SMGroup

Pigment Dispersion Syndrome and Pigmentary Glaucoma

Nurullah Koçak[1] and Emrullah Beyazyıldız[1]*

[1]Samsun Research and Training Hospital, Turkey

*Corresponding author: Emrullah Beyazyıldız, Samsun Research and Training Hospital, Turkey, Email: dremrullah@hotmail.com

INTRODUCTION

Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) are two different spectra of a disease characterized by dispersion of pigment granules from iris pigment epithelium, and their accumulation in different anterior segment regions. While intraocular pressure is normal and no glaucomatous damage is observed in pigment dispersion syndrome, secondary glaucomatous optic neuropathy is observed in pigmentary glaucoma.

History

Vertically located pigment accumulation at the corneal endothelium was firstly identified by Krukenberg at the end of the 1800s. He argued that the pathology occurs due to proximity of congenital pupillary membrane to cornea in the early stages of embryogenesis. Then in 1901, Von Hippel suggested that the released iris pigments can raise intraocular pressure by blocking aqueous outflow. In 1909, Levinsohn stated that pigment stored in the anterior chamber originates from iris pigment epithelium. In 1958, this theory was supported by Scheie demonstrating transillumination defect in such patients. The first pigmentary glaucoma case was reported by Sugar in 1940, nearly 40 years after Krukenberg's description. In 1966, as a result of 25 years of observations about the disease, Sugar described such related features as myopia, bilaterality, young ages and male. One of the most important definitions of the pathophysiology was made by Campbell in 1979 as concavity in the iris mid-periphery and iridolenticular contact.

Epidemiology

The incidence of PDS was reported as 2.5%. PG constitutes 1.5% of all glaucoma cases. In the USA, the annual incidence rates of PDS and PG are estimated as 4.8/100,000 and 1.4/100,000 respectively. The rate for PDS's conversion to PG ranges between 6% -43%. In another study, it was observed that in 5 years 10% of the cases and in 10 years 15% of the cases converted to PG. Typically, the involvement is seen young (between 20-40 year old age) and myopic patients. With slight male gender predominance, PDS is observed in both sexes in approximately equal proportions. PG, on the other hand, is observed in male sex significantly more frequently (78%-93% of the cases). It was reported to be seen in Asian race more frequently. It is seen in Caucasians more commonly as compared to black race and among black people there is a phenotypic difference as no transillumination defect is detected among blacks.

Genetics

Majority of the cases are sporadic. Apart from sporadic cases, it shows dominant incomplete penetrance. Nitric oxide synthase located in the 7th chromosome, muscarinic acetylcholine receptor gene and human Cyclops gene regions were hold responsible. Apart from this, there are reports for myocilin gene located in the 1st chromosome, LOXL1 gene in the 15th chromosome and LRP1B gen regions located in the 2nd chromosome.

Pathophysiology

After pigment dispersion was begun to be identified, many ideas were proposed about its pathophysiology. First, iris pigment dispersion and angle anomalies were associated with congenital mesodermal dysgenesis. In another theory, it was suggested that primary atrophy or degeneration of the iris caused the pathology. Defining a family with familial Krukenberg spindles suggested that genetic etiology could also be effective. In the late 1970s, Campbell showed a correlation in pigment dispersion cases between the number of zonules making insertion to front capsule of the lens and number and location of transillumination regions. There were an average 65-80 pieces of lens zonules ending in the front capsule of the lens, while there were about 65-80 transillumination slits in the iris. Based on that, he suggested that the contact between the zonules ending in the front capsule of the lens and iris mid-periphery caused pigment discharge from posterior iris. The theory suggested by Campbell regarding PDS and PG is still valid today. Subsequent anterior segment OCT and ultrasound biomicroscopy studies support this theory. Concave configuration of iris, formation of a flap-valve as a result of increased iris lens contact surface, increase in the pressure of the anterior chamber and its being higher than posterior chamber hence leading to increased friction due to the iris pushed towards posterior is defined as formation of reverse pupillary block. Reverse pupillary block can be triggered by physiological events such as winking, accommodation, eye movements and exercise. Changes in the front surface of the lens during accommodation forces aqueous towards anterior chamber angle and also increases iris lens contact, thus lead to formation of reverse pupillary block. During exercise,

increase in the posterior iris concavity triggers dispersion, and decrease in the aqueous outflow leads to distinct increase in the intraocular pressure. During blinking, aqueous, secondary to temporary vector forces is pumped into the anterior chamber from posterior chamber and increase in the pressure in the anterior chamber leads to posterior bowing of the iris which in turn leads to pigment dispersion.

Unlike other types of glaucoma, PG enters burn-out phase with the increasing age. Pigmentation in trabecular meshwork begins to decrease gradually, especially starting from the lower quadrant. As a result of decrease in the pigmentation, intraocular pressure reduces over time. Decrease in the pigmentation and presence of glaucomatous findings cause patients to receive mistakenly primary open-angle glaucoma (POAG) or normotensive glaucoma (NTG) diagnoses. Over time, different theories have been proposed to explain decrease in the pigment dispersion. Campbell suggested that increased axial length of the lens raises iris and moves it away from lens zonular complex, thus dispersion decreases. Relative pupillary block and functional bowing iris, seen in the patients with relative miosis that occurs with age who receive miotic therapy for a long time, moving peripheral iris away from the zonules help this situation. Another theory explains it as lack of pigment to be released due to friction in time.

Clinical Features

The classic triad of the disease is spindle-shaped pigmentation in corneal endothelium, transillumination defects in the iris and pigment accumulation in the irido-corneal angle. During biomicroscopic examination, movement of the aqueous circulating in the anterior chamber and pigment located in the corneal endothelium may be seen as a line and it is called Krukenberg spindle. It is not pathognomonic for PDS. Sometimes it can be seen as intense concentric pigmentation in inferior cornea periphery. It is seen more frequently in female sex and hormonal factors were implicated. When examined histologically, melanin pigments are observed in endothelial cells. While pleomorphism and polymegathism were identified in endothelial cells, function and cell loss were not observed. In patients with PDS, it is observed that the angle of the anterior chamber is wide and open in such a way that ciliary body band can be seen. Although there is no difference between the axial lengths of the eyes in patients with unilateral PDS, the anterior chamber of the affected eye is deep. Intense dark brown pigmentation is seen in the trabecular region and other angle regions and it is called Sampaolesi line. While pigment is seen in Schwalbe line in exfoliation syndrome, it is usually only in posterior trabecular in PDS. Pigmentation is equally distributed in all quadrants. Histologically, melanin granules are observed in trabecular endothelial cells. Pigment particles flying in the anterior chamber can be mistakenly evaluated as uveitis reaction. After dilation, pigment discharge may increase and pigment dispersion towards anterior chamber in pupil range may be observed. The pigment amount can be measured by laser fluorometer. The accumulation of pigment in the concentric grooves on the front surface of the iris can sometimes cause heterochromia appearance in the light-colored irises. Also, radial, slit-shaped, mid-peripheral transillumination defects can be seen in the iris. Width of the defects and degree of

the Krukenberg spindle are correlated. Defect can be detected by directing light onto the iris in a perpendicular way or by using posterior scleral transillumination. Unlike PDS, transillumination defect is located peripapillary, not mid-peripheral, in pseudoexfoliation (PXF) syndrome. In the patients with asymmetric PDS, pupil is larger in the eye that has more transillumination. Anisocoria, mydriasis and heterochromia can mimic congenital Horner's syndrome. Pigments can accumulate on the lens surface in PDS. In 1938, Zentmayer identified storage in the rear face of the lens for the first time and this formation was named Zentmayer line. When same formation is observed in the junction of zonular complex and posterior capsule, it is named as Scheie line. Posterior segment, as well as anterior segment, can be affected by PDS. Retinal pathologies such as lattice degeneration (20%, 33%), retinal tears (12%) and retinal detachment (5.5-% to 6.6%) can be observed.

Risk factors for PDS, PG conversion

Rate of PDS's conversion to PG varies in a wide range of 6%-43%. It was observed that in 5 years 10% of the cases and in 10 years 15% of the cases converted to PG. Some risk factors were detected in PG cases. There is a family history of glaucoma in 4%-21% of the PDS cases. The family history of glaucoma is seen 26%-48% in the PG cases. Although hereditary factors are not specific to PDS and PG, they are risk factors in terms of glaucoma development. Having an initial intraocular pressure over 21 mm Hg is an important risk factor in terms of PG development. Every 1 mm Hg increase in intraocular pressure leads to 1.4 times increased risk in the risk of conversion. Presence of Krukenberg spindle was also found to be a risk in terms of conversion to PG. When patients with non-glaucomatous PDS and patients with PG are compared, it was found that Krukenberg spindle is observed more frequently in patients with PG. This can be explained as that more pigment dispersion leads to PG development more frequently. In terms of PDS development, no difference was found between two sexes except for slight male gender predominance. In terms of PG, male gender is a distinct risk factor. In terms of refraction, most of the cases with PDS have myopia, and a very small patient group has hyperopia. Also a positive correlation between increased degrees of myopia and PG conversion was identified. In compliance with the theory of Campbell, high myopia results in deep anterior chamber, increased lens zonules-iris contact results in increased pigment dispersion.

PIGMENTARY GLAUCOMA

When autopsy studies conducted in human eyes and primate eyes were examined, it was seen that aqueous outflow decreases due to pigment blockage in trabecular channels. Endothelial cells in trabecular meshwork phagocyte pigments. Increased phagocytic load results in cell death and necrotic debris and pigment in the environment are removed by macrophages. Trabecular cell death results in collapse, sclerosis and obliteration that develop in the channels result in increase in the intraocular pressure.

Clinical Features

Majority of the patients are asymptomatic. In some of the cases, on the other hand, blurred vision and headache attacks may occur after physical exercise. Corneal edema development, seconder to increased intraocular pressure, leads to appearance of halos around the lights. It is a type of glaucoma that causes an average 29 mm Hg intraocular pressure during diagnosis. In long-term analyses, intraocular pressure was found to be >31 mm Hg in 25% of the patients, and >39 mm Hg in the 12.5% of the patients. Compared to PAAG, intraocular pressure tends to be in a wider range. The burn-out phase, entered with advancing age, provides convenience in achieving the desired IOP. Visual field defects and optic disc appearance are similar to PAAG. In asymmetrical PG cases, glaucoma is more severe in the eye that has more pigment dispersion. With laser fluorometric studies, IOP was found more in the eye where pigment is more in the aqueous. Pigmentation level of trabecular meshwork and severity of glaucoma are correlated but there is no correlation in PDS cases between trabecular pigmentation level and conversion to PG.

Differential Diagnosis

PDS and PG may show similarities in many cases:

PAAG

Pigmentation may be seen in trabeculum but unlike homogenous distribution in PDS, it demonstrates density in the lower part of the angle. Iris transillumination defects and Krukenberg spindle are not observed. Compared to PG, they are seen in older ages.

PXF syndrome

Transillumination defect is also seen in PXF but unlike mid-peripheral involvement in PDS, it is seen in pupillary margin. The involvement in trabeculum is different than homogenous involvement in PDS and in patched-shape. Often patients over 60 are affected. Characteristic PXF is observed in different regions of the anterior chamber.

Pseudophakic pigmentary glaucoma

Pigment release occurs as a result of friction of optic and haptic of intraocular lens with the posterior surface of the iris

Uveitis

Iris pigment epithelitis results in pigment release from the iris and inflammatory cells flying in the anterior chamber. Patchy trabecular hyperpigmentation, iris atrophy and transillumination defects can be observed. Especially herpetic uveitis can occur with iris atrophy and increased intraocular pressure.

Ocular surgery and trauma

An intraocular surgery undergone and blunt or penetration trauma might cause pigment cells in the aqueous, trabecular hyperpigmentation and transillumination defects, similar to those in PDS. Trauma and surgical history of the patients should be carefully examined.

Apart from these, long-term mydriasis, diabetes, intraocular tumors and rhegmatogenous retinal detachment also lead to a similar appearance with PDS.

Treatment

Medical treatment

Prevention of pilocarpine pupil dilatation and correction of posterior bowing of the iris have a reducing effect on the pigment dispersion. It's causing ciliary spasm, cataract development and retinal detachment limit its use. Young patients cannot tolerate it well. Prostaglandin derivatives are potent ocular hypotensive agents but they do have a specific effect on PG. As in other types of glaucoma, they can be used as first-line agents in PG as well. Causing increased pigmentation in the iris does not limit its use in patients with PG. α-adrenergic agonists, beta blockers and carbonic anhydrase inhibitors are used in PG as other types of glaucoma. Dapiprazole and thymoxamine coherence, as selective alpha-adrenergic antagonists, triggers miosis without causing spasms and reduces dispersion. Irritation effect limits their use.

Laser trabeculoplasty

Since pigment amounts are more, laser absorption is higher, so better results are achieved as compared to PAAG. Avoiding excessive treatments in the angles with high pigment loads, and starting treatment with low laser powers is important. Argon laser trabeculoplasty yields better results in young patients than older patients. It is thought that cells in trabecular meshwork respond better to laser treatment in young patients, and outflow increases more through remodeling occurring in the trabecular meshwork due to increased metabolism. Over time, initial activity reduces; the success was reported as 45% in the 6-year period. Reason for the decrease in the success is scar development in trabecular meshwork and high absorption as well as overtreatment. Selective laser trabeculoplasty provide similar effect with lower laser power by targeting pigment cells. But after SLT, increase in intraocular pressure in some patients was reported. After laser trabeculoplasty, at least one third of the patients require trabeculectomy within 5 years.

Laser iridotomy

It prevents reverse pupillary block formation by correcting iris contour, reducing excessive iris-lens contact, equalizing anterior and posterior chamber pressures. After iridotomy, the iris's having planar configuration was shown with ultrasound biomicroscopy. A decrease in anterior chamber volume and lens zonules-iris contact is seen. Decreases in the intraocular pressure

might be observed. There are studies reporting that in the long-term follow-ups it is not superior to medical treatment. If, there is no PG under the age of 40 with PDS, or there is PG in one eye and PDS in the other eye, laser iridotomy can be planned for those patients having increased intraocular pressure.

Trabeculectomy

Trabeculectomy is needed more frequently as compared to PAAG. Surgical results are not very successful due to younger patient population. The additional use of antimetabolites can improve surgical outcomes. There are opinions that only iridectomy reduces progression by flattening the iris and reducing posterior bowing.

References

1. Sugar HS, Barbour FA. Pigmentary glaucoma: a rare clinical entitiy. Am J Ophthalmol. 1949; 32: 90-92.

2. Levinsohn G. Beitragzurpathologische Anatomie und Pathologiedes Glaukoms. Arch Augenheilkd. 1909; 62: 131-154.

3. Sugar HS. Pigmentary glaucoma: a 25-year review. Am J Ophthalmol. 1966; 62: 499-507.

4. Campbell DG. Pigmentary dispersion and glaucoma. A new theory. Arch Ophthalmol. 1979; 97: 1667.

5. Siddigui Y, Ten Hulzen RD, Cameron JD, Hodge DO, Johnson DH, et al. What is the risk of developing pigmentary glaucoma from pigment dispersionsyndrome? Am J Ophthalmol. 2003; 136: 794-799.

6. Farrar SM, Shields MB. Current concepts in pigmentary glaucoma. Surv Ophthalmol. 1993; 37: 233-252.

7. Migliazzo CV, Shaffer RN, Nykin R, Magee S. Long-term analysis of pigmentary dispersion syndrome and pigmentary glaucoma. Ophthalmology. 1986; 93: 1528–1536.

8. Scheie HG, Cameron JD. Pigment dispersion syndrome: a clinical study. Br J Ophthalmol. 1981; 65: 264-269.

9. Andersen JS, Pralea AM, DelBono EA, et al. A gene responsible for the pigment dispersion syndrome maps tochromosome 7q35-q36. Arch Ophthalmol. 1997; 115: 384-388.

10. Vincent AL, Billingsley G, Buys Y, Levin AV, Priston M, Trope G, et al. Digenic inheritance of early-onset glaucoma: CYP1B1, a potential modifiergene. Am J Hum Genet. 2002; 70: 448-460.

11. Faucher M, Anctil JL, Rodrigue MA, Duchesne A, Bergeron D, Blondeau P, et al. Founder TIGR/myocilin mutations for glaucoma in the Que´becpopulation. Hum Mol Genet. 2002; 11: 2077-2090 .

12. Alward WLM, Kwon YH, Khanna CL, Johnson AT, Hayreh SS, Zimmerman MB, et al. Variations in the myocilin gene in patients with open-angle glaucoma. Arch Ophthalmol. 2002; 120: 1189-1197.

13. Mikelsaar R, Molder H, Bartsch O, Punab M. Two novel deletions (array CGH findings) in pigment dispersion syndrome. Ophthalmic Genet. 2007; 28: 216-219.

14. Wolf C, Gramer E, Mu¨ ller-Myhsok B, Pasutto F, Gramer G, Wissinger B, et al. Lysyloxidaselike 1 gene polymorphisms in German patients with normal tension glaucoma, pigmentary glaucoma and exfoliation glaucoma. J Glaucoma. 2010; 19: 136-141.

15. Lichter PR, Shaffer RN. Diagnostic and prognostic signs in pigmentary glaucoma. Trans Am Acad Ophthalmol Otolaryngol. 1970; 74: 984-998.

16. Bick MW. Pigmentary glaucoma in females. Arch Ophthalmol. 1957; 58: 483-494.

17. Dinc UA, Kulacoglu DN, Oncel B, et al. Quantitative assessment of anterior chamber parameters in pigmentary glaucoma using slit-lamp optical coherence tomography. Eur J Ophthalmol. 2010; 20: 702-707.

18. Evans WE, Odom RE, Weenas EJ. Krukenberg's spindle: a study of 202 collected cases. Arch Ophthalmol. 1941; 26: 1023-1056.

19. Wilensky JT, Buerk KM, Podos SM. Krukenberg's spindles. Am J Ophthalmol 1975; 79: 220-225.

20. Prince AM, Ritch R. Clinical signs of the pseudoexfoliationsyndrome. Ophthalmology. 1986; 93: 803–807.

21. Zentmayer W. Association of an annular band of pigment on the posterior capsule of the lens with a Krukenberg spindle. Arch Ophthalmol. 1938; 20: 52.

22. Weseley P, Liebmann J, Walsh JB, Ritch R. Lattice degenerationof the retina and the pigment dispersion syndrome. Am J Ophthalmol. 1992; 114: 539–543.

23. Farrar SM, Shields MB, Miller KN, Stoup CM. Risk factors for the development and severity of glaucoma in the pigment dispersion syndrome. Am J Ophthalmol. 1989; 108: 223–229.

24. Donaldson DD. Transillumination of the iris. Trans Am OphthalmolSoc. 1974; 72: 89–106.

25. Schenker HI, Luntz MH, Kels B, Podos SM. Exercise-induced increase of intraocular pressure in the pigmentary dispersion syndrome. Am J Ophthalmol 1980; 89: 598–600.

26. Lindquist NG, Larsson BS, Stjernschantz J. Increased pigmentation of iridial melanocytes in primates induced by a prostaglandin analogue. Exp Eye Res. 1999; 69: 431–436.

27. Grierson I, Jonsson M, Cracknell K. Latanoprost and pigmentation. Jpn J Ophthalmol. 2004; 48: 602–612.

28. Wand M, Grant WM. Thymoxamine hydrochloride: an alpha-adrenergic blocker. SurvOphthalmol 1980; 25: 75–84.

29. Mastropasqua L, Carpineto P, Ciancaglini M, Gallenga PE. The usefulness of dapiprazole, an alpha-adrenergic blocking agent, in pigmentary glaucoma. Ophthalmic Surg. 1996; 27: 806–809.

30. Ritch R, Liebmann J, Robin A, et al. Argon laser trabeculoplasty in pigmentary glaucoma. Ophthalmology. 1993; 100: 909–913.

31. Breingan PJ, Esaki K, Ishikawa H, Liebmann JM, Greenfield DS, Ritch R. Irido lenticular contact decreases following laser iridotomy for pigment dispersion syndrome. ArchOphthalmol. 1999; 117: 325-328.

32. Niyadurupola N. Pigment dispersion syndrome and pigmentary glaucoma a major review. Clin Experiment Ophthalmol. 2008; 36: 868–882.