REVIEW ARTICLE

Pigment dispersion syndrome: A brief overview

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ABSTRACT

Background: Pigment dispersion syndrome (PDS) is characterized by dispersion of pigment in the anterior chamber structures and can present with deposits on the central corneal endothelium or Krukenberg spindle, iris trans-illumination spoke-like defects, and increased pigmentation in the iridocorneal angle. It is more common in myopic patients with a predominance in young males in the third to fifth decade of life that affects about 1–2% of the population. PDS is a risk factor and can give lead to a rise in intraocular pressure (IOP) and secondary glaucoma. Pigmentary glaucoma (PG) can develop from PDS in the presence of elevated IOP coupled with glaucomatous optic neuropathy, retinal nerve fiber thinning, and/or visual field defects. PDS and PG have the same clinical features, representing different levels of severity on the same clinical spectrum.

Relevance for Patients: Early diagnosis, appropriate management, and follow-up of patients with PDS are important to prevent vision deterioration or blindness due to glaucomatous optic neuropathy.

1. Introduction

Pigment dispersion syndrome (PDS) is characterized by the presence of melanin pigment granules that circulate within the aqueous humor (AH) and accumulate on different structures found in the anterior chamber (AC) of the eye, including corneal endothelium, lens surface, zonules, iris, iridocorneal angle, and trabecular meshwork (TM) [1]. The pigment granules that accumulate in the angular structures and TM can give rise to reduced aqueous outflow, leading to elevated intraocular pressure (IOP). PDS can cause ocular hypertension (OHT) and can lead to secondary IOP rise that can damage the optic nerve in terms of pigmentary glaucoma (PG) development, which is a secondary type of glaucoma. PG can form when elevated IOP cause glaucomatous optic neuropathy, retinal nerve fiber layer (RNFL) thinning, and/or visual field defects [2]. PDS and PG in reality reflect different levels of severity on a continuum disease spectrum. PDS is an important risk factor in the development of OHT and PG [3]. There are different forms of glaucoma, the most prominent being primary open-angle glaucoma (POAG). PG is considered a secondary form of open-angle glaucoma [1-3]. PDS is normally diagnosed in the clinical presentation of a variety of signs and symptoms, which include fine pigment deposits on the central part of the corneal endothelium, radial mid-peripheral transillumination iris defects, and pigmentation in TM [1-3]. The mechanisms behind the formation of PDS are due to the constant rubbing and friction between pigment iris epithelium and lens structures during pupil movements, which tend to occur in the presence of reverse pupillary block and posterior bowing of the iris [1-3]. Some studies have theorized a burn-out phase or pigment reversal later in life in some patients, in which signs of PDS or PG are less evident.

With regards to historical notions, in 1899, Friedrich Krukenberg first described the presentation of vertical accumulation of pigment on the corneal endothelium [4], which

is now commonly referred to as Krukenberg spindle. This clinical characteristic was later associated with glaucoma by Von Hippel in 1901, who claimed AH outflow obstruction due to accumulation of pigment [5]. The first case of PG was reported by Sugar in 1940 [6]. Nine years later, the same author reported PG in 2 male myopes showing Krukenberg spindle, transillumination iris defects, pigment accumulation in the TM, and OHT [7]. He later published a 25-year review on PDS and PG based on 147 patients [8]. Levinsohn discovered pigment in the TM and hypothesized origination from the iris [9].

In terms of number of people with glaucoma, PDS and PG, there are over 75 million people affected by glaucoma worldwide. The prevalence is 3.5 % for those people aging from 40-80 years, with an expected increase to reach over 110 million by the year 2040 [10]. In Caucasian countries, glaucoma is due to PG and PDS in 1-1.5% of patients [1]. PDS and PG are more common in Caucasian patients with myopia between 20 and 40 years of age with an even distribution between males and females for PDS and a slight a slight male predominance for PG [11,12]. PDS is a risk factor to develop PG, especially in the presence of OHT and an anatomic myopic predisposition, with a lifetime conversion rate of 10–50% [1,13,14].

The aim of this brief overview is to provide a quick review for clinicians regarding important points and brief take home messages to remember when diagnosing, treating, and managing patients with PDS. A better understanding of PDS is of utmost importance in the differential diagnosis, treatment, and management of patients with PDS and PG to avoid the onset and/or progression of irreversible glaucomatous structural and functional damage.

2. Pathophysiology and clinical features

The cause of PDS is the release of pigment and accumulation in structures in the AC, which can give rise to increases in IOP and lead to PG. It was originally thought that PDS and PG had a congenital etiology, due to pigment loss from the iris from congenital mesodermal dysgenesis [15] or atrophy or degeneration of the iris pigment epithelium (IPE) [16,17]. Possible genetic factors have been hypothesized to explain the familial presence of Krukenberg spindle [18]. Although the low incidence of familial PDS and PG, studies have reported a possible autosomal dominant inheritance for PDS [19] and multifactorial pattern of inheritance [20], which may play a role in the clinical expression of factors related to iris color, gender, and refractive error. Anderson *et al*. [21] reported a possible gene responsible for PDS located on chromosome 7Q35-q36 based on an autosomal dominant pattern observed in patients from 4 Irish families with PDS. Studies have reported several genetic locus associated with PDS, which include Glycoprotein nmb (GpnmbR150x), Gene GPDS1 (glaucoma-related PDS 1), and (OMIM ID 600510) [22].

The release of pigment showers in the AC is mainly due to the friction and rubbing between the IPE and posterior surface and zonules of the lens, which is favored by the backward posterior bowing of the iris that can be found in moderate myopic eyes that have more space [23] and by reverse pupillary block mechanisms due to increased iridolenticular touch [24]. Ultrasonographical studies [25] have shown that events leading to increased friction and contact between AC structures that favor reverse pupillary block include physiological events such as accommodation, blinking, eye movements, head positions, and exercise. The increased contact between the iris and lens structures in eyes at risk of having a deep AC and/or a large iris can create a ball-valve mechanism in certain conditions in which the AH moves from the posterior chamber (PC) to the AC in a unidirectional mode, thus creating a high pressure in the AC that favors further apposition between the iris and lens surface [26]. The AH trapped in the AC can cause posterior bowing and further friction between the peripheral posterior iris and zonules and lens structures leading to pigment dispersion showers.

In 2016, a large meta-analysis was performed in a Cochrane review based on 5 randomized controlled trials regarding the common features and effects of treatment for PG [27]. The study reported the common features found in PDS, which include structural disturbance in the ipe, dispersion of melanin granules (on the lens, iris, cornea, and TM), and friction between anatomic structures in the AC. The deposited pigment granules can lead to damage to the TM that can cause a buildup of AH, leading to high IOP with glaucomatous optic neuropathy. Topical therapy tends to be the first-line treatment, similar to other forms of glaucoma. The Cochrane review showed that there was inadequate evidence to use peripheral iridotomy to treat PG, and further studies are needed to evaluate the clinical use of this laser treatment in PDS and PG patients.

PDS tends to be asymptomatic and is usually detected during a routine or urgent ophthalmic examination for other reasons. Headaches, halos around illuminated sources, and episodes of blurring have been reported in some patients, especially after exercise, prolonged reading, or certain head movements due to OHT spikes favored by PDS [28,29]. The clinical presentation of PDS includes pigment showers in the AC, Krukenberg spindle, iris trans-illumination defects, and increased pigmentation in TM [1-3]. Patients with PDS tend to have myopia and a relatively deep AC, which favor the backward bowing of the iris towards the zonules and reverse pupillary block mechanisms [24,25]. PDS can give rise to OHT, which can become PG in the presence with glaucomatous visual field defects, optic neuropathy, and/or RNFL thinning.

Pigment showers in the AC arise from melanin pigments released due to the chronic mechanical friction between the IPE and zonule structures in predisposed eyes. Krukenberg spindles are vertical-shaped deposits on the corneal endothelium, which may or not be present in PDS [1]. Histological studies have shown that the melanin granules appear within the corneal endothelium cells, thus suggesting pigment phagocytosis and not simply pigment depositing on the cornea [30,31]. Patients with PDS have been shown to have relatively normal endothelium cell counts and function, with possible pleomorphism and polymegathism [32].

Various case reports have also reported a less common feature that is sometimes overlooked in PDS and PG eyes. Central

profound pigment deposits near the equator can also be found on the posterior lens capsule, probably due to a communication between posterior chamber and the posterior lens capsule and anatomic anomalies in Wiegers ligament [33-38].

Studies have shown that the AC of patients with PDS tended to be deeper when compared to patient age-and refraction-corrected individuals with POAG [39]. The greater AC space in these patients can favor the backward movement of the iris and touching of the IPE with the lens structure. The release of pigment from the IPE causes iris trans-illumination defects with a spoke-like pattern, which can be visible when light is projected perpendicularly through the pupil. These are present in more than 85% of individuals with PDS that are more evident in eyes with light-colored irises [13]. The iris often shows pigment that can deposit within the iris furrows on the anterior portion [19]. The chronic rubbing and friction of the IPE with the zonule structures can lead to pigment loss of the iris, anisocoria, hyperplastic dilator muscles, heterochromia, and mydriasis [1].

The backward bowing of the iris in individuals with PDS was first described as a possible etiology by Campbell in 1979 [40]. These eyes tend to have a large iris, which can bend backward in the mid-peripheral portion in the presence of a deep AC and favor irido-lenticular rubbing and friction. Reverse pupillary block can occur, causing a ball-valve mechanism in which AH travels in a unidirectional manner from PC to the AC, giving rise to OHT and greater pressure in the AC that favors the movement of the iris backward and increase contact between IPE and zonule lenticular structures [24,26]. Physiological activities, such as exercise, accommodation, blinking, and head movements can trigger episodes of a reverse pupillary block [26], which can explain the episodic symptoms of headache and blur in some patients with PDS.

Gonioscopy normally shows increased pigmentation of the TM in individuals with PDS [20]. The dark pigmentation in TM tends to be homogenous, whole circumference, and prominent inferiorly probably due to gravity, as opposed to patchy-patterned as seen in patients with pseudoexfoliation syndrome (PEX), which can help in the differential diagnosis [41,42]. Similar to the corneal endothelium, histological studies have shown the presence of phagocytosed pigment granules in endothelial cells of the TM [43]. It is thought that chronic overload of phagocytosed pigment in the TN can give rise to apoptosis, cell necrosis, and anatomic structural alterations of this structure, which can lead to a decreased outflow of AH, OHT, and PG [44].

It is important to remember that the diagnosis PDS is clinical and may be challenging due to a wide variety of clinical features. PDS may present with any of the following signs, which include Krukenberg spindle (pigment deposition on the endothelium), pigment granules on the iris, concave configuration of the peripheral iris, spoke-like transillumination defects of the iris, pigment deposition on the anterior lens capsule, pigment deposition on the posterior lens capsule (Scheie stripe or Zentmeyr line, recent observations also include deposition on the more central part of the posterior lens capsule), and pigmentation of TM using gonioscopy (line similar to Sampaolesi's line).

3. Differential diagnosis

PEX can give rise to trans-illumination defects of the iris, and deposits in the AC, however, the iris defects in PEX tend to be located along the pupillary margin as opposed to the mid periphery of the iris, and TM pigmentation appear to be patchy, with deposits in the AC that are dandruff-like flakes rather than dark pigment material [36]. Both PEX and PDS are important risk factors for OHT due to decreased outflow of AH in TM, which can lead to pseudoexfoliation glaucoma and PG in the presence with visual field damage and glaucomatous optic neuropathy and RNFL thinning.

Trauma, ocular surgery, uveitis, and infection can all give rise to deposits in the AH, iris defects, and elevated IOP [45]. Debris and inflammatory cells secondary to certain ophthalmic conditions can appear as pigment showers. Uveitis-Glaucoma-Hyphema syndrome, or Ellingson syndrome, which is a rare complication after intraocular lens implants that can cause iris transillumination defects, pigmentary dispersion, elevated IOP, and hyphema must be considered in the differential diagnosis after cataract surgery [46]. Although seldom seen, certain intraocular tumors, such as uveal melanomas, can give rise to pigment deposits, iris trans-illumination defects, and OHT [47]. Other conditions such as Horner syndrome, Posner Schlossman syndrome, cataract surgery, rhegmatogenous retinal detachment, diabetes, and long-term use of mydriasis medication can show clinical signs of non-transparent AH, deposits, iris defects, and IOP spikes. A thorough ophthalmological examination, and accurate and detailed history, coupled with instrumental testing if needed, can help in the differential diagnosis to determine the proper individualized management and treatment. Instrumental testing that can assist in diagnosis and management include visual field testing, optical coherence tomography, and ultrasound biomicroscopy.

4. Management and treatment

PDS is a risk factor for PG, in which OHT can arise due to the reduced and less efficient outflow mechanisms of the AH by the dispersion of pigment that causes irreversible functional and structural damage. The only treatment available for glaucoma is geared at reducing IOP, be it using local drop therapy, laser, and/or surgery. If PDS does not show elevated levels of IOP, therapy may not necessarily be required, however, periodical ophthalmologic examinations with instrumental testing, if needed, is important. In pigmented races, such as Asians, Africans, and people of color, pigment dispersion is highly dangerous for visual function due to high volume of pigment in the IPE layer of the iris. Reverse pupillary block and pigment dispersion warrant more active and aggressive interference in the pigmented races. The time period between follow-ups needs to be determined on a case-by-case basis, in which age, disease severity, other risk factors, coexisting ophthalmologic conditions, etc., need to be considered.

Several studies have proposed staging the condition in determining how aggressive management and therapy need to be [2]. Richter *et al*. described four stages [48] based on the IOP and pigment dispersion activity in PDS, which include: (1) stable

IOP in the presence of inactive pigment dispersion; (2) stable IOP in the presence of active pigment dispersion; (3) PG and OHT in the presence of active pigment dispersion; and, (4) PG and OHT or normal IOP in the presence of inactive pigment dispersion. Three clinical stages have been recently proposed [3,49] to assist in dealing with PDS, which include: (1) Asymptomatic pigment dispersion induced by physiological factors such as exercise, accommodation, and stress that does not give rise to OHT; (2) PG with evident pigment in TM, high IOP, and (3) glaucomatous functional and morphologic damage; and pigment clearing from TM with normalizing IOP levels that tend to occur with aging. Gandolfi *et al.* [50] suggest that provocative testing using phenylephrine based on the number of pigmented particles released in individuals with PDS can assist in identifying those high-risk patients in developing elevated IOP over time and could probably benefit in preventative laser peripheral iridotomy (LPI), mainly by inducing iris flattening to reduce concavity, posterior iris bowing, and reverse pupillary block. It is important to note that although these methods of staging have been proposed in studies, clinicians may not necessarily advocate and use them in a routine clinical setting when managing patients.

PDS usually does not express itself until adulthood, and does not convert to PG. PDS is a risk factor; however, several longitudinal studies suggest that most PDS eyes never develop PG [14]. The difference could partially be due to the ability of the TM to tolerate or remove pigment particles and control AH outflow mechanisms. Other studies, however, have reported conversion rates that vary, which can be as high as 50% in some cases. Siddiqui *et al.* reported that that 10% of PDS eyes developed PG after 5 years, and 15% developed PG after 15 years [13].

The age of the individual is an important factor when managing PDS. Some authors theorize that some patients may develop a burn-out phase later in life in which signs of PDS or PG are less evident. Some also call it pigment reversal sign. In these patients, IOP can stabilize and less pigment can be seen in the TM, normally with the inferior TM clearing first [1]. A reduction in IOP-lowering medication can sometimes be seen in PG patients with normal IOP levels in this phase of burnout. Some authors have stated that the presence of less pigment in the TM and normal IOP can lead to the misdiagnosis of PG patients as having POAG or normal-tension glaucoma [3].

With regard the influence of race, is important to note that Krukenberg spindle, spoke-like iris transillumination defects, and homogeneous TM pigmentation is typical and classic findings in Caucasians. However, in the pigmented races, iris transillumination defects are usually absent. Nevertheless, PDS in pigmented races like Asian and people of color is highly sight threatening because the volume of pigment granules in IPE layer is huge and may cause very serious TM pigmentation and rapid AH outflow blockage, resulting in constant high IOP and glaucomatous neuropathy and blindness. In clinical practice, the burnout phase is scarcely seen in pigmented PDS patients.

With regards to diagnosis, PDS tends to be first seen during a routine eye examination. The patients are usually asymptomatic and seek the clinician for an eye examination or prescription glasses. The clinical signs regarding pigment deposits in in the AC structures and cornea are evident with examination at the slit-lamp, in addition to the spoke-like iris transillumination defects. A new simple method to detect iris spoke-like patterns using an automatic refractometer has been recently been proposed, which is simple and can be useful in a routine clinical setting [51]. Pigment accumulation can be seen with gonioscopy. PDS conversion to PG is diagnosed and managed with the same methods and instruments used in managing glaucoma, which include tonometry, visual field examination, and optical coherence tomography.

The treatment and management of glaucoma are based on lowering IOP to target levels in ranges that prevent or slow down irreversible glaucomatous morphological and visual field damage. Therapy can consist of IOP-lowering drops, laser, and surgery. PDS is an important risk factor in developing PG. As with all types of glaucoma, IOP elevation in PDS/PG is addressed in the same manner.

Local therapy to treat elevated IOP and glaucoma includes beta-blockers, alpha-agonists, prostaglandins, miotics, and topical carbonic anhydrase inhibitors. Miotics tend to be poorly tolerated. Beta-blockers and prostaglandins have shown effective results in lowering IOP in patients with PDS/PG [2].

Laser therapy can be applied to the iris and/or the TM. Argon and selective laser trabeculoplasty, respectively, known as ALT and SLT, can be used to enhance outflow at the TM. ALT has been reported to be effective in younger patients with PG [52]; however, success rates tend to diminish over time probably due to pigment release, overtreatment, high energy absorption of the TM, and permanent tissue scarring. SLT, which shows a greater, effective, and selective absorption of energy in tissues with pigment is theoretically an interesting option in these patients, especially considering that SLT can be repeated over time. Studies regarding SLT in PG, however, showed success rates at 1 year of 85% dropped to 14% after 4 years, with a failure rate occurring at about 27 months [53]. Moreover, SLT has been shown to give IOP spikes after treatment, especially in individuals with heavily pigmented TM, thus should be used with caution in PG patients with previous treatments with ALT, heavily pigmented TM, and those using multiple glaucoma IOP-lowering medications [54].

LPI has been proposed in several studies to address the morphological and anatomical predisposition of PDS eyes at risk of OHT [20,40], mainly by inducing iris flattening to reduce concavity, posterior iris bowing, and reverse pupillary block, thus creating a proper equilibrium of AH flow from the PC to AC. Numerous long-term systematic studies and reviews [27,55-57], however, have shown that LPI had little benefit and scarce clinical differences in risk of IOP rises when compared to eyes that did not undergo treatment and that LPI could be considered in very select cases in young individuals that show irido-zonular contact with UBM with normal IOP.

Surgery can be considered when target pressures are not reached with maximal IOP-lowering drop therapy and/or laser, or in patients that do not tolerate drops. Surgery is usually considered as a second or third option, considering the invasiveness and risks related to surgery. As with other forms of glaucoma, traditional

trabeculectomy is effective in lowering IOP; however, risks related to surgery remain to be important. Alternative surgical methods [58-62] such as canaloplasty, goniotomy, Ab interno trabeculectomy, trabectome, minimally invasive glaucoma surgery techniques, and modern implants show fewer surgical risks, however, offer limited success rates in achieving IOP target levels. When surgery is needed, patients must be assessed on a case-to-case basis to determine the best individual option.

5. Conclusions

PDS is a relatively common entity with a wide variety of clinical features. Early diagnosis, patient education, and treatment of patients at risk are of great socioeconomical and individual importance. It is usually identified on routine ophthalmologic visits. Patients are usually asymptomatic. Therefore, preventive ophthalmic visits are of utmost importance. Individuals that show OHT and PG need prompt treatment to avoid irreversible glaucomatous morphological and functional damage and progression over time. Patient education, correct diagnosis, and proper clinical management can limit the need for aggressive treatments and prevent sight-threatening conditions such as end-stage glaucoma.

Conflict of Interest

The author declares no conflict of interest.

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