Received: 11 April 2023 | Accepted: 13 March 2024

DOI: 10.1111/aos.16680

Acta Ophthalmologica

ORIGINAL ARTICLE

Peripheral hypertrophic subepithelial corneal opacification – Role of tear secretion, medication and systemic diseases

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Abstract

Background: Peripheral hypertrophic subepithelial corneal opacification (PHSCO) is a corneal disease that may severely affect vision. The major goal of this study was to test the hypothesis that tear secretion, medication and systemic diseases are associated with PHSCO.

Methods: This is a retrospective, case–control study conducted at the Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz. We analysed medical records of patients diagnosed with PHSCO. Sex, age, Schirmer's test II, general medication and medical history were assessed and compared to an age- and sex-matched control group from the Gutenberg Health Study (GHS).

Results: One hundred ninety-five eyes of 112 patients with PHSCO were included. Eighty-eight patients were female with a mean age of 55.3 ± 14.7 years (23–89 years) and 24 patients were male with a mean age of 59.3 ± 12.6 years (38–84 years). In 83 patients (74.1%) both eyes were involved. The Schirmer's test II was significantly reduced in patients with PHSCO compared to the GHS control group ($p < 0.001$). Patients with PHSCO were more frequently administered artificial tears and steroid eye drops ($p < 0.001$) and were more hyperopic than healthy controls ($p = 0.01$). Systemic diseases or medication did not differ markedly between PHSCO and healthy controls.

Conclusion: Reduced tear secretion and more frequent use of artificial tears in patients with PHSCO suggest a link between PHSCO and dry eye disease. The results of the study do not support our hypothesis that PHSCO is associated with systemic diseases. Interestingly, patients with PHSCO were less frequently on β-blockers than control subjects.

KEYWORDS
artificial tears, dry eye, peripheral hypertrophic subepithelial corneal opacification, Salzmann degeneration, Schirmer's test

1 | INTRODUCTION

Peripheral hypertrophic subepithelial corneal opacification (PHSCO) is a rare disease, which is characterised by solitary or multiple bluish-white elevations of the corneal surface, which typically start in the periphery and may progress towards the corneal centre causing marked visual impairment by refractive changes and/or by covering the visual axis (Maust & Raber, 2003). The disease was first described as corneal 'degeneration', but because it is still not known, whether the opacification results from degeneration or dystrophy, we use the term 'opacification'. It is still also not clearly defined if PHSCO belongs to the same clinical entity as Salzmann's nodular degeneration (SND) (Sundmacher, 2012), but recently, new details

The results of the study were partly presented at the Congress of the German Ophthalmologic Surgeries (DOC) 2022.

were described to distinguish between PHSCO and SND (Raber & Eagle, 2022). Histopathological findings are similar (Schargus et al., 2015), but PHSCO tends to present bilaterally and symmetrically (Raber & Eagle, 2022). Furthermore, the opacities of PHSCO are larger and localised more peripherally (Raber & Eagle, 2022).

The superficial fibrosis is localised between the corneal epithelium and the Bowman's layer (Maust & Raber, 2003). PHSCO is mostly located in the nasal and upper nasal quadrant (Riedl et al., 2018). Corneal vascularisation is present in two-thirds of the patients, whereby optical coherence tomography angiography (OCT-A) provides more detailed information on vascularisation in PHSCO compared with conventional slit lamp microphotography (Riedl et al., 2018). We recently described markedly lower endothelial cell density, higher polymegathism and pleomorphism in PHSCO compared to healthy controls (Riedl et al., 2020). As no spontaneous remission has been reported in PHSCO so far, the opacifications have to be surgically removed when it comes to a decrease in visual acuity. Superficial keratectomy or phototherapeutic keratectomy are typical treatment options. We previously demonstrated that the astigmatism of the anterior and posterior corneal surface decreases markedly after surgery (Riedl et al., 2021).

In recent years, some further new findings about PHSCO have been published, but many questions remain unanswered. The purpose of the present study was to test the hypothesis that PHSCO is associated with systemic and ocular medications as well as general diseases. Since middle-aged women are particularly often affected, we assumed a possible connection between PHSCO and the substitution of hormones.

2 | MATERIALS AND METHODS

This retrospective, case–control study is a follow-up study with the same study group as in our previous publication (Riedl et al., 2023) and was performed at the Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz. According to local law ('Landeskrankenhausgesetz' §36, §37), no ethical approval was required, and no informed consent was obtained from the patients.

The inclusion criteria were: all genders; age ≥18 years; uni- or bilateral PHSCO defined as prominent bluish-white subepithelial deposits extending from the limbus towards the central cornea.

Medical records of all patients with PHSCO were analysed between April 2018 and April 2021 for sex, age, spherical equivalent (SE), Schirmer's test II (with local anaesthesia, cut-off level 10 mm) values, topical ocular and self-reported systemic medication and general diseases. Only diseases and medications reported by at least 10 patients were analysed. An age- and sex-matched control group (4:1) from the Gutenberg Health Study (GHS) (Höhn et al., 2015), a population-based study in Mainz/Mainz-Bingen, was used for comparison. The GHS is a prospective, ongoing, single-center, interdisciplinary, population-based cohort study, in which the ophthalmological section assesses the prevalence and incidence of ocular diseases and explores risk factors, genetic determinants and association with systemic diseases and conditions. The GHS complies with Good Clinical Practice, Good Epidemiological Practice and the ethical principles of the Declaration of Helsinki. The study protocol and study documents were approved by the local ethics committee of the Medical Chamber of Rhineland-Palatinate, Germany (reference no. 837.020.07; original vote: 22.3.2007).

2.1 | Statistical methods

For descriptive analyses, mean and standard deviation were calculated for approximately normally distributed data if skewness was lower than 1, otherwise median and interquartile range are presented. The study groups were compared with chi-square test in case of dichotomous variables and the Kruskal–Wallis test in case of continuous variables. This in an exploratory study, we defined an alpha error of 5%.

Conditional logistic regression with the use of univariate factors (SE, Schirmer-test, artificial tears, cortisone eyedrops, systemic diseases and systemic medication) was carried out.

Statistical analysis was carried out using R (R Core Team, 2022).

3 | RESULTS

This study involved 195 eyes of 112 patients. Eighty-eight patients (78.6%) were female with a mean age of 55.3 ± 14.7 years (range: 23–89 years) and 24 patients (21.4%) were male with a mean age of 59.3 ± 12.6 years (range: 38–84 years). In 29 patients, one eye was affected, whereas in 83 patients (74.1%) both eyes were involved. The Schirmer's test II was significantly reduced in patients with PHSCO compared to the control group (median: 5.5 mm in the unilateral PHSCO group, 7 mm in bilaterally affected patients and 25 mm in the control group; $p < 0.001$). Sixty-two per cent of the unilaterally affected patients and 63% of the bilaterally affected patients were administering artificial eye drops, whereas only 8% of the control group were using artificial eye drops ($p < 0.001$, Table 1). Steroid eye drops were also more frequently used in subjects with PHSCO ($p < 0.001$).

3.1 | Systemic disease and systemic medication

Tables 2 and 3 provide data on systemic diseases and medication in all study groups. None of the self-reported diseases displayed differences regarding their frequency between patients with PHSCO and the GHS control group. Hashimoto thyroiditis, depression, COPD, rheumatism and previous breast cancer as well as all other listed systemic medications did not differ between the

TABLE 1 Descriptive statistics, spherical equivalent, Schirmer's test II values, artificial tears, cortisone eye drops for patients with peripheral hypertrophic superficial corneal opacification (unilateral and bilateral separately) and the control group.

	PHSCO unilateral ($n=29$)	PHSCO bilateral ($n=83$)	GHS control group ($n=403$)	p-value for any group differences
Mean age (IQR), years	57 [50, 66]	56 [48, 67]	57 [50, 66]	0.338
Sex, f (%)	19 (65.5)	65 (78.6)	307 (76.2)	0.135
SE (mean±SD), diopters	−0.35 (3.26)	0.56 (3.42)	−0.56 (2.99)	0.01*
Right eye		0.59 (3.44)		
Left eye		0.53 (2.81)		
Schirmer's test (median IQR), mm	5.5 [3, 9.25]	7 [4, 10]	25 [16, 31]	<0.001*,#
Right eye		6.5		
Left eye		7.5		
Artificial tears, *n* (%)	18 (62.1)	71 (63.4)	34 (8.4)	<0.001*,#
Steroid eye drops, *n* (%)	3 (10.3)	3 (3.6)	3 (0.7)	<0.001#

Note: In the bilateral PHSCO group, the mean value from both eyes was taken.

Abbreviations: f, female; IQR, interquartile range; SD, standard deviation; SE, spherical equivalent in diopters.

Posthoc testing: *Significant difference between bilateral and control group, #Significant difference between unilateral and control group.

TABLE 2 Absolute numbers, percentage and p-values of self-reported diseases of patients with peripheral hypertrophic superficial corneal opacification (unilateral and bilateral separately) and for the control group.

Self-reported diseases	PHSCO unilateral ($n=29$)	PHSCO bilateral ($n=83$)	GHS control group ($n=403$)	p-value
Arterial hypertension, *n* (%)	8 (27.6)	21 (25.3)	148 (36.7)	0.26
Hashimoto thyroiditis, *n* (%)	3 (10.3)	6 (5.4)	16 (4.0)	0.25
Depression, *n* (%)	2 (6.9)	5 (4.5)	20 (5.0)	0.76
COPD, *n* (%)	3 (10.3)	5 (4.5)	24 (6.0)	0.23
Rheumatism, *n* (%)	2 (6.9)	6 (5.4)	27 (6.7)	0.81
Previous breast cancer, *n* (%)	1 (3.4)	5 (4.5)	11 (2.7)	0.61

Abbreviations: COPD, chronic obstructive pulmonary disease; PHSCO, peripheral hypertrophic subepithelial corneal opacification.

TABLE 3 Absolute numbers, percentage and p-values of systemic medication of patients with peripheral hypertrophic superficial corneal opacification (unilateral and bilateral separately) and for the control group.

	PHSCO unilateral ($n=29$)	PHSCO bilateral ($n=83$)	GHS control group ($n=403$)	p-value
β-blocker use, *n* (%)	1 (3.4)	9 (8.0)	75 (18.6)	0.02*
Proton pump blocker use, *n* (%)	2 (6.9)	6 (5.4)	50 (12.4)	0.10
Acetylsalicylic acid, *n* (%)	3 (10.3)	8 (7.1)	48 (11.9)	0.29
Calcium channel inhibitors, *n* (%)	2 (6.9)	3 (3.6)	49 (12.2)	0.06
ACE inhibitors, *n* (%)	3 (10.3)	6 (7.2)	48 (11.9)	0.46
Hydrochlorothiazid, *n* (%)	1 (3.4)	4 (4.8)	6 (1.5)	0.92
Vit D3, *n* (%)	3 (10.3)	6 (5.4)	43 (10.7)	0.14
L-Thyroxin, *n* (%)	5 (17.2)	16 (19.3)	95 (23.6)	0.14

*Significant difference in the global analysis, but only $p=0.07$ between PHSCO unilateral and control and between PHSCO bilateral and control, respectively.

groups. Notably, significant differences were detected in β-blocker use ($p=0.02$).

3.2 | Univariate analysis

In univariable analyses, PHSCO was associated with hyperopic SE (OR = 1.17 [95% CI: 1.06; 1.29], $p=0.01$), lower Schirmer's test II values (OR = 0.76 [95% CI: 0.69; 0.84], $p=0.001$) and steroid eye drop application (OR = 10.09 [95% CI: 2.178; 54.57], $p=0.01$).

4 | DISCUSSION

The study reveals that PHSCO is associated with both hyperopic spherical equivalent and a reduced Schirmer's test value. In addition, patients with PHSCO are more

frequently administered artificial tears and steroid eye drops. Systemic medication differed between the PHSCO and the control group with regard to β-blocker application, which was higher in the control group, suggesting that β-blockers are more likely to be protective than risk factors for PHSCO. No association was observed between systemic diseases and PHSCO.

We recently reported on reduced Schirmer's test II values in patients with PHSCO (Riedl et al., 2020, 2023). Likewise, in the present study, Schirmer's test II values were lower in patients with both unilateral and bilateral PHSCO compared to the control group. Common risk factors for dry eye disease are female gender and menopause (Lurati, 2019; Messmer, 2015). Both would apply to our patient's collective (78.6% female, mean age 55.3 years). The reduced Schirmer's test II values, suggestive of dry eye disease, may also explain the more frequent application of artificial tears and steroid eye drops in patients with PHSCO.

The spherical equivalent showed significant differences between patients with PHSCO and the control group. Due to the hypertrophic corneal opacification, PHSCO often results in flattening of the cornea and therefore a hyperopic shift and an increased corneal astigmatism (Germundsson & Fagerholm, 2004; Jeng & Millstein, 2006; Riedl et al., 2021). Recently, we reported that not only the astigmatism of the corneal anterior surface is increased but also the astigmatism of the posterior surface (Riedl et al., 2021). Both showed a marked reduction after superficial keratectomy, which leads also to a myopic shift due to surgical removal of the subepithelial corneal opacification and normalisation of the corneal shape (Riedl et al., 2021).

Various links between systemic medication and eye diseases are already known. For example, selective serotonin reuptake inhibitors, diuretics, β-blockers and antidepressants have been associated with the promotion of dry eye disease (Germundsson & Fagerholm, 2004; Jeng & Millstein, 2006; Kocer et al., 2015; Messmer, 2015; Mrignaz et al., 2013; Rakofsky et al., 2021). Moreover, amiodarone and chloroquine are recognised inducers of cornea verticillata (Chew et al., 1982; Lacava, 2010; Seiler et al., 1977). The present study revealed differences in the use of antihypertensive medication. Remarkably, control patients from the GHS group were more frequently taking antihypertensives, especially β-blockers. Intriguingly, β-adrenoceptors were shown to be expressed in the cornea, limbus, conjunctiva and lacrimal glands and involved in corneal regeneration, the pathophysiology of allergic conjunctivitis and dry eye disease (Böhm et al., 2023; Diebold et al., 2001; Jun et al., 2022; Ruan et al., 2023; Yuan et al., 2021). Considering the local application of β-blockers to the eye with limited side effects, exploring the potential of β-adrenoceptors as targets for treating PHSCO is warranted.

4.1 | Strengths and limitations

With 195 eyes of 112 patients, this is the largest reported cohort of patients with PHSCO. The comprehensive data collection of patients' age, sex, SE, Schirmer's test II, use of artificial tears and steroid eye drops as well as systemic medication and systemic diseases enabled us to further shed some light on the pathophysiology of PHSCO. Based on these data, neither systemic diseases nor systemic drugs appear to contribute to the development of PHSCO.

One major limitation of the study is its retrospective design. Hence, regarding the more frequent use of artificial tears and steroid eye drops in patients with PHSCO, it is hard to discern in which cases the drops were employed before the PHSCO diagnosis or specifically for PHSCO treatment. Given this uncertainty, suggesting that the use of artificial tears and steroid eye drops constitutes a risk factor for PHSCO remains speculative. We posit that due to the prevalent use of these medications and the low incidence of PHSCO, it is more plausible that individuals with PHSCO were utilising these treatments more frequently to address symptoms associated with dry eye disease and PHSCO. Dry eye disease, in turn, may serve as a triggering factor for PHSCO.

While the Schirmer's test II, SE and eye drops have been measured and prescribed by our department, the information on systemic diseases and systemic medication is based on information provided by the patients themselves. In our department, we ask each PHSCO patient separately about the use of oral contraceptives and hormone replacement therapy (also in the past), as we assume an association. So, the former intake and, if applicable, the active ingredient is documented in the medical history. The control group (which was age- and sex-matched) was only asked about current medication intake. Since the average age was 56 years, taking oral contraceptives was the exception here. A different control group is therefore required to compare a possible association between PHSCO and previous oral contraception or hormone replacement therapy. Furthermore, Schirmer's test was only measured in 114 eyes of 64 patients, which can bear the risk of selection bias. Moreover, the higher rate.

5 | CONCLUSION

This study does not present evidence supporting an association between PHSCO and systemic diseases. Notably, patients with PHSCO exhibited a lower frequency of β-blocker usage among systemic medications. Further investigation is required to explore whether β-adrenoceptors might play a protective role in the development of PHSCO. The observed reduction in tear secretion and the increased use of artificial tears in patients with PHSCO imply a potential connection between PHSCO and dry eye disease.

AUTHORS CONTRIBUTIONS

Conceptualization, J.C.R and A.G.; Methodology, J.C.R.; Software, A.G, AKS.; Validation, J.C.R. and A.G; Formal Analysis, J.C.R. and A.G.; Investigation, J.C.R., A.M., J.W-P, A.G.; Resources, J.C.R., I.S., M.E.B., N.P., A.G; Data Curation, J.C.R., A.M., A.G.; Writing – Original Draft Preparation, J.C.R. and A.G..; Writing – Review & Editing, J.C.R., J.W.-P., I.S., M.E.B., A.G.,

N.P.; Visualization, J.C.R; Supervision, A.G.; Project Administration, J.C.R.,A.K.S., I.S., M.E.B., A.G.

FUNDING INFORMATION

Schuster AK holds the professorship for ophthalmic healthcare research endowed by 'Stiftung Auge' and financed by 'Deutsche Ophthalmologische Gesellschaft' and 'Berufsverband der Augenärzte Deutschlands e.V.' Riedl JC, Misirkhanova A, Wasielica-Poslednik J, Schmidtmann I, Beutel ME, Pfeiffer N, Gericke A: none.

CONFLICT OF INTEREST STATEMENT

Pfeiffer N receives financial support and grants from Novartis, Ivantis, Santen, Thea, Boehringer Ingelheim Deutschland GmbH & Co. KG, Alcon and Sanoculis. Schuster AK receives research support from Allergan, Bayer, Heidelberg Engineering, PlusOptix and Novartis. Riedl JC, Misirkhanova A, Wasielica-Poslednik J, Schmidtmann I, Beutel ME, Gericke A: none.

DATA AVAILABILITY STATEMENT

All data are presented in the article.

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How to cite this article: Riedl, J.C., Misirkhanova, A., Wasielica-Poslednik, J., Schuster, A., Schmidtmann, I., Beutel, M.E. et al. (2024) Peripheral hypertrophic subepithelial corneal opacification – Role of tear secretion, medication and systemic diseases. *Acta Ophthalmologica*, 102, e956–e960. Available from: https://doi.org/10.1111/aos.16680