Slide 1

Exfoliative and Pigmentary Glaucoma

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Disclosures and Special Request

Paid consultant for:

- Alcon Pharmaceuticals, Bausch and Lomb, Carl Zeiss Meditec, NiCox

Special Request:

Interactive remotes don't work on your TV, so please don't take them home! ☺

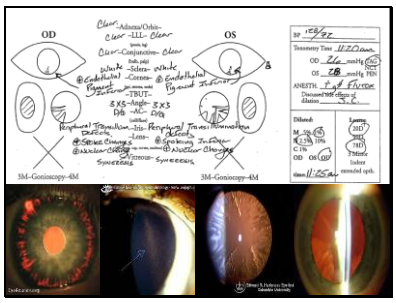
Commitment to change:

- write down three things that you "learned" from this presentation that you can incorporate into your practice to improve patient care

Slide 3

CASE

Slide 4



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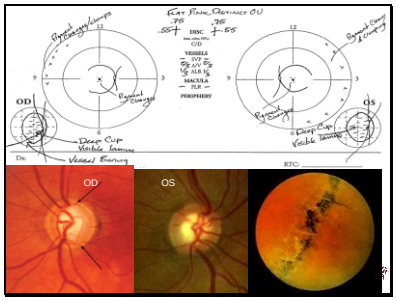

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Pigment Dispersion Syndrome (PDS) and Pigment Dispersion Glaucoma (PDG)

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Pigment Dispersion Syndrome: PDS

- The typical patient with PDS is:
  - young (20–40 years) and
  - myopic
- The US prevalence of PDS has been estimated to be approximately 2.5%
  - Prevalence in non-Caucasians is low and may be a result of different iris anatomy or different behavior of the iris in non-Caucasians

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Pigment Dispersion Syndrome: PDS

- tends to affect men and women in roughly equal numbers, although there might be a slight male preponderance with 58–67% of PDS patients being male in some reports
  - However, 78–93% of PDG patients are male

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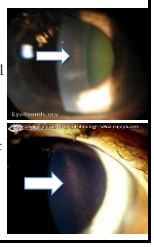
PDS Clinical Features

- ***Krukenberg spindles***
  - The Krukenberg spindle refers to pigment deposition on the corneal endothelial surface that typically occurs in a vertical spindle-shaped pattern.
    - characteristic pattern is thought to occur secondary to aqueous convection currents within the anterior chamber



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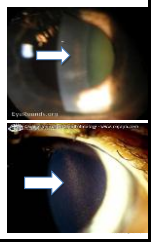
PDS Clinical Features

- ***Krukenberg spindles***
  - not always present in PDS and are not pathognomonic of PDS.
  - presence of a Krukenberg spindle has been found to be more common in PDG



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PDS Clinical Features

- *Krukenberg spindles*
  - development is more common in women
    - may suggest a hormonal influence in their development
  - histological examination has revealed melanin granules on and within endothelial cells
    - suggesting that the pigment is phagocytosed.

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PDS Clinical Features

- *Endotheliopathy*
  - Endothelial cells in PDS show:
    - pleomorphism (abnormal shape) and
    - polymegathism (abnormal size)
  - However, normal endothelial cell counts have been reported and patients with PDS have normal corneal thickness,
    - suggesting that endothelial function is not compromised

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PDS Clinical Features

- *Pigment showers:*
  - Circulating AC pigment may be identified in PDS patients and can be mistaken for uveitic inflammatory cells.
  - In many individuals, pupil dilation, either naturally (or especially with phenylephrine), can be associated with a pigment cloud entering the AC through the pupil

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PDS Clinical Features

- Iris trans-illumination defects:
  - not always present in PDS eyes, but are present in most (86%) cases
    - more obvious in light-colored eyes.
  - PDS trans-illumination defects are commonly located in the mid-peripheral iris and occur with a spoke-like pattern

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PDS Clinical Features

- *Iris trans-illumination defects:*
  - The extent of transillumination and the degree of Krukenberg spindle pigmentation are positively correlated with the degree of pigment dispersion
  - The iris defects are developmental rather than being a congenital occurrence
  - The iris trans-illumination defects of pseudo-exfoliation syndrome (PXF) differ from those in PDS,
    - being peri-pupillary rather than mid-peripheral

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MULTISPECTRAL DIAGNOSTIC IMAGING OF THE IRIS IN PIGMENT DISPERSION SYNDROME

- Near infrared (NIR) imaging techniques currently provide the most sensitive means to detect and record iris transillumination
- modified digital camera system is used
  - requires adaptations to be truly practical in clinical and research settings.

MULTISPECTRAL DIAGNOSTIC IMAGING OF THE IRIS IN PIGMENT DISPERSION SYNDROME, Roberts, Daniel et. al., 2012

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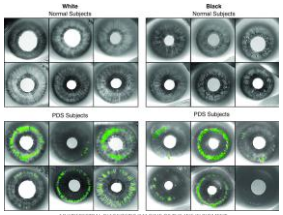
MULTISPECTRAL DIAGNOSTIC IMAGING OF THE IRIS IN PIGMENT DISPERSION SYNDROME



MULTISPECTRAL DIAGNOSTIC IMAGING OF THE IRIS IN PIGMENT DISPERSION SYNDROME, Roberts, Daniel et. al., 2012

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PDS Clinical Features

- *Iris trough pigmentation and heterochromia*
  - In eyes with PDS there is often pigment deposition on the anterior iris surface
    - preferentially within iris furrows
  - In asymmetric cases there may be heterochromia
    - the more affected eye having a darker iris as a result of pigment deposition onto its anterior surface

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PDS Clinical Features

- *Anisocoria*
  - In asymmetric cases of PDS, the eye with the greater iris trans-illumination tends to have a larger pupil
  - The larger pupil may be a consequence of the hyperplastic dilator muscle that is associated with the loss of iris pigment epithelium in eyes with PDS

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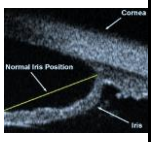
PDS Clinical Features

- ***Backward bowing of the iris***
  - The backward bowing of the mid-peripheral iris, described is of key importance in the etiology of PDS.
  - It has been proposed that the iris is relatively too large for the eye thus making posterior bowing of the iris and iridodonesis more inevitable



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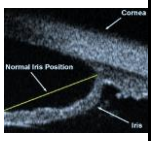
PDS Clinical Features

- ***Backward bowing of the iris***
  - Hypothesized that the iris of PDS eyes are more flaccid and prone to be pressed against the lens (Aptel, 2011)
  - posterior bowing of the peripheral iris is probably the result of an intermittent pressure gradient between the anterior-posterior chamber known as reverse pupillary block.
    - supported by the change of iris configuration after laser peripheral iridotomy (LPI), when the iris returns to a planar configuration.



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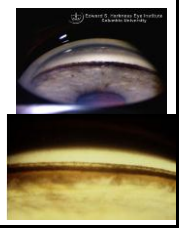
PDS Clinical Features

- Gonioscopy:
  - The characteristic gonioscopic feature is the increased TM pigmentation tends to be homogenous
    - in contrast to the patchy involvement in PXF syndrome
  - The full circumference of the TM tends to be affected, although pigmentation is more prominent inferiorly
    - possibly owing to gravity.



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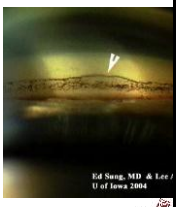
PDS Clinical Features

- Gonioscopy:
  - Histologically, the melanin is located within the TM cells indicative of their phagocytic properties
- Pigment deposition also occurs at Schwalbe's line
  - producing a thin, dark line similar to **Sampaolesi's line** in PXF syndrome.
  - tends to be more prominently pigmented inferiorly.



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PDS and IOP

- the elevated IOP in patients with PDS is caused by a reduction in outflow facility
  - aqueous flow remains normal.
- Uveoscleral outflow remains unchanged in PDS (Toris 2010)
- Increased uveoscleral outflow may be a plausible explanation for "normal IOP" in PDS cases despite the pigment dispersion process compromising the outflow facility

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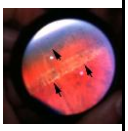
PDS Clinical Features

- *Posterior segment*
  - Lattice retinal degeneration has been reported to be evident in 20–33% of cases of PDS and PDG, which is greater than would be expected for the associated myopia
  - Retinal breaks also occur more frequently than in normal eyes, affecting 12% of eyes with PDS and PDG
  - Retinal detachments have been reported to occur in 5.5–6.6% of PDS cases
    - higher than expected for the degree of myopia and is independent of miotic use



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Pigment Dispersion Glaucoma (PDG)

- The **typical PDG patient is young (30–50 years) and myopic**
  - degree of myopia in groups of PDS patients that develop PDG is higher than those who do not develop PDG
- Unlike PDS, **PDG is much more prevalent in men**, with 78–93% of PG patients being male
  - tends to occur at an earlier age in men, at 34–46 years, whereas women tend to develop PDG a decade or so later at 43–53 years of age
  - in addition to occurring earlier in men, PDG tends to be more aggressive in men than women

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PDS/PDG Conversion

- Estimates of the proportion of patients with PDS that have PDG have ranged from 6% to 43%
  - large degree of variation that reflects widely differing study inclusion criteria
- It is generally considered that patients with PDS will develop PG (after diagnosis):
  - 5–10% at 5–6 years,
  - 15% at 15 years,
  - 35% developing PG at 35 years.

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Pigment Dispersion Glaucoma (PDG)

- **Symptoms**
  - The majority of patients with PDG are asymptomatic.
    - headaches and episodes of blurred vision have been reported, particularly after physical exercise.
    - patients may describe seeing haloes around point sources of light, probably owing to pigment showers (often after intensive exercise) associated with IOP spikes and corneal edema
      - these patients also tend to have Krukenberg spindles reflecting the greater degree of pigment dispersion during exercise

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Pigment Dispersion Glaucoma (PDG)

- *IOP*
  - **PDG tends to be a high-tension type of glaucoma with a mean IOP of 29 mmHg at diagnosis**
    - in one long-term analysis
      - 25% of the patients had an IOP >31 mmHg at diagnosis, with 12.5% having an IOP of >39 mmHg
  - there is a tendency for the glaucoma to 'burn-out' with increasing age, with target IOPs becoming progressively easier to reach.

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Pigment Dispersion Glaucoma (PDG)

- *IOP*
  - the presence of OH (IOP > 21 mmHg) at the initial diagnosis of PDS has been identified as the most important factor for conversion to PDG
    - Siddiqui found that each 1 mmHg rise in IOP increased the risk of conversion from PDS to PG by a factor of 1.4

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Pigment Dispersion Glaucoma (PDG)

- In normal eyes and those with POAG, exercise usually lowers IOP
  - In PDS/PDG, however, exercise induces pigment dispersion that may result in reduced aqueous outflow and significant IOP elevation
- Laser peripheral iridotomy (LPI) can prevent the exercise-induced phenomenon by relieving reverse-pupillary block and preventing posterior bowing of the iris
- the exercise-induced IOP elevation can be inhibited pharmacologically with pilocarpine, but not with b-blockers

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Pigment Dispersion Glaucoma (PDG)

- Patients with PDS and PDG generally fall in to one of the four clinical groups:
  - ***Inactive pigment dispersion with stable IOP.***
    - This group includes PDS patients and those with burnt-out PDG.
  - ***Active pigment dispersion with stable IOP.***
    - This group includes PDS and PDG patients. The TM has not been overwhelmed by pigment and the aqueous outflow facility is sufficient to maintain IOP.

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Pigment Dispersion Glaucoma (PDG)

- Patients with PDS and PDG generally fall in to one of the four clinical groups:
  - ***Active pigment dispersion with progressive glaucoma and elevated IOP.***
    - These PDG patients may later have inactive pigment dispersion and the IOP may return to normal or they may progress to group four.
  - ***Inactive pigment dispersion with progressive glaucoma and normal or elevated IOP.***
    - This group of PDG patients are likely to have permanently damaged TM and, as a result, have poor aqueous outflow facility with high IOP. However, they may also develop a progressive, normal tension type glaucoma.

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Pigment Dispersion Glaucoma (PDG)

- *Visual field defects*
  - visual field progression has been reported to be common in PDG
    - 28–44% of cases progressing in 11–17 years
    - perhaps a reflection of the degree of IOP elevation
- In asymmetric cases of PDG
  - the glaucoma has been found to be more severe in the eye with the greater degree of pigment dispersion
  - the degree of TM pigmentation has been reported to correlate with severity, but the degree of trabecular pigmentation at presentation of PDS is not necessarily a predictor of conversion to PDG.

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Pigment Dispersion Glaucoma (PDG)

- The mechanism of reduced outflow is not one of simple TM channel blockage with pigment
  - discovered that TM endothelial cells phagocytose pigment
    - phagocytic overload of the trabecular endothelial cells leads to their death
    - these necrotic cells, together with the pigment, are then cleared away by macrophages
  - the loss of TM cells results in the improper function of the meshwork channels, outflow obstruction and elevated IOP

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Pathologic Phases of PDS

- Phase 1:
  - pigment acutely obstructs the intertrabecular spaces where trabecular endothelial cells have a high capacity for phagocytosis of pigment granules, and this is believed to remove them from the trabecular meshwork aqueous pathways.
- Phase 2
  - continual migration of the trabecular endothelial cells eventually leads to trabecular beam degeneration and collapse; and subsequent increase in IOP

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Pigment Dispersion Glaucoma (PDG)

- **PDG: BURN-OUT PHASE**
  - Unlike many other forms of glaucoma, PDG has a tendency to enter a final quiescent phase with advancing age.
  - Reduced pigment dispersion and IOP normalization have been noted in patients over a 10-year period
  - Long-term follow-up studies have shown an age-related reduction in degree of TM pigmentation and a tendency to IOP normalization with the requirement for fewer anti-glaucoma medications

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PDG: Treatment

- **Pilocarpine**
  - Pilocarpine is almost an ideal therapy for PDG.
  - Pilocarpine lowers IOP, prevents pupil dilation, reverses posterior iris bowing and inhibits exercise-induced rises in IOP, probably as a result of the drug-induced change in iris configuration
  - However, pilocarpine has a poor side effect profile (accommodative spasm, increased risk of retinal detachment, cataract formation and systemic parasympathomimetic side-effects, such as dry mouth).

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PDG: Treatment

- Prostaglandin analogues are potent ocular hypotensive agents, but have no specific anti-PDS effects.
- The enhancement of uveoscleral outflow may be beneficial in PDS/PDG patients and latanoprost has been shown to be more effective in reducing IOP in PDG patients than timolol
- Increased iris pigmentation occurs with prostaglandin analogues, but this does not lead to increased pigment dispersion as it primarily affects the iris stromal melanocytes and not the iris pigment epithelium
- Thus, prostaglandin analogues are not contraindicated in PG and in clinical practice are often used as first-line agents.

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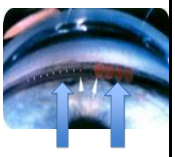
PDG: Treatment

- Argon laser trabeculoplasty (ALT) has been shown to be particularly effective in PDG
  - success may be due to the greater energy absorption by the pigmented TM.
  - ALT in young PDG patients seems to be more effective than in older patients, unlike with POAG
  - the success of ALT diminishes with time, with a reported success rate of only 45% at 6 years



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PDG: Treatment

- A laser peripheral iridotomy (LPI) equalizes the pressure between the AC and the PC
  - relieving reverse-pupillary block, flattening the iris and reversing posterior iris bowing to prevent further pigment release.
- The advantageous effect of iridotomy was found to be more significant in patients <40 years
  - probably a reflection of the condition being more likely to be in an active phase in younger patients
- LPI alone is unlikely to be beneficial in eyes that already have permanent trabecular damage and/or progressive glaucoma because it does not in itself reduce IOP.

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LPI and PDS/PDG Conversion

- Scott (2010) study suggests that there is no benefit o YAG LPI in preventing progression from PDS with OHT to PG within 3 years of follow-up.
  - suggest little benefit in performing the procedure in eyes with established OHT.
- However, patients with PDS, minimal trabecular meshwork damage, and no OHT may benefit from a procedure that reduces the dispersion of pigment.

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CASE

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Case

- 67 year old white male presents to the clinic noticing that his left eye is a bit blurry
  - PMHx: history of high cholesterol for which he is taking a statin
  - POHx: no history of eye surgeries or trauma
  - FOHx: aunt has glaucoma for which she takes drops

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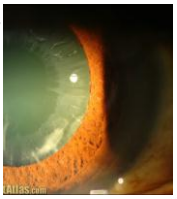
Case

- VA: 20/20 OD, 20/30 OS
- PERRL no APD
- Pachy: 540, 550 OD, OS
- IOP: 16, 40
- Fundus eval: see photos
- OD: c/d 0.45/0.45
- OS: c/d 06/0.5
- HVF: see photos



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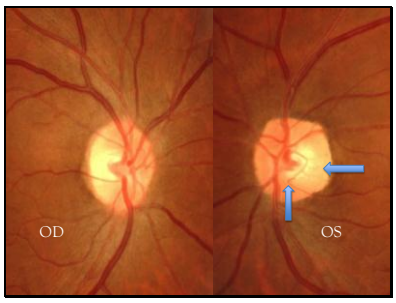

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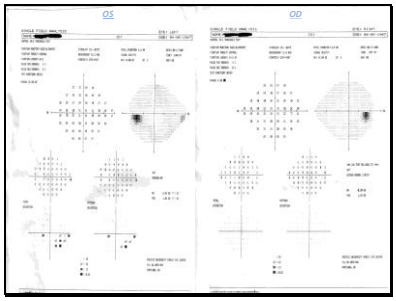

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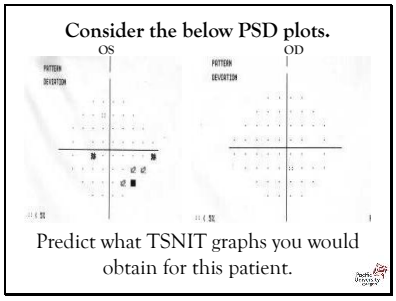

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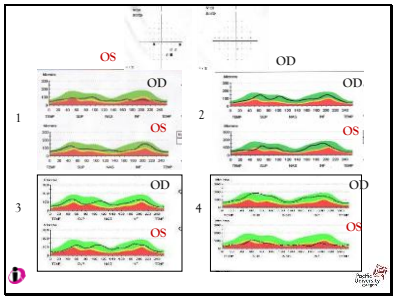

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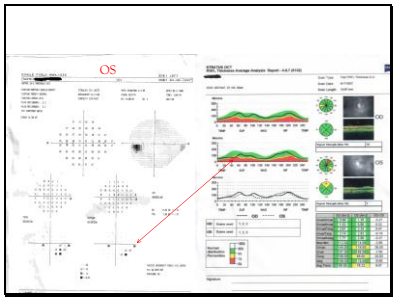

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What We Did.

- We discussed with the patient:
  - appears he has early glaucomatous changes
    - early nasal step OS,
    - reduced NFL OS
  - Elevated IOP

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Follow up

- Patient returned 14 days later for a follow up and his IOP had decreased from 40 to 22 in the left eye on the Travatan Z.
- Is this good enough????

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Pseudoexfoliation Syndrome/Glaucoma (PXS/PXG)

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PXS/PXG

- Characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues
- PXS is reported to be the most common identifiable cause of open-angle glaucoma
  - However, not all participants with PXS develop glaucoma

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Systemic Manifestations

- Pseudoexfoliation material (PXM) deposits around blood vessels of connective tissue.
- It has been identified as a generalized disorder of the extracellular matrix, involving the:
  - skin, extraocular muscles, heart, lung, liver, kidney, and meninges in addition to the eye
  - PXF was found to be associated with increased risk for cardiovascular or cerebrovascular morbidity in some studies

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Demographics

- PXS and pseudoexfoliative glaucoma (PXG) prevalence is increased in white populations (Australia and Scandinavia).
- The prevalence is as high as approximately 20% in Finland and over 25% in Iceland, but only 5% in parts of Denmark
  - Interestingly, the incidence in an Arizona Navajo population is as high as 38%.

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Increases with Age

- In Finland, the incidence rose from 10% for persons aged 60 to 69 years old to 33% in persons 80 to 89 years old.
- Increased incidence with age was also found in populations in Norway, Japan, Australian aborigines, and in the United States.
- Eyes with exfoliation may convert to PXG at a rate of approximately 30% per decade

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Epidemiology

- Ambient temperature and sun exposure may be important environmental triggers of PXS.
  - PXS is more prevalent in populations with relatively high UV exposure
- To date a number of genes have been linked to PXS, of which LOXL1 appears to be the most relevant in many populations
  - studies indicate that although *LOXL1* risk genotypes are present in 92% or more of patients with PXS, they are also seen in 74% or more of control participants, suggesting that other genetic or environmental factors contribute to PXS.

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PXF/PXG

- Pseudoexfoliation glaucoma (PXG) is a severe type of glaucoma with a higher risk of blindness.
  - PXG is associated with a higher maximum and mean intraocular pressure (IOP) at the time of diagnosis, and a higher 24-hour pressure curve than primary open angle glaucoma (POAG)
  - PXG patients were seen to have significantly greater mean visual field defects at presentation than POAG patients

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PXF/PXG

- Pseudoexfoliation glaucoma (PXG) is a severe type of glaucoma with a higher risk of blindness.
  - the IOP is harder to control in PXG than POAG
  - PXG is more difficult to manage clinically, with a higher incidence of treatment failure than POAG.

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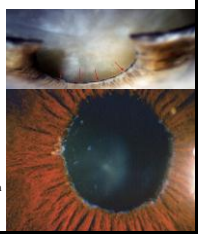
PXS Clinical Features

- PXS is defined by the presence of pseudoexfoliative material either at the pupil margin or on the lens capsule.
- PXS typically presents unilaterally.
  - Why this occurs remains unknown.
  - The fellow eye develops signs of pseudoexfoliation in more than 40% of cases



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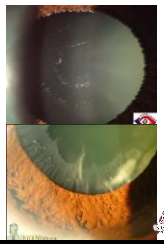
PXS Clinical Features

The most commonly recognized feature is the **3-ring sign** on the anterior lens capsule

- formed by a central disk, a peripheral ring, and a clear zone, which separates the two.
- the clear zone varies in diameter and may exhibit curled edges.



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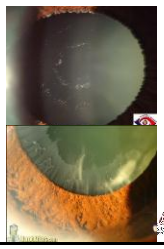
PXS Clinical Features

Peripupillary iris atrophy is a common and distinctive finding.

- It is best visualized using infrared transillumination



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PXS Clinical Features

- Other signs of pseudoexfoliation syndrome are:
  - insufficient mydriasis,
  - posterior synechiae,
  - pigment deposition on the iris surface,
  - deposition of pigment and pseudoexfoliation material on the corneal endothelium,
  - pigment liberation after pupillary dilation, and
  - pseudoexfoliation 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.

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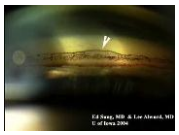
PXS Clinical Features

- Gonioscopy shows a discontinuous pigmentation of the trabecular meshwork
  - usually less dense than seen in pigmentary glaucoma.
- 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 pseudoexfoliation has been reported.



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PXS/PXG Treatment

- Glaucoma in pseudoexfoliation is more resistant to medical therapy and has a poorer prognosis than primary open-angle glaucoma
- Combined therapy is required at the time of diagnosis in many patients with PXG whose target pressures cannot be easily reached with mono-therapy.
- Elevated IOP leads to glaucoma development in about 50% of patients

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PXS/PXG Treatment

- The treatment of pseudoexfoliation glaucoma is the same as that of primary open-angle glaucoma;
  - 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.

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PXS/PXG Treatment

- 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.
- Selective laser trabeculoplasty (SLT) has been shown to be equivalent to argon laser trabeculoplasty in terms of lowering IOP at 1 year.
  - theoretical advantage of SLT is that SLT is a repeatable procedure because it does not seem to produce thermal damage to the trabecular meshwork.

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PXS/PXG Surgical Treatment

- 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
  - patients with pseudoexfoliation glaucoma have higher IOP, they tend to undergo glaucoma filtering surgery more frequently than patients with primary open-angle glaucoma.

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PXS/PXG Surgical Treatment

- **Cataracts occur more commonly in patients with pseudoexfoliation syndrome**
  - weakness of the zonular fibers, spontaneous lens subluxation, and phacodonesis also can be present
  - cataract surgery alone or combined cataract surgery and glaucoma filtering surgery in the presence of pseudoexfoliation is associated with a higher incidence of intraoperative complications, most notably zonular dialysis, vitreous loss, and lens dislocation.

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PXS and Alzheimer's?

- AD is a progressive neurodegenerative disorder characterized by neuronal and synaptic loss in the cerebral cortex leading to cognitive impairment, behavioral deficits and dementia.
- Cognitive areas, particularly the hippocampus, are most severely affected.
- Late-onset sporadic AD is most prevalent, affecting as many as half of the U.S. population over 85 years, whereas early-onset familial forms of the disease account only for about 5% of the total cases.

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PXS and Alzheimer's?

- Although largely overlooked, visual impairment is also a common finding in AD patients, with a number of reports suggesting that it may result from undiagnosed glaucoma.
- The loss of specific neuronal populations is perhaps the most fundamental process shared by glaucoma and AD.
  - Visual dysfunction in glaucoma primarily results from the death of RGCs with axonal degeneration extending to the brain.

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PXS and Alzheimer's?

- In a study by Cumurcu (2013) it was demonstrated that Alzheimer's type dementia was statistically significantly increased in the PXS group as compared to the age- and sex- matched control groups
  - an increased AD prevalence in patients with PSX when compared with the control group.
- patients with Alzheimer's disease have a higher incidence of PXS, characterized by the accumulation of an abnormal amyloid-like material in the anterior segment of the eye.