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PERSPECTIVES OR EXPERT OPINIONS

Pigment dispersion syndrome and pigmentary glaucoma: a review and update

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Abstract

Introduction Pigment dispersion syndrome (PDS) is a condition where anomalous iridozonular contact leads to pigment dispersion throughout the anterior segment and the released pigment is abnormally deposited on various ocular structures.

Clinical presentation The clinical presentation of PDS is defined by the presence of pigmented cells on the corneal endothelium, an increase of pigmentation of the trabecular meshwork, and mid-periphery transillumination defects of the iris. This syndrome, more common in myopes, is usually bilateral and can be associated with ocular hypertension or glaucoma. Secondary open-angle pigmentary glaucoma (PG) can develop due to reduction of the outflow of aqueous humour and consequent increase in intraocular pressure leading to glaucomatous optic neuropathy. Diagnosis of PG is commonly between 40 and 50 years of age, occurring more frequently in men. The advent of ultrasound biomicroscopy and anterior segment optical coherence tomography has contributed to enhancing our knowledge on the condition. Typical alterations of the anterior segment are the posterior insertion of the iris and iris concavity. Treatment of PG should be initiated early to hinder disease progression, glaucomatous damage, and vision loss. Management is based on medical therapy, laser iridotomy, selective laser trabeculoplasty, and filtration procedures.

Conclusions The differential diagnosis of PDS with other disorders can be challenging and awareness of the condition together with meticulous ophthalmologic examination allows early diagnosis followed by appropriate management strategies. The present review is a comprehensive report on the clinical characteristics, pathogenesis, current management, and status quo of PDS and PG.

Keywords Pigment dispersion syndrome · Pigmentary glaucoma · Trabecular meshwork · Iris

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transillumination · Krukenberg spindle · Ultrasound biomicroscopy

Introduction

The ophthalmic condition defined as pigment dispersion syndrome (PDS) can lead to elevated intraocular pressure (IOP) and pigmentary glaucoma (PG) ultimately resulting in visual loss. PDS is characterized by pigment localized on the corneal endothelium, iris transillumination defects largely restricted to the mid-peripheral sections, and heightened trabecular meshwork pigmentation. PG is defined when these characteristics cause an increase in IOP and glaucomatous optic neuropathy. In PDS, there is spread of pigment from the iris pigment epithelium and its abnormal accumulation onto various parts of the anterior segment [1]. Pigment on the trabecular meshwork can lead to trabecular alterations and increased IOP. This can be associated with glaucomatous optic neuropathy. PG, considered a secondary open-angle glaucoma, is often under diagnosed as it occurs in the third or fourth decade of life [1–4]. The differential diagnosis of PDS can be challenging and meticulous examination of patients is warranted. PDS should be differentiated from secondary glaucoma caused by trauma, medication such as corticosteroids, inflammation, tumours, and pseudoexfoliation. Early diagnosis and treatment of PG are fundamental to prevent disease progression.

History

Krukenberg identified pigment accumulation on the corneal endothelium in 1899 [5] but the association between glaucoma and pigmented cells was first reported by Von Hippel in 1901 [6]. Sugar described the first case of PG in 1940 [7] and Levinsohn discovered pigment on the trabecular meshwork hypothesizing its origin from the iris [8]. In 1949, Sugar and Barbour described the characteristic features of PG in two young men with myopia presenting Krukenberg spindles, iris transillumination defects, increased pigmentation of the trabecular meshwork, and ocular hypertension which increased with mydriasis and decreased with pilocarpine [9]. This finding was followed by a comprehensive review of PG in 147 patients by Sugar and other authors [10, 11–14]. PG was considered a rare condition in the past but today there is increased awareness of the condition and appropriate diagnosis and management strategies are mandatory.

Epidemiology

Over 70 million people suffer from glaucoma worldwide [15]. PG and PDS account for 1–1.5% of glaucoma cases in Caucasian countries [16]. In the literature, reports of the risk of developing PG from PDS are estimated as between 35 and 50% [16]. A recent article with a mean follow-up of over 4 years reported a rate of 37.5% [17]. PDS occurs in patients between 20 and 40 years of age. Myopia is found in about 80% of patients and is a risk factor for PDS; the more myopic the eye, the more it is likely to be affected [16]. Many studies have reported that the mean age of PG diagnosis, more frequent in young Caucasian men, is between 40 and 50 years [16]. PG is rare in black and Asian populations; however, the incidence could be underestimated in subjects with darker and thicker iris anatomy as this can veil diagnosis [18, 19]. Differential diagnosis should be made with oculodermal melanocytosis and phakomatosis pigmentovascularis where ocular hyperpigmentation is frequently associated with glaucoma [20–22]. Interestingly, congenital abnormalities due to mesodermal migration have been suggested to have a role in the development of PDS/PG [23] and a genetic anomaly occurring in the third trimester seems to be generally accepted as an etiological factor of PDS and PG [24].

Genetics

PDS has been reported as an autosomal dominant disease with incomplete penetrance [25]. Familial aggregation is a characteristic of both PG and PDS, but it does not necessarily reflect a Mendelian pattern, and unspecified, multiple genes coupled with environmental influences can cause these conditions [26]. Chromosome 7q35-q36 may be related to or increases the risk for PDS [25]. Recent research showed that the

Swedish population is more prone to PG on account of the psuedoefoliation (PEX) syndrome [26]. The PEX syndrome and pseudoexfoliative glaucoma are associated with single nucleotide polymorphisms within the LOXL1 gene and a recent study showed that haplotypes of LOXL1 are also associated with an increased risk of PDS and PG [26]. The authors hypothesized that mutation of the LOXL1 gene could lead to defects of the stromal elastic fibres of the iris in PDS and PG [26].

Pathophysiology

The clinical triad of PDS consists in the Krukenberg spindle, radial mid-peripheral iris transillumination defects, and pigment accumulation on the trabecular meshwork. The iris shows a concave aspect, which frequently inserts into the posterior ciliary body band [27, 28]. Pigment in the anterior segment is transported by convective currents of the aqueous and accumulated on the structures of the anterior part of the eye. The typical corneal pigmentation or Krukenberg spindle generally appears as a central, elongated, brown band on the corneal endothelium which becomes smaller and lighter over time. However, the absence of this sign does not rule out PDS [29, 30]. There is also an overload of pigment in the endothelial cells of the trabecular meshwork, which can lead to endothelial cell death [16, 31]. Failure of the trabecular beams due to necrosis of endothelial cells can result in decrease in outflow channels and IOP elevation [31, 32]. The degree of pigmentation of the trabecular meshwork is not necessarily a predictor of conversion from PDS to PG but the amount of pigmentation is connected with the severity of PG [1, 24].

In 1970, Campbell found a direct connection between the extension and position of iris transillumination defects and bundles of zonules that inserted into the anterior lens surface in PDS [7, 33]. The typical position and the vicinity of the zonular bundles with the mid-peripheral iris and transillumination defects indicated that the bundles were the cause of loss of pigment from the posterior iris [34]. Thus, it was suggested that frequent friction with iris movements was the cause of pigment dispersion and iris transillumination [35, 36]. Campbell reported on a typical backward bowing of the iris [33]. Moroi et al. [37] suggested another mechanism related to the presence of elongated anterior zonules inserted centrally on the anterior lens capsule, which damage the iris pigment epithelium and cause pigment dispersion. A congenital posterior insertion of the iris has also been defined as a PDS characteristic [38]. Backward bowing of the iris may be observed with gonioscopic examination and posterior bowing of the iris with iridozonular contact is shown with ultrasound biomicroscopy [39, 40–42].

In comparison with other forms of glaucoma, the earlier onset of PG in myopia may be due to rapid growth of the eye, creating adjunctive space for the peripheral iris to move posteriorly [33]. Campbell introduced the idea of reverse pupillary block as the main mechanism for increase in IOP, which was confirmed by Karickhoff in 1992 [7, 33, 43]. Extended irido-lenticular contact in eyes with PDS could create a ball valve mechanism where unidirectional movement of aqueous from the posterior to the anterior chamber results in elevated pressure in the anterior chamber with posterior iris bowing and closure of the iris valve [31, 44, 45]. In the literature, there are some reports on the possible involvement of the posterior segment of the eye in PDS and PG based on the observation that the pigment epithelium of the iris and the retinal pigment epithelium share the same embryological derivation [46–48].

Physiological mechanisms such as blinking, accommodation, and exercise have been reported to influence the reverse pupillary block mechanism [43]. Blinking forces the movement of aqueous humour from the posterior to the anterior chamber with a vector pressure that leads to posterior iris bowing, iridozonular friction, and pigment dispersion. Liebmann reported that when blinking is prevented a flattening of the iris profile with reduction of iridozonular contact is observed [45]. Accommodation also involves posterior bowing of the iris and constriction of the pupil followed by pupil dilatation during the relaxation phase. Pavlin suggested that iridozonular friction during these phases causes pigment dispersion [49]. Interestingly, accommodative power diminishes with advancing age and this coincides with the burnout phase of PG. Similarly, exercise can give rise to pigment dispersion with a mechanism linked to pupil dilatation and posterior iris bowing [16]. In support of this theory pilocarpine, by inducing miosis, can limit

exercise-induced pigment release and consequent increase in intraocular pressure [50–52].

Histopathology

Histologically, PDS is featured by the presence of melanin granules throughout the anterior chamber: on the corneal endothelium, trabecular meshwork, and the anterior surface of the lens. The characteristic Krukenberg spindle is not due to free pigment cells adherent to the cornea but rather to phagocytosed pigment cells in the endothelium [36, 53]. Pleomorphism (abnormal shape) and polymegathism (abnormal size) characterize the endothelial cells [36]. Nevertheless, the presence of normal endothelial cell counts as well as a normally thick cornea in PDS patients suggest that endothelial function is not at risk. Pigment accumulation is also found on Schwalbe's line visible as a dark line. Ultrastructural studies have shown the presence of pigmented epithelial melanosomes in the trabecular meshwork and melanin inside the trabecular cells suggesting their phagocytic capabilities [54, 55] (Figs. 1, 2).

Richardson reported that endothelial cells phagocytose pigment granules deposited on the trabecular meshwork [55]. These cells subsequently degenerate liberating cellular debris. The trabecular lamellae progressively lose their endothelial covering and come into direct contact with the aqueous humour, degenerating and collapsing on each other, thus, obliterating the interlamellar spaces and, ultimately, reducing aqueous humour outflow [53].

Diagnosis and clinical features

Slit lamp examination, gonioscopy, IOP measurement, fundus assessment, visual field analysis, and retinal nerve fibre evaluation with optical coherence tomography are the standard procedures for glaucoma diagnosis. Further diagnostic procedures such as ultrasound biomicroscopy and optical coherence tomography of the anterior segment should be carried out when Krukenberg spindle, iris transillumination defects, and pigment accumulation on the trabecular meshwork are observed.

Examination of the anterior chamber shows an increased depth both in the central and peripheral areas [56]. The Krukenberg spindle and iris transillumination defects can be detected with slit lamp observation (Figs. 3, 4). Iris transillumination is seen in about 86% of patients in the form of spoke-like defects, which should be differentiated from mottled defects in normal eyes with light irises [33]. Transillumination defects in PDS have a typical pattern of red reflexes of the fundus similar to the rosetta window of a church, also known as the church-window sign. Asymmetric transillumination may create anisocoria and it has been suggested that this may be due to irritation of the

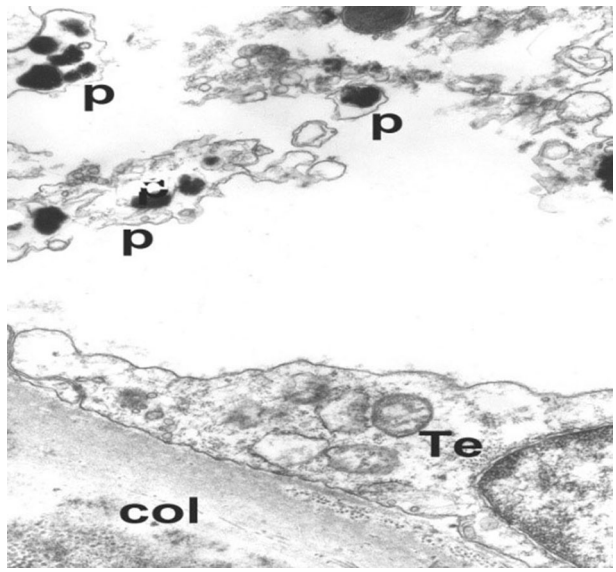

Fig. 1 Intracellular accumulation of pigment granules (p) in several processes of trabecular cells. Trabecular endothelial cells (Te) are well preserved. (col: collagen). Magnification ×2500. (Courtesy of Prof Janos Feher)

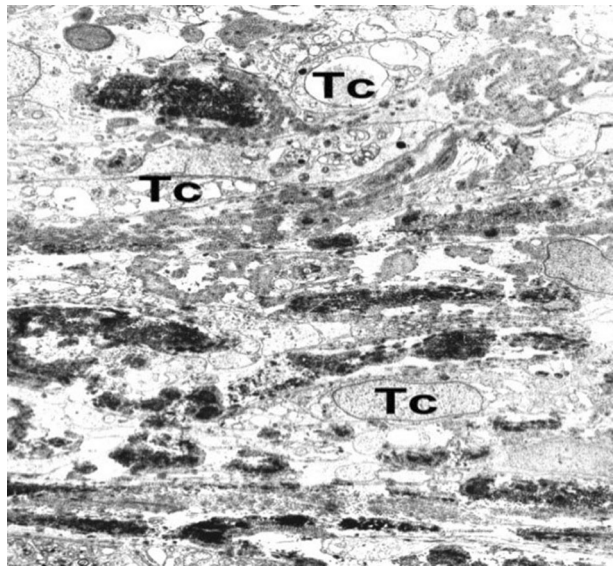

Fig. 2 Corneoscleral trabecular meshwork formed by highly condensated electrodense trabecular sheets. Only a few trabecular cells (Tc) can be seen. Their cytoplasm is very poor in organelles but contains several vacuoles. Magnification ×7000. (Courtesy of Prof Janos Feher)

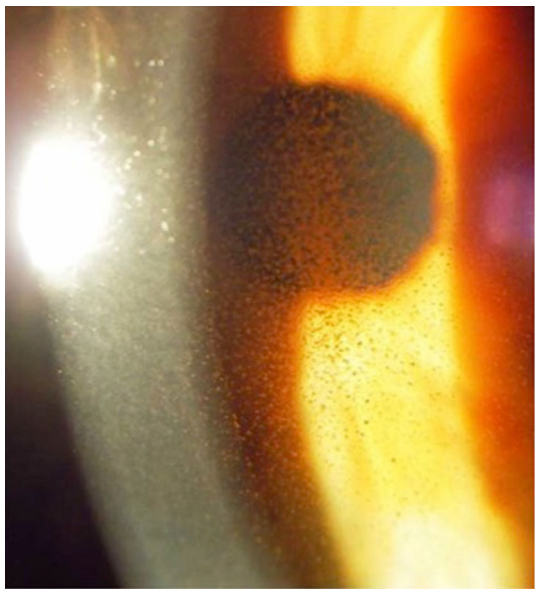

Fig. 3 Kruckenberg spindle in pigmentary glaucoma. Slit lamp examination shows pigment on the corneal endothelium

iris by zonules or alterations of dilator muscles, which should be considered during anterior segment surgery [33, 57]. IOP elevations in PDS, measured with applanation or non-contact tonometry, are generally in the 30 mmHg range but occasionally there are higher spikes associated with episodes of pigment release and corneal oedema [16, 58, 59]. A patient with PDS may refer symptoms of headache and sporadic blurry vision, especially in the context of extreme physical activity [50].

Fundoscopy can reveal glaucomatous optic nerve neuropathy in patients with PG. Myopes have a two-sixfold increased risk of developing glaucoma, [60] and patients with PG frequently have myopic refractive defects. The advent of excimer laser surgery has led to an increasing number of patients with iatrogenically thinned corneas; therefore, history of past refractive surgery should be taken into consideration when measuring IOP as corneal thickness alterations may cause erroneous evaluation and bias the diagnosis of PG [60–62].

The typical gonioscopic aspect of PDS is increased and homogenous pigmentation on the trabecular meshwork, unlike the pigmentation observed in PEX syndrome, which is characteristically patchy. In PDS, the whole circumference of the trabecular meshwork is involved, although pigmentation is more intense in the inferior part. However, the characteristic pigmentation of the trabecular meshwork can change with age and in older patients the "pigment reversal sign" can be observed where pigmentation is more intense in the superior part of the trabecular meshwork. The Sampaolesi line, frequently observed but not exclusive to PDS, is a pigmented line located in the inferior part of the chamber angle anterior to Schwalbe's ring. Similar to endothelial pigment deposits, pigment in the trabecular meshwork is phagocytosed. In PDS, circumferential pigment deposition at the site of anterior

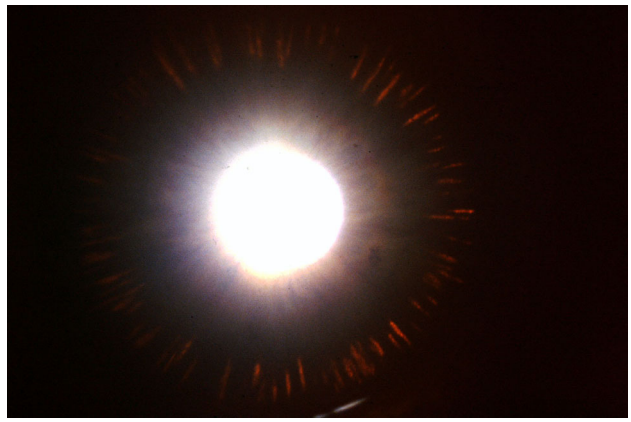

Fig. 4 Transillumination defects in pigment dispersion syndrome. Slit lamp image shows transillumination defects of the iris in the mid-peripheral areas

hyaloid attachment to the posterior lens periphery is known as Eggers line and pigment deposits on the posterior capsule along the insertion of the zonules are referred to as the Scheie stripe or Zentmayer line [16].

The characteristic posterior bowing of the iris and iridozonular contact can be observed with ultrasound biomicroscopy [39–42], which demonstrates the existence of a specific site of contact between the concave iris and the zonular fibres and between the iris and the ciliary processes (Fig. 5) [41, 42].

Since the advent of optical coherence tomography as a valid technique for the early diagnosis of glaucoma, evidence shows the diagnostic value of ganglion cell layer and retinal nerve fibre layer thickness measurement [63–66]. Arigfoglu et al. evaluated 102 patients using SDOCT and visual field analysis and found a lower average retinal nerve fibre layer thickness in patients with PG with respect to PDS. Furthermore, these authors showed that the superior and inferior ganglion cell complex was thinner in eyes with PG and concluded that the evaluation of retinal nerve fibre layer and ganglion cell complex thickness using SDOCT is a useful parameter in distinguishing PG from PDS [67].

The incidence of lattice degeneration and retinal breaks in PDS/PG is between 20 and 33.3%, and 12%, respectively, and about half of the latter cases lead to retinal detachment. However, these patients are frequently myopes and have a higher chance of peripheral retinal lesions [68].

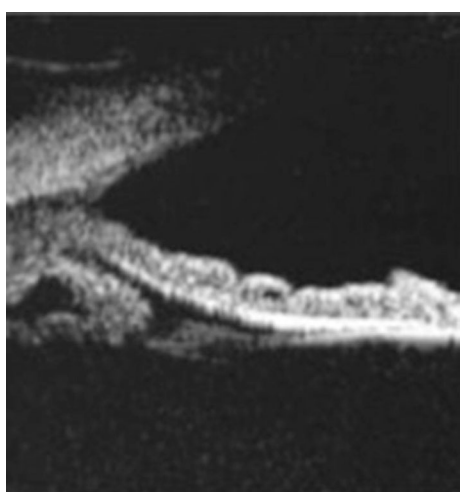

Fig. 5 Ultrasound biomicroscopy image in pigmentary glaucoma. The iris is bowed posteriorly towards the zonules and posterior chamber

Differential diagnosis

Pigment dispersion syndrome typically involves both eyes [54] whereas PEX glaucoma affects only one eye in 50% of patients and occurs in older patients. The differential diagnosis of PDS can be challenging and meticulous examination is warranted to make a distinction from other conditions where there is dissemination of pigment. In PEX, the pigmentation of the trabecular structures is patchy as the entire boundary of the trabecular meshwork is not always involved. Iris defects, sometimes present in PEX, are localized at the pupillary border whereas typical transillumination defects in PDS are in the mid-peripheral iris. The presence of white pseudoexfoliative material on the pupillary border and on the anterior lens surface indicates a clear diagnosis of PEX [69, 70].

Pigment granules in the anterior chamber may be confused with inflammatory cells making differential diagnosis with uveitis difficult [71]. Indeed, anterior uveitis, with flow of pigment, inflammatory cells, and debris into the anterior chamber, may be incorrectly assessed as PDS. Moreover, iris transillumination defects, high IOP, and trabecular meshwork pigmentation can be the result of herpetic uveitis [72]. Intraocular tumours such as uveal melanomas, and choroidal metastases manifesting with masquerade syndromes, can present with pigment dispersion and increase in IOP [73–75]. Of note is the increased risk of melanomas in patients presenting oculodermal melanocytosis and phakomatosis pigmentovascularis, which can be associated with glaucoma and pigment dispersion [22, 76, 77].

Iris transillumination deficit may be caused by diabetes due to thinning of the pigment epithelium of the iris [78]. Characteristics typical of PDS can also be caused by intraocular surgery or trauma [16]. Indeed, following cataract surgery transillumination defects can be observed. Furthermore, some types of intraocular lenses have increased contact with the iris (such as in those fixated at the sulcus) and can induce pigment dispersion. The trabecular meshwork may also become pigmented in these cases and can be associated with increased outflow resistance and elevated IOP [16]. Retinal detachment can lead to increased pigment cells visible in the anterior chamber, trabecular meshwork, and in the vitreous; however, high IOP levels are seldom encountered.

Pigment dispersion, trabecular meshwork pigmentation, and iris transillumination defects are increasingly observed in the elderly population. In addition, pigment loss and increase in trabecular meshwork pigmentation are caused by mydriasis over long periods of time.

Medical treatment

Among patients with PDS, only some will develop increase in IOP or PG. Comprehensive ophthalmologic examination is advisable, especially during the pigment liberation phase of the disease. Reduction of IOP in progressive glaucomatous optic neuropathy is fundamental to prevent vision loss. However, as the stage and degree of pigment liberation, IOP, and glaucomatous optic neuropathy widely differ, therapy should be tapered to each individual patient [79, 80]. Moreover, as in other forms of glaucoma, patients with open-angle glaucoma may have depression and hypochondriasis which can lead to reduced compliance to therapy [81, 82]. There are reports in the literature suggesting that type A personalities are frequently those with PDS/PG [83] and have greater variations in IOP with more significant visual field changes [84].

Numerous studies have reported an arrest of PG with age, called the burnout phase, which occurs after about 10 years of disease and may be due to an increase in the antero-posterior diameter of the lens with consequent distancing of the iris from zonular fibres [16]. Follow-up times can be lengthened when there is a decrease in pigment liberation and trabecular pigmentation as there is also a reduction of IOP. In this phase, topical anti-glaucoma medication can be tapered.

The principal aim of the initial medical therapy consists of lowering IOP. Reduction of aqueous humour production using a topic beta-blocker is efficacious but topical prostaglandins can be used as first-line treatment as they enhance uveoscleral outflow [86, 87]. The iris surface colour changes associated with the use of prostaglandins may be due to increased melanin production by iris melanocytes but there is no evidence that this worsens pigment dispersion [87–89]. Alpha-agonists are effective in PG, but allergy in some patients makes the long-term use of dipivefrin difficult, whereas brimonidine 0.2% is well tolerated [3, 90, 91]. Parasympathic mimetics may be used with the aim to reduce pupillary block and iridozonular contact, thus, diminishing pigment liberation [24]. Pilocarpine, through pupillary constriction, causes reduction of iridolenticular friction and increase of aqueous outflow; therefore, it has been considered optimal in treating PG [50]. However, miotics in young individuals are hardly accepted because of the subsequent spasm of accommodation and blurred vision but the use of lower dose pilocarpine such as 0.5%, where available, could be better tolerated in terms of disabling adverse effects. Although there is an increased prevalence of lattice degeneration and retinal breaks in PG patients, Scheie et al. [3] did not find an increased incidence in patients treated with pilocarpine. Nevertheless, attentive examination of the peripheral retina should be carried out when therapy with miotics is considered. Topical

carbonic anhydrase inhibitors are also effective and well sustained in the treatment of PG.

Systemic medication, such as trycyclic antidepressants, antipsychotics, and selective serotonin reuptake inhibitors, has been reported to induce uveal alterations and accommodative disorders causing iris bowing and potential pigment dispersion. The drug topiramate is known to induce ciliochoroidal effusion with anterior displacement of the lens-iris diaphragm leading to glaucoma in some patients. Thus, initiation of this type of therapy should be carefully evaluated in patients with PDS and PG where iris concavity is present [92, 93].

The advancing age of the population and pathologies such as age-related macular degeneration and retinal thrombotic events has increased the use of intravitreal anti-vascular endothelial growth factor and steroidal treatment; however, increase in IOP must be kept in mind when considering these therapeutic options and patients must be carefully evaluated to consider any cases of previously undiagnosed glaucoma in PDS patients [94, 95].

Laser and surgical management

Argon laser trabeculoplasty may be performed when medical therapy is not sufficient in the management of PG. Unfortunately, following a satisfactory initial response, IOP can rise again in many cases, possibly due to secondary damage and scarring of the trabecular meshwork. Thus, younger patients seem to have a better response [96]. Selective laser trabeculoplasty (SLT) has been reported to yield a 20% reduction in IOP in 85% of patients with PG at 1 year with maintenance of results in only 14% after 2 years [97]. However, frequently caused IOP elevations following SLT have been reported [98] requiring subsequent trabeculectomy [99–101].

Yag-laser iridotomy reduces the iris concavity present in most patients with PDS by creating pressure balance between the anterior and posterior chambers. Moreover, it may reverse backward bowing of the iris by flattening the iris, resulting in reduced iridozonular contact, pigment dispersion, and IOP increase [102–104] (Fig. 6). However, the elimination of the posterior bowing of the iris with laser peripheral iridotomy to alter the course of the condition is still in debate and a recent review concluded that there is insufficient evidence to draw conclusions on the role of laser iridotomy in preventing or reducing glaucoma progression as some authors reported a flatter iris but not a significant reduction of IOP [105–107]. Given that this procedure is not efficacious in patients with damage of the trabecular anatomy or long standing glaucoma, various authors evaluated the efficacy of laser iridotomy in preventing conversion of PDS to PG. Gandolfi et al. [108] in 2014 conducted a 10-year follow-up of eyes with PDS and concluded that peripheral laser iridotomy may reduce the rate of IOP elevation in eyes with a high risk of transformation to PG. However, Scott et al. [109] in a randomized trial with 3 years of follow-up did not find that laser iridotomy prevented the progression of PDS with high IOP to PG.

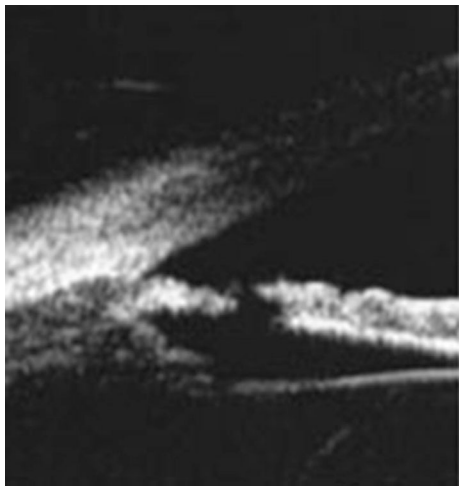

Fig. 6 Ultrasound biomicroscopy image in pigmentary glaucoma. Laser iridotomy is clearly visible, there is flattening of the iris and decreased iridozonular contact with respect to image in Fig. 5

Changes in the optic nerve combined with visual field alterations are the main factors to evaluate when considering filtering surgery [80, 110, 111]. When medical therapy and laser procedures fail, the surgical management of PG, similar to primary open-angle glaucoma, is standard filtration surgery with trabeculectomy [112].

Conclusions

PDS and PG represent two different stages of evolution of the same condition characterized by abnormal

iridozonular contact, pigment dispersion and deposit in the anterior segment. The disorder affects both sexes; however, glaucoma is more frequently encountered in men at an earlier age. Ultrasound biomicroscopy has enriched our knowledge on the condition and shows the typical posterior bowing of the iris and iridozonular contact. Novel imaging methods together with the typical clinical manifestations of the conditions allow early diagnosis of the condition. However, differential diagnosis with other pathologies can be challenging. At present, management of PDS consists of observation. The first-line treatment option for PG is medical therapy, which should be initiated early to prevent progression of disease. Although miotic therapy may impede pigment liberation, it is not well tolerated in younger patients; therefore, other IOP lowing topical medications can be employed. Yag laser iridotomy creates a planar configuration of the iris and reduces pigment release with reduction of IOP and laser trabeculoplasty reduces IOP; however, both procedures have given variable results. Trabeculectomy is still the surgical treatment of choice when medical and laser treatment is not sufficient or is unsuccessful. Long-term management of PG is fundamental in order to prevent glaucomatous optic nerve damage and visual loss.

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