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The Heritability of Pigment Dispersion Syndrome and Pigmentary Glaucoma

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Abstract

Purpose: Pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG) are presumed to be inherited in an autosomal dominant manner. Herein, we examine relatives of patients with PDS and PG in order to determine the heritability of this disease.

Design: Prospective, cross-sectional study.

Methods: A total of 101 patients with PDS were prospectively recruited over eleven months. Four of the patients had PDS without ocular hypertension (OHT) or glaucoma, 6 had PDS and OHT, and 91 had PG. Criteria for PDS were two of three signs: Krukenberg spindle, mid-peripheral iris trans-illumination defects (TIDs), and/or heavy trabecular meshwork (TM) pigmentation. Criteria for PG were PDS and two of three signs: intraocular pressure (IOP) greater than 21 mmHg, glaucomatous optic nerve damage, and/or glaucomatous visual field loss. Ninety-nine first-degree relatives living within a 100-mile radius of Iowa City, Iowa were examined in the clinic to determine the probability of familial transmission.

Results: A total of 10/99 (10.10%) first-degree relatives were diagnosed with PDS (1 with PDS alone, 2 with PDS and OHT and 7 with PG). Seven families with at least two affected members were identified. The majority of affected family members (8/10) showed moderate to heavy TM pigmentation and either Krukenberg spindle or TIDs.

Conclusions: Most of our cases our of PDS are sporadic and the risk to first-degree relatives is lower than previously reported. However, there are families with apparent autosomal dominant inheritance of PDS in which the risk to relatives may be high.

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Introduction

When Sugar and Barbour first described pigmentary glaucoma (PG) in 1949 they felt that it was a “rare clinical entity.”¹ It is now recognized that PG and the underlying pigment dispersion syndrome (PDS) are common disorders. Pigment dispersion syndrome is characterized by abnormal loss of iris pigment epithelium with dispersion throughout the anterior segment of the eye. This pigment is deposited along the corneal endothelium as a Krukenberg spindle, in the trabecular meshwork as a dark band, on the anterior surface of the iris, and at the junction of the posterior zonules and lens capsule as a Scheie stripe or Zentmayer ring. The pigment originates when a back-bowed iris causes the iris pigment epithelium to abrade against packets of lens zonules, resulting in characteristic radial slit-like mid-peripheral trans-illumination defects in the iris.² A subset of patients with pigment dispersion syndrome develop an elevated intraocular pressure (IOP) due to progressive trabecular dysfunction caused by the dense trabecular pigment. Some of these patients with elevated IOP will develop glaucomatous optic nerve head damage and are considered to have PG.³

In 1966, Sugar reviewed 147 cases of PG, reporting many additional characteristics including; bilaterality, frequent association with myopia, greater incidence in men than in women, and a relatively young age at onset.⁴ Bick, in 1956, first proposed that concentric atrophy of the iris pigment epithelium (IPE) is the primary lesion in PG.⁵ Later, many others including Scheie and Fleischhauer,⁶ Sugar,⁴ and Kupfer et al.⁷ advocated this concept. Kupfer and colleagues studied the histopathology of iris tissue and trabecular meshwork from PDS patients and described outer pigment epithelial cell loss with marked thinning of the remaining outer layers of iris.⁷ Campbell described mechanical rubbing between anterior zonular packets and iris pigment epithelium to be causative in the pathogenesis of PDS and PG.² The location and number of the trans-illumination defects correlated with the position and number of the underlying zonular bundles. He hypothesized that iridozonular friction during pupillary movement disrupts the IPE, releasing pigment into the posterior chamber.

Kaiser-Kupfer et al. proposed a hereditary basis for pigment dispersion due to abnormal pigment epithelium of the iris and the ciliary body, which increases the vulnerability to contact with zonules and subsequent mechanical rubbing.⁸ In 1996, Ritch proposed a unification hypothesis of pigment dispersion, which postulated that a gene affecting some aspect of the development of the middle third of the eye early in the third trimester could be the cause.⁹ This hypothesis could explain the abnormally high incidence of lattice degeneration of the retina and retinal detachment in PDS patients and the high susceptibility of IPE cells to disruption.

Other conditions can also lead to release of iris pigment without all of the classic features of PDS. Iris trauma from iris cysts, injury, surgery, or abrasion from an artificial lens implant or a subluxed crystalline lens may cause release of iris pigment.^{10–12} Pigment release from the iris has also been detected in patients with diseases that are frequently associated with lens dislocation and secondary glaucomas, such as exfoliation syndrome and Marfan syndrome.^{13,14} A recent report of PG in a patient with Marfan syndrome without a subluxed lens

suggested that mutations fibrillin-1 or other genes associated with microfibrils might have a role in PDS/PG.¹⁵

Prior studies have suggested a hereditary basis for PDS and PG. A positive family history of glaucoma has been found in 4% to 26% of patients with PDS and/or PG.^{16–18} The largest study to date was by Mandelkorn et al.¹⁹ who reported 23 patients in four families with PDS and observed this syndrome to be transmitted in an autosomal dominant pattern in three of the four families, independent of refractive error, iris color and gender. A genetic basis for dispersion of iris pigment and glaucoma in mice also provides support for a genetic basis for PG in humans.²⁰

The purpose of our prospective study was to examine the familial prevalence and of the type of inheritance in a large cohort of family members of patients with PDS and PG.

Materials and methods

In this cross-sectional study patients were identified in the Glaucoma Service, Department of Ophthalmology and Visual Sciences at University of Iowa Carver College of Medicine over an eleven-month period. Consecutive patients with PDS and PG were evaluated after obtaining an informed consent for participation in the study. Approval for this Health Insurance Portability and Accountability Act-compliant study was prospective and was obtained through the Institutional Review Board of University of Iowa, Iowa City, IA and all research adhered to the tenets of the Declaration of Helsinki.

A total of 101 unrelated individuals with PDS and PG were prospectively enrolled. We excluded patients with pigment dispersion secondary to other conditions such as trauma, iris cysts, iritis, intraocular lens implant, pseudoexfoliation of the lens capsule, etc. A complete past ocular history was obtained including previous history of ocular hypertension and glaucoma and family history of glaucoma. Patients were also asked whether they had first-degree relatives, more than 18 years of age, who lived within a 100-mile radius of Iowa City, Iowa and whether they would be willing to be evaluated for PDS.

A standardized ophthalmic examination was carried out, which included slit lamp biomicroscopy looking for a Krukenberg spindle that was graded from 0 to 4 (0= none, 1= few flecks, 2= subtle spindle, 3= dense spindle, 4= diffuse pigment). Intraocular pressure (IOP) was measured with Goldmann applanation tonometer. Gonioscopy was performed with a Posner or Sussman four-mirror lens. Trabecular meshwork (TM) pigmentation was graded from 0 to 4 (0 = no pigment, 1 = light pigment, 2 = moderate pigment, 3 = heavy, non confluent pigment, 4= confluent, heavy pigment). The iris contour was also graded (back-bowed, flat or convex). Infrared transillumination was performed to evaluate the iris for transillumination defects. This technique has been described previously.²¹ Refractive error was determined by autorefractometer (Topcon, Tokyo, Japan). Biometry (IOL Master, Carl Zeiss Meditec, Dublin, CA) determined anterior chamber depth (ACD), keratometry and axial eye length (AEL). Optic nerve status was determined by evaluation with an indirect fundus lens and the vertical and horizontal cup-to-disc ratio determined. Humphrey visual fields (Humphrey instruments, Carl Zeiss Meditec, Dublin, CA) and optical coherence

tomography (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA) were obtained to evaluate the severity of glaucoma. A total of 99 first-degree relatives within a 100-mile radius also underwent standardized ophthalmic examination to determine the presence of PDS and/or PG. There is a potential for misclassification of PDS in very young people, as the disease may not manifest until the 20s or 30s, therefore we did not examine family members under 18 years of age. The first-degree relatives ranged in age from 19 to 99 years (mean age 54.30 ± 18.76 years, median age 53 years). All of the first-degree relatives underwent a complete ophthalmological examination similar to the patients, including slit-lamp biomicroscopy, applanation tonometry, gonioscopy, and infrared videography to identify iris trans-illumination defects. In addition, their refractive status was evaluated with an auto-refractometer and their AEL and ACD recorded. Relatives were asked whether they knew their highest prior IOP measurement and the higher of the historical or measured IOP was recorded.

Based on our examination, the subjects were separated into one of three categories: **1. PDS:** At least two of three characteristics in at least one eye: Krukenberg spindle, mid-peripheral iris trans-illumination defects, or heavy TM pigmentation (Grade 2 or higher); **2. PDS with OHT:** PDS + IOP > 21 mmHg; and **3. PG:** PDS plus at least two of the three characteristics in at least one eye: IOP > 21 mm Hg; glaucomatous optic nerve head damage (CDR > 0.5 or CDR asymmetry > 0.2) with neuroretinal rim loss; or glaucomatous visual field defect.

We describe PDS/PG cases as familial if we were able to identify an affected family member on our examination. If we were not able to identify an affected relative we called the patient sporadic, recognizing that there are possibly affected relatives that we did not have the chance to evaluate. It is also possible that some sporadic cases may represent disease caused by recessive genes that have not yet been discovered.

Results

Of the 101 probands with PDS, four had PDS without ocular hypertension (OHT) or glaucoma, 6 had PDS with OHT, and 91 had PG. Because the patients were recruited from a tertiary glaucoma practice the probands were skewed towards patients with glaucoma and cases of PDS without glaucoma were under-represented.

Features of probands

Age of diagnosis and gender

The age at diagnosis ranged from 12 to 75 years. The mean age at diagnosis was 42.49 ± 13.10 years (41.52 ± 13.87 years for men and 44.17 ± 11.54 years for women). The median age at diagnosis was 43 years for men and 46 years for women. Sixty-four (63.37%) of the probands were men and 37 (36.63%) were women with a male: female ratio of 1.73:1. The mean age at diagnosis of the probands who were found to have an affected family member (familial PDS) was 30.5 years, compared to 43.73 years for sporadic PDS.

Race

The patient population was predominantly Caucasian (93.07%), with only two patients being Caucasian Hispanic (1.98%), one patient each of African American, East Asian, South Asian, Mediterranean, and Native American origins. For comparison, the population of the state of Iowa in 2017 was 91.1% Caucasian, 6.0% Hispanic, 3.8 % African American and 2.6% Asian (US Census Bureau 2017 Estimate).

Clinical features

Table 1 describes the clinical features of the probands with PDS. A Krukenberg spindle on slit lamp biomicroscopy was found in 79.10% (159/201) of eyes. One eye could not be examined for Krukenberg spindle because it had undergone corneal endothelial transplantation. Iris transillumination defects were seen in 76.26% (151/198) of eyes on infrared videography and asymmetric trans-illumination was observed in 13.13% (13/99) of patients. Four eyes of two patients could not be trans-illuminated because of dilation (2 eyes) or technical difficulties with the infrared camera (2 eyes). The majority, 60.10% (119/198) of eyes, demonstrated both corneal endothelial pigment as well as iris transillumination defects.

The anterior chamber angles of all eyes reported in this study were open. Gonioscopy revealed heavy TM pigmentation (grade 2 or higher) in 96.53% (195/202) of eyes. Asymmetric TM pigmentation was present in 11.88 % (12/101) of patients. The iris contour was found to be in a characteristic concave mid-peripheral configuration in only 14.85% (30/202) of eyes, while other patients had a more flat (77.72%) or a convex (2.97%) configuration. The contour of six eyes (2.97%) could not be evaluated because of pilocarpine usage.

Of the 126 phakic eyes, 113 (89.68%) were myopic, 10 (7.93%) were hyperopic and 3 (2.38%) were emmetropic. The mean AEL was 25.39 ± 1.90 mm (range 20.67–35.9) with the majority of eyes (87.56%) being longer than the published normal mean of 23.67 mm.²²

Family history of glaucoma and inheritance in PDS

A positive family history of glaucoma was elicited in 58.41% (59/101) of our patients, but only 6.93% (7/101) of the patients reported having a known relative with PDS or PG.

Ninety-nine first-degree relatives of 44 of the 101 probands were available for examination. Of these 44 probands, seven (15.91%) had first-degree relatives with PDS. There were seven families with two or more affected individuals. Five had only two affected individuals (three with an affected father and son, one with an affected father and daughter and one with two affected brothers). Two probands had more than one first-degree relative with PDS (Figures 1&2).

In total, 10 (10.10%) of 99 first-degree relatives were diagnosed with PDS (1 with PDS, 2 with PDS with OHT and 7 with PG). All of the families are Caucasian. All of the family members were examined in the clinic by a single examiner (AT). However during the study, a proband (Family 2 in Figure 1) belonging to a large PDS family, previously examined by our group presented to the clinic and we therefore included five of those first-degree relatives examined earlier for the purpose of this study.

In the affected family members Krukenberg spindles were found in 14 of 20 eyes (70.00%). Mid-peripheral iris transillumination defects were detected in 13 of 20 eyes (65.00%). Moderate to heavy trabecular meshwork (2+) pigmentation was present in 16 of 20 eyes (80.00%).

Table 2 compares the clinical features between affected and unaffected relatives. Eleven of 20 eyes (55%) from family members with PDS had myopia of -1D or worse. Only one patient had significant iris concavity. It is interesting that the unaffected relatives were, on average, more myopic than the affected relatives and had slightly longer axial eye lengths although this was not statistically significant ($p=0.08$).

Among the first-degree relatives there were four individuals with primary open angle glaucoma (POAG), two with OHT and one with normal tension glaucoma (NTG).

Discussion

Since the initial suggestion of a genetic etiology underlying familial Krukenberg spindles^{23,24} and reports of familial pedigrees with PDS/PG,^{19,25–27} PG has been largely considered to be a disorder with autosomal dominant transmission.

Scheie and Cameron studied 407 patients with PDS and/or PG and reported a positive family history of glaucoma in 4% of the patients with PDS, and in 16% of the patients with PG.¹⁶ They concluded that the “low incidence suggests a multifactorial inheritance pattern or trait of variable penetrance and expressivity.”

Becker et al.²⁸ suggested an association between HLA-B13 and Bw17 and PDS, and an increased prevalence of HLA-B12 when PG is present but these findings have not been replicated by others.^{29,30} Krukenberg spindles have been described in three separate mother and daughter pairs^{23,24,31} and in twins.²⁶ The inheritance pattern of PDS and PG has been explored in various studies.^{32,33} Roth et al. described eight families with PDS, concluding that it was inherited in an autosomal dominant fashion.²⁶ Mandelkorn et al. described four families with PDS and observed this syndrome to be transmitted in an autosomal dominant pattern from parent to offspring in three of the four families, independent of refractive error, iris color and gender.¹⁹ Several routes of inheritance (father-to-son, father-to-daughter, mother-to-son, mother-to-daughter) were observed. Sugar suggested that PG was inherited in an “autosomal dominant multifactorial” manner.³³ Bovell et al. identified and phenotypically characterized six North American families with autosomal dominant PDS.³⁴ However, an autosomal recessive pattern of inheritance was suggested by Stankovic in his study of one family with PG in four generations.²⁷

A genetic locus for PDS has been mapped to chromosome 7q35-q36 in Caucasians with autosomal dominant PDS and PG.³⁵ However, this linkage has not been replicated. In 2018 Lahola-Chomiak and colleagues reported that non-synonymous sequence variations in the premelanosome protein (PMEL) gene were found in two PDS/PG families.³⁶ Seven additional non-synonymous variants were found in targeted screening of 394 PDS/PG patients from three cohorts.³⁶

Linnér suggested an association between PG and myopia.³⁷ The association between PG and myopia was also explored by Bovell et al.,³⁴ Stankovic et al.²⁷ and Campbell et al.³⁸ Moreover, myopia was also prevalent in the affected subjects in the chromosome 7q families reported by Anderson et al.³⁵

We identified seven pedigrees with PDS. In these pedigrees, transmission from parent to child was observed in six of seven pedigrees. Specifically, transmission of PDS was noted from father-to-daughter (1 family), father-to-son (3 families), mother-to-son (2 families), and mother-to-daughters (1 family). These transmission patterns exclude X-linked and mitochondrial inheritance in at least some cases of familial PDS. Overall, the frequent vertical transmission of disease in these pedigrees suggests that some cases of PDS may have an autosomal dominant mode of inheritance. However, none of the pedigrees demonstrated transmission of PDS through three generations, which is typically required as strong evidence for autosomal dominant inheritance. Autosomal recessive or pseudo-dominance, cannot be ruled out.

The risk of a first-degree family member developing glaucoma in our study was 10.10%. This risk for our predominantly-Caucasian Iowa population may not be the same in all other populations. This may overestimate the risk because one of the probands was a member of a previously identified PDS/PG family. While this risk is lower than some prior reports,¹⁹ it is still higher than the general population. A slit lamp examination-based screening in a population undergoing glaucoma screening found the prevalence to be 2.45%.³⁹ We may have found a higher prevalence, not only because we were examining PDS/PG relatives instead of the general population, but also because we used infrared videography to look for iris trans-illumination and gonioscopy to make the diagnosis.²¹ If we relied on slit lamp examination for Krukenberg only we would have found a prevalence of 7.07% in these relatives. Therefore, using only slit lamp examination for Krukenberg spindles, these PDS/PG relatives were only at 2.89 times higher risk of being diagnosed than what has been reported in the general population.³⁹

It is possible that we missed some cases of PDS/PG because some relatives were too young to develop the disease. To decrease the likelihood of this we limited our evaluation of first-degree relatives to individuals over age 18. The mean age of the examined relatives was 54.30 ± 18.76 years, and the median age was 53 years. It is also possible that some relatives were so old that they may have “burned-out” and lost signs of PDS. There were four relatives with POAG, two with OHT and one with NTG. The use of infrared iris transillumination and gonioscopy (looking for angle pigmentation and Scheie stripes) would make it unlikely, but not impossible, that subtle PDS would have been missed.

This is the largest study on PDS and PG subjects with a complete office-based ophthalmic examination including infrared videography. The gender predilection in our study reveals a 2:1 prevalence of males-to-females with PG, which correlates well with previous reports.^{3,32,40}

In this study population, there was a predominance of myopic (89.68 %) eyes. These figures are consistent with others who found a strong correlation between myopia and PDS.

Krukenberg had noted in his original report in 1899 that all three of the PDS patients he described were myopic.⁴¹ Since then, the association of myopia with PDS and PG has been explored in various studies, that have found a prevalence of myopia ranging as low as 6.6% to as high as 78.2% among PDS patients.^{2,4,16,19,42,43} Mandelkorn et al. found a predominance of myopia (16/23) in their PDS population.¹⁹ Stankovic felt that myopia may be considered as a part of PDS/PG disease spectrum and a polygenic inheritance could account for this spectrum.²⁷ Myopic individuals have been shown to have a positive pressure response to topical steroids, even in the absence of any evidence of glaucoma.⁴⁴ This was substantiated by Farrar et al., who felt that refractive error has prognostic significance in patients with PDS and PG.¹⁸ They found that PG patients had a more myopic mean refractive error (OD -3.53D, OS -3.65D), when compared to PDS patients (OD -1.91D, OS -1.88D), thus concluding that myopia was one of the independent risk factors for PDS and PG. In our study, PG patients were found to have longer axial eye lengths, figures being consistent with earlier observation by Lord et al., who studied the keratometry and axial eye length in PDS and PG patients and reported a mean of 25.98±2.00 mm.⁴⁵ The fact that most did not demonstrate iris concavity on gonioscopy was not surprising because many of these patients were older and 76 of 202 eyes were pseudophakic.

In conclusion, we found that most of our cases of PDS and PG are sporadic. The risk to most family member is lower than previously reported. However, there are a few families with an apparent autosomal dominant inheritance pattern.

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Highlights

- The risk to first-degree relatives of patients with pigment dispersion syndrome is about 10%.
- The risk is substantially lower than previously reported.
- The inheritance, when present, appears to be autosomal dominant.
- PDS/PG relatives were only at about 3 times more risk than the general population.

Figure 1.
Pedigree of family 1, with three affected members (filled symbols). Arrow indicates proband.

Figure 2.
Pedigree of family 2, with four affected members (filled symbols). Arrow indicates proband.

Table 1.

Features of Probands with Pigment Dispersion Syndrome and Pigmentary Glaucoma

Feature	Number/eyes	Percent
Krukenberg spindle	159/201	79.10
Iris TIDs	151/198	76.26
TM pigmentation	195/202	96.53
Grade 2	62/202	30.69
Grade 3	72/202	35.64
Grade 4	61/202	30.20
Iris contour	157/202	77.72
Flat	30/202	14.85
Concave	9/202	4.46
Convex	6/202	2.97
Eyes on pilocarpine		

TID = transillumination defect

TM = trabecular meshwork

Table 2.

Clinical features of relatives of patients with Pigment Dispersion Syndrome and Pigmentary Glaucoma

Feature	Affected (n=10)	Unaffected (n=89)
Male: Female ratio	1.5:1 (6:4)	0.4:1 (28:62)
Refraction (Diopters)	-1.42 $\pm$ 1.55	-2.00 $\pm$ 3.05
OD Mean	-1.11 $\pm$ 1.66	-2.35 $\pm$ 3.13
OS Mean		
IOP (mmHg)	24.39 $\pm$ 7.64	19.83 $\pm$ 5.85
OD Mean	24.0 $\pm$ 18.06	19.72 $\pm$ 5.52
OS Mean		
AEL (mm)	24.17 $\pm$ 0.90	24.70 $\pm$ 1.92
OD Mean	24.09 $\pm$ 1.01	24.68 $\pm$ 1.64
OS Mean		

IOP = intraocular pressure

AEL = axial eye length