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Review

Pigment dispersion syndrome and pigmentary glaucoma – a major review

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Abstract

Pigment dispersion syndrome (PDS) is an interesting condition that can lead to secondary open angle glaucoma. Pigmentary glaucoma is primarily a disease of young people, myopes and men. PDS is characterized by the presence of Krukenberg spindles, iris trans-illumination defects, trabecular meshwork pigmentation and backward bowing of the iris. Posterior bowing of the iris causes rubbing of the pigmented iris epithelium against lens structures, liberation of pigment and trabecular meshwork changes that result in reduced aqueous outflow with the risk of glaucoma. Peripheral laser iridotomy can reverse backward bowing of the iris and may prevent progression of pigmentary glaucoma.

Key words: pigment dispersion syndrome, ocular hypertension, pigmentary glaucoma, peripheral laser iridotomy.

History

Vertical pigment deposition on the corneal endothelium was identified by Krukenberg in the late 1800s.[1] He considered this to be a congenital anomaly caused by the approximation of the pupillary membrane to the cornea during early embryogenesis.[1] However, it was not until 1940 that Sugar described the first case of pigmentary glaucoma (PG).[2] As is often the case in medical history there has been a great deal of controversy behind our eventual understanding of PG.[3,4] A key historical event was the proposal by Von Hippel in 1901 that pigment obstructed aqueous outflow and had a role in elevating intraocular pressure (IOP).[5] A source of the pigment was proposed 8 years later by Levinsohn, who demonstrated pigment within the trabecular meshwork (TM) and suggested an origin from the iris.[6] Later, others[7,8] suggested a causal relationship between pigment deposition and glaucoma, although at that time many opposed this concept.[3,4]

In 1949, Sugar and Barbour reported the detailed clinical features of two cases of PG.[9] Both were myopic patients with corneal endothelial pigment deposition, iris transillumination defects, heavy TM pigmentation and elevated IOP. In 1966, Sugar published a 25-year review of 147 PG cases confirming these findings,[10] but the term 'Sugar-glaucoma' was, perhaps unfairly, never introduced.

Definitions

- Pigment dispersion syndrome (PDS): an ocular condition characterized by dispersion of iris pigment throughout the eye. PDS can be associated with ocular hypertension (OH) or glaucoma and is usually bilateral.
- Pigmentary ocular hypertension (POH): pigment dispersion syndrome with elevated IOP and no glaucomatous optic neuropathy.
- Pigmentary glaucoma (PG): glaucomatous optic neuropathy in association with PDS.

Pigment dispersion syndrome

Demography

The typical patient with PDS is young (20–40 years) and myopic.[4,10–14] PDS is as common in women as in men,[4,13] although there might be a slight male predominance[12,15,16] and affects Caucasians more than other racial groups.[11,14,17,18]

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. The characteristic pattern is thought to occur secondary to aqueous convection currents within

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the nasal and temporal halves of the anterior chamber (AC) that may be influenced by blinking.[10] Krukenberg spindles are not always present in PDS and are not pathognomonic of PDS. Krukenberg spindle development is more common in women,[19,20] which may suggest a hormonal influence in their development.[21] Histological examination of Krukenberg spindles has revealed melanin granules on and within endothelial cells, suggesting that the pigment is phagocytosed.[22,23] Phagocytosis may account for the consistent form of spindles, not to be expected if the pigment deposits were entirely a surface phenomenon.[10]

Endotheliopathy

Endothelial cells in PDS show pleomorphism (abnormal shape) and polymegathism (abnormal size).[24] However, normal endothelial cell counts have been reported and patients with PDS have normal corneal thickness, suggesting that endothelial function is not compromised.[24,25]

Anterior chamber depth

Caprioli reported that the ACs of patients with PDS were deeper than those with primary open angle glaucoma (POAG) when corrected for age and refraction.[26] The ACs of eyes with PDS appear deepest at 3.5 mm below axis[27], and in asymmetric cases the ACs were deeper in the most affected eye, suggesting that deep ACs have a role in the pathogenesis.[28,29] Male PDS patients have been shown to have deeper ACs than female PDS patients.[30] The deeper ACs of men, myopes and young people reported in biometric studies correlate well with the clinical characteristics of PDS and PG.[14,29]

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.[10,31,32] The degree of pigment showering can be quantified using laser flarometers.[31]

Iris trans-illumination defects

Iris trans-illumination defects are not always present in PDS eyes, but are present in most (86%) cases, being more obvious in light-coloured eyes.[16] PDS trans-illumination defects are commonly located in the mid-peripheral iris and occur with a spoke-like pattern.[33] The extent of trans-illumination and the degree of Krukenberg spindle pigmentation are positively correlated with the degree of pigment dispersion.[31] The iris defects are developmental rather than being a congenital occurrence.[33–35]

To detect iris trans-illumination defects, light should be projected though the pupil in a plane perpendicular to the iris. Alternatively, the defects can be illuminated posteriorly by scleral trans-illumination. Iris trans-illumination defects may be seen in normal, particularly blue, eyes. In normal eyes, however, the defects tend to be subtle, more mottled and less spoke-like. The iris trans-illumination defects of pseudo-exfoliation syndrome (PXF) differ from those in PDS, being peri-pupillary rather than mid-peripheral.[36]

Iris trough pigmentation and heterochromia

In eyes with PDS there is often pigment deposition on the anterior iris surface, this being deposited preferentially within iris furrows.[10,14] 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.[10,37–39]

Anisocoria

In asymmetric cases of PDS, the eye with the greater iris trans-illumination tends to have a larger pupil.[40–42] 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.[34,43–45] Mechanical irritation of smooth muscle cells, as the iris rubs against the zonules in eyes with PDS may cause the mydriasis.[40] Also, the presence of an efferent defect in the most affected eye has been suggested as a cause of pupil enlargement.[41] Anisocoria and heterochromia, with mydriasis and a darker iris in the more affected eye of asymmetric PDS cases, may mimic congenital Horner's syndrome in the fellow eye.[46]

Iris pathology

Histology has revealed that there is loss of pigment epithelium within the iris trans-illumination defects.[33,35,44,45,47] Scanning electron microscopy of early defects have shown disruption of pigment epithelial cell membranes with dispersion of their pigment granule contents.[33] As the trans-illumination defects progress, there is loss of the entire iris pigmented epithelial layer within these defects.[33] A delay in iris melanogenesis has been reported in PDS[45] and iris angiographic studies have revealed vascular hypoperfusion with associated iris hypoplasia in cases of PDS.[48] Histological studies have shown hyperplasia of the iris dilator muscle, often associated with areas of loss of iris pigment epithelium.[35,43–45] Marked iris processes are also a feature of PDS.[49]

Backward bowing of the iris

The backward bowing of the mid-peripheral iris, described by Campbell,[33] is of key importance in the aetiology of PDS. It has been proposed that the iris in PDS is effectively too large for the eye, thus making posterior bowing of the iris and iridodonesis more inevitable.[4,50]

Gonioscopy

The characteristic gonioscopic feature of PDS is increased TM pigmentation,[10,13] which tends to be homogenous, in

contrast to the patchy involvement in PXF syndrome.[36] The full circumference of the TM tends to be affected, although pigmentation is more prominent inferiorly, possibly owing to gravity. Histologically, the melanin is located within the TM cells indicative of their phagocytic properties.[15,22,35,44,45,51–54]

Pigment deposition also occurs at Schwalbe's line,[4] producing a thin, dark line similar to Sampaolesi's line in PXF syndrome. In a similar manner to the TM, Schwalbe's line tends to be more prominently pigmented inferiorly.

The backward-bowing of the iris may be noticed at gonioscopy, and a congenitally more posterior iris insertion compared with controls has been described as a PDS feature that may have aetiological importance.[55] A greater-than-expected number of iris processes anterior to the scleral spur is another reported feature of PDS,[49] although not a consistent finding.

Lens and zonules

Pigment in PDS may be deposited on the lens surface. The pigment deposition often looks like a subtle Krukenberg spindle on the anterior capsule. Pigment may also be deposited on the posterior lens surface, a feature first described by Zentmayer in 1938.[56] Despite Zentmayer's initial description, pigment accumulation occurring at the junction of the zonules and posterior capsule has tended to be called Scheie's stripe.[13,57]

Posterior segment

In addition to effects within the anterior segment of the eye, PDS may affect the posterior segment. Lattice retinal degeneration has been reported to be evident in 20–33% of cases of PDS and PG, which is greater than would be expected for the associated myopia.[58,59] Retinal breaks also occur more frequently than in normal eyes, affecting 12% of eyes with PDS and PG.[58] Retinal detachments have been reported to occur in 5.5–6.6% of PDS cases, again higher than expected for the degree of myopia and is independent of miotic use.[4,11,13]

Pigmentary glaucoma

Demography

The typical PG patient is young (30–50 years) and myopic.[10–14] Unlike PDS, however, PG is much more prevalent in men, with 78–93% of PG patients being male.[10,12,13,16,37]

Symptoms

The majority of patients with PG are asymptomatic. However, headaches and episodes of blurred vision have been reported, particularly after physical exercise.[60,61] 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 oedema.[60–62] These patients also tend to have Krukenberg spindles reflecting the greater degree of pigment dispersion during exercise.

Clinical features

The features of PG are similar to PDS, but with elevated IOP and glaucomatous optic neuropathy.

IOP

Pigmentary glaucoma tends to be a high-tension type of glaucoma with a mean IOP of 29 mmHg at diagnosis.[16] In one long-term analysis of PG, 25% of the patients had an IOP >31 mmHg at diagnosis, with 12.5% having an IOP of >39 mmHg.[12] There is a tendency to a greater range of IOP at diagnosis compared with POAG. In a 25-year review of patients with PG, Sugar noted an IOP range of 24–56 mmHg at diagnosis.[10] Although the particularly high IOP might be more difficult to control in PG than in POAG, there is a tendency for the glaucoma to 'burn-out' with increasing age, with target IOPs becoming progressively easier to reach.

Visual field defects

Unfortunately, visual field progression has been reported to be common in PG, with 28–44% of cases progressing in 11–17 years, perhaps a reflection of the degree of IOP elevation.[12,16]

Optic disc cupping

The morphology of the optic disc and retinal nerve fibre layer in PG has been reported to be no different from that in POAG.[63]

Degree of pigmentation

In asymmetric cases of PG, the glaucoma has been found to be more severe in the eye with the greater degree of pigment dispersion.[15] Laser flarometry studies have shown that the greater the number of melanin granules in the aqueous, the greater the IOP.[64] The degree of TM pigmentation has been reported to correlate with severity,[13,65] but the degree of trabecular pigmentation at presentation of PDS is not necessarily a predictor of conversion to PG.[12]

Filtration blebs

Pigment deposition has been noted within the filtering blebs of PG patients,[38] but it remains unknown as to whether this adversely affects trabeculectomy function.

Retinal detachment

The incidence of retinal detachment in patients with PG has been reported to be slightly higher (7.6–10%) than for PDS.[13,66,67] The higher rate of retinal detachment in PG

patients is probably not a consequence of pilocarpine therapy as the incidence of retinal detachment in patients treated with miotics is similar to those not on miotics.[13]

Differential diagnosis

There are several conditions with features similar to PDS/PG (with or without elevated IOP):

Pseudo-exfoliation syndrome

Pseudo-exfoliation syndrome can be associated with iris trans-illumination defects, TM pigmentation and elevated IOP. However, iris trans-illumination in PXF tends to occur at the pupillary margin rather than in the mid-peripheral iris.[36,68] The pigmentation of the TM is patchy compared with the uniform pigmentation in PDS/PG.[36] PXF also tends to affect an older population (usually >60 years), and is unilateral in 50% of cases, on the basis of clinical examination.[14,36,69] The diagnosis of PXF is aided by the presence of characteristic whitish PXF deposits throughout the anterior segment.[36]

Uveitis

Anterior uveitis can cause iris pigment epithelitis with the release of pigment, inflammatory cells and debris into the AC, which can be mistaken for PDS.[70] The loss of pigment epithelial cells is often associated with iris trans-illumination defects.[70] Herpetic uveitis is a common cause of iris trans-illumination defects associated with elevated IOP.[68] Furthermore, uveitis can cause patchy increased TM pigmentation.

Intraocular surgery and trauma

Intraocular surgery or trauma (blunt or penetrating) can cause features similar to PDS, with iris trans-illumination defects, aqueous pigment cells, increased TM pigmentation and possibly an elevated IOP. The history will aid diagnosis, and the presence of posterior chamber intraocular lenses, particularly sulcus-fixated lenses (that more closely approximate the iris), is a relatively common cause of pigment dispersion. The TM may be heavily pigmented in pseudophakic eyes and can be associated with increased outflow resistance, elevated IOP and glaucoma.[71–77]

Intraocular tumours

Intraocular tumours, in particular anterior uveal melanomas, may be a cause of pigment or tumour cell dispersion into the AC and IOP elevation.[78,79]

Age

Pigment dispersion increases with age in normal eyes and can lead to age-related TM pigmentation.[80,81] It is also more common for the aged iris to have more trans-illumination defects.[68]

Rhegmatogenous retinal detachment

Rhegmatogenous retinal detachment may produce pigment cells that are apparent in the AC as well as in the vitreous. Retinal detachment may be associated with increased TM pigmentation and rarely can cause an elevated IOP due to outflow obstruction with retinal pigment cells or photoreceptor outer segments.[82,83]

Long-term or frequent mydriasis

Long-term or frequent mydriasis can cause pigment dispersion and increased TM pigmentation.[61,84–86]

Diabetes

Diabetes may be a cause of iris trans-illumination defects. The accumulation of glycogen causing vacuolization and thinning of the iris pigment epithelium, together with hypoxia due to an impaired iris microvascular circulation, may be responsible for the iris trans-illumination defects.[68,87,88] Diabetic trans-illumination defects are often associated with dispersion of pigment into the AC, although a degree of this may be secondary to the frequent mydriasis that diabetics undergo for retinal examination, therapy or surgery.[68,87]

Mechanism of IOP elevation

Studies of human autopsy eyes[51] and non-human primate eyes[89] have shown that the perfusion of pigment into these eyes causes reduced aqueous outflow. However, the mechanism of reduced outflow is not one of simple TM channel blockage with pigment. In 1977, Richardson discovered that TM endothelial cells phagocytosed pigment.[53] Current understanding is that phagocytic overload of the trabecular endothelial cells leads to their death (Fig. 1) and that the necrotic cells, together with the pigment, are then cleared away by macrophages.[90] The loss of TM cells causes collapse and fusion of the denuded trabecular beams, resulting in obliteration of the meshwork channels, outflow obstruction and elevated IOP.[53,90,91]

Mechanism and aetiology of PDS and PG

Originally, PDS/PG was considered to have a congenital aetiology. Congenital mesodermal dysgenesis was thought to be the cause of iris pigment loss and the cause of a developmental drainage angle anomaly.[37,38] Other theories suggested that primary atrophy or degeneration of the iris pigment epithelium led to PDS/PG.[34,35,44,45] It has also been proposed that a genetic abnormality affecting the middle third of the eye during the third trimester may be the cause of PDS/PG, which could explain the association with retinal lattice degeneration, retinal tears and retinal detachment.[4]

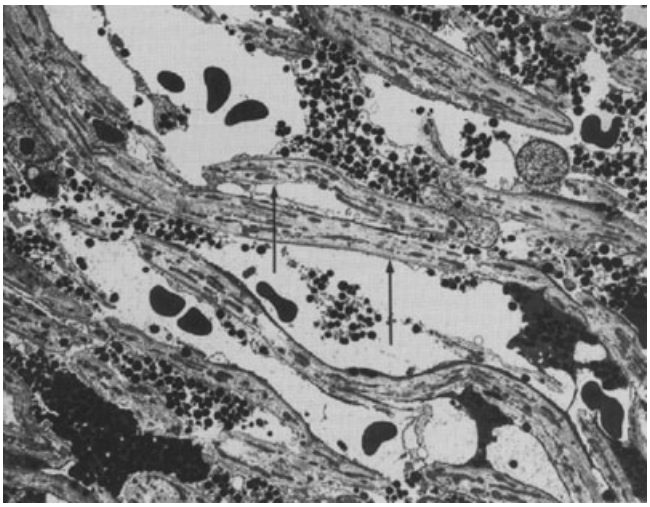

Figure 1. Transmission electron micrograph of corneoscleral meshwork in pigmentary glaucoma. Note denudation (absence of cellular covering) of trabecular sheets (arrows), pale cytoplasm and fragmented cell membranes of trabecular cells, and necrotic nuclei without cytoplasm. Most melanin granules are intracellular, contained within either intact or partially ruptured trabecular cells (specimen 1362; uranyl acetate-lead citrate, original magnification ×1800). (Reprinted from Alvarado JA and Murphy CG[90] with permission of *Archives of Ophthalmology*.)

A possible genetic aetiology has been suggested in reports of familial Krukenberg spindles[92–94] and familial pedigrees with PDS/PG.[28,95–100] Several authors have reported an autosomal dominant inheritance of PDS.[28,95,97,99,101] However, an autosomal recessive inheritance of PG in four generations of a family has also been described.[98] Mandelkorn[95] reported several modes of inheritance of PDS in five families, suggesting that factors such as gender, iris colour and refractive error may have a role in clinical expression of the condition. The low incidence of familial PDS and PG suggests a multifactorial pattern of inheritance or trait of variable penetrance and expressivity.[13]

A possible gene responsible for PDS/PG has been reported to map to chromosome 7q35-q36 and has been identified in 28 of 54 patients from four Irish families with autosomal dominant PDS or PG.[102] The specific gene itself has yet to be characterized, but candidate genes mapped to this region of Chromosome-7 include a homeobox gene,[103] a gene associated with human Cyclops,[104] a muscarinic cholinergic receptor gene[105] and the nitric oxide synthetase gene.[102,106]

In pathological studies performed in the late 1970s, Campbell discovered a close correlation between the number and location of iris trans-illumination defects and bundles of zonules that inserted into the anterior lens surface in PDS eyes.[33] On average, there were 65–80 bundles of zonules inserting into the anterior capsule of each eye, and there were 65–80 corresponding iris radial trans-illumination defects.[33] The radial distribution and the close proximity of the anterior zonular bundles with the mid-peripheral iris and trans-illumination defects suggested that it was these bundles that were responsible for causing the loss of pigment from the posterior iris.[33] The importance of the finding that zonules inserted into the anterior capsule as bundles (Fig. 2) is that bundles of fibres are more likely to cause rubbing of pigment off the posterior iris than single strands.[33] Campbell also reported backward bowing of the peripheral iris in many patients with PG and concluded that it was this bowing that resulted in contact and friction between the posterior pigmented iris epithelium and the zonular bundles.[33] It was proposed that persistent and frequent friction with all iris movements was the cause of pigment dispersion and the subsequent development of iris trans-illumination. The presence of posterior bowing of the iris and irido-zonular contact in PDS eyes has been confirmed by ultrasound biomicroscopy (Fig. 3).[3,50,107]

Campbell's theory is supported by clinical correlations for the condition. The relatively early onset of PG, compared with other forms of glaucoma, may reflect early enlargement of the myopic eye, allowing more room for the peripheral iris to bow posteriorly.[33] Dark irides have heavy pigmentation and thicker, more compact, iris stroma that may prevent backward bowing of the iris and account for the lower rate of PDS/PG in non-Caucasians.[3,33] The 'burn-out' phase of PG may be due to the age-related increase in lens axial length pushing the iris forward and away from its contact with the zonular bundles.[33] The age-related relative miosis may also pull the iris away from the zonular bundles, contributing to the cause of the final 'burn-out' phase of PG.[33]

With Campbell's observations of PDS and PG, the concept of reverse-pupillary block was proposed as the principal causative mechanism.[33,108] Karickhoff[108] and others[109] had observed that some eyes with deep ACs, which were pseudophakic or undergoing cataract surgery, developed posterior bowing of the iris caused by a reverse-pupillary block; a result of a higher aqueous pressure in the AC than the posterior chamber (PC). The similar iris configuration seen in PDS/PG led to Campbell's[33] and Karickhoff's[108] theory of reverse-pupillary block. Reverse-pupillary block is not unique to eyes with PDS or pseudophakia and can be caused by blinking, accommodation or eye movements in normal eyes.[108,110,111]

The sequence of events leading to reverse-pupillary block described by Karickhoff[108] and confirmed by ultrasonographic studies[50] has been shown to be initiated by physiological events such as blinking, accommodation, eye movements, exercise and certain head positions.[108] It has been reported that the portion of iris in contact with the lens acts as a simple flap-valve allowing aqueous to pass from the PC to the AC, but not in the opposite direction.[108] The currently accepted mechanism is that a physiological event causes aqueous to be pumped through the flap valve of the iris from the PC to the AC. The process eventually results in a higher pressure within the AC (relative to the PC) that causes the flap valve of the iris to close leading to reverse-pupillary block. The reason that reverse-pupillary block occurs more readily in PDS eyes, compared with normal eyes, is that eyes with PDS have greater irido-lenticular

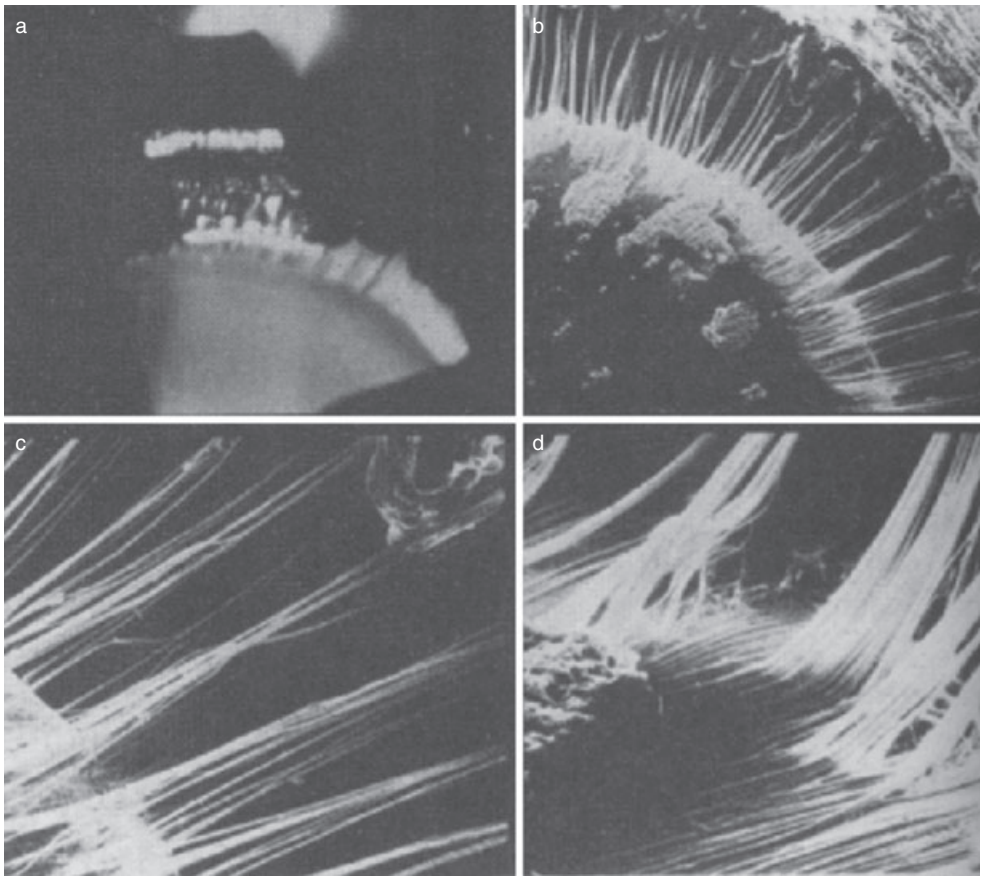

Figure 2. Normal human anterior zonular anatomy. Prominent anterior zonular packets are shown following iris removal. (a) Slit-lamp photograph (at original magnification ×16). (b) Scanning electron microscopic view (at original magnification ×30). (c) Enlarged view of B, showing zonular packets (at original magnification ×100). (d) Insertion of zonular packets into lens (at original magnification ×400). (Reprinted from Campbell DG[33] with permission of *Archives of Ophthalmology*.)

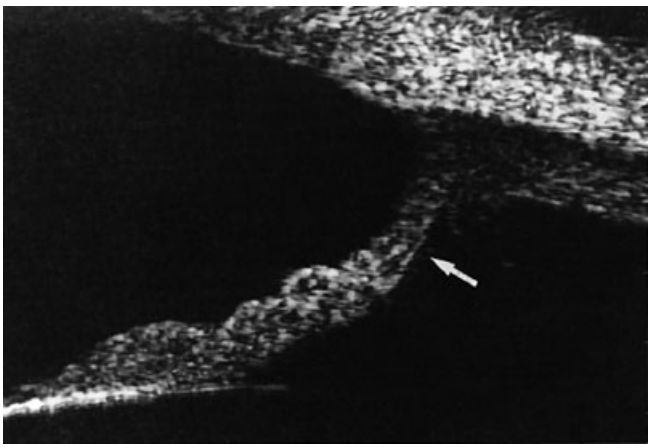

Figure 3. Ultrasound biomicroscopic image of concave iris in patient with pigmentary glaucoma, with zonule (arrow) extremely close to, and likely touching, posterior iris surface. (Reprinted from Pavlin CJ *et al.*[107] with permission of *Canadian Journal of Ophthalmology*.)

contact preventing equilibration between the pressure in the AC and PC.[110] The trapped aqueous at a higher pressure in the AC causes posterior bowing of the peripheral iris leading to friction between the posterior iris pigmented epithelium and zonular bundles, which results in the subsequent dispersion of pigment.

PG: BURN-OUT PHASE

Unlike many other forms of glaucoma, PG 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.[65] An age-related reduction in pigment dispersion has been supported by documented reversal of iris trans-illumination defects, although this tends to be more frequently seen in patients treated with pilocarpine.[12,15,33,112] Long-term follow-up studies have also shown an age-related reduction in degree of TM pigmentation and a tendency to IOP normalization with the requirement for fewer anti-glaucoma medications.[12,33,37,65,112] As the burn-out phase occurs, the increased pigmentation of the inferior angle tends to clear before the pigmentation of the superior angle leading to a relatively darker band superiorly: the pigment reversal sign.[4] The clearance of pigment may increase the facility of aqueous outflow and cause resolution of the glaucomatous process.[33] It has been proposed that reversal of the pigmentary signs of PG in older patients can lead to a misdiagnosis of POAG, or normal tension glaucoma when associated with IOP normalization.[113]

There may be several reasons for the tendency of PG to burn-out with advancing age. Campbell has suggested that the increasing axial length of the lens with age lifts the peripheral iris away from contact with the lens-zonule bundle complexes, thus reducing pigment dispersion.[33]

Furthermore, age-related relative miosis and the long-term treatment of some patients with miotic therapy (commonly used in the past) may cause a relative pupil block, and the functional iris bombe may lift the peripheral iris away from the zonular bundles.[33] Another reason for reduced pigment dispersion with time may be that once the zonules have rubbed the entire posterior pigment epithelium off the iris in areas of irido-zonular contact, no further release of pigment is possible, an assumption being made that no regeneration occurs. The tendency to easier control and IOP normalization with increasing age in patients with PG may also be related to age-related, relative ciliary body shut-down resulting in reduced aqueous production.

Epidemiology

The US prevalence of PDS has been estimated to be approximately 2.5% and the incidence of PDS has been reported to be 4.8/100 000 population per year.[16,114] The US incidence of PG (cf. PDS) has been found to be 1.4/100 000 population per year.[16] Hence, PDS/PG represents an important condition that accounts for 1–1.5% of glaucoma cases seen in the Western world.[18,115] The prevalence of PDS in non-Caucasians is low and may be a result of different iris anatomy or different behaviour of the iris in non-Caucasians.[11,13,14,17,18] The more heavily pigmented irides may also mask subtle iris trans-illumination defects and lead to an underestimation of incidence and prevalence in non-Caucasians.

Estimates of the proportion of patients with PDS that have PG have ranged from 6% to 43%, a large degree of variation that reflects widely differing study inclusion criteria.[13,19,57] It is generally considered that 5–10% of patients with PDS will develop PG at 5–6 years after diagnosis,[16,20] 15% at 15 years,[16] with 35% developing PG at 35 years.[12] However, other studies have estimated higher PDS to PG conversion figures of 20% at 7 years,[116] or even 50% at 4 years.[11] The actual figures of conversion from PDS to PG will remain unknown without a large community-based population survey, particularly as most cases of PDS remain undetected, there being a bias towards detecting only those patients with glaucoma or ocular hypertension.

Risk factors for conversion from PDS to PG

Family history of glaucoma

Studies have shown that 4–21% of PDS patients have a family history of glaucoma.[13,16,117] However, the percentage of PG patients with a family history of glaucoma has been reported to be much higher, at 26–48%.[11,16] Family members with glaucoma do not necessarily have PG and therefore the hereditary factor may be for a susceptibility to develop glaucoma rather than to specifically develop PDS or PG.

Gender

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.[4,12,13,15,16] However, for PG, men greatly outnumber women with 78–93% of PG patients being male.[10,12,13,16,37] PG tends to occur at an earlier age in men, at 34–46 years, whereas women tend to develop PG a decade or so later at 43–53 years of age.[3,10,11,13,15,116] In addition to occurring earlier in men, PG tends to be more aggressive in men than women.[11,37] Interestingly, however, for patients with POH, the incidence of progression to PG seems to be equal for both genders.[12]

Refraction

The majority (38–100%) of PDS patients are myopic (> -1.00 D),[10,13,16,116] some (12–42%) are emmetropic (-1.00 D to 1.00 D),[10,13,116] and only a minority (2–13%) are hypermetropic ($> +1.00$ D).[10,13,116] Studies have shown that the degree of myopia in groups of PDS patients that develop PG is higher than the degree of myopia in those who do not develop PG.[16,116] The preponderance of myopia among patients with PG supports Campbell's theory,[33] as the more myopic eyes, with their tendency to have deeper ACs, have more contact between iris and zonules leading to greater pigment dispersion. Further support for Campbell's hypothesis has been the finding that the higher the degree of myopia, the lower the age of conversion from PDS to PG.[116,118]

Krukenberg spindle

The presence of a Krukenberg spindle has been found to be more common in PG eyes than in eyes with non-glaucomatous PDS,[11] suggesting that a spindle may be predictive of PDS eyes that may develop PG. The predictive nature of a Krukenberg spindle is not unexpected as the amount of pigment deposited in a spindle has been shown to reflect a greater degree of pigment dispersion.[31]

Initial 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 PG.[16,116] Siddiqui[16] found that each 1 mmHg rise in IOP increased the risk of conversion from PDS to PG by a factor of 1.4, although in contrast, high initial IOP was not identified as a significant conversion risk factor in an earlier study.[12]

Pupil dilation

Pharmacological pupil dilation can induce pigment showers[31,32] and can raise the IOP significantly in eyes with PDS/PG.[85,119] However, Epstein[61] found that the majority of

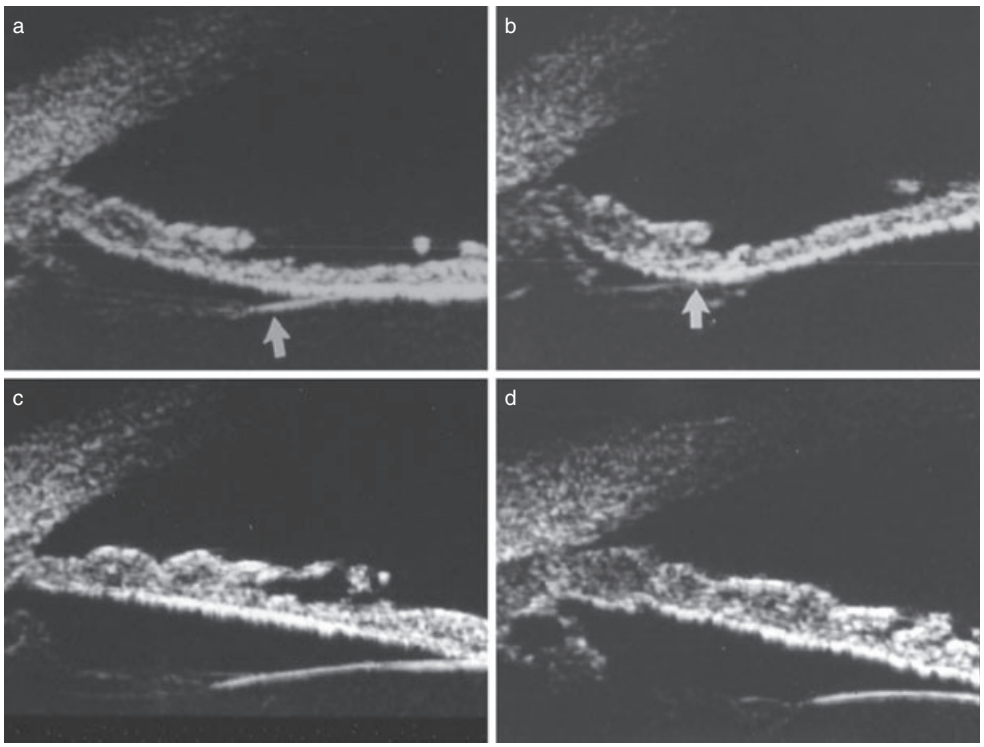

Figure 4. (a) Ultrasound biomicroscopic image of a cross-section of the inferior iris in a patient with pigmentary glaucoma on distance fixation. The iris has a concave configuration. The posterior iris surface is not in contact with the peripheral lens margin and zonule (arrow). (b) On near fixation, the iris concavity increases. The posterior iris surface is now in contact with the peripheral lens margin and zonule (arrow). (c) Following laser iridotomy, the iris has a straight configuration on distance fixation. (d) The iris configuration remains straight on near fixation following iridotomy. (Reprinted from Pavlin CJ *et al.*[129] with permission of *SLACK Incorporated*).

patients had no greater than a 2 mmHg elevation in IOP despite pigment liberation following instillation of 10% phenylephrine.

Exercise

In normal eyes and those with POAG, exercise usually lowers IOP.[120–125] It has been suggested that increased plasma osmolarity, increased blood lactate, decreased blood pH, changes in haemodynamic factors during exercise, or an exercise-induced increase in outflow facility, might have a role in reducing IOP during exercise.[121,123,126] In PDS/PG, however, exercise induces pigment dispersion that may result in reduced aqueous outflow and significant IOP elevation.[60–62,127] Exercise can increase the posterior iris concavity that is likely to induce pigment dispersion.[128] It has been proposed that the increased pulse rate and volume within the choroidal circulation during exercise causes increased cyclical aqueous movement posteriorly, this exacerbating the backward bowing of the iris in the presence of reverse-pupillary block.[128] Laser iridotomy (LI) can prevent the exercise-induced phenomenon by relieving reverse-pupillary block and preventing posterior bowing of the iris.[128] Furthermore, the exercise-induced IOP elevation can be inhibited pharmacologically with pilocarpine, but not with β-blockers.[60–62,127] It is probable that pilocarpine, unlike β-blockers, prevents friction between the iris and the zonular bundles by preventing exercise-induced pupil dilation and by altered iris configuration.

Accommodation

Accommodation can be associated with posterior iris bowing and thus has the potential to increase pigment dispersion.[111,129] High-resolution ultrasonography has shown that accommodation induces anterior movement of the lens, thus decreasing AC depth.[129] It is considered that the resultant increase in AC pressure, compared with the pressure in the PC, causes increased posterior bowing of the iris as aqueous is prevented from passing through the flap-valve of the iris. Thus, Pavlin's group has proposed that the increased posterior bowing with accommodation allows more irido-zonular contact and causes increased pigment dispersion.[129] In support of their own hypothesis it has been shown that an LI can inhibit the increased posterior bowing of the iris induced by accommodation (see Fig. 4).[129]

The concepts proposed by Pavlin's group[129] are attractive in explaining the young age of onset for PG compared with other types of glaucoma. Accommodation is active in the young, which may lead to more pigment dispersion at a young age. In contrast, accommodative power declines with age, which may account for the burn-out phase of PG. However, the effect of accommodation on iris profile in PDS/PG has been found to be highly variable, with some irides increasing in concavity, others remaining unchanged and some reducing in concavity.[130] The effect of accommodation on iris configuration is unlikely to be the sole factor in the aetiology of PDS. Pigment dispersion may depend on a number of factors that include the duration and degree of accommodation, pupil diameter and blinking.

Blinking

Normal blinking can create transient vector forces that pump aqueous from the PC to the AC, increasing AC

pressure to cause posterior iris bowing.[131] Blinking, therefore, has the potential to increase irido-zonular contact and friction, leading to pigment dispersion. In support of the effect of blinking on pigment dispersion, studies have shown that prevention of blinking for prolonged periods results in a flattening of iris profile, reducing irido-zonular contact and the associated pigment dispersion.[110]

Management of PDS and PG

The management of each case of PDS, POH or PG has to be individually tailored with respect to the advantages and disadvantages of therapy for the particular patient. In addition, the management should depend on the state of disease activity. Patients with PDS and PG generally fall in to one of the four clinical groups:[15]

1 *Inactive pigment dispersion with stable IOP.* This group includes PDS patients and those with burnt-out PG.
2 *Active pigment dispersion with stable IOP.* This group includes PDS and PG patients. The TM has not been overwhelmed by pigment and the aqueous outflow facility is sufficient to maintain IOP.
3 *Active pigment dispersion with progressive glaucoma and elevated IOP.* These PG patients may later have inactive pigment dispersion and the IOP may return to normal or they may progress to group four.
4 *Inactive pigment dispersion with progressive glaucoma and normal or elevated IOP.* This group of PG 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.

During the active phases of the disease the management of the condition may need to be aggressive. However, it is also important to remember that during the quiescent phases the management should be less intensive. As with the management of all forms of glaucoma, prevention of progressive disease is an ideal, but adverse consequences of therapy should be considered, as these may be more symptomatic than the condition itself.

In addition to identifying the signs of PDS/PG in the assessment of these patients, examination after exercise should be considered in certain circumstances, especially when visual symptoms occurring during or after exercise have been reported. Increased pigment dispersion with posterior iris bowing during exercise may aggravate the disease process and these patients may therefore require more aggressive management of their condition.[60–62,127,128] The recognition of posterior bowing of the iris during exercise, accommodation, with pupil size and with time is also important as flattening the iris plane with LI may be all that is required to prevent pigment dispersion and control the condition in these patients.

Medical therapy

Pilocarpine

Pilocarpine is almost an ideal therapy for PG. Pilocarpine lowers IOP, prevents pupil dilation, reverses posterior iris bowing[33,50,107] and inhibits exercise-induced rises in IOP, probably as a result of the drug-induced change in iris configuration.[60–62,127] 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).

α-adrenergic agonists

Adrenaline and dipivefrin are particularly efficacious in PG compared with their efficacy in other types of glaucoma.[13,132,133] The increased efficacy of α-adrenergic agonists in PG might be explained by adrenergic hypersensitivity in patients with PDS/PG and may reflect the impression that PDS affects people with Type-A personalities and those with a possible predisposition to cardiovascular disease.[133] However, adrenaline and dipivefrin have a poor side-effect profile commonly causing conjunctival hyperaemia and adrenochrome deposition.

β-adrenergic antagonists (β-blockers) and carbonic anhydrase inhibitors)

β-blockers and carbonic anhydrase inhibitors are useful ocular hypotensive agents, often used to treat POH/PG, but do not have specific anti-PDS effects.

Prostaglandin analogues

Prostaglandin analogues are potent ocular hypotensive agents, but have no specific anti-PDS effects. The enhancement of uveoscleral outflow may be beneficial in PDS/PG patients and latanoprost has been shown to be more effective in reducing IOP in PG patients than timolol.[134] 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.[135,136] Thus, prostaglandin analogues are not contraindicated in PG and in clinical practice are often used as first-line agents.

α-adrenergic antagonists

Thymoxamine or dapiprazole specifically inhibit the α-adrenergic receptors of the iris dilator muscle. Inhibition of α-adrenergic receptors is ideal for PDS/PG as it causes miosis and reversal of posterior iris bowing without the ciliary muscle contraction and unwanted accommodation produced by pilocarpine.[33,137,138] α-adrenergic antagonists also reduce exercise-induced IOP rises, probably as a consequence of pupil constriction and altered iris configuration.[139] However,

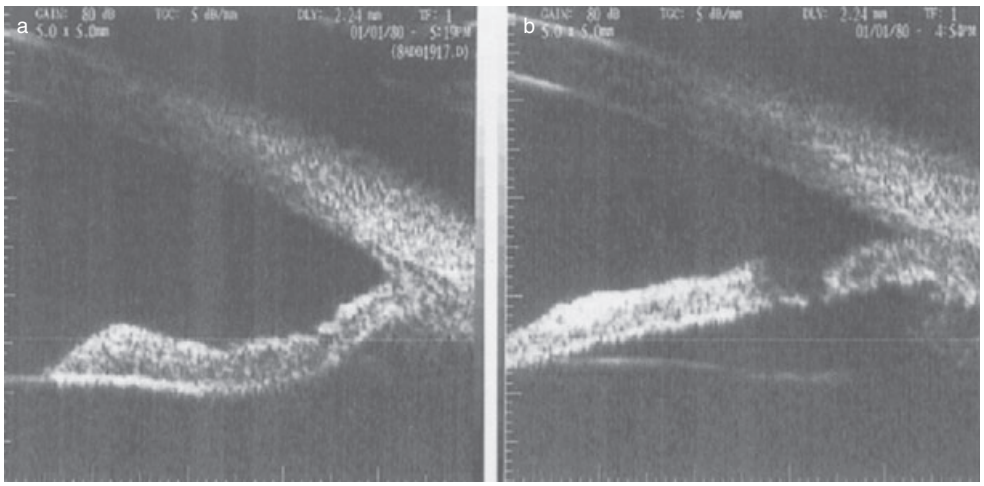

Figure 5. (a) Ultrasound biomicroscopic image showing the iris concavity of a patient with pigmentary glaucoma before iridotomy. (b) Ultrasound biomicroscopic image showing flattening of the iris configuration following iridotomy in the same eye. (Reprinted from Chen MJ *et al.*[163] with permission of *British Journal of Ophthalmology*.)

the treatment of PG with α-adrenergic antagonists has not been evaluated with controlled trials and topical α-adrenergic antagonists are not widely available.

Laser trabeculoplasty

Argon laser trabeculoplasty (ALT) has been shown to be particularly effective in PG.[117,140–149] The reason for this success may be due to the greater energy absorption by the pigmented TM. In PG, ALT in young patients seems to be more effective than in older patients, unlike with POAG.[142,144,149,150] The location of pigment in the inner meshwork in young patients compared with the outer meshwork and around Schlemm's canal in older patients may explain this phenomenon.[149] It is possible that the absorption of laser energy by the innermost TM cells of young patients may improve outflow more effectively than the absorption of laser energy by cells in the deeper meshwork in older patients.[149] ALT may work by causing 'trabecular tightening' with expansion of intertrabecular spaces or may stimulate an increase in the numbers, or metabolic function, of TM cells.[151–153] Young eyes may be more responsive to ALT because of their ability to increase the number of TM cells or their metabolism.[149]

The success of ALT diminishes with time, with a reported success rate of only 45% at 6 years.[149] The time-related reduction of efficacy may be due to secondary damage and scarring of the TM,[142] and the high energy absorption of pigmented tissues may be a cause of over-treatment in some cases, the damage having a long-term detrimental effect on aqueous outflow. Selective laser trabeculoplasty (SLT) may have an advantage in this respect, as it causes less damage to the TM than ALT.[154] The selective absorption of energy by pigmented TM cells rather than non-pigmented cells allows less energy to be used with SLT than ALT. Despite the targeted treatment to pigmented TM cells, the degree of TM pigmentation does not seem to affect the success rates of SLT.[154] In fact, SLT has been reported to cause a marked and persistent increase in IOP in certain PG eyes, requiring subsequent trabeculectomy.[155] Hence, SLT should be used with caution in cases of PG and close post-laser observation is advised.

Laser iridotomy

Kurwa was the first to report the successful use of peripheral LI as a therapy for PG in 1984.[156] However, iridotomy was not widely accepted as a treatment for PG because a pathophysiological explanation for treatment effect could not be offered. It was not until 1991 that LI was popularized by Campbell[157] after it was noted that the iris flattened after treatment. Campbell's[33] and Karickhoff's[108] concept of reverse-pupillary block and posterior iris bowing as a cause of pigment dispersion provided the explanation for the treatment effect of LI. A peripheral iridotomy equalizes the pressure between the AC and the PC, relieving reverse-pupillary block, flattening the iris and reversing posterior iris bowing[49,107,108,158–163] (Fig. 5) to prevent further pigment release.[164] Gandolfi and Vecchi[32] have shown that LI prevented long-term rises in IOP in patients with PDS. In their study, only 5% of eyes randomly assigned to treatment with LI had an increase in IOP of >5 mmHg, compared with 52% in the control group, over a 2-year period. 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.[32]

A peripheral LI alone is not the universal answer to treating PDS/PG and, unfortunately, is not successful in all cases.[165] Because of the effect of LI in reducing pigment release by flattening the iris, it is likely to be useful only in active stages of the disease and only if there is significant posterior bowing of the iris. Peripheral LI 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.[162,166] It is probable, therefore, that LI would be most beneficial prior to the development of PG. Offering LI to patients with PDS might be appropriate as a prophylactic procedure, much like the use of LI to prevent angle closure in eyes with closeable angles. However, it remains controversial

as to whether performing a procedure in a patient with no manifest disease is appropriate, particularly as liberation of pigment from the LI may further damage the TM and/or cause IOP spikes. The ideal eye to be treated with LI would have PDS with significant iris bowing and an increase in pigment dispersion or increase in IOP with exercise or pupil dilation. The ideal patient would have PG in the fellow eye, suggesting that the eye with PDS is likely to progress to PG without treatment, the aim of the LI being to reduce pigment release.

Trabeculectomy

Trabeculectomy has been reported as the most effective treatment for PG, with fewer eyes deteriorating compared with eyes on medical therapy.[12] However, the need for filtration surgery needs to be balanced with the slightly higher incidence of visual acuity loss secondary to cataract formation and retinal detachment compared with medical treatment.[12] It may be argued that the iridectomy alone is all that is needed to prevent progression of PG owing to its effect of relieving reverse-pupillary block and flattening the iris profile to reduce pigment dispersion.

Summary

PDS and PG represent two ends of a spectrum of a fascinating condition. It is a type of glaucoma with a known aetiology and pathophysiological mechanism. However, the more we understand about the condition, the more questions are raised: Should we tell our patients not to exercise? Should we tell our patients not to read books? Should we tell our patients not to blink? Clearly 'No', but is an iridotomy more acceptable? Should further evidence be forthcoming, the role of iridotomy in the management of patients with PDS may become more evidence based. In particular, it will be important to determine when and in whom such therapy would be beneficial in both the short and long term.

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