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Case Report

# BILATERAL SEROUS CHORIORETINOPATHY AND PIGMENTARY GLAUCOMA – WHAT IS THE ASSOCIATION?

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SUMMARY – We present a patient with concurrent pigmentary glaucoma, bilateral central serous chorioretinopathy and unilateral optic disc pit, and propose a possible association of these conditions. Comprehensive ophthalmic examination of a 36-year-old man who was complaining of blurry vision and pain in the eyes showed reduced visual acuity on the left eye, elevated intraocular pressure in the right eye, bilateral signs of pigment dispersion syndrome, and bilateral central serous chorioretinopathy, combined with optic disc pit in the left eye. Visual field and optical coherence tomography findings demonstrated functional and structural glaucoma changes. Choroidal circulation abnormalities were observed by angiographic methods. Genetic and developmental anomalies of the external layer of the optic disc cup that gives rise to many anterior and posterior eye segment structures suggest a possible association of a clinical condition characterized by the combination of pigmentary glaucoma, central serous chorioretinopathy and optic disc pit. Future research would enable to determine proper diagnostic protocols, treatment and follow-up procedures for this chronic-progressive disorder.

Key words: *Pigmentary glaucoma; Central serous chorioretinopathy; Retinal pigment epithelium; Genetics; Embryology*

## Introduction

During eye development, most of the eye tissue develops from the ectoderm with extraocular muscles and vascular endothelium developing from the mesoderm[1-3]. The optic cup is an embryologic structure of neuroectoderm origin composed of two layers that give rise to many tissues in the eye[1-3]. The internal layer of the optic cup develops into anterior ocular structures, such as the non-pigmented ciliary epithelium, posterior iris pigment epithelium (IPE), and pupil muscles, while its posterior portion forms the neurosensory retina[1-3]. The external layer of the optic cup forms the retinal pigmented epithelium (RPE), the anterior IPE, and the pigmented ciliary epithelium[2,3]. *In vitro* and *in vivo* studies have shown similar morphological development of the RPE and IPE, and similar expression patterns of specific transcription factors and function, such as the ability to synthesize melanin, suggesting their common origin[2,3]. In addition, neural crest cells in the optic cup take part in the development of other ocular structures including the corneal endothelium and trabecular meshwork[1].

Since a complex interaction between various embryologic tissues is essential for normal development

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of the organ, pathologic neuroectodermal signaling could halt normal growth of the eye[1]. Dysgenesis of the neuroectoderm can contribute to numerous ocular disorders such as retinal detachment, glaucoma, and anterior segment malformations[4].

This paper aims to present a case of a patient with pigmentary glaucoma (PG) with concurrent bilateral acute central serous chorioretinopathy (CSCR) and optic disc pit in one eye. To the best of our knowledge, there is only one published paper reporting a patient with combined pigment dispersion syndrome (PDS) and unilateral chronic CSCR[5].

## Case Report

A 36-year-old Caucasian male presented with pain in both eyes, gradual decline of visual acuity in the left eye during the last two months, and metamorphopsia in the last few days. He was otherwise healthy and there was no history of the use of any medication, however, he revealed that he had a stressful situation at work. His family history disclosed that his brother had been observed and treated for chronic CSCR. The patient provided written informed consent to publicize this case report and accompanying images.

Our patient's best-corrected visual acuity was 0.0 on his right eye and 0.2 on his left eye obtained by the LogMAR visual acuity chart. Slit-lamp examination showed pigment deposits (Krukenberg's spindle) on the corneal endothelium and discrete iris transillumination defects. Intraocular pressures measured by applanation tonometry were 32 and 15 mm Hg in the right and left eye, respectively. Gonioscopy demonstrated a wide open angle, a densely pigmented trabecular meshwork, and concave configuration of the iris root (Fig. 1A).

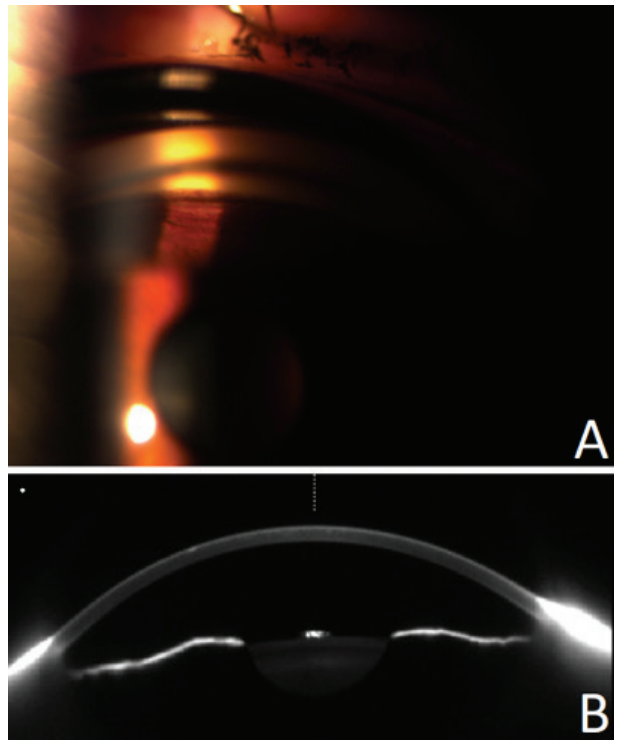


*Fig. 1. (A) Gonioscopy presents a widely open iridocorneal angle, dense pigment accumulation on the trabecular meshwork, and posterior iris insertion; (B) corneal tomography demonstrates deep anterior chamber and iridolenticular contact of a concave iris and a backward configuration of the iris root.*

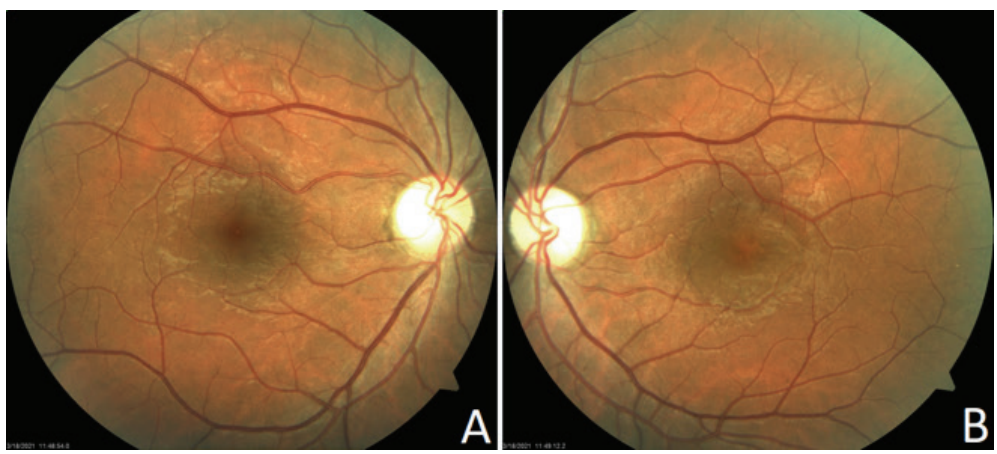


*Fig. 2. Color fundus photography: (A) right eye localized retinal detachment in the upper parafoveolar area; and (B) left eye foveolar serous chorioretinopathy. Images of the optic nerve head (ONH) did not present optic disc pit (A and B).*

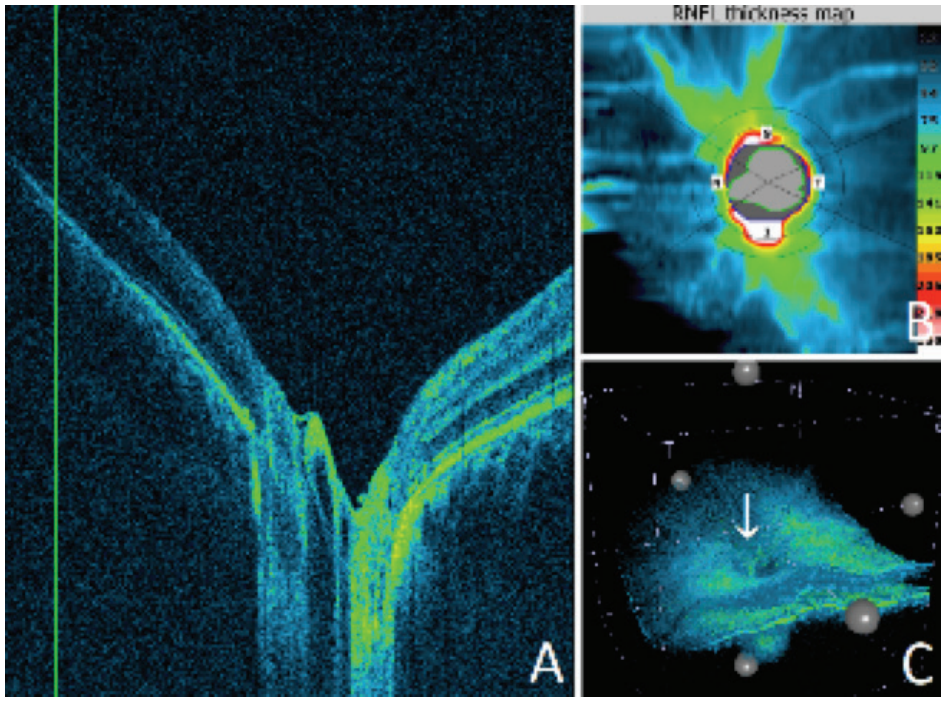


*Fig. 3. Optical coherence tomography (OCT) scans of the left optic nerve head (ONH). Horizontal OCT scan through the left optic disc at the location of the pit displays a wide cup with a small recess in the nasal aspect of the cup (A). The retinal nerve fiber layer (RNFL) thickness map shows a reduced peripapillary RNFL thickness in the nasal area of ONH with focal small nasal excavation of the neuroretinal rim, which could implicate incomplete closure of the embryonic fissure. The thickest RNFL is in the inferior part (B). OCT 3-dimensional reconstruction of ONH showed excavation in the nasal area, which confirmed the presence of the optic disc pit (C).*

Fundus examination showed bilateral glaucomatous optic nerve head (ONH) cupping, as well as bilateral neurosensory retinal detachment in the macula, extrafoveolar in the right eye, and central in the left eye. In addition, left ONH revealed small grayish cupping close to the nasal edge of the optic disc rim that resembled optic disc pit (ODP) which, however, was not detected by the fundus camera on fundus photographs obtained by Visucam (Carl Zeiss Meditec AG, Jena, Germany) (Fig. 2). On the other hand, optical coherence tomography (OCT) horizontal scans and 3D reconstruction of the left ONH obtained by SD-OCT Copernicus HR (OPTOPOL Technology, Zawiercie, Poland) finally demonstrated the location of a small ODP on the left eye (Fig. 3 A-C). OCT B-scan images of both maculae showed serous detachment of the neurosensory retina (Fig. 4A-D).

Retinal nerve fiber layer analysis of OCT imaging of ONH showed thinning in the superior and inferior part confirming optic nerve neuroretinal rim loss in that area. Visual field testing obtained by the Octopus 900 G program (Haag-Streit AG, Köniz, Switzerland) showed bilateral arcuate scotomas. The OCULUS Pentacam (OCULUS Optikgeräte GmbH, Wetzlar, Germany) revealed a deep anterior chamber and backward bowing of the iris, as well as corneal thickness of 625 microns in the central cornea (Fig. 1B). Specular microscopy showed normal density of the corneal endothelium. An electrooculogram (EOG) was performed with the Roland RETI-port/scan 21 unit (Brandenburg, Germany) and Arden`s index was found to be in the normal range.

Fluorescein angiography (FA) obtained by Visucam (Carl Zeiss Meditec AG, Jena, Germany) demonstrated focal leakage in terms of the early point-like hyperfluorescence that gradually enlarged in the upper parafoveolar region, as well as along the temporal margin of the ONH in the right eye and in the temporal

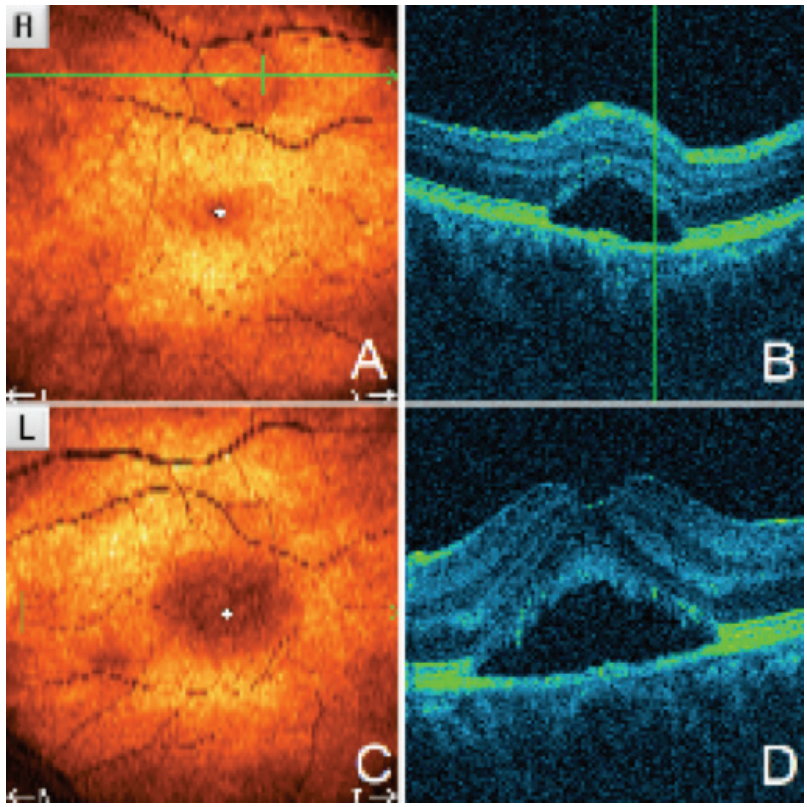


*Fig. 4. Optical coherence tomography (OCT) horizontal scans of both maculae demonstrate low-reflective space corresponding to the accumulation of serous fluid which separates the sensory retina from the retinal pigmented epithelium (RPE). Extrafoveolar location of changes with the loss of integrity of the underlying RPE is shown in the right eye (A-B). In the left eye, neurosensory retinal detachment is present in the center of macula, with mild disturbance of the adjacent RPE layer (C-D).*

part of the macula in the left eye (Fig. 4A-D). Indocyanine green angiography (ICGA) showed dilatation of the large choroidal vessels, discrete in the right eye and more noticeable in the left eye (Figs. 4E-F, 5). A review of clinical findings was highly suggestive of a diagnosis of acute CSCR in both eyes together with PG and left eye optic disc pit.

Glaucoma therapy was provided by prescribing topical and systemic carbonic anhydrase inhibitors, which resulted in normalization of the intraocular pressure.

## Discussion

This case report is the first to date in the literature that describes a patient with both CSCR and PG. Earlier, Kourkoutas *et al.* have reported a patient with concurrent PDS and unilateral chronic CSCR[5]. However, our patient had CSCR in both eyes, and additionally ODP in the left eye. The incidence of ODP has been reported to be 1 *per* 11,000 cases and it may occur together with retinal schisis, serous macular detachment, and maculopathy[6,7]. Both PDS and CSCR are typically seen in middle-aged men[8,9]. The conditions are of unknown etiology, mostly multifactorial, with genetics and environmental factors contributing to their development[9,10].

Given the fact that RPE and IPE are both derived from the neuroectoderm, it raises concern that genetic abnormalities during embryonic development of the eye resulted in structural changes in our patient. Additionally, his family history emphasized the possible genetic influence. Family history of CSCR proposed its genetic background, hence mutations in many different genes were investigated[10,11]. The inher-

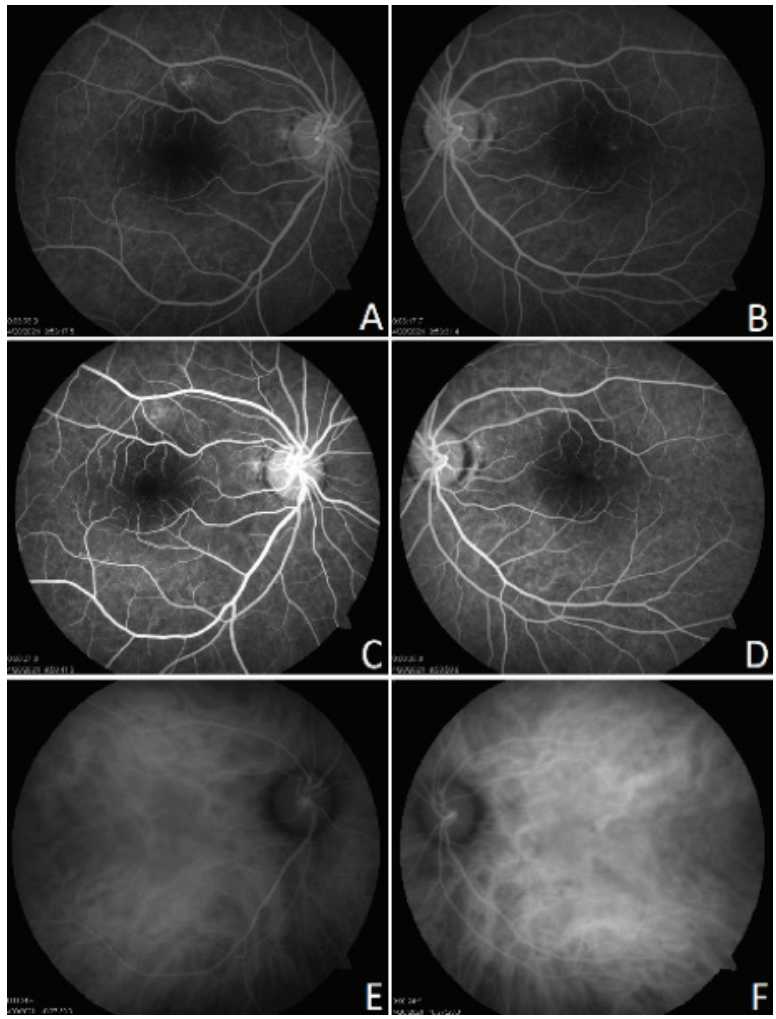


*Fig. 5. Fluorescein angiography shows increasing hyperfluorescent spots with intense late leakage indicating defects in the retinal pigment epithelium in the superior part of the macula in the right eye (A, C), as well as in the temporal part of the macula in the left eye (B, D). Hyperfluorescence in terms of window effect was further noted in the area adjacent to the temporal margin of the optic nerve head in the angiogram of the right eye (A, C). Indocyanine green angiography (ICGA) shows dilated large choroidal vessels at the posterior pole of both eyes, more pronounced on the left eye (E-F).*

itance pattern is currently unknown, but the mode of inheritance seems to be autosomal dominant. Additionally, it is suggested that PDS and PG possess a hereditary basis for developmental abnormality of the iris and/or related iris support structures with the release of pigment, which has been observed by histopathologic findings of the iris in some eyes with PDS. The precise mode of transmission of PDS has yet to be defined, but autosomal dominant inheritance with combinations of mutations in more than one gene, or from common variants in many genes, have been described[9].

Since the optic cup is derived from neuroectoderm and gives rise to many ocular structures, this may have broad clinical significance. Defects in optic cup embryogenesis can result in diverse ocular conditions and dysgeneses such as coloboma, morning glory syndrome, and Axenfeld-Rieger syndrome[4].

The optic disc pit in our patient's left eye suggested another possible defect of neuroectoderm signaling. In the literature, there are some reports of optic disc pit combined with malformations of the anterior eye segment[12]. Our patient had a very thick cornea, around 625 μm. Goktas and Goktas demonstrated that the

eyes with an optic disc pit have a smaller back radius of corneal curvature compared to other eyes[12]. It is possible that embryologic factors in the development of optic disc pit influence the development of the cornea, which both also are of neuroectodermal origin.

Some previous studies presented patients with PDS combined with RPE degenerations[13]. Furthermore, some authors report EOG abnormalities in patients with PDS, indicating disturbances in the integrity and function of the RPE[14]. *In vitro* studies have shown that IPE cells and RPE cells acquire specific properties which provide many common functions. Research has revealed the possibility of using IPE cells to carry viral material for gene transfer to the retina in order to substitute the defective RPE layer. Furthermore, subretinal transplantation of cultured autologous IPE cells was proposed as a new treatment modality for retinal diseases with RPE dysfunction[2,3]. In this case, the patient's normal EOG findings showed normal functional reserve of the RPE and the photoreceptors, presenting only localized retinal changes. At this time, however, close monitoring is necessary in order to identify the possible disease progression.

In cases with PDS, it was suggested that the release of pigment from the iris might not be caused exclusively by reverse pupillary block, first proposed by Campbell, but that an inherent abnormality of the IPE has to be present in order to result in the release of pigment granules during mechanical rubbing against the lens zonulas[15]. In addition, due to angiographic findings which have shown hypoperfusion of the iris in patients with PDS, some investigators speculated that the pigment dispersion might be related to a developmental anomaly of the mesodermal structures of the iris[9]. Although controversial, some reports proposed that PDS might be related to mutual mechanical, developmental, and trophic abnormalities involving other structures than the eyeball, such as dynamic fluctuations in the gradient between intraocular and intracranial pressures[16,17].

Increasing evidence implicates abnormal choroidal circulation to be the cause of CSCR as seen on ICGA. Due to the increased hydrostatic pressure in vessels of the choriocapillaris, fluid leaks through a defect of the RPE to the subretinal space and detaches the neurosensory retina[10]. On the other hand, various reports confirmed the connection between macular serous detachment or retinoschisis and ONH defects (congenital and acquired disorders such as ODP)[18]. They suggest that vitreous fluid passes into the retina and subretinal space through a break in the translucent membrane overlying ONH defects[18]. CSCR in our patient's left eye could be explained by the presence of both the ICGA abnormalities and optic disc pit. The absence of optic disc pit and normal ICGA findings leave the mechanism of neurosensory detachment in the right eye unexplained, although the hyperfluorescent locus along the temporal side of the right ONH, presented on FA, increases the possibility of leakage from an unrecognized ONH anomaly or defect in the RPE.

Similar to our patient, there is a report of a patient with concurrent ODP maculopathy and PG with advanced disc cupping, with no visible pit on fundus examination[19]. However, the authors detected space by SD-OCT that resembled congenital pit, masked by the acquired neuroretinal rim loss[19]. In our case, ODP was suspected on fundus examination of the left eye, but it was finally confirmed by 2D and 3D SD-OCT reconstruction of the left eye ONH. These findings suggest that OCT examination is a sensitive diagnostic tool for ODP detection in patients with ONH glaucomatous cupping and CSCR, while glaucomatous cupping may mask small pits, which can explain their lack of visibility on fundus examinations and fundus photographs.

This paper suggests the possible genetic and developmental connections between PDS/PG and ONH/RPE anomalies, so the question is whether there is a need to screen these conditions when one of them already exists in the patient. Additional investigations with more respondents are required to prove this presumed association, as well as its extent, in order to find proper diagnostic algorithms and possible future treatment (gene therapy), as well as follow-up protocols for these chronic-progressive disorders.

## Conclusion

In conclusion, for the first time, this work presents a rare combination of pigmentary glaucoma, acute CSCR, and optic disc pit in the same presenting case. A proposed explanation for this rare clinical combination of conditions might be that developmental anomalies of the external layer of the optic cup also involve both the anterior and posterior parts of the

eyeball. Further studies are required to define whether there is a connection among those conditions, and to what extent, and whether there is a need for screening of these conditions when one of them already exists. By increasing our knowledge about the genetics and pathogenesis of these conditions, more appropriate therapeutic algorithms can be determined, resulting in better treatment outcomes.

## References


1. Heavner W, Pevny L. Eye development and retinogenesis. Cold Spring Harb Perspect Biol. 2012 Dec 1;4(12):a008391. doi: 10.1101/cshperspect.a008391.
2. Wang X, Xiong K, Lu L, Gu D, Wang S, Chen J, *et al*. Developmental origin of the posterior pigmented epithelium of iris. Cell Biochem Biophys. 2015;71(2):1067-76. doi: 10.1007/s12013-014-0310-0.
3. Thumann G. Development and cellular functions of the iris pigment epithelium. Surv Ophthalmol. 2001;45(4):345-54. doi: 10.1016/s0039-6257(00)00195-8.
4. Rosen D, Mahabadi N. Embryology, Optic Cup. StatPearls [Internet]. Treasure Island (FL) StatPearl Publishing, 2022.
5. Kourkoutas D, Tsakonas G, Karamaounas A, Karamaounas N. Chronic central serous chorioretinopathy in a patient with pigment dispersion syndrome: a possible correlation. Case Rep Ophthalmol Med. 2017;2017:5857041. doi: 10.1155/2017/5857041.
6. Kranenburg EW. Crater-like holes in the optic disc and central serous retinopathy. Arch Ophthalmol. 1960;64:912-24. doi: 10.1001/archopht.1960.01840010914013.
7. Brown GC, Augsburger JJ. Congenital pits of the optic nerve head and retinochoroidal colobomas. Can J Ophthalmol. 1980;15(3):144-6.
8. Bahadorani S, Maclean K, Wannamaker K, Chu ER, Gresores N, Sohn JH, *et al*. Treatment of central serous chorioretinopathy with topical NSAIDs. Clin Ophthalmol. 2019;13:1543-8. doi: 10.2147/OPTH.S202047.
9. Farrar SM, Shields MB, Miller KN, Stoup CM. Risk factors for the development and severity of glaucoma in the pigment dispersion syndrome. Am J Ophthalmol. 1989;108(3):223-9. doi: 10.1016/0002-9394(89)90110-4.
10. Giannopoulos K, Gazouli M, Chatzistefanou K, Bakouli A, Moschos MM. The genetic background of central serous chorioretinopathy: a review on central serous chorioretinopathy genes. J Genomics. 2021;9:10-9. doi: 10.7150/jgen.55545.
11. Oosterhuis JA. Familial central serous retinopathy. Graefes Arch Clin Exp Ophthalmol. 1996;234(5):337-41. doi: 10.1007/BF00220710.
12. Goktas A, Goktas S. Common embryological links to the optic pit and anterior segment structures. Optom Vis Sci. 2010;87(8):585-7. doi: 10.1097/OPX.0b013e3181e64ee3.
13. Kadayifçilar S, Tatlipinar S, Eldem B, Irkeç M. Pigment dispersion syndrome and butterfly-shaped pattern dystrophy of the retinal pigment epithelium. Eye (Lond). 2000 Aug;14 ( Pt 4):663-5. doi: 10.1038/eye.2000.164.
14. Scuderi GL, Ricci F, Nucci C, Galasso MJ, Cerulli L. Electro-oculography in pigment dispersion syndrome. Ophthalmic Res. 1998;30(1):23-9. doi: 10.1159/000055450.
15. Campbell DG, Schertzer RM. Pathophysiology of pigment dispersion syndrome and pigmentary glaucoma. Curr Opin Ophthalmol. 1995;6(2):96-101. doi: 10.1097/00055735-199504000-00015.
16. Georgalas I, Ladas I, Georgopoulos G, Petrou P. Optic disc pit: a review. Graefes Arch Clin Exp Ophthalmol. 2011;249(8):1113-22. doi: 10.1007/s00417-011-1698-5. Epub 2011 Jun 3.
17. Jain N, Johnson MW. Pathogenesis and treatment of maculopathy associated with cavitary optic disc anomalies. Am J Ophthalmol. 2014;158(3):423-35. doi: 10.1016/j.ajo.2014.06.001. Epub 2014 Jun 14.
18. Zumbro DS, Jampol LM, Folk JC, Olivier MM, Anderson-Nelson S. Macular schisis and detachment associated with presumed acquired enlarged optic nerve head cups. Am J Ophthalmol. 2007;144(1):70-4. doi: 10.1016/j.ajo.2007.03.027. Epub 2007 May 9.
19. Maidana DE, Sanz S, Lillo J, Arruga J. Serous macular detachment associated with optic nerve head cupping in pigmentary glaucoma. Can J Ophthalmol. 2014;49(2):e56-9. doi: 10.1016/j.jcjo.2014.01.003.

Sažetak

## OBOSTRANA SEROZNA KORIORETINOPATIJA I PIGMENTNI GLAUKOM – KOJA JE POVEZNICA?

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Prikazujemo slučaj bolesnika s pigmentnim glaukomom, obostranom centralnom seroznom korioretinopatijom i jednostranom jamicom optičkog diska te predlažemo moguću povezanost navedenih stanja. Sveobuhvatnim oftalmološkim pregledom 36-godišnjaka koji se žalio na zamagljen vid i bol u očima ustanovila se smanjena vidna oštrina lijevog oka, povišen očni tlak u desnom oku, obostrani znakovi sindroma disperzije pigmenta, obostrana centralna serozna korioretinopatija te jamica optičkog diska lijevo. Nalazi vidnog polja i optičke koherentne tomografije pokazali su glaukomske funkcionalne i strukturne promjene. Abnormalnosti koroidne cirkulacije uočene su angiografskim metodama. Genetske i razvojne anomalije vanjskog sloja čašice optičkog diska iz kojega se razvijaju strukture prednjeg i stražnjeg segmenta oka ukazuju na moguću vezu u kliničkom stanju koje obilježava kombinacija pigmentnog glaukoma, centralne serozne korioretinopatije i jamice optičkog diska. Buduća istraživanja bi omogućila utvrđivanje odgovarajućih dijagnostičkih postupaka, protokola liječenja i praćenja ovoga kronično-progresivnog stanja.

Ključne riječi: *Pigmentni glaukom; Centralna serozna korioretinopatija; Mrežnični pigmentni epitel; Genetika; Embriologija*