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The prevalence of exfoliation syndrome in Turkey

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ABSTRACT.

Purpose: **To investigate the prevalence of the exfoliation syndrome and its relationship with ocular and cardiovascular diseases in the Central Anatolia region of Turkey.**

Methods: **This cross-sectional and population-based study was conducted at the Sivas Province among the population aged 40 years and over. The diagnosis of XFS was made when exfoliative material was found on the anterior lens capsule or iris on slit-lamp examination. The subjects were divided into an XFS group and a non-XFS group according to the presence of exfoliative material, and the groups were compared for the presence of glaucoma, cataract, age-related macular degeneration, phacodonesis, hypertension, diabetes mellitus, coronary artery disease, smoking and alcohol-use frequency.**

Results: **XFS was present in 63 subjects consisting of 42 males (8.0%) and 21 females (3.6%) for an overall rate of 5.7% (95% CI: 0.054–0.060). Once we adjusted the values for age, we found a statistically significant relationship of increased age and male gender with the presence of XFS (p = 0.001, p = 0.027, respectively). The relationship between XFS and glaucoma, cataract and phacodonesis was found to be statistically significant (p = 0.001). No relationship was found between exfoliation syndrome and hypertension, diabetes mellitus and coronary artery disease.**

Conclusion: **The prevalence of exfoliation syndrome was 5.7% in this population-based study. There was a statistically significant relationship between XFS and advancing age and male gender.**

Key words: cataract – coronary artery disease – exfoliation syndrome – glaucoma

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Introduction

Exfoliation syndrome (XFS), the most common cause of secondary open-angle glaucoma worldwide, is an age-related and a generalized disease of the extracellular matrix, characterized by the production and progressive accumulation of fibrillar extracellular material in many ocular and extraocular tissues and is often associated with glaucoma (Ritch 2014). Its ocular manifestations involve all of the anterior segment structures (Ritch 2014). Exfoliation syndrome seems to be a systemic disorder as the extracellular fibrillar material is found in many organs in the body, including the skin, lungs, liver, gallbladder, blood vessels, heart and cerebral meninges (Schlötzer-Schrehardt et al. 1992). It can be seen together with various systemic vascular diseases (Schumacher et al. 2001; Wang et al. 2014).

The study was conducted in the Turkish Central Anatolian city of Sivas, which has a population of 623 000. Some characteristics of the city are that it is the Turkish province with the largest number of villages and it is the second highest Central Anatolian city with an altitude of 1285 m. The Central Anatolia region has a continental climate with one of the lowest amounts of rainfall in the country. While there are three different hospital-based studies from the Eastern Mediterranean (Adana Province), Middle Black Sea (Tokat Province) and Central Anatolia (Sivas Province) regions of Turkey, no population-based epidemiological study has been conducted in our country (Yalaz et al. 1992; Cumurcu et al. 2010; Kılıç et al. 2014). The aim of this population-based study was therefore to investigate the XFS prevalence and its relationship with systemic diseases such as diabetes mellitus (DM), HT, coronary artery disease (CAD), smoking and alcohol use.

Materials and methods

This cross-sectional and population-based study was conducted at the Sivas Province between August 2014 and February 2015. The study was conducted according to the Helsinki Declaration principles after consent was obtained from the Cumhuriyet

University Medical Faculty Clinical Studies Ethics Committee. All participants also provided a consent form.

This study was conducted on individuals aged 40 years and over living in central Sivas or its town and villages. The number of subjects to be included was determined as 1500 following power analysis. Once the 1500 subjects were distributed proportionately to the urban and rural location according to the age distribution of the population aged 40 years and over, we proceeded as follows: 1 – we made lists of the individuals aged 40 years or over in the city centre, towns and villages using the records from selected Family Health Centers, 2 – we randomly selected subjects from these lists, 3 – we invited the subjects selected from the city centre to our clinic and examined them. The subjects from town centres and villages were examined by inviting them to temporary clinics. We were able to examine only 1220 subjects during the study duration and excluded from the statistical evaluation the 113 subjects who were pseudophakic or aphakic.

A detailed ophthalmic and systemic history of the patients was obtained. All subjects underwent comprehensive ophthalmic examination. This examination consisted of a visual acuity test with a Snellen chart, slit-lamp examination, intra-ocular pressure (IOP) measurement with the air puff tonometer, gonioscopy and dilated fundus examination. We also performed visual fields, ultrasonic pachymetry and retinal nerve fibre layer analysis in patients with glaucoma or suspected of having glaucoma. Suspicion of glaucoma was defined as an IOP over 21 mmHg, C/D ratio of 0.4 or more and asymmetrical C/D difference of at least 0.2 between the two eyes. We set up temporary clinics in the town centres and villages and examined previously informed subjects. This examination consisted of visual acuity with the Snellen scale, IOP measurement with air puff tonometry, anterior segment examination with slit-lamp biomicroscopy, gonioscopy and fundus examination through a dilated pupil. Cases with glaucoma or suspected of having glaucoma were invited to our clinic for more advanced investigations. The diagnosis of XFS was made when exfoliative material was found on the anterior lens capsule or iris on slit-lamp examination.

Glaucoma was defined as an IOP over 21 mmHg, glaucomatous optic nerve damage, visual field defect, decreased retinal nerve fibre layer thickness and a previous history of glaucoma surgery or the presence of a bleb. We graded all nuclear, cortical and posterior subcapsular cataracts using the conventional (0–4) grading system. Possible phacodonesis was evaluated with slit-lamp biomicroscopy. Dilated fundus examination was used to detect age-related macular degeneration (AMD), if any. We obtained information on HT, DM, CAD, smoking, and alcohol intake using standard queries. The subjects were divided into an XFS group and a non-XFS group according to the presence of exfoliative material and the groups were compared for the presence of glaucoma, cataract, AMD, phacodonesis, HT, DM, CAD, smoking and alcohol-use frequency.

Statistical method

We used the SPSS 22.0 (Chicago, IL, USA) program to evaluate the data. The chi-square test, *t*-test and logistic regression analyses were used for descriptive statistics. Statistical significance was accepted as $p < 0.05$. The Hosmer–Lemeshow goodness of fit was used to determine the appropriateness of the model for logistic regression analysis, and the chi-square value was found to be 5.19 ($p = 0.52$).

Results

A total of 1107 individuals were evaluated within the scope of the study. All subjects were indigenous central Anatolians. The relationship of XFS and age, gender and the other related factors is shown in Table 1. The relationship between XFS and advancing age was found to be statistically significant (Table 2). Exfoliation syndrome was present in 63 subjects consisting of 42 males (8.0%) and 21 females (3.6%) for an overall rate of 5.7% (95%CI: 0.054–0.060). The difference between male and female genders was statistically significant ($\chi^2 = 9.28$ and $p = 0.002$). The condition was bilateral in 31 of the 42 (73.8%) male subjects and 16 of the 21 female subjects (76.2) for a total of 47 bilateral (74.6%) and 16 unilateral (25.4%) subjects.

The glaucoma prevalence was significantly higher in the XFS group than the non-XFS group ($p = 0.001$). The mean age was 72.9 ± 5.5 and 62.2 ± 9.4 years and the mean IOP 16.9 ± 5 and 15.8 ± 3.2 mmHg in the two groups, respectively. A strong relationship was found between XFS and glaucoma and cataract according to the results of the logistic regression analysis adjusted for age, but a similar relationship was not found between XFS and AMD (Table 3). Table 4 presents the logistic regression analysis results and XFS correlation. Once we adjusted the values for age, a statistically significant relationship of increased age and male gender with the presence of XFS was found ($p = 0.001$, $p = 0.027$, respectively).

Discussion

The XFS prevalence varies by ethnicity and geographic location. Reported rates in different countries are 0–16.1% (Forsius 1979; Colin et al. 1988; Kozobolis et al. 1997; Nouri-Mahdavi et al. 1999; Miyazaki et al. 2005; Arnarsson et al. 2007; Viso et al. 2010; Landers et al. 2012). The XFS

Table 1. XFS-related factors.

	XFS ($n = 63$)	Non XFS ($n = 1044$)	Tests	p
Age mean ± SD	69.6 ± 8.2	54.1 ± 10.1	$t = 11.93$	0.001F
Mean IOP ± SD	16.9 ± 5	15.8 ± 3.2	$t = 2.50$	0.013
Gender (Female/Male)	21/42	560/484	$\chi^2 = 9.8$	0.002
Glaucoma, *n* (%)	12 (19)	11 (1.1)	Fisher's exact test	0.001
Cataract, *n* (%)	36 (57.1)	125 (12)	$\chi^2 = 97.5$	0.001
AMD, *n* (%)	8 (12.7)	23 (2.2)	$\chi^2 = 24$	0.001
Phacodonesis, *n* (%)	4 (6.3)	0	Fisher's exact test	0.001
Hypertension, *n* (%)	24 (38.1)	304 (29.1)	$\chi^2 = 2.3$	0.130
Diabetes mellitus, *n* (%)	12 (19)	158 (15.1)	$\chi^2 = 0.7$	0.403
CAD, *n* (%)	14 (22.2)	83 (8)	$\chi^2 = 15.1$	0.001
Smoking, *n* (%)	9 (14.3)	197 (18.9)	$\chi^2 = 0.8$	0.364
Alcohol use, *n* (%)	0 (0)	8 (7.7)	Fisher's exact test	0.625

Table 2. XFS rate according to age and gender.

Age groups	Female (XFS+, %)	Male (XFS+, %)	Total
40–49	0/238	0/170	0/408
50–59	1/169 (0.6)	3/154 (2.0)	4/323 (1.6)
60–69	12/119 (10.1)	14/132 (10.6)	26/251 (10.4)
70+	8/55 (14.5)	25/70 (35.7)	33/125 (26.4)
Total	21/581 (3.6)	42/526 (8.0)	63/1107 (5.7)
	χ^2 = 19.03* p = 0.001	χ^2 = 53.02* p = 0.001	

* The 40–49 years old age group has not been included in the analysis.

Table 3. Relationship between XFS and glaucoma, cataract and AMD.

	Glaucoma	Cataract	AMD
XFS (Absent)	1	1	1
XFS Exp(B)	8.57	2.39	1.65
95% CI for Exp(B)	3.24–22.69	1.29–4.43	0.67–4.07
p	0.001	0.001	0.238

Table 4. Associations for XFS using logistic regression analysis.

Variables		Exp(B)	95% CI for Exp(B)	p
Gender	Female (Reference)	1		
	Male	1.91	1.08–3.39	0.027
Age	50–59 (Reference)	1		
	60–69	8.91	3.06–25.93	0.001
	70+	26.37	9.03–77.05	0.001
CAD	Absent (Reference)	1		
	Present	1.37	0.69–2.75	0.370

frequencies in the hospital-based studies conducted in Eastern Mediterranean, Middle Black Sea and Central Anatolia regions of Turkey were 7.2%, 12.2% and 10.1%, respectively (Yalaz et al. 1992; Cumurcu et al. 2010; Kılıç et al. 2014). The XFS prevalence was found to be 5.7% (95%CI: 0.054–0.060) in this population-based study.

XFS rates are higher in hospital-based studies. This study has demonstrated the difference between a hospital-based study and a population-based study conducted at the same region. The XFS prevalence was 6.5% for the 45 years and older population in this study but 10.1% in the previous hospital-based study (Kılıç et al. 2014). The higher rate in the hospital-based study could be due to the increased presentation of exfoliative glaucoma patients at the hospital for their routine follow-ups compared to normal subjects. Cataracts are also more common in patients with XFS, causing them to go to the hospital more often.

Recent studies show that environmental factors may play a role in the development of XFS. Stein et al. (2011) reported an increased XFS frequency with increase in the annual number of sunny days, decreased mean high July temperature, decreased mean January low temperature and lower elevation above sea level. Dewundara & Pasquale (2015) reported that XFS prevalence tends to increase as a function of latitude. They also reported that solar exposure and colder temperatures could be environmental factors in the pathogenesis of XFS. Sivas Province has colder temperatures and high altitude.

We found that the XFS frequency increased significantly with age, similar to other studies (Arnarsson et al. 2007; Viso et al. 2010; Landers et al. 2012). We found XFS to be more common in males in this study as in the previous hospital-based one and the difference was statistically significant (Exp(B): 1.91 OR: 1.88, CI: 1.08–3.39 p = 0.027) (Kılıç et al. 2014). Some studies reported higher rates in both genders but most found no significant relationship between gender and XFS (Kozobolis et al. 1997; Miyazaki et al. 2005; Astrom & Linden 2007; Al-Bdour et al. 2008; You et al. 2013).

We found a strong relationship between XFS and glaucoma (Exp (B):8.57 CI: 3.24–22.69 p = 0.001), similar to other studies (Al-Bdour et al. 2008; Viso et al. 2010; Anastasopoulos et al. 2011). The glaucoma prevalence was 36.3% in the previous hospital-based study and 19% in this study (Kılıç et al. 2014). Hospital-based studies have similarly found high rates of glaucoma (Rao et al. 2006; Al-Bdour et al. 2008; Shazly et al. 2011). The relationship between cataract and XFS is well known (Casson et al. 2007; Al-Bdour et al. 2008). The cataract prevalence in this population-based study (57.1%) was lower than in our previous hospital-based study (75%) (Kılıç et al. 2014). Phacodonesis greatly increases the risk during cataract surgery (Shingleton et al. 2010). We found a statistically significant relationship between XFS and cataract and phacodonesis in this study (p = 0.001).

We had found a statistically significant relationship between XFS and CAD in our previous hospital-based study but did not find such a relationship in this population-based study (Exp(B):1.37 CI: 0.69–2.75, p = 0.370) (Kılıç et al. 2014). A positive relationship between cardiovascular disease and XFS has been reported in many studies, but there is no study reporting increased mortality rates in XFS patients (Mitchell et al. 1997; Ringvold et al. 1997; Shrum et al. 2000; Visontai et al. 2006; Andrikopoulos et al. 2014; Svensson & Ekström 2015). A relationship between XFS and cardiovascular disease was not found by several other studies (Tarkkanen 2008; Tarkkanen et al. 2008; Spečkauskas et al. 2012). In conclusion, case–control studies focusing on geographical, ethnic and cultural differences are needed to better understand the relationship between XFS and cardiovascular diseases.

To our knowledge, this population-based study is the first from Turkey to investigate the prevalence of XFS. The unilateral or bilateral XFS rate in individuals aged 40 years and over in this population-based study was 5.7%. There was a statistically significant relationship between XFS and advancing age and male gender in this study.

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