Exfoliation syndrome

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Abstract

Exfoliation syndrome, previously known as pseudoexfoliation syndrome, is characterized by the production and progressive accumulation of a fibrillar extracellular material in lens, ciliary body, zonules, iris, trabecular meshwork, corneal endothelium, conjunctiva and orbital structures. Ocular hypertension or glaucoma develops within 10 years in approximately 40 percent, a risk approximately a ten times higher than that found in the general population. Annual checkups for early detection of glaucoma should be done so that medical management, laser trabeculoplasty and glaucoma surgery can be planned. This would help preserve the visual acuity for a longtime.

Keywords: Artificial intelligence, ophthalmology, diabetic retinopathy, digital screening, machine learning.

Introduction

Exfoliation syndrome (XFS), previously known as pseudoexfoliation syndrome, is an age-related disease characterized by the production and progressive accumulation of a fibrillar extracellular material in ocular tissues throughout the anterior segment like lens, ciliary body, zonules, iris, trabecular meshwork, corneal endothelium, conjunctiva and orbital structures. It is now known to be a systemic disease related in part to genetic and environmental factors with close associations with systemic pathology, including cardiovascular and cerebrovascular diseases.

Pathophysiology

Exfoliation syndrome an ocular manifestation of a systemic disease. Defects in elastin metabolism has been proposed to be responsible for the synthesis of exfoliative material since association with specific mutations of the lysyl oxidase-like protein 1 (LOXL1) gene, which is important in elastin metabolism, is strongly associated with XFS and exfoliation glaucoma (XFG). Histochemically, exfoliative material is made of glycoconjugates surrounding a protein core. The origin of exfoliative material is unclear; however, evidence suggests emergence from intraocular cells (trabecular and corneal endothelium, ciliary and lens epithelium and iris) and extraocular cells (fibrocytes, vascular and muscle).

Ocular pathology associated with XFS includes peripupillary iris depigmentation, trabecular meshwork hyperpigmentation (an early feature), secondary open-angle and/or angle-closure glaucoma, cataract, lens subluxation, corneal endothelial compromise and central retinal vein occlusion.

Clinical Features

XFS is three times more common in females than males. This condition rarely occurs before 50 years of age and the incidence increases steadily with age. XFS typically presents unilaterally. The fellow eye develops signs of exfoliation in more than 40% of cases, but exfoliation material can almost always be demonstrated in fellow eyes on electron microscopy and conjunctival biopsy.

Lens

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, in between (Figure 1).

Fig. 1: Image of exfoliation material on the lens capsule, demonstrating classic findings of central disc, lucid interval (arrowhead) and peripheral band.

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. The translucent zone most
likely is created by the physiologic rubbing of the
posterior surface of the iris against the lens.

**Iris** Fine flaky white material can be seen on the
pupillary border of the iris without dilation(Figure 2).

Physiological rubbing of iris against the lens scrapes
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. Peripupillary
iris atrophy is a common and distinctive finding. It is
best visualized using infrared transillumination (Figure 3).

**Pupil** Eyes with XFS often dilate poorly. Eyes with
XFS may also constrict less well to topical 4%
pilocarpine. Even without mydriatics, the pupil in the
involved eye may be smaller. Pigment dispersion in
the anterior chamber is common after pupillary
dilation and may be profuse causing marked IOP
elevation.

**Cornea** Scattered flakes of pseudoexfoliative
material may be observed on the endothelial surface
of the cornea. A greater than normal frequency of
cornea guttata in eyes with XFS has been suggested.

**Zonules and Ciliary Body** Exfoliation
material(XFM) may be detected earliest on the ciliary
processes and zonules and this creates a tendency to
spontaneous subluxation or dislocation of the
crystalline lens in advanced cases.

**Anterior Chamber Angle** Gonioscopy shows a
discontinuous pigmentation of the trabecular
meshwork, pigment characteristically is deposited on
the Schwalbe line or anterior to the Schwalbe line (the
Sampaolesi line)(Figure 4).

**Fig. 2 :** XFM on pupillary border. Photograph courtesy
of Dr Robert Ritch, MD. XFS, exfoliation syndrome.

**Fig. 3 :** Typical diffuse iris sphincter region
transillumination. Photograph courtesy of Dr Robert
Ritch, MD. XFS, exfoliation syndrome.

**Vitreous** After cataract extraction, XFM may be
found on the vitreous face or on vitreous strands when
the face is ruptured, on the posterior capsule and on
IOLs indicating that the presence of the lens is
unnecessary for its continued formation.

**Glaucoma in Exfoliation Syndrome**
Glaucoma is a secondary event. Exfoliation syndrome
itself does not cause optic nerve damage. Glaucoma
occurs more commonly in eyes with XFS than in
those without it, about six times more. Glaucoma in
XFS has a more serious clinical course and worse
prognosis than POAG. There is a significantly higher
frequency and severity of optic nerve damage at the
time of diagnosis, worse visual field damage, higher
baseline IOP, greater diurnal fluctuation of IOP, poorer response to medications, more severe clinical course, more rapid progression, and more frequent necessity for surgical intervention. Exfoliative glaucoma undergoes periods of exacerbations and remissions and appropriate management.

**Mechanism of Open Angle Glaucoma**
Blockage of the trabecular spaces by XFM promotes accumulation of pigment and cellular debris in the juxtacanalicular tissue, which causes obstruction of the aqueous channels and limits access to the Schlemm canal that leads to narrowing of the canal lumen, collapse of its walls, disruption of its endothelium, and partial obliteration.

**Mechanism of Angle Closure Glaucoma**
Zonular laxity allows forward movement of the lens, causing decreased anterior chamber depth and pupillary or angle closure glaucoma. Nuclear cataract is often more frequently found in eyes with XFS than in eyes without it. Patients with XFS are much more prone to having complications at the time of cataract extraction. Pupillary diameter and zonular fragility (and/or phacodonesis) have been suggested as the most important risk factors for capsular rupture, zonular dehiscence and vitreous loss (5-10 times more common) and should serve as a warning sign to the surgeon. Posterior capsular opacification is more in eyes with XFS compared to those without XFS. Late postoperative decentration of IOLs and capsular bags was reported to be significantly higher in eyes with XFS and was also related to zonular weakness. Capsule contraction syndrome is particularly common in eyes with XFS, particularly if the capsulorrhexis is small, and can lead to IOL displacement.

**Work Up**
History- Patients may be asymptomatic, or they may complain of decreased visual acuity secondary to cataract or glaucomatous visual field changes. Slit lamp examination- Pseudo exfoliation syndrome is diagnosed clinically by slit lamp examination with an 85% sensitivity rate and a 100% specificity rate. In an undilated eye, pupillary border may show XFM with peripupillary iris transillumination defects. On dilated examination, characteristic 3 ring sign on the anterior lens capsule may be seen. Presence of glaucomatous disc damage will indicate XFL glaucoma.

**Gonioscopy** shows a discontinuous pigmentation characteristically on the schwalbe's line or anterior to it (sampolesi line).

**Investigations**- Preoperative assessment prior to cataract extraction includes Ultrasound Biomicroscopy to diagnose any zonular laxity or lens subluxation. Specular microscopy can be done to ascertain reduced endothelial cell density or morphologic changes in size and shape of the endothelial cells.

In pseudoexfoliative glaucoma, Visual Fields are confirmatory of any glaucomatous disc damage. The glaucomatous disc changes and visual fields defect pattern is the same as in POAG. Various imaging technologies like Optical coherence tomography (OCT) and confocal scanning laser ophthalmoscope (Heidelberg retina tomograph [HRT]) are also 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 POAG. Anterior Segment OCT can suggest presence of any synecial angle closure or reduced depth of the anterior chamber.

**Differential Diagnosis**
Pigmentary glaucoma: characteristic signs are Krukenberg spindle, mid peripheral iris transillumination defects and homogenously darkly pigmented trabecular meshwork/sampolesi line. It is common in young males with myopia. Uveitis: Photophobia is a common symptom. In both exfoliative and uveitic glaucomas, corneal endothelial deposits are common. The ragged peripheral anterior synechiae of some inflammatory glaucomas in not seen in exfoliative glaucoma however angle closure due to narrow angles in not very uncommon in exfoliative glaucoma.

Capsular delamination/True exfoliation: Trauma, exposure to intense heat(glass blowers), or severe uveitis can cause peeling off of a thin membrane of anterior lens capsule.

**Primary amyloidosis**
- Primary open angle glaucoma
- Fuchs heterochromic uveitis
Treatment of Exfoliative Glaucoma

Medical Management

Glaucoma associated with XFS tends to respond less well to medical therapy than does POAG. Prostaglandins are effective in XFL glaucoma because they facilitate trabecular outflow directly and also by having an inhibitory action on matrix metalloproteinases and reducing the formation of exfoliative fibrils. Latanoprost is associated with a narrower range of diurnal IOP fluctuation.

XFG was reported to respond less favorably to timolol therapy than eyes with COAG, but some studies suggest an equal or greater ocular hypotensive response.

Dorzolamide is almost as effective as timolol and also is additive with it.

Cholinergic agents are effective and probably have a greater additive effect with beta-blockers in XFS than COAG.

Aqueous suppressants by decreasing aqueous secretion, result in decreased aqueous flow through the trabecular meshwork. Reduced perfusion results in failure of the meshwork to survive. Continued administration of oral acetazolamide produces a reduction in outflow facility and an elevation of IOP to greater than baseline after discontinuation.

Theoretically, miotics should be the first line of treatment. However, frequent presence of nuclear sclerosis in such patients, chance of development of posterior synechiae and tendency to cause pigment release with miotics make them less popular.

Lasers

Laser trabeculoplasty is particularly effective in XFL glaucoma owing to the relatively pigmented angles however the amount of IOP reduction is modest and long-term success drops to approximately 35–55% at 3–6 years. Also, eyes with XFS may have a greater post-laser inflammatory reaction than eyes without.

Selective laser trabeculoplasty (SLT) has been shown to be equivalent to Argon laser trabeculoplasty in terms of lowering IOP. The theoretical advantage of SLT is that SLT is a repeatable procedure because it does not produce thermal damage to the trabecular meshwork.

Laser iridotomy is the procedure of choice for angle-closure glaucoma. Angle-closure glaucoma caused by anterior lens movement or subluxation may also require argon laser peripheral iridoplasty to mechanically pull the iris away from the trabecular meshwork.

Surgery

If IOP remains uncontrolled following medical and/or laser treatment, surgical management is warranted. Trabeculectomy has similar efficacy and safety outcomes in XFG as in POAG.

Glaucoma drainage device implantation is also an option, especially in eyes with previous conjunctival manipulation.

Trabeculotomy as well as trabecular aspiration (TA) have been shown to be effective in the management of XFG. TA aims to improve trabecular outflow by removing pigment and exfoliative material.

Trabeculotomy combined with phacoemulsification is more effective than cataract surgery alone in reducing postoperative IOP and the necessity for antiglaucoma medication but not as effective as phaco-trabeculectomy.

There is some support for the use of Trabectome as well as the use of iStent, but prospective studies with longer follow-up are needed before one can recommend widespread use of these and possibly other microinvasive glaucoma surgical approaches.

Deep sclerectomy has been proposed in XFG, and one study found that patients with XFG had significantly higher success following deep sclerectomy with an implant compared with patients with POAG.

The role of endoscopic cyclophotocoagulation (ECP) in XFG is minimal as exfoliation material accumulates on the ciliary body and zonules, and high laser energy can result in rupture of ciliary processes with significant inadvertent haemorrhage.

Taken together, non-medical management of XFG is guided by mechanism, stage of glaucoma, degree of IOP elevation, ocular and systemic factors and patient and care provider preferences.

Cataract extraction in Exfoliation Syndrome

It is recommended not to delay cataract surgery. Moreover, a significant IOP-lowering effect has been found following cataract surgery in patients with PXF. Plausible theories for this include: washing out of fibrillar material from the angle, structural
alterations such as deepening of anterior chamber angle, decrease in irido-lenticular contact and inflammation leading to better aqueous outflow (trabeculoplasty-like effect).

**Conclusion**

Key recommendations to prevent complications during cataract extraction are summarised in the box below.

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XFS patients have approximately a 40% chance of developing ocular hypertension or glaucoma within 10 years, a risk approximately a tenfold higher than that found in the general population58 hence they should have annual checkups for early detection of glaucoma. Exfoliative glaucoma patients should also be more frequently followed up than POAG patients as progression can occur more rapidly.

**References**


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