Relation between Pseudoexfoliation Syndrome and Age-Related Cataract

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KEYWORDS

Pseudoexfoliation syndrome, cataract, glaucoma, extracellular matrix, ocular disease.

ABSTRACT

Background: Pseudoexfoliation syndrome (PXF) is a widespread, age-related systemic disease characterized by an atypical deposition of fibrillar extracellular materials. PXF syndrome is closely intertwined with ocular pathologies, particularly with regard to glaucoma and cataract development, and can have a significant impact on both visual function and general wellbeing.
Objective: The present study aims to review pathogenesis, clinical features, risk factors, and epidemiologic trends of PXF, with a strong focus placed on its association with age-related glaucoma and cataracts.
Methods: A thorough review of current literature was conducted in an attempt to assess the biochemical, genetic, and environmental factors responsible for PXF. In addition, the study covers its ocular complications, its challenging diagnostics, and its therapeutic options.
Results: PXF represents a key etiological factor in secondary open-angle glaucoma and increases surgical complications in cases of cataract. Genetic predisposition, oxidative stress, and environmental factors contribute towards its development and progression. PXF varies in prevalence geographically, with a high prevalence in older age groups.
Conclusion: Early and continued observation in cases of PXF is important in preventing severe loss of vision. Progress in an understanding of molecular processes involved in PXF could lead to effective therapeutic interventions. Targeted therapeutic interventions and preventive strategies will require additional studies to develop them.

Introduction

Pseudoexfoliation syndrome (PEXS) is an age-associated systemic disorder characterized by abnormal production and turnover of extracellular matrix (ECM), leading to the progressive deposition of extracellular, fibrillary, white flaky deposits in different tissues and organs of the body. ECM is a 3-dimensional network of interacting macromolecular effectors that apart from tissue support and integrity affects growth factors availability, cell signaling and functional properties such as oxidative stress (OS) pathways [1]. The most affected ocular tissues reveal deposition of Pseudoexfoliation material (PEXM) in the pupillary margin of the iris [2].

These aterations are responsible for pathological changes and sequelae in the anterior part of the eye, such as cataracts, zonular weakness, phacodonesis, lens subluxation/dislocation, iris rigidity and synechiae, blood-aqueous barrier dysfunction, melanin dispersion, capillary haemorrhage, poor mydriasis, radial body complication, trabecula impairment, keratopathy, and even retinal vein occlusion in the posterior eye segment [3].

Research has revealed a correlation between pseudoexfoliation syndrome and diabetes mellitus, arterial hypertension, and ischemic heart disease [4].

Ophthalmic effects of PXF

PXF ocular manifestations are directly evident through visualization of fibrillary material deposition using slit lamp biomicroscopy. PXF can be seen unilaterally or bilaterally. Unilateral cases may become bilateral over time, as this is a systemic disease that increases in severity with age. Whether unilateral or bilateral, PXF has significant ocular morbidities, all of which can result in significant visual impairment or blindness. This highlights the importance of investigation to better understand the etiology of PXF with a goal of identifying curative, rather than temporizing, treatments [5].

1) Glaucoma

Glaucoma, a progressive optic neuropathy, is defined by structural alterations in the retina and optic nerve, including selective loss of retinal ganglion cells (RGCs) and thinning of the retinal nerve fiber layer (RNFL), alongside functional visual field (VF) deficits typically located at the sites of these structural changes [6].

Glaucoma is a leading cause of blindness globally and results in progressive visual field loss due to optic nerve damage. Glaucoma often occurs in the setting of elevated intraocular pressure (IOP). Globally, PXF is the leading cause of the open-angle glaucoma, accounting for up to 25% of all glaucoma cases. Conversely, 15 to 30 percent of those diagnosed with PXF will subsequently develop PXF glaucoma (PXG). PXG demonstrates increased severity compared with other forms of primary open-angle glaucoma (POAG). In PXG, increased IOP results from the deposition of fibrillary material in the trabecular meshwork, the drain of the eye [7].

2) Cataract

Cataract is the leading cause of preventable blindness and vision loss, accounting for 51% of global blindness. Cataract is present when the natural lens becomes opaque and can result in low night vision, decreased vision, blindness, double vision, and decreased contrast sensitivity. Most cataracts involve central, nuclear lenticular changes and are age-associated. Cataract blindness disproportionately affects low-resource areas worldwide due to limited access to preventative eye care services [8].

Age-related cataract is the predominant cause of blindness worldwide, responsible for 51% of all cases. The majority of cataract cases arise in developing nations [9].

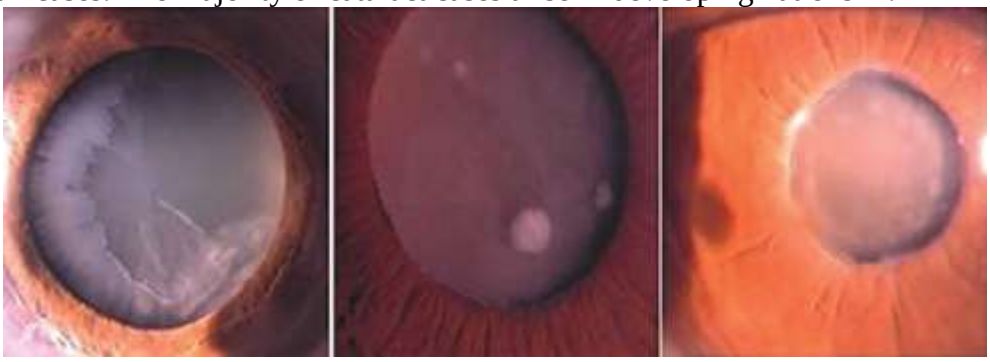

Figure 1: Cataract development is associated with pseudoexfoliation syndrome.

3) Other ocular manifestations

Other less well-characterized ocular manifestations of PXF include lens dislocation and dry eye syndrome. As a result of ocular surface and eyelid fibrillary deposition, tear production and osmolarity are altered, resulting in decreased tear break up time, poor tear quality, and dry ocular surface. Individuals with PXF are therefore at a higher risk for developing dry eye disease. Lens dislocation may occur in individuals with PXF after cataract surgery. Additionally, research has shown that individuals with PXF are at a higher risk of developing intraocular lens dislocations than individuals having cataract surgery without PXF [10].

Epidemiological risk of PXF

1) Age

PXF is an age-related disease as its risk increases with age. Clinical evidence of PXF is uncommon under 40 to 50 years of age. To date, only 12 cases of PXF have been identified in those aged less than 40 years. In contrast, PXF can affect up to 25% of individuals aged 60+ years old [11].

2) Sex

As is the case with other medical conditions, including osteoarthritis, stroke, and lupus, women experience PXF at higher rates than men. This may because in most places around the globe, women live longer than men, and age is a risk factor for PXF. Additionally, women in low-resource countries/regions have poorer detection and prevention of PXF due to less access to general preventative and medical care [12].

Environmental factors affecting PEXS onset and progression:

Nutrition plays an essential role in the progression and pathogenesis of PEXS (Figure 1). A diet containing nutrients such as selenium can regulate the PEXS onset and progression. OS has also been linked to PEXS pathogenesis in the presence of nutrient deficiences. Specifically, regular consumption of dietary fibre-rich vegetables and fruits, particularly when started from a young age, has been related to a lower risk of PEXS occurrence, signifying an antioxidative and protective role against this condition. Similarly, mild to moderate caffeine consumers were less likely to present PEXS than those who consume a lot of coffee. It has been proposed that caffeine consumption on a long-term basis may contribute to a continuous PEXM accumulation in the eye [13].

Moreover, caffeine consumption has been shown to increase plasma homocysteine (Hcy) concentrations. Since Hcy has also been found elevated in AH, tear fluid and serum of PEXS patients, it could be suggested that the Hcy-increasing effect of caffeine may signify a good association between coffee consumption and PEXS. It is also known that Hcy has pro-oxidant action. Its high concentrations may participate in the abnormal ECM repair detected in PEXS and other tissues, thus explaining the high vascular risk observed in PEXS patients. Therefore, it would be rational for such patients, especially those with bilateral eye involvement, to have total serum Hcy levels screened [13].

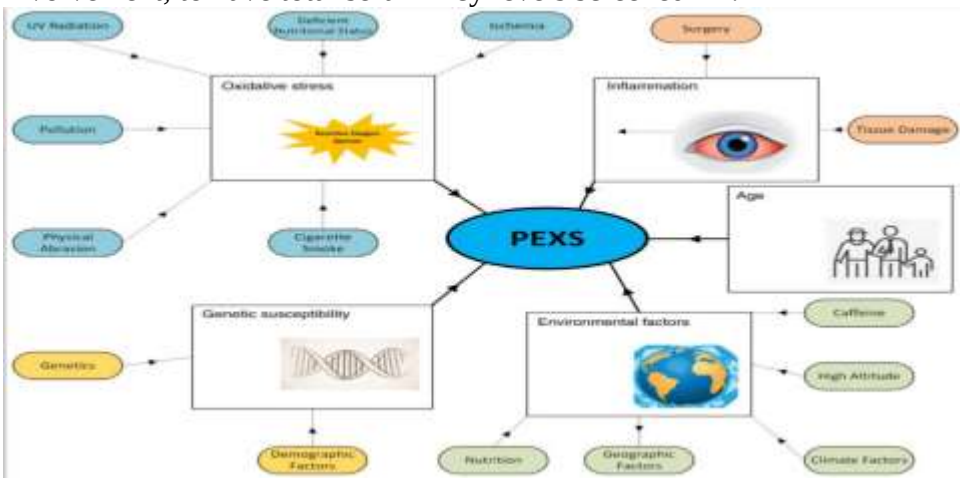

Figure 2: Factors associated with the onset and progression of PEXS. PEXS, pseudoexfoliation syndrome [13].

Genetic susceptibility of PEXS

Genetic studies conducted in populations worldwide clearly suggest a significant role of genetics in the pathogenesis of PEXS (Figure 1). Initially, the genetic basis of PEXS was uncovered through a genome-wide association study (GWAS) conducted on northern Europeans. Two single nucleotide polymorphisms (SNPs), rs1048661, and rs3825942, located in the coding region of the lysyl oxidase-like one gene (LOXL1), were linked to the development of PEXS in Scandinavians [14].

Pathogenesis of PEXS

The pathogenesis of PEXS manifested mainly through the generation and deposition of insoluble fibrillary extracellular material on connective tissues and tissues close to the bloodstream. Other pathological changes that contribute to the PEXS include dysregulated degradation and ECM production, increased inflammation, and enhanced OS. Since PEXM is insoluble, it aggregates at the trabecular meshwork and blocks the normal flow of AH and thus, increasing the intraocular pressure in the eye. Although the primary cause is not yet understood, it is hypothesized that the PEXM deposition is one of the reasons for complications, including cataracts, zonular weakness, and lens dislocation [13].

1) LOXL1

Defects in the functions of LOXL1 are one of the major contributors to abnormal deposits of PXEM in ocular tissues. LOXL1 essentially maintains the homeostasis of fibrillar ECM via regulating the generation, maintenance and repair of the elastic connective tissue. LOXL1 essentially acts as a framework element ensuring spatially defined elastin deposition. Particularly, LOXL1 is involved in the crosslinking of elastin and collagen through its pro-peptide, which binds to both fibulin-5 and tropoelastin to target elastic microfibrils at elastogenesis sites [15].

2) TGF-β1

Another critical protein involved in the ECM remodelling and the pathogenesis of PEXS is tumor growth factor-β1 (TGF-β1), a fibrosis-associated growth factor found in high levels, specifically in fibrotic diseases and experimental fibrosis models. Increased TGF-β1 levels were noted in the AH of PEXS patients, and it has been associated with the production of several elastic fibrillary elements, like fibrillin-1, that comprise the PEXM [16].

Notably, TGF-b1 is one of the most vital factors that triggers the expression of both LOXL1 and fibrillin-1, which is the critical element of PEXS fibrils. Additionally, these factors also seemed to activate the construction of a specific elastic microfibrillar network into PEXS-like fibrils, suggesting the contribution of TGF-β1 in the PEXM deposition [17].

3) Clusterin

Studies suggest that TGF-β1 activation causes downregulation of clusterin (CLU), a molecular chaperone essential for folding denatured and misfolded proteins in the AH during the PEXM generation. CLU is a glycoprotein component of biological fluids and is found at higher levels in ocular cells. CLU isoforms act as an extracellular chaperone that reduces abnormal aggregation of proteins by favouring their unfolded state for proper refolding [18].

4) Fibulin-5

Studies have suggested that LOXL1 activity is tightly regulated by fibulin-5 (FBLN5), an extracellular scaffold protein. FBLN5 plays a crucial role in the activation of LOXL1, thereby controlling the deposition of elastin in the ECM. Notably, FBLN5 activates LOXL1 via binding to the N-terminus of LOXL1. Studies have suggested that two polymorphisms that have been found in the noncoding part of the FBLN5 gene could be a risk factor for PEXS [19].

Clinical Manifestations

It is important to emphasize that PES is a significant ocular problem. Most patients with pseudoexfoliation are asymptomatic. Older patients should be carefully examined for diagnosis of pseudoexfoliation by biomicroscopy. Pupillary dilation is necessary to detect deposits on the lens surface. Classic signs of PES include fluffy, white deposits at the anterior lens surface and pupillary margins [20].

1) Intraocular pressure

Eyes with PES were shown to have higher IOP than non-involved fellow eyes. This difference is approximately 2 mmHg. Diurnal IOP fluctuation is also greater in patients with PES than in non-pseudoexfoliation subjects [21].

2) Tear film

PEM is associated with reduction in tear secretion and tear film stability. A study demonstrated that tear osmolarity in both eyes of clinically unilateral PES patients is higher compared to normal subjects [22].

3) Cornea

Small, fluffy, white pseudoexfoliation deposits may be observed on the corneal endothelium in patients with pseudoexfoliation **(**Figure 3) together with some pigment deposition on the central corneal endothelium (Figure 4) [20].

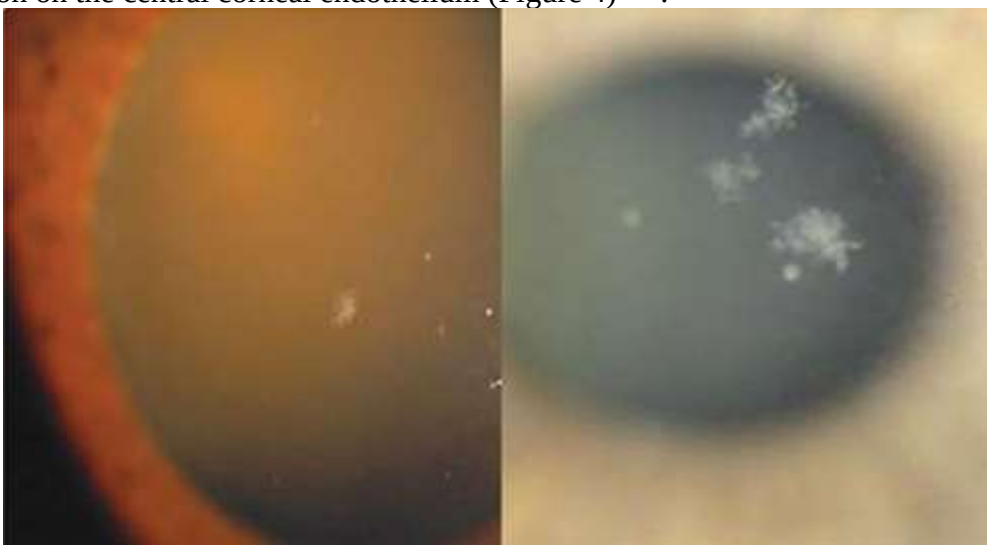

Figure 3: Pseudoexfoliation material deposition on the corneal endothelial surface in pseudoexfoliation syndrome [20].

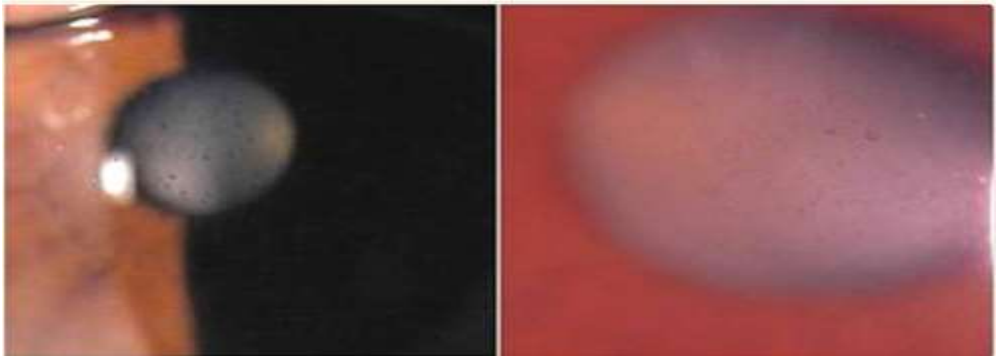

Figure 4: Pigmentary deposits on the corneal endothelial surface in pseudoexfoliation [20].

4) Iris

Deposits of PEM on the pupillary border and stroma and muscle tissues of the iris are among the changes seen anterior to the lens (Figure 5). Pseudoexfoliation is associated with pigment loss from the pigment epithelium over the iris sphincter, loss of pupillary ruff, and transillumination defect of the pupillary border. The iris appears to be more rigid and often dilates poorly [23]

Figure 5: White deposits or flakes and "moth-eaten" pattern on the pupillary margin [20].

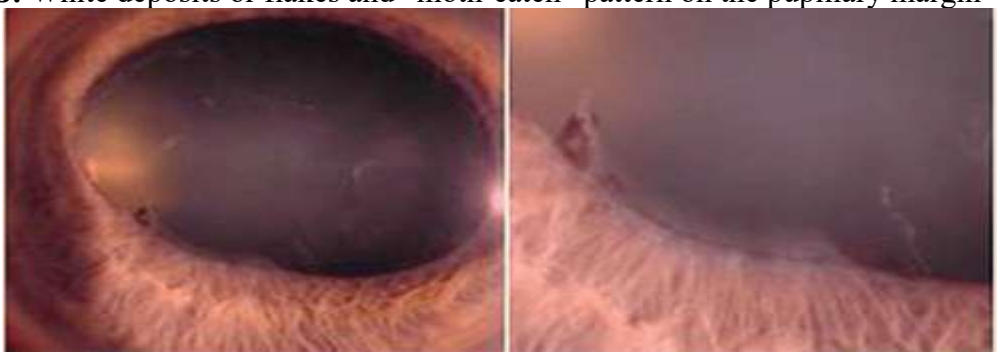

Figure 6: Pigment loss from the peripupillary pigment epithelium of the iris and synechiae between the pupillary border of the iris and anterior lens surface [20].

5) Lens

PES can be diagnosed by the observation of deposits of white material on the anterior lens surface. The epicapsular deposition appears as a homogenous diffuse ground-glass or matte film on the lens surface. As the epicapsular layer thickens, focal defects occur in the mid-peripheral zone. The classic appearance consists of a central disk, peripheral zone, and clear intermediate area. Eventually, pseudoexfoliation deposition with various appearances can be observed on the anterior lens surface (Figure 7). PEM can also be found on the surface of an implanted posterior chamber intraocular lens and the hyaloid face [20].

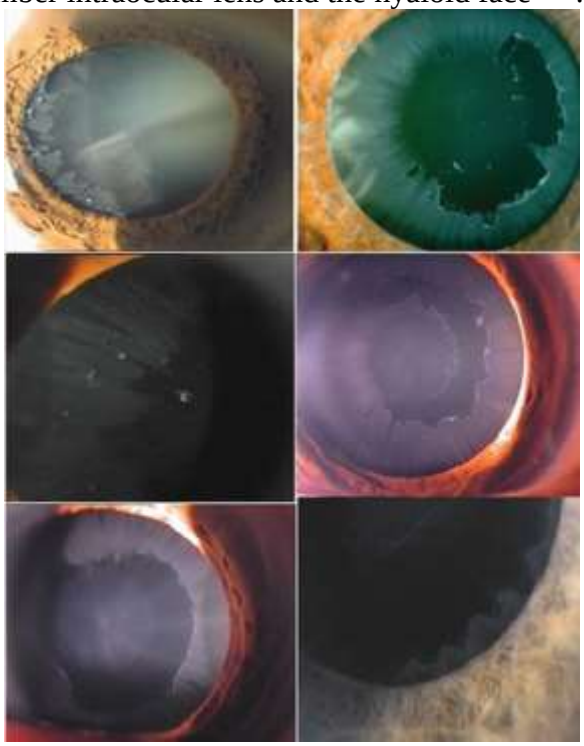

Figure 7: Pseudoexfoliation deposition on the anterior lens surface has a variable presentation. The classic appearance consists of a central disk, peripheral zone, and clear intermediate area separating the two areas [20].

6) Anterior chamber angle

The defining gonioscopic feature of PES is increased trabecular meshwork pigmentation, which often manifests as patchy involvement. The pigmentation is more prominent inferiorly. It is not as dense as that seen in pigmentary glaucoma (Figure 8). Small dust-like white pseudoexfoliation deposits may be observed at the angle [24].

In patients with pseudoexfoliation, gonioscopically determined angle pigmentation correlates more significantly with a higher presenting IOP than with the quantity of PEM on

the anterior lens capsule. The involved eye may have a narrower angle than the non-involved fellow eye [24].

Figure 8: Increased trabecular pigmentation may be seen in the anterior chamber angle during gonioscopy, usually on Schwalbe's line [20].

7) Zonules

Small dots and flakes of pseudoexfoliation deposits can be found earliest on the ciliary processes and zonules. Deposits on zonules may explain the clinically observed zonular weakness and lens subluxation or dislocation (Figure 9). Deposition of PEM on the zonules can be determined by high-resolution ultrasound biomicroscopic examination [25].

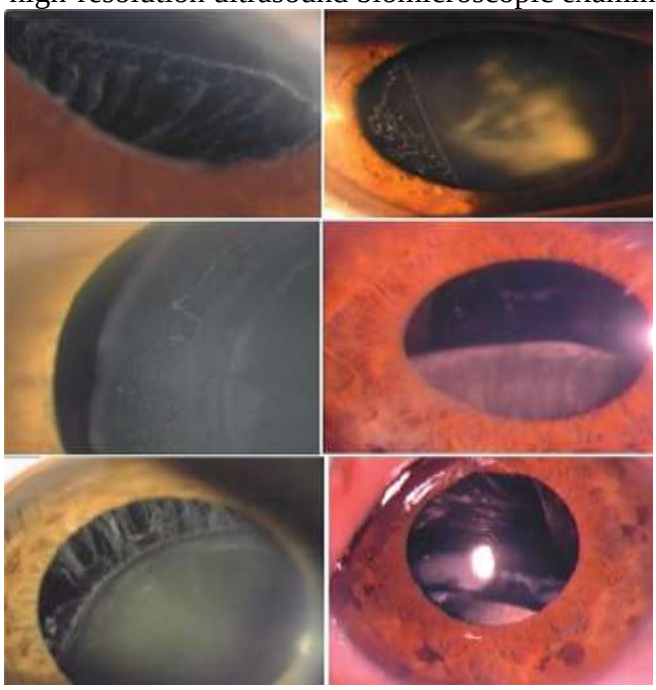

Figure 9: Patients with pseudoexfoliation can develop zonular weakness and lens subluxation or luxation caused by the progressive accumulation of pseudoexfoliation material [20].

pseudoexfoliation glaucoma

pseudoexfoliation glaucoma (PEG) may cause increased outflow resistance as a result of progressive accumulation of pseudoexfoliation material (PEM) in the trabecular meshwork, which contributes to alteration of retrobulbar blood flow and optic nerve microvascular blood flow, as well as elastosis of the lamina cribrosa [26].

Optical coherence tomography (OCT), one of several new technologies developed to evaluate structural alterations, has the potential to produce high resolution cross-sectional images of the retina in vivo (with axial resolution of 8–10Mm2 and quantifiable measurement of retinal thickness) [27].

Pathogenesis of pseudoexfoliation glaucoma

In recent decades, many clinical findings have contributed to our understanding of the pathomechanisms underlying PEG. Increased outflow resistance is related to the progressive accumulation of PEM in the trabecular meshwork and Schlemm's canal cells. Subsequent

degenerative changes in Schlemm's canal and juxtacanalicular tissues are causes of elevated IOP [26].

The additional pathogenetic factor contributing to pressure elevation is melanin dispersion. IOP-independent factors may contribute to glaucomatous damage as well. Reported IOP-independent factors include impaired ocular and retrobulbar blood flow velocities and increased accumulation of elastic fibers in the lamina cribrosa [28].

Types of glaucoma

IOP may rise over 50 mmHg despite a wide-open angle. Angle-closure glaucoma may be associated with PES (Figure 10). It is a relatively rare entity. Chronic or acute angle-closure glaucoma may occur. Pseudoexfoliation is known to cause zonular weakness, anterior lens subluxation or dislocation, posterior synechia and increased iris rigidity, and occludable angles. In addition, neovascular glaucoma may develop after central retinal vein occlusion with PEG (Figure 11) [29].

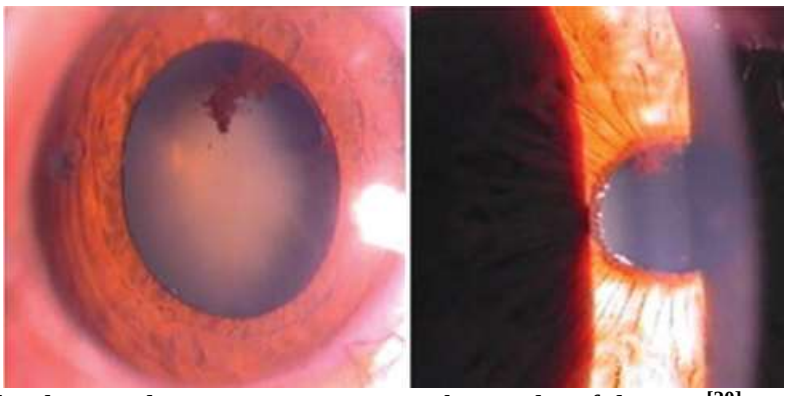

Figure 10: Angle-closure glaucoma in patients with pseudoexfoliation [20].

Figure 11: Neovascular glaucoma and Pseudoexfoliation [20].

Prognosis

The time of conversion from PES to glaucoma may take years. The risk of developing glaucoma is cumulative and IOP is an important risk factor. PEG has a more severe clinical course and a worse prognosis than POAG. Patients should be monitored at regular intervals [23].

Treatment

Numerous antiglaucoma medications, such as βadrenergic receptor antagonists, PG analogs, carbonic anhydrase inhibitors, adrenergic receptor agonists, cholinergic medications, and rho-kinase inhibitors, are currently on the market that reduce intraocular pressure (IOP) by increasing aqueous outflow and/or decreasing aqueous production. PG analogs are usually used as a first-line treatment for glaucoma patients because of their once-daily dosing advantage and effective IOP reduction [30].

PXF around the globe

1) Asia

As the largest continent globally, the most populous, and with many different cultures and communities in every region, the prevalence of PXF varies across Asia [31]. In Northern China, in one hospital-based study of 8,205 cataract patients aged 60+ years old, PXF was found to be quite low and found in only 0.55% of study participants [32]. In Pakistan, the prevalence of PXF has been reported to be 6.45% of the population. This was confirmed by a prospective study of 1,890 participants aged 45 to 87 years old that found that 40% of those with PXF had high IOP [33].

2) Africa

Several studies conducted in Africa have shown that the prevalence of PXF varies by geographic location. A cross-sectional study of 2,142 Congolese patients, (57.5% men) showed the prevalence of PXF was 1.7% [34].

3) Australia

There have been several studies conducted in Australia to identify the prevalence of PXF [35]. The Visual Impairment Project study cohort consisted of three distinct populations, including 3,271 urban participants aged 40 to 98 years old, 1,473 nursing home participants aged 46 to 101 years old, and 1,473 rural participants aged 40 to 95 years old. The sex breakdown was 46%, 21%, and 48% men, respectively [36]. Prevalence of PXF was 0.98% in the overall population but 6.0% in those aged 80–89 [35].

4) Europe

PXF prevalence has been well studied throughout regions in Europe [37]. The highest PXF in Europe reported was among Icelanders, Finns, Russians, and Lapps residing in Novosibirsk, Russia of 21% [38]. The lowest prevalence of PXF has been reported in the Greenland indigenous population at 0%, in a population-based study of those were 60+ years old which included multiple ethnicities [39].

5) North America

The prevalence of PXF can differ throughout North America's geography as the population is ethnically and racially diverse. In the Navajo American Indian population of Arizona, the prevalence of PXF was 38% [40], as seen in a hospital-based study which included 50 Navajo participants aged 60+ years old [40]. A prospective study conducted in the Southeastern Region of the US found the prevalence to be 1.6% in 1,216 female and 905 male participants aged 60+ years old [41].

6) South America

PXF prevalence differs across South America [42]. In a study that included 159 participants aged 50+ years old in Peru, the prevalence of PXF was 4.4% [43] and increased with age. Prevalence of PXF in Paraguay has been reported to be 17.1% in 268 female and 200 male patients aged 50+ years old with a diagnosis of senile cataract [42].

Conclusion:

Pseudoexfoliation syndrome (PXF) is an age-related condition with both systemic and ocular consequences, notably its close relationship with glaucoma and the formation of cataracts. The pathophysiologic mechanisms of PXF are characterized by the abnormal deposition of extracellular fibrillary material causing progressive ocular dysfunction, for example, raised intraocular pressure, lens subluxation, and failure of the trabecular meshwork. Epidemiological research has proposed that worldwide PXF incidence is determined through a complex interrelationship between genetic, nutritional, and environmental factors. Despite significant improvements in an understanding of PXF's genetic and biochemical pathophysiologic processes, effective modalities for therapy have not yet developed. Prompt diagnosis and ongoing observation and follow-up are critical for arresting long-term loss of vision and improving patient prognosis. Emerging studies must target the development of therapeutic modalities designed to stop disease progression and its complications. Integration of a multidisciplinary model that incorporates genetics, ophthalmology, and public health

programs is critical for arresting PXF's impact and its consequences for worldwide ocular health.

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