Case 6 – Pseudoexfoliation Syndrome

This case will outline the presentation of a patient with pseudoexfoliation with raised intraocular pressure. The management of patients with pseudoexfoliation syndrome will be discussed. Genetic risk factors for pseudoexfoliation syndrome will also be briefly described.

Case Presentation:

A 63 year old Caucasian male presented to his optometrist for a routine eye examination. His previous ocular history was unremarkable aside from a congenital colour vision defect. However, he did mention that he had been experiencing intermittent blurred vision in the right eye (like ‘vaseline’ over the eye), lasting a couple of hours, two to three times per week for the last six months. His family ocular history included proliferative diabetic retinopathy (mother). The patient had a history of hypothyroidism and was taking thyroxine for this. He was also taking hytrin for an enlarged prostate.

The optometrist’s initial findings are given below:

<table>
<thead>
<tr>
<th></th>
<th>Right Eye</th>
<th>Left Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best-corrected visual acuity</strong></td>
<td>6/6-</td>
<td>6/6</td>
</tr>
<tr>
<td><strong>Ishihara colour plates</strong></td>
<td>1/14</td>
<td>1/14</td>
</tr>
<tr>
<td><strong>Pupils</strong></td>
<td>No RAPD</td>
<td></td>
</tr>
<tr>
<td><strong>Refraction</strong></td>
<td>+0.75/-0.50 x 117</td>
<td>+0.25/-0.25 x 056</td>
</tr>
<tr>
<td><strong>Slit lamp biomicroscopy</strong></td>
<td>Early cataract, evidence of pseudoexfoliative material on anterior lens, transillumination at pupil margin</td>
<td>Early cataract</td>
</tr>
<tr>
<td><strong>IOP (Goldmann)</strong></td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td><strong>Pachymetry</strong></td>
<td>531</td>
<td>524</td>
</tr>
</tbody>
</table>

Optic nerve photographs are shown in figure 1.

Visual field results are given in figure 2, and figure 3 shows the OCT scan of the peripapillary retinal nerve fibre layer.

Question 1:

Describe the optic nerve, visual field and OCT findings, and formulate a working diagnosis based on these results and the findings at the initial examination.

The right optic nerve is slightly larger than the left (average to large size in the right eye, average optic nerve size in the left). The cup to disc ratio is also slightly larger in the right eye (0.6 vs. 0.5). There is no focal thinning of the neuroretinal rim in either eye. There is no evidence of a focal retinal nerve fibre layer defect in the colour photographs. There are no disc haemorrhages. Overall
there is mild optic disc asymmetry, but no evidence of glaucomatous optic neuropathy.

A 24-2 SITA-Standard Humphrey visual field assessment was performed in each eye. In the right eye the test was reliable, and the visual field is normal. The left eye had 27% fixation errors and is mildly unreliable. There are a few points of mildly reduced visual field sensitivity compared to age-matched normals, however, there is no evidence of a glaucomatous visual field defect.

The peripapillary retinal nerve fibre layer scans are of good quality (32/40 on the Heidelberg Spectralis OCT), and there are no defects in the automated layer segmentation. Based on comparison with a normative database, the patient’s RNFL values are within normal limits. Looking at the line graph of the peripapillary RNFL values, there is no focal thinning of this layer. There is some mild asymmetry between the two scans, as may be expected based on the optic disc appearance.

Taking these results into account, combined with the clinical examination records, the working diagnosis is right pseudoexfoliation syndrome with ocular hypertension. There is no evidence of glaucoma.

Question 2:
What is the significance of the intermittent blurred vision?

Some patients with pseudoexfoliation will experience acute IOP spikes, which can lead to transient blurred vision. These pressure spikes may sometimes be accompanied by ocular pain and the patient may report seeing haloes.

Question 3:
What other investigation is required? What would you expect to see?

It is necessary to perform gonioscopy to assess the anterior chamber angle in this patient.

The anterior chamber may be more narrow in pseudoexfoliation syndrome, particularly inferiorly relative to superiorly. Continued monitoring of the angle is required. You would expect to see irregular pigmentation of the trabecular meshwork, with large, darkly pigmented particles. Pigment deposition anterior to Schwalbe’s line results in the characteristic Sampaolesi line (this is the same line of pigment deposition that is observed in patients with pigment dispersion syndrome).
Question 4:
Describe the classical ocular clinical signs of pseudoexfoliation syndrome and pseudoexfoliative glaucoma

Approximately one-third to one-half of cases are clinically unilateral at detection, but 14-43% of cases can become bilateral over the course of five to ten years.

The clinical findings in pseudoexfoliation syndrome include a classic pattern of flaky white material on the anterior lens surface. The characteristic pattern is a central translucent disc of material, surrounded by a clear zone, and then a more peripheral granular greyish-white ring with scalloped edges. This is best visualised with a dilated pupil (however, affected eyes may dilate poorly). It has been postulated that the clear zone is caused by movement of the iris. In some cases the central disc of material may not be present. This flaky pseudoexfoliative material can also be seen on the iris, in the angle and on the corneal endothelium. The fibrillar material is also deposited on the zonules. The iris transillumination defects in pseudoexfoliation syndrome are located at the pupil margin. Atrophy of the pigmented pupil ruff can also be observed.

Gonioscopy findings have been described in the answer to question 3.

In the eye, the fibrillar pseudoexfoliative material is produced by the pre-equatorial lens epi-epithelium, the corneal epithelium, the iris, the vascular endothelial cells, the ciliary epithelium and the trabecular endothelium. The fibrils are composed of microfibrils, which each measure 8 – 10 nm in diameter. The microfibril subunits have a coating of electron-dense amorphous material which conceals the microfibrillar nature.

Patients with pseudoexfoliative glaucoma will have the above signs, in combination with elevated pressure and glaucomatous changes to the optic nerve. It is possible to have pseudoexfoliation syndrome with elevated IOP and no glaucomatous optic nerve findings, as was the case for the patient outlined here.
Figure 1: Right and left optic nerve head
Figure 2: Right and left Humphrey visual field results
Figure 3 – OCT scan of the peripapillary retinal nerve fibre layer
Question 5:

Is the pseudoexfoliative material found elsewhere in the body?

Pseudoexfoliation syndrome is a common age-related disorder of the extracellular matrix affecting the eye and visceral organs. Pseudoexfoliative material has been detected in the lung, liver, kidney, brain, heart, skin and gall bladder.

Systemic diseases including angina, aortic aneurysm and dementia have been linked to pseudoexfoliation syndrome, although the association between the conditions remains controversial.

Question 6:

What is the prevalence of pseudoexfoliation syndrome? What is the prevalence of glaucoma in patients with pseudoexfoliation?

Reported prevalence rates vary considerably, and prevalence increases with age. The prevalence of pseudoexfoliation syndrome is highest in Nordic countries at up to 40% of the population over the age of 80. In many other parts of the world, including Australia and Asia, prevalence is low. In the Blue Mountains Eye Study the prevalence of pseudoexfoliation in subjects aged between 49 and 97 years was 2.3%.

Psuedoexfoliation is a major risk factor for glaucoma. The proportion of patients with pseudoexfoliation and glaucoma varies in different populations. In all populations, the majority of individuals with pseudoexfoliation do not have glaucoma. In countries with predominantly Caucasian populations (Australia, Greece, Iceland) approximately 12 to 15% of patients with pseudoexfoliation have glaucoma. In non-Caucasian populations, this percentage is lower.

Question 7:

What are the risk factors for progression from pseudoexfoliation syndrome to pseudoexfoliative glaucoma?

The reasons why a proportion of patients with pseudoexfoliation develop glaucoma and others do not is not fully understood. In two population-based studies, patients with pseudoexfoliation syndrome and no glaucoma had similar clinical characteristics (cup to disc ratio, central corneal thickness, optic disc size and percentage of patients with IOP above 21 mmHg) to those without pseudoexfoliation.

In a ten year prospective study, factors associated with the progression of pseudoexfoliation syndrome to pseudoexfoliative glaucoma include the presenting IOP, the difference in IOP (compared with the fellow eye), and the degree of pupillary dilation.
The presence of pupil ruff atrophy has been found to be associated with RNFL thinning on OCT in patients with pseudoexfoliation syndrome but no glaucoma. This may predict early glaucomatous changes.

Prognosis is poor for patients with pseudoexfoliative glaucoma, and these patients often present with more advanced visual field loss.

Question 8:
What are the genetic and environmental risk factors for the development of pseudoexfoliation syndrome and pseudoexfoliative glaucoma?

Differences in the worldwide prevalence rates of pseudoexfoliation syndrome are primarily due to the differences in genetic and environmental factors. A simple inheritance model has not been identified. This suggests that inheritance is complex and is based on the interplay between multiple environmental and genetic factors. Genetic factors may contribute to the subsequent development of glaucoma in patients with pseudoexfoliation syndrome.

In 2007, the LOXL1 gene was identified as a potential risk factor for both pseudoexfoliation syndrome and pseudoexfoliative glaucoma in a genome-wide association study in individuals from Iceland and Sweden. However, this gene has low specificity as a number of controls also carry this gene. In ocular tissues of patients with pseudoexfoliation syndrome, dysregulated LOXL1 has been found.

There is increasing evidence that cellular stress conditions, including oxidative stress, hypoxia and low grade chronic inflammatory processes contribute to the pathogenesis of pseudoexfoliation syndrome.

Question 9:
How is pseudoexfoliative glaucoma treated?

The patient outlined in this case was treated with prostaglandin therapy (latanoprost 0.005% at night in the right eye only). He was reassessed six weeks later and his IOP was 13 in the treated right eye, and 18 in the untreated left eye. This is an excellent response (an IOP reduction of 50% from baseline). The patient continues to have regular reviews and has not developed glaucomatous optic nerve changes or a visual field defect.

Patients with pseudoexfoliative glaucoma do not always respond well to medical therapy with anti-glaucoma medications. Close monitoring is required. Patients with pseudoexfoliative glaucoma frequently need to undergo laser therapy to lower IOP, or glaucoma surgical procedures.

Selective laser trabeculoplasty, as discussed in other cases, is able to be performed, with favourable results, in patients with pseudoexfoliation and raised intraocular pressure. One small study reported a mean reduction of 31.4% in pseudoexfoliation eyes at 18 months. It has been shown that the effect of
selective laser trabeculoplasty does not differ between pseudoexfoliative glaucoma and other types of glaucoma.

Patients with pseudoexfoliative glaucoma respond well to argon laser trabeculoplasty.

Recent studies suggest that results following trabeculectomy in eyes with pseudoexfoliative glaucoma are similar to those in patients with primary open angle glaucoma. Mitomycin C and 5-Fluorouracil are used to enhance the success rate.

Question 10:
What is the difference between pseudoexfoliation syndrome and true exfoliation?

Pseudoexfoliation and true exfoliation are different clinical entities. True exfoliation of the lens capsule is rare. In true exfoliation, the anterior layer of the lens capsule delaminates and appears as a thin membrane in the anterior chamber. The cause of true exfoliation is not fully understood but it has been attributed to infrared radiation, inflammation, trauma and idiopathic causes. There have also been documented cases following cataract surgery. True exfoliation was first documented in glassblowers, who were exposed to open fires.

The relationship between true exfoliation and glaucoma is not known. There have been cases reported in the scientific literature of pseudoexfoliation and true exfoliation being observed in the same patient.

Question 11:
Why should cataract surgery be performed with extra caution in patients with pseudoexfoliation syndrome?

Several population studies have shown a cross-sectional association between psuedoexfoliation and cataract diagnosis, although others have not found a similar association.

Damage to the zonules is a key feature of pseudoexfoliation, and this, combined with poor pupil dilation can lead to increased complications during cataract surgery, including capsular rupture, zonular dialysis, vitreous loss and retained lens fragments.

A thorough pre-operative examination, and a well-planned surgical technique can mean that the intraoperative complications are reduced in frequency and are less severe. The use of ultrasound biomicroscopy can help to identify the presence of pseudoexfoliative material on the zonules, as well as other zonular abnormalities.

Post-operatively, patients with pseudoexfoliation require close monitoring for complications, including inflammation, IOP spikes and intraocular lens
dislocation. Early post-operative spikes are commonly encountered in patients with pseudoexfoliation. It has also been reported that endothelial cell loss is more pronounced following cataract surgery in eyes with pseudoexfoliation syndrome than in those without.

References and Recommended Reading

Question 1:
On Humphrey visual field testing, in order for the test to be considered reliable, fixation losses should be less than?

A. 10%
B. 15%
C. 20%
D. 25%
E. 30%

Question 2:
What type of glaucoma is pseudoexfoliative glaucoma?

A. Primary open angle glaucoma
B. Secondary open angle glaucoma
C. Phacolytic glaucoma
D. Angle closure glaucoma
E. Phacomorphic glaucoma

Question 3:
What is the cause of transient blurred vision in patients with pseudoexfoliation syndrome?

A. Transient ischaemic attacks
B. Subluxation of the crystalline lens
C. The presence of fibrillar material on the visual axis
D. Intraocular pressure spikes
E. Pupillary miosis

Question 4:
Which of the following is not a clinical sign of pseudoexfoliation syndrome?

A. Peripheral grey-ring of flaky material on the anterior lens surface
B. Atrophy of the pigmented pupillary ruff
C. Iris transillumination defects at the pupil margin
D. Glaucomatous optic neuropathy
E. Deposits of fibrillary material on the corneal endothelium

Question 5:
An acute increase in IOP may lead to transient visual blurring in pseudoexfoliation syndrome.

**TRUE or FALSE?**

**Question 6:**
What are the characteristic gonioscopic findings in patients with pseudoexfoliation syndrome?

A. A wide open angle with a moderately pigmented trabecular meshwork  
B. A wide open angle, particularly inferiorly, with dense pigmentation of the trabecular meshwork  
C. A narrow angle with no visible trabecular pigmentation and Sampaolesi line anterior to Schwalbe’s line  
D. Any angle configuration with a densely pigmented trabecular meshwork  
E. A relatively narrow angle, particularly inferiorly (relative to superior) with patchy pigmentation of the trabecular meshwork and Sampaolesi line

**Question 7:**
In pseudoexfoliation syndrome, flaky white material is deposited on anterior segment structures including the:

A. Iris  
B. Trabecular meshwork  
C. Anterior lens surface  
D. Zonules  
E. All of the above

**Question 8:**
With regard to pseudoexfoliation syndrome, which of the following is true?

A. All cases of pseudoexfoliation syndrome are unilateral  
B. All cases of pseudoexfoliation syndrome are clinically bilateral  
C. Pseudoexfoliation syndrome may be clinically unilateral or bilateral  
D. Clinically unilateral cases of pseudoexfoliation syndrome cannot become bilateral over time  
E. Patients with clinically bilateral signs of pseudoexfoliation show more advanced disease

**Question 9:**
Which of the following is not a risk factor for progression from pseudoexfoliation syndrome to pseudoexfoliative glaucoma?

A. Central corneal thickness
B. Presenting IOP
C. Presence of pupil ruff atrophy
D. Difference in IOP between eyes
E. Degree of pupil dilation

Question 10:
Pseudoexfoliation syndrome is always inherited in an autosomal dominant pattern
TRUE or FALSE?

Question 11:
What is the diameter of the microfibrils that make up the fibrillary pseudoexfoliative material?
A. 1 – 3 nm
B. 4 – 6 nm
C. 8 – 10 nm
D. 13 – 15 nm
E. 16 – 18 nm

Question 12:
What is the prevalence of glaucoma in Caucasian populations with pseudoexfoliation?
A. Less than 5%
B. 12 – 15 %
C. 5 – 10%
D. 20 – 25 %
E. Greater than 40%

Question 13:
Which region has the highest prevalence of pseudoexfoliation syndrome?
A. Eastern Europe
B. Northern Africa
C. South America
D. Nordic countries
E. Australasia

Question 14:
Where in the body has the pseudoexfoliative material been found?
A. Heart
B. Brain
C. Liver
D. Lungs
E. All of the above

Question 15:
Patients with pseudoexfoliative glaucoma have a poorer prognosis than those with primary open angle glaucoma
TRUE or FALSE?

Question 16:
In the Blue Mountains Eye Study, what was the prevalence of pseudoexfoliation in participants aged 49 and over?
A. 1%
B. 2.3%
C. 5.9%
D. 10.2%
E. 14.2%

Question 17:
Which of the following is false with regard to the treatment of patients with pseudoexfoliative glaucoma?
A. Argon laser trabeculoplasty is not a suitable treatment modality as it causes thermal damage to the trabecular meshwork
B. Patients may not respond well to topical ocular anti-hypertensive medications
C. Selective laser trabeculoplasty has been shown to be effective in lowering IOP in patients with pseudoexfoliative glaucoma
D. The success rate of trabeculectomy in pseudoexfoliative glaucoma is similar to that in primary open angle glaucoma
E. Antimetabolite agents may be used to enhance the success of trabeculectomy surgery

Question 18:
In patients with pseudoexfoliative glaucoma, what is the mean reduction in IOP from baseline at 18 months with selective laser trabeculoplasty?
A. 12%
B. 25%
Question 19:
Which of the following genes has been associated with pseudoexfoliation syndrome?

A. ZFN9  
B. PXF2  
C. FXN  
D. LOXL1  
E. PES6

Question 20:
Endothelial cell loss following cataract surgery is more pronounced in patients who have pseudoexfoliation than those who do not

TRUE or FALSE?

Question 21:
With regard to cataract surgery in patients with pseudoexfoliation, which of the following is false?

A. Poor pupil dilation is a potential issue in patients with pseudoexfoliation  
B. Damage to the zonules does not increase the risk of intra-operative or post-operative complications  
C. The small pupil can be dilated pharmacologically or mechanically  
D. A thorough pre-operative examination can reduce the likelihood of intra-operative complications  
E. Ultrasound biomicroscopy can be used pre-operatively to detect zonular abnormalities

Question 22:
In true exfoliation syndrome...

A. The lens capsule delaminates at the equator and is deposited on the zonules  
B. The anterior capsule of the lens delaminates and appears as a thin membrane in the anterior chamber  
C. The posterior capsule of the lens delaminates and appears as a thin membrane in the posterior chamber  
D. Glaucoma is observed in all patients
E. Anterior vitreous humour migrates into the anterior chamber giving the appearance of exfoliative material

Question 23:
Which of the following is not thought to be a cause of true exfoliation syndrome?
   A. Exposure to intense heat
   B. Exposure to infrared radiation
   C. Ocular trauma
   D. Ocular inflammation
   E. Neovascular glaucoma

Question 24:
Which of the following is not an important post-operative complication in patients with pseudoexfoliation?
   A. IOP spikes
   B. Inflammation
   C. Endothelial decompensation
   D. Non-arteritic anterior ischaemic optic neuropathy
   E. Intraocular lens dislocation

Question 25:
True exfoliation and pseudoexfoliation cannot be observed simultaneously in the same patient.
TRUE or FALSE?