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The characteristics of pseudoexfoliation glaucoma in Ankara, the capital of Turkey

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Abstract

Purpose: The purpose of the study was to study the profile, clinical characteristics, and associated ocular and systemic comorbidities of pseudoexfoliation glaucoma (PEXG) in a cross-sectional multicentric study.

Methods: A total of 7500 eyes of 3750 subjects with glaucoma and suspected glaucoma underwent complete ophthalmic evaluation including history, visual acuity testing, slit-lamp examination, applanation tonometry, gonioscopy, and dilated examination of the optic disc and fundus between March 15, 2015, and May 16, 2015. Patients with PEXG were identified and their data were analyzed with respect to age, sex, intraocular pressure, ocular, and systemic diseases.

Results: A total of 1180 eyes of 666 subjects had PEXG (mean age: 72.7±9.0 years (38–97 years)). The percentage of the patients with PEXG within patients with glaucoma (4604 eyes of 2541 subjects) was 26.2%. Male-to-female ratio was 402/264 (60.3%/39.6%). One hundred and three patients (15.4%) had a positive family history. Four hundred and seventy-four patients (71.17%) had an additional systemic disease and the most prevalent comorbidities were hypertension and diabetes mellitus. Five hundred and fourteen patients (77.1%) had bilateral disease. The most common surgery performed in patients with PEXG was trabeculectomy (281 eyes; 23.8%). Six hundred and thirty-six patients (95.5%) had open angle glaucoma and 30 patients had closed angle glaucoma (4.5%).

Conclusion: PEXG is common in Turkey and one-quarter of glaucoma patients were found to have PEXG in this hospital-based study. In addition, with this multicentric study, we were able to document the demographic properties of PEXG in a large study population in the Central Anatolian metropolitan area.

Keywords: Characteristic; comorbidity; glaucoma; pseudoexfoliation.

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Pseudoexfoliation (PEX) syndrome is an idiopathic, generalized disorder that is characterized by the production and accumulation of a fibrillar extracellular material in many ocular tissues.^[1] Despite extensive research, the exact chemical nature of the fibrillar material is unknown. It is believed to be secreted multifocally; in the iris pigment epithelium, the ciliary epithelium, and the peripheral anterior lens epithelium.^[2]

PEX has a worldwide distribution and prevalence rates vary from 10 to 20% of the general population over the age of 60 years.^[3] To the best of our knowledge, there are three hospital-based epidemiologic studies on the prevalence or characteristics of PEX in Turkey. According to these studies, the prevalence of PEX in Turkey varies between 10.1% and 12.2%.^[4–6] Other hospital-based studies have shown a prevalence of 9.1% in Jordanians,^[7] 0.4% in Chinese,^[8] 6.5% in Pakistani,^[9] 7.4% in Indians,^[10] and 9.6% in Iranians.^[11] Kılıç et al.^[12] reported a new population-based study about the prevalence of PSX in Turkey. In this study, a total of 1107 individuals were evaluated and the authors reported a prevalence of 6.5% over 40 years of age.

PEX predisposes to a number of ocular comorbidities, the most severe being glaucoma, known as PEX glaucoma (PEXG).^[1,13] PEX is reported to be the most common identifiable cause of open angle glaucoma and PEXG accounts for approximately 25% of all open angle glaucomas worldwide.^[14,15] PEXG has a more serious clinical course and a worse prognosis than primary open angle glaucoma.^[16,17] It is believed that the fibrillary material moves into the aqueous humor and is carried to the trabecular meshwork, following the normal flow. Obstruction of the trabecular meshwork by this fibrillary material and pigment causes elevation of the intraocular pressure (IOP) leading to glaucoma.^[18] PEX is now suspected to be a systemic disorder and has been associated preliminarily with stroke, systemic hypertension, and myocardial infarction in some studies,^[19] whereas other studies did not report an association of PEX with cardiovascular or cerebrovascular morbidity or mortality.^[20,21] In fact, pseudoexfoliative like material has been found in lungs, skin, liver, heart, kidney, gallbladder, blood vessels, extraocular muscles, and meninges by electron microscopy.^[22]

This research is a part of a hospital-based cross-sectional, prospective, multicentric study designed to determine the characteristics of glaucoma in Ankara. Ankara is the capital and second largest city of Turkey, additionally, this city located in the center of country. The ophthalmology clinics that joined this study are reference centers accepting patients from different parts of the country. In this

study, we aimed to include a large population with glaucoma. For this current work, we analyzed only the data of the patients with PEXG and studied the profile, clinical characteristics, and associated ocular and systemic comorbidities of these patients.

Materials and Methods

This study was conducted between March 15, 2015, and May 16, 2015. The patients who presented and/or were referred to the glaucoma units of nine tertiary ophthalmology centers in Ankara and were diagnosed with glaucoma in either one eye or both eyes were included in the study. In brief, of the 3750 individuals with glaucoma and suspected glaucoma who underwent clinical examination, 2541 fulfilled the inclusion criteria of glaucoma and were eligible for the study. The study was carried out after approval by the Institutional Research and Ethics Board of the Gülhane Military Medical Academy (2015–27). Adherence to the Declaration of Helsinki for research involving human subjects was confirmed. Written informed consent was taken before proceeding for the recording of information and confidentiality was ensured.

Data were entered into a standardized form that had been constructed before the commencement of the study. All data collections were performed under the supervision of a glaucoma specialist. In this current study, patients with PEXG were identified and their data were analyzed with respect to age, sex, ocular parameters, and systemic diseases. We have to underline that the patients with only PEX (without glaucoma) were excluded from the study.

Examination Procedures

The examination included detailed medical and ophthalmic history; visual acuity testing using Snellen chart; slit-lamp examination; Goldmann applanation tonometry; gonioscopy using Goldmann three-mirror system; visual field examination (24–2 full-threshold test (stimulus size III) on a Humphrey automated perimeter (Humphrey Instruments, Inc., Dublin, California, USA); and dilated fundus examination. Visual field evaluation was performed to all patients except patients in category 3. Subjects with open angles had dilated their pupils with 5% phenylephrine and 1% tropicamide eye drops. Patients with typical pseudoexfoliative material on the anterior lens surface in either or both eyes were labeled as having PEX. Only eyes where the diagnosis was absolutely certain were included in the study. The aphakic and pseudophakic patients who were undoubtedly diagnosed as “PEXG” according to the reliable file data were included in this study. Stereoscopic evalua-

tion of the fundus and the optic disc with the +90 D lens was performed.

The patients who were found to have narrow or occludable angles on gonioscopy were first offered laser iridotomy treatment. The rest of the evaluation was then deferred to a later date. An angle was considered occludable if the pigmented trabecular meshwork was not visible in 180° or more of the angle.

The presence of glaucoma was defined under the guidelines according to the International Society for Geographical and Epidemiological Ophthalmology (ISGEO) Classification.^[23,24] Eyes with an ophthalmoscopic vertical cupping to disc ratio (C/D ratio) or C/D ratio asymmetry >97.5th percentile for the normal population, or a neuroretinal rim width reduced to <0.1 C/D ratio (between 11 and 1 o'clock or 5 and 7 o'clock) that also showed a definite visual field defect consistent with glaucoma was then assessed under category 1 criteria (structural and functional evidence). When perimetry was not possible, glaucoma was considered to be present if category 2 (advanced structural damage with unproven field loss) criteria were fulfilled (C/D ratio 99.5th percentile in the absence of any other explanation), or if category 3 (optic disc not seen, field test impossible) criteria were fulfilled when disc assessment was not possible (visual acuity <3/60 and IOP >99.5th percentile, or visual acuity <3/60 and the eye shows evidence of glaucoma filtering surgery, or medical records confirm glaucoma). Cutoff points for 97.5th and 99.5th percentile for ophthalmoscopic C/D ratio were accepted as 0.7 and 0.9, respectively. Cutoff points for 97.5th and 99.5th percentile of ophthalmoscopic C/D ratio asymmetry were accepted as 0.2 and 0.3. Cutoff point for 97.5th percentile of IOP was accepted as 22 mmHg.^[24,25]

Criteria for blindness were defined as best-corrected visual acuity less than 3/60 in the worse eye for monocular blindness and less than 3/60 in the better eye for binocular blindness.^[26,27]

For calculation of values such as mean IOP, C/D ratio, and index of visual field test, only one eye of each patient with bilateral disease was considered. In those with bilateral PEXG, only the worse eye was included. Worse eye was selected depending on the amount of visual field damage and C/D ratio. In patients with unilateral PEXG, the eye with PEXG was included.

Best-corrected visual acuity was measured with a decimal visual acuity chart and converted into logMAR units for analysis. Number of current glaucoma medications and previous glaucoma surgeries were recorded.

Data were entered and analyzed using the Statistical Program for Social Sciences (SPSS version 21.0 for Windows software). Chi-square test was used to compare discrete variables and Mann–Whitney U-test was used to compare ordinal data. $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 1180 eyes of 666 subjects had PEXG. Thus, the prevalence of PEXG in the patients with glaucoma (4604 eyes of 2541 subjects) was 26.2%.

Men outnumbered women in the PEXG patients. Four hundred and two cases (60.4%) were male and 264 cases (39.6%) female with a male-to-female ratio of 1.52/1.

Fifty-one patients (7.6%) were diagnosed with PEXG during this study period. The remaining 615 patients (97.5%) had the disease for more than 1 year. One hundred and three patients (15.4%) had a positive family history.

Mean age of the patients with PEXG was 72.7 ± 9.0 years (38–97 years). Table 1 shows age distribution of the patients. Prevalence of PEXG increased with age and was highest among subjects aged between 70 and 80 years. Large proportion of all PEXG patients (92.1%) was over 60 years old.

The big amount (71.2%) of the patients had additional systemic disease and the most prevalent comorbidities were hypertension (53.0%) and diabetes mellitus (18.4%). Table 2 shows the systemic diseases of the patients with PEXG.

Table 1. Age distribution in the study population

Age range (years)	No. of subjects	Percentage (%)
49>	7	1.1
50–59	45	6.8
60–69	184	27.6
70–79	259	38.9
80<	171	25.7

Table 2. The systemic diseases of the patients with pseudoexfoliation glaucoma

Age range (years)	No. of patients	Percentage (%)
Hypertension	353	53.0
Diabetes mellitus	123	18.4
Heart disease	104	15.6
Lung disease	45	6.7
Thyroid disease	29	4.3
Vasospastic disorder	8	1.2
Migraine	5	0.7
Anemia	3	0.4
Neurologic disorder	2	0.3

Table 3. The characteristics of patients with pseudoexfoliation glaucoma

	Mean	Median	Range
BCVA (LogMAR)	0.5±0.6	0.2	0-2
C/D	0.8±0.2	0.7	0.5-1.0
MD	-13.4±9.2	-8.3	-32.1-1.8
PSD	6.6±3.4	5.6	1.1-22.1
Number of drugs	1.7±1.6	2	0-5

BCVA: Best-corrected visual acuity; C/D: Cupping to disc ratio; MD: Mean deviation; PSD: Pattern standard deviation.

Table 4. The comparison of IOP, C/D ratio, and visual field test index between patients with unilateral and bilateral disease

	Bilateral	Unilateral	p-value*
IOP			
Mean	17.3±7.2	15.1±5.5	0.051
Median	16	15	
Minimum-maximum	3-47	6-50	
C/D			
Mean	0.7±0.3	0.7±0.4	0.67
Median	0.7	0.7	
Minimum-maximum	0.5-1.0	0.5-1.0	
MD			
Mean	-12.7±9.3	-10.7±8.5	0.022
Median	-10.2	-7.8	
Minimum-maximum	-31.8-1.4	-32.1-1.8	
PSD			
Mean	6.4±3.3	5.8±3.4	0.032
Median	6.6	5.1	
Minimum-maximum	1.4-14.6	1.1-16.2	

*Mann-Whitney U-test. IOP: Intraocular pressure; C/D: Cupping to disc ratio; MD: Mean deviation; PSD: Pattern standard deviation.

Six hundred and thirty-six patients (95.5%) had open angle glaucoma and 30 patients had closed angle glaucoma (4.5%). The gender distribution in patients with closed angle glaucoma (11 men and 19 women) was different from the patients with open angle glaucoma (393 men and 243 women) ($p=0.018$; $\chi^2=5.59$). The age, IOP, C/D ratio, and visual field test index were similar between open angle and closed angle glaucoma groups ($p>0.05$).

The mean IOP was 16.7 ± 6.5 mmHg, ranging from 3 to 56 mmHg (median: 16 mmHg). The IOP obtained from the medical history as the highest IOP was named as "maximum IOP". Maximum IOP was 30.96 ± 8.66 mmHg, ranging from 25 to 66 mmHg (median: 29.00 mmHg). Table 3 shows the overall characteristics of our patients.

Five hundred and fourteen patients (77.1%) (298 men and 216 women) had bilateral disease and 152 patients (22.9%) (100 men and 52 women) had unilateral disease. The

Table 5. The most common surgery types performed in patients with pseudoexfoliation glaucoma

	No. of eyes	Percentage (%)
Argon/selective laser trabeculoplasty	18	1.5
Trabeculectomy	308	26.1
Once only	281	
Twice or more	27	
Seton surgery	8	0.6
Cyclodestruction	5	0.4
Non-penetrative glaucoma surgery	8	0.6

men-women ratio in patients with unilateral PEXG (1.92/1) was significantly higher than the patients with bilateral disease (1.37/1) ($p=0.034$; $\chi^2=4.518$). The mean ages of patients with uni- and bilateral PEX were 69.6 ± 9.7 (range: 38-97 years; median: 69 years) and 74.2 ± 8.3 years (range: 38-92 years; median: 75 years), respectively, the difference being significant (Mann-Whitney U-test, $p\leq 0.001$). Table 4 shows the comparison of IOP, C/D ratio, and visual field test index between patients with unilateral and bilateral disease. IOP and C/D ratio were found to be similar between patients with unilateral and bilateral disease, however, visual field test index of patients with unilateral disease was better than bilateral disease.

The most common glaucoma surgery performed was trabeculectomy (281 eyes; 23.8%). Table 5 shows the most common surgery types performed in patients. Four hundred and fourteen eyes (35.1%) were pseudophakic and 9 eyes (0.8%) aphakic.

On the basis of ISGEO criteria, 431 (64.7%) of the patients were in category 1, 208 (31.2%) were in category 2, and 27 (4.0%) were in category 3. Monocular blindness was present in 168 (25.2%) patients, while binocular blindness was present in 17 (2.6%) patients.

Discussion

There are extensive variations in design or sampling methods of studies about PEX and PEXG. In addition, there are genetic, geographical, or racial variations in these study groups. Because of that, comparisons between studies on prevalence and characteristics of PEX are difficult. We want to emphasize that only the patients (1180 eyes of 666 patients) with PEXG were included in this study. We also determined a PEXG prevalence of 26.2% among patients with glaucoma, similar to other studies.^[14,15]

Conflicting reports exist regarding the association between gender predilection and prevalence of PEX. There are stud-

ies reporting a higher PEX frequency in females.^[28,29] Other studies reported that there was no sex predilection.^[7,30,31] In our study, men outnumbered women and the male-to-female ratio was 1.52/1. Similar to our study, some authors reported that^[32,33] PEX was more common among males than in females in their countries. In two studies from Turkey, Yalaz et al.^[4] and Kılıç et al.^[6] found PEX to be more common in males, but Cumurcu et al.^[5] found that women were more frequently affected than men.

PEX has a greater prevalence in the older population.^[3,9,32,34] and increasing age has been universally accepted as a significant risk factor for the development of PEX.^[32,35] In our study, we found that the mean age of the patients with PEXG was 72.7±9.0 years. Prevalence of PEXG increased with age and was highest among subjects aged between 70 and 80 years. About 92.1% of all PEXG patients were over 60 years old which is comparable to the previously published reports.^[5,30,36]

Open angle glaucoma is more prevalent in patients with PEX compared to angle closure glaucoma.^[37,38] Various studies reported that the prevalence of occludable angle was between 4% and 23% in patients with PEX.^[30,37,39] In our study, 95.67% of the patients had open angle glaucoma and 4.32% had closed angle glaucoma. The gender distribution in patients with closed angle glaucoma was different from the patients with open angle glaucoma. We observed that closed angle glaucoma was more common in women and open angle glaucoma was more common in men.

In this study, 77.1% of patients had bilateral disease and the remaining 22.9% had unilateral disease which is comparable to the previously published reports.^[7,31,38,40] The men-women ratio in patients with unilateral PEX (1.92/1) was found to be significantly higher than the patients with bilateral disease (1.37/1). The mean ages of people with uni- and bilateral PEXG were 69.6±9.66 and 74.17±8.26 years, respectively, the difference being significant ($p \leq 0.001$). These findings are similar to those of other studies.^[30,41] It has been known that unilateral PEX converts to bilateral disease in up to 50% of patients within 5–10 years.^[10,38] The patients with unilateral disease were found to be approximately 5 years younger than the cases with bilateral disease in our study. This may be related to the conversion to bilateral disease within 5–10 years.

There is a well-known association between PEX and cataract.^[5,7,9,42] We did not directly record cataract as a finding or investigate the frequency of cataract among the patients with PEXG, however, we detected that 35.08% of eyes were

pseudophakic and 0.76% aphakic. Because of that, it seems that the cataract frequency in PEXG patients in our study was lower than the previous studies.^[4–6,8] Regarding the cataract frequency in PEX cases in studies conducted in Turkey, the authors found a frequency of between 44% and 85%.^[4–6]

Recent studies have highlighted the association between PEX and visual morbidity rates.^[30,42] Similarly, in the current study, blindness was strongly associated with the presence of PEXG. Monocular blindness due to glaucoma was present in 25.2% of patients, while binocular blindness due to glaucoma was present in 2.6% of patients. Thomas et al.^[42] found that 4.1% of patients with PEX were blind due to glaucoma and it was comparable with our study.

The relationship between PEX and cardiovascular diseases still remains controversial. Many studies have shown a positive relationship between cardiovascular diseases and PEX.^[19,43–45] The Blue Mountains Eye Study reported a significant relationship between PEX and a history of hypertension, a history of angina or combined angina or myocardial infarction, and a history of stroke.^[19] Of the studies from Turkey, Citirik et al.^[20] showed a significant relationship between coronary arterial disease and PEX, but Emiroglu et al.^[21] found no relationship. Kılıç et al.^[6] found no relationship between PEX and hypertension or diabetes mellitus in their study, but a significant relationship was found to be with coronary arterial disease. However, there are a lot of studies which have found no relationship between PEX and cardiovascular disease.^[46–48] In our study, we detected that 53% of patients had hypertension, 18.46% of patients diabetes mellitus, and 16.81% of patients cardiovascular disease.

As a result, this work was conducted in Ankara as a cross-sectional multicentric study. Our study had some limitations. This study was hospital based rather than population based. However, only the PEXG patients who were defined with strict criteria by nine different ophthalmology clinics were included in this study. In addition, with this multicentric study, we were able to document the demographic properties of PEXG in a large study population in the Central Anatolian metropolitan area. We think that the data of this study would contribute to the literature and will be a base for the future population-based studies in Turkey.

Ethics Committee Approval: This study was approved by Gülhane Military Medical Academy Ethics Committee (2015–27).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: S.G.G., A.A., A.B.; Design: A.A., A.B.; Supervision: A.A., A.B.; Resource: S.G.G., A.A., A.B., U.E., O.T., T.T., U.E., A.Y., T.M., Z.A., A.K., O.E.K.; Materials: S.G.G., A.A., A.B.,

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