=0.10; 1.01 ± 1.64 *vs* 0.99 ± 2.70dB, p=0.30, respectively), no significant difference was found in optic disc functional parameters between groups (p>0.05).

PRP was associated with a reduced inferior and nasal RNFL thickness (controls versus PRP group: 118.67 ± 12.60 *vs* 104.05 ± 17.64 μm, p=0.01; 79.50 ± 12.70 *vs* 70.05 ± 12.21 μm, p=0.04, respectively), as previously described for scleroderma, a secondary cause of RP, and for chronic migraine, suggesting that it might be a RNFL thinning pattern characteristic of conditions associated with vasospasm.[6,8] No correlation was found between age, duration of PRP diagnosis or annual frequency of vasospastic events and RNFL (p>0.05).

Optic disc VD was also significantly reduced in PRP patients, particularly in the center and inner ring area (controls *versus* PRP group: 2.42 ± 0.90 *vs* 2.13 ± 0.60 mm^{-1}, p=0.04; 15.90 ± 2.10 *vs* 14.20 ± 0.43 mm^{-1}, p=0.02, respectively), which is in accordance with İncekalan TK *et al* (2022), who also found a reduced density of the superficial peripapillary capillary plexus in patients with PRP and SRP.[11] There was no correlation between age, duration of PRP diagnosis or annual frequency of vasospastic events and optic disc VD (p>0.05). Our results could suggest that a reduced ocular perfusion was at least partially responsible for the differences in optic disc morphology in PRP patients, however no correlation was found between central, inner ring, outer ring or full area optic disc superficial VD on multivariate regression analysis in our study. As such, as postulated previously by İncekalan TK *et al* (2022), although ocular arteriolar vasospasm may be associated with a reduced optic disc VD in patients with PRP, it is possible that these vascular changes may be at least partially reversible in cases of primary RP, and therefore not sufficiently significant to be considered a risk factor for optic disc morphologic damage and progressive NTG development.[12] Additional physiopathological mechanisms predisposing to optic disc morphologic damage, duration and severity of vasospastic events and/or association with other vasospastic conditions, independently of IOP and vascular changes, may therefore be involved in RNFL thinning in patients with PRP.

Our findings suggest that PRP may be associated with reduced optic disc superficial VD and greater predisposition to optic nerve structural damage, the latter apparently not explained by age, severity of the disease nor the optic disc vascular changes. Further studies are required to determine if there is an increased risk of long-term visual impairment and whether prompt ophthalmologic evaluation and adequate treatment are useful in these patients.

Our limitations included small sample size, lack of comparison with SRP patients, lack of arterial blood pressure measurement and ocular perfusion pressure calculation and optic disc assessment based on a single evaluation. Additionally, there were limitations regarding VD measurements:

- The deep capillary plexus (DCP) was not assessed in our study. However, it is known that the inner plexiform layer is supported by both the superficial vascular complex and the intermediate capillary plexus (ICP), which forms the deep vascular complex along with the DCP.[13] Changes in the deep vascular complex may therefore be at least partially inferred based on superficial VD evaluation, as a reduction in intermediate capillary density would have influence on deep vascular complex. Additionally, it seems that the inner retinal layers, which are mainly supported by the superficial vascular complex are more susceptible to ischemic damage in patients with cardiovascular disease.[14]
- The distance from the disc border to the rings was different between subjects (because the rings are fixed), therefore the differences found in our study could have been due to vessel measurements at a different distance from the disc.
- The central area of the VD analysis pattern may not be reliable, as it mostly captures the optic nerve head optically hollow area.
- Large retinal vessels were not excluded from the analysis.

In conclusion, vasospastic conditions have been proposed as major risk factors for NTG development. Our study suggests that PRP may be associated with reduced optic disc vascular density and RNFL thinning. These results alert to the importance of investigating a possible association between PRP and long-term glaucoma development. Further studies, with a greater population size and long-term optic disc evaluation are required to corroborate our results.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors declare that they had a substantial and direct intellectual contribution in the design and elaboration of this article, that they participated in the analysis and interpretation of the data, in the writing of the manuscript, in the revision of versions and critical revision of its content and in the approval of the final version, agreeing who are responsible for the accuracy and completeness of all work.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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ETHICAL DISCLOSURES

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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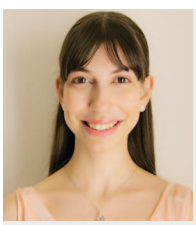

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