Major Review

Pseudo Exfoliation Syndrome:
An identifiable cause of Open Angle Glaucoma

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Introduction

Pseudo exfoliation syndrome (XFS) is an age-related, generalized disorder of the extracellular matrix characterized by the production and progressive accumulation of an abnormal fibrillar extracellular material in many ocular tissues and is the most common identifiable cause of open-angle glaucoma worldwide. Exfoliation syndrome plays an etiologic role in open-angle glaucoma, angle-closure glaucoma, cataract, and retinal vein occlusion. Glaucoma occurs more commonly in eyes with XFS than in those without it; in fact, XFS has recently been recognized as the most common identifiable cause of glaucoma. Patients with XFS are also predisposed to develop angle-closure glaucoma, and glaucoma in XFS has a more serious clinical course and worse prognosis than primary open-angle glaucoma.

History

In 1917, a Finnish ophthalmologist named Lindberg first described pseudo exfoliation syndrome. This entity is characterized by flakes of granular material at the pupillary margin of the iris and throughout the inner surface of the anterior chamber. It is also associated with secondary open-angle glaucoma, known as pseudo exfoliation glaucoma, which is the most common identifiable form of secondary open-angle glaucoma worldwide. Dvorak-Thebold suggested the term pseudo exfoliation to differentiate it from true exfoliation or lamellar delamination of the lens capsule found in glassblowers. True exfoliation syndrome is due to heat or infrared-related changes in the anterior lens capsule. Despite extensive research, the exact chemical composition of exfoliation material (XFM) remains unknown. An overproduction and abnormal metabolism of glycosaminoglycans have been suggested as one of the key changes in XFS. The protein components of XFM include both noncollagenous basement membrane components and epitopes of the elastic fiber system such as fibrillium. Regardless of etiology, typical exfoliation fibers have been demonstrated electron microscopically in close association with the pre-equatorial lens epithelium, the nonpigmented ciliary epithelium, the iris pigment epithelium, the corneal endothelium, the trabecular endothelium, and with almost all cell types of the iris stroma, such as fibrocytes, melanocytes, vascular endothelial cells, pericytes, and smooth muscle cells.

Pathophysiology

Pseudo exfoliation syndrome is a common ocular manifestation of a systemic disease, known to cause disease primarily in the eye. Exact etiology of this condition remains unknown. Exfoliation syndrome appears to be a disease of elastic tissue microfibrils. Despite extensive research, the exact chemical composition of exfoliation material (XFM) remains unknown. An overproduction and abnormal metabolism of glycosaminoglycans have been suggested as one of the key changes in XFS. The protein components of XFM include both noncollagenous basement membrane components and epitopes of the elastic fiber system such as fibrillium. Regardless of etiology, typical exfoliation fibers have been demonstrated electron microscopically in close association with the pre-equatorial lens epithelium, the nonpigmented ciliary epithelium, the iris pigment epithelium, the corneal endothelium, the trabecular endothelium, and with almost all cell types of the iris stroma, such as fibrocytes, melanocytes, vascular endothelial cells, pericytes, and smooth muscle cells.

Pseudo exfoliation material is associated with abnormalities of the basement membrane in epithelial cells and has a wide distribution throughout the body. Pseudo exfoliative material has been found in the walls of the vortex veins and the central retinal artery. Extraocular tissues involved include lung, skin, liver, heart, kidney, gallbladder, blood vessels, extraocular muscle, connective tissue in the orbit, and meninges. In the anterior segment of the eye, it is characterized by deposition of pseudo exfoliative amyloid like material on the anterior lens capsule, ciliary body, zonules, pupillary margin of the iris, corneal endothelium, anterior vitreous, and trabecular meshwork.

Some investigators believe that the iris pigment epithelium, the ciliary epithelium, and the peripheral anterior lens epithelium produce this pseudo exfoliative amyloid-like material, which moves into the aqueous humor and is carried to the trabecular meshwork, following the normal flow. Obstruction of the trabecular meshwork by this fibrillar material and pigment associated with degenerative changes in the Schlemm canal and the juxtacanalicular area causes elevation of the intraocular pressure (IOP) with associated glaucoma.

Zenkel et al have studied genes differentially expressed in anterior segment tissues and have postulated that pseudo exfoliation syndrome is a stress-induced elastic microfibrillopathy.

Frequency

Regional

In Asia, the prevalence in a Japanese population was 3.4%. Hospital-based studies showed a prevalence of 6.45% in Pakistan and 7.4% in India. A prevalence rate of 0.4% in patients aged 60 years or older was identified in China.

International

Roth and Epstein reported that pseudo exfoliation glaucoma was present in 12% of patients with glaucoma. In the Framingham study, prevalence of pseudo exfoliation syndrome was 1.8%. In a prospective study, Cashwell and Shields found that the prevalence of pseudo exfoliation syndrome in the south eastern United States was 1.6% of the total population and in 6% of an open-angle glaucoma subpopulation. Because of the increased mean age of populations, pseudo exfoliation syndrome may become more prevalent in the future. Prevalence of pseudo exfoliation...
syndrome in Europe was found to be 4.7% in England, 6.3% in Norway, 4% in Germany, 1.1% in Greece, and 5.5% in France.

Bartholomew reported an 8.2% prevalence of pseudo exfoliation syndrome in the Bantu tribes of South Africa.4

Race

Although it occurs in virtually every area of the world, a considerable racial variation exists in the incidence of pseudo exfoliation glaucoma. In Scandinavian countries, more than 50% of cases of open-angle glaucoma are caused by pseudo exfoliation syndrome. Pseudo exfoliation syndrome is relatively rare among African Americans and Eskimos. It was not observed at all in the Inuit who live throughout the Canadian Arctic. Prevalence is high in the Sami people who are indigenous of northern Europe. Among the Bantu tribes of South Africa, exfoliation was found in 19% of patients in a glaucoma clinic. In Saudi Arabia, Summanen and Tonjum reported a prevalence of pseudo exfoliation syndrome of 13%. Prevalence of pseudo exfoliation syndrome in Spanish Americans in New Mexico was estimated to be 3-6%.

Mortality/Morbidity

In a retrospective study, Shrum et al found no association between ocular pseudo exfoliation and cardiovascular or cerebrovascular mortality.5 However, other authors have found that pseudo exfoliation is linked with Alzheimer disease, senile dementia, cerebral atrophy, chronic cerebral ischemia, stroke, transient ischemic attacks, heart disease, and hearing loss. Vessani et al found that homocysteine levels were higher among patients with pseudo exfoliation syndrome and pseudo exfoliative glaucoma compared with controls.6 Roedl et al reported increased homocysteine concentrations in tear fluid and plasma of patients with pseudo exfoliation glaucoma.7 Elevated plasma homocysteine levels have been described as a risk factor for cardiovascular disease.

Sex

Pseudo exfoliation syndrome is more common in females than in males. In a series by Kozart and Yanoff, pseudo exfoliation syndrome was 3 times more common in women than in men.8

Age

Pseudo exfoliation syndrome is rarely seen before age 50 years, and its incidence increases steadily with age.

Clinical Evaluation

History

Patients may be asymptomatic, or they may complain of decreased visual acuity secondary to cataract or glaucomatous visual field changes.

Physical

Pseudo exfoliation syndrome is diagnosed clinically by slit lamp examination with an 85% sensitivity rate and a 100% specificity rate.

- Pseudo exfoliative material can be seen on the pupillary border of the iris without dilation. Pseudo exfoliative material is seen in the image below.
- The most commonly recognized feature is the 3-ring sign on the anterior lens capsule, formed by a central disc, a peripheral ring, and a clear zone, which separates the two. The clear zone varies in diameter and may exhibit curled edges.
- The central disc measures 1-2.5 mm in diameter and has well-demarcated borders.
- The peripheral ring typically is seen after pupillary dilation. Its size is variable, and its inner border has many radial striations.

Figure 1 - Pseudoexfoliation on lens capsule

- The translucent zone most likely is created by the physiologic rubbing of the posterior surface of the iris against the lens. It screes the pseudo exfoliative material from the surface of the lens. This scraping results in a secondary pigmentary dispersion syndrome, with a loss of melanin from the iris pigment epithelium at the pupillary margin adopting a sawtooth-like morphology. Accumulation of melanin granules in the trabecular meshwork ensues. Peripupillary iris atrophy is a common and distinctive finding. It is best visualized using infrared transillumination.
- Gonioscopy shows a discontinuous pigmentation of the trabecular meshwork, usually less dense than seen in pigmentary glaucoma. Also, pigment characteristically is deposited on the Schwalbe line or anterior to the Schwalbe line (the Sampaolesi line). A high incidence of narrow, or occludable, angles in eyes with pseudo exfoliation has been reported.
• Elevated IOP leads to glaucoma development in about 50% of patients. Puska et al reported that the conversion rate from pseudo exfoliation syndrome to pseudo exfoliation glaucoma was 3.2% per year. Jeng et al found that, in patients with pseudo exfoliation, the probability of developing glaucoma was 44% after 15 years, and, in a study by Grodum et al, 55.1% of patients developed glaucoma after a mean of 8.7 years.

• When glaucoma develops, it is frequently referred to as capsular glaucoma. Patients with pseudo exfoliation syndrome have higher IOP than patients with primary open-angle glaucoma. Because of these higher IOPs, visual field loss and optic nerve damage are more pronounced.

• Other signs of pseudo exfoliation syndrome are insufficient mydriasis, posterior synechiae, pigment deposition on the iris surface, deposition of pigment and pseudo exfoliation material on the corneal endothelium, pigment liberation after pupillary dilation, and pseudo exfoliation material covering the ciliary processes and the zonules. Phacodonesis, lens subluxation, and corneal endothelial decompensation can be present. An associated nuclear cataract is a common finding.

• Pseudo exfoliation syndrome typically presents unilaterally. Why this occurs remains unknown. The fellow eye develops signs of pseudo exfoliation in more than 40% of cases, but pseudo exfoliation material can almost always be demonstrated in fellow eyes on electron microscopy and conjunctival biopsy.

• Pseudo exfoliation syndrome is associated with reduced ocular blood flow, iris hypoperfusion, and anterior chamber hypoxia.

• Oxidative damage and free radicals may play a role in the disease. A decrease in ascorbic acid concentrations, increased 8-iso-prostaglandinF2a concentrations, and increased malondialdehyde concentrations have been reported.

Causes

Whether pseudo exfoliation syndrome occurs as part of a genetic process or in association with other diseases is not clear. Familial aggregation supports the notion that it may be inherited as an autosomal dominant trait with incomplete penetrance and late onset. Its frequency increases with age; however, it is not part of normal aging. Possible predisposing factors include ultraviolet light, northern latitudes, and altitude. Climate factors may not play a definitive role in the pathogenesis of the disease.

The exact nature of pseudo exfoliation material remains unknown, although its close association with zonular fibers supports the idea of pseudo exfoliation syndrome as a type of elastosis, affecting elastic microfibrils. It seems to arise from abnormal aggregation of elastin microfibrillar components.

• In 2007, Thorleifsson et al studied Icelandic and Swedish patients with glaucoma. They found that 2 nonsynonymous single-nucleotide polymorphisms (SNPs) (rs1048661, R141L; rs3825942, G153D) in exon 1 of the lysyl oxidase-like protein 1 gene (LOXL1) represent a major susceptibility variant for pseudo exfoliation syndrome and support the idea that the variant confers risk of glaucoma by causing pseudo exfoliation syndrome. These findings have been corroborated by Fingert et al in the United States. By fluorescence in situ hybridization, Kenyon et al mapped the human LOXL gene to 15q24-q25.

• The risk of pseudo exfoliation glaucoma is 700 times in individuals homozygous for the high-risk haplotypes. The 2 non-synonymous changes are highly associated with pseudo exfoliation syndrome and account for more than 99% of all pseudo exfoliation glaucoma cases from Iceland and Sweden and 88% of cases in Iowa. Fan et al found a strong association between non-synonymous single-nucleotide polymorphisms G152D, but not R141L, and pseudo exfoliation in a clinic-based population from the Northeastern United States.

• The LOXL1 gene has been associated with the lysyl oxidase family of proteins that has important roles in elastogenesis. LOXL1 pro-peptide binds to both tropoelastin and fibulin-5 and alterations of the gene could affect the catalytic activity of the protein producing modifications in the elastin fibers, a major pathophysiological component of the syndrome. LOXL1 serves as a cross-linking enzyme and to ensure proper spatial deposition of elastin.

• The high-risk haplotype of LOXL1 alleles is very common in Caucasians with a frequency of approximately 50% in the general population, 25% being homozygous for the haplotype. This indicates that, even though LOXL1 represents a significant risk factor for pseudo exfoliation, most persons with high-risk LOXL1 alleles do not have the condition. Therefore, other factors that remain to be identified must be involved.

• This finding in 2007 that two common single nucleotide polymorphisms in the coding region of the lysyl oxidase-like 1 (LOXL1) gene located on chromosome 15 were specifically associated with XFS and XFG should help in planning therapy. LOXL1 is a member of the lysyl oxidase family of enzymes, which are essential for the formation, stabilization, maintenance, and remodelling of elastic fibers and prevent age-related loss of elasticity of tissues. LOXL1 protein is a major component of exfoliation deposits and appears to play a role in its accumulation and in concomitant elastotic processes in intra- and extraocular tissues of XFS patients. This discovery should open the way to new approaches and directions of therapy for this protean disorder.
Glaucoma is a secondary event. Blockage of the trabecular spaces by pseudo exfoliation material promotes accumulation of pigment and cellular debris, which causes obstruction of the aqueous channels and limits access to the Schlemm canal. Accumulation of pseudo exfoliation material in the juxtacanicular tissue adjacent to the Schlemm canal leads to narrowing of the canal lumen, collapse of its walls, disruption of its endothelium, and partial obliteration. These changes appear to be the causative factors for chronic IOP elevation and pseudo exfoliation glaucoma.

- Zonular laxity allows forward movement of the lens, causing decreased anterior chamber depth and pupillary or angle closure glaucoma.
- Pseudo exfoliation syndrome itself does not produce optic nerve damage.

**Imaging Studies**

Various imaging technologies are being used to document and monitor changes due to glaucomatous damage in the optic disc and the retinal nerve fiber layer. These imaging techniques are similar to that in open angle glaucoma.

Optical coherence tomography (OCT) is a valuable tool in the evaluation of glaucoma. OCT provides a cross-sectional view of the scanned retinal area that allows differentiation between the retinal layers. The thickness of the retinal nerve fiber layer can be measured using this technique. The confocal scanning laser ophthalmoscope (Heidelberg retina tomograph [HRT]) provides topographical measures of the optic disc as well as indirect measurements of the retinal nerve fiber layer thickness. OCT and HRT have been used to help in the diagnosis and follow-up of patients with glaucoma. Both OCT and HRT have shown a high correlation between the retinal nerve fiber layer thickness and the visual field mean defect during achromatic perimetry. The GDx Nerve Fiber Analyzer has been reported to be a valuable tool in helping the clinician to discriminate between healthy eyes and glaucomatous eyes. Gonioscopy and visual field testing

**Histologic Findings**

Gottanka et al found marked differences in the optic nerve between primary open-angle glaucoma and pseudo exfoliation glaucoma.17 Eyes with primary open-angle glaucoma were found to have axon loss associated with more connective tissue in the septa and surrounding the central retinal vessels and a decrease in the density of capillaries as compared with eyes with pseudo exfoliation glaucoma where the capillary density did not change with axon loss.

**Medical Care**

- Patients with pseudo exfoliation syndrome should have annual eye examinations for early detection of glaucoma. Glaucoma in pseudo exfoliation is more resistant to medical therapy and has a poorer prognosis than primary open-angle glaucoma.
- The treatment of pseudo-exfoliation glaucoma is the same as that of primary open-angle glaucoma; however, topical medications tend to be less effective. Miotics lower IOP, but they aggravate the blood-aqueous barrier dysfunction and decrease iris mobility, thereby increasing the risk of posterior synechiae and cataract formation.
- Argon laser trabeculoplasty is frequently used with excellent initial success. Its hypotensive effect may be facilitated by enhanced heat absorption because of increased trabecular pigmentation.
- According to a published study, selective laser trabeculoplasty (SLT) has been shown to be equivalent to argon laser trabeculoplasty in terms of lowering IOP at 1 year. The theoretical advantage of SLT is that SLT is a repeatable procedure because it does not seem to produce thermal damage to the trabecular meshwork.

**Surgical Care**

- If medical therapy and laser therapy are unsuccessful to control the glaucoma, trabeculectomy can be performed with similar success rates to that of primary open-angle glaucoma. Because patients with pseudo exfoliation glaucoma have higher IOP, they tend to undergo glaucoma filtering surgery more frequently than patients with primary open-angle glaucoma.
- Cataracts occur more commonly in patients with pseudo exfoliation syndrome. Weakness of the zonular fibers, spontaneous lens subluxation, and phacodonesis also can be present. Therefore, in these patients, cataract surgery alone or combined cataract surgery and glaucoma filtering surgery in the presence of pseudo exfoliation is associated with a higher incidence of intraoperative complications, most notably zonular dialysis, vitreous loss, and lens dislocation. This occurs 5 times more frequently than in other cases. Naumann 1988, Seorolil 1998 and Shingleton 2006.
- The increased intra-operative posterior capsule complication rate appears to correlate with the level of cataract maturity. Modern surgical techniques involving the use of capsulorrhexis, small-incision surgery, and better viscoelastics have improved the surgical outcome. Capsular tension rings have been used to decrease surgical stress on the zonules. Intraoperative modification to reduce zonular stress should include (a) lower the bottle height for less anterior chamber dynamics and zonular stress. (b) More energy to remove lens and not to move it. Careful performance of I & A steps, newer phaco Ozil, Stellaris and Signature help reduce turbulence within the anterior chamber.
Several zonular support devices like iris (Figure 2) refractors and capsule tension ring along with newer OVD’s help in achieving better surgical outcome. Simple standard CTR or modified CTR (Cionis) can be placed (Figure 3). Ahmed CTR can be placed before phaco (Figure 4). Henderson modified CTR can be placed to facilitate cortical cleaning (Figure 5).

Postoperative cataract surgery complications can occur after uneventful operations due to continued destabilization of the zonules and capsular contraction and posterior capsular opacifications. Owing to increase in ageing population, more will have PXF. In PXF, there is likelihood of late in the bag dislocation (Fig. 6).

Shingleton in 2006 estimated this to be 2 in 100 cases of PXF. Davis et al 2009 quoted 50% of in the bag explants to be due to PXF. In order to prevent in the bag dislocation, the following measures could be resorted to:

1. CTR – may not prevent dislocation
2. Early YAG to prevent phimosis (either radially or circumferentially).
3. Suturing the haptic to the sclera
4. Placement of lens in the sulcus

Jacobi et al described a non-filtering surgical technique
consisting of trabecular aspiration with or without cataract removal with encouraging results. The operation attempts to increase the outflow facility along the trabecular meshwork by removing pretrabecular and trabecular debris using an externally applied suction device.

In summary, XFG does not respond well to anti-glaucoma medications. They tend to progress faster, are more refractory to treatment and often present with co-existing lens changes. The presence of XFS should alert the clinician to the increased risks of intraocular surgery, most commonly zonular dehiscence, capsular rupture, and vitreous loss during cataract extraction. Therefore, the decision of cataract or combined surgery should be weighed with caution in these patients. Heightened awareness of this condition and its associated clinical signs are important in the detection and management of glaucoma, and preoperative determination of those patients at increased risk for surgical complications.

References