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ARTICLE

Endothelial cell density in children with posterior polymorphous corneal dystrophy: a longitudinal case-control study

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Abstract

Objective To evaluate longitudinal endothelial cell characteristics of children with posterior polymorphous corneal dystrophy (PPCD).

Methods In this prospective case-control study, children with PPCD were followed with slit-lamp photography and non-contact specular microscopy. Patient's eyes were subdivided according to the clinical subtypes of PPCD (vesicular, band, diffuse, and unaffected) and the number of lesions present on the posterior corneal surface. Findings were then compared with age-matched controls.

Results Thirty eyes of 15 patients with PPCD with a mean age 10.5 ± 3.1 years were analysed. Mean follow-up was 3.0 ± 1.0 years. PPCD morphology was vesicular in 40%, diffuse in 37%, band type in 10% and 13% had no detectable lesions despite contralateral involvement. Fourteen eyes (47%) had ≥5 endothelial lesions. Patients with PPCD had significantly lower endothelial cell densities (ECD) at recruitment (1918.9 ± 666.3 vs. 3340.1 ± 286.5 cells/mm^2, $p < 0.007$) and at final follow-up (1793.1 ± 684.6 vs. 3265.2 ± 304.3 cells/mm^2, $p < 0.007$) compared to age-matched controls. The lowest ECDs were found in eyes with diffuse type PPCD and those with ≥5 posterior corneal lesions, while clinically unaffected eyes in patients with confirmed PPCD in fellow eye had a normal ECD. However, the rates of annual ECD decline were not significantly different between eyes with PPCD in general, between the subgroups of PPCD and the normative groups.

Conclusion Endothelial cell density is significantly reduced among children with PPCD and depends on the clinical subtype and the number of posterior corneal lesions present. However, annual ECD loss is similar between normal eyes and those with PPCD.

Introduction

Posterior polymorphous corneal dystrophy (PPCD) is an uncommon inherited disorder first described by Koeppe in 1916. Several gene mutations are implicated in the aetiology of PPCD, including *OVOL2*, *COL8A2*, *ZEB1* and *GRHL2* genes [1]. Pathologically, the Descemet membrane is abnormally thickened, due to the replacement of the corneal endothelium by multi-layered epithelial-like cells and production of aberrant basement membrane [2].

Clinically, PPCD may present on rare occasions as infantile corneal clouding due to the presence of stromal edema [3–5]. However, PPCD typically presents later in life as a bilateral but asymmetric disease diagnosed during otherwise routine examination. In both adults and in children, characteristic lesions on the Descemet membrane and the corneal endothelium can be seen as vesicle-like, band-like (also described as snail-track type) or diffuse posterior corneal opacities [2, 6–8]. While most patients with PPCD remain asymptomatic into adulthood, young children with PPCD may develop amblyopia due to asymmetric or unilateral corneal involvement. It has also been suggested that PPCD is a slowly progressive condition [4, 9], with some developing visually significant corneal stromal and

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epithelial oedema due to endothelial dysfunction at a relatively young age [2, 10].

Currently, the manner of disease progression in children is uncertain [11–13]. Herein, we present the longitudinal endothelial cell status assessed by specular microscopy in 15 paediatric patients with PPCD compared with an age-matched normative cohort.

Methods

The study was approved by the Research Ethics Board at the Hospital for Sick Children, Toronto, ON, Canada with adherence to the tenets of the Declaration of Helsinki. Informed consent was obtained from patients' guardians prior to participation in the study. All patients under the age of 18 years between July 2013 and July 2018 who were diagnosed with PPCD were recruited, patients underwent prospective specular microscopy and age-matched normative patients identified from our database were used as the control group. Patient demographics and clinical details, including age, previous medical and surgical history, best corrected visual acuity (BCVA, recorded in logMAR equivalent), ocular alignment assessment and cycloplegic refraction were obtained. Slit-lamp biomicroscopic features were documented with clinical photography and were used to determine the number of lesions present and the clinical subtype (vesicular, band, diffuse and unaffected) [11]. Changes in clinical appearance between follow-up appointments were also documented. When possible, keratometric (K) and central pachymetric values were obtained from corneal tomography (Pentacam, Oculus, Wetzlar, Germany).

Specular microscopic analysis

All specular images of the central cornea were taken using a non-contact technique (Konan Medical USA, Torrance, CA) during all follow up visits. For cooperative individuals, images were acquired with the patient seated upright and with central fixation, allowing images to be obtained from the same corneal region multiple times. In one patient, images were taken during examination under anaesthesia in the left lateral decubitus position using a validated technique [14]. Specular images were analysed by one masked and one unmasked investigator. A third masked investigator would adjudicate the final analysis if there was a difference greater than 5% in endothelial cell density (ECD). The semi-automated 'center' method was used to mark the centres of as many contiguous cells as possible (minimum 75 cells). The ECD (cells/mm^2), hexagonality (HEX%) and coefficient of variance (CV) of cell shape were then calculated using Konan CellChek software. Statistical analysis was performed with Microsoft Excel for Mac (Irvine, CA). Statistical significance was defined as $p < 0.05$, and Bonferroni adjustment was performed in the setting of multiple statistical comparisons.

Results

Sixteen patients were included in this study, with 10 male and 6 female participants. One patient did not return for further assessment and was therefore excluded from further analysis. Of the remaining 15 patients, mean age at presentation was 10.5 ± 3.1 years (range: 5.5 – 15.2 years). Mean follow-up was 3.0 ± 1.0 years (range: 1.0 – 4.5 years).

The baseline demographics of the patients with PPCD are shown in Table 1. Eleven subjects had bilateral involvement. Four eyes were clinically normal and hence 26 out of 30 eyes (87%) demonstrated PPCD lesions. The two most common morphologies were vesicular (40%) and diffuse type (37%) of PPCD. Fourteen eyes (47%) had ≥ 5 posterior corneal lesions identified on slit lamp biomicroscopy: one was band type; two were vesicular type; and the rest were diffuse type PPCD (Fig. 1). The morphology in each eye did not change from one type to another, and the number of lesions did not change during the course of the study. None of the patients developed corneal ectasia or oedema at any time during the study.

The mean BCVA of the group was 0.19 ± 0.15 logMAR. Among the 15 patients, 4 patients (2 bilateral and 2 unilateral PPCD) had heterophoria, which were well controlled without the need of strabismus surgery. While 5 patients had reduced BCVA that would meet the criteria of amblyopia as conventionally defined (inter-eye difference in BCVA by >2 lines or reduction of BCVA by ≥2 lines

Table 1 Baseline demographics of paediatric subjects with posterior polymorphous corneal dystrophy.

	Initial	Follow-up
Gender: M:F (%)	10:5 (67% : 33%)	
BCVA (logMAR)	0.19 ± 0.15 (0.00 – 0.50)	0.18 ± 0.18 (−0.10 – 0.60)
RSE (D)	−0.5 ± 2.3 (−4.5 – +2.9)	−1.1 ± 2.2 (−5.0 – +2.4)
Cylindrical error	1.3 ± 1.3 (0.0 – 4.5)	1.2 ± 1.3 (0.0 – 5.0)
Keratometric values (D)		
Average	44.6 ± 2.3 (40.1 – 48.3)	45.0 ± 2.8 (40.0 – 51.1)
Flat	43.8 ± 2.3 (39.7 – 48.1)	44.0 ± 2.8 (39.5 – 50.2)
Steep	45.4 ± 2.6 (40.5 – 50.7)	46.0 ± 2.9 (40.4 – 52.0)
CCT (μm)	568.4 ± 57.0 (495 – 678)	566.7 ± 54.5 (494 – 671)
Clinical morphology		
No lesion	4 (13%)	
Band	3 (10%)	
Diffuse	11 (37%)	
Vesicular	12 (40%)	

BCVA best corrected visual acuity, *RSE* refractive spherical equivalent, *D* dioptres, *μm* microns

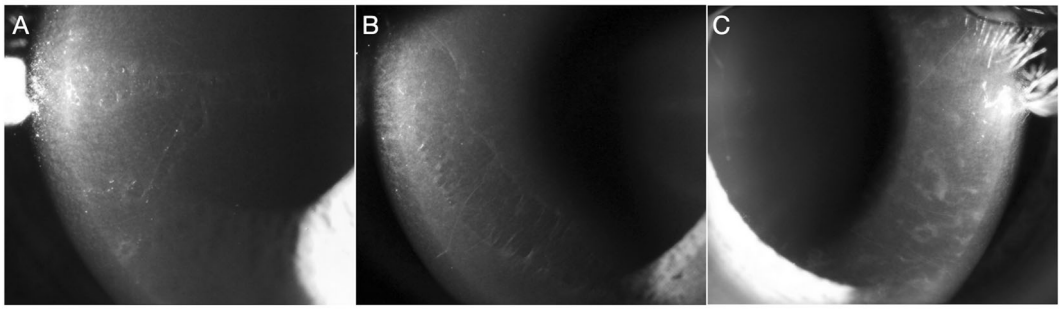

Fig. 1 Clinical characteristics of posterior polymorphous corneal dystrophy (PPCD). Posterior corneal lesions as seen in **A** vesicular type, **B** band type, **C** diffuse type of PPCD.

compared to age-appropriate normative values), they were 8–15 years old at first presentation, none had BCVA worse than 20/50, and all had PPCD lesions affecting the visual axis to account for the reduced vision. As such, amblyopia treatment was discussed with parents and decision was reached to not initiate patching. Amblyopia treatment was not initiated in any of the participants, as those with reduced vision unilaterally were all beyond the amblyogenic period. Mean refractive spherical equivalent (RSE) was -0.5 ± 2.3 D. On corneal topography, the mean average keratometric (K) value was 44.6 ± 2.3D, while the mean steep K was 45.4 ± 2.6 D. Mean central corneal thickness (CCT) was 568.4 ± 57.0 µm. After a mean follow-up of 3.0 ± 1.0 years, apart from a significant myopic shift in RSE ($p = 0.001$), all other parameters of the cohort remained stable.

Table 2 shows the corneal endothelial parameters in eyes with characteristic PPCD lesions ($n = 26$). Eyes with PPCD had significantly lower ECD compared to age-matched control group at study recruitment (1918.9 ± 666.3 cells/mm^2 vs. 3340.1 ± 286.5 cells/mm^2; $p < 1 \times 10^{-8}$) and at follow-up (1793.1 ± 684.6 cells/mm^2 vs. 3265.2 ± 304.3 cells/mm^2; $p < 1 \times 10^{-8}$), During the course of the study, mean ECD of PPCD eyes significantly reduced (1918.9 ± 666.3 cells/mm^2 to 1793.1 ± 684.6 cells/mm^2, $p = 0.0002$), yielding a rate of 1.9 ± 3.7% endothelial cell loss per year. The annual rate of ECD loss was comparable to control group ($p = 0.95$). The morphological parameters of the endothelial cells in PPCD patients did not significantly change during follow-up (CV, $p = 0.76$; HEX, $p = 0.58$). Similarly, no significant differences were detected in either CV or HEX between the PPCD group and age-match control.

To assess for differences between the various subtypes of PPCD, including those which were clinically normal in unilateral PPCD, further analysis was performed, and the results are shown in Table 3 and Fig. 2. Apart from the band type PPCD, all other types of PPCD were found to have significantly lower mean ECD at recruitment and at follow-up compared to their respective age-matched controls after adjustments ($p < 0.006$). In participants with unilateral PPCD involvement, mean ECDs in eyes without corneal

Table 2 Corneal endothelial characteristics in children with posterior polymorphous corneal dystrophy and age-matched control.

	PPCD ($n = 26$)	Control ($n = 26$)
Follow-up duration (years)	3.0 ± 1.0	1.3 ± 0.5
ECD (cells/mm^2)		
Initial	1918.9 ± 666.3	3340.1 ± 286.5*
Follow-up	1793.1 ± 684.6	3265.2 ± 304.3*
Rate of ECD loss (%)	1.9 ± 3.7%	2.0 ± 1.5%
CV		
Initial	27.8 ± 3.9	26.1 ± 3.5
Follow-up	27.6 ± 3.6	24.9 ± 3.2
HEX (%)		
Initial	65.4 ± 7.9	71.8 ± 9.3
Follow-up	66.4 ± 7.0	72.5 ± 8.0

Statistically significant differences are marked with asterisks ($p < 0.007$).

ECD endothelial cell density, *CV* coefficient of variance, *HEX* hexagonality

Table 3 Endothelial cell densities (ECD) in children with different subtypes of posterior polymorphous corneal dystrophy (PPCD) and respective age-matched control.

	ECD (cells/mm^2)	
	PPCD subgroup	Control subgroup
Vesicular ($n = 12$)		
Initial (cells/mm^2)	2240.4 ± 810.8	3248.7 ± 294.0*
Follow-up (cells/mm^2)	2151.7 ± 803.5	3179.4 ± 328.1*
Band ($n = 3$)		
Initial (cells/mm^2)	1952.5 ± 475.6	3425.7 ± 211.3
Follow-up (cells/mm^2)	1754.2 ± 397.5	3327.0 ± 249.4
Diffuse ($n = 11$)		
Initial (cells/mm^2)	1559.1 ± 274.1	3416.5 ± 287.4*
Follow-up (cells/mm^2)	1412.6 ± 340.6	3341.8 ± 290.1*
No Lesion ($n = 4$)		
Initial (cells/mm^2)	3307.5 ± 482.0	3343.8 ± 425.7
Follow-up (cells/mm^2)	3158.6 ± 378.0	3294.8 ± 404.6

Statistically significant differences are marked with asterisks ($p < 0.006$).

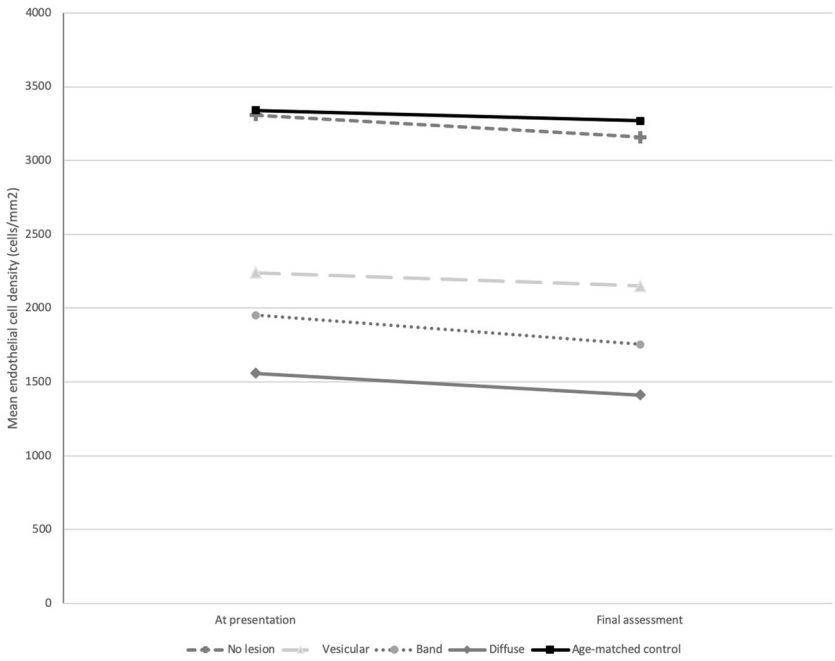

Fig. 2 Endothelial cell densities (ECD) among subjects with posterior polymorphous corneal dystrophy (PPCD) and age-matched control. While the mean ECDs were lower among the eyes with PPCD lesions compared to those without corneal lesions and in age-matched control, the annual rate of ECD loss were not significantly different.

lesions (shown as 'No lesion' in Table 3 and Fig. 2) were similar to those in age-matched controls, both at recruitment and at follow-up. Finally, none of the PPCD subgroups had statistically significant differences in annual rate of ECD loss compared to their respective age-matched controls (band PPCD vs. control, $p = 0.45$; vesicular PPCD vs. control, $p = 0.40$; diffuse PPCD vs. control, $p = 0.63$; no lesion PPCD vs. control, $p = 0.68$).

Potential associations between the effect of the number of posterior corneal lesions and the specular microscopic characteristics were explored, and the results are shown in Table 4. Cross-sectional comparisons with age-matched controls showed those with ≥5 PPCD lesions had a significantly lower mean ECD than those with 1–4 lesions at recruitment ($p = 0.0002$) and at follow-up ($p = 0.0007$). However, the mean annual rate of ECD loss in both groups did not differ significantly from their respective age-matched controls (control vs. 1-4 lesions: $p = 0.29$; control vs. ≥5 lesions, $p = 0.40$).

Discussion

In the largest paediatric study to date, we report the longitudinal changes in corneal endothelial cells in children diagnosed with PPCD and contrast them with age-matched controls. The key findings are that eyes with PPCD, particularly the vesicular or diffuse subtypes, demonstrated a significantly lower ECD than those in the control group. In addition, the mean ECD among eyes with ≥5 lesions characteristic of PPCD is significantly lower than those with fewer corneal lesions. However, in all of the analyses, the annual rates of ECD loss in any subtypes of PPCD were not significantly different to those seen in the age-matched normative controls.

There is a paucity of studies describing the changes in the corneal endothelium in children affected by PPCD [3, 11, 12]. Early work by Laganowski and colleagues who used large-field specular microscopy to study 48 cases of PPCD reported that ECDs were lower in eyes with PPCD than normally expected [11]. However, although a number of children were observed in each of the three types of PPCD, the authors did not specify the number of children within each group and did not separately analyse the paediatric data. Ahn et al. reported the clinical and corneal endothelial features in seven Korean children (10 eyes) diagnosed with PPCD in a retrospective study in 2017 [12]. The authors compared them to four children without corneal findings, and found that children with PPCD had significantly lower ECD compared with the normal control (1733.0 ± 543.9 vs. 3320.8 ± 175.1 cells/mm^2; $p < 0.001$). However, repeat measurement after 3 years showed no significant differences compared with the initial ECDs in the PPCD-affected eyes. Importantly, the study did not contain any children with diffuse type PPCD lesions, and differences between the various subtypes of PPCD were not investigated. Furthermore, it was unclear whether the phenotypically normal cornea in cases of unilateral PPCD are comparable to an otherwise healthy cornea.

In this prospective longitudinal study, our cohort consisted of children with all the different clinical subtypes of PPCD. In keeping with previous literature [11, 12], the

Table 4 Corneal endothelial characteristics according to number of corneal lesions identified on clinical examination.

	No lesions ($n = 4$)		1 – 4 lesions ($n = 12$)		5 or more lesions ($n = 14$)	
	PPCD	Control	PPCD	Control	PPCD	Control
ECD (cells/mm^2)						
Initial	3307.5 ± 482.0	3343.8 ± 425.7	2386.0 ± 698.5*	3340.6 ± 299.2	1518.6 ± 258.8*	3435.0 ± 276.0
Follow-up	3158.6 ± 378.0	3294.8 ± 404.6	2299.4 ± 648.0*	3269.1 ± 311.2	1359.1 ± 326.6*	3363.3 ± 282.3
Annual ECD loss (%)	1.4 ± 1.4	1.7 ± 0.3	0.8 ± 3.7	2.0 ± 1.4	2.9 ± 3.6	1.9 ± 1.5
CV						
Initial	28.3 ± 3.3	24.0 ± 1.4	25.8 ± 2.7	25.8 ± 4.2	29.6 ± 3.9	26.3 ± 3.0
Follow-up	29.5 ± 4.7	21.8 ± 1.7	26.3 ± 2.9	24.9 ± 3.4	28.8 ± 3.8	24.9 ± 3.1
HEX (%)						
Initial	61.5 ± 11.0	75.3 ± 3.1	70.0 ± 7.5	72.3 ± 9.8	61.6 ± 6.1	71.4 ± 9.2
Follow-up	62.4 ± 8.8	72.0 ± 14.7	68.0 ± 7.7	75.0 ± 7.0	65.0 ± 6.4	70.4 ± 8.4

Intragroup longitudinal analysis revealed significant differences in endothelial cell density (ECD) in all groups. Asterisks: statistically significant intergroup differences ($p < 0.003$).

predominant clinical morphology was vesicular PPCD. Indeed, among the 44 subjects who successfully underwent specular microscopy with Laganowski et al, 42% were vesicular type [11]. However, 37% of eyes displayed diffuse type PPCD, which was previously thought to be uncommon. There may be geographic differences in the distribution of PPCD subtypes, and further studies would help to clarify this. As a tertiary referral unit, it is also possible that our cohort is biased toward the more clinically striking forms of PPCD, as they would be more easily identified in the community.

We also observed variations in ECD reduction among different types of PPCD, with vesicular type being the least and diffuse type the most severe. To the best of our knowledge, this correlation between ECD and phenotypical appearances has not been previously described in detail. Results from studies by Laganowski et al. [11] and Ahn et al. [12] appear to support our observation. In the former, the authors were able to calculate the ECD in eyes with vesicular PPCD but not the others, which could be due to the increasingly severe alterations to the posterior corneal surface [11]. In the study by Ahn et al, although diffuse type PPCD was not included in the study, all of the 8 eyes with band type lesions had lower ECD than the 2 eyes with vesicular PPCD at all time points of the study [12].

Bozkurt and colleagues have previously shown that the posterior corneal lesions in PPCD contained abnormal or an absence of endothelial cells along with atypical deposits that are hyperreflective on in vivo confocal microscopy [15]. Therefore it may be postulated that the presence of more posterior corneal lesions is indicative of reduced numbers of viable endothelial cells. Indeed, we found that eyes with ≥5 posterior corneal lesions had significantly lower ECD compared to those with 1–4 corneal lesions and those in the control group. As such, the subtype of PPCD and the number of lesions seen clinically may be useful predictors of corneal endothelial decompensation and failure with increasing age and in the event of intraocular surgeries. Patients with these high-risk characteristics should be monitored more closely and counselled accordingly if they require intraocular surgery.

While we found that eyes with PPCD have significantly lower ECD compared to the controls at all time points of the study, the annual rates of ECD loss were comparable between the two groups (1.9% vs. 2.0%, respectively). The different phenotypes of PPCD also had similar rates of ECD decline as our control subjects. This finding is in contrast with that by Ahn and colleagues, who reported a 13.3 ± 10.1% reduction ECD over 3 years among subjects with PPCD, and only 0.45 ± 1.93% among normal control ($p = 0.03$) [12]. However, it is important to note that the authors did not find any significant difference in absolute ECD between recruitment and follow-up investigations among both the PPCD and the normal control group. This discrepancy is likely due to the fact of a small cohort and a different control group size ($n = 4$). Interestingly, the right eye of subject 5 in the study experienced a 39% reduction of ECD over 3 years (the remainder ranged from 4 to 18%), which may explain their widely distributed rates of ECD loss over 3 years. Further study will help to confirm the findings, but even if the annualized decline rate among subjects with PPCD were similar to that among normal children, those with diffuse PPCD and/or large numbers of posterior corneal lesions would be prone to earlier corneal decompensation due to reduced initial reserve of corneal endothelial cells.

We were able to compare the endothelial features among the clinically normal eyes in children with unilateral PPCD versus those from a normative cohort. To this end, we did not find any significant differences in any of the

endothelial characteristics, and the mean annual rates of ECD loss were consistent with previously reported figures of 1.1–2.9% per year in children [16–18]. Therefore, our findings suggest that the corneal endothelial cells are negatively affected by PPCD only when there are characteristic phenotypic changes on the cornea.

Despite being the largest report in children, a small sample size is a limitation of our study, due to the rarity of this diagnosis in children. Specular microscopy images only a small area of the cornea, and there may be variations of ECD in each eye depending on the presence or the absence of posterior corneal lesions in the sampling area. Therefore, eyes with diffuse PPCD would be more likely to have generalized reduction of ECD, and the differences against other subtypes may in fact be even more significant. Another limitation of our study is that genotyping was not available to our patients due to funding and availability. At present the genotype-phenotype correlation is not known for disease severity or endothelial prognosis in PPCD. Future studies to compare the phenotypic features of PPCD lesions with specific mutations are needed. However, the clinical implications of lower ECD, and hence their endothelial reserve, in children is important to consider when intraocular surgery is indicated in these eyes.

In conclusion, PPCD is associated with a significant reduction of corneal endothelial cells, the severity of which is dependent on the clinical characteristics and the number of posterior corneal lesions present. However, the annual rate of endothelial decline among all types of PPCD is similar to that measured in normal eyes. Prognosis and likelihood of children with PPCD having corneal decompensation could therefore be stratified according to their presenting clinical characteristics.

Study highlights

What was known before

- PPCD is an uncommon inherited disorder with characteristic vesicle-like, band-like or diffuse posterior corneal opacities.
- In children, PPCD could result in amblyopia due to asymmetric or unilateral corneal involvement.
- PPCD is also thought to be a slowly progressive condition; if so, children may be at risk of developing visually significant corneal oedema at a young age.

What this study adds

- This is the largest longitudinal paediatric study using specular microscopy to assess the corneal endothelium.
- Children with PPCD have lower endothelial cell densities, and the degree of reduction varies depending on the clinical subtype of PPCD.
- However, children with PPCD has similar annual rate of endothelial cell loss to age-matched normative control.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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