Observational Study

Changes of trabecular meshwork pigmentation in patients with pigment dispersion syndrome
A 15-year study

Rongyao Zhou, MD, Qi Tang, MD, Liping Pu, MD, Guoping Qing, MD, PhD∗

Abstract
To report the changes of trabecular meshwork (TM) pigmentation and clinical outcomes of patients with pigment dispersion syndrome (PDS) after resolution of reverse pupillary block.

Twenty one eyes of 11 PDS patients were followed up periodically for 15 years after resolution of reverse pupillary block with either Nd: YAG laser peripheral iridotomy (LPI) or trabeculectomy. Visual acuity (VA), best-corrected visual acuity (BCVA), slit lamp examination, intraocular pressure (IOP), Humphrey visual field analysis (VFA), gonioscopy and stereoscopic funduscopy were performed on admission and every 6 months postoperatively. TM pigmentation was quantitatively evaluated and graded every 5 years after the treatment, in which the circumference of anterior chamber angle was divided into 4 quadrants: superior, inferior, nasal and temporal. Postoperative IOP, VA, BCVA, VFA, TM pigmentation and adjunctive anti-glaucoma medications were main outcome measurements and compared with baseline.

Eleven patients (9 males, 2 females) were identified as PDS according to the diagnostic criteria, with average age of 38.25 ± 6.93 years (range, 31–55 years) at initial diagnosis. The mean IOP level was 33.1 ± 9.8 mmHg (range, 22–56 mmHg) at diagnosis. Ten PDS eyes received LPI, and the other eleven eyes underwent uneventful trabeculectomy. The median TM pigmentation score of the 21 PDS eyes was 16 (interquartile range [IQR], 15–16) on admission, which changed to 14 (IQR, 13–15), 13 (IQR, 12–14), 12 (IQR, 10.5–12) at 5-, 10-, 15-year follow-up visits respectively. The decrease rate of TM pigmentation was 37% in inferior quadrant, while in nasal, temporal, and superior quadrant the reduction rate was 28%, 23%, and 18%, respectively, at the last follow-up visit. Majority of these enrolled eyes (19/21) had stable VA and BCVA with average endpoint IOP of 15.1 ± 3.4 mmHg.

TM pigmentation in PDS patients attenuates with time after reverse pupillary block was resolved, in which the inferior quadrant seems faster than the other quadrants.

Abbreviations: AC = anterior chamber, BCVA = best-corrected visual acuity, IOP = intraocular pressure, IPE = iris pigment epithelium, IQR = interquartile range, LPI = laser peripheral iridotomy, PDS = pigment dispersion syndrome, PG = pigmentary glaucoma, TM = trabecular meshwork, VA = visual acuity, VFA = Humphrey visual field analysis.

Keywords: laser peripheral iridotomy, pigment dispersion syndrome, reverse pupillary block

1. Introduction

Pigment dispersion syndrome (PDS) is an ocular disorder characterized by melanin pigment granule liberation from the iris pigment epithelium (IPE) due to mechanical disruption between the IPE and lens zonule and/or ciliary processes.[1–3] The released pigment granules are carried by aqueous convection currents and deposit on anterior segment structures including corneal endothelium, iris surface, trabecular meshwork (TM), lens surfaces and zonules. Accumulation of pigment in the TM may lead to increased resistance of aqueous humor outflow which will result in the development of pigmentary glaucoma (PG).[4–6] In one study, the greatest risk factor for predicting conversion from PDS to PG was found to be IOP at the initial examination.[7] The cumulative probability for developing PG over a 15-year period was 46% in eyes with an initial IOP of 21 mmHg or more, compared with only 2% in eyes with an IOP of less than 21 mmHg.

Reverse pupillary block and abnormal posterior iris bowing have been postulated to be the cause of pigment granule dispersion and pathogenesis of PDS. In 1979, Campbell proposed that the pathogenesis of the condition involved mechanical rubbing of the posterior iris against packets of lens zonules during physiologic pupillary movement.[8] Based on this theory, the
cause-oriented management of PDS should be first to eliminate reverse pupillary block and mechanical rubbing between the zonule packets and IPE layer.\textsuperscript{[9,10]} Furthermore, to lower the elevated IOP and to prevent development or progression of glaucoma. In 1992, Karickhoff suggested that laser peripheral iridotomy (LPI) may be a potential treatment for PG.\textsuperscript{[11]} He postulated that LPI may relieve the posterior bowing of the peripheral iris by equalizing the pressure in the anterior and posterior chambers. This would eliminate contact between the iris pigment epithelium and the lens zonules, thereby arresting pigment dispersion and progression of PG. LPI is always utilized to resolve the reverse pupillary block in PDS eyes with or without ocular hypertension.\textsuperscript{[12]} Trabeculectomy is frequently employed in severe PDS cases with highly elevated IOP especially when secondary PG is complicated. In both LPI and trabeculectomy, the reverse pupillary block can be eliminated and the iris contour becomes flattened. Thus, the pigment showering may be stopped completely.

Preliminary success of eliminating reverse pupillary block has been reported by both Karickhoff and by Campbell and Schertzer.\textsuperscript{[13,14]} Later, Gandolfi, and Vecchi showed that an Nd: YAG LPI reduced the incidence of ocular hypertension in PDS in a randomized control trial of 21 patients.\textsuperscript{[15]} In this study, we have followed up 11 PDS patients for 15 years since they had consented to take part in a prospective interventional study of PDS in Beijing Tongren Eye Center, Beijing.

2. Materials and methods

Twenty one eyes of 11 Chinese (9 males, 2 females) participants in this study identified as PDS and received LPI or trabeculectomy including iridectomy from January to December of 2005 were included in this study. The diagnostic criteria for PDS included at least 2 of the following 3 signs: homogeneous moderate to heavy TM pigmentation (≥Scheie II), lenticular/zonular pigment granule dusting, and corneal endothelial pigmentation in a Krukenberg spindle pattern.\textsuperscript{[3,16,17]} PDS eyes with 2 or more of the following signs were diagnosed with PG: initial IOP > 21 mmHg, glaucomatous optic nerve damage (increased cupping or glaucomatous disk appearance), or visual field defect. Exclusion criteria included a history of uveitis, trauma, previous ocular surgery or anterior segment laser treatment, or any evidence of exfoliation material.

All selected participants received detailed ophthalmic examinations before the treatment: visual acuity (VA), best corrected visual acuity (BCVA), IOP measurement, slit lamp examination, gonioscopy, funduscopic examination, ultrasound biomicroscopic, and Humphrey SITA standard 30 to 2 visual field analysis (VFA). Systemic and ocular medical histories were also recorded.

To evaluate the TM pigmentation, the circumference of the anterior chamber (AC) angle was divided into 4 sections: superior, inferior, nasal, and temporal. Each was scored from 0 to 4 based on the Scheie’s TM pigmentation classification system.\textsuperscript{[18]} The TM pigmentation score of each particular PDS eye was the sum up of 4 quadrants. The rate of pigmentation reduction in each quadrant was calculated by the formula: the rate of pigmentation reduction = (initial TM pigmentation−TM pigmentation on latest visit)/ initial TM pigmentation. In order to avoid inter-physician bias, slit lamp examination, funduscopic evaluation of the optic disk, gonioscopy and TM pigmentation evaluation were performed by the same doctor (QGP), which were repeated every 5 years on follow-up visits.

Statistical analyzes were performed with SPSS 20.0 statistics (IBM SPSS Statistics for Windows, NY, USA). Continuous variables were expressed as mean ± standard deviation if they were verified to comply with the normal distribution. On the other hand, if they did not comply with the normal distribution, the median and interquartile range would be used to represent them. Mean IOPs on follow-up visits were compared with baseline using the paired sample t-test. TM pigmentation scores were compared with baseline using the Friedman test and Wilcoxon test. P values < .05 were considered as statistically significant.

We certify that all applicable institutional and governmental regulations concerning the ethical use of human subjects were followed during this study. The research also followed the tenets of the Declaration of Helsinki. Informed consents were obtained from each participant after explanation of the nature of the study, which had been approved by the Institutional Review Board of Beijing Tongren Hospital, Capital Medical University.

3. Results

Eleven consecutive PDS patients (9 males, 2 females) completed this study, with average age of 38.25 ± 6.93 years (range, 31–55 years) at the time of diagnosis. Majority of the patients (10/11) were identified before the fourth decade. The average age of the male and female subjects was 38.6 ± 7.52 years (range, 31–55 years) and 36.5 ± 3.54 years (range, 34–39 years), respectively.

Most (10/11) patients had myopia of −0.5D or greater, with a mean refractive error of −6.60 ± −6.07 (range, −24.75 to −0.75) spherical equivalent diopters. The mean IOP at initial diagnosis was 33.1 ± 9.8 mmHg (range, 22–56 mmHg). The median of VA, BCVA and anti-glaucoma medications were 0.05 (interquartile range [IQR], 0.02–0.2), 1.0 (IQR, 0.3–1.2), and 1.5 (IQR, 0.25–2), respectively. Ten of the 11 patients had bilateral PDS, but the extent of optic nerve damage and visual field defect was asymmetrical among the participants in this study (Table 1).

A total of 21 eyes of these patients were identified and included in this study, among which 10 eyes were identified as PDS, the...
other 11 eyes were diagnosed as PG according to the diagnostic criteria. Most of the patients were affected bilaterally except 1 eye from one of the patients, which had mild TM pigmentation but neither were Krukenberg spindle nor lenticular/zonular pigmentation. The ten PDS eyes underwent LPI after enrollment. Eleven of the PG eyes received trabeculectomy including iridectomy. All enrolled patients completed the research protocol. Ultrasound biomicroscopic showed marked posterior bowing of the

Figure 1. Ultrasound biomicroscopic view of the iris before and after operation. (A) Marked posterior bowing of the iris and increased contact between the iris pigment epithelium and the zonules and anterior surface of the lens are visible before operation. (B) After the operation the iris contour became flattened.
midperipheral iris, and a large area of contact between the IPE and the lens zonules or anterior surface of the lens. After the operation, the iris contour became flattened. (Fig. 1). Reverse pupil block was reserved in all patients. Heavy homogeneous TM pigmentation was seen in all PDS eyes (Fig. 2), which manifested as a “mascara line” on gonioscopy.

The median TM pigmentation score of the 21 PDS eyes at the time of diagnosis was 16 (interquartile range [IQR], 15–16), which changed to 14 (IQR, 13–15), 13 (IQR, 12–14), 12 (IQR, 10.5–12) at 5-, 10-, 15-year follow-up visits respectively (Fig. 3). Notably, 8 of the PDS eyes which had received LPI as treatment had increased inferior TM pigmentation while the other eyes had decreased extent of pigmentation at the 5-year follow-up visit. Especially, the rate of pigmentation reduction in inferior quadrant was 37%, while that in nasal, temporal, and superior quadrant was 28%, 23%, and 18%, respectively, in 15 years. A decline trend of TM pigmentation was noticed in all PDS eyes since enrollment (Fig. 4). The change was statistically significant when compared to baseline. \( P = .001, < .001, < .001, \) respectively.

On the last follow-up visit fifteen years after treatment, all enrolled eyes had satisfactory IOP control. The mean IOP of these study eyes was 15.1 ± 3.4 mmHg (range, 8–20 mmHg), which was statistically lower than baseline \( (P < .001) \) (Table 2). The median of anti-glaucoma medications was 0 (IQR, 0–1).

Majority of these enrolled eyes (19/21) had stable VA and BCVA. The median of VA and BCVA were 0.1 (IQR, 0.04–0.2) and 1.0 (IQR, 0.6–1.2), respectively. Nevertheless, 3 of subjects had worse VA and BCVA, and lost 2 lines or more of letters on Snellen chart due to cataract formation. Visual field in the majority of eyes (19/21) were unchanged when compared with the baseline. Enlargement of scotoma in VFA was confirmed in 2 PG eyes.

4. Discussion

In this study, 21 PDS eyes received trabeculectomy or LPI as main treatment, and were followed up regularly for 15 years. The results have demonstrated that eliminating reverse pupil block had satisfactory IOP control, visual function was well preserved after 15 years of surgery in PDS eyes and TM pigmentation attenuated with time.

Irido-zonular rubbing has been postulated to be the cause of pigment dispersion in PDS. As causal treatment, reverse pupillary block should be first eliminated to prevent further dispersion of the pigment. There were some controversies on recommending LPI on Caucasian patients with PDS for its treatment benefits. Ophthalmologists who do not prefer LPI believe that the disease has a self-restrictive characteristic as well as burnout phase in the fourth decade of the patient.\(^{[18]}\) On the other hand, the conversion rate from PDS to PG is relatively low in Caucasian. Nevertheless, the other researchers think LPI may have a positive treatment effect on PDS which may halt the disease from progression.

![Figure 2. TM pigmentation attenuated after trabeculectomy in a PG eye. (A) Heavy homogeneous TM pigmentation at enrollment. (B) TM pigmentation 15 years later.](image)

![Figure 3. Evolution of TM pigmentation during the study course. \( P < .05. \)](image)

![Figure 4. A decline trend of TM pigmentation in 15 years. In particular, the rate of pigmentation reduction is more significant in inferior quadrant than in the other quadrants.](image)
pigmented races, however, PDS has a high conversion rate to PG and may cause severe visual disability in the 30-second. Previous studies have shown that in Chinese patients with PDS, 94% of the PDS patients had increased IOP of ≥21 mmHg and 83% of them have already converted to PG at their initial diagnosis. Pathological studies revealed that the IPE layer in iris of Caucasian is thin with quite limited pigment melanin in the IPE and iris stroma. The pigment can be exhausted due to years of irido-zonular friction and reach out to a “burnout phase” when no more pigment could be liberated from the IPE layer, IOP stops from progression even with continuous reverse pupillary block and irido-zonular contact. However, in pigmented races, the IPE layer is much thicker with very heavy pigment volume in the iris stroma and IPE layer. Pigment showering can last for a long time if the reverse pupillary block cannot be eliminated. Large amount of pigment melanin deposits on the TM surface and enter the lumen of the meshwork, resulting in rapid elevation of IOP and serious glaucomatous neuropathy. PDS in pigmented races is potentially blinding which may happen at the third decades. It is critical to eliminate the reverse pupillary block in the management of PDS in pigmented races to preserve residual visual acuity.

Currently, there is quite limited procedure for ophthalmologists to clear pigment granules on the surface or in the lumen of the TM. As the causes of elevated IOP and glaucomatous neuropathy, TM pigmentation caused high interest among ophthalmologists. The evolution of TM pigmentation after abrupt cessation of irido-zonular contact is still not clear. The purpose of this study is to characterize the changes of TM pigmentation posterior to elimination of reverse pupillary block, which may help understand the pathogenesis of the disease and to improve clinical management and outcomes. The results of this 15-year study have shown that hyper-TM pigmentation decreased over time, which also had been reported in previous reports on gross observation under gonioscopy. In this study, we used the Scheie’s grading system to quantify the TM pigmentation, which allows better quantification of TM pigmentation and precise comparison between baseline and follow-up visits. All 4 quadrants of the circumference of AC were compared between initial level and posttreatment levels. An identical decline trend in TM pigmentation around the circumference of the AC was revealed in all subjects.

The limitations of this study were those to be expected of a small sample and uncontrolled study. Due to the low prevalence of PDS in Chinese, it is not easy to enroll enough patients for both investigation and control. In most of the patients, we enrolled both eyes for study in that the IOP will not be influenced by the contralateral eye. The follow-up interval for the patients was 5 years for TM pigmentation evaluation and comparison. TM pigment change seems to be a slow process.

In summary, after 15 years of observation, we have discovered that eliminating reverse pupil block in PDS eyes has a beneficial effect on IOP control, visual function preservation, and TM pigmentation attenuation. Such findings provide new insight into the pathogenesis and characteristic of PDS.

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### Table 2

Comparison of IOP in PDS patients at diagnosis and the last visit.

| Group | Eyes | IOP (mmHg) |
|-------|------|------------|
| Initial | 21 | 33.1 ± 9.8 |
| Last visit | 21 | 15.1 ± 3.4 |
| t values | | 6.98 |
| P values | | <.001 |

**IOP** = intraocular pressure, **PDS** = pigment dispersion syndrome.
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