In-Depth Characterization of Cystoid Macular Edema in Retinitis Pigmentosa Using Swept-Source Optical Coherence Tomography

Caracterização do Edema Macular Cistóide na Retinopatia Pigmentar com Recurso a Tomografia de Coerência Óptica *Swept-Source*

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Recebido/Received: 2023-10-17 | **Aceite/Accepted:** 2024-05-23 | **Published online/Publicado online:** 2024-10-07 | **Publicado/Published:** 2024-12-20

DOI: https://doi.org/10.48560/rspo.33236

ABSTRACT

INTRODUCTION: Retinitis pigmentosa (RP) may be complicated by cystoid macular edema (CME), which contributes to central vision loss. The underlying pathophysiology of RP-associated CME (RP-CME) and its impact in prognosis remains uncertain.

Our objective was to investigate the association between cystoid spaces (CS), retinal morphometric parameters and clinical data in RP-CME using swept-source optical coherence tomography (SS-OCT).

METHODS: Prospective study conducted at an IRD referral center in Portugal. Consecutive RP patients with evidence of CME were recruited from the Retinal Dystrophies Clinic and invited to undergo SS-OCT (Zeiss PLEX Elite 9000). Morphometric assessment using the in-built software was performed by 2 independent graders (CC and CN) and included: central point outer nuclear layer thickness (CPONLT), ellipsoid zone area (EZA), central macular thickness (CMT), CS location (central point, central millimeter, outside central millimeter), CS retinal layer involvement and CS size. Clinical data, such as gender, age, genetic variants, best-corrected visual acuity (BCVA), lens status and vitreomacular interface status were registered.

RESULTS: We enrolled 40 eyes from 21 patients (71.5% male; mean age 47.3±15.2 years). In 61.90% the inheritance pattern was autosomal recessive, 80.95% had non-syndromic disease and 90.48% had bilateral CME. Mean BCVA was 68.06±14.55 ETDRS letters. CS were found in the inner nuclear layer in 100% of eyes and in the outer nuclear layer in 50%. CS involved the central point or central millimeter in 85% eyes (17 eyes each); 6 cases (15%) showed CS outside central millimeter. Size and retinal layer involvement were not associated with BCVA (p=0.548 and p=0.285). CS in the central point were associated with higher EZA when compared to those without central point involvement (p=0.009). EZA and CPONLT correlated with BCVA (r=0.351, p=0.0286 and r=0.387, p=0.0462).

CONCLUSION: CS involving the central point were associated with higher EZA values, showing that central point involvement happens in less severe disease stages with more preserved visual function. The correlation between CPONLT and BCVA highlights the importance of this

outer retinal layer for visual function in RP-CME. Further studies are needed to obtain a profound understanding of this entity along with the true impact of CS in visual function.

KEYWORDS: Macular Edema; Retinitis Pigmentosa; Tomography, Optical Coherence.

RESUMO

INTRODUÇÃO: O edema macular cistóide (EMC) pode complicar a retinopatia pigmentar (RP), contribuindo para perda de visão central. A fisiopatologia subjacente ao EMC associado à RP (EMC-RP) e o seu impacto prognóstico permanecem incertos.

O objetivo foi investigar a associação entre espaços cistóides (EC), parâmetros morfométricos da retina e dados clínicos no EMC-RP, com recurso a tomografia de coerência óptica *swept-source* (SS-OCT).

MÉTODOS: Estudo prospetivo realizado num centro de referência de distrofias hereditárias da retina (DHR) em Portugal. Doentes com RP com evidência de EMC foram recrutados do nosso centro e convidados a realizar SS-OCT (Zeiss PLEX Elite 9000). A avaliação morfométrica foi realizada por 2 avaliadores independentes (CC e CN) e incluiu: espessura da camada nuclear externa do ponto central (ECNEPC), área da zona elipsoide (AZE), espessura macular central (EMC), localização dos EC (ponto central, milímetro central, fora do milímetro central), envolvimento da camada retiniana e tamanho dos EC. Dados clínicos - sexo, idade, variantes genéticas, melhor acuidade visual corrigida (MAVC), *status* do cristalino e da interface vítreomacular foram registados.

RESULTADOS: Foram incluídos 40 olhos de 21 doentes (71,5% homens; idade média 47,3±15,2 anos). Em 61,90% o padrão de hereditariedade foi autossómico recessivo, 80,95% apresentavam doença não-sindrómica e 90,48% apresentavam EMC bilateral. A MAVC média foi de 68,06±14,55 letras ETDRS. EC foram encontrados na camada nuclear interna em 100% dos olhos e na camada nuclear externa em 50%. EC envolveram o ponto central ou milímetro central em 85% dos olhos (17 cada); 6 casos (15%) apresentaram EC fora do milímetro central. Tamanho e envolvimento da camada retiniana não mostraram associação com a MAVC (p=0,548 e p=0,285). EC no ponto central associaram-se a maiores AZE, quando comparados com aqueles fora do ponto central (p=0.009). AZE e ECNEPC correlacionaram-se com a MAVC (r=0.351, p=0.0286 e r=0.387, p=0.0462).

CONCLUSÃO: EC no ponto central associam-se a maiores AZE, sendo o envolvimento do ponto central ocorrente em estadios menos graves com função visual mais preservada. A correlação entre ECNEPC e MAVC destaca a importância desta camada externa na função visual no EMC-RP. Mais estudos são necessários para obter profunda compreensão desta entidade e do seu impacto na visão.

PALAVRAS-CHAVE: Edema Macular; Retinite Pigmentar; Tomografia de Coerência Óptica.

INTRODUCTION

Retinitis pigmentosa (RP; OMIM #268000) corresponds to a group of inherited retinal disorders (IRDs) where progressive rod-cone degeneration is observed. RP is the single most frequent IRD, with an estimated prevalence of 1 in 4000 individuals, i.e. affecting approximately 2.5 million people worldwide.[1] According to the IRD-PT,[2,3] there are over 300 genetically tested non-syndromic RP patients from all over Portugal currently managed at Centro Hospitalar e Universitário de Coimbra (CHUC).

Visual symptoms usually start in the second or third decades of life, with night blindness as a frequent early manifestation, followed by progressive visual field constriction.[4] Some RP hallmarks are optic disc pallor, retinal vessel attenuation, and mid-peripheral bone spicule hyperpigmentation, although the exuberance of each symptom and its impact in visual function is variable, having in mind the phenotypic heterogeneity that characterizes the disease. Reduced or non-detectable electroretinogram (ERG) responses under both scotopic and photopic conditions are common. As the disease progresses, a concentric loss of the outer retinal layers is observed, with significant visual field loss, and in advanced disease, macular atrophy with foveal involvement can be found, with severe central visual acuity loss.[5,6] Histologically, one may have disorganization of the retinal structure, particularly in the periphery, with loss of photoreceptors, some areas of preserved cones and gliosis.[7]

The classical idea that in retinitis pigmentosa (RP) visual function loss occurs concentrically, bilaterally and symmetrically, and that central visual acuity is preserved until late in the disease course is no longer an acquired fact, were it not for the phenotypical heterogeneity that characterizes the disease.[8] Central visual acuity loss may be attributed to macular atrophy, choroidal neovascularization (CNV), cystoid macular edema (CME), and vitreomacular interface disorders (VMID). In particular, CME may complicate RP and the association between both is known for a long time,[9] however the pathophysiology of CME in RP is still a matter of debate. The reported prevalence of CME varies in the literature but studies have shown that it may affect up to 50% of eyes.[10,11] Considering the detrimental effect that CME can have on central visual acuity, it is mandatory to screen RP patients for this potentially treatable complication.[12] Optical coherence tomography (OCT) revolutionized the diagnosis and management of retinal diseases and is currently the most frequently used imaging method to establish the presence of CME in RP.[10,13,14]

Breakdown of the blood retina barrier (BRB), retinal pigment epithelium (RPE) pump mechanism failure and/or Muller cell edema and dysfunction have been proposed etiologies for CME development in RP.[15] Cystoid spaces (CS) are commonly located in the inner nuclear layer, suggesting that BRB dysfunction may be one of the main culprits.[15,16]

In a recent publication, we have shown that CME could be found in 15.9% (23/145) of eyes with non-syndromic RP and 20% (13/65) of eyes with syndromic RP. In this study, CME, foveal thickness, cataract surgery and loss of integrity of the outer retinal layers were initially found to be significantly associated with BCVA. However, on mixed-effects multivariable linear regression analysis, only foveal thickness remained significant, which supports the clinical notion that patients with thinner retinas, suffering from long-standing degeneration, have worse visual acuity and that CME seems to be observed in eyes with better vision, although the reason for this is not fully elucidated.[10] As previously reported by others,[17,18] in our cohort there was no association between CME and age, gender, cataract surgery or inheritance pattern. However, Testa *et al*[19] reported that CME was significantly associated with female gender and autosomal-dominant inheritance and was less likely to exist in pseudophakic patients. Liew *et al*[20] found that CME was more likely to be found in autosomal-dominant forms of RP as opposed to X-linked forms and that it was more likely to occur in younger patients and less likely to occur in the presence of ERM or cataract.

To sum up, the burden of CME in RP is high.[10] Having this in mind, we aimed to investigate the association between cystoid spaces, retinal morphometric parameters and clinical data in RP-CME using swept-source optical coherence tomography (SS-OCT). We expect to increase our understanding of CME pathophysiology in RP, ultimately aiming to establish outcome measures and endpoints for a better management. Furthermore, as we are entering an era of targeted gene therapies for RP, a thorough analysis of the characteristics of CME across different RP genotypes is crucial.

MATERIAL AND METHODS

STUDY DESIGN

We performed a prospective study conducted at an IRD referral center (Centro Hospitalar e Universitário de Coimbra, CHUC, Portugal [JM1]). CHUC is the only Portuguese healthcare provider that integrates the European Reference Network for Rare Eye Diseases (ERN-EYE), a cross-border cooperation platform between specialists for the diagnosis and treatment of rare eye diseases. This places CHUC in a privileged position to provide specialized care to IRD patients in general, and RP patients in particular. Consecutive RP patients with evidence of CME were recruited from this IRD Clinic and invited to undergo SS-OCT (Zeiss PLEX Elite 9000).

Informed consent was obtained for every included subject. The study was approved by the local Ethics Committee and followed the tenets of the Declaration of Helsinki for biomedical research.

GENETIC TESTING

Genetic testing was clinically oriented in all probands and coordinated by a medical geneticist from the Medical Genetics Unit of our center. A next-generation sequencing approach was used and, when deemed necessary, complemented by multiplex ligation–dependent probe amplification and/ or sequencing of *RPGR*-ORF15. Peripheral blood samples were collected from all probands and available relatives for genetic analysis. The genomic DNA was extracted using a genomic DNA extraction and purification kit based on the manufacturer's protocol. Variants were classified in accordance with the American College of Medical Genetics and Genomics (ACMG).[21] All variants classified as pathogenic (class V) or likely pathogenic (class IV) were further confirmed by Sanger sequencing. Whenever possible, segregation analysis was performed in family members. Published cDNA sequences for the identified genes were compared with the sequencing results. Genetic counseling provided by a medical geneticist was granted to all subjects.

DATA COLLECTION AND GRADING

Clinical and demographic data were collected from all patients. All patients underwent a complete ophthalmologic examination comprising best-corrected visual acuity (ETDRS letters), anterior segment biomicroscopy, dilated fundus biomicroscopy and intraocular pressure measurement. Complementary, multimodal retinal imaging included ultra-wide field color fundus photography and fundus autofluorescence (Optos California, Optos GmbH, Germany) and swept-source OCT (Zeiss PLEX Elite 9000). Patients with low-quality scans due to nystagmus or significant media opacities were excluded from the analysis.

Lens status was recorded and patients classified as phakic or pseudophakic.

Vitreomacular interface status was also graded, regarding vitreous attachment (attached or detached) and presence of macular hole or pseudohole, lamellar hole, epiretinal membrane (ERM) and vitreomacular traction (VMT). ERM were graded according to the ERM SD-OCT classification proposed by Govetto *et al*.[22]

Morphometric assessment using the in-built software was performed by 2 independent graders (CC and CN), and included: (1) central point outer nuclear layer thickness (CPONLT): manually measured in horizontal scans (Fig. 1); (2) ellipsoid zone area (EZA): ellipsoid width was manually measured in horizontal and vertical scans (Fig. 1); also, by assuming that the OCT EZA is a semi-oval structure, each of the vertical and horizontal widths were considered a diameter, therefore, EZA was calculated using the formula $EZA=\pi((D1+D2)/4)^2$; (3) central macular thickness (CMT): given by the SS OCT-angiography through macular thickness analysis (Angio (6 x 6 mm) (100kHz)); (4) Cystoid Spaces analysis: manually measured regarding: (4.1) location: central point, central millimeter or outside central millimeter; (4.2) retinal layer involvement: inner nuclear layer or inner nuclear layer + outer nuclear layer/outer plexiform layer; (4.3) size of the largest CS in the central millimeter (Fig. 1): CS width and length were measured in axial scans and according to the greatest measure, CS were classified as: small: 0-150 µm, medium: 150-300 µm, large: 300-450 µm or very large: >450 µm.

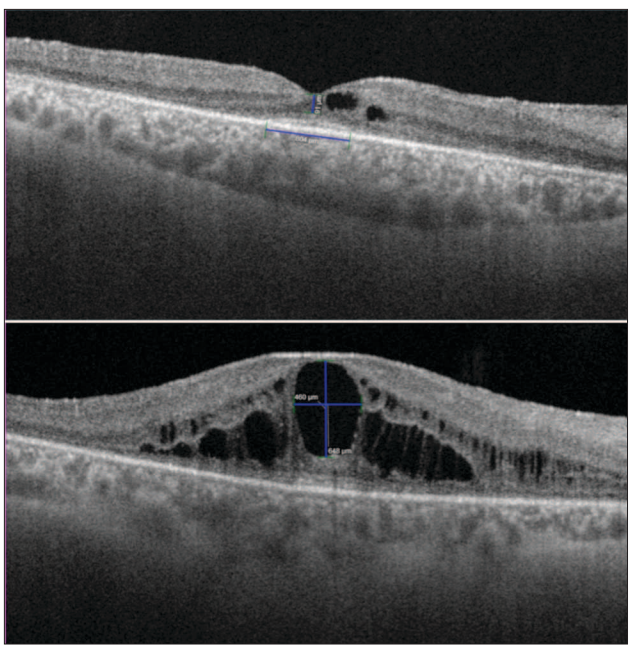

Figure 1. On top: EZ length and CPONLT measurements in horizontal scan. At bottom: CS size measurement (width and length).

DATA ANALYSIS

A descriptive analysis was conducted to all study variables. Continuous variables were expressed as mean±standard deviation. BCVA was expressed mainly in ETDRS letters. Demographic and baseline data were described according to each variable type. Continuous variables were analyzed by means of two-tailed parametric tests, such as T test or, when warranted, non-parametric tests, such as Mann Whitney test. Chi-square test was used for analysis of categorical outcome variables.

Correlations between the different parameters were tested using the Pearson and/or the non-parametric Spearman correlation coefficients.

Statistically significant results were considered for p-values lower than 0.05 adjusted for multiple comparisons when needed. For statistical analysis, GraphPad Prism Software for Windows, version 8.4.2 (GraphPad Software Inc, California, USA) and SPSS version 26 (SPSS, Inc., Chicago, IL, USA) were used.

RESULTS

STUDY POPULATION

We enrolled 40 eyes from 21 patients [mean age 47.3±15.2 years (range 17-75 years); 71.5% (n=15) male]. Complete data is presented in Table 1.

GENETIC INFORMATION

Autosomal-recessive inheritance was the most frequently observed inheritance pattern (n=13; 61.9%), followed by autosomal-dominant (n=2; 9.52%) and X-linked (n=1; 4.76%). Three patients (14.28%) corresponded to simplex cases and 2 patients (9.52%) are genetically unsolved. Seventeen patients (80.95%) had non-syndromic disease, while 4 patients (19.05%) had syndromic disease - 3 (75%) with Usher syndrome type I and 1 (25%) with Usher syndrome type IV. Seven (50%) pathogenic variants, 4 (28.57%) likely pathogenic and 3 (21.43%) variants of unknown significance were found in the cohort.

Of the genetically solved cases, *EYS* gene was the most commonly mutated gene (n=6, 42.86%).

CLINICAL DATA

Clinical and Epidemiological data are shown on Table 1.

MORPHOMETRIC PARAMETERS

Morphometric parameters are shown on Table 1.

Of note, in 13 patients (all with CS in the CP), the central point location of the CS precluded this measurement, so this item in these patients was further classified as non-measurable.

ASSOCIATIONS AND CORRELATIONS

Association between CMT, EZA and BCVA and CS location: Patients with CS in the CP showed higher CMT values (415±121 µm), compared to those with CS in the CM and OCM (303±119 µm) (p=0.0015). They also showed higher

Table 1. Baseline characteristics of the study population and morphometric parameters.

Baseline characteristics of the study population	
Patients (n)	21
Eyes (n)	40
Gender (n,%)	
Male	15 (71.5%)
Female	6 (28.5%)
Age (mean±SD)	47.3±15.2 years
BCVA (mean±SD)	
logMAR	0.33±0.29
ETDRS letters	68.06±14.55
Inheritance pattern (n,%)	
AR	13 (61.9%)
AD	2 (9.52%)
XL	1 (4.76%)
Simplex cases	3 (14.28%)
Still undetermined cases	2 (9.52%)
Non-syndromic RP (n,%)	17 (80.95%)
Syndromic RP (n,%)	4 (19.05%)
Lens status (n,%)	
Phakic	31 (77.50%)
Clear lens	19 (61.29%)
Cataract (all posterior subcapsular)	12 (38.71%)
Pseudophakic	9 (22.50%)
Vitreomacular interface status (n,%)	
Bilateral CME (patients)	19 (90.48%)
ERM (eyes)	9 (22.50%)
PVD (eyes)	5 (12.50%)
VMT (eyes)	1 (2.50%)
Morphometric parameters	
CS location	
CP	17 eyes (42.50%)
CM	17 (42.50%)
OCM	6 eyes (15%)
CS retinal layer involvement	
INL	40 eyes (100%)
INL+ONL	20 eyes (50%)
Ganglion Cell Layer	7 eyes (17.5%)
CS size	
Very large	7 (17.50%)
Large	6 (15%)
Medium	12 (30%)
Small	15 (37.50%)
Mean CMT	121±42 µm
Mean CPONLT	121±42 µm
Mean EZA width and area	
Horizontal scan	1832±1163 µm
Vertical scan	1219±951 µm
Area	2550367 µm^2

SD: standard deviation; BCVA: best-corrected visual acuity; AR: Autosomal-recessive; AD: autosomal-dominant; XL: X-linked; RP: retinitis pigmentosa; CME: cystoid macular edema; ERM: epiretinal membrana; PVD: posterior vitreous detachment; VMT: vitreomacular traction; CS: cystoid spaces; CP: central point; CM: central millimeter; OCM: out of central millimeter; INL: inner nuclear layer; ONL: outer nuclear layer; CMT: central macular thickness; CPONLT: central point outer nuclear layer thickness; EZA: ellipsoid zone area.

EZA values (2488007±1790057) than patients with CS in the CM and OCM (2150205±4201149) (p=0.009). These data are summarized in Table 2.

Table 2. Separated analysis CS in CP *vs* CS in CM and OCM.

Anatomical structure or clinical feature	CS in CP	CS in CM and OCM	*p*-value
CMT	415±121 µm	303±119 µm	0.0015*
EZA	2488007±1790057 µm	2150205±4201149 µm	0.009*
BCVA	69.18±14.76 ETDRS letters	67.24±14.66 ETDRS letters	0.569*

* Mann-Whitney U test.

BCVA: best-corrected visual acuity; CS: cystoid spaces; CP: central point; CM: central millimeter; OCM: out of central millimeter; CMT: central macular thickness; EZA: ellipsoid zone area.

Table 3. Association of the (1) interdependence between CS location, CS retinal involvement and CS size and the (2) influence of lens status on these parameters.

CS location and CS retinal involvement			*p*-value
	INL	INL + ONL	
CP	3	14	**0.004**
CM and OCM	17	6	
CS location and CS size			
	large and very large	small and medium	
CP	10	7	**0.0022**
CM and OCM	3	20	
CS retinal layer involvement and CS size			
	large and very large	small and medium	
INL	3	17	**0.0181**
INL + ONL	10	10	
Lens status and CS location			
	pseudophakic	phakic	
CP	1	15	**0.0445**
CM and OCM	8	16	
Lens status and retinal layer involvement			
	pseudophakic	phakic	
INL	8	19	**0.0080**
INL + ONL	1	12	
Lens status and CS size			
	pseudophakic	phakic	0.120
large and very large	1	12	
small and medium	8	19	

CS: cystoid spaces; CP: central point; CM: central millimeter; OCM: out of central millimeter; INL: inner nuclear layer; ONL: outer nuclear layer; EZA: ellipsoid zone area.

Association of the interdependence between CS location, CS retinal layer involvement and CS size: Patients with CS in the CP had CS located mostly in the INL+ONL, while patients with CS in CM and OCM had CS located mostly in the INL (p=0.004). Additionally, patients with CS in the CP had CS sized large or very large, while patients with CS in CM and OCM had CS sized small and medium (p=0.0022). Large and very large CS were located mostly in the INL+ONL, while small and medium CS were located mostly in the INL (p=0.0181). Chi-Square test was used. These data are summarized on Table 3.

Influence of lens status on CS location, CS retinal layer involvement and CS size: Pseudophakic patients were more prone to have CS in the CM and OCM, while phakic patients had approximately the same rate, p=0.0445. Pseudophakic patients were also more prone to have CS in the INL while phakic patients had a trend to have CS in the INL+ONL, p=0.0080. Finally, pseudophakic patients had a trend to have small and medium CS, the same happening with phakic patients, p=0.120. Chi-Square test was used. These data are summarized on Table 3.

Association between CS retinal layer involvement and CS size and EZA and BCVA: BCVA and EZA did not significantly differ between patients with CS in the INL and in the INL+ONL. Patients with medium and small CS showed lower EZA values and worse BCVA, although a not statistically significant difference was noted. These data are summarized on Table 4.

Correlation between CPONLT and CMT with BCVA and EZA: CPONLT positively correlated with BCVA, with a statistically significant correlation (r=0.387, p=0.0462), and with EZA, although a not statistically significant correlation was found (r=0.311, p=0.114). EZA positively correlated with BCVA (r=0.351, p=0.0286). Table 5 summarizes these data.

Table 4. Separated analysis of: (1) CS in INL vs CP in INL+ONL and (2) small and medium CS versus large and very large CS.

CS in INL *vs* CS in INL+ONL			***p*-value**
Anatomical structure or clinical feature	CS in INL	CS in INL+ONL	
EZA	2453468±4420068 µm	2115446±1902009 µm	0.161*
BCVA	66.28±14.88 ETDRS letters	69.85±14.35 ETDRS letters	0.285*
Small and medium CS *vs* large and very large CS			***p*-value**
Anatomical structure or clinical feature	small and medium CS	large and very large CS	
EZA	2157324±3808431 µm	2584591±2312205 µm	0.147*
BCVA	66.95±14.00 ETDRS letters	68.15±16.20 ETDRS letters	0.548*

* Mann-Whitney U test.

BCVA: best-corrected visual acuity CS: cystoid spaces; CP: central point; CM: central millimeter; OCM: out of central millimeter; INL: inner nuclear layer; ONL: outer nuclear layer; EZA: ellipsoid zone area.

Table 5. Correlation of anatomical structure and BCVA and EZA

Anatomical structure	Correlation with BCVA	Correlation with EZA
CPONLT	r=0.387*, p=0.0462	r=0.311*, p=0.114
CMT	r=-0.069*, p=0.711	r=0.050*, p=0.788
EZA	r=0.351*, p=0.0286	Not applicable

* Pearson correlation coefficient.

BCVA: best-corrected visual acuity; EZA: ellipsoid zone area; CPONLT: central point outer nuclear layer thickness; CMT: central macular thickness.

DISCUSSION

Pathogenesis of CME in RP is not fully understood, although theories include the breakdown of BRB, RPE pump mechanism failure and/or Muller cell edema and dysfunction. The presence, location and amount of fluid accumulation, as markers of severity or activity, are paramount to treatment and management decisions in clinical practice. Obtaining a deeper understanding of the mechanisms behind CME in RP may facilitate the identification of targeted and more effective therapies, so we studied the role of the CS different characteristics in the clinical outcomes of RP patients with cystoid macular edema, as well as the contributions of each one to the pathogenesis of this complex entity.

CS in CP were associated with higher CMT values, showing that centrally located CS are more prone to induce central thickness changes. However, in terms of BCVA and EZA, this was not of great impact, as demonstrated by the weak correlations between CMT and these parameters. In this field, RP-CME does not seem to differ from other pathologies, such as Irvine-Gass syndrome[23] or diabetic macular edema,[24] in which improvements in BCVA do not seem to significantly correlate with CMT. Still regarding CS location, patients with centrally located CS showed significantly better EZAs and better (although a not statistically significant difference) BCVAs. This may suggest that CS have a protective effect on the preservation of the outer retina, although its presence may interfere with central vision, which is just one measure of the current visual function. Taking this into account, it remains controversial if in an exhaustive effort should be made to completely resolve the edema in these patients. Additionally, patients with CS in the CP had CS located mostly in the INL+ONL instead of just in the INL, which depicts even better this protective effect, eventually for having CS closer to the outer retinal layers. This is in favor of the theory of the Muller cells dysfunction,[25] as these patients may benefit from the fact that the inner nuclear layer is not damaged by the CS compression. Another thing to note was that patients with CS in the CP had CS sized large or very large mostly instead of medium and small, and this was dramatically more evident

when looking at patients with CS in CM and OCM, that had mostly CS sized small and medium instead of very large and large.

In terms of retinal layer involvement, we demonstrated that it does not seem to have a direct relationship with BCVA and EZA. Additionally, large and very large CS were located mostly in the INL+ONL instead of just in the INL, supporting the aforementioned theory that CS may have a protective role on the outer retina and as the compression effect is distributed through the inner and outer retina, Muller cells are not as damaged as if the biggest CS were mostly located in the inner layers. Despite all this and once more, our study also showed that CS size does not seem to directly impact BCVA and EZA, so a missing link is still to investigate. The limited effect of the CME size on the BCVA in the RP-CME paradigm contrasts with the impact of CME seen in patients with diabetic macular edema and branch retinal vein occlusion,[26] once more showing that RP-CME is a distinct entity.

Pseudophakic patients were more prone to have CS in the CM and OCM instead of in the CP and to have CS mostly in the INL instead of in the INL+ONL. This may signify that lens status must be taken into account when approaching these patients, and a remodeling of the edematous retina is suggested to happen when cataract surgery is performed.

CPONLT positively correlated with BCVA, highlighting the importance of the outer retinal layers for visual function in RP-CME. In one study, the inner retinal layers seemed to be more preserved in RP patients with CME, unlike in RP patients without ME and that, in contrast, the outer retinal status was similar in RP eyes with ME and RP eyes without ME.[27] However, another study suggested a high negative correlation between the outer retinal degeneration and the size of the cysts,[28] so this measure has to be taken into account to understand its true role.

BCVA and EZA showed a positive and statistically significant correlation, showing that although in some cases a residual central point EZ preservation is compatible with a functional BCVA, higher EZA values are more compatible with better BCVAs.

Our study is unique due to its methodology; however, it has some limitations. The first one is related to our sample, which is relatively small. Further studies with larger cohorts are needed to obtain a profound understanding of this entity along with the true clinical impact of CS in visual function. Second, it does not take into account temporal changes with long-term follow-up analyses. Third, the associations and correlations found here may not necessarily imply direct causation, as RP-CME is complex and it is impossible to include all the intervenients in one study at the same time. Additionally, the changes noted here may not be enough to explain the CME pathogenesis on their own, as CME is a dynamic entity and the anatomical and structural features may affect each other and contribute asymmetrically to the evolution of the CS phenotypes. Finally, we did not take into account possible confounding factors, such as systemic conditions and treatment already instituted (although the last is mostly similar in all patients with indication for treatment).

In the future, we seek to identify the location and quantify the presence of abnormal extracellular fluid accumulation, and investigate this feature as a possible biomarker for the characterization of RP, aiming an improved mapping of the location and extent of retinal fluid accumulation, better characterization of the distribution of abnormal fluid in the different retinal layers, as well as their relative involvement, as reliably as fluorescein angiography and OCT-A, and establish outcome measures and endpoints for a better management.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

CC and CN: Responsible for gathering the data, presenting the results, and writing the manuscript.

MS, SS and PM: Performing OCT acquisition.

JPM: Concept, design of the study and revision of the manuscript and supervised this project and contributed with their expertise to its conclusion.

RS and JM: Supervised this project and contributed with their expertise to its conclusion.

All authors: read and approved the final manuscript.

CC e CN: Responsáveis pela recolha dos dados, apresentação dos resultados e redação do manuscrito.

MS, SS e PM: Realização da aquisição da OCT.

JPM: Conceito, desenho do estudo e revisão do manuscrito e supervisionou este projeto e contribuiu com a sua experiência para a sua conclusão.

RS e JM: Supervisionaram este projeto e contribuíram com a sua experiência para a sua conclusão.

Todos os autores: leram e aprovaram o manuscrito final.

RESPONSABILIDADES ÉTICAS

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

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

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.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

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).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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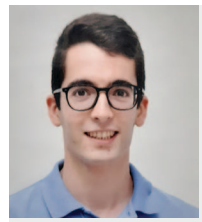

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