Received: 28 March 2022 | Accepted: 19 November 2022

DOI: 10.1111/aos.15303

Acta Ophthalmologica

ORIGINAL ARTICLE

Risk factors for peripheral hypertrophic subepithelial corneal opacification

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Abstract

Background: To evaluate the phenotype, tear secretion and refractive changes of patients diagnosed with peripheral hypertrophic subepithelial corneal opacification (PHSCO).

Methods: This is a retrospective, interventional case series conducted at the Department of Ophthalmology, University Medical Center of the Johannes Gutenberg University Mainz. Medical records of patients diagnosed with PHSCO were analysed. Sex, age, fluorescein tear film breakup time (FTBUT), Schirmer Test II, iris colour and hair colour were assessed. Objective refraction was evaluated at different time points and, in case of surgery, 1 month and 1 year postoperatively.

Results: One hundred ninety-five eyes of 112 patients (78.6% female, 21.4% male; mean age 56.2 ± 14.3) were included. The median FTBUT was 6 sec. (Q1: 4/Q3: 8.75; range 1–20 s) (measured in 70 eyes of 36 patients), the median Schirmer Test II was 8 mm (Q1: 5/ Q3:15; range 1–35 mm). In 83 patients (74.1%) both eyes were involved. In 86 eyes of 64 patients (55.3%) superficial keratectomy was performed. Sphere and cylinder changed significantly 1 month and 1 year postoperative compared to the pre-operative objective refraction, while there was no significant change between 1 month and 1 year postoperatively.

Conclusion: We found that PHSCO occurs mostly bilaterally in middle-aged women and appears to be associated with decreased tear production and reduced tear film stability.

KEYWORDS

corneal astigmatism, dry eye, peripheral hypertrophic subepithelial corneal opacification, salzmann degeneration, schirmer test

1 | INTRODUCTION

Peripheral hypertrophic subepithelial corneal degeneration was first described in 2003 (Maust & Raber, 2003). Because it is unknown at present whether the opacification results from dystrophy or degeneration, we use the term 'opacification' instead of 'degeneration'. It is also heavily debated whether peripheral hypertrophic subepithelial corneal opacification (PHSCO) belongs to the same clinical entity as Salzmann's nodular degeneration (SND), but Raber et al. recently reported several new findings to distinguish between PHSCO and SND (Raber & Eagle Jr, 2021). While both diseases are rare and have similar morphological characteristics, PHSCO tends to present bilaterally and symmetrically. Furthermore, the authors describe that the opacities of PHSCO are larger and localized more peripherally than typical SND opacities (Raber & Eagle Jr, 2021). PHSCO is characterized by solitary or multiple bluish-white elevations, rising above the corneal surface (Järventausta, Holopainen, & Zalentein, 2014; Järventausta, Tervo, et al., 2014; Maust & Raber, 2003). The opacities are also frequently vascularized and are characterized by superficial fibrosis between the corneal epithelium and Bowman's layer histological (Maust & Raber, 2003; Riedl et al., 2018). Light microscopy showed no signs of active ocular inflammation, but abundant collagen deposition in the fibrotic areas (Jarventausta, Tervo, et al., 2014). Initially, just an involvement of the corneal surface was assumed, but we recently also observed an involvement of the corneal

back with increased astigmatism of the posterior corneal surface and a reduction in endothelial cell density (ECD) (Riedl et al., 2020). Moreover, patients with PHSCO also frequently develop dry eye disease with reduced tear secretion and often complain about foreign body sensation (Riedl et al., 2018; Jarventausta, Holopainen, & Zalentein, 2014). Superficial keratectomy is a potential treatment option for patients with progressive disease and decreasing visual acuity (Riedl et al., 2021).

Our personal observation was a high percentage of blue iris colour among patients with PHSCO. This impression was also supported by the eyes presented in the study of Gore et al. (2013). Hence, one of the goals of the present study was to test the hypothesis that PHSCO is associated with blue iris colour and blonde hair. To further shed some light on the aetiology of PHSCO, we evaluated patient's characteristics, tear production and stability as well as objective refraction in the course of time and after surgery.

2 | MATERIALS AND METHODS

This retrospective, interventional case series 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, since no patient was prospectively involved in this study.

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

Medical records of all PHSCO patients were analysed for age, gender, tear film break-up time (TFBUT), Schirmer Test II performed under topical anaesthesia for 5 min, eye colour and hair colour, Furthermore, objective refraction at first presentation and at the follow-up after 1 year, 2 years, 3 years and 4 years as well as the refraction 1 month and 1 year after surgery were evaluated. Indications for surgery were reduced visual acuity either due to a change in refraction or a central corneal opacification as well as strong foreign body sensation. Corrected distance visual acuity (CDVA) was tested with Snellen charts and transformed into logMAR.

2.1 | Surgery

All surgeries were performed by two surgeons (A.G. or J.W-P.) under topical anaesthesia with lidocaine eyedrops. First, the epithelium was scraped at the border of the affected area and the fibrous tissue was removed using a colibri forceps and a hockey knife. Fibrovascular tissue was sometimes cut at the limbus using Vannas scissors. In each patient, a Merocel® sponge (Beaver-Visitec International) thrush soaked with mitomycin C 0.02% was applied onto the keratectomized area for 30 followed by a thorough wash with balanced salt solution (BSS). At the end of the surgery, a bandage contact lens (Air Optix Night & Day, Alcon) was applied for 5 days. The postoperative medication included ofloxacine eyedrops 3 mg/mL for 5 days (Floxal®, Dr. Gerhard Mann GmbH, Berlin, Germany) and dexamethasone eyedrops 1 mg/mL for 6 weeks (Dexa EDO®, Dr. Gerhard Mann).

2.2 | 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 were presented. A paired t-test was used to detect differences between variables, and the Bonferroni correction was applied for multiple testing to reduce critical alpha. Data of first presentation were compared against the 1 year follow-up, 2 years follow-up, 3 years follow-up and 4 years follow-up. Postoperative results (1 month and 1 years) were compared to pre-operative results. To take inter-eye correlation into account, we used the mean value from both eyes in patients with bilateral involvement for statistical analysis. Statistical analysis was carried out using SPSS 24.0 software (IBM Corp., IBM SPSS Statistics for Macintosh, version 24.0).

3 | RESULTS

One hundred ninety-five eyes of 112 patients were included in this study. Eighty-eight patients were female with a mean age of 55.3 ± 14.7 years (range: 23–89 years) and 24 patients were male with a mean age of 59.3 ± 12.6 years (range: 38–84 years). Age distribution is shown in Figure 1. In 83 patients both eyes were involved (Figure 2) whereas in 29 patients PHSCO was detected in only one eye. The distribution of iris colour is shown in Figure 3. Most of the patients had a blue iris followed by brown iris. Thirty-four patients had brown hair followed by dark blonde hair (Figure 4). The median FTBUT was 6 s. (Q1: 4/Q3: 8.75; range 1–20 s) (measured in 70 eyes of 36 patients), the median Schirmer Test II was 8 mm (Q1: 5/ Q3:15; range 1–35 mm) (measured in 114 eyes of 64 patients). Refractive change over time for conservatively followed up patients are shown in Table 1 for 28 eyes and Figure 5 illustrate photographs of PHSCO: (a) first presentation, (b) 1 year follow-up, (c) 2 years follow-up, (d) 3 years follow-up. *p*-values were calculated for the follow-up visits compared to the first presentation. No changes

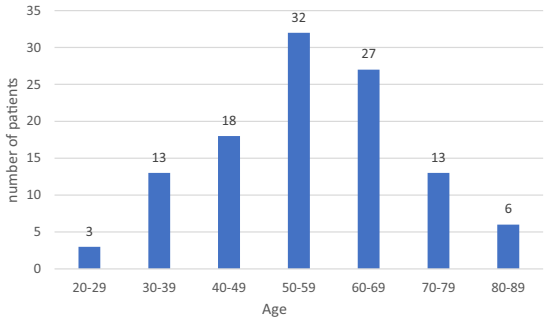

FIGURE 1 Age distribution of patients with PHSCO ($n = 112$).

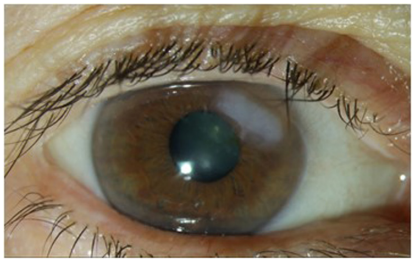

FIGURE 2 Typical superior nasal location of PHSCO.

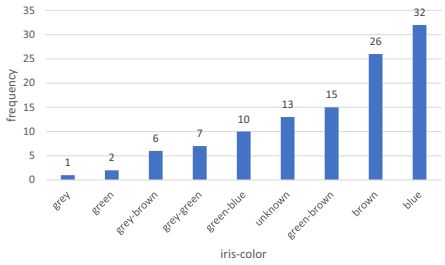

FIGURE 3 Distribution of the iris colour of patients with PHSCO ($n = 112$).

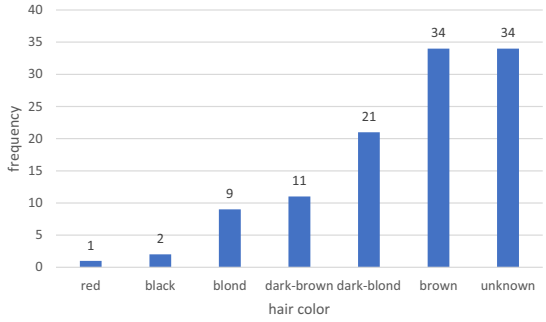

FIGURE 4 Distribution of the hair colour of patients with PHSCO ($n = 112$).

were observed for the 1 year-, 2 years, 3 years and 4 years follow-up. Eighty-six eyes of 62 patients (46 female) underwent superficial keratectomy (nine eyes in combination with PTK). Objective refraction was analysed in 34 eyes of 24 patients 1 month postoperatively and 1 year after surgery. Sphere and cylinder changed significantly after 1 month and after 1 year compared to the preoperative objective refraction, while there was no significant change between 1 month and 1 year postoperatively, Table 2 and Figure 6b. The median time between the first presentation and the surgery was 21 months (Q1:6/Q3:69; range 0–279). Pre- and postoperative photographs of the cornea are shown in Figure 7.

4 | DISCUSSION

The major goal of this study was to characterize patients with regard to phenotype, age distribution, tear secretion and stability, and changes in objective refraction with and without surgery. Several major new findings emerge from this study. First, this study confirms that PHSCO predominantly affects middle-aged women and presents mostly bilaterally. However, PHSCO does not appear to be associated with a specific hair or iris colour. Second, in the time course of 4 years, most patients with PHSCO had only minimal disease progression. Changes of refraction and BCVA over 4 years were not statistically significant. This finding is important to give affected patients an outlook about the further course of the disease. Third, we found sustained reduction of the cylinder after superficial keratectomy, while sphere, axis, SE and CDVA were similar to pre-operative values 1 year after surgery.

The mean patients' age at first presentation as well as the predominant occurrence in women with a ratio of approximately 4:1 supports the already existing literature that reported a predominance of PHSCO in middle-aged women (Maust & Raber, 2003; Jarventausta, Holopainen, & Zalentein, 2014). In the present study, the incidence of bilaterality was 74% with symmetric characteristics (Figure 4), which is in line with recent findings of Raber & Eagle Jr, 2021, who reported that 81.6% of all cases had bilateral manifestation (Raber & Eagle Jr, 2021). We did not find any predisposition with regard to iris or hair colour. Most of the included eyes had blue iris colour, but were closely followed by brown iris colour. With these results, we could not confirm our primary hypothesis that PHSCO occurs most often in people with blue iris colour and blonde hair.

We already reported reduced tear secretion in patient with PHSCO in one of our previous studies, in which 38 eyes of patients with PHSCO were compared with 38 eyes of age-matched controls (Riedl et al., 2020). In the previous study, the mean Schirmer Test result was significantly lower in patients with PHSCO compared with age-matched controls (9.8 ±4.4 mm vs. 14.3 ± 5.7 mm; PHSCO vs. controls). This assumption is supported by the present large study. With a Schirmer's test of 8 mm (median) measured in 114 eyes (mean age 54.5 years), the tear secretion is much lower than in the normal population. Hampel et al. recently investigated 1999 volunteers (mean age 59 years) from the same geographical region as our patients and reported mean Schirmer's test results of 23.2 mm and 22.9 mm for the left eye (Hampel et al., 2020). Smaller tear fluid quantity was associated with male sex, higher age, lower socioeconomic status and season in the study of Hampel et al. (Hampel et al., 2020).

FTBUT, a marker of tear film stability, has been determined in 70 eyes of 36 patients from our present patient cohort. The median FTBUT was 6 s. in our patients, which is under the normal limit of 10 s (Lemp et al., 1971; Lemp & Hamill, 1973). However, FTBUT depends on various factors, such as the observer, holding/not holding the lid during the procedure, the use of anaesthetic eye drops prior to determination of FTBUT as used for the Schirmer's test II etc. (Lemp & Hamill, 1973). Due to these confounding factors, which cannot be excluded retrospectively, we cannot conclude from our data that FTBUT is definitely reduced in patients with PHSCO. A prospective controlled study is warranted in this regard.

The objective refraction was evaluated over a four-year time period. According to our clinical experience,

TABLE 1 Development of objective refraction and visual acuity from first presentation to 4 years thereafter for conservatively followed up patients.

	First presentation (n = 28 eyes)	1 year follow-up (n = 28 eyes)	2 years follow-up (n = 28 eyes)	3 years follow-up (n = 28 eyes)	4 years follow-up (n = 28 eyes)
Sphere (D)	0.55 ± 2.3 (−3.25; +5.5)	1.42 ± 2.9 (−3.5; +6.5)	1.02 ± 2.8 (−3,25; +6.5)	1.12 ± 3.06 (−3.25; +8.5)	−1.1 ± 3.66 (−7.25; +7.25)
Cylinder (D)	−2.48 ± 2.25 (−7; 0)	−2.75 ± 2.45 (−7.25; −0.25)	−1.8 ± 3.24 (−7.25; 0)	−2.77 ± 2.54 (−7.25; −0.5)	−1.1 ± 3.66 (−7.25; +2.25)
Axis (°)	88.4 ± 56.9 (0–178)	94.9 ± 47.6 (2–179)	88.5 ± 47.1 (6–179)	99.4 ± 53.8 (2–180)	67.4 ± 58.3 (0–169)
SE (D)	−0.7 ± 1.9 (−4.13; +2.75)	0.04 ± 2.26 (−4.6; +3.25)	−0.39 ± 2.4 (−5; +2.9)	−0.2 ± 2.8 (−5.25; +5.4)	0.13 ± 3.1 (−5.75; +6.4)
Visual acuity CDVA (logMAR)	0.175 ± 0.27 (0–1)	0.19 ± 0.27 (0–1)	0.2 ± 0.18 (0–0.6)	0.21 ± 0.2 (0–0.6)	0.17 ± 0.18 (0–0.6)

Abbreviations: CDVA, corrected distance visual acuity (logMAR); D, Diopter; SE, spherical equivalent.

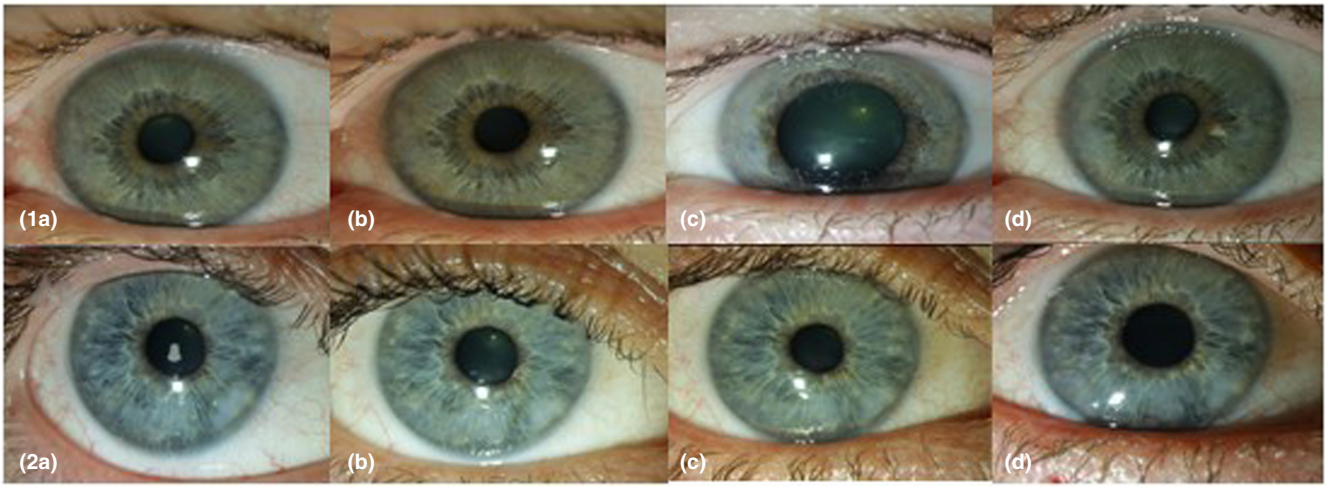

FIGURE 5 Patients with PHSCO: (a) first presentation, (b) 1-year follow-up, (c) 2-years follow-up, (d) 3-years follow-up. First patient: PHSCO located between 8 and 10 o'clock; second patient: PHSCO located between 2 and 8 o'clock.

TABLE 2 Development of objective refraction in operated patients: Pre-operative; 1 month postoperatively (n = 34 eyes), 1 year postoperatively (n = 34 eyes).

	Pre-op	1 month postop	1 year postop	p-value 1 month vs. 1 year postoperative
Sphere (D)	2.3 ± 4.1 (−8; 10.75)	−0.3 ± 2.3* (−6; 5.25)	−0.23 ± 2.1 (−4; 4)	0.26
Cylinder (D)	−4.2 ± 2 (−7.5; −0.5)	−1.6 ± 1.9** (−6.75; 2.75)	−1.57 ± 1.6** (−5; 1.5)	0.94
Axis (°)	79.5 ± 49.7 (3–179)	78.8 ± 61.1 (4–179)	81.6 ± 60.2 (3–179)	0.83
SE (D)	0.22 ± 3.9 (−10.5; 7.3)	−1.13 ± 2.4 (−7.75; 2)	−0.56 ± 2.16 (−6.13; 1.75)	0.17
Visual acuity CDVA (logMAR)	0.32 ± 0.32 (0–1)	0.21 ± 0.19 (0–0.5)	0.17 ± 0.22 (0–1)	0.47

Abbreviations: CDVA, corrected distance visual acuity (logMAR); D, Diopter; SE, spherical equivalent (decimal).

*Statistical difference ($p \leq 0.0167$) compared to first presentation (Bonferroni correction).

**Statistical difference ($p < 0.001$) compared to first presentation.

we assume a slow course of progression, with stable periods of several years. There are significant changes in refraction between the time of diagnosis and the one year follow-up and they remain stable afterwards. However, we do not know how long the corneal opacities have already existed before the patients presented to us. We assume, that the opacities are mostly asymptomatic until foreign body sensation and/or reduced visual acuity due to progression of the opacification towards the corneal centre and progressive irregular astigmatism occur (Riedl et al., 2021).

The objective refraction before and after superficial keratectomy was also evaluated in this study to analyse the clinical significance of the corneal changes after surgery. The refractive cylinder decreased from a mean preoperative value of −4.2 ± 2 D to a mean postoperative value of −1.6 ± 1.9 D 1 month after surgery and to −1.57 ± 1.6 D 1 year after surgery. One month and 1 year after surgery there was a marked reduction of hyperopia (myopic shift), which has also already been reported in previous studies of PHSCO and Salzmann's nodular degeneration (Bowers et al., 2003; Jeng & Millstein, 2006; Khairredin et al., 2011;

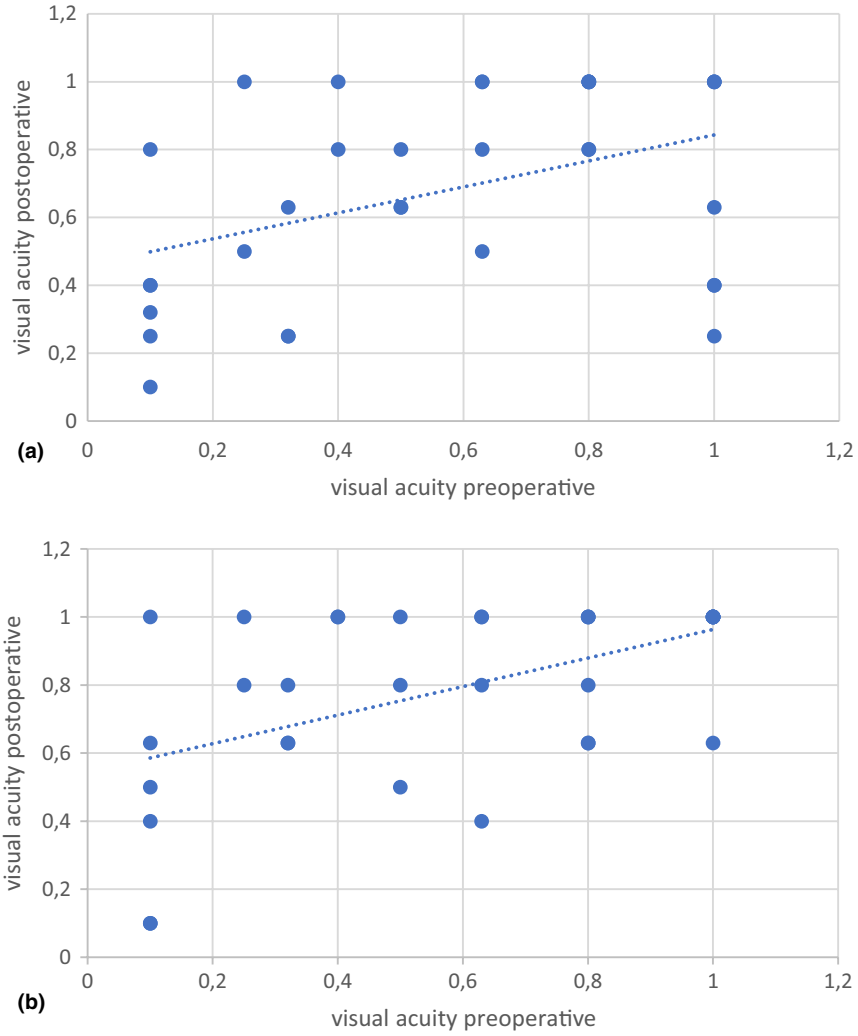

FIGURE 6 (a) Visual acuity pre- and 1-month postoperative. Data point above the diagonal indicates improved vision. Visual acuity is shown in Snellen. (b) Visual acuity pre- and 1 year postoperative. Data point above the diagonal indicates improved vision.

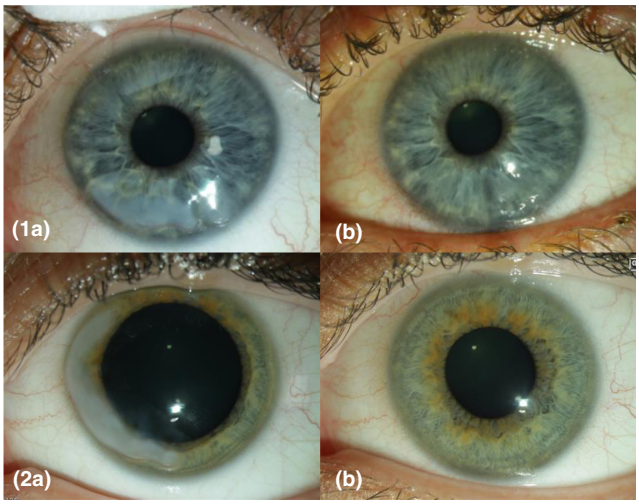

FIGURE 7 Patients with PHSCO: (a) pre-operative (b) 1 year postoperative.

Riedl et al., 2021). Of note, while sphere and cylinder significantly improved 1 month after surgery, there was no significant change 1 month after surgery compared to one year after surgery. Notably, visual acuity increased 1 month after surgery. Similar visual improvement after superficial keratectomy in PHSCO was shown in the study of Järventausta et al. and in previous studies using PTK or a combination of PTK and superficial keratectomy for removing corneal changes in Salzmann's nodular degeneration instead of superficial keratectomy alone (Germundsson & Fagerholm, 2004; Jarventausta, Tervo, et al., 2014, Jarventausta, Holopainen, & Zalentein, 2014).

5 | STRENGTHS AND LIMITATIONS

Of note, this is a large cohort of patients with PHSCO. The comprehensive data collection of patients' phenotypes, photographs, FTBUT, Schirmer's tests as well as a 4 years follow-up of objective refraction and refraction after surgery enabled us to describe corneal changes in PHSCO.

One major limitation is the retrospective study design with the review of medical charts only. Existing data is relied on, which could lead to inaccuracies, especially with regard to eye colour and hair colour. While undocumented eye colour could be supplemented by evaluating existing photographs, the hair colour of 34 patients is still unknown. Furthermore, both, the hair and eye colour were evaluated subjectively without comparing a fabric card. Also, results of Schirmer test II and FTBUT were assessed retrospectively, which may lower their reliability

due to different operational and environmental factors, such inter- and intra-observer bias, air humidity and ambient temperature. Moreover, Schirmer test II and FTBUT results were only determined in subgroups of the cohort, which bears the risk of selection bias. Unfortunately, the change of objective refraction could not be evaluated in all 195 eyes over the 4 years of follow-up. The longer the time interval between the initial diagnosis, the fewer patients were followed up. Not all patients came regularly for follow-up after 1 year. This could be due to a lack of symptoms. As long as the opacities are stable and there is no change in the objective refraction and thus no reduction in visual acuity, the patients often have no complaints. Other patients come regularly because of self-interest, reduced visual acuity or dry eye disease.

Third, the study does not contain a control group to show the differences between the surgical procedure and the spontaneous progression of the disease, because all progressive cases received surgery So far, our clinical experience shows no spontaneous recovery of PHSCO and there are no reports on spontaneous recovery of PHSCO in the literature.

In conclusion, we found that PHSCO occurs mostly bilaterally in middle-aged women and appears to be associated with decreased tear production and reduced tear film stability.

AUTHOR CONTRIBUTIONS

This study contains parts of the thesis of Aminat Misirkhanova.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

The authors have no financial interests or any conflicts of interest.

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How to cite this article: Riedl, J.C., Misirkhanova, A., Musayeva, A., Wasielica-Poslednik, J., Pfeiffer, N. & Gericke, A. (2023) Risk factors for peripheral hypertrophic subepithelial corneal opacification. *Acta Ophthalmologica*, 101, 443–448. Available from: https://doi.org/10.1111/aos.15303