Pseudoexfoliation syndrome is characterized by the development of white, dandruff-like flakes on the lens, pupillary margin, and other anterior segment structures in older patients. Pseudoexfoliation material has recently been found in sites other than the eye, and may be a diffuse basement membrane disease, or represent a generalized form of elastosis. Although the condition appears most frequently in patients with Scandinavian heritage, it occurs in almost all races and in all climates. In the United States, up to 28% of patients with open-angle glaucoma are found to have pseudoexfoliation syndrome, whereas in the Nordic countries this may be as high as 47%. 

Over time, nearly one half of all patients with pseudoexfoliation will have glaucoma, and, of patients with pseudoexfoliation syndrome and no glaucoma at the initial examination, 15% will develop elevated pressure after 10 years. Pseudoexfoliation glaucoma is more difficult to control than primary open-angle glaucoma, with higher intraocular pressures and a poorer response to medication. In addition, pseudoexfoliation may cause weakened zonules and poorly dilating pupils, predisposing the eye to complications during cataract surgery. Although no systemic disease is associated with pseudoexfoliation, the diagnosis of the condition by careful biomicroscopy should alert the clinician to the potential for glaucoma both at the initial examination and in the future, as well as for difficulties in cataract surgery.

**BACKGROUND**

Pseudoexfoliation syndrome was first described in patients from Finland, in whom it was noted in almost half of the patients with glaucoma. Initially thought to be an exfoliation or delamination of the lens capsule, as seen in glassblowers, several theories later arose as to the origin of the material. Some researchers felt that pseudoexfoliation was an abnormal precipitation of material upon the lens capsule, rather than an abnormality of the capsule itself, and termed it pseudoexfoliation. Recent studies have again pointed to the lens capsule as one source of the material, and have also found it in a variety of ocular and extraocular sites. Opinions on the exact terminology for the condition remain mixed, prompting a variety of other names, including senile pseudoexfoliation of the lens capsule, senile uveal pseudoexfoliation, fibrillopathia epitheliocapsularis, the basement membrane pseudoexfoliation syndrome, and glaucoma capsulare.

**EPISTEMOLOGY**

Numerous studies report high prevalence rates from Nordic countries, but this syndrome has also been described in most other peoples of the world. Prevalence rates vary not only among races, but also depending upon examination techniques. These include pupillary dilation, the examiner’s experience level, population age, and whether the data are collected prospectively or retrospectively. Prospective studies using pupil dilation are most likely to detect this condition because its early manifestations may be subtle. Pseudoexfoliation is common in Finland, where prevalence is 20%, and Norway, but less common in Denmark, Austria, and Switzerland, where the prevalence is 2% in each country. It has been reported in 10% of
blacks with glaucoma in South Africa, yet in only 0.4% of blacks in Louisiana, whose ancestral homes were mainly West Africa. Rates in other populations tend to be similar or lower: 4.4% in Peruvian Indians, 2% in India, and 1.8% in Massachusetts; and 0.2% in Japanese.

Currently, no studies have identified a specific inheritance pattern for pseudoexfoliation. This may be due to its onset late in life, when a patient’s parents have died and before their children are old enough to develop the condition.

Pseudoexfoliation syndrome is more common after age 50, and nearly doubles in incidence with each successive decade. Forsius reported a prevalence of 10% among Finns age 50 to 69 years, among Finns age 70+ years. The Framingham study found a 0.6% prevalence for people age 52 to 64, rising to 5.0% by age 75 to 85. In the few cases occurring in patients under age 40, all eyes had undergone prior intraocular surgery or trauma.

The high prevalence rates in Nordic countries might suggest that northern latitudes, cold air, hours of sunlight, or some other climate-related factor contributes to producing the pseudoexfoliation syndrome. However, no strong evidence for this exists. This syndrome is common in Laplanders but rare in Eskimos, who live at similar latitudes. It is also common in Saudi Arabia (13.2%), which has a different climate with more intense sunlight than the northern latitudes. Attempts to connect pseudoexfoliation with ultraviolet light exposure have been mixed, and this condition is not correlated with clinical signs characteristically associated with ultraviolet exposure, such as pterygia, climatic keratopathy, or cataract.

Pseudoexfoliation syndrome appears unilateral in about 50% of patients at the time of diagnosis. Because most theories of pathogenesis suggest a metabolic or degenerative cause, which should occur bilaterally, pseudoexfoliation may be a bilateral process with an asymmetric presentation. This is supported by the observations that, in clinically diagnosed unilateral pseudoexfoliation syndrome, up to 76% of uninvolved fellow eyes can have exfoliative material on their ciliary processes, although some, but not all, studies suggest that trabecular material can be present in such eyes.

How could a presumed systemic or genetic condition be unilateral? Although pseudoexfoliation syndrome may present unilaterally, most studies agree it is a bilateral condition with an asymmetric presentation.

**PATHOGENESIS**

Pseudoexfoliation material appears in many regions of the ocular anterior segment, as well as outside the eye, supporting the possibility that this is a generalized metabolic condition. Although the exact nature of the pseudoexfoliation material is currently unknown, it appears to play a prominent role in obstructing aqueous humor outflow and causing glaucoma.

**PATHOLOGY**

**Intraocular Pathology**

Pseudoexfoliation material arises in a variety of sites within the eye. Clinicians are most likely to see it on the anterior lens capsule, where it occurs in several regions, often in the peripheral granular zone (Fig. 20–1A–C). The posterior capsule does not appear involved, whereas the material seems to arise from the equator. Of interest, pseudoexfoliation material can appear on the vitreous face and anterior surface of intraocular lenses, often 5 or more years after cataract surgery. This suggests that the material is not produced by the anterior capsule, but gets deposited there from the aqueous humor.

Pseudoexfoliation also arises from the basement membrane region of the ciliary processes. Ultrastructurally, the material coats the ciliary processes and appears intermixed with a multilaminar basement membrane, whereas the zonules themselves appear intact. Accumulation of pseudoexfoliation material at the insertion of the zonular fibers into the ciliary body may weaken this attachment, leading to zonular rupture and lens dislocation.

In the iris, pseudoexfoliation material can appear in the iris pigment epithelium and blood vessel walls and on the anterior stroma. Clinically, it can be especially prominent on the pupillary margin. Microscopically, exfoliative material is intermixed with a duplicated and disorganized basement membrane of the iris pigment epithelial cells, which also show degeneration and disruption. The iris vasculature may contain subendothelial accumulations of material, often in conjunction with disrupted basement membranes. These changes may occlude the lumen in some areas, and produce dropout and leakage of iris vessels as seen with fluorescein angiography.

In the trabecular meshwork, pseudoexfoliation material appears in the aqueous channels of the uveal meshwork, the intertrabecular spaces, just anterior to Schlemm’s canal (Fig. 20–2A,B). These locations suggest deposition of material from the aqueous, although some, but not all, studies suggest that trabecular cells can produce this material directly. In advanced cases with glaucoma, the pseudoexfoliation material appears to disrupt Schlemm’s canal, causing it to fill with fibrous tissue and occlude the lumen of the
A curled edge of pseudoexfoliation material appears at the margins of the central disc (c) and peripheral regions. Note broken zonular fibers (z) at the equator in the foreground (20X). (B) Zonular fibers at the peripheral and equatorial region of the lens appear with granular balls of pseudoexfoliation material (arrowheads) (100X) that (C), at higher power, appear to consist of tangled balls of fine filaments (1000X).

Extraocular Pathology

Pseudoexfoliation material has been found in both the bulbar and the palpebral conjunctiva,5,19-22 where it is associated with both stromal and vascular elastic fibers.21,23,24 Streeten et al. reported an intermingling of the pseudoexfoliation fibrils with elastic fibrils and suggested
that the pseudoexfoliation syndrome may be a type of elastosis, resulting from an abnormal aggregation of components related to elastic microfibrils.

Several studies have found pseudoexfoliation material in sites distant from the eye, including skin from the eyelid, buttocks, and behind the ear. Here, too, it demonstrated a predilection for elastic fibers and appeared influenced by an accompanying dermal elastosis. Additional extraocular sites consist of the connective tissue of the heart, lungs, liver, gallbladder, kidney, and cerebral meninges. The lamina cribrosa of the optic disc appears to undergo elastosis to a greater extent than would be expected by intraocular pressure effects alone, although pseudoexfoliation material has not been identified in this region.

Despite the microscopic appearance of pseudoexfoliative material in these other tissues, patients do not have an increased mortality rate, although one study reported an association of pseudoexfoliation with vascular disease, including histories of angina, hypertension, or stroke.

**Composition of Pseudoexfoliation Material**

Many enzymatic, histochemical, and immunologic tests have been performed on pseudoexfoliative material. Under transmission electron microscopy, it appears as a tangle of filaments and fibrils embedded in an amorphous ground substance thought to consist of proteoglycans. The small filaments appear similar to elastic microfibrils, and the larger thick fibrils resemble aggregations of the small filaments. Light microscopy and lectin staining concur that proteoglycans are probably present in pseudoexfoliation material.
The nature and origin of pseudoexfoliation material are currently in dispute. Some contend that this material is related to abnormal production of basement membranes, whereas other evidence suggests that it results from elastic fiber degeneration.

Current theories suggest that pseudoexfoliation material may arise either from abnormal basement membrane, or from a degeneration of the elastic fiber system. Basement membranes are a mixture of material secreted by epithelial cells throughout the body. In addition to its association with duplicated, disrupted, or degenerated basement membranes, pseudoexfoliation material labels with antibodies directed against several components of basement membranes, including laminin, fibronectin, elastin, and the proteoglycans heparan sulfate and chondroitin sulfate. Naumann and colleagues concluded that pseudoexfoliation material is a “multicomponent expression of a disordered extracellular matrix synthesis, including the incorporation of the principal noncollagenous basement membrane components.”

Elastic tissue consists of a central core of an amorphous, insoluble protein (elastin), surrounded by microfibrils. Streeter has demonstrated that elastin, tropoelastin, and fibrillin are all present in pseudoexfoliation material. In addition, pseudoexfoliation material shares light microscopic staining characteristics with zonular fibers, which are similar in amino acid composition and structure to microfibrils of elastin.

Pseudoexfoliation material is intimately related to areas of elastosis throughout the body, and Streeter and colleagues consider pseudoexfoliation to be a type of elastosis. They have also noted pseudoexfoliation material arising from fibroblasts and other local cells. They have also commented, however, that pseudoexfoliation material may be a product of local basement membrane-secreting cells.

**PATHOGENESIS OF PSEUDOEXFOLIATION GLAUCOMA**

Histologic evidence suggests that this form of glaucoma is secondary to accumulation of pseudoexfoliation material within the trabecular meshwork (see Fig. 20–2A,B). In a study of 19 autopsy eyes, maximum intraocular pressure measured clinically during life and average intraocular pressure while on treatment were both related to the amount of material within the juxtacanalicular region of the trabecular meshwork. In most cases of glaucoma the trabecular meshwork appeared otherwise intact. However, advanced cases demonstrated disorganization of the juxtacanalicular region and a decrease in the size of Schlemm’s canal. Ultrastructurally, the trabecular meshwork from eyes with pseudoexfoliation glaucoma differ from those with primary open-angle glaucoma, and lack the excess tendon sheath material found in advanced cases of primary open-angle glaucoma.

The heavy pigmentation of the meshwork seen on clinical gonioscopy may also contribute to the development of pseudoexfoliative glaucoma, and some investigators have suggested a relationship between the amount of pigment seen with gonioscopy and the incidence of glaucoma. Histologically, pigment is present within trabecular cells and occasionally within the intertrabecular spaces. However, these changes do not appear to narrow the outflow spaces enough to produce elevated pressure.
SECTION IV THE GLAUCOMAS

FIGURE 20–3 Biomicroscopic manifestations of pseudoexfoliation include (A) target-like appearance of the anterior lens capsule, with a central disc of gray pseudoexfoliation material surrounded by the clear “intermediate zone” and the outermost white peripheral zone. (B) Pseudoexfoliation material may extend through the intermediate zone to connect the central disc and peripheral zone. (C) Repeated pupillary movement separates material from the capsule, and can release it to other anterior segment structures, including the corneal endothelium (D). Following cataract extraction, pseudoexfoliation material can appear on the vitreous face (E) and posterior chamber intraocular lens implants, in a pattern that suggests deposition beneath the iris. (Figure 20–3C courtesy of Julia Whiteside-Michel, M.D.)

TABLE 20–1 DIAGNOSIS OF PSEUDOEXFOLIATION

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>None until extensive visual field loss</td>
<td>White material and flakes on anterior lens capsule, pupillary margin, zonules, corneal endothelium, and trabecular meshwork</td>
</tr>
<tr>
<td></td>
<td>Patchy to confluent peripupillary iris transillumination defects</td>
</tr>
<tr>
<td></td>
<td>Loss of pigment ruff from pupillary border</td>
</tr>
<tr>
<td></td>
<td>Moderate to dense segmental pigmentation of the trabecular meshwork</td>
</tr>
<tr>
<td></td>
<td>Limited pupillary dilation</td>
</tr>
<tr>
<td></td>
<td>Phacodonesis and iridodonesis</td>
</tr>
<tr>
<td></td>
<td>Zonular rupture during cataract surgery</td>
</tr>
<tr>
<td></td>
<td>Elevated intraocular pressure</td>
</tr>
<tr>
<td></td>
<td>Glaucomatous optic nerve damage and visual field defects</td>
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</tbody>
</table>
patchy, “moth-eaten” peripupillary iris transillumination that results from constant rubbing of the iris on the anterior lens capsule (Fig. 20–A,B).

Gonioscopy often reveals moderate to dense segmental pigmentation of the trabecular meshwork and the inferior Schwalbe’s line. Although this pigmentation is characteristically dark brown or black, it is not as dense or homogeneous as that seen in pigmentary glaucoma (Fig. 20–C).

Characteristic glaucomatous optic nerve damage with generalized or focal neuroretinal rim erosion and characteristic visual field defects may be present on diagnosis, or may develop over time. The extent of this injury generally correlates with the degree and duration of the pressure elevation.

Although several studies comment on finding gonioscopically narrow angles in eyes with pseudoexfoliation syndrome, none have documented an increase in the incidence of acute angle closure attacks. However, weakened or ruptured zonular fibers could allow lens subluxation, resulting in secondary angle closure, or acute angle closure from pupillary block (Fig. 20–D).

At the time of discovery, 6 to 24% of patients with pseudoexfoliation have either glaucoma or elevated intraocular pressure. Approximately 50% of patients with...
pseudoexfoliation syndrome will ultimately be diagnosed with glaucoma, either during the initial examination or at a later time, with reports ranging from 20 to 85%.3,6,75,81,83

PEARL... Beware of glaucoma at the time of discovery of pseudoexfoliation syndrome. Initial examination should always include careful optic disc evaluation, and visual field testing and diurnal intrascleral pressure measurement in cases with suspicious discs or intrascleral pressures.

DIFFERENTIAL DIAGNOSIS

Few things are easily confused with pseudoexfoliation syndrome (Table 20–2). Many patients diagnosed with open-angle glaucoma actually have pseudoexfoliation syndrome with glaucoma. Surveys of patients with established open-angle glaucoma indicate that between 3 and 47% of these open-angle glaucoma cases are pseudoexfoliation glaucoma, with figures in the United States ranging up to 28%.3,5,64 These percentages probably increase with advancing age.

All patients with primary open-angle glaucoma should be carefully examined for evidence of subtle pseudoexfoliation, particularly after dilation. Distinguishing pseudoexfoliative glaucoma from primary open-angle glaucoma has direct clinical importance. Aside from their increased potential for complications during cataract surgery, intraocular pressure in eyes with pseudoexfoliation glaucoma is generally more unpredictable and refractory to medical therapy than in eyes with primary open-angle glaucoma.

In pigmentary glaucoma, the trabecular pigmentation is dense, even, and dark brown or black compared to the irregular, more segmental pigmentation of pseudoexfoliation. The iris transillumination defects of pigmentary glaucoma are elongated radial spokes in the periphery of the iris, whereas those of pseudoexfoliation syndrome appear as moth-eaten patches around the pupil, often with some loss of the pupillary ruff.24 Although uveitis may produce synechiae, fibrin, or cyclitic membranes that involve the anterior lens capsule with whitish debris, this lacks the homogenous granular appearance and characteristic flakes of exfoliative material.

Table 20-2: Differential Diagnosis of Pseudoexfoliation Glaucoma

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary open-angle glaucoma</td>
<td>Lack of pseudoexfoliation material within the anterior segment</td>
</tr>
<tr>
<td></td>
<td>Lack of increased, or patchy trabecular meshwork pigmentation</td>
</tr>
<tr>
<td>Pigmentary glaucoma</td>
<td>Kruckenberg spindle</td>
</tr>
<tr>
<td></td>
<td>Lack of pseudoexfoliation material</td>
</tr>
<tr>
<td></td>
<td>Radial, midperipheral iris transillumination defects</td>
</tr>
<tr>
<td></td>
<td>Heavier, more confluent trabecular meshwork pigmentation</td>
</tr>
<tr>
<td></td>
<td>Pigment on iris, lens equator, and zonules</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Fibrin, cyclitic membrane less homogenous than true pseudoexfoliation material</td>
</tr>
<tr>
<td></td>
<td>Irregular, lighter trabecular meshwork pigmentation</td>
</tr>
</tbody>
</table>

PEARL... Beware the development of glaucoma in pseudoexfoliation syndrome. Because half of patients may ultimately have glaucoma, patients with pseudoexfoliation and no glaucoma should be examined at least every 1 to 2 years.

Laser trabeculoplasty is especially effective in pseudoexfoliation glaucoma, with reported initial success rates up to 80%.85,86 These increased success rates may result from the higher prelaser intraocular pressures and generally increased trabecular pigmentation in these patients.

However, as in primary open-angle glaucoma, success rates decrease with time, averaging 50% or less by 5 years. Although mixed, most reports suggest that retreatment with laser is less successful than the initial treatment.86 Numerous studies have commented on the failure of long-term medical treatment and late failures of laser trabeculoplasty85,87-89 in pseudoexfoliative glaucoma. In one, 61% of patients had undergone either laser trabeculoplasty (35%) or glaucoma surgery (26%) by the time they...
In this same group of patients, 25% became blind in at least one eye, and 8% in both eyes. Both eyes became blind in 15% of patients with bilateral pseudoxefoliation glaucoma.

In patients who do not respond to medications or laser, routine filtration surgery can achieve success rates similar to those of surgery in patients with primary open-angle glaucoma.83

Cataract Surgery

Weakened attachments of the zonular fibers to the ciliary body can cause subluxation of the crystalline lens in pseudoxefoliation syndrome.48 Thus, plus poor pupillary dilation, also predisposes these eyes to surgical complications during cataract surgery, with a five- to ten-fold increase in the incidence of cataract surgery, with a five- to ten-fold increase in the rate of zonular breaks, capsular dialysis, or vitreous loss.90–93

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