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ORIGINAL PAPER

Correlation between age and corneal edema in pediatric patients with Peters anomaly

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Abstract

Purpose To evaluate corneal edema in different-aged pediatric patients with Peters anomaly and to correlate in vivo with ex vivo histopathologic findings.

Methods A retrospective cross-sectional study was performed. The medical records of patients diagnosed with Peters anomaly who underwent examination under anesthesia (EUA) between 2011 and 2015 were reviewed. Eyes in which central corneal thickness (CCT) measurements were taken were included. The thickest point in the CCT pachymetric map was used to objectively quantify corneal edema. Correlation between CCT and age was calculated. Additionally, a retrospective review of histopathologic studies of excised corneal buttons from pediatric eyes with Peters anomaly between 2011 and 2015 was performed.

Results Eighteen eyes of 12 children were included. Mean age was 14 ± 15 months, and mean CCT was 842 ± 304 μm. A significant inverse correlation was noted between the CCT and the age of the patients, with lower CCT values in older children ($r = 0.6$; $P = 0.01$). Seven excised corneal buttons that underwent penetrating keratoplasty were reviewed. All corneal buttons showed absence of Descemet membrane and localized absence of endothelium. However, three specimens showed presence of corneal endothelium in areas of absent or attenuated Descemet membrane.

Conclusions In Peters anomaly, the CCT decreases with age, possibly due to a decrease in corneal edema. Histopathologic studies show cases of endothelial expansion in areas of absent or attenuated Descemet membrane. This may contribute to improved endothelial function and decreased edema with age.

Keywords Peters anomaly · Descemet membrane · Anterior segment coherence tomography · Corneal endothelium

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Introduction

Peters anomaly is a rare congenital eye disease in which a malformation of the anterior segment results in diffuse corneal edema and a central corneal opacity

secondary to an absence of Descemet membrane and endothelium in the area of the corneal opacity [1]. Since the corneal edema and central opacity can impair visual development resulting in deprivation amblyopia, intervention is required as early as possible, particularly in bilateral cases [1]. Currently, penetrating keratoplasty (PK) is the preferred treatment for this pathology, although it is often challenging with high risk of graft failure in pediatric patients [2].

Recent reports have documented cases of corneal edema spontaneously decreasing with time in eyes with other types of endothelial dystrophies and in cases of lost endothelium by accidental damage [3]. These changes have been thought to occur due improved endothelial function by enlargement or proliferation of endothelial cells over areas of previously absent endothelium. We hypothesize that changes in corneal edema could occur with age in pediatric eyes with Peters anomaly through similar mechanisms.

Recently, the use of anterior segment optical coherence tomography (AS-OCT) has gained popularity in the evaluation of corneal diseases as it provides cross-sectional corneal imaging and analysis, allowing identification of the opacity morphology as well as depth, which are important factors in surgical planning. In cases of Peters anomaly, it can reveal valuable information about corneal thickness, iridocorneal adhesions, and lamellar defects [4].

The purpose of this study is to evaluate correlation between corneal edema or thickness and age in patients with Peters anomaly. CCT measurements obtained with AS-OCT were used to evaluate corneal edema in eyes of different-aged pediatric patients with this anomaly. As a secondary objective, histopathologic readings of excised corneal tissue in eyes with Peters anomaly were analyzed to further explore the hypothesis of improved endothelial function. To our knowledge, this is the first study to utilize in vivo and ex vivo findings to investigate the changes in corneal edema in this condition. These findings may guide the indications and nature of surgical intervention in patients with Peters anomaly and may establish a potential role for endothelium-sparing procedures in management.

Methods

We conducted a retrospective review of medical records and of pathology specimens of patients with the diagnosis of Peters anomaly. This study was approved by the Institutional Review Board of University of Miami and is adherent to the tenets of the Declaration of Helsinki and compliant with the Health Insurance Portability and Accountability Act.

Financial claims data were searched to identify all patients with diagnosis of Peters anomaly (ICD-10 Q13.4, ICD-9 743.44) and anterior segment dysgenesis (ICD-10 Q15.9, ICD-9 743.8) who underwent EUA (CPT-92018) at our tertiary referral center between 2011and 2015. As an institutional practice, all patients with findings suspicious of Peters anomaly and/or anterior segment dysgenesis involving the visual axis and incapable of cooperating with a comprehensive clinic-based examination undergo EUA. Patients were included if they presented with diagnosis/characteristics of Peters anomaly type I and II, and during EUA underwent AS-OCT examination with the iVue platform (Optovue Inc., Freemont, CA) with measurement of the central corneal thickness. Intraoperative CCT measurements obtained with AS-OCT were used as a measurement of corneal edema.

The following data were extracted from the medical record: age; morphologic characteristics of anterior segment structures including cornea, anterior chamber, iris and lens; and corneal thickness measurement. Subjective morphologic analysis of AS-OCT images of the central 6-mm zone of all corneas was performed (Fig. 1). The thickest point in the CCT pachymetric map was recorded. Statistical analyses were performed using SPSS software, version 21.0 (SPSS, Chicago, IL, USA). Values are presented as means (± standard deviation). Pearson's correlation was used to assess the correlation between the age of the patient at time of imaging and the central corneal thickness. P values less than 0.05 were considered statistically significant.

To identify the histopathologic mechanism behind the observed in vivo finding, histopathologic slides of all patients with diagnosis of Peters anomaly who underwent penetrating keratoplasty from 2011 to 2015 were reviewed. Hematoxylin-and-eosin- and periodic acid–Schiff (PAS)-stained slides were examined using an Olympus BH-2 light microscope (Olympus Optical

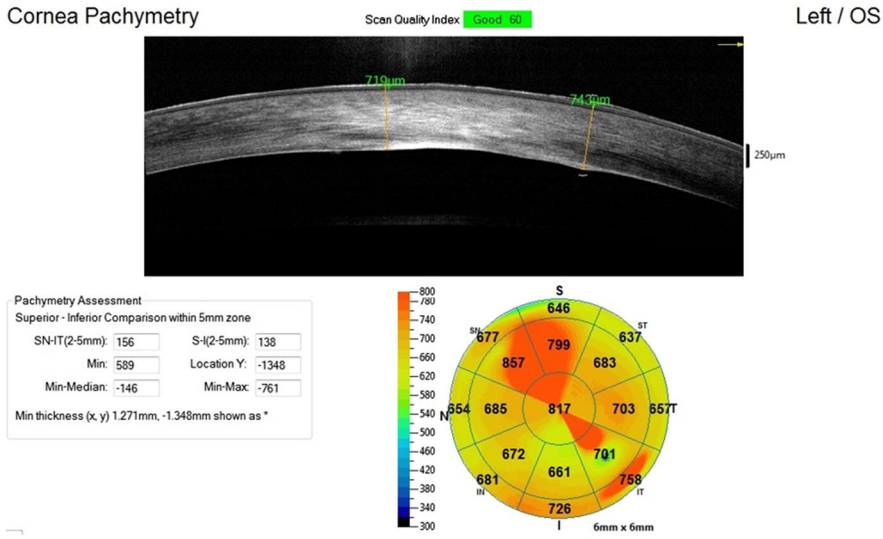

Fig. 1 Anterior segment spectral domain optical coherence tomography scan of the central 6-mm zone of the cornea with a pachymetric map display showing corneal thickening and absence of Descemet membrane

Co., Tokyo, Japan) by the Ocular Pathology Department of our institution.

Results

A total of 18 eyes of 12 children (mean age 14 ± 15 months) with Peters anomaly were included in the study. All eyes presented with the clinical characteristics of Peters anomaly, including corneal edema, corneal opacities, and iridocorneal adhesions. None of the eyes met the Childhood Glaucoma Research Network definition of glaucoma associated with non-acquired ocular anomalies or systemic disease/syndrome at the time of EUA [5].

All eyes underwent anterior segment AS-OCT examination and CCT measurement. Mean CCT measurement was 842 ± 304 µm. (Table 1) A statistically significant inverse correlation between the age of the examined patients and the CCT was observed ($r = 0.6$; $P = 0.01$) (Fig. 2).

A total of seven excised corneal buttons from penetrating keratoplasties on children with Peters anomaly underwent histopathologic examination using PAS stain. The typical findings of Peters anomaly were seen in all specimens, including focal absence of Descemet membrane and endothelium in the area of the corneal opacity, and iridocorneal adhesions at the edges. However, two specimens showed additional evidence of corneal endothelium present in areas of absent or attenuated Descemet membrane (Fig. 3a, b). Furthermore, a third corneal tissue (Fig. 3c) revealed the presence of a retrocorneal membrane with underlining attenuated and variably present endothelium.

Table 1 Age (months) and corneal thickness (µm) of pediatric patients with Peters anomaly

Age (months)	Corneal thickness (µm)
1	1004
2	954
2	937
2	831
2	1270
5	817
6	1808
6	779
7	836
8	673
11	755
11	745
16	715
16	651
23	719
35	711
48	508
48	445

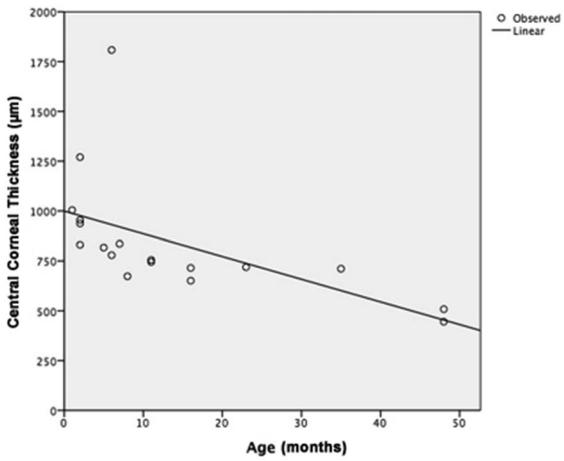

Fig. 2 Corneal thickness (µm) inversely correlated with the patients' age (months) (linear correlation coefficient $R = 0.6$) with lower corneal thickness values in older children ($r = 0.6$, $P = 0.01$)

Discussion

Central corneal thickness measurements vary depending on age, race, and functionality of the endothelial cell layer. There are currently limited data regarding CCT values on children, and the effect of age is still uncertain. A study published by the Pediatric Eye Disease Investigator Group found that median CCT in anatomically normal eyes increases modestly with age from 1 to 11 years [6]. Hussein et al. [7] reported a slow and mild increase in CCT in children up to age 9, achieving adult thickness by 5 years of age. Conversely, other investigators have found no association between CCT and age in pediatric patients [8, 9].

In this study, we found that central corneal thickness was inversely correlated with patient age ($P = 0.01$) in patients with Peters anomaly. In anatomically normal eyes, the corneal endothelium performs the function of preserving transparency by maintaining the cornea in a state of relative dehydration. Absence or damage of this cell layer, as in cases of Peters anomaly, endothelial dystrophies, and surgical trauma, will cause accumulation of fluid and corneal swelling with loss of transparency. This corneal edema will present as increased CCT values. We believe our findings showing a decrease in CCT with age in Peters anomaly may be secondary to a decrease in corneal edema due to improved endothelial function with age.

Historically, it has been thought that the corneal endothelium lacks mitotic and reparative capabilities. However, since the 1980s, an increasing number of reports suggest that corneal endothelial cells might be able to spontaneously repopulate in areas with absent Descemet membrane and endothelium, by either

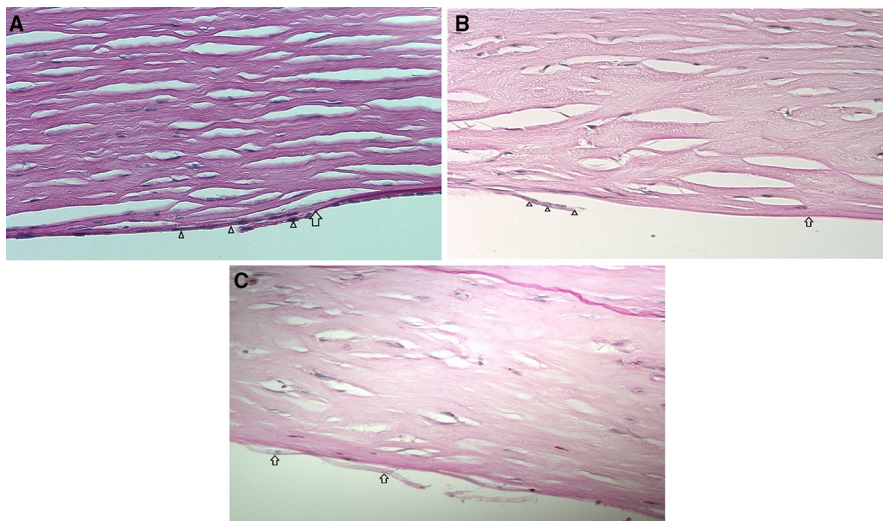

Fig. 3 **a**, **b** Histopathologic slides of two corneal buttons demonstrating the presence of corneal endothelium in areas of absent or attenuated Descemet membrane (arrows: point at areas of termination of Descemet membrane; arrow heads: point at endothelium present in areas with absent or attenuated Descemet membrane). **c** Histopathologic slide of a corneal button demonstrating the presence of a retrocorneal membrane, with underlining attenuated and variably present endothelium (arrows)

cellular enlargement with migration or cellular proliferation [3, 10–13]. With the use of confocal microscopy, studies in patients with Fuchs endothelial dystrophy and posterior polymorphous corneal dystrophy have found evidence of endothelial repopulation after Descemet stripping, with consequent rapid clearance of corneal edema [3, 10, 13]. In addition, several reports of spontaneous endothelial barrier reformation with improvement in corneal edema have been described in cases of intentional and accidental endothelial damage occurring in corneal and non-corneal procedures [3, 12]. In these cases, a functional endothelial barrier reformed despite incomplete or no corneal endothelial cell transplantation.

Corneal clouding in Peters anomaly shares a comparable etiology of dysfunctional corneal endothelium as the previously reported cases. This pathology is histologically characterized by an absence of both Descemet membrane and endothelium in the area of the corneal opacity, with iridocorneal adhesions at the edges [1, 14]. Our histopathologic studies confirmed these typical characteristics in our specimens. However, in three of our specimens it was also noticed that there were some areas with presence of endothelium in zones of absent or attenuated Descemet membrane. These findings are comparable to similar results found in studies of patients with other endothelial dystrophies in which spontaneous repopulation of endothelium has been evidenced in areas with absent Descemet membrane. [11]. Currently, it remains unknown whether this endothelial self-repair involves migration or proliferation of the remaining host endothelium or a combination of both phenomena. However, clinical and objective measurement of corneal deturgescence with a decrease in CCT evidences a substantial improvement in endothelial function with age in patients with Peters anomaly. Nevertheless, further studies with a larger number of histologic specimens would be needed to determine this possible endothelium proliferation or migration over time.

These findings may provide valuable therapeutic considerations. For many years, intervention for Peters anomaly in patients lacking a clear peripheral cornea has centered around PK. However, performing PK in children is challenging and the prognosis for graft survival ranges from 30 to 60% [2, 15]. This is thought to be due to a combination of factors which include difficulty in obtaining an accurate eye examination, delayed recognition of complications, and the extensive nature of the disease process. Nevertheless, PK continues to be the surgical treatment of choice for children at high risk of amblyopia due to lack of a clear cornea, as it replaces all layers of the cornea including the defective Descemet and endothelial layers. However, further studies of endothelial changes in patients with Peters anomaly may suggest a possible therapeutic benefit of endothelium-sparing procedures over PK.

This study presents some limitations due to the retrospective nature of the series. The authors believe that prior CCT measurements from the corneas that underwent histopathologic studies would have provided useful information in the evaluation of our hypothesis. However, this information was not available in the medical records. In addition, the authors consider the possibility of selection bias. Although EUA is standard of practice in our institute for all younger patients unable to be examined at slit lamp, patients with more severe disease may require EUA earlier in life. Therefore, in these cases CCT may be correlating with disease severity rather than age. In addition, as pathologic specimens came from severe Peters cases requiring PK, our retrospective cross-sectional cases may not share the same endothelial mechanisms.

In conclusion, use of SD-OCT demonstrated decreased corneal thickness in older patients with Peters anomaly. In addition to histopathologic studies evidencing the presence of endothelium in areas of absent Descemet membrane, these changes may suggest gradual recovery of the endothelium as a possible mechanism for the improved corneal thickness. These findings may better help us understand the natural history of Peters anomaly and thus permit the proposal of endothelium-sparing techniques to improve surgical outcomes and minimize the risk of allograft rejection.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

Ethical approval A retrospective chart review was performed and approved by the University of Miami Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent As this study was a retrospective chart review, a waiver of informed consent was deemed appropriate by the IRB.

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