

Review of pseudoexfoliation syndrome: Prevalence, Ocular clinical profile and related complications evaluated by different diagnostic methods

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Abstract:

Pseudoexfoliation syndrome (PEX) is an age-related, worldwide, the multisystemic disease has significant variations in prevalence in a different race, lifestyle, and geographic area. It is diagnosed by the appearance of grayish-white fibrilla granular material on several extraocular and ocular tissues, including lens surface, iris surface, pupillary margin, zonules, corneal endothelium, trabecular meshwork, and ciliary process. Ocular hypertension, glaucoma, and cataracts are more frequently present in patients with PEX.

In this article, the prevalence of PEX in different aged groups and population, its clinical presentation, related complications are presented.

Keywords: Pseudoexfoliation syndrome, pseudoexfoliative material, glaucoma, cataract, OCT, EDI-OCT, OCTA

Introduction:

Pseudoexfoliation syndrome (PEX) is an age-related complex multisystemic disease characterized by the production and progressive accumulation of abnormal extracellular fibrilla-granular deposition. Pseudoexfoliative material (PEM) is detected in all ocular and several other extraocular tissues in visceral organs such as the heart, lungs, liver, kidneys, cerebral meninges, gallbladder, vessel walls, optic nerve and skin. PEX are strongly associated with systemic comorbidities or comorbidities, including cardiovascular diseases, such as aortic aneurysms and cerebrovascular diseases such as dementia. In eyes, PEM can be detected on the lens, iris surface, pupillary margin, corneal endothelium, furthermore, zonules, ciliary processes, vitreous face, even on vitreous strands if the anterior hyaloid is ruptured. (1-7)

Lindberg ⁽⁸⁾ was first described exfoliation syndrome in 1917, as the presence of small whitish-gray material deposited on the pupillary margin, later in 1926, Vogt ⁽⁹⁾ named this disorder "capsular glaucoma" and explained

that presence of whitish material on the pupillary border could come from peeling of the anterior lens capsule. Subsequently, in 1954 Dvorak-Theobald ⁽¹⁰⁾ used the term "pseudoexfoliation syndrome," after observing the presence of PEM on the anterior lens capsule, zonules, and ciliary body.

PEM has been proposed a kind of elastosis that results from excessive production of elastic microfibrillar components, and/or insufficient breakdown of the basement membrane. PEM is composed of the amyloid-beta peptide, laminin, collagen, fibrillin, elastin, and other elastic fibers evaluated by both unique light-microscopy and ultrastructural examination. (11-16)

The exact pathogenesis and etiology of PEX are not fully explained, and multiple epidemiological factors play a role in the pathogenesis of PEX, including environmental and geographic factors such as increased sun exposure, living in lower latitudes, lifestyle, and dietary factors, genetic predisposition, and aging have been postulated. (1-3,7,16)

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Prevalence :

Even PEX was used to be known as “Viking disease”, because it frequently presents in northern European countries, especially Scandinavians, it has been reported in all countries and different races. (7,14,15)

Several population-based studies showed that the prevalence of PES across the globe, varying from 0% to nearly 40%. The prevalence of PES has been shown to vary significantly between several ethnic populations and geographic localization, due to differences in examination methods such as with or without pupillary dilatation in addition to inclusion criteria.

Epidemiological studies have reported that the PEX occurs 0% in Eskimos, 1–2% in the United States, 1.5% in Northern Nigeria, 2.1% in the Chinese population, 1.87–9.7 % in India, 3.8 - 4.14% in Upper Egypt, 4.5% in Malays, 4.7% in Australians, 6.45% in Pakistan, 11% in Turkey, 19.53% in Yemen, 25% in the Scandinavian countries, and 38% in Navajo Indians. (17-29)

Age and PEX:

PEX is an age-related disease, and its prevalence increases markedly with aging that more commonly presents after the age of 60 years. Forsius et al. (30) reported that the incidence of this syndrome doubled every decade after the age of 50 years. The occurrence of PEX is negligible in the middle-aged population, such as 0.7% younger than the age of 50, but it increases to 22.2% in the subjects above the age of 80 years in Saudis. (15) Similarly, in the Tanjong Pagar survey, the prevalence of PEX was reported by 0.2% in the age of 40 years that rose to 0.7% in subjects over 60 years of age in Chinese Singaporean. (19) Jonas et al. (31) reported that the prevalence of PEX is 0.95% at Central Indian populations at the age of 30 and above. The prevalence was reported 5% in Americans aged between 75–85 years and 6.25% in Australians aged 85 years or older. (25) In the Reykjavik Eye Study reported that the overall 12-year incidence increased from 6.5% in aged 50–59 years at baseline to 10.6% in the subject at 70–79 years of age in Iceland. (32) Govetto et al. (33) reported that PEX was not observed in patients younger than 50 years. However, the prevalence is progressively

increased with the aging that it presents 6.1% between 50 - 60 years old, 7.3% between 60- 70 years old, 19.1% between 70 - 80 years old, and 31.7% over 80 years old subjects among the patients scheduled for cataract surgery. Similarly, Al-Shaer et (28) observed PEX in 10.1% of patients aged between 41 and 50 years and 28.8% over the 81 years old. Joshi and Singanwad (5) found PEX in 4.42% cases of 51–60 year-age group, which further increased to 35.8% in subjects older than the 81-year-age group.

Gender Distribution:

In the literature, there are conflicting studies presented about the gender-wise distribution of PEX, but most of the reports showed no sex predominance. In the series of Al-Saleh et al. (15), the prevalence of the disease among males was 3.7%, while 3.4% in females. It was reported that the male to female ratio of PEX was 1:1.27 in India. Similarly, Moreno et al. (34) reported an equal frequency of PEX among men and women in the Spanish population. However, female predominance was observed in the Reykjavik study. (29)

In contrast, exfoliation syndrome was more common in men in some series. including Australians, Indians, Turkish, and Yugoslavs. (15) In a series reported from China, PEX prevalence is 0.4% in males, and no cases were observed in females, while in Nepal, its prevalence among males was more than four times higher than that of females.(35,36) The exact mechanism of the higher rate of PEX in males is not well explained but, it has been attributed to the fact that men are longer outdoor working that may cause more exposed the provoking climatic conditions.(1)

Laterality in PEX:

Even the PEX is a systemic disease, and it may present with unilateral as well as bilateral involvement. Joshi and Singanwad (5) observed bilateral involvement in 38.1%, whereas unilateral involvement in 62% of cases. In contrast to their observation, Gelaw and Tibebu (37) reported that 33.3% of unilateral involvement, whereas 66.7% of bilateral involvement. Similarly, 52% of unilateral and 48% of bilateral PEX cases were reported in The Blue Mountains study. (14) Several researches observed high conversion rates from unilateral to bilateral cases in time, such as in the Reykjavik study,

in which 70% case converted to the bilateral case in 12 years (29,32) Puska and coworkers⁽³⁸⁾ have reported that 32% conversion from unilateral to bilateral PEX.

Vesti et al.⁽³⁹⁾ stated that the PEX is never strictly unilateral; the no exfoliative fellow eyes also show some similar morphological alterations and demonstrate exfoliative material on the immune histochemical study. Similarly, ultrastructural studies by electron microscopy demonstrated the presence of PEM in the clinically normal fellow eye of unilateral cases. A classic slit-lamp finding of grayish-white fibrillar depositions on the anterior lens capsule represents a late stage of this syndrome, which is preceded by a chronic, progressive preclinical course. (1,12,13,40)

Ophthalmic features in PEX:

Correct diagnosis of PEX can be made only by observing pathognomonic grayish-white fibrillar exfoliative material on the different parts of anterior segment structures such as lens surface after pupillary dilatation, iris surface and pupillary border by slit-lamp examination.

Lens and Cataract:

Chronic progressive accumulation of PEM on the anterior lens capsule increased both the precapsular layer of the lens and irido-lenticular contact. Continuously rubbing of the iris over the lens surface during pupillary movement cause typical focal defects on the mid-peripheral zone of the precapsular layer of the lens. This hallmark of the characteristic pattern consists of three distinct zones of PEM; the most central disk-shaped zone corresponding nearly to the pupil diameter, the peripheral zone can only become visible after the full pupillary dilatation, a clear intermediate zone in between two zones. Idakwo et al.⁽¹⁸⁾ observed that all patients had the PEM on the peripheral zones of the lens. Several studies reported a similar feature that PEM can be observed in almost all cases, while the central disk is reported not to be present in 20%–60% of cases with PES. (1,12,13,16,41,42) [Fig 1-3]

Fig 1: Pseudoexfoliation material on the central disk shaped zone



Fig 2: Fibrillo granular deposition of Pseudoexfoliative material in midperipheral zone

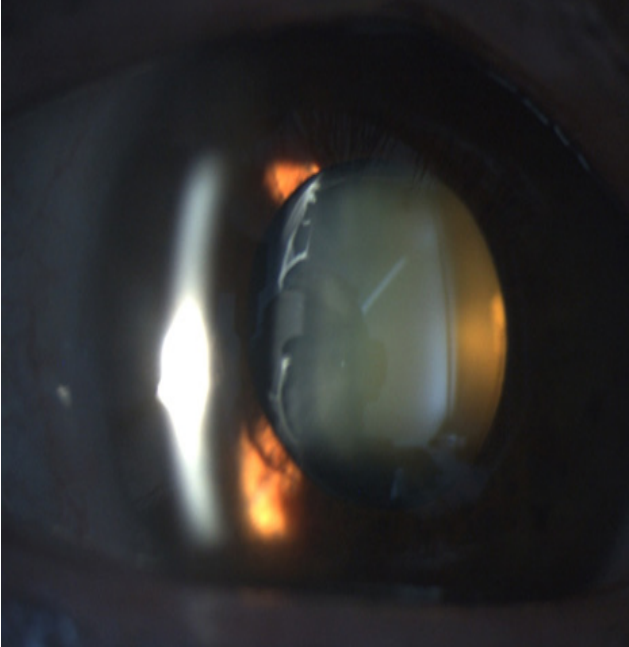
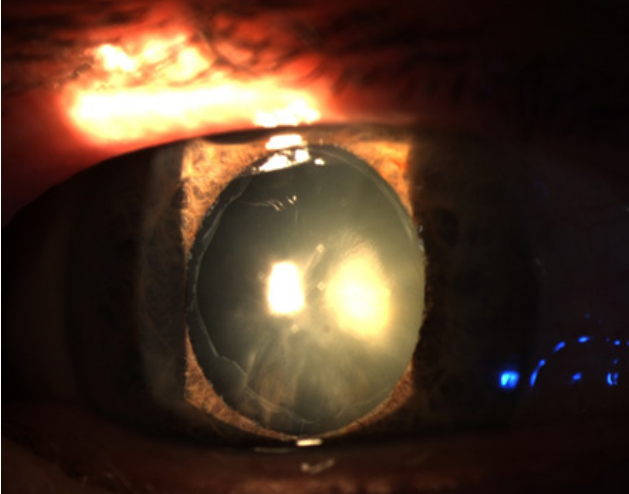


Fig 3: Pseudoexfoliative material in peripheral zone



PEM may also appear on the intraocular lens surface, on the posterior capsule, anterior hyaloid surface, and lens zonules. The deposition of PEM leads to zonules become more fragile, wreaked, and reduced zonular integrity is clinically presented with phacodonesis with eye movements and a reduction in cornea lenticular distance, owing to a forward shift of the lens with unstable zonules. In some advanced cases, zonular fragility increases the risk of zonular dialysis, lens subluxation, or dislocation. Zonular dialysis occurs up to 10 times more frequently in eyes with PEX comparing to normal eyes. The incidence of spontaneous lens subluxation or phacodonesis is changing from 8.4% to 10% in eyes with PEX.(41-44)

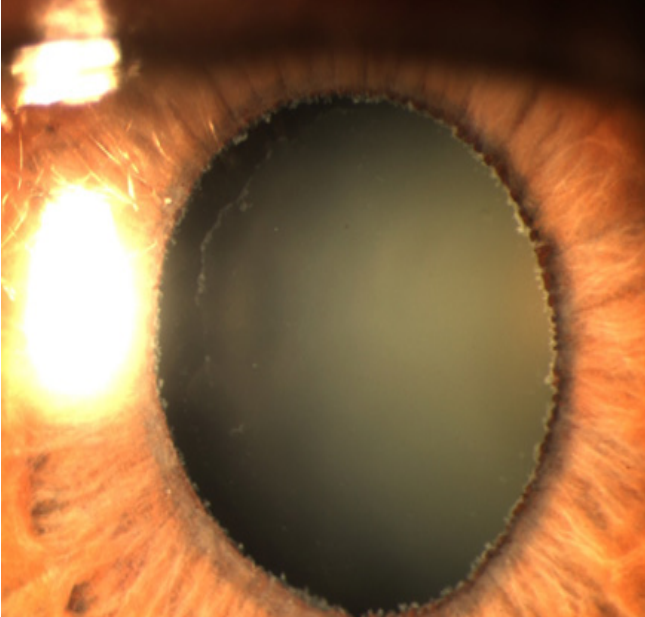
A cataract is frequently present in this disease. Al-Saleh et al. ⁽¹⁵⁾ reported the cataract in 26% of their subjects. Joshi et al. ⁽⁵⁾ reported the 22.1% of PEX in patients scheduled for cataract surgery. In their study, the frequency of cataract type was reported as 11.5% nuclear, 11.1% cortical cataract, whereas 43.4% hyper mature cataract, among the eyes with PEX. Grade VI cataract based on Lens Opacity Classification System III (LOCS-III) was reported 41.3% in their patient. They reported that a high prevalence of hyper mature cataracts with advanced grade is due to the late presentation of patients for surgery in rural India.

Population-based with long follow-up studies showed that PEX was a strong predictor of cataract development, that increased risk 2 -3 fold in multivariate analysis.(45)

Iris:

As a result of abrasive movements of the iris over the anterior lens surface, a dandruff-like PEM over the pupillary margin, loss of pupillary ruff, iris sphincter transillumination, as well as patchy iris depigmentation were seen as common appearance of PES. Al-Saleh et al. ⁽¹⁵⁾ study flakes on the pupil margin were reported in 62.3% of the eyes with PEX contrast to their report the Joshi and Singanwad ⁽⁵⁾ observed PEM distribution on the pupillary margin is only 15.9% eyes while its accumulation on combination of the iris, pupil, and lens in 30.9% of eyes in PEX. [Fig 4]

Fig 4: Dandruff like Pseudoexfoliative over the pupillary margine



Increased pigment dispersion in the anterior chamber after pupillary dilation, cause pigment accumulation on the iris surface as well as trabecular meshwork and corneal endothelium. Iris vascular abnormalities such as blood-aqueous barrier dysfunction, degenerated, narrowed, and even completely obliterated vessels due to intravascular aggregates of PEM with large molecular weight proteins are common clinical features in advanced stages of PEX. Pupil ruff atrophy and patchy iris depigmentation may also caused by recurrent ischemic attacks combined with mechanical disruption due to irido-lenticular contact. Due to accumulation of flakes on the pupil margin combined with atrophy cause poor pupillary dilatation in more than 40% of cases. (1,5,15,46)

Cornea:

Diffuse, scattered flakes of PEM on the corneal endothelial surface frequently be observed. Relatively homogeneous pigment particle accumulation on the central endothelium may cause the Krukenberg spindle pattern in some cases. Direct involvement of corneal endothelial cells by PEM and pigment particles, slowly progressing accumulation of extracellular matrix, fibroblastic alternation in the endothelium, hypoxic changes in the anterior chamber, cause a decrement of corneal endothelium density evaluated by specular microscopy studies. PEX associated corneal endotheliopathies are increased the risk of endothelial decomposition and corneal

edema even after minimally invasive surgical manipulations and only with moderate rises in IOP. Decreased corneal stroma and corneal basal epithelial cells cause thinning of corneal thickness as another morphologic alteration of disease. (47-49) Besides, a decreased in sub-basal neural integrity has been correlated with the decreased in corneal sensitivity and impaired tear film stability. (16)

Anterior Chamber Angle and Glaucoma :

An early sign of PES, dispersed melanin pigment accumulate on the peripheral cornea, anterior to Schwalbe’s line, present with undulating dark pigmented lines named as Sampaolesi line. Moderate to excessive pigmentation observed on trabecular meshwork in 56% of PEX is a prominent feature of clinically evident cases. (1,3,5,21)

In addition to the slit-lamp examination, Ultrasound-biomicroscopic evaluation shows several other morphological alterations such as increase lens thickness, decreased central anterior chamber depth, abnormalities of the zonules, and occludable angles. Optical coherence tomography (OCT) investigations of anterior segment demonstrated, decreased anterior chamber angle, increased iris convexity during pupillary dilatation, narrower angle widening, and increased irido-lenticular contact. In cases diagnosed unilateral PEX with the slit-lamp examination, have similar features to some degree in clinically normal fellow eyes, demonstrated either by Ultrasound-biomicroscopy or OCT. (42,43,50,51)

A strong correlation between increased intraocular pressure and PEX has been reported by several reports. In the Blue Mountain study, eyes with PEX in either eye have a two- to a threefold higher risk of glaucoma.(14) In Thessaloniki Eye Study, glaucoma was observed 15.2% of eyes with PEX, which was higher than that of in eyes without PEX (4.7%).(3) The high rate of pseudoexfoliative glaucoma (PXG) was reported in different other series such as 16.7% in Govetto et al. (34) series, similarly 16.7% in South Indian study, 26% in Yildirim et al. (28), 30.3% in Shazly et al. (28), 34%in Sood et al. (52) report. Different types of glaucoma can be present among the eyes with PEX; PXG was reported 14% and Ocular Hyper Tension (OHT) 9% in eyes with PEX,

according to the Blue Mountains Eye Study. (14) Rao and coworkers (51) observed glaucoma in 25% and OHT in 20% of unilateral cases while more than 50% (675 of 1250 eyes) glaucoma in bilateral cases with PEX.

Even the mechanism of increased intraocular pressure in PEX has been evaluated by numerous investigators, it is not exactly explained. It has been suggested that accumulation of PEX material may block normal trabecular drainage of aqueous humor, which in turn results in increase intraocular pressure. Pigment dispersion from iris-pigment epithelium during pupillary movement and its accumulation in the anterior chamber angle is another mechanism for increased IOP and glaucoma development. Besides, increased lens thickness may cause Lens induced and Primary Angle Closure Glaucoma (PACG). In the series of Rao et al. (51) PACG was observed in 13.7%, Lens induced in 3.7%, and Normo Tension glaucoma in 0.8% in eyes with PEX. PEX progress continuously from a milder form to more severe forms, with eventually develop glaucomatous optic nerve damage, and vision loses. Visual field defects are more severe at the time of diagnosis and progress more rapidly with frequent vascular ischemic episodes in PXG compared with non-exfoliative glaucoma. PXG is difficult to treat with medication and more prone to have complications at the time of surgery. (3,14,15,28)

Posterior Segment Involvement evaluation by different diagnostic methods:

Hemodynamic and vascular structures are significantly effected in PEX eyes, which are demonstrated by various imaging methods.

The PEX material accumulation in the vascular structures may damage the vessel walls, then disrupt the normal perfusion and cause hypoxia or even recurrent silent ischemic attacks in both anterior and posterior segments. Yüksel et al. (53) reported a significant reduction in peak systolic and diastolic flow in the ophthalmic artery, central retinal artery, and short posterior ciliary arteries in eyes with PEX. Several hemodynamic studies evaluated by color Doppler ultrasound showed an increase in vascular resistance and a decrease in flow in the optic nerve head and peripapillary area in eyes with PEX in. Several studies reported that mainly ischemic Central Retinal Vein Occlusion

(CRVO) and Branch Retinal Vein Occlusion risk increased due to disruption of retrobulbar circulation in eyes with PEX. (54-56)

The superficial retinal vascular plexus is the main vascular supply for the ganglion cells in the retinal nerve fiber layer (RNFL). El-tutar et al.⁽⁵⁷⁾ observed the significant RNFL and superficial retinal layer thinning in eyes with PEX comparing to healthy non-PEX eyes by OCT evaluation, as an indirect evidence of the reduced blood flow and vessel density in the superficial retinal layers. Rao⁽⁵⁸⁾ found that Significant RNFL thinning in one or two quadrants in 48 of 59 bilateral and 18 of 32 unilateral eyes with PEX. The fellow eyes of patients with unilateral PEX have prominent RNFL thinning even in the absence of PEM anywhere in the eye as an indicator of early glaucoma.

Besides, the superficial retinal thinning, a significant reduction in choroidal thickness was demonstrated by enhanced depth imaging-OCT(EDI-OCT) in eyes with PEM comparing to healthy eyes. According to several comparative studies, these EDI-OCT findings may be caused by ischemia due to a reduction in the choroidal blood flow from existing vasculopathy by the PEM. (59,60)

Optical coherence tomography angiography (OCTA) is a recently developed imaging modality that evaluates retinal and choroidal microvascular structures without the using a contrast agent. OCTA as a non-invasive angiography obtained the images by measuring the red blood cell velocity. To date, it has been used in the diagnosis of various retinal vascular pathologies. (61,62)

Park and Yoo⁽⁶²⁾ showed a significantly lower peripapillary vessel density in patients with PXG comparing to primary open-angle glaucoma (POAG) even without any significant difference in terms of RNFL thickness. Similarly, Rebolleda et al.⁽⁶³⁾ observed significantly lower capillary density in PXG compared to that in POAG with the similar glaucoma damage levels. These findings supported the other authors' studies by OCTA, suggest that the indirect evidence of damage caused by PEM, particularly in the endothelium of the peripapillary small vessels. (61,62, 64)

In addition, to a decrease in peripapillary vessel density, decrement macular foveal vessel density with avascular zone enlargement was reported. In OCTA measurements, both the superficial capillary plexus and the deep capillary plexus were enlarge in PEX eyes compared to healthy eyes. (61,62, 64)

Çınar et al.⁽⁶¹⁾ reported that the OCTA measurements showed significantly lower flow in the total, parafoveal, and foveal area both in foveal superficial and deep capillary plexus in PEX eyes than that in healthy eyes. Further, more vessel densities were significantly lower in these areas both in foveal superficial and deep capillary plexus in PEX eyes comparing to healthy eyes. At the same time, the differences were not significant between PEX eyes and fellow non-PEX eyes. These results showed that the PEX-related vascular pathology starts before the clinically detected PEM accumulation. OCT and OCTA are very useful diagnostic tools for identifying the development of PEX-associated delicate pathologies even before clinical diagnoses of PEX.

In conclusion, PEX is an age-related systemic disease that occurs worldwide, and its prevalence rates vary extensively based on racial, ethnic, geographic factors in addition to age and gender. This extracellular matrix disorder characterized by fibrillar material in different tissues such as on the lens surface, iris surface, pupillary margin, lens zonules, corneal endothelium, trabecular meshwork, and ciliary body. As a result of progressive accumulation PEM and chronic destruction in different parts of anterior segment tissues, PEX is associated with high incidence visual disruption due to different types of glaucoma and cataract development. In addition to RNFL involvement, a decrease in retinochoroidal circulation and vessel densities may be developed even before clinically diagnosed with PEX. The further advance studies will help to understand the pathophysiology of PEX and its early diagnosis even before the development of clinical signs.

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