Original Article

Abnormalities of tear function in patients with pseudoexfoliation

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Abstract

Background and Aim: Pseudoexfoliation (PEX) seems to affect the tear secretion and tear film stability by altering cell morphology in conjunctiva. We aimed to study the abnormalities of tear secretion and tear film that can occur in patients with PEX material on lens.

Methods: In this prospective non-randomized study, Group 1 consisted of 30 eyes of 15 normal subjects without PEX material on lens serving as controls and Group 2 consisted of 43 eyes of 30 patients with PEX at least in one eye. Patients with ocular surface disorder, PEX glaucoma, previous ocular surgeries and adnexal abnormalities were excluded. To study the tear function, Schirmer's two and tear film break-up time (TBUT) were performed in all eyes.

Results: Average Schirmer's and TBUT in Group 1 were 22.05 ± 4.4 mm and 14.75 ± 2.5 s respectively, whereas in Group 2 they were 10.6 ± 7 mm and 5.6 ± 2.8 s and the differences were clinically significant ($P < 0.001$). Within Group 2, among the 17 unilateral PEX syndrome the average Schirmer's and TBUT in eyes with PEX material was 11.7 ± 6.4 mm and 6.4 ± 1.8 s respectively whereas in fellow uninvolved eye they were 12.9 ± 5.9 mm and 6.6 ± 2.1 s. This difference was not statistically significant ($P = 0.065$).

Conclusion: PEX syndrome causes unstable tear film and reduced tear secretion.

Key words: Dry eye, pseudoexfoliation, Schirmer's test, tear function

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INTRODUCTION

John G. Lindberg, in 1914, was first to describe pseudoexfoliation (PEX). He found that this phenomenon was more common in cataractous eyes and in patients with glaucoma.[1] Since its discovery, PEX syndrome has undergone extensive research for its unique structure and its effects on the eye. Patients of PEX can develop corneal endotheliopathy, sphincter atrophy of the iris, poor mydriasis, iris neovascularization, transillumination defects and flaky material on the lens capsule, zonular dialysis and spontaneous dislocation of the lens. They are also more predisposed to goblet cell loss and dry eye. Cataract surgery and glaucoma medications can induce the risk of dry eye in such patients.[2]

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Our study has assessed the tear function abnormalities in PEX and compare the findings in eyes without PEX.

MATERIALS AND METHODS

In this prospective non-randomized study, Group 1 consisted of 30 eyes of 15 normal subjects and Group 2 consisted of 30 patients with PEX syndrome at least in one eye. The study was approved by Institute Ethics Committee. Patients diagnosed to have PEX syndrome in the lens or iris were included in Group 2 of the study. Patients with ocular surface disorder, PEX glaucoma, previous ocular surgeries and adnexal abnormalities were excluded. The demographic profile, slit lamp examination for zones of pseudoexfoliative material, laterality of PEX and grading of cataract were documented. To detect tear film changes, Schirmer's 2 test and tear film break up time (TBUT) were performed.

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Schirmer's 2 test

After instilling a drop of proparacaine in the eyes and waiting for 30 s, the eyelids were gently wiped with cotton. About five mm of Schirmer's strip was bent and placed in the inferior fornix between the medial two-third and lateral one-third and readings are measured after 5 min. The length of the wetted filter paper was directly read on the scale. The value of <10 mm was considered as abnormal and was suggestive of dry eye.

TBUT

The TBUT is an important clinical test for estimating tear film stability. Tear break-up was measured after instilling fluorescein dye and observing with the use of a blue exciter and yellow barrier filter, while the patient refrains from blinking. The TBUT is the time which elapses from the last blink to the first appearance of a dark spot in the fluorescein-stained film and is seen to evolve in a characteristic way with time. The normal TBUT varies between individuals and also varies in the same person at different times of the day. In general, a break-up time of <10 s suggests an unstable tear film.

Conjunctival impression cytology

The conjunctival impression cytology (CIC) was studied under light microscopy. Nelson grading was used to grade the slides.

Grade 1

The epithelial cells are small with eosinophilic staining cytoplasm. The nuclei are large and basophilic with nucleocytoplasmic ratio of 1:2. The goblet cells are abundant, plump and oval and have intensely periodic acid Schiff (PAS) reaction positive cytoplasm.

Grade 2

The epithelial cells are larger and polygonal and occasionally multinucleated with variably staining cytoplasm. The nuclei are small with nucleocytoplasmic ratio of 1:4 to 1:5. The goblet cells are markedly decreased, less intensely PAS positive with poorly defined cellular borders.

Grade 3

The epithelial cells are large and polygonal with basophilic staining cytoplasm. The nuclei are small and pyknotic and in many cells completely absent. The nucleocytoplasmic ratio is more than 1:6. Goblet cells are completely absent.[3]

Statistical analysis

Statistical analysis in this study was performed using GraphPad Instat (Version 3, USA) software. The results of Schirmer's test and TBUT were analyzed by unpaired Student's *t*-test.

RESULTS

The study included 30 eyes of 15 normal subjects and 43 eyes of 30 patients with PEX. Seventeen (56.6%) of the 30 patients in the study group had unilateral PEX and the rest 13 (43.4%) had bilateral presentation. The mean age of the patients in Group 1 and Group 2 was 59.4 ± 6.1 years (range 51-72) and 66.27 ± 6.7 years (range 55-80) respectively.

Among the eyes with PEX, 67.4% of cases had PEX material in both zone 1 and zone 3. 20.9% of cases had only in zone 1 and 13.9% had only in zone 3. Hence, 81.3% of case had PEX material in zone 3 [Figures 1 and 2]. The average mydriasis in eyes with PEX syndrome was 4.9 mm and in eyes without PEX syndrome was 5.5 mm.

Average Schirmer's and TBUT in Group 1 were 22.05 ± 4.4 mm and 14.75 ± 2.5 s respectively whereas in Group 2 the values were 10.6 ± 7 mm and 5.6 ± 2.8 s and the differences were statistically significant ($P < 0.001$) [Table 1]. Within Group 2, among the 17 unilateral PEX syndrome the average Schirmer's and TBUT in eyes with PEX material was 11.7 ± 6.4 mm and 6.4 s respectively whereas in fellow uninvolved eyes the values were 12.9 ± 5.9 mm and 6.6 s. This difference was not statistically significant ($P = 0.065$) [Table 1].

In Group 1, CIC score was Stage 1-66.7%, Stage 2-33.3%, Stage 3-0% which was significantly lower when

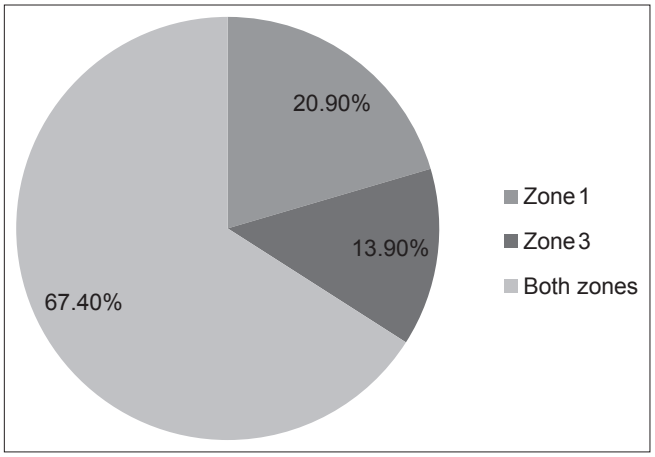

Figure 1: Distribution of pseudoexfoliative material in different zones of the lens

Table 1: Schirmer's test and TBUT in eyes with and without PEX syndrome

Parameter	Group 1 (controls)	Group 2	Group 2 PEX eyes only	Group 2 non-PEX eyes only
Schirmer's test (mm)	22.05±4.4	10.6±7*	11.7±6.4	12.9±5.9
TBUT (s)	14.75±2.5	5.6±2.8*	6.4±1.8	6.6±2.1

TBUT: Tear film break-up time, PEX: Pseudoexfoliation, *: $P<0.001$

compared to Group 2. In eyes with PEX, 60% had Stage 3 cytology with total loss of goblet cells, 37.2% had Stage 2 and 2.3% had Stage 1 [Figure 3].

DISCUSSION

The present study was conducted to assess the tear film changes in eyes with PEX. These were compared to age-matched control eyes without PEX and also fellow uninvolved eyes of unilateral PEX patients. We did not include patients of PEX glaucoma as this condition and its treatment with anti-glaucoma medications are known to affect the ocular surface and influence the results. Only patients of similar age and gender were included in the control group to prevent the results being influenced by the decreased tear function produced by increasing age.

The PEX syndrome is characterized by the widespread production and progressive accumulation of an abnormal extracellular fibrillar material in many ocular and extraocular tissues, including skin and connective tissue portions of various visceral organs. In India, epidemiological studies have revealed the prevalence of PEX to range from 3% to 10% and this increases progressively after 50 years.[4] Some investigators have found a greater incidence in females while some found that PEX glaucoma is more common in males.[5]

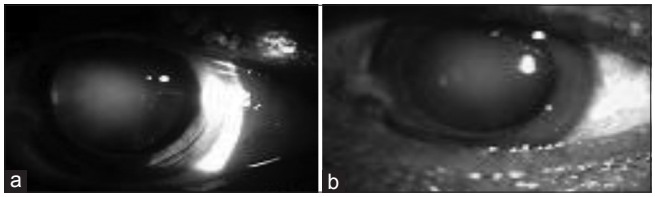

Figure 2: (a) Immature cataract with pseudoexfoliation. (b) Immature cataract without pseudoexfoliation

It has now become common knowledge that unilateral PEX syndrome is an early manifestation of bilateral disease. Tarkkanen found that 48% of the 418 patients of PEX studied had unilateral disease,[5] using transmission electron microscopy of conjunctival specimens and anterior lens capsule obtained during cataract surgery in 32 consecutive patients with unilateral PEX syndrome. Parekh *et al*. concluded the presence of PEX material in either of the samples in 26 of the 32 patients. The results suggest that the seemingly uninvolved eye in a patient with clinically unilateral PEX syndrome has an 81% likelihood of being affected ultrastructurally.[6] Other studies demonstrate that 43% of the fellow eyes develop manifestations of PEX syndrome over 6-7 years, 13% over 6 months to 16 years and 15% over 15 years.[7,8] In the present study, nearly 56.6% of PEX cases were unilateral and 43.4% of cases were bilateral in our study.

According to a study by Rao and Kaliaperumal, 95% of PEX syndrome can be successfully diagnosed prior to dilatation by the presence of PEX material in the pupillary ruff.[9] In this study, 67.4% of cases had PEX material in both zone 1 and zone 3. Out of which only 20.9% of cases had in zone 1 and 13.9% only in zone 3.

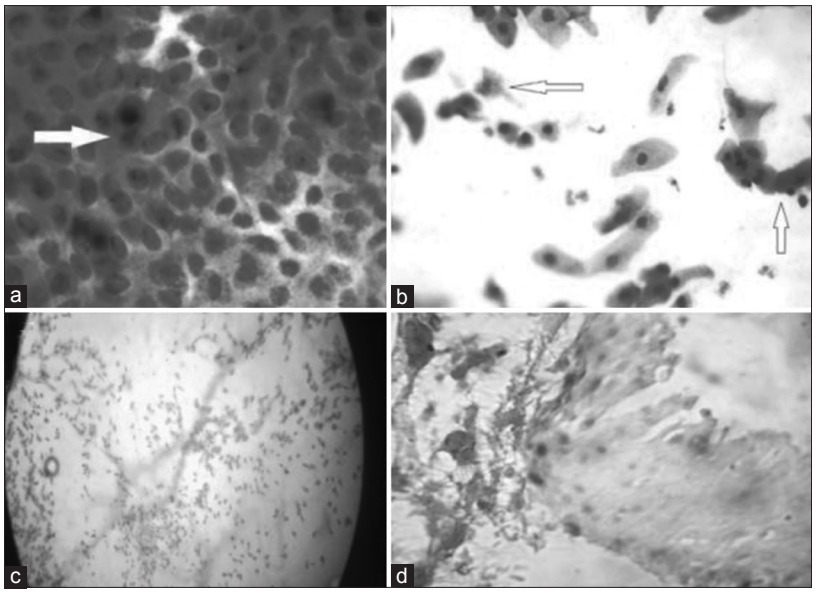

Figure 3: (a) Stage 1 - Conjunctival impression cytology in eyes with pseudoexfoliation syndrome showing plump periodic acid Schiff positive goblet cells amongst normal appearing epithelial cells. (b) Stage 2 - Conjunctival epithelial cells showing periodic acid Schiff positive material amidst pleomorphic epithelial cells with increased nuclear cytoplasmic ratio. (c) Stage 3 - Conjunctival impression cytology with total absence of goblet cells and polygonal epithelial cells with increased nuclear cytoplasmic ratio. (d) Conjunctival biopsy showing periodic acid Schiff positive material on the surface of the conjunctival epithelium

The accessory lacrimal glands of Krause and Wolfring located in the substantia propria of conjunctiva play a role in producing tears. Schirmer's 2 test (with corneal and conjunctival anesthesia) reflects mainly basic tear secretion and this test is reported to be more sensitive in the diagnosis of mild cases of keratoconjunctivitis sicca than Schirmer's test without anesthesia. The mucous layer of the tear film is secreted by the goblet cells also located in the conjunctiva. The TBUT evaluates the sufficiency of the mucous layer of tear film and shows that mucin secretion levels are affected by conjunctival goblet cell density.

In the present study, the mean Schirmer's value and TBUT were significantly lower in PEX patients when compared to the control group. Among the 17 unilateral PEX syndrome the same values in eyes with PEX material were less compared to the fellow uninvolved eyes. However, this difference was not found to be statistically significant. A study by Kozobolis *et al*. conducted a study in eyes with PEX syndrome and found a significant positive correlation between the conjunctival involvement in PEX and decreased tear secretion and tear film stability.[10] Similarly, in a study by Erdoğan *et al*., which included an additional group of PEX glaucoma, the mean values of TBUT and Schirmer's were lower in PEX and PEX glaucoma groups than in control group.[3]

Cho *et al*., in their study have shown that cataract surgery itself can induce dry eye to some extent which can be manifested in patients who already have symptoms of dry eye.[11] Anti-glaucoma medications like timolol can also lead to dry eye and corneal epithelial changes.[12] Again using such drugs in patients with PEX syndrome increases the likelihood of occurrence of symptoms of dry eye.

Defects in the zonular-elastic microfibrillar system might induce the PEX process.[13] Garner *et al*. took tissue from 8 patients between 75 and 88 years with PEX syndrome and subjected it to histopathological procedures which principally detected elastic fibers. PEX materials were found to be always cellular and eosinophilic that form tufts or delicate fibrils aligned perpendicular to the surface to which they are attached giving a characteristic carpet tuft or hoar frost appearance. In alcian blue/PAS stained section, PEX material appeared to have 2 components, magenta stained core with a coating of alcinophilic substance. It was also observed that the staining responses of zonular fibers were virtually identical to that of pseudoexfoliative material.[14]

Though, the report of the present study was similar to other studies in assessing tear function in PEX, we excluded patients of glaucoma with PEX. Moreover we compared the tear function tests in eyes with PEX versus fellow eyes without PEX, which was not assessed in other studies.

Tear is important for maintaining clarity of cornea, decreasing lenticular haziness, providing clear vision and improving defense mechanism of the eye. Hence, the reduced tear function leads to xerophthalmic manifestations in PEX, which will not only reduce the corneal and lenticular clarity and efficiency but also will decrease the ophthalmic local defense mechanism. Therefore, future studies in larger sample size are warranted to assess the impairment of local immune mechanisms in patients with PEX.

CONCLUSION

PEX is a common ophthalmological problem in India, which is more common in males. This study reveals that PEX syndrome causes tear film abnormalities and decrease in number of goblet cells which can even precede the appearance of PEX in lens or iris. Thus, the findings of the present study suggest the abnormality of tear physiology in patients with PEX syndrome. Future studies should address how the improvement in tear functions can help in the better management of PEX.

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