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A Case–Cohort Study of Exfoliation Risk Factors and Literature Review

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Abstract

The purpose of the study is to evaluate the risk factors associated with exfoliation in a case-cohort setting and literature review. This single-center, prospective, case-cohort study was carried out from January 2010 to April 2020 on patients operated for cataract surgery by a single surgeon in Lebanon. Forty‑nine consecutive patients with exfoliation syndrome (XFS) and 62 consecutive control patients were identified and further investigated for selected systemic (diabetes mellitus, systemic hypertension, asthma, or atopy) and ocular variables (baseline vision, severity of nuclear sclerosis, glaucoma, eye rubbing, history of dry eye, or allergic eye disease). The mean baseline Snellen visual acuity was 20/283 in XFS versus 20/145 in control cases ($P = 0.012$). XFS also demonstrated significantly denser nuclear sclerosis than controls ($P = 0.00958$). By univariate analysis, allergic conjunctivitis (15 [30.6%] vs. 2 [3.2%]; $P < 0.001$), dry eye (20 [40.8%] vs. 13 [21.0%]; $P = 0.0133$), and habitual rubbing of the eyes (33 [67.3%] vs. 19 [30.6%]; $P < 0.001$) were associated with the presence of XFS. Habitual ocular rubbing was closely associated with allergic conjunctivitis (odds ratio [OR] = 13.0; 95% confidence interval [CI]: 2.8–58.8; $P = 0.032$). After multivariable analysis, the following variables showed significant results: glaucoma (OR = 34.5; 95% CI: 4.4–250; $P = 0.010$), duration of surgery (OR = 5.6; 95% CI 2.43–12.9; $P < 0.001$), and habitual ocular rubbing (OR = 4.42; 95% CI: 1.97–9.90; $P = 0.029$). This study shows a novel potential correlation between eye rubbing and XFS in a Lebanese cohort. Chronic eye rubbing induces or may exacerbate preexistent zonular damage in subjects with XFS, hence the need to better manage concurrent ocular surface disorder in these patients.

Keywords:

Allergic conjunctivitis, cataract, dry eye, exfoliation syndrome, lens zonules, ocular rubbing, phacoemulsification, pseudoexfoliation syndrome

Introduction

Exfoliation syndrome (XFS) is currently a global disease affecting an estimated 70 million people, worldwide.[1] XFS appears to be a syndrome targeting ocular tissues with deposition of fibrillary material on the lens capsule with similar deposits in other parts of the body, such as the skin, kidneys, liver, heart, and lungs. XFS material is a mixture of several biologic components made of amyloid, laminin, elastic fibers, and collagen basement membrane.[2] The causes of XFS are not well known,[3,4] especially with animal models lacking,[5,6] leaving researchers with the human Tenon's capsule fibroblasts as a model system for the study of XFS.[7] Advanced age appears as a major risk factor as well as some genetic factors.[8] Some evidence exists for the association between XFS and lysyl oxidase-like 1 (LOXL1) protein gene implicated in elastin formation and maintenance and less so with the calcium channel protein gene CACNA1A, and the extracellular matrix chaperon clusterin protein. Known environmental risk factors for the disease have included

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solar exposure,[9] ambient temperature, living at more northern latitudes,[10] dietary factors,[9,11] and infectious etiology.[12] The possible relationship between XFS and selected ocular and systemic factors was investigated in a Lebanese cohort.

Methods

This is a prospective data registry of all patients undergoing phacoemulsification in one surgical suite by a single surgeon (AMM) from January 2010 to April 2020. All patients provided written informed consent in accordance with the Declaration of Helsinki. Institutional Review Board (Rafic Hariri University Hospital, Beirut, Lebanon) approval was obtained for this study. Data were anonymized to maintain confidentiality. Systemic factors recorded have included age, gender, hypertension, diabetes mellitus, coronary artery disease, morbid obesity, Alzheimer neurodegenerative disorder, and intake of alpha agonists for benign prostatic hypertrophy and any major disease (migraine, cancer). Recorded ocular factors were preoperative and postoperative best-corrected visual acuity (BCVA), intraocular lens power, presence of XFS, glaucoma, macular degeneration, and diabetic retinopathy. Seven hundred and fifteen patients (mean age: 74 years) were enrolled in this study, and 387 of them underwent bilateral cataract removal. Surgeries were performed on 1097 eyes (599 right eyes and 498 left eyes) and were nearly equally distributed among men (509) and women (588). A case–cohort study was designed in which cases with XFS and controls without XFS were drawn from within this large prospective study. We selected a consecutive (most recent to less recent date of surgery) control group. In addition, we conducted a survey on these two groups to collect additional ocular and systemic variables between January 2010 and April 2020 (approved by the Institutional Review Board at Rafic Hariri University Hospital). This survey was done by phone call to answer the presence of habitual ocular rubbing before glaucoma topical therapy, history of therapy for either dry eye or allergic conjunctivitis, skin atopy or asthma, erectile dysfunction, and sensorineural hearing loss. The survey was carried by a blinded operator (KAJ). The subjects who answered positively for ocular rubbing (before glaucoma therapy) were contacted a second time to fill an ocular rubbing score.

We included all patients with significant cataract and visual acuity 20/40 (6/12) or less and with any accompanying ocular morbidity (keratoconus, XFS, glaucoma, maculopathy, reduced endothelial cells [<1800 cells/mm^2], and central corneal opacity) or systemic morbidity (controlled diabetes mellitus, controlled systemic hypertension, stable stroke, and controlled angina) and Alzheimer's disease or adult Down's syndrome. Exclusion criteria included refusal to sign an informed consent, recent conjunctivitis of any kind, uncontrolled systemic hypertension or diabetes mellitus, active proliferative diabetic retinopathy, active untreated neovascular macular degeneration, Marfan syndrome, homocystinuria, systemic amyloidosis, true XFS[13] (history of radiotherapy, glass blowing, excessive heat exposure from oven burning or metal welding), and eyes that require concomitant vitrectomy (for vitreous hemorrhage or retinal detachment).

Preoperatively, we carried out slit lamp examination, before and after pupillary dilatation, with one drop of tropicamide (Mydriacyl® 1%, Alcon, Fort Worth, Texas, USA), fundoscopy, tonometry, measurement of BCVA, and ocular measurement with an optical biometer (IOL Master 700; Carl Zeiss Meditec AG, Jena, Germany). Target refraction was emmetropia. In the final analysis, only the first operated eye in subjects with bilateral exfoliation was included. In the control group, the first operated eye of consecutive subjects without XFS was enrolled. BCVA was measured by the same surgeon (AMM) using Snellen visual charts. Nuclear hardness was graded after pupillary dilation on the slit lamp (Haag-Streit® slit lamp 900 [Haag-Streit AG, Koeniz, Switzerland]) by the same surgeon using the 5-level Emery-Little Classification System (soft, semi-soft, medium hard, hard, and rock-hard). Glaucoma diagnosis relied upon intraocular pressure above 21 mmHg, glaucomatous optic disc cupping >0.7, and typical glaucoma-related visual field loss. A rubbing score has been designed to assess numerically the intensity of the ocular friction [Table 1].

Statistical analysis

Statistical analyses were performed using SPSS version 22 (IBM, Chicago, IL, USA), and *t*-test was used for testing the difference between the means of two independent samples. Multivariate analysis was carried using simple discriminant analysis when the dependent variable is categorical variable broken into yes and no using ANOVA and confirmed by cross-tabulation and Pearson's Chi-square test. Significance is set at $P < 0.05$.

Literature search

The databases of Medline, Embase and Google Scholar were systematically searched by one of us (AMM) for relevant articles published between 1975 and May 2020 using the search terms: exfoliation or pseudoexfoliation AND risk factors; exfoliation or pseudoexfoliation AND young age and using forward searching, checking references in major reviews (on exfoliation/pseudoexfoliation), and in all retrieved articles. Only comparative studies showing positive results with statistical significance set at $P < 0.05$ for the associated risk factors were included in the final tabulations.

Results

The number of surveyed patients was 49 in the XFS group and 61 in the control group [Tables 2 and 3]. The completion rate of telephone survey approached 100% as patients or their close relatives (in case of death) completed the survey, for example, the survey in the control group was completed by 57 patients or by their mates in four deceased patients (100% response); likewise, the survey in the XFS group was completed by 45 patients or by their mates in 3 of 4 deceased patients (98% response). All enrolled subjects were Caucasians. The two groups were not different for gender, diabetes mellitus, coronary artery disease, or morbid obesity [Table 2]. XFS patients had longer follow-up because of the need to monitor for future or current glaucoma. XFS group was significantly older (by 7.4 years) than the control group. There was no significant difference for the presence of diabetes mellitus, systemic hypertension, coronary artery disease, morbid obesity, asthma or skin atopy, sensorineural hearing loss, or use of oral alpha-agonist for benign prostatic hypertrophy. Erectile dysfunction occurred in 12 of 22 XFS males (54.5%) versus 3 of 17 control males (17.6%) ($P = 0.0069$). Additional systemic findings in the XFS group not listed in Table 2 included migraine in 4, rheumatoid arthritis in 3, stroke in 2, and temporal arteritis or sarcoidosis or interstitial lung fibrosis or colon cancer or lung cancer or toxic goiter or Parkinson's or sleep apnea in one case each. Additional systemic findings in the control group included breast cancer in two cases and sleep apnea or carotid stenosis or Parkinson's or migraine in one case each.

Eye-wise, the two groups were not different for baseline astigmatism, presence of posterior subcapsular cataract, baseline refraction (measured indirectly by the inserted intraocular lens power), and final BCVA [Table 3]. The two groups were different in terms of several ocular characteristics. The mean baseline spectacle-corrected Snellen visual acuity was 20/270 in the XFS versus 20/145 in the control ($P = 0.032$). Duration of surgery was near double in XFS than in controls (36.0 min vs. 17.4 min; $P < 0.001$), partly from higher grades of severity of nuclear sclerosis in the eyes with XFS ($P = 0.023$). Glaucoma (18 [36.7%] vs. 1 [16.1%]; $P < 0.001$), allergic conjunctivitis (before glaucoma therapy) (17 [34.7%] vs. 2 [3.2%]; $P < 0.001$), dry eye (before glaucoma therapy) (21 [42.9%] vs. 13 [21.0%]; $P = 0.0074$), and rubbing score of the eyes (before initiation of glaucoma medical therapy) (8.69 vs. 2.11; $P < 0.001$) were significantly more common in the XFS group. Other ocular findings in six patients with XFS and not listed in Table 2 included: Sjogren's syndrome in 3, chronic

Table 1: Rubbing score is the sum of the items listed (all before initiation of glaucoma eye drops)

Parameter	Score of 1	Score of 2	Score of 3	Score of 5
Rubbing episode per day	<5/day	6-10/day	>10/day	
Seasonal or yearly rubbing	Occasional	Seasonal	Year round	
Rubbing years divided by 5 (years)	5	10	15	25
Rubbing severity	Mild	Moderate	Severe	
Physician noted rubbing before eye exam				X
Rubbing compulsive or stress-induced			X	
Vernal or allergic conjunctivitis of childhood			X	
Habitual crying			X	
History of drops for ocular allergy	X			
History of drops for dry eye	X			
Rub the skin	X			
Asthma or atopy or allergic rhinosinusitis	X			

Table 2: Potential systemic risk factors for pseudoexfoliation by univariate analysis

	Mean±SD or total number (%)		*P*
	Pseudoexfoliation (*n*=49)	Control (*n*=61)	
Age	78.4±9.0	71.0±10.3	<0.001
Gender	21 male (42.9)	25 male (41.0)	0.42
Diabetes mellitus	11 (22.4)	18 (29.5)	0.20
Systemic hypertension	18 (36.7)	29 (47.5)	0.13
Coronary artery disease	15 (30.6)	13 (21.3)	0.13
Morbid obesity	2 (4.1)	2 (3.3)	0.413
Asthma or atopy	7 (14.6)	8 (13.1)	0.41
Sensorineural hearing loss	14 (28.6)	12 (19.7)	0.14
Erectile dysfunction	12 (54.5)	3 (17.6)	0.0069
Oral alpha agonist intake	6 (31.2)	8 (32.0)	0.45

SD: Standard deviation

Table 3: Potential ocular risk factors for pseudoexfoliation by univariate analysis

	Mean±SD or total number (%)		*P*
	Pseudoexfoliation (*n*=49)	Control (*n*=61)	
Baseline spectacle corrected visual acuity (logMAR)	−1.13±−0.60	−0.86±0.70	0.032
Final spectacle corrected visual acuity (logMAR)	−0.29±−0.40	−0.20±0.27	0.15
Baseline astigmatism	1.03±0.69	1.19±0.85	0.27
Follow-up (months)	25.5±37.2	8.6±18.7	0.002
Duration of surgery (min)	36.0±24.3	17.4±6.2	<0.001
Nuclear sclerosis grade	3.1±1.3	2.4±1.6	0.023
Intraocular lens power (D)	20.4±3.8	19.4±4.8	0.257
Floppy iris	2 (4.1)	9 (14.8)	0.032
Glaucoma	18 (36.7)	1 (1.6)	<0.001
Dry eyes therapy	21 (42.9)	13 (21.3)	0.0074
Allergic conjunctivitis therapy	17 (34.7)	2 (4.1)	<0.001
Posterior subcapsular cataract	0.31±0.71	0.21±0.41	0.20
Grade 1	7 (14.3)	13 (26.5)	
Grade 2	1 (2.0)	0	
Grade 3	2 (4.1)	0	
Nuclear sclerosis grade	3.10±1.60	2.46±2.55	0.011
1 Soft	5 (10.2)	15 (24.6)	
2 Semi-soft	6 (12.2)	10 (16.4)	
3 Medium-hard	20 (40.8)	20 (32.8)	
4 Hard	12 (24.5)	11 (18.0)	
5 Rock-hard	6 (12.2)	5 (8.2)	
Total rub score	8.69±7.85	2.11±4.09	<0.001
	0-9, 25 (51.0)	0-9, 53 (86.9)	
	>10, 23 (46.9)	>10, 8 (13.1)	

anterior blepharitis in 2, severe ocular rosacea in 2, and large old herpetic corneal scar in 1, while a single patient in the control group had chronic anterior blepharitis.

A multiple regression was run to predict the potential risk factors for XFS [Table 4]. These variables significantly predicted the occurrence of XFS ($F = 6.68$; $P < 0.001$; $R^2 = 0.642$): duration of cataract surgery ($P < 0.001$), glaucoma diagnosis ($P = 0.004$), history of local therapy for allergic conjunctivitis ($P = 0.044$), and ocular rubbing score ($P < 0.001$).

For XFS patients, 48 completed the survey, 30 admitted rubbing, and 18 denied rubbing. Of note, 23 XFS patients were witnessed rubbing the eyes in the clinic (all before any potential therapy for glaucoma). Severity of rubbing: 3 severe, 10 moderate, and 17 mild; frequency of daily rubbing: more than 10 times in 6, between 5 and 10 in 1, and <5 times in 23; rubbing was throughout the year in 13, seasonal in 6, and occasional in 11. Years of rubbing: 10 reported >20 years, 8 had between 11 and 20, 8 had between 6 and 10, and 4 had <6 years. For the 61 control patients who completed the survey, 14 admitted rubbing and 47 denied rubbing. Five control patients were witnessed ocular rubbing in the clinic (all before any potential therapy for glaucoma). Severity of rubbing: 1 severe, 2 moderate, and 11 mild; frequency of daily rubbing: more than 10 times in 1 and <5 times in 13; rubbing was throughout the year in 4, seasonal in 4, and occasional in 6. Years of rubbing: 4 had >20 years, 1 had between 11 and 20, 4 had between 6 and 10, and 5 had <6 years.

Literature review of positive risk factors for XFS in general [Tables 5-7][14-81] and XFS in young subjects [Table 8][82-99] was tabulated and this information was used to synthesize the literature findings with the current study findings.

Discussion

In the Lebanese cohort under investigation, XFS was associated with advanced age, glaucoma, habitual ocular rubbing, and longer time for cataract surgery. While advanced age [Table 6],[39-70] glaucoma [Table 5],[14-38] and longer surgery duration[100] are well established risk factors for XFS [Table 5],[14-38] ocular rubbing has received little attention in the literature.

What are the causes of ocular rubbing in exfoliation syndrome?

A major precipitating factor in the cohort under investigation is the presence of dry eye and to a lesser extent the presence of allergic conjunctivitis. Rubbing was associated in the current study with dry eye, and dry eye is a known feature in XFS patients.[101] XFS patients have lower basal tear test

Table 4: Multiple regression analysis of risk factors for pseudoexfoliation

Variable	*P*	OR	CIs	
			Lower	Upper
Nonocular variables				
Female gender	0.843	0.90	0.50	2.31
Older age	0.001*	4.02	1.80	8.96
Diabetes mellitus	0.404	0.90	0.43	1.98
Systemic hypertension	0.255	0.64	0.30	1.38
Coronary artery disease	0.266	1.63	0.69	3.86
Morbid obesity	0.823	1.26	0.17	9.25
Sensorineural hearing loss	0.275	1.63	0.67	6.46
Erectile dysfunction	0.014*	5.75	1.31	25.0
Asthma or atopy	0.825	1.13	0.38	3.38
Use of alpha antagonists	0.892	0.924	0.298	2.868
Ocular variables				
Better baseline vision	0.001*	0.26	0.12	0.58
Better final vision	0.35	0.75	0.35	1.63
Baseline astigmatism	0.15	0.57	0.26	1.23
Higher nuclear sclerosis severity	0.039*	2.40	1.03	5.57
Posterior subcapsular cataract	0.91	1.05	0.42	2.63
Higher intraocular lens power	0.081	2.00	0.91	4.39
Duration of surgery	0.000*	5.92	2.55	13.8
Follow-up (month)	0.003*	3.28	1.50	7.19
Floppy iris	0.068	0.25	0.052	1.22
Dry eye treatment	0.015*	2.77	1.20	6.37
Allergic eye treatment	0.000*	15.6	3.40	15.6
Glaucoma	0.000*	34.5	4.44	250
Total rub score	0.000*	6.12	2.64	14.2

*Significant variables (*P*<0.05). OR: Odd ratio, CI: Confidence interval

scores, decreased tear breakup time, loss of goblet cell density (by impression conjunctival cytology),[101] and significant Meibomian gland dysfunction.[23] These ocular surface disorders have been attributed partly to deposition of exfoliation material in the conjunctiva.[102,103] Possible other explanations have included: degenerative disease of the ocular surface with deposition of neurodegenerative proteins similar to that found in Alzheimer's or Parkinson, autoinflammatory disease of the conjunctiva, and vascular insufficiency [Table 9]. Allergic conjunctivitis was also associated with rubbing but to a lesser extent in the present Lebanese study with one subject having XFS and vernal catarrh. Asthma and abnormal pulmonary function tests (obstructive airway disease) have been associated with XFS [Table 6].[39-70] Batur *et al*.[66] in 60 patients with XFS without pulmonary disease detected a significant decline in pulmonary function tests versus 52 controls matched for age, gender, and smoking history. Similarly, in the Reykjavik Eye Study, a population-based study involving 1045 subjects (108 XFS) followed for 5 years, asthma was significantly associated with XFS (odds ratio 1.91; [95% confidence interval 1.00–3.62]) by multivariate analysis.

What are the consequences of ocular rubbing on the eye?

Acute rubbing of the eye can cause transient astigmatism,[107,108] elevated intraocular pressure,[109,110] and corneal hydrops.[111] Chronic rubbing has been linked with the development of keratoconus,[112,113] cataract,[114] optic disc cupping,[115] and retinal detachment.[116] Küchle[84] reported 2 young subjects with keratoconus necessitating penetrating keratoplasty at ages 31, 37 and 40 years with XFS detected between 4 and 6 years after surgery. Küchle attributed this temporal relationship to possible slow virus transmitted from the donor cornea. We propose that rubbing caused the concomitant keratoconus and XFS. This is further confirmed by analysis of XFS in young subjects [Table 8]:[82-99] Half of young subjects with a reported risk for XFS had keratoconus. Out of 35 subjects with XFS under 45 years of age, detailed clinical data were available in 18:9 having some kind of corneal ectasia and 9 having had intraocular surgeries (2 after penetrating trauma and 7 had primary glaucoma). The decreased endothelial cell count in XFS[28] could be due to XFS material accumulation[30] or from eye rubbing as rubbing per say decreases endothelial cell density.[117,118]

Zonular stretching in health, trauma, and exfoliation syndrome

The function of the zonules is mechanical with its relatively elastic fibers able to stretch up to four times their original length before breaking, but this elasticity declines markedly with age. Biochemically, a zonule consists of a microfibril backbone comprised fibrillin and a restricted set of glycoproteins (80% being FBN1 and LTBP2).[119] LOXL1, a crosslinking enzyme responsible collagen and elastin biogenesis, is detected at significant levels, and this enzyme is implicated in the pathogenesis of XFS. Assia *et al*.[120] tested the stretching capability of lens zonules in 40 postmortem human eyes. They found that zonules can slowly stretch up to 3.82 mm in young subjects before rupturing. That value of maximal zonular stretch tended to decrease with the age by 0.5 mm for every 5 years in normal eyes, while eyes with XFS had even more friable zonules. Similarly, Saber *et al*.[121] found a median mechanical zonular stretch tolerance of 3.00 mm on postmortem eyes that previously had extracapsular extraction. The zonular apparatus is involved extensively in XFS. Ultrasound biomicroscopic grading of zonular changes in XFS included uneven and disrupted zonules, followed by patchy deposits on the zonules. A more severe grade involves diffuse granulation over thickened zonules[122] with web-like structure in between zonules. The end stage is extensive loss of zonules.[123] Similarly, occult zonular defects were present on ultrasound biomicroscopy in 21 of 49 patients (42.9%) following ocular trauma.[124] XFS was detected in a study of young amateur boxers.[125] How much the eye is indented around the limbus during ocular rubbing or ocular trauma? In acute blunt trauma, the damage is one time

Table 5: Literature review of articles showing positive ocular risk factors in pseudoexfoliation

First author (year of publication)	City, country	Sample size	Type of study	Risk factor	*P* value or hazard ratio
Akdemir (2016)	Istanbul, Turkey	50 XFS, 20 XFS with glaucoma, 65 controls	Clinic-based cross-sectional study	Dry eye	<0.001
Kozobolis (2004)	Crete, Greece	40 XFS and 40 controls	Prospective, cross-sectional study	Dry eye	0.01
Kozobolis (1999)	Crete, Greece	57 XFS versus 60 controls	Cross-sectional study	Dry eye	<0.002
Öncel (2012)	Istanbul, Turkey	31 XFS and 31 controls	Clinic-based case-control study	Dry eye	0.001
Rao (2018)	Odisha, India	55 XFS with 40 controls	Clinic-based case-control study	Dry eye	<0.001
Škegro (2015)	Zagreb, Croatia	40 XFS and 40 controls	Clinic-based case-control study	Dry eye	<0.01
Noori (2019)	Pune, India (Asian Indian)	100 XFS and 100 controls	Clinic-based comparative study	Dry eye	0.003
Kaliaperumal (2014)	Puducherry, India	30 XFS and 15 controls	Clinic-based comparative study	Dry eye	<0.001
Pujar (2019)	Karnataka, India	30 XFS and 30 controls	Clinic-based comparative study	Dry eye	<0.001
Potemkin (2016)	Saint Peterburg, Russia	66 XFS and 64 controls	Clinic-based comparative study	Meibomian gland dysfunction	<0.05
Landers (2012)	Central Australia	1884 with 72 XFS	Clinic-based cross-sectional study	Climatic keratopathy	<0.001
Resnikoff (1991)	Bamako, Mali, East Africa	2446	Countryside survey	Climatic keratopathy	6.4 (1.2-33.1) (*P*=0.02)
Forsisus (2002)	Peru (7 XFS), Novosibirsk (41 XFS in Russia), Åland (41 XFS in Finland)	International Biological Programme for study populations living in extreme climates	Samples of extreme climate International Biologic Programme	Climatic keratopathy	<0.05
Yazgan (2015)	Zonguldak, Turkey	45 healthy, 43 XFS and 30 XFS Glaucoma eyes	Clinic-based cross-sectional study	Decreased Corneal Hysteresis	<0.001
Romero-Aroca (2011)	Taragona, Spain	2342 with 309 XFS	Population-based cross-sectional study	Increased corneal endothelial polymorphism, polymegathism, cell loss	<0.001
Yenerei (2011)	Istanbul, Turkey	52 XFS and 42 controls	Clinic-based cross-sectional study	Decreased Corneal hysteresis and Corneal Resistance Factor	<0.05
Palko (2017)	World literature	Literature before September 2016	Meta-analysis	Decreased corneal nerves	4 studies had *P*<0.05
Palko (2017)	World literature	Literature prior to September 2016	Meta-analysis	Decreased corneal endothelial cell count	9 of 11 studies had *P*<0.05
Topouzis 2019	Thessaloniki, Northern Greece	1468 with 19.6% XFS	Longitudinal, population-based study	More hyperopia	0.72 per mm (0.57-0.92)
McCarty 2000	Victoria, Australia	3271 with 0.98% XFS	Cluster, stratified sampling	Glaucoma	3.80 (1.73-8.33)
Sorkou 2020	Greece	42 XFS versus 72 controls	Cross-sectional clinic based	Glaucoma	0.002
Hietanen 1992	Helsinki, Finland	305 consecutive patients (77 XFS) scheduled for cataract surgery	Cross-sectional clinic based	Glaucoma	<0.001 (33.8% of XFS vs. 10.8% in non XFS)
Rotchford 2003	South Africa	1840 with 7.7% XFS	Cluster-based random cross-sectional sampling	Glaucoma	2.5 (1.4-4.5)
Mitchell 1999	Sydney, Australia	3654 (Blue Mountains Eye Study)	Cross-sectional study	Glaucoma	5.0 (2.6-9.6)
Forsman 2007	Kökar island in southern Finland	595	Population-based eye examination	Glaucoma	11.9 (6.2-22.9)
Bikbov (2020)	Ufa, Bashkortostan, Russia	5899	Population-based cross-sectional study	Glaucoma	2.40 (1.36-4.23) (*P*=0.003)

XFS: Pseudoexfoliation

Table 6: Literature review of articles showing positive systemic nonvascular risk factors in pseudoexfoliation

First author (year of publication)	Country	Sample size	Type of study	Risk factor	*P* value or OR (95% CI)
Kim 2016	South Korea	13,223	Korean National Health and Nutrition Examination Survey	Increasing age	1.04 (0.99-1.09) *P*=0.016
Krishnadas 2003	Southern India	5150	Population-based cross-sectional study	Increasing age	<0.001
Rotchford 2003	South Africa	1840 with 7.7% XFS	Cluster-based random cross-sectional sampling	Increasing age	<0.001
Jonas 2013	Central India	4711 with 69 XFS	Population-based, cross-sectional study	Increasing age	1.11 (1.09-1.13) *P*<0.001
Arnarsson (2010)	Reykjavik, Iceland	1045	Reykjavik eye study population-based study	Increasing age	0.001
Pavičić-Astaloš (2016)	Zagreb, Croatia	5349 with 188 XFS	Clinic-based cross sectional study	Increasing age	<0.001
Bikbov (2020)	Ufa, Bashkortostan, Russia	5899	Population-based cross-sectional study	Increasing age	1.09 (1.07-1.11) *P*<0.001
You (2013)	Beijing, China	3468 (Beijing Eye Study)	Population-based cross-sectional cohort study	Increasing age	1.08 (1.04-1.10) *P*<0.001
Hepsen (2007)	Ankara, Turkey	72 XFS and 65 control with cataract	Clinic-based cross-sectional study	Increasing age	<0.001
Berhanu (2020)	Baso and Worena District, Central Ethiopia	682	Population-based cross-sectional study	Increasing Age	0.038
Hiller 1982	Massachusetts, USA	2675	Population-based survey (Framingham Eye Study)	Female gender predominance	2.3:1 female: male (significant)
Ekström 2019	Tierp, Sweden	1065 with 78 XFS	Population survey	Female gender predominance	1.59 (1.16-2.18)
Topouzis 2019	Thessaloniki, Northern Greece	1468 with 19.6% XFS	Longitudinal, population-based study	Female gender predominance	0.02
Arnarsson (2007)	Reykjavik, Iceland	1045 with 108 XFS	Reykjavik Eye Study population based study	Female gender predominance	<0.001
Krishnadas 2003	Southern India	5150	Population-based cross-sectional study	Male gender predominance	0.01
Yalaz (1992)	Adana, Turkey	1356	Clinic-based cross-sectional study	Male gender predominance	<0.001
Jonas 2013	Central India	4711 with 69 XFS	Population-based, cross-sectional study	Lower body mass index	0.88 (0.82-0.95) *P*=0.001
Arnarsson (2010)	Reykjavik, Iceland	1045	Reykjavik Eye Study population based study	Fruit intake	0.20 (0.04-0.91) *P*=0.04
Pasquale 2012	USA	78,977 women from nurses' health study and 41,202 men from health professionals follow-up study with 360 XFS	Longitudinal population-based study	Caffeine intake	≥3 cu*P*s coffee daily increased risk of XFS glaucoma 1.66 (1.09-2.54) *P*=0.02
Kang 2014	USA	78,977 women from nurses' health study and 41,202 men from health professionals follow-up study with 360 XFS	Longitudinal population-based study	Folate intake	XFS glaucoma associated with highest quintile (Q5; ≥ 654 µg/day) 0.75 (0.54-1.04) *P*=0.02
Tijani 2017	Rabat, Morocco	260 scheduled for cataract surgery	Retrospective clinic-based	Smoking	5.2 (1.35-20.15) *P*=0.01
Pasquale 2014	USA and Israel	118 XFS and 106 controls; Israel 67 XFS and 72 controls	Clinic-based, case-control studies	Higher latitude	Each degree of latitude away from equator associated with 11% increased odds of XFS 1.11 (1.05-1.17); *P*<0.001

Contd...

Table 6: Contd...

First author (year of publication)	Country	Sample size	Type of study	Risk factor	*P* value or OR (95% CI)
Pasquale 2014	USA and Israel	United States: 118 XFS and 106 controls; Israel: 67 XFS and 72 controls	Clinic-based, case-control studies	Solar exposure	Every hour weekly sPent outdoors during summer, over lifetime 1.04 (1.00-1.07) *P*=0.03
Arakaki 2020	Kumejima, Okinawa, Japan	3762	Population-based survey ≥40 years	Working outdoor	2.18 (0.99-4.82) *P*=0.04
Wirostko 2016	Utah, USA	132,772 women in Utah Medicare	Cross-sectional analysis	Pelvic Organ Prolapse	1.56 (1.42-1.72)
Besch 2018	Utah, USA	Hospital charts compared with population controls	Chart review University of Utah Healthcare medical records	Indirect Inguinal Hernia	2.3 (1.4-3.5) (*P*=0.03)
Sorkhabi (2012)	Tabriz, Iran	30 XFS and 30 controls	Clinic-based prospective comparative study	Markers of inflammation and peripheral endothelial dysfunction	0.002
Dursun (2015)	Sivas, Turkey	26 XFS, 26 XFS with glaucoma, 26 controls with cataract	Clinic-based prospective comparative study	Increased oxidative stress	<0.05
Yazdani (2008)	Tehran, Iran (Caucasian race)	83 subjects with XFS and 83 controls	Prospective clinic-based case-control study	Sensorineural hearing loss	6.69 (3.49-11.79) *P*<0.001
Papadopoulos (2012)	Patras, Greece (Caucasian race)	94 XFS and 44 controls	Prospective clinic-based case-control	Sensorineural hearing loss	0.007
Sarenac-Vulovic (2014)	Kragujevac, Serbia	20 XFS, 20 XFS with glaucoma, 20 controls	Clinic-based cross-sectional study	Sensorineural hearing loss	6.5 (*P*=0.03)
Singham (2014)	Kuala Lumpur, Malaysia	68 XFS and 55 controls	Prospective clinic-based case-control study	Sensorineural hearing loss	3.00 (1.25-7.19) *P*=0.01
Cumurcu (2013)	Turgut, Turkey (Caucasian race)	67 XFS and 67 controls	Clinic-based cross-sectional study	Alzheimer neurodegenerative impediment	*P*<0.001
Linnér (2001)	Goteborg, Sweden	11 of 39 Alzheimer had XFS (clinic) versus 23 of 476 (population survey) had XFS	Clinic-based versus population survey	Alzheimer neurodegenerative impairment	5.84 (2.87-11.98)
Turgut Coba (2018)	Antalya, Turkey	31 XFS and 31 controls	Case-control study	Peripheral Neurosensory impairment	<0.05
Arnarsson (2010)	Reykjavik, Iceland	1045	Reykjavik Eye Study population-based study	Asthma	1.91 (1.00-3.62)
Batur (2018)	Van, Turkey	60 XFS and 52 controls	Clinic-based comparative study	Decreased pulmonary function tests	0.036
Yaşar (2019)	Eskişehir, Turkey	2009 with 100 XFS	Population-based, cross-sectional study	Depressive disorder	0.024
Cumurcu (2006)	Tokat, Turkey	41 XFS glaucoma, 32 POAG and 40 controls	Clinic-based comparative study	Depressive disorder	007
Scharfenberg (2019)	Leipzig, Germany (Caucasian)	Patients with ophthalmological operations	Hospital-based retrospective case-control study	Benign prostatic hypertrophy	2.3 (1.4-3.7)
Gökce (2015)	Ankara, Turkey	34 XFS and 58 controls	Clinic-based comparative study	Erectile dysfunction	0.002

XFS: Pseudoexfoliation, CI: Confidence interval, OR: Odds ratio, POAG: Primary open-angle glaucoma

and severe, while with severe repetitive rubbing, the damage is cumulative progressive and infinitesimal. The eyeball is deformed with shortening of anteroposterior length and distension of the equatorial region, leading to stretch of the zonules [Figure 1a and b]. Delori *et al*.[126] demonstrated in a pig eye model that blunt trauma causes indentation of the cornea with lens–cornea touch and backward displacement of the lens together with

Table 7: Literature review of articles showing positive systemic vascular risk factors in pseudoexfoliation

First author (year of publication)	Country (race if available)	Sample size	Type of study	Risk factor	*P*-value or hazard ratio (95% CI)
Vardhan (2017)	Tamil Nadu, India	930 XFS and 476 controls	Cross-sectional clinic-based study	Systolic hypertension	0.001
Alpastan (2012)	Konya, Turkey	31 XFS and 29 controls	Case-controlled observational study	Increased aortic stiffening	0.021
Yüksel (2006)	Kocaeli, Turkey	25 XFS, 24 XFS glaucoma and 25 controls	Clinic-based comparative study	Decreased middle cerebral artery velocity	0.005
Yüksel (2006)	Kocaeli, Turkey	16 XFS, 21 XFS glaucoma and 18 controls	Clinic-based case-control study	Ischemic brain damage	<0.05
Kocabeyoglu 2013	Ankara, Turkey	40 XFS and 40 controls	Clinic-based prospective comparative study	Cerebrovascular disease	0.026
Kan (2017)	Samsun, Turkey	50 cerebrovascular disease and 50 controls	Cross-sectional case-control study	Ischemic cerebrovascular disease	0.02
Chung (2018)	worldwide	1308 XFS in 11 studies	Meta-analysis before 2017	Cerebrovascular disease	1.76 (1.40-2.22)
Chung (2018)	worldwide	9583 XFS in 20 studies	Meta-analysis before 2017	Cardiovascular disease	1.61 (1.37-1.90)
Rumelaitienė (2020)	Kaunas, Lithuania	1033 followed 10 years with XFS prevalence increasing from 10.3% to 34.2%	Longitudinal population-based study	Ischemic heart disease	1.5 (*P*=0.014)
Djordjevic-Jocic (2012)	Nis, Serbia	60 XFS, 60 XFS glaucoma, 60 open-angle glaucoma and 60 with cataract	Clinic-based 4-group comparison	Infrarenal AAA	<0.05
Sarenac-Vulovic (2014)	Kragujevac, Serbia	20 XFS, 20 XFS glaucoma, 20 controls	Clinic-based cross-sectional study	Abdominal aneurysm	10% versus 0% *P*=0.018
Wang 2014	Meta-analysis	16 studies 8533 XFS and 135,720 controls	Meta-analysis before 2014	Vascular disease	1.72 (1.31-2.26) for any vascular disease, 1.61 (1.22-2.14) for coronary heart disease, 1.59 (1.12-2.23) for cerebrovascular disease, and 2.48 (1.30-4.72) for aortic aneurysm

AAA: Abdominal aortic aneurysm, XFS: Pseudoexfoliation, CI: Confidence interval, OR: Odds ratio

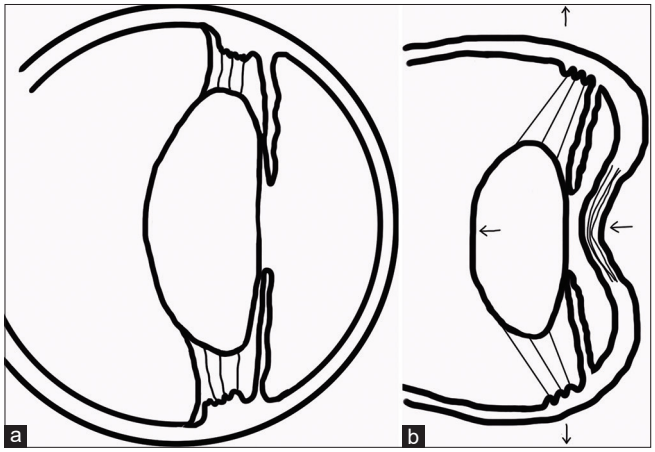

Figure 1: Sketch of a cross-section of the anterior globe centered around the zonules. (a) Normal section. (b) Section during rubbing. With vigorous knuckle rubbing or blunt trauma to the central cornea, the cornea indents with retraction of the lens and stretching of the ciliary body causing sudden elongation of the zonules

widening of the pars plana. This causes severe zonular stretching over several milliseconds [Figure 1b]. Second, there is compression of the angle, iris, ciliary body, anterior vitreous, lens over the area rubbed, resulting in squeezing injury to the zonules [Figure 2a and b]. Third, XFS material can act as cutting fulcrum when eye is rubbed or traumatized. Note that flaccid cornea, or eyes with hypotony, or have more distortion of cornea and more indentation of the globe.

Delori *et al*.[126] used the technology of high-speed cinematography and single-flash high-speed photographs to document the globe deformation in 75 pig eyes immersed in gelatin, with high impact pellet to the center of the cornea. The distance between the posterior pole of the lens to the vitreous base elongated by 28% at 0.4 ms and shrank by 13% (from baseline) at 1 ms before resuming baseline level. If we extrapolate similar changes in humans, this deformation translates to sudden distension of the zonules by around 3 mm. The same applies after vigorous rubbing, but the distension of the zonules is slower and milder as witnessed by rubbing videos by volunteer on dynamic medical imaging (Investigating Eye Rubbing with Dynamic Medical Imaging, www.defeatkeratoconus.com). The equator of the vitreous base measures around 21 mm

Table 8: Systematic literature review of patients with early onset pseudoexfoliation pseudoexfoliation (<age 45 years)

Author publication date	Age at diagnosis of XFS (years)	Primary ocular disease	Surgery	Trauma	Remarks and Country
Keratoconus (or allergic conjunctivitis)					9 patients
Yüksel (2005)		Developmental cataract	Extracapsular cataract extraction with sulcus posterior chamber implant age 6	No	Corneal topography revealed a central steepening resembling keratoconus Turkey
Konstas (1997)	13	Congenital glaucoma	Trabeculectomy in infancy	No	Allergic conjunctivitis and lid dermatitis Greece
Küchle (1992)	42	Keratoconus	Penetrating keratoplasty both eyes with XFS appearing 4-5 years later in both eyes	No	Germany
Küchle (1992)	37	Keratoconus	Penetrating keratoplasty at 31 years	No	Germany
Hørven (1967)	35	Keratoconus	Penetrating keratoplasty age 24	No	USA
Konstas (1992)	42	Keratoconus age 19	Penetrating keratoplasty age 29 with long radial iridotomy	No	Only right eye had XFS Greece
Sampaolesi (1997)	3 patients: 21 and 2 other young cases	Keratoconus	Penetrating keratoplasty	Not mentioned	Argentina
Ocular surgery					9 patients 2 with penetrating trauma and 7 with glaucoma
Sugar (1976)	26	Penetrating trauma	Repair of laceration age 11 months	Penetrating trauma	USA
Fakhraie (2012)	30	Traumatic glaucoma and cataract	Repair of limbal-scleral laceration	Limbal-scleral laceration age 4 years	Iran
Hørven (1967)	31	Juvenile glaucoma	Iridencleisis age 16	No	USA
Fakhraie (2012)	13	Congenital glaucoma	Goniotomy age 6 months then trabeculectomy age 2 years both eyes	No	Only right eye had XFS Iran
Amini (2012)	43	Juvenile glaucoma	Argon laser trabeculoplasty age 28; then posterior lip sclerotomy; then trabeculectomy	No	Only left eye had XFS Iran
Amini (2012)	40	Juvenile glaucoma	Trabeculectomy age 27 then Ahmed valve	No	2 episodes of blebitis; Only left eye had XFS Iran
Amini (2012)	40	Juvenile glaucoma	Argon laser trabeculoplasty age 36 then trabeculectomy age 37	No	Only left eye had XFS Iran
Amini (2012)	18	Congenital glaucoma	Trabeculotomy age 1 year; then trabeculectomy twice; then Ahmed valve	No	Only left eye had XFS Iran
Kumar (2019)	28	Developmental glaucoma	Trabeculectomy age 2	No	India
Survey or case report					17 patients
Hørven (1967)	31	NM	NM	NM	USA
Hørven (1967)	35	NM	NM	NM	USA
Bartholomew (1971)	7 XFS <40 years	NM	NM	NM	Bantu tribe South Africa
Tarkkanen (1962)	31	NM	NM	NM	Finland
Taylor (1977)	35	NM	NM	NM	Australia
Summanen (1988)	38	NM	NM	NM	Saudi Arabia
Khanzada (1985)	32	NM	NM	NM	Pakistan
Joannides (1961)	39	NM	NM	NM	Greece
Als (1980)	2 XFS <40 years	NM	NM	NM	Iceland
Oliveira (2006)	42	NM	NM	NM	USA

NM: Not mentioned, XFS: Pseudoexfoliation

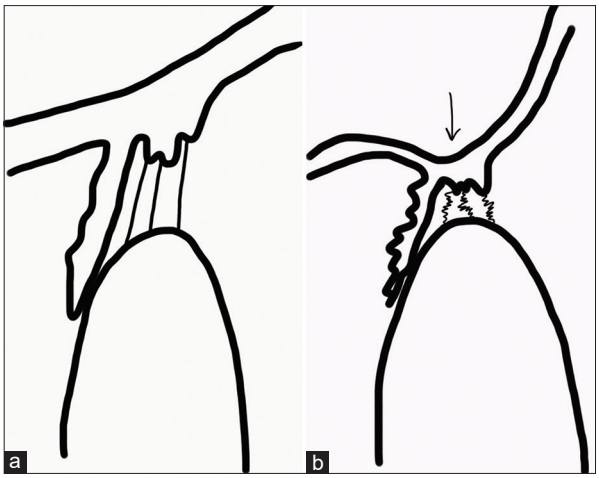

Figure 2: (a) Small section through limbus. (b) Section of limbus after ocular rubbing on the limbal area. If rubbing center on the limbus or pars plana, there is contusion of the zonules by a smashing effect

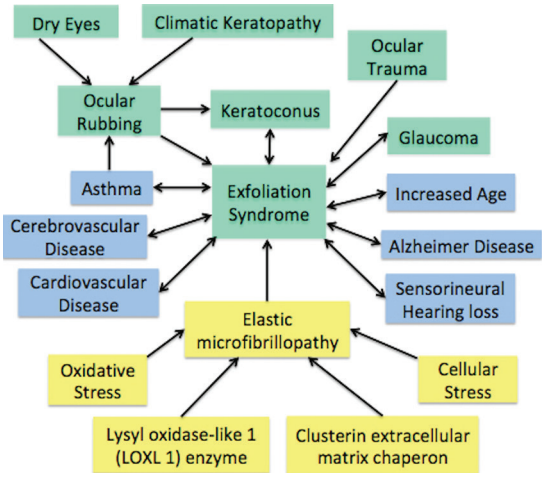

Figure 3: Proposed pathophysiology of associated ocular, systemic, and biochemical factors in relation to exfoliation syndrome

Table 9: Possible causes of ocular rubbing, dry eye and allergic conjunctivitis in pseudoexfoliation subjects

1. Decreased basal tear secretion[14-22]
2. Loss of goblet cells[101]
3. Meibomian gland dysfunction[23]
4. Deposition of XFS material in conjunctiva[102,103]
5. Degenerative changes in conjunctiva similar to changes in Alzheimer (Presinilin) or Parkinson (alpha synuclein)[7,63,64]
6. Auto inflammatory disease of ocular surface[57,58,104,105]
7. Vaso-occlusive disorder (loss of limbal vascular pattern)[106]
8. Asthma association with XFS[42,66]
9. Keratoconus associated with young patients having XFS[82,87]

XFS: Pseudoexfoliation

in normal eyes and expands by 28% or near 3.0 mm on either side of the zonules over a fraction of a millisecond in pellet or rub model. Superfast distension of the zonules leads to more breakage than gradual distension; hence, the breakage distension at high speed is estimated to be around 1 mm or so.[127]

Itching from atopy or dry eye is a trigger for chronic aggressive rubbing. Other causes of ocular rubbing include several disorders associated with an obsessive-compulsive form of ocular rubbing: Tourette syndrome,[128] Leber's congenital amaurosis, retinitis pigmentosa,[129] and the extreme form of the oculo-digital reflex also known as the pop-eye phenomenon.[130] To control chronic rubbing that may be the cause of XFS, there is a need for an increased vigilance and care of the eyes in XFS patients in the form of: education, meticulous therapy of ocular surface disease (preservative free antiallergic and lubricant, therapy of meibomian gland dysfunction or blepharitis), wearing of safety glasses, psychologic consultation or need for/ pharmacotherapy. Larger studies are needed to delineate the subset of XFS that relate to environmental factors.

Based on the above data [Tables 2-9], we propose that ocular rubbing [Figure 3] leads in susceptible eyes to keratoconus, iridoschisis, disruption of zonules, and partial tears of anterior capsule around zonules.[113,131-133] Following severe rubbing, the intraocular pressure can rise to 100 mmHg[109] with collapse of peripheral anterior chamber, with the zonules becoming stretched or compressed by the posterior part of the iris, leading to tearing.

The current study suffers from the shortcoming of any survey and from the small number of participants. However, the strength of the study includes near absence of nonresponse (high nonresponse rate can result in bias of the measures of outcome) and combining the current data with data from the systematic literature review, leading to a proposed comprehensive pathophysiology of XFS. Scientific evidence has shown that XFS is a multifactorial disease involving complex interaction of possible genetic and environmental factors. Our study and review of the literature point to a new factor (ocular rubbing) implicated in the pathogenesis of XFS and hence the need to better manage concurrent ocular surface disorder in these patients. Further studies with larger numbers of patients are needed to delineate more clearly the contribution of ocular rubbing, ocular surface disease, and other ocular or systemic or genetic factors [Tables 5-8] to the development of XFS.

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Conflicts of interest

There are no conflicts of interest.

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