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Original Article / *Özgün Araştırma*

Evaluation of the Ocular Surface Parameters in Pseudoexfoliation Syndrome and Conjunctivochalasis

Psödoeksfoliasyon Sendromu ve Konjonktivaşalazisli Olgularda Oküler Yüzey Parametrelerinin Değerlendirilmesi

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Summary

Purpose: To evaluate the ocular surface parameters in pseudoexfoliative (PEX) patients with conjunctivochalasis (CCh).

Material and Method: Fifty-three eyes of 53 patients with PEX syndrome and 107 eyes of 107 subjects without PEX were enrolled in this study. All subjects were categorized into two groups according to the presence or absence of CCh. The ocular surface characteristics were evaluated with standard tear break-up time testing (BUT), lissamine green (LG) staining of the conjunctiva and cornea, and Schirmer I test with topical anesthesia. Patients were also assessed with the Ocular Surface Disease Index (OSDI) questionnaire with respect to the severity of their subjective symptoms. The Mann-Whitney U-test, student's t-test, and logistic regression analysis were used for statistical evaluations.

Results: Among the 160 subjects, 30 (56.6%) in the PEX group and 38 (35.5%) in the control group had CCh (p=0.018). Logistic regression adjusted to gender and age showed that eyes with PEX were 2.3 times (odds ratio, 95% CI: 1.1 to 4.6) more likely to develop CCh than eyes without PEX (p=0.015). There were significant differences in the BUT scores, Schirmer values, LG staining scores and the OSDI scores of patients who had PEX and those without PEX.

Discussion: The frequency of CCh is significantly higher in patients with PEX syndrome. Both PEX and CCh affect the ocular surface test results. It seems reasonable to evaluate and follow up PEX patients for CCh and ocular surface disease.. *(Turk J Ophthalmol 2012; 42: 332-5)*

Key Words: Pseudoexfoliation syndrome, conjunctivochalasis, ocular surface

Özet

Amaç: Psödoeksfoliasyon sendromu ve konjonktivaşalazisi olan hastalarda oküler yüzey parametrelerinin değerlendirilmesi.

Gereç ve Yöntem: Psödoeksfoliasyon sendromu olan 53 hastanın 53 gözü ve psödoeksfoliasyonu olmayan 107 hastanın 107 gözü çalışmaya dahil edildi. Tüm hastalar konjonktivaşalazisin varlığına göre iki alt gruba ayrıldı. Oküler yüzey parametreleri göz yaşı kırılma zamanı testi (BUT), topikal anestezi ile Schirmer testi ve lissamin yeşili (LG) ile kornea ve konjonktiva boyanması ile değerlendirildi. Ayrıca, semptomların şiddetinin değerlendirilmesi amacıyla hastalara oküler yüzey hastalık indeks (OSDI) skorlaması uygulandı. İstatistiksel analizde Mann-Whitney U testi, Student-t testi ve lojistik regresyon analizi kullanıldı.

Sonuçlar: Değerlendirmeye alınan 160 hastada, psödoeksfoliasyon sendromu bulunan hastaların 30'unda (%56,6), kontrol grubunun 38'inde (%35,5) konjonktivaşalazis saptandı (p=0,018). Lojistik regresyon analizinde yaş ve cinsiyet düzeltmesi yapıldığında, konjonktivaşalazis sıklığının psödoeksfoliasyonu olanlarda olmayanlara göre 2.3 kat (odds oranı, %95 CI: 1.1 to 4,6) daha fazla olduğu görüldü (p=0,015). Psödoeksfoliasyonu olan hastalar ile kontrol grubu arasında BUT skorları, Schirmer testi değerleri, LG boyanması ve OSDI skorları arasında istatistiksel olarak anlamlı fark saptandı.

Tartışma: Konjonktivaşalazis sıklığı psödoeksfoliasyon sendromlu hastalarda daha fazla görülmektedir. Hem psödoeksfoliasyon varlığı hem de konjonktivaşalazis oküler yüzey parametrelerini etkilemektedir. Psödoeksfoliasyon sendromlu olgular konjonktivaşalazis ve oküler yüzey hastalığı varlığı açısından değerlendirilmeli ve takipleri yapılmalıdır. *(Turk J Ophthalmol 2012; 42: 332-5)*

Anahtar Kelimeler: Psödoeksfoliasyon sendromu, konjonktivaşalazis, oküler yüzey

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Introduction

Pseudoexfoliation (PEX) syndrome is a common age-related condition and is characterized by the excessive synthesis and deposition of abnormal elastic fibrillar material in intra- and extraocular tissues. PEX is correlated with several ophthalmic conditions, including glaucoma,[1] cataract,[2] increased risk of intraoperative complications during cataract surgery,[3,4] decreased tear secretion and tear film stability[5] and changes in corneal sensitivity and dry eye findings.[6] PEX syndrome has been described as a specific type of stress-induced elastosis.[7] Dysregulated expression of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) have been implicated in many disease processes accompanied by abnormal matrix production, such as proliferative vitreoretinopathy,[8] secondary cataract formation,[9] the pathogenesis of pterygia[10,11] and conjunctivochalasis (CCh).[12]

The purpose of this study was to determine the association between PEX syndrome and CCh and the influence of PEX on ocular surface parameters, employment of ocular surface disease index (OSDI) scores, tear break-up time testing (BUT), lissamine green (LG) staining and Schirmer testing.

Materials and Methods

One hundred and sixty eyes of 160 patients with or without PEX syndrome were included in this prospective study. The Tenets of the Declaration of Helsinki were followed throughout the study. Informed consent was obtained from all patients and the study was carried out with approval from the Institutional Review Board. All patients underwent a complete ophthalmic examination including best-corrected visual acuity testing, slit-lamp examination, intraocular pressure determination and fundus examination. Subjects were categorized into two groups on the basis of the presence or absence of PEX. A diagnosis of PEX syndrome was based on the characteristic PEX material on the anterior lens surface following mydriasis. Patients without PEX features constituted the control group. Both the PEX syndrome and control groups were categorized into two subgroups according to the presence or absence of CCh. CCh was defined by the presence of a redundant conjunctival fold on the inferior eyelid margin and was graded according to the severity of involvement.[13] Grade 1 CCh was defined as the presence of redundant conjunctiva at the temporal location only; Grade 2 CCh was defined as the presence of redundant conjunctiva at both temporal and nasal inferior lid margins; and Grade 3 CCh was defined as the presence of redundant conjunctiva along the entire inferior lid margin. Subjects who used topical IOP-lowering drugs or topical artificial tears, who had a history of ocular surface surgery or ocular trauma, who had ocular surface disorders, and who were using contact lenses were excluded from the study.

The ocular surface characteristics of all patients were evaluated with standard tear break-up time testing (BUT), LG staining of the conjunctiva and cornea, and Schirmer I test with topical anesthesia. The tests were performed in exactly the same order for all subjects in one session, and all patients were examined under the same temperature and humidity conditions. BUT measurements were obtained after an application of sterile fluorescein strips moistened with preservative-free lubricating eye drops (Refresh eye drops, Allergan Inc., Irvine, California). The patient was instructed to blink several times for a few seconds and the BUT was measured as the time between the last blink and the appearance of the first corneal dry spot. The Schirmer I test was performed after the instillation of a topical anesthetic (proparacaine hydrochloride 0.5%, Alcaine, Alcon Laboratories Inc., Belgium). Sterilized strips of filter paper were placed in the inferior fornix, between the lateral third and the middle third of the eyelid, for five minutes with the patient looking straight ahead. The ocular surface staining was evaluated after an application of an LG strip in the lower conjunctival sac. Using white light, the staining of the cornea and the conjunctiva was graded on a scale of 0 to 5 according to the Oxford Scheme.[14]

Patients were also assessed with the Ocular Surface Disease Index (OSDI, Allergan Inc, Irvine, California) questionnaire on the basis of the severity of their subjective symptoms. The OSDI was developed to provide a rapid assessment of the severity of symptoms of OSD and their impact on vision-related function.[15] Briefly, the twelve items of the OSDI questionnaire are graded on a scale of 0-4: 0 indicates the presence of symptoms none of the time; 1= some of the time; 2= half of the time; 3= most of the time; 4= all the time. Total OSDI scores were calculated for each patient using the formula: OSDI= (sum of scores for all questions answered) x 25/ (total number of questions answered). Thus, the OSDI was scored on a scale of 0 to 100.

Data analysis was performed using the SPSS 15.0 (Statistical Package for Social Sciences, SPSS Inc. Chicago, IL, United States) software package. The Mann-Whitney U-test was used to compare ocular surface parameters between the subgroups of CCh subjects for PEX syndrome and the control group. A p-value of 0.05 was accepted as statistically significant. Logistic regression was implemented for an analysis of PEX in association with the development of CCh.

Results

Fifty-three eyes of 53 patients with PEX syndrome (26 female, 27 male) and 107 eyes of 107 normal subjects (58 female, 49 male) were enrolled in this prospective study. The mean age of the patients with PEX and without PEX syndrome was 65.2±5.4 years (range= 52-83 years) and 64.7±5.4 years (range= 57-79 years), respectively. There were no significant differences with respect to age (p=0.601, t-test) and sex (p=0.539, chi-square test) between the two groups. Among the 160 subjects, 30 (56.6%) in the PEX group and 38 (35.5%) in the control

group had CCh (p=0.018). Among the 30 subjects with CCh in the PEX group, 13 had Grade 1 and 17 had Grade 2 CCh. In the control group, 24 had Grade 1 and 14 had Grade 2 CCh. Comparison of ocular surface parameters of patients with and without CCh in the PEX and control groups are summarized in Table 1 and Table 2. Logistic regression adjusted to gender and age showed that eyes with PEX were 2.3 times (odds ratio, 95% CI: 1.1 to 4.6) more likely to develop CCh than eyes without PEX (p=0.015). CCh is also associated with aging (OR=1.07, 95% CI: 1.0 to 1.1, p=0.021), but not associated with gender (OR=1.06, 95% CI: 0.5 to 2.0, p=0.848).

Discussion

One of the findings of this study is that there may be an association between PEX syndrome and development of CCh. We demonstrated that eyes with PEX were 2.3 times more likely to develop CCh than eyes without PEX. When the pathophysiology of PEX is evaluated, studies have shown that complex changes in the MMP-TIMP balance and reduced MMP activity in aqueous humor may promote abnormal matrix accumulation.[16] In addition, elevated levels of fibrogenic transforming growth factor-β1 (TGF- β1),[17] decreases in antioxidative factors, increases in oxidative stress markers,[18] and deficiencies in clusterin[19] have been shown in aqueous humor in patients with PEX. These findings suggest that PEX syndrome has been described as a specific type of stress-induced elastosis, elastic microfibrillopathy with the excessive production and abnormal aggregation of elastic microfibril components.[19] MMPs and TIMPs participate in connective tissue degradation and remodelling. An increase of proteases over their inhibitors is associated with abnormal matrix degradation. Li et al.[12] suggested that the ratio between MMPs and TIMPs produced by CCh fibroblasts is higher than those produced by normal conjunctival fibroblasts. Meller et al.[20] found mRNA and protein overexpression of MMP-1 and MMP-3 in CCh fibroblasts and increased expression of MMPs with inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). They suggested that the ocular surface inflammation might stimulate collagenolytic action that may be linked to elastotic degeneration of conjunctiva.

CCh is more prevalent in older people and it has been reported to be one of the age-related diseases of the eye. Mimura et al.[21] suggested that the prevalence of CCh increases dramatically with age (61.5% between 31 to 40 years, 100% 91 to 100 years). In an epidemiologic study performed among Chinese patients, the prevalence of CCh was found 44% of the time, and it was confirmed that CCh is a common eye disease in the elderly population.[22] In our study, logistic regression showed that aging increases the risk of CCh 1.07 times. However, aging was not found to be as strong risk factor as PEX in the development of CCh.

In our study, we were able to demonstrate significant differences in several ocular surface test results of patients with PEX and CCh compared to the control group. These differences were more evident in Grade 2 than in Grade 1 CCh. Thus, our results suggest that PEX may be an important co-pathogenetic factor in the deterioration of ocular surface tests results in patients with CCh. Decreased tear secretion and tear film stability in patients with PEX have been reported in previous studies.[5,6,23,24] In these studies, both Schirmer test and BUT values were significantly lower in the PEX patients than in patients without PEX. It has been suggested that PEX seems to alter goblet cell morphology and affects tear film stability. However, the changes in goblet cell morphology cannot explain the reduction of Schirmer test scores; studies have implicated that dry eye findings can be correlated with changes in corneal sensation.[6]

To our knowledge, this is the first study that investigates the relationship between PEX and CCh and the ocular surface changes in patients with CCh and PEX who do not use any antiglaucoma drugs. Our results suggest that CCh was significantly higher in PEX eyes compared with normal subjects. In addition, the presence and severity of CCh is associated with both objective and subjective alterations of ocular surface parameters in PEX patients. In conclusion, it seems reasonable to evaluate and follow up PEX patients for CCh and ocular surface disease. Further research is required to investigate the pathogenesis of CCh and the relationship between PEX syndrome and development of CCh.

Table 1. Comparison of ocular surface parameters patients with conjunctivochalasis in subjects with and without pseudoexfoliation as evaluated with Mann-Whitney U test

	Patients with PEX (n=30)	Patients without PEX (n=38)	p
BUT (second)	6.6±2.2	9.5±3.2	<0.001*
LG staining (grade)	1.3±0.9	0.8±0.9	0.082
Schirmer test (mm)	8.9±3.7	11.7±5.1	0.017*
OSDI score (points)	16.0±12.2	7.8±7.6	0.005*

*Indicates statistical significance from control subjects. BUT: Break-up time; LG: Lissamine green; OSDI: Ocular Surface Disease Index

Table 2. Comparison of ocular surface parameters patients without conjunctivochalasis in pseudoexfoliative and normal subjects as evaluated with Mann-Whitney U test

	Patients with PEX (n=23)	Patients without PEX (n=69)	p
BUT (second)	10.3±1.6	11.8±2.1	0.004*
LG staining (grade)	0.1±0.3	0.1±0.3	0.877
Schirmer test (mm)	12.7±2.6	16.0±3.5	<0.001*
OSDI score (points)	5.5±4.7	2.2±3.4	0.001*

*Indicates statistical significance from control subjects. BUT: Break-up time; LG: Lissamine green; OSDI: Ocular Surface Disease Index.

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