In Vivo Confocal Microscopic Evidence of Keratopathy in Patients with Pseudoexfoliation Syndrome

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PURPOSE. To measure the density of cells in different layers of the cornea and to determine whether morphologic changes of the subbasal corneal nerve plexus are present in eyes with the pseudoexfoliation (PEX) syndrome.

METHODS. Twenty-seven patients with unilateral PEX syndrome and 27 normal controls were investigated. All eyes underwent corneal sensitivity measurements with an esthesiometer and in vivo confocal microscopic study. Densities of the epithelial, stromal, and endothelial cells were measured. The density and tortuosity of the subbasal corneal nerve plexus were also evaluated.

RESULTS. Eyes with PEX syndrome had significantly lower cell densities in the basal epithelium (P = 0.003), anterior stroma (P = 0.007), intermediate stroma (P = 0.009), posterior stroma (P = 0.012), and endothelium (P < 0.0001) than in the corresponding layers of normal eyes. PEX eyes also had lower subbasal nerve densities and greater tortuosity of the nerves than normal eyes. Fellow eyes of patients with PEX also had significantly lower densities of the basal epithelial and endothelial cells than the normal eyes. Corneal sensitivity was significantly decreased in PEX eyes, and this was significantly correlated with the decrease of basal epithelial cell and subbasal nerve densities.

CONCLUSIONS. These results have shed light on understanding of the pathogenesis of decreased corneal sensitivity in eyes with PEX syndrome. PEX syndrome is probably a binocular condition for which keratopathy of the fellow eye also requires observation. (Invest Ophthalmol Vis Sci. 2011;52:1755–1761) DOI:10.1167/iovs.10-6098

The pseudoexfoliation (PEX) syndrome is a common age-related disorder of the extracellular matrix and is frequently associated with severe chronic secondary open angle glaucoma and cataract.1-3 The prevalence of PEX syndrome varies widely in different racial and ethnic populations. In addition, the prevalence of PEX is dependent on the age and sex distribution of the population examined, the clinical criteria used to diagnose PEX, and the ability of the examiner to detect early stages and more subtle signs of PEX. For example, the highest rates in studies of persons older than 60 years of age have been reported to be approximately 25% in Iceland and more than 20% in Finland.4,5 The ocular manifestation of PEX syndrome is the production and progressive accumulation of abnormal extracellular fibrillar material in almost all the inner wall tissues of the anterior segment of the eye. This characteristic alteration predisposes the eye to a broad spectrum of intraocular complications including phacomatosis and lens subluxation, angle closure glaucoma, melanin dispersion, poor mydriasis, blood-aqueous barrier dysfunction, posterior synechiae, and other related complications.1-3

The PEX syndrome is associated with corneal endotheliopathy, and this has been suggested to be the cause of the so-called atypical non-guttae Fuchs endothelial dystrophy.5,6 PEX endotheliopathy, a slowly progressing disease of the corneal endothelium, is usually bilateral but is often asymmetrical. It can lead to early corneal endothelial cell decompensation, which can then induce severe bullous keratopathy, a vision-threatening disorder.

Clinical signs of PEX syndrome include decreased corneal sensitivity, thinning of the central corneal thickness, and impaired tear film stability.7-9 However, the underlying cause of these clinical findings has not been well investigated, possibly because objective and accurate in vivo examination techniques are not available.

Recent advances in imaging technology have improved the ability of these instruments to diagnose different ocular diseases. The Rostock Cornea Module (Heidelberg Engineering, Heidelberg, Germany), consisting of a contact lens system attached to the Heidelberg Retina Tomograph II (Heidelberg Engineering), is such an instrument. It uses laser scanning technology to investigate the cornea at a cellular level, and structures such as the subbasal nerve plexus, which cannot be seen by slit-lamp microscopy, can be clearly seen.10,11

In vivo confocal microscopy (IVCM) was used by Martone et al.12 to examine one eye with PEX syndrome, and noncontact IVCM was used by Sbeity et al.13 to study PEX, PEX-suspect, and normal eyes. However, there has not been a detailed and quantitative study of the morphologic changes in the corneas of eyes with PEX syndrome.

Thus, the purpose of this study was to examine the underlying pathogenesis of PEX keratopathy and to obtain evidence to explain clinical findings such as the decreased corneal sensitivities observed in patients with PEX syndrome. To accomplish this, we used IVCM to determine cell densities in different corneal layers of eyes with PEX syndrome and their clinically unaffected fellow eyes. These findings were compared with those in normal control eyes. The nerve densities in the subbasal layer were also analyzed, and their relationship with the alterations of clinical corneal sensitivity were analyzed.
SUBJECTS AND METHODS

Subjects

We studied 27 patients (16 men, 11 women; mean age, 74.4 ± 6.3 years; age range, 65–90 years) with diagnoses of unilateral PEX syndrome. In all eyes, exfoliation material (XFM) was seen by slit-lamp microscopy at the pupillary border or on the anterior lens capsule. Eyes with PEX syndrome were placed in the PEX group, and clinically normal fellow eyes were placed in the PEX fellow eye group. Age and sex-matched normal subjects (16 men, 11 women; mean age, 72.7 ± 6.5 years; age range, 61–92 years) were also studied. One eye from the normal control group was randomly selected and used in the statistical analyses. Exclusion criteria included Stevens-Johnson syndrome, lymphoma, sarcoidosis, corneal dystrophy, injury, inflammation, systemic therapy with drugs with known corneal toxicity; treatment with topical anti-glaucoma drugs, steroids, or NSAIDs; contact lens wear; pre-therapy with drugs with known corneal toxicity; treatment with topical anti-glaucoma drugs, steroids, or NSAIDs; contact lens wear; previous ocular surgery; and other ophthalmic diseases.

The procedures used conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after an explanation of the nature and possible consequences of the procedures. The protocol used was approved by the Ethics Committee of Ehime University School of Medicine.

Corneal Sensitivity Measurements

Measurement of the corneal sensitivity was performed with a Cochet-Bonnet nylon thread esthesiometer, as described. The examination was begun with a 60-mm length of nylon filament applied perpendicularly to the central cornea, and the tests were continued by shortening the filament by 5 mm each time until the subject felt the contact of the filament. Each subject was measured twice with a between-test interval of at least 5 minutes, and the average of two measurements was used for the statistical analyses.

In Vivo Confocal Microscopy

IVCM was performed on all subjects with the Rostock Corneal Module of the Heidelberg Retina Tomograph II (HRT-II-RCM; Heidelberg Engineering). After topical anesthesia with 0.4% oxybuprocaine (Santen Pharmaceuticals, Osaka, Japan), the subject was positioned in the chin and forehead holder and instructed to look straight ahead at a target to make sure that the central cornea was scanned. The objective of the microscope was an immersion lens (magnification ×63; Zeiss, Chester, VA) covered by a polymethylmethacrylate cap (TomoCap; Heidelberg Engineering). Comfort gel (Bausch & Lomb, Berlin, Germany) was used to couple the applanating lens cap to the cornea. The polymethylmethacrylate cap was applanated onto the center of the cornea by adjusting the controller, and in vivo digital images of the cornea were seen on the monitor screen. When the first layer of superficial epithelial cells was seen, the digital micrometer gauge was set to zero, and then a sequence of images was recorded as the focal plane was gradually moved toward the endothelium. Each subject underwent scanning three times at intervals of at least 15 minutes.

The laser source of the HRT-II RCM is a diode laser with a wavelength of 670 nm. Two-dimensional images consisting of 384 × 384 pixels covering an area of 400 × 400 μm were recorded. The digital resolution was 1.04 μm/pixel transversally and 2 μm/pixel longitudinally, as stated by the manufacturer.

Image Analyses

Central corneal images of all subjects were taken, and the three best-focused images from the superficial epithelium, basal epithelium, subbasal nerve plexus, anterior stroma, intermediate stroma, posterior stroma, and endothelium were selected for analyses. The selected images were randomly presented to two masked observers (XZ, SO) for evaluation. All data are presented as averages of three images.

Cell Density Analyses

Morphologic characteristics and densities in the different layers of the cornea in the PEX and PEX fellow eyes were assessed and compared with those of normal controls. Superficial epithelial cells were identified as polygonal cells with clearly visible cell borders, bright cytoplasm, and dark nuclei. Basal epithelial cells were identified as the layer just above the amorphous-appearing Bowman membrane. Basal cells had bright borders, a uniform shape, and nonhomogeneous cytoplasm. The anterior stroma was identified as the first layer immediately beneath the Bowman membrane, and the posterior stroma was identified as the layer just anterior to the Descemet membrane and the endothelium. The intermediate stroma was defined as the layer halfway between the anterior and posterior stroma. The corneal endothelium consisted of a monolayer of regularly arranged hexagonal cells with dark borders and bright reflecting cytoplasm.

After selecting a frame of the image and manually marking the cells inside the frame (>50 cells), cell densities were calculated automatically by the software installed in the instrument. Cells partially contained in the area analyzed were counted only along the upper and right margins. The results are expressed in cells per square millimeter.

Analyses of Subbasal Nerve Plexus

The subbasal nerve plexus layer is located between the Bowman membrane and the basal epithelial layer through which numerous nerve fibers pass. The density and tortuosity of the subbasal nerve plexus were analyzed as described. Two parameters were analyzed: the long nerve fiber density (LNFD) was determined by dividing the number of long nerves by the image area (0.16 mm²), and the nerve branch density (NBD) was determined by dividing the total number of long nerves and their branches by the image area. Nerve tortuosity was classified into 4 gradings: grade 1 = approximately straight nerves; grade 4 = very tortuous nerves with significant convolutions throughout their course.

Statistical Analyses

Data were analyzed with statistical software (JMP, version 8.0 for Windows; SAS Japan Inc., Tokyo, Japan). All data are expressed as the mean ± SD. The differences of cell densities between PEX eyes and normal controls or between PEX fellow eyes and normal controls were evaluated with two-tailed Student’s t-tests. The differences of cell densities between PEX eyes and their fellow eyes were evaluated by paired t-tests. The Wilcoxon rank sum test was used to compare the values of corneal sensitivity, LNFD, NBD, and the nerve tortuosity between PEX patients and normal controls. Spearman’s correlation was used to determine the correlation among the parameters of basal epithelial cell density, subbasal nerve density, and corneal sensitivity. P < 0.05 was considered statistically significant.

RESULTS

The mean age was not significantly different between patients with PEX and normal controls (two-tailed Student’s t-tests, P = 0.725). Eyes with PEX showed typical whitish exfoliation material on the pupillary border or on the anterior lens capsule on slit-lamp examination. Pigmented keratoprecipitates and slight folding of Descemet membrane were also detected in some patients. Fellow eyes of PEX eyes and normal control eyes appeared normal by slit-lamp microscopy.

Corneal Sensitivity

The mean corneal sensitivity was 47.8 ± 5.6 mm for PEX eyes and 53.7 ± 4.9 mm for PEX fellow eyes. This difference was significant (P = 0.005; Wilcoxon rank sum test). Mean corneal
sensitivity was 55.6 ± 4.7 mm for the normal control subjects, and the corneas of eyes with PEX were significantly less sensitive than those of normal control eyes (P < 0.0001). The difference in corneal sensitivity between PEX fellow eyes and normal controls was not significant (P = 0.378).

**Cell Densities**

The density of the corneal superficial epithelial cells was 872.6 ± 95.3 cells/mm², and that for the basal epithelial cells was 4829.7 ± 462.1 cells/mm² in PEX eyes. Densities for the corresponding layers in PEX fellow eyes were 910.4 ± 80.8 cells/mm² and 4996.7 ± 438.7 cells/mm², and densities for the normal control eyes were 886.4 ± 101.7 cells/mm² and 5446.4 ± 639.9 cells/mm². The density of the basal epithelial cells was significantly lower for PEX eyes and PEX fellow eyes than for the control eyes (P = 0.003 and P = 0.015, respectively; two-tailed Student’s t-tests; Fig. 1). The difference in the density of the basal epithelial cells between PEX eyes and PEX fellow eyes was not significant (P = 0.589; paired t-test). Differences in the densities of the superficial epithelial cells among the three experimental groups also were not significant (Fig. 1).

Densities of the cells in the three stromal layers of PEX eyes, PEX fellow eyes, and normal control eyes are shown in Figure 2. Compared with normal controls, the cell densities of PEX eyes were significantly lower in all three layers of the stroma (anterior stroma, P = 0.007; intermediate stroma, P = 0.009; posterior stroma, P = 0.012; two-tailed Student’s t-tests). The densities in these three stromal layers in PEX fellow eyes were also lower, but the decrease was not significant (P = 0.196; P = 0.261; P = 0.08; respectively; Fig. 2).

Endothelial cell densities were 2240.7 ± 236.6 cells/mm², 2386.6 ± 200.8 cells/mm², and 2738.7 ± 233.2 cells/mm² for PEX eyes, PEX fellow eyes, and normal eyes, respectively. Differences between PEX eyes and normal controls (P < 0.0001; two-tailed Student’s t-test; Fig. 1) and between PEX fellow eyes and normal controls were significant (P = 0.001). The difference in endothelial cell density between PEX and PEX fellow eyes was not significant (P = 0.754; paired t-test).

There was a higher degree of pleomorphism and polymegethism in PEX eyes than in control eyes. The coefficient of variation (CV) of the cell area was 45.2% ± 8.7%, and the percentage of hexagonal cells (HEX) in PEX eyes was 30.5% ± 10.3%. Both values are significantly different from those of normal control eyes (CV, 30.6% ± 5.6%, P = 0.016; HEX, 50.3% ± 6.8%, P = 0.008; two-tailed Student’s t-test). PEX fellow eyes also showed a similar tendency of increased pleomorphism and polymegethism, but the differences were not statistically significant.

**Subbasal Nerve Plexus**

The LNFD and NBD were significantly decreased in PEX eyes (17.4 ± 6.3 and 32.2 ± 8.3 nerves/mm², respectively) compared with those in normal controls (35.9 ± 8.2 and 72.2 ± 8.8 nerves/mm²; P < 0.0001 and P < 0.0001, respectively; Wilcoxon rank sum test; Fig. 3). PEX fellow eyes also had decreased LNFD and NBD, but these changes were not
significantly different from those of the controls (31.5 ± 7.8 and 69.9±9.4 nerves/mm²; P = 0.093 and P = 0.301).

Confocal images of PEX eyes showed extremely tortuous nerve fibers, thinning of nerves, short nerve sprouts, fewer branches from the main nerve trunk, and highly reflective inflammatory infiltrates in close vicinity of the subbasal nerves. Representative confocal images of the three groups are shown in Figure 4. In PEX eyes, 85.2% (23 of 27 eyes) had grade 3 subbasal nerve tortuosity, and the degree of tortuosity in PEX eyes was significantly higher than that of the controls (3.2 ± 0.7 vs. 1.6 ± 0.6; P < 0.0001; Wilcoxon rank sum test). The degree of tortuosity in PEX fellow eyes was also greater than that of normal controls, although the difference was not significant (2.1 ± 0.9 vs. 1.6 ± 0.6; P = 0.054).

It was our impression that PEX eyes had more inflammatory cells, including dendritic cells, infiltrating the subbasal cell layer and anterior stroma, and these changes were more severe in eyes with decreased subbasal nerve densities and lower corneal sensitivities (Fig. 4).

**Correlation between Corneal Sensitivity and Subbasal Nerve Density and Basal Epithelial Cell Density**

Spearman’s correlation analyses showed that there was a significant positive correlation between corneal sensitivity and the subbasal nerve densities (LNFD, r = 0.764, P < 0.0001; NBD, r = 0.634, P < 0.0001; Spearman correlation coefficient). Corneal sensitivity was also significantly and positively correlated with basal epithelial cell density and significantly and negatively correlated with subbasal nerve tortuosity (Table 1).

**Confocal Microscopic Detection of Hyperreflective Material**

IVCM showed hyperreflective material, probably XFM, in the subbasal epithelial layer or the anterior stroma of 22 of the 27 PEX eyes (81.5%). The hyperreflective material was also observed abundantly in the endothelia of all PEX eyes. Five of 27 (18.5%) PEX fellow eyes showed hyperreflective deposits in the subbasal epithelial layer or anterior stroma, and 14 of 27 (51.9%) had endothelial surface deposits of hyperreflective material. In sharp contrast, none of the normal eyes showed hyperreflective material in the subbasal epithelial or anterior cornea.

**TABLE 1.** Correlation among Corneal Sensitivity, Subbasal Nerve Fiber Density, Tortuosity, and Basal Epithelial Cell Density

<table>
<thead>
<tr>
<th>Corneal Sensitivity</th>
<th>Spearman Correlation Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long nerve fiber density</td>
<td>0.7640</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Nerve branch density</td>
<td>0.6341</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Subbasal nerve fiber tortuosity</td>
<td>-0.8250</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Basal epithelial cell density</td>
<td>0.6971</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

* Statistically significant.
stromal layers, and only two (7.4%) had a small amount of hyperreflective material on the endothelial surface (Figs. 5, 6).

**DISCUSSION**

The manifestations of PEX syndrome in the anterior segment are widely known to affect intraocular surgery with poor mydriasis and intensive postoperative inflammation. The fact that aggregates of XFM can be identified in autopsy specimens of the heart, lung, liver, kidney, and other organs in patients with ocular PEX suggests that the ocular PEX syndrome is part of a general systemic disorder. In fact, PEX syndrome has been reported to be associated with cardiovascular diseases, chronic cerebral disorders, Alzheimer disease, and acute cerebrovascular events. Two single nucleotide polymorphisms in the lysyl oxidase-like 1 (LOXL1) gene have been recently identified as strong genetic risk factors for PEX syndrome and PEX glaucoma.

IVCM with the HRTII-RCM provides a new imaging method that allows rapid, noninvasive, high-resolution, and microstruc-
tural examination of the cornea. Only two studies have used IVCM to study the corneas of patients with PEX syndrome. Martone et al. reported the findings in one case, and they reported that IVCM can detect hyperreflective deposits and dendritic cells infiltrating the basal epithelial cell layer. Fibrillar subepithelial structures were found, and the endothelial layer showed cellular anomalies. In a prospective observational case series, Sbeity et al. used noncontact IVCM to detect XFM on the lens surfaces and corneal endothelia of PEX eyes and their fellow eyes.

Our study was the first to use IVCM to investigate cell densities in different layers of the cornea and to determine alterations of subbasal nerve density and tortuosity in PEX and PEX fellow eyes. Our results showed a significant decrease in the densities of the corneal endothelial cells in PEX eyes and their fellow eyes, which is in agreement with earlier observations by specular microscopy. In addition, the clear confocal images allowed us to detect pleomorphisms and polymegathisms of the endothelial cells. All PEX eyes and 51.9% of PEX fellow eyes showed deposits of hyperreflective material in the endothelium, indicative of either pigment granules or XFM. In agreement with Sbeity et al., we believe that the pleomorphic and irregular deposits found on the corneal endothelium most likely represent XFM rather than pigment granules, which are round and uniform in size. In addition, a number of patients who had no visible pigment keratoprecipitates on slit-lamp microscopy were found to have abundant large and irregular hyperreflective deposits on the endothelium in the confocal images.

PEX syndrome–associated corneal endotheliopathy has been suggested to be caused by one or a combination of the following alterations: hypoxic changes in the anterior chamber, accumulation of extracellular matrix, fibroblastic changes of the endothelium, and increased concentration of TGF-β. Our confocal microscopic findings suggest that the XFM, possibly at different stages of the normal course of PEX, may be deposited on the endothelium or may migrate from the endothelial cells that undergo fibroblastic changes. Our findings also showed that hyperreflective materials are found not only on the endothelium of PEX eyes but also in their fellow eyes, indicating that the fellow eyes might be at a preclinical stage of PEX syndrome. A bilateral decrease in the endothelial cell counts and morphologic alterations of endothelium support the idea that PEX is a binocular and systemic abnormality. Patients with unilateral PEX syndrome may have asymmetric manifestation of this slowly progressing disease.

Of clinical significance was our finding that the decreased stromal cell densities observed by IVCM could possibly explain the report that the central corneas of PEX eyes were thinner than those of normal subjects. The pathogenesis of the decrease of stromal cell density in PEX eyes warrants future study. Because XFM deposits were simultaneously observed in the anterior stroma of PEX eyes, we suggest that the XFM may be somehow causative for this alteration, perhaps by inducing apoptosis of the keratocytes. Other pathogenic factors, such as altered levels of cytokines or chemokines in the cornea, could also be responsible, and this definitely warrants future investigation. In addition, PEX fellow eyes also had lower cell counts in the stroma, although the difference was not statistically significant. We suggest that the cause of the binocular differences in our study might have been because the two eyes were at different stages of the PEX process, and PEX fellow eyes may still be at a preclinical stage of PEX syndrome.

Other important findings were found in the subbasal nerve plexus. Our results showed that the subbasal nerve density was significantly lower and the nerves were mostly tortuous, with beading and thinning in PEX eyes. Interestingly, PEX fellow eyes also had similar alterations, though the changes were not significant. These findings support the idea that PEX syndrome is a binocular abnormality that is expressed in both eyes but to different degrees. The important clinical significance of our study is that our correlation analyses showed that the decreased subbasal nerve density and increased tortuosity were significantly correlated with decreased corneal sensitivity. These results provide evidence, for the first time, that the cause of the decreased corneal sensitivity in eyes with PEX syndrome is the decreased subbasal nerve density. For patients with PEX syndrome, it would be practical and feasible to examine corneal sensitivity to assess the severity of PEX keratopathy and perhaps to predict the progression of PEX syndrome. In addition, detection of the morphologic changes in cell densities and subbasal nerve abnormalities by IVCM in the fellow eyes indicates that it is a sensitive tool for the diagnosis of preclinical stage of PEX syndrome. Our findings showed that PEX keratopathy may develop before any clinically visible XFM deposits are detected on the lens capsule or iris. If these findings are confirmed, then keratopathy may be the first event of the ocular complications of PEX syndrome. These findings also indicate that clinically unaffected fellow eyes of patients with PEX syndrome are probably at risk for PEX syndrome, and more frequent ophthalmologic examinations are necessary.

This study has increased our understanding of the keratopathy of this most likely systemic abnormality. Whether the alternations of the subbasal corneal nerves are primary or secondary changes of the disease must be determined. Because of the increase in the elastic microfibril components and imbalances in the matrix metalloproteinases (MMPs) and tissue inhibitors of MMP in eyes with PEX syndrome, PEX fibrils accumulate in the tissues. Our findings that XFM deposits were frequently observed close to the subbasal epithelial layer or anterior stroma support the idea that besides an abnormal aggregation of elastic microfibrils into exfoliation fibers (the elastic microfibril hypothesis), other extracellular matrix components, such as basement membrane components, may possibly interact and become incorporated into the composite XFM (the basement membrane hypothesis). In addition, our observation of an infiltration of dendritic cells in close vicinity of the subbasal nerve plexus layer indicates the possibility that accumulation of extracellular XFM may induce inflammatory responses, which then recruit antigen-presenting cells such as immunocompetent dendritic cells. This excessive deposition of XFM and infiltration of dendritic cells may play a role in the neuropathy of the subbasal nerve plexus, resulting in decreased corneal sensitivity in patients with PEX syndrome.

Some limitations were present this study. First, the IVCM scans a very small area of the cornea, which may generate biases among different portions of scanning of different groups. As mentioned, efforts were taken to scan the center of the cornea of each subject. In addition, we also confirmed our findings by scanning the midperipheral and peripheral portions of the cornea (data not shown).

Second, IVCM images may not represent the true histologic changes of the cornea. By applying the same criteria for image evaluation, we can conclude that the differences between the studied groups were still detected. Furthermore, it was our impression that fewer keratocytes were seen in the stromas of corneal specimens obtained from PEX syndrome patients with penetrating keratoplasty.

Future investigations, including a thorough and quantitative analysis of the exfoliation material by confocal imaging, are needed. In addition, the correlations between IVCM findings with endothelial barrier function should be determined. If the confocal findings can provide clues for preclinical stages of endothelial barrier dysfunction of the cornea in PEX syndrome, their clinical significance can be used in designing an early treatment protocol.
In summary, our study demonstrated that eyes with PEX syndrome have decreased cell densities in the cornea. The subbasal nerve density was also significantly decreased, and this was significantly correlated with clinically decreased corneal sensitivity. Our study sheds light on understanding the cause of impaired corneal sensitivity in patients with PEX syndrome. The PEX syndrome is probably a bilateral event in which the keratopathy of the fellow eye also must be observed.

References