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Review article

Pigment dispersion syndrome and its implications for glaucoma

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ABSTRACT

Pigment dispersion syndrome (PDS) represents a clinical spectrum of a relatively common and usually underdiagnosed phenomenon produced by spontaneous pigment dispersion from the iris into the anterior segment. PDS is often bilateral, has no gender predisposition, and presents at a young age, particularly in myopes. Although most patients experiencing an episode of pigment dispersion are asymptomatic, extreme photophobia, ocular pain, redness, and blurred vision may occur. Other characteristic signs are iridolenticular contact, concave iris configuration, 360° peripheral iris transillumination, and pigment deposition on the anterior chamber angle or the corneal endothelium (Krukenberg spindle). Early PDS diagnosis is crucial to detect patients with pigment-related ocular hypertension (POHT) that can eventually lead to pigmentary glaucoma (PG). The latter represents a sight-threatening condition in which mechanical, environmental, and genetic factors contribute to optic nerve damage. In this review, we update the pathogenic mechanisms involved in the clinical spectrum of the disease. We describe its clinical presentation, ophthalmologic manifestations, and complications, including the factors influencing the development of POHT and PG. Because PDS has variable clinical presentations that lead to misdiagnoses, we emphasize the differential diagnosis and the actual therapeutic strategies according to disease status.

1. Introduction

Pigment dispersion syndrome (PDS) is a distinct clinical entity characterized by intraocular pigment dispersion from the iris epithelium with deposition throughout the anterior segment. PDS can cause pigment-related ocular hypertension (POHT) or pigmentary glaucoma (PG).[58] Therefore, early detection and understanding of the pathogenesis are of relevance for establishing adequate therapy to prevent vision loss. Misdiagnosis of pigment dispersion with other anterior segment entities that present with similar clinical manifestations frequently occurs. The diagnosis of PDS is primarily clinical,

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and most patients respond well to medical or laser therapy, although surgery is necessary in some cases.[30] The prognosis of PDS depends on the potential development of POHT or PG. The dispersion of iris pigment is classified as PDS with normal intraocular pressure (IOP), PDS with POHT, or PG.[78]

2. Historical background

Friedrich E. Krukenberg first identified a vertical pigment deposition on the corneal endothelium in 1899. At that time, this finding was not related to pigment dispersion but instead was considered a congenital anomaly.[42] Two years later, Von Hippel[32] proposed that pigment deposition in the trabecular meshwork was an etiologic factor of glaucoma; however, it was not until the 1940s that Sugar described PG.[85] Evans and coworkers further described the Krukenberg spindle in 202 cases.[19] Sugar and Barbour first made an association of PG with the pigment dispersion in the AC,[84] whereas Sugar and coworkers fully documented the clinical features of PG in their clinical observations over 25 years.[86] Despite investigations aiming to determine the incidence of PDS and PG, the results remain inconclusive. This probably relates to disease underdiagnosis.[72] A study of 799 eyes (407 patients) with PDS by Scheie and Cameron classified PDS with normal IOP and high IOP, with and without glaucomatous damage.[72] In this study, patients with normal IOP prevailed. Also, male patients predominated over females (ratio = 3:2) in the PG subset.[72] Amongst the most common clinical features in this large series were heavy trabecular meshwork pigmentation (85.1%), mild myopic refractive error (62%), and transillumination defects (57.9%).[72] Approximately two-thirds of PG eyes showed an adequate response to medical therapy. On the other hand, nonresponders required one or various filtering procedures.[72] Speakman found a reduction in pigment dispersion after a 10-year follow-up in most patients.[81] Nonetheless, some patients continued to show increase dispersion of pigment. PDS and POHT may be self-limited in some cases, leading to therapy discontinuation.[81]

3. Epidemiology

There is inconclusive information regarding the epidemiology of PDS. A possible explanation is the variety of clinical manifestations and its asymptomatic nature, leading to a misdiagnosis or underdiagnosis, respectively. Nonetheless, PDS affects 2–4% of patients during the second to fourth decades of life.[58,75] A study of African descendants showed a PDS prevalence of 15 cases per 10,000 inhabitants.[69] A study on patients seeking refractive surgery found a PDS prevalence of 25.9% (165/637 eyes); however, these data may be biased due to the high prevalence of myopic patients involved in this study.[16] Myopia represents a risk factor for PDS development. Moreover, myopia has a positive correlation with PDS severity; the more myopic the eye is, the more likely it will be affected.[21,27] In a large white population with glaucoma, PDS accounted for only 2.45% of the cases.[68] Furthermore, in another PDS series 20% of the patients had POHT, while 25.60% had PG.[81] Studies report a risk of 35% to 50% for developing PG in patients with PDS.[58] Mastropasqua and coworkers, in a retrospective longitudinal study, found that 20% of eyes with an initial diagnosis of PDS developed PG.[51] In 85.8% of these patients, the conversion to PG occurred within the first ten years from PDS diagnosis. Moreover, three studies that examined patients longitudinally suggest that up to 50% will eventually develop PG.[21,53,64] Contrary to the common belief, the PDS ratio is equal in males and females; however, in POHT and PG, there is a marked male predominance.[65,72] Caucasian men between 40 and 50 years seem to be more prone to develop PG than Asians and African-Americans.[58,59] Nevertheless, the incidence could be underestimated in subjects with darker and thicker irides, which can mask the diagnosis.[49] A study of Latin American patients followed for at least four years showed a PG rate of 37.5%.[24]

4. Clinical features

4.1. *Pigment dispersion syndrome (PDS)*

PDS can be a fortuitous finding during a routine ophthalmologic examination, particularly in myopic patients. Symptoms are absent or can vary from patient to patient, encompassing a clinical spectrum ranging from a red eye and mild discomfort to severe ocular pain, photophobia, blurred and halo vision. In young patients, these symptoms usually occur during or after exercise.[81] A thorough clinical history, review of systems, and careful slit-lamp examination are essential for achieving an accurate diagnosis. Intraocular pressure (IOP) measurement, gonioscopy, and fundus examination are also mandatory. The most relevant slit-lamp finding is a faint to marked Krukenberg spindle that is more prominent in the inferior corneal endothelium as a result of the aqueous humor currents within the AC (Fig. 1A). Blinking and hormonal variations influence Krukenberg spindle development.[24,86] Of note, the Krukenberg spindle is not always present in PDS and is not pathognomonic of the entity.[58] A slightly concave midperipheral iris, along with a spoke-like 360° degree transillumination defects, are also common (Fig. 1B). A careful search for transillumination defects is required to avoid missing them. Pigment deposition on the anterior surface of the iris is also a feature, especially within iris furrows.[20,86] Pigment deposition can also occur on the anterior lens capsule (Fig. 1C). Scheie and Fleischhauer reported that pigment deposition might occur on the lens zonules and posterior capsule, the so-called "Scheie stripe."[73] Occasionally, the Scheie line presents as the first sign of PDS.[71]

Although PDS is mostly a bilateral condition, asymmetry occurs, giving a heterochromatic appearance. The more affected eye usually has a darker iris from iris pigment deposition.[58,86] Patients with PDS usually have a deep anterior chamber (AC), suggesting a role of AC depth in pathogenesis.[36,58] Free pigment in the AC is often seen in patients with active dispersion, although it is not always present. Importantly, the ophthalmologist must differentiate pigment from inflammatory cells, as this can confuse the examiner and lead to misdiagnosing PDS as acute anterior uveitis in a patient with prominent symptoms.[25] Inflammatory cells are generally round, bigger, and whiter, while the pigment is small, tanned-

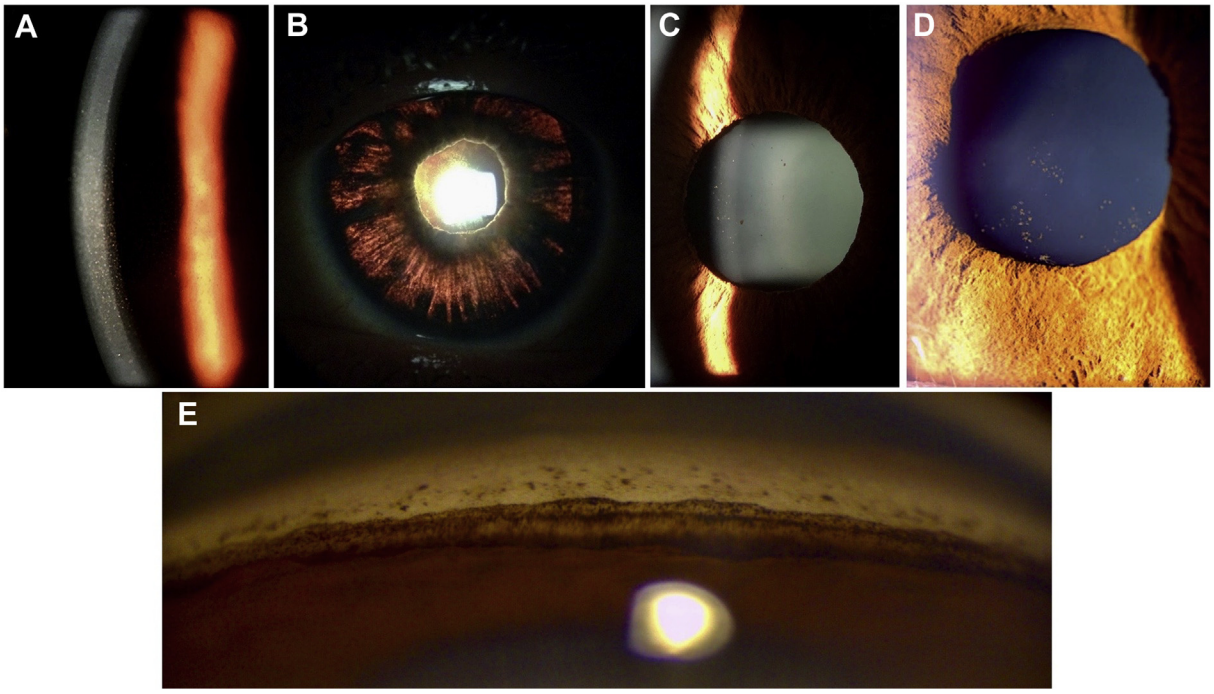


Fig. 1 – Composite image of the most prominent clinical findings in patients with pigment dispersion syndrome. *A:* Marked pigment deposition along the inferior endothelial surface, also known as Krukenberg spindle. *B:* Spokelike 360° degree iris transillumination defects seen by retro illumination technique. *C:* Pigment deposition on the anterior capsule of the lens. *D:* Loss of continuity and irregular pupil contour associated with pigment on the anterior capsule of the lens. *E:* Indirect gonioscopy image of an open angle showing heavy homogenous pigmentation of the trabecular meshwork.

brown particles with sharper edges. The assessment of inflammatory cells or pigment in the AC is performed before pupil dilation, as some eyes disperse pigment with pharmacologic mydriasis. Long standing PDS might cause irregularities in the pupil contour (Fig. 1D). In asymmetric cases where pupil irregularities and transillumination defects are present, excluding herpetic uveitis is mandatory. Gonioscopy and fundus examination are essential in the assessment of PDS patients. The angle is usually open, and characteristic pigment deposition is often seen in the inferior trabecular meshwork. Trabecular meshwork pigmentation in PDS is more homogenous than in pseudoexfoliation syndrome (Fig. 1E).[61] In some cases, pigmentation of the Schwalbe line occurs, giving the appearance of a Sampaolesi line.[58] Sampaolesi line is a brown pigment at or anterior to Schwalbe line observed in PDS or pseudoexfoliation syndrome. Other important gonioscopic findings in PDS are backward-bowing of the iris and higher than expected number of iris processes, although these are not consistently present.[58]

The disc color, appearance, and cupping of the optic nerve require careful assessment in PDS eyes. Optical coherence tomography (OCT) analysis of the retinal nerve fiber layer and ganglion cell complex is also important, the latter in order to identify the presence of glaucomatous damage.[8] Eyes with PDS have a higher risk of retinal detachment, regardless of the severity of myopia.[72] Retinal detachment occurs most often in mildly myopic, phakic males.[72] Lattice degeneration is also more prevalent in PDS patients than in the general population; therefore, it is essential to search for any peripheral retinal alterations by performing indirect ophthalmoscopy with scleral depression and/or a three-mirror lens.[95]

4.2. *Pigmentary ocular hypertension (POHT)*

POHT in the setting of PDS tends to be more prevalent in males.[72] POHT has the same clinical findings of PDS. The higher prevalence of PDS in young adults makes this group more prone to have POHT. Monitoring the IOP must be rigorous since each 1 mmHg rise above 21 mmHg increases the risk for developing PG by 1.4 times.[78] During acute episodes of pigment dispersion, the IOP can vary up to 8.08 mmHg compared to the same patients' basal IOP.[29] Symptoms include ocular pain, injection, photophobia, and halo vision. Patients may experience symptomatology during or after exercise. Gonioscopy and fundus examination are essential for the diagnosis of POHT. The clinical appearance of the optic nerve, OCT of the retinal nerve fiber layer thickness, and ganglion cell segmentation should be assessed, along with visual field testing. If there is structural optic nerve damage or visual field changes, the patient has PG. Frequent optic nerve assessments are essential in patients with POHT.

4.3. *Pigmentary glaucoma (PG)*

Like POHT, PG is more prevalent in males. Up to 78–93% of PG patients are males.[58] A community-based retrospective study found a low risk for developing PG due to PDS with an estimated conversion rate of 10% at 5 years, increasing to 15% at

15 years. This study also demonstrated that the most important predictive factor for the conversion is an IOP >21 mmHg at the initial diagnosis.[78] Similarly, a longitudinal study of patients with PDS who developed PG had significantly higher IOP levels (24.6 ± 4.0 mmHg) during the acute episode of pigment dispersion compared to those who did not develop glaucoma (22.5 ± 10.64 mmHg) at the end of follow-up. This study suggests that a significant IOP variation (mean, 8.5 mmHg) during and after dispersion events is also a potential risk factor for the development of PG.[29]

PG patients tend to have a more prominent Krukenberg spindle related to the pigment showers that occur while exercising. Some patients might have subacute attacks characterized by corneal edema and blurred vision.[23] Although the degree of trabecular meshwork pigmentation does not represent a risk factor for developing PG in patients with PDS,[53] in those with established PG, the amount of pigmentation is related to the disease severity.[58] Optic nerve cupping and visual field defects point to the diagnosis of PG. The visual field deterioration must correspond with the anatomical damage in the retinal nerve fiber layer and ganglion cell complex observed in glaucomatous neuropathy.[8] Visual field defects are also present and tend to progress unless adequate treatment controls the IOP. SITA-SWAP (blue on yellow) protocol visual field assessment is more sensitive in detecting visual field defects. PG is more challenging to control than primary open-angle glaucoma.[72] Similar to POHT recommendations, frequent follow-up and close IOP monitoring are necessary for PG patients. The evolution of PG over time usually leads to a phase of declining pigment liberation. Speakman described reduced pigment dispersion and ocular pressure normalization over 10 years.[81] This gonioscopic finding is known as the "pigment reversal sign." Inferior angle pigmentation tends to clear before the superior angle, leading to a darker trabecular meshwork superiorly.[58,65] Frequent gonioscopy and pressure monitoring are essential to identify patients with PG undergoing this phase. Hence, the pigment reversal sign can help to decide when to discontinue antiglaucomatous therapy. Mastropasqua and coworkers described different risk factors that predispose the conversion from PDS to PG, establishing different grades of PDS (Table 1).[51] Although PDS tends to affect men and women in almost equal numbers, as previously noted, PG development is far more common in men.[58] The prevalence of myopia in patients with PDS ranges from 38% to 100%. Moreover, the higher the degree of myopia, the greater the risk for developing PG.[58,59] The presence of POHT (IOP >21 mmHg) at the moment of PDS diagnosis is the most important risk factor for conversion to PG.[78] Table 2 shows the main risk factors that predispose the conversion from PDS to PG.

Table 1 – Grading of pigment dispersion syndrome*

Grade	Clinical findings
0	Iris touch with the zonule and/or Krukenberg spindle, and angle pigmentation
1	Iris touch with the zonule, Krukenberg spindle, and/or pigment granules on the iris, and/or lens anterior capsule pigment deposits, and angle pigmentation
2	Iris touch with the zonule, endothelial pigment deposits, and/or pigment granules on the iris, and/or lens anterior capsule pigment deposits, and grade-1 angle pigmentation, and IOP ≤21 mmHg, and normal visual field
3	All previous findings and visual field defects consistent with the diagnosis of PG.

IPP, intraocular pressure; PG, pigmentary glaucoma.
* Adapted from Mastropasqua L, et al. *Ann Ophthalmol Glaucoma* 1996; 28: 301–307.

Table 2 – Main risk factors for conversion from pigment dispersion syndrome to pigmentary glaucoma

Risk factor	Percentage of risk (%)
Family history of glaucoma in[56]:	
■ PDS	4–21
■ PG	26–48
Gender of patients with PG[51,76]:	
■ Males	78–93
■ Females	7–22
Presence of myopia in patients with[27]:	
■ PDS without POHT	6.1
■ PDS with POHT	21.1
■ PG	72.9
Presence of Krukenberg spindle in PDS[76]	94.7
Race of patients with PG[21]:	
■ White	96.0
■ Black	4
Risk of conversion since PDS diagnosis[76]:	
■ 5 years	10
■ 15 years	15
Initial IOP[76]:	
■ ≥21 mmHg	46
■ <21 mmHg	2

PDS, pigment dispersion syndrome; PG, pigmentary glaucoma; POHT, pigmentary ocular hypertension.

5. Diagnosis

The diagnosis of PDS is mostly clinical and often challenging because most patients experience asymptomatic pigment dispersion episodes. The degree of pigment release and clinical findings may vary widely; therefore, PDS is often missed or misdiagnosed.[72] In the presence of diagnostic doubt, imaging analysis using ultrasound biomicroscopy (UBM) and anterior segment OCT (AS-OCT) can discern between PDS and other clinical entities. Different imaging features such as an increased anterior chamber volume,[7] increased iridolenticular contact area,[37] and increased iris posterior bowing during accommodation may aid in the diagnosis of challenging cases (Table 3).[1]

5.1. *Ultrasound biomicroscopy (UBM)*

Image diagnostic tools help identify the structural configurations and characteristics that predispose to iridozonular and iridolenticular contact. The UBM allows detailed *in vivo* visualization of the anterior segment structures. In PDS patients, UBM evaluates the relationship of the peripheral iris and the zonular structures during light and accommodative pupillary reflexes and after exercise and scleral indentation.[34,55] A 50 Hz

transducer probe is required to acquire a useful image of the iridocorneal structures. A radial cut should be obtained in at least one meridian (usually the temporal limbus). In PDS eyes, it is possible to observe a posterior iris insertion to the sclera, a concave iris profile paralleled by a deeper anterior chamber, and a flaccid stroma.[55] Table 4 shows the different measurements required for a complete analysis of PDS eyes. The insertion of the iris into the ciliary body is more posterior in PDS eyes than is usual. A significantly greater scleral spur to iris root distance and a greater Schwalbe line to iris root distance, particularly in the temporal quadrant, corroborate this finding. The same anatomic change is also present in a group of patients with asymmetric PDS, where the insertion of the iris is more posterior in the most affected eye.[37]

Iris concavity can be measured in the posterior iris surface using an angle caliper or by measuring the distance of the iris to a traced line from the most peripheral to the most central point of the pigment epithelium at the site of highest iris concavity or convexity (Fig. 2).[46,60]

Mora and coworkers used the receiver operating characteristic (ROC) analysis to obtain the most sensitive iridocorneal parameters to differentiate between eyes with PDS/PG and healthy controls, with and without accommodative stimuli. The iridocorneal angle in near vision was the most discriminatory parameter, with a cutoff point of 53° yielding an 87.5% sensitivity and specificity. Iris concavity in near vision was also a highly sensitive parameter (sensitivity of 79.2%) with a cutoff of 166.6°. This evidence confirms the importance of the iris movement behavior in PDS.[55] Carassa and coworkers reported that about 50% (12/23) of eyes with PDS do not have iris deflection at baseline.[14] After repeating the UBM during accommodation, only three eyes experienced iris deflection <0. Blinking also influenced the iris configuration. A UBM analysis demonstrated that, after a mean time of 4.4 minutes without blinking, the iris configuration changed from a concave to a most convex position in PDS eyes.[46] Also, without blinking, iridozonular contact disappeared in all the patients who present it.[46] Regarding the effect of exercise on a scleral indentation in PDS eyes, Jensen and coworkers described an increased iris concavity after 10 minutes of bicycle exercise in two patients with PG and the opposite after scleral indentation.[34] Imaging studies are also useful for monitoring treatment response. Rectification of the iris plane after Neodymium-YAG laser peripheral iridotomy and significant iridozonular separation distance after the use of 2% pilocarpine drops are two different UBM findings in PDS eyes.[60]

Table 3 – Anterior segment ocular coherence tomography and ultrabiomicroscopy findings in pigment dispersion syndrome, pigmentary ocular hypertension, and pigmentary glaucoma

UBM Findings	AS-OCT Findings
■ Concave iris configuration	■ Increased AC volume
■ Increased iridolenticular contact area	■ Increased iridolenticular contact area
■ Increased distance from SS to iris insertion	■ Small iris volume-to-length ratio
■ Increased lens thickness	■ Increased AC depth
■ Increased iris posterior bowing during accommodation	■ Increased AOD
Specific measurements analyzed in PDS	■ Increased TISA at 500 μm and 750 μm from the SS
■ AC depth	
■ Iris-lens contact	
■ Iridozonular contact	
■ Iridocorneal angle	
■ Iris concavity or iris deflection*	
■ Iris insertion	
■ SS to iris root distance	
■ Schwalbe line-iris root distance	

AS-OCT, anterior-segment optical coherence tomography; UBM, ultrabiomicroscopy; PDS, pigment dispersion syndrome; AC, anterior chamber; AOD, angle opening distance; TISA, trabecular iris space area; SS, scleral spur.

* The iris concavity/deflection is obtained by measuring an angle in the posterior iris surface or measuring the distance of the posterior iris to a line from the most peripheral to the central point of the iris epithelium.

5.2. AS-OCT

AS-OCT also evaluates the anterior chamber depth, anterior chamber width, pupil diameter, iris volume, and concavity in PDS eyes.[15,48,77] A study using the Visante® OCT (Carl Zeiss, Dublin, CA) to compare similar refraction eyes with PDS and PG *versus* healthy controls showed that PDS eyes have a larger AC volume and iridolenticular contact area, as well as a higher iris volume-to-length ratio than healthy controls.[7] In the same study, multivariate analysis showed that a deeper AC with a larger volume had a significant prediction on the greater iridolenticular contact area. The angle opening distance (AOD) and the trabecular iris space area (TISA) at 500 μm and 750 μm from the scleral spur were also significantly greater in eyes with PDS and PG compared with controls using the slit-lamp (SL)-OCT (Heidelberg Engineering, Heidelberg, Germany).[12] On the other hand, there was no difference in anterior chamber measurements between eyes with PDS and PG.[12]

5.3. Posterior-segment OCT

PDS eyes with an elevated IOP, structural optic nerve assessment (retinal nerve fiber layer, cup-to-disc ratio, and ganglion cell complex analysis) with the spectral-domain or swept-source OCT is essential to further classify the entity as POHT or PG and to monitor disease progression or therapeutic control.

OCT has become a crucial tool for diagnosing and monitoring glaucoma. The parameters evaluated by OCT represent surrogate measures of glaucomatous structural changes reflected as retinal nerve fiber layer and macular thickness thinning. In particular, the loss of macular ganglion cells eventually results in visual field abnormalities, with reports of almost 40% ganglion cell loss before any detectable visual field defect appears.[76] One study found a lower inferior and superior ganglion cell complex and retinal nerve fiber layer thickness as expected when comparing PDS, PG, and healthy patients.[8] These findings emphasize the discriminative power of OCT measures for detecting glaucomatous damage in PDS individuals. Nevertheless, there are reports of slightly lower retinal nerve fiber layer thickness in PDS than in healthy

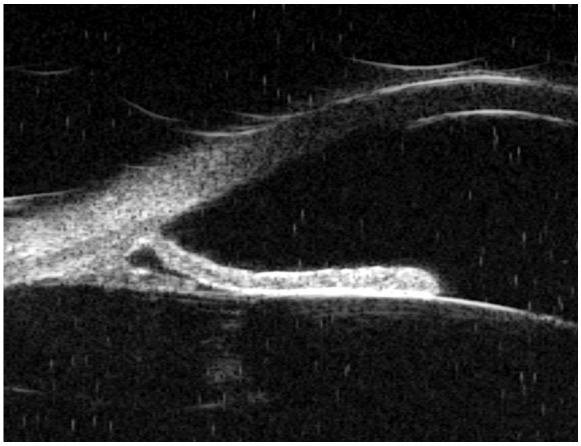


Fig. 2 – Ultrasound biomicroscopy of a nonaccommodating eye with an undilated pupil under photopic conditions with classic signs of PDS consisting of concave iris with posterior insertion, contact of the iris with the lens, zonula, and ciliary body.

individuals, possibly explained by intermittent IOP spikes during exercise-induced pigment release.[54] To our knowledge, there is only one study that compared the ganglion cell complex thickness among PG, PDS, and healthy eyes.[8]

The stage of glaucomatous damage influences the relevance of OCT parameters in glaucoma. In early preperimetric stages, the damage to the macular ganglion cell complex with discrete retinal nerve fiber layer thinning can occur in glaucoma suspects or POHT eyes. On the other hand, late in the disease, optic nerve OCT parameters are less useful in detecting progression when the nerve fiber layer thickness reaches a floor effect, about 40–50 mm, not decreasing any further. This OCT image analysis limitation is changing since emerging evidence shows that the macular ganglion cell complex's thickness may represent a parameter for early detection and late monitoring of advanced disease.

5.4. *Posterior-segment OCT angiography (OCTA)*

Recently, OCTA has emerged as a novel, noninvasive imaging technique that enables the study of retinal and optic disc blood flow. The first report of reduced capillary density and flow index at the superficial disc tissue and lamina cribosa in patients with glaucoma dates to 2014.[35] Nonetheless, the optic nerve is not an ideal image target because of artifacts related to its intricate anatomy. The ideal scans for glaucoma are the superficial plexus at the peripapillary retina and macula.[47] In both, the reduced vessel density provides adequate diagnostic accuracy for glaucoma. We found no studies with findings in PG.

The advantages of OCTA besides diagnosis and monitoring glaucoma progression are the correlation with visual field parameters, adding another parameter for detecting structural changes.[96]

Finally, it is crucial to recognize factors that undermine OCT accuracy and could influence a treatment strategy. The first factor is signal strength, which can be variously affected by cataracts, media opacities, corneal edema, blinking, eye movements, and dry eye. The lower signal often yields a diminished retinal nerve fiber layer than is seen with a higher quality exam. The scan centration and alignment are directly related to adequate patient fixation, which can be difficult in eyes with reduced visual acuity. Another factor is segmentation errors of the neuroretinal tissue that often result in misleading information.

5.5. *Automated visual fields*

Standard automated perimetry measures the functional assessment of glaucomatous damage. There are some differences in the pattern of visual field between PG and primary open-angle glaucoma. The temporal field appears to be more susceptible to damage in POAG in comparison with PG.[57] Therefore, the nasal optic disk damage is less likely to be related to PG itself. A possible explanation for PG visual field findings can be the younger age at presentation and the association with myopia that could influence perimetric results.

6. Differential diagnosis

Table 4 summarizes the most relevant features of the differential diagnosis of PDS. Any anterior segment condition that causes iris depigmentation, pigment dispersion, deposition, and morphologic changes can confuse the examiner with PDS. Intraocular inflammatory conditions like Fuchs uveitis, herpetic uveitis, Posner-Schlossman syndrome, and Vogt-Koyanagi-Harada disease can resemble PDS. Distinct clinical features of Fuchs uveitis are unilateral diffusely distributed stellate KPs, atrophy of the anterior pigment border layer, and iris' stromal atrophy, heterochromia, prominent iris and angle vessels, and cataract formation.[3] Herpetic uveitis is usually associated with an active dendritic corneal ulceration or subepithelial scarring from an old epithelial keratitis episode. The anterior uveitis is associated with medium to large-size KPs. Characteristic features include transillumination defects, sectoral iris atrophy, and lack of pigment in the inferior trabecular meshwork, posterior iris synechiae, and cataract formation.[91,94] Unilateral, recurrent, nongranulomatous anterior uveitis, endotheliitis, and IOP elevation that can result in chronic secondary glaucoma are features of Posner-Schlossman syndrome. Extensive bilateral, peripheral iris transillumination due to severe depigmentation can occur in young patients with chronic recurrent VKH disease.[87,9] On the other hand, PDS can masquerade as acute anterior uveitis as both disorders can share common symptoms, including ocular pain, photophobia, redness, and blurred vision.[25]

Other disorders that can produce iris depigmentation, atrophy, and transillumination defects are Horner syndrome, pseudoexfoliation syndrome, trauma, and acute angle-closure glaucoma.[67] More recently, a moxifloxacin-related pigment dispersion disorder, also known as acute bilateral iris transillumination (BAIT), presents as an abrupt onset of usually bilateral pigment dispersion, lack of iris concavity, and history of the systemic use of fluoroquinolones.[90] Another similar clinical entity called bilateral acute depigmentation of the iris (BADI) features an acute, bilateral, and symmetric

Table 4 – Differential diagnoses of pigment dispersion syndrome and its main clinical characteristics

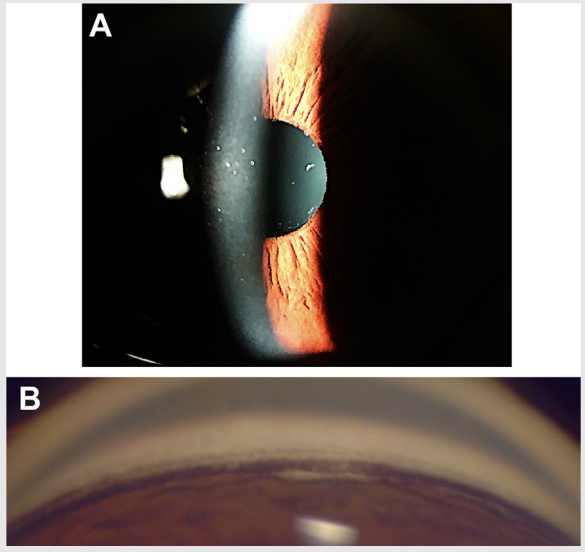
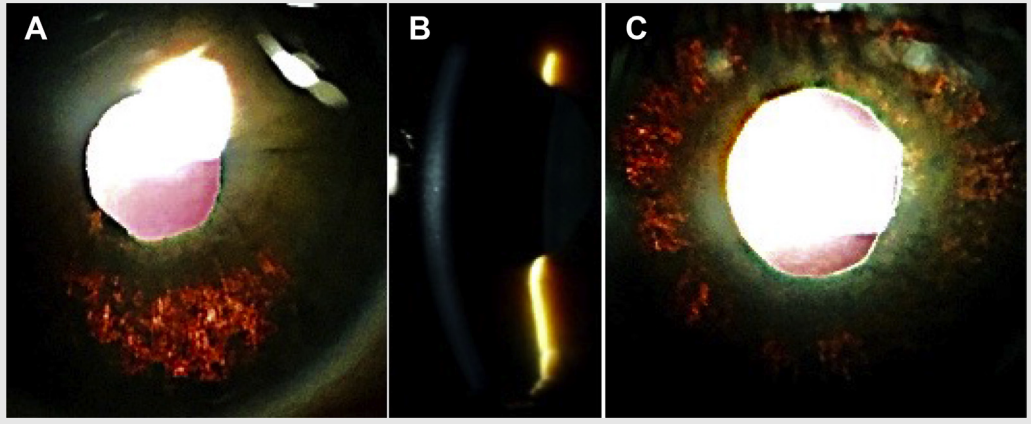
Disease	Distinguishing clinical features	Clinical appearance
Pseudoexfoliation Syndrome	Late age, insidious onset, chronic unilateral (76%) disease. Exfoliation material deposits on the iris sphincter, pupillary margin, anterior lens capsule, and corneal endothelium. Pigment loss at iris sphincter and Schwalbe's line pigment deposition (Sampaolesi line) are common. Cataract and secondary glaucoma are frequent complications. Figure A. Pseudoexfoliation flakes on the corneal endothelium resembling pigment and on the anterior lens capsule. **B.** Sampaolesi line.	
Bilateral Acute Iris Transillumination (BAIT)	Prior history of upper respiratory tract infection (75%) in a female (87%) and systemic moxifloxacin administration (81%). Ocular hypertension (100%), diffuse iris transillumination defects (100%), atonic pupil with sphincter paralysis (100%). Final distorted pupillary borders (60%). **Figures A–C.** Iris TIDs and irregular pupil contour OU. **B.** Pigment deposition on the corneal endothelium and concave iris OS in a patient treated with oral moxifloxacin for an upper respiratory infection.	

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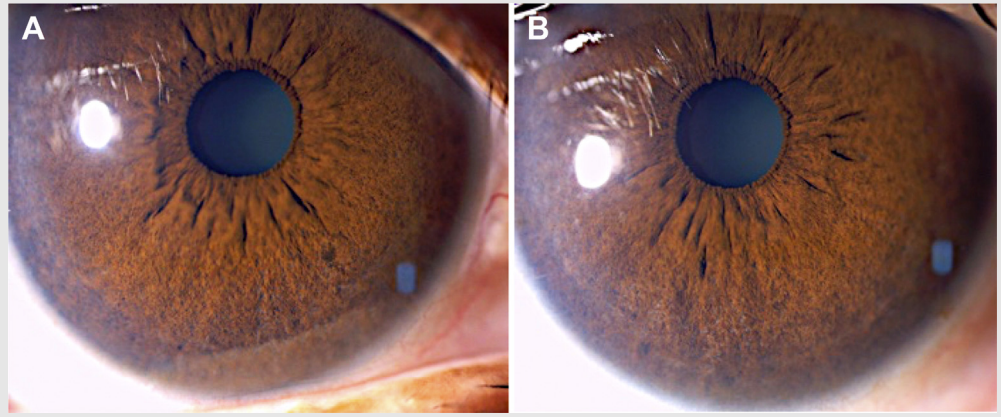
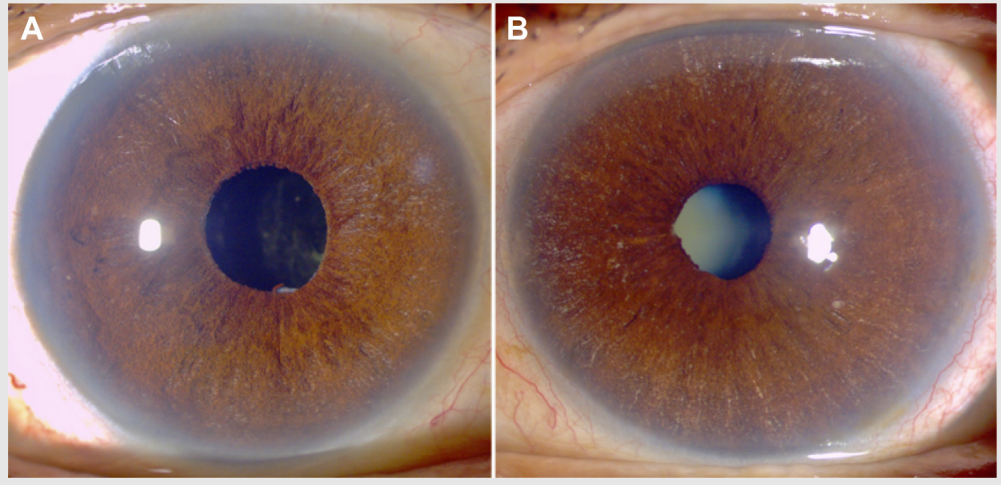
Table 4 – (*continued*)

Disease	Distinguishing clinical features	Clinical appearance
Bilateral Acute Depigmentation of the Iris (BADI)	Young patients (15–25 years) with sudden-onset bilateral ocular discomfort and red-eye. Symmetrical diffuse or patchy iris stromal depigmentation (100%), Krukenberg spindle, circulating pigment in the anterior chamber, and heavy pigment deposition in angle. No iris transillumination defects, inflammatory KPs and anterior chamber cells are seen. **Figures A–B.** 28 y/o Hispanic female patient with dark iris showing diffuse patchy iris depigmentation and heavy pigment deposition in the angle OU (BADI).	
Posner-Schlossman Syndrome	Self-limited recurrent episodes of markedly elevated IOP (40–60 mmHg) and mostly unilateral nongranulomatous iridocyclitis (94%) in young (20–50 years) patients. Fine KPs, open anterior chamber angles. CMV-positive (62%), female gender (56.6%), glaucoma development (26.4%). Figure A. 58 y/o Hispanic female with multiple attacks of P-S syndrome OD, showing iris depigmentation (slight heterochromia) and secondary glaucoma, after cataract surgery. **B.** Unaffected left eye.	

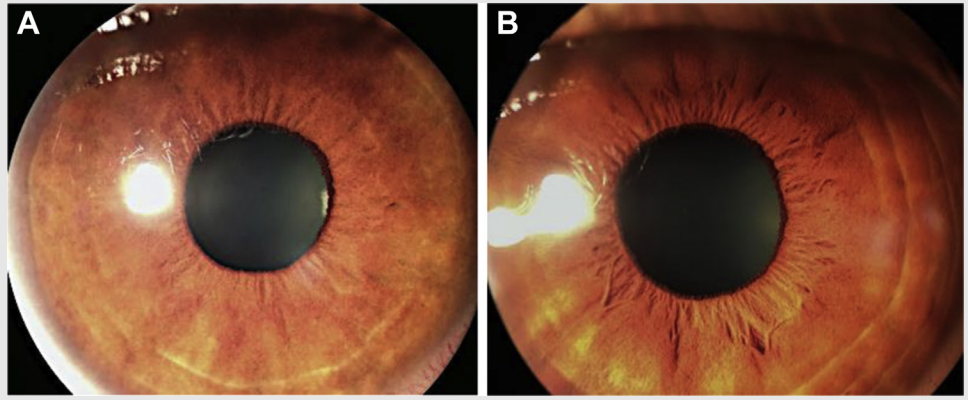
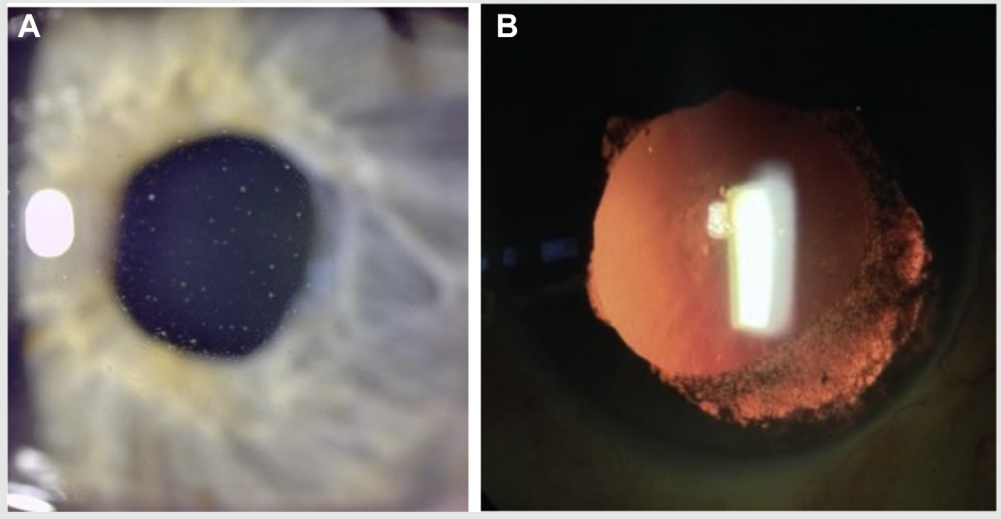
Fuchs' Uveitis	Unilateral (95.2%) chronic anterior uveitis, stellate small or medium-sized KPs (90.2%) of diffuse distribution, persistent inflammatory AC cells, iris heterochromia in light-colored iris, cataract formation (85.6%), decreased vision (79.9%), and glaucoma (26.4%) at presentation. **Figure A**. 36 y/o Hispanic male with brown iris and Fuchs uveitis OD, showing subtle heterochromia, but notably atrophy of the anterior border layer with smoothness of the iris rugosity and crypts attenuation. **B.** Healthy left eye.	
Herpetic Anterior Uveitis	Unilateral recurrent uveitis, granulomatous KPs (92.9%), corneal ulcer or scarring (57.0%), transient IOP elevation (50.8%) during recurrent attacks of inflammation. Sectorial iris atrophy with or without iris transillumination defects (48.2%), posterior synechiae (26.3%), pupil distortion (25.4%). Cataract and glaucoma are common complications. Figure A. Fine, tanned KPs, and sectorial iris stromal atrophy in a patient with recurrent attack of herpetic uveitis. **B.** Sectorial TID and pupillary atrophy in another herpes varicella uveitis patient.	

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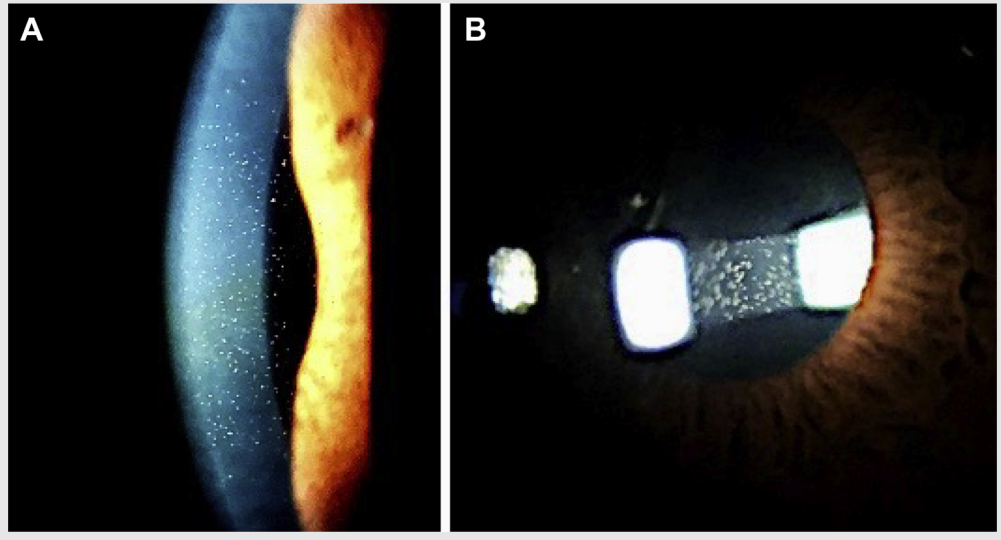
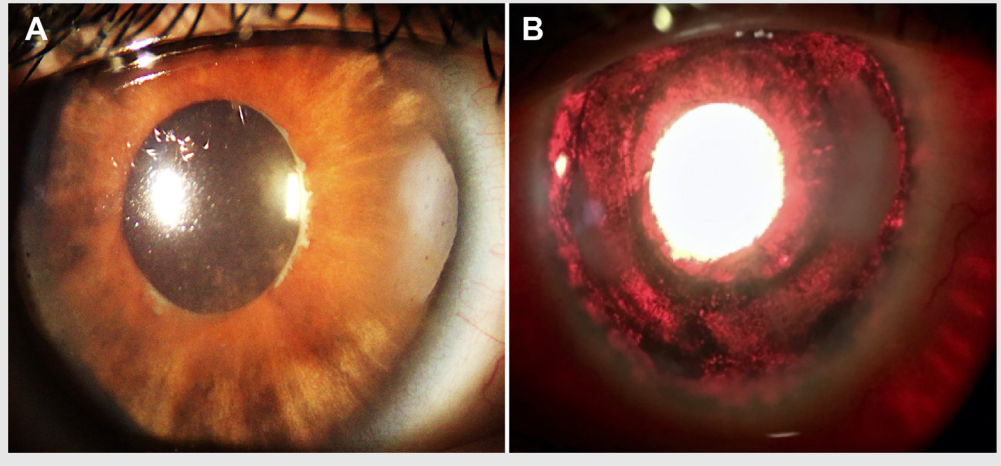
Table 4 – (*continued*)

Disease	Distinguishing clinical features	Clinical appearance
Acute Autoimmune Anterior Uveitis	Acute onset of red-eye, pain, photophobia, and blurred vision, similar symptoms of an episode of pigment dispersion. Usually unilateral, AC cells, absence of AC pigment, small-medium size KPs, frequent posterior iris synechiae, absence of iris TIDs, absence of trabecular meshwork pigmentation. Low or normal IOP. Figure A. Fine, diffuse KPs in a patient with idiopathic acute anterior uveitis. **B.** Anterior chamber cells and flare in HLA-B27 associated uveitis.	
Vogt-Koyanagi-Harada Disease	Prodrome of severe headache and neck rigidity (49%), tinnitus (36%), dysacusia (32%). Chronic, bilateral, granulomatous panuveitis with vitreous cells (38%), AC cells (36%), large KPs (22%), Koeppe (15.6%), and Busacca iris nodules (5.5%). Late vitiliginous fundus appearance (58%), nummular chorioretinal scars (46%). Late poliosis (28%) vitiligo (20%), and alopecia (18%). Figure A. Right eye of an 18 y/o female with VKH panuveitis showing band keratopathy, extensive iris stromal atrophy and inflammatory precipitates on the IOL. **B.** 360° iris TID of the same eye, showing the edge of the IOL optical zone and the haptics.	

KPs, keratic precipitates; IOP, intraocular pressure; OHT, ocular hypertension; CMV, cytomegalovirus; XFM, exfoliation material; VKH, Vogt-Koyanagi-Harada; AC, anterior chamber; TIDs, transillumination defects; TM, trabecular meshwork.

depigmentation of the iris stroma without pupillary effection or iris transillumination defects.[7]

Other rare disorders that can resemble PDS include ring melanoma of the iris and the anterior segment. UBM imaging analysis is crucial to distinguish ring melanoma of the anterior chamber from PG. Another lesion that confuses with PDS is the presence of bilateral iris epithelial cysts.[31,82] With UBM, iris pigment epithelial cysts show thin hyperreflective walls and appear acoustically hollow. On the other hand, the ciliary body and iris melanomas are acoustically denser.[31] Nevertheless, in patients with dense pigment but with absent clinical findings (Scheie line, Krukenberg spindle, among others), secondary causes of pigment liberation need to be ruled out, mainly to exclude uveal melanoma, a life-threatening disease.[31]

7. Pathogenesis

Fig. 3 depicts the complex and inconclusive pathogenic pathways involved in PDS. Recent studies regarding PDS's genetic characteristics agree that there is an intricate inheritance pattern in which sporadic cases are present. Several genetic loci can play a central role in the inheritance of this disease, such as 7q35-q366 and 18q11-q21.[5,6,93] To date, a single responsible gene is not known, and it is possible that many cases of PDS result from a combination of gene mutations contributing.[44] A study to determine the hereditary patterns on PDS patients' relatives found that most cases within the PDS clinical spectrum are sporadic, with only 10.1% of first-degree relatives diagnosed with PDS, a lower risk than previously described.[88]

On the other hand, congenital abnormalities of mesodermal migration and primary iris degeneration relate to PDS; this could explain the high incidence of lattice degeneration and retinal brakes existing in these patients.[70] Pigment dispersion occurs from the pigment epithelium of both iris and ciliary body. Such pigment release occurs secondary to idiopathic atrophy of the pigment layers of the iris.[72]

Among several theories regarding the etiology of PDS, the hypoperfusion and iris hypoplasia,[23] mechanical contacts and rubbing of the iris against the zonular bundles,[13] and the reverse pupillary block theory stand out.[14]

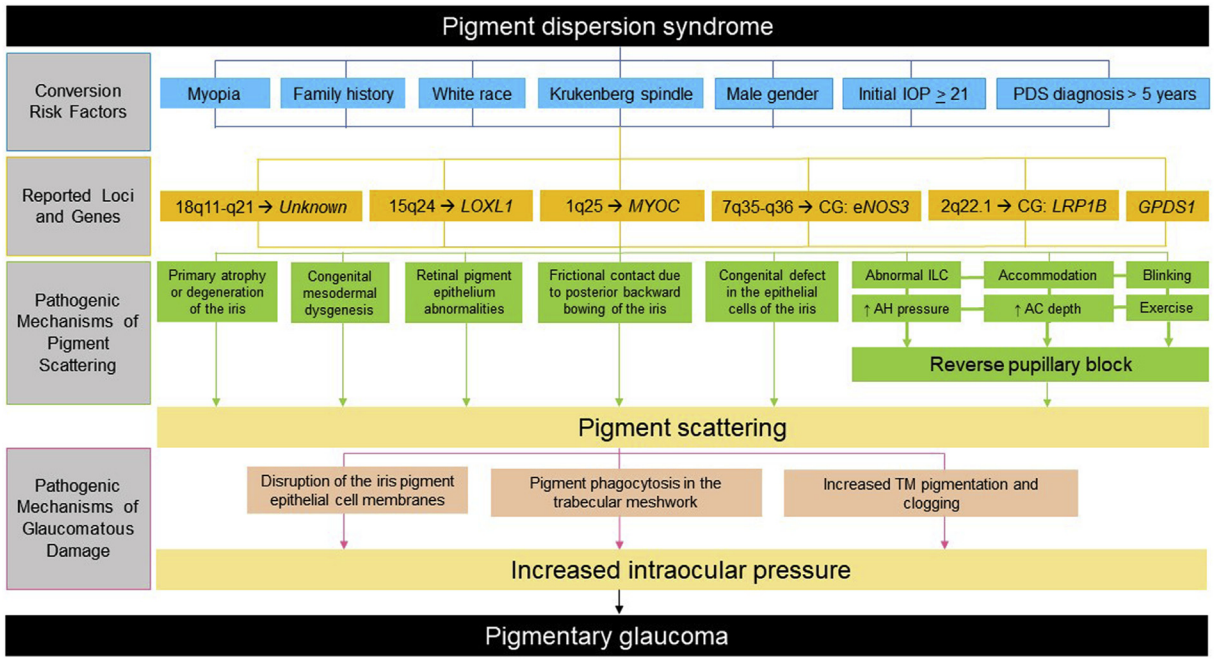
Campbell found a close correlation between the proximity of the anterior zonular bundles with the mid-peripheral transillumination defects, suggesting mechanical rubbing of the posterior iris pigment as the cause of PDS.[13,58] Several other clues that favor pigment rubbing are the backward bowing of the iris, deep anterior chamber, and myopic eyes. The most probable mechanism causing PDS is the reverse-pupillary block.[14] Karickhoff reported that higher aqueous pressure in the anterior chamber might cause a backward bowing of the iris as the posterior chamber collapses.[38,58] Physiological events such as blinking, accommodation, ocular movements, and exercise trigger the reverse-pupillary block.[38,58] Eyes with PDS have a more extensive iridolenticular contact area, favoring the rise in the AC aqueous humor pressure.[58] The relative higher pressure in the anterior chamber will lead to a reverse pupillary block with subsequent pigment dispersion.

Histologic and UBM findings corroborate the unique structural findings of PDS.[58] The correspondence of iris transillumination defects with lens zonule bundles inserted in the anterior capsule reflects the iris concavity as a pigment release mechanism. The regression phase of PG seen with the aging process is probably related to the decrease of iridozonular contact, explained by the increase of axial lens length and age-related miosis. Pigment dispersion is associated with POHT and PG. More than just pigment deposition in the trabecular meshwork is needed to explain the increase of IOP in these patients. Since the 1970s, specific studies elucidate the mechanism by which pigment affects the aqueous humor outflow. Richardson reported that pigment phagocytosis by endothelial cells of the trabecular meshwork produces dysfunction of the aqueous humor outflow mechanism.[63] Age-related ocular changes, such as increased lens axial length and iris shape changes, are identified as factors that favor the resolution of PG.[58]

A recent genome-wide association study calculated the single-nucleotide polymorphism hereditability of PG and identified the disease's genetic associations.[79] Although not significant, the single-nucleotide polymorphism in PG showed a moderate correlation with myopia and a strong one with iris pigmentation. Moreover, there was no shared genetic basis between PG and POAG.[79]

8. Pathology

The importance of knowledge of the histopathological findings in PDS relies on the increased risk of PG development with subsequent vision loss in this group of patients. Unfortunately, the exact converting mechanism remains unknown.[26] Although pigment granules released by different mechanisms could hinder aqueous humor outflow by clogging the trabecular meshwork; different studies have failed to support this theory.[26] Histologically, the major finding in PDS is the presence of pigment granules distributed within the anterior chamber, including the corneal endothelium, trabecular meshwork, and the anterior surface of the lens.[75] In the corneal endothelium, there is pleomorphism and polymegathism of endothelial cells secondary to phagocytosed pigment cells. This phagocytosed pigment also represents the characteristic Krukenberg spindle.[45,75] There is a decreased, but not statistically significant, endothelial cell density in patients with PDS and PG compared to healthy controls.[45] Pigment accumulation is also present on the Schwalbe line as a visible dark line on gonioscopy.[58] In the trabecular meshwork, light and electron microscopy studies show a marked loss of trabecular cells.[26,89] A study comparing the aqueous outflow facility in cynomolgus monkeys' eyes perfused with experimental pigment *versus* sham-manipulated fellow eyes found a significant decrease in outflow facility in perfused eyes. Nonetheless, after a one-week evaluation, outflow facility values returned to baseline. The hindmost suggests that other factors besides pigment



IOP, intraocular pressure; PDS, pigment dispersión syndrome; TM, trabecular meshwork; ILC, iridolenticular contact; AC, anterior chamber; AH, aqueous humor

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Fig. 3 – Interrelation between the risk factors and pathogenic mechanisms leading to pigment dispersion and favoring glaucomatous damage.

deposition contribute to converting PDS to PG.[18] These findings can be explained by the capacity of the trabecular meshwork macrophages to phagocytose pigment granules.[4] Unfortunately, this pigment phagocytosis and renewal capacity of the trabecular meshwork has a threshold. A study evaluating the morphologic changes in the trabecular meshwork of eyes with PDS and PG found that when the amount of cell loss after pigment deposition surpassed the renewal capacity threshold, the trabecular lamellae fuses and collapses the intertrabecular spaces. Also, increased deposition of extracellular matrix material occurs in the subendothelial region of the Schlemm canal.[26,89] This extracellular matrix material deposition is hypothesized to occur because of decreased outflow facility.[89] The latter finding contrasts the fact that in POAG and corticosteroid-induced glaucoma, the deposition of extracellular matrix material is related to the induced factors of the disease itself. Meanwhile, in PG, the extracellular matrix material appears to accumulate secondary to trabecular meshwork cell loss.[89] Regarding the role of the juxtacanalicular tissue in outflow resistance, a study evaluated the melanin granule distribution within the trabecular meshwork and its impact on outflow resistance in normal eyes and eyes with PG, PDS, and POAG.[56] In PG eyes, the percentage of pigment distribution in the juxtacanalicular tissue was 3.5 ± 1.2%, in the corneoscleral meshwork 53.0 ± 8.7%, and the uveoscleral meshwork 43.5 ± 9.6%. In PDS eyes, values were 0.8 ± 0.5% in the juxtacanalicular tissue, 51.0 ± 1.0% in the corneoscleral meshwork, and 48.2 ± 1.5% in the uveoscleral meshwork.[56] When evaluating the outflow facility with a hydrodynamic model of the juxtacanalicular tissue, there were no significant differences in resistance in any group (PG, PDS, POAG, and normal eyes).[56] These findings are consistent with the fact that other mechanisms are involved in developing glaucoma in PDS.

9. Management

The appropriate management of PDS and PG depends on the disease stage defined by pigment dispersion activity, development of OHT, and the degree of glaucomatous neuropathy. There are three critical phases in the natural course of PDS/PG. The first one is the active pigment dispersion phase that develops in early adulthood, mostly asymptomatic. The triggering mechanisms that release the pigment into the anterior chamber include exercise, emotional stress, and pharmacologic mydriasis.[58] The trabecular meshwork remains functional and clears the pigment, preserving the aqueous natural outflow. A high IOP is not always present despite the flush of pigment release. Eventually, the trabecular meshwork becomes heavily pigmented, and OHT develops, defining the second stage of the disease, with the consequent optic nerve damage. As mentioned before, the estimated lifetime risk of conversion from PDS to PG is between 35–50% and increases with time.[66] Among the great risk factors for the development of PG are active pigment release and high myopia.[21] Finally, the third stage arises when the pigment starts to clear from the trabecular meshwork. The IOP normalizes in some cases, and the iris transillumination defects become less prominent. This stage's gonioscopy hallmark is a darker and denser

pigment in the upper than in the lower angle quadrants, known as the "pigment reversal sign."[66] Fig. 4 summarizes the medical, laser, and surgical therapies for PDS, POHT, and PG.

9.1. *Pigment dispersion therapy*

As it changes the iris configuration, pilocarpine can be useful in controlling pigment dispersion.[72] For active pigment dispersion, 2% pilocarpine every eight hours has a relatively safe side-effects profile. Limiting physical activity is often recommended as pigment dispersion may be precipitated by exercise, probably by changes in the iris shape. The use of laser peripheral iridotomy (LPI) in PDS and PG is controversial; however, it seems to have a place in certain PDS patients. LPI reduces the iris concavity and backward bowing present in most patients with PDS. This procedure generates a pressure equilibrium between the anterior and posterior chambers,[75] restraining the iris and zonular fibers' friction.[43]

Iris flattening after LPI reduces iridozonular contact; hence, decreasing up to a 65% pigment release into the anterior segment.[51] Nonetheless, the procedure does not directly correct the iris concavity and low insertion; neither prevents the exposure and damage done by pigment to the trabecular meshwork.[52] There are different functional outcomes of LPI studied in PDS and PG, including the risk of conversion to glaucoma, IOP reduction, and the need for further glaucoma surgery. One study demonstrated a 10-year reduction in the IOP of PDS eyes. These patients had specific characteristics: concave iris, pigment release upon pharmacologic dilation, and an average baseline IOP. Age is important, as the largest IOP reduction effect occurs in patients <40 years, consistent with the exacerbation of reverse pupillary block associated with the accommodation reflex.[92] A Cochrane review did not find evidence to support the effect of LPI in preventing or reducing visual field progression in PDS and PG.[52] Nevertheless, an LPI randomized control trial that classified 72 patients with PDS into high-risk and low-risk IOP elevation based on pupil dilation with a 10% phenylephrine provocative test showed that 62% of untreated eyes had an IOP elevation >5 mmHg, compared to only 14% of the treated group. Whereas in the low-risk group, only 4 of 35 eyes developed hypertension.[22] This study emphasized the importance of using the pharmacologic mydriasis as a pigment-release provocative test to identify high risk eyes that benefit from LPI.

In the setting of PDS and POHT, a controlled clinical trial, including 166 patients randomized to LPI in one eye and the fellow eye used as a control, found that both groups were similar in subjects requiring medical treatment or demonstrating visual field progression after three years. The results suggested that LPI did not prevent the conversion of PDS hypertensive eyes to PG.[74] Once the trabecular meshwork function is affected by pigment, topical hypotensive therapy is required. Although a laser flattening effect occurs in PG eyes after LPI in comparative studies against medical treatment, there are no differences in visual acuity, IOP control, and pigment dispersion between groups. Pilocarpine 1% achieves better control of the IOP.[52] Finally, the need for filtering glaucoma surgery was similar in a series of PG patients randomized to LPI.[52] The trials discussed above demonstrate that LPI effectively changes iris concavity, but its benefit in reducing the PDS conversion into PG and the glaucoma progression is questionable. The results suggest that early LPI would benefit young PDS patients with functional trabecular meshwork and iris concavity evidence. In summary, LPI can help patients younger than 40 years with no POHT and iridozonular contact demonstrated by UBM. Nevertheless, there is insufficient evidence on the role of LPI in PDS patients for the prevention and conversion to PG.[52]

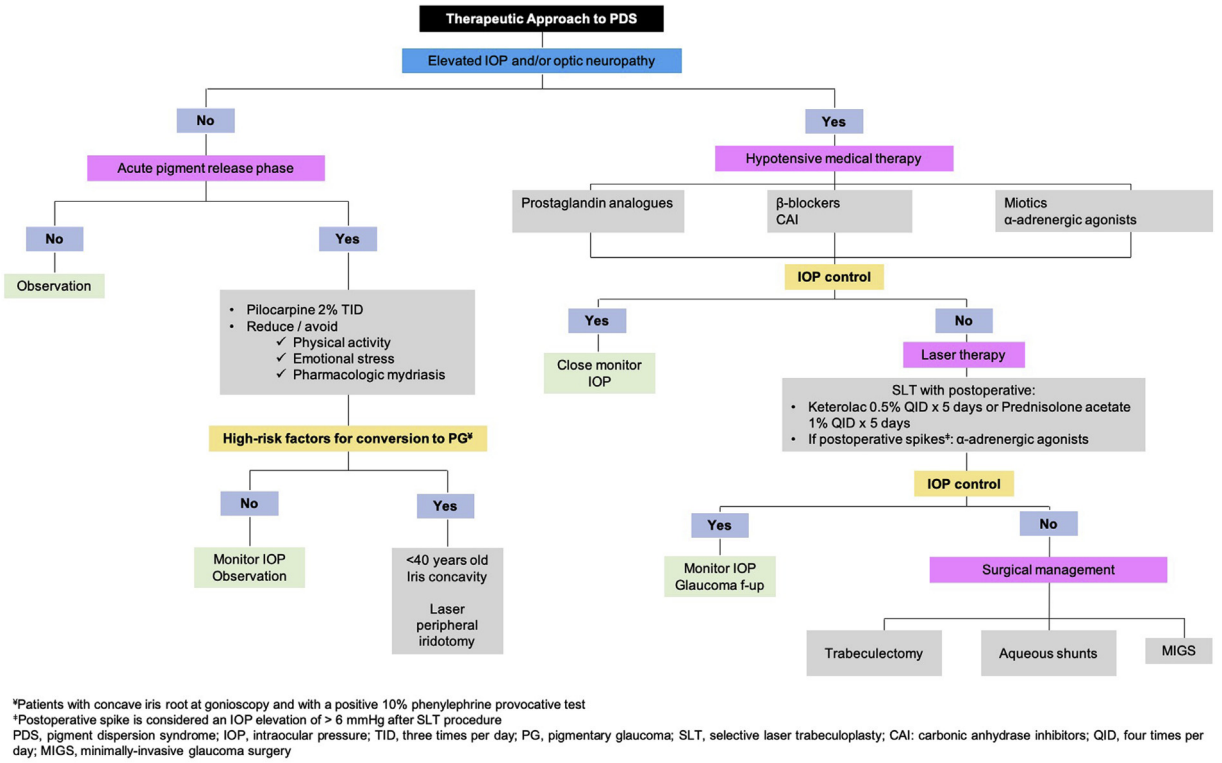
9.2. *Pigmentary ocular hypertension (POHT) and glaucoma (PG) therapy*

9.2.1. *Medical therapy*

Hypotensive medical treatment is the first-line approach in PG. Nevertheless, the unique features of PG eyes require special consideration for other nonmedical treatment strategies. Cholinergic agonists such as pilocarpine have the advantage of reducing pigment liberation by blocking the pupil in miosis, reducing iridozonular contact, and lowering the IOP by facilitating aqueous humor outflow.[72] Despite these theoretical advantages, pilocarpine use is limited by poor tolerance related to visual disturbances associated with miosis, ocular surface disease, and the potential risk for retinal tears or detachment, particularly in myopic patients. Safer drugs such as prostaglandin analogs, beta-blockers, and alpha agonists are now preferred. Latanoprost proved to be more effective than timolol in controlling the IOP in a 12-month randomized clinical trial of patients with PG.[50] Despite lowering the IOP by facilitating uveoscleral flow, prostaglandin analogs do not address the pigment liberation mechanism. Escalation from PG therapy is the same as for POAG. After prostaglandin analogs, β-adrenergic antagonists, carbonic anhydrase inhibitors, and alpha-adrenergic drugs can control the IOP. When acceptable IOP levels are unreached with medical therapy, laser therapy is usually enough to do so.

9.2.2. *Laser therapy*

The use of laser therapy is a reasonable option in PG and may be particularly effective because of the higher energy absorption by the trabecular meshwork pigment.[58] Performing gonioscopy ensures a wide-open angle and quantifies the amount of pigment deposited in the trabecular meshwork. The factors related to the effectiveness of argon laser trabeculoplasty are different compared to POAG. According to studies, young individuals have a better response. On the other hand, a longer duration of the disease foretells inadequate response.[11] The use of selective laser trabeculoplasty (SLT) has become more popular owing to its repeatability and safety profile, with an IOP-lowering effect comparable to medical therapy.[11] The exact mechanism of action of SLT is unknown; however, a stimulation effect on the trabecular meshwork is probable.[41,83] A study of SLT treatment of PG showed a 20% IOP reduction in 85% of the eyes at one year, dropping to 14% at two years.[10] Therefore, in most cases, supplementation with topical antiglaucoma medications is necessary. If SLT becomes a therapeutic option for PG eyes, there are special considerations to take in advance. The inflammation and IOP spikes are the most common complications in PG eyes treated with SLT.[40] There are high-risk factors reported for post-SLT IOP elevation, including



¥Patients with concave iris root at gonioscopy and with a positive 10% phenylephrine provocative test
‡Postoperative spike is considered an IOP elevation of > 6 mmHg after SLT procedure
PDS, pigment dispersion syndrome; IOP, intraocular pressure; TID, three times per day; PG, pigmentary glaucoma; SLT, selective laser trabeculoplasty; CAI: carbonic anhydrase inhibitors; QID, four times per day; MIGS, minimally-invasive glaucoma surgery

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Fig. 4 – Stepwise therapeutic decisions for the management of pigment dispersion syndrome and its progression to pigmentary glaucoma.

intensely pigmented TM, the use of multiple topical medications, and having previous argon laser trabeculoplasty. Eventually, in high-risk patients, the SLT may precipitate the need for filtering surgery.[30] One must select the least amount of energy to obtain bubbles, typically around 0.4 mJ per spot.[33] The IOP should be measured within an hour after treatment to identify spikes (>6 mmHg) and decide if therapy with an alpha-agonist hypotensive drop is necessary. The use of short-term topical antiinflammatory treatment with 0.5% ketorolac or 1% prednisolone four times a day is advised since these drugs influence the effectiveness of SLT.[28]

9.2.3. *Surgical therapy*

Inadequate IOP control and evidence of visual field defect progression on maximal antiglaucoma therapy are clear indications for glaucoma surgery. Filtering surgery remains the first choice in advanced or uncontrolled PG. Intraoperative practical considerations are administering antifibrotic agents to prevent bleb scarring and minimize the anterior chamber's shallowing, avoiding vitreous base and peripheral retina traction. Aqueous shunts are reserved for eyes with failed trabeculectomy but not as a primary procedure.

The use of minimally invasive glaucoma surgery (MIGS) techniques offers a better safety profile than traditional glaucoma surgery, avoiding the bleb formation by shunting aqueous across the obstructed trabecular meshwork into the Schlemm canal. The first MIGS approved in 2004 was the Trabectome® (Neomedix Inc. Tustin, CA, USA). It consists of an *ab interno* trabeculectomy using a handheld electrode. In a one-year study comparing PG with POAG eyes, the Trabectome combined with or without cataract surgery had similar IOP and medication reduction rates. An IOP <21 mmHg and 20% reduction from baseline occurred in 92% of PG and 86% of POAG eyes.[2]

The Kahook® dual-blade (New World Medical, Rancho Cucamonga, CA, USA) is a single-use ophthalmic knife used to perform a goniotomy and remove the trabecular meshwork. A multicenter case series of 52 open-angle glaucoma eyes treated with phacoemulsification combined with the Kahook dual-blade found a mean IOP reduction of 26.2% and a 50% decrease in the number of preoperative medications at one year.[17] The most common adverse effects were pain (7.7%), posterior capsule opacification (3.8%), and IOP spikes >10 mmHg. There are no studies on the effectiveness of the Kahook dual blade in PG eyes.

Another popular MIGS procedure is the iStent® (Glaukos Corporation, San Clemente, CA, USA), an implant designed to bypass the trabecular meshwork. The device has exclusive FDA approval for the management of POAG in combination with cataract surgery. There are no specific studies for PG and the first generation iStent. The second-generation iStent Inject includes two preloaded devices for perpendicular insertion in the trabecular meshwork. The new device has a reported IOP lowering effect of 33% at six months in a series of 35 phakic eyes with POAG; however, 3 eyes with PG developed IOP spikes and required filtrating surgery, which limits the use as a single procedure.[39] There are few studies of efficacy and safety on the use of iStent in PG. In a case series of 24 eyes of 12

patients with PG implanted with one iStent combined with cataract surgery, a 25% IOP reduction was reported in a month.[37] There were no pressure spikes and no patients requiring additional surgery. The use of iStent combined with cataract surgery can be considered in such cases. Further studies are needed to evaluate the role of the trabecular microbypass in this population.

9.3. *Complications, prognosis, and visual outcome*

The main complication of PDS is the development of PG, a sight-threatening condition. Iridozonular contact, pigment dispersion, and deposition in the anterior chamber are PDS and PG's hallmarks. They both probably represent different stages of the same condition rather than two different diseases.[75] The pathogenic mechanisms of PDS and PG are still unknown, and adequate evidence with extended follow-up addressing both entities' outcomes is scant. Nevertheless, evidence points out that patients with PG are at higher risk for developing post-SLT IOP elevations (up to 46 mmHg). Such postlaser IOP elevations can occur even in POAG or POHT patients, but in lesser proportions.[80] The latter represents how the response to first-line therapies, such as SLT, is highly unpredictable in patients with PG. A recent study in a Chinese population evaluated 18 eyes with PG diagnosis for trabeculectomy's long-term efficacy and safety.[62] The mean IOP after eight years of follow-up was 13.7 + 2.5 mmHg, significantly lower than baseline. Moreover, both the visual acuity and automated visual field analysis (mean deviation) remained stable in 83.3% (15/18) of the eyes after follow-up.[62] Even though the efficacy of trabeculectomy in the safety and clinical profile of the patients enrolled in this study, larger prospective, randomized studies are needed to elucidate the long-term outcomes of PDS and PG patients.

10. Conclusions

Ophthalmologists need to be familiar with PDS's clinical spectrum, its early diagnosis, the different clinical entities that resemble it, and its therapeutic alternatives, as it is a disease frequently misdiagnosed or overlooked. Careful ophthalmologic examination is essential to crafting a thorough differential diagnosis. Frequent follow-up to determine secondary hypertension and glaucoma is indicated. Patients with POHT or PG need periodic evaluation for visual field defects and optic nerve structural changes. Also, PG patients require aggressive antiglaucoma therapy to prevent optic nerve damage. These patients are more challenging to control than those with POAG and frequently require escalation of therapy to obtain adequate IOP control. Pigment dispersion activity and IOP behavior mandate a tailored-therapeutic approach according to individual needs.

Finally, by searching the literature exhaustively on the clinical spectrum between PDS and PG, it becomes evident that scientific reports on the subject are scant and that there is a lack of large cohort randomized controlled clinical trials on therapeutic modalities for the disorder.

11. Methods of literature search

The authors conducted an extensive literature search using the National Library of Medicine's PubMed and Google Scholar database for all English language articles published until April 2020. The following search terms were used: *pigment dispersion, pigment dispersion syndrome, pigmentary ocular hypertension, pigmentary glaucoma, pigment dispersion syndrome and eye, pigmentary glaucoma and surgical management, minimally invasive glaucoma surgery and pigmentary glaucoma, pigmentary glaucoma and medical management, pigment dispersion therapy, trabecular pigment, and pigment dispersion and ocular hypertension*. Case reports, case series, letters to the editor, review articles, and original articles were included. Relevant references within articles found were also included. Excluded were articles with the previously mentioned terms in other languages.

12. Declarations of interest

Declarations of interest: The authors declare no commercial interests nor financial disclosures.

13. Disclosure

Disclosure: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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