TITLE: A Case of Bilateral Pigment Dispersion Syndrome Following Many Years of Uninterrupted Treatment with Atropine 1% for Bilateral Congenital Cataracts

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Abstract

PURPOSE: Describe an unusual case of bilateral pigment dispersion syndrome (PDS) following years of uninterrupted treatment with Atropine 1% for bilateral congenital cataracts, speculate on potential mechanisms leading to this condition.

DESIGN: Case report.

CASE: A 45-year-old Caucasian patient on long term treatment with Atropine 1% ointment since his infancy for bilateral congenital cataracts developed pigmentary dispersion syndrome (PDS) with secondary ocular hypertension (OHT).

RESULTS: The patient showed all the hallmarks of PDS with secondary OHT. An anterior segment Swept- Source OCT was obtained to review the iris profile. The patient showed good pressure response to topical prostaglandin therapy.

CONCLUSIONS: This is the second case report of PDS in a patient with chronic use of topical Atropine. The proposed mechanisms for pigment dispersion are discussed and the possibility raised of dispersion being a potential side effect of the drug.

KEYWORDS: Pigmentary Dispersion Syndrome, PDS, Atropine, Ocular Hypertension, Congenital Cataracts.

CASE REPORT

A 45-year-old Caucasian gentleman was referred by his optician to the Glaucoma Clinic for raised intraocular pressure and disc cup asymmetry. He had congenital cataract treated uninterruptedly since early childhood with Atropine 1% ointment once every 5 days and esotropia with left amblyopia. He also reported a family history of congenital cataract. On examination his best corrected visual acuities were 6/12 in the right and 2/60 in the left, amblyopic eye. Both eyes showed a significant degree of compound myopic astigmatism (right eye: sphere -4.00/ -5.00x110°; left eye: sphere -3.00/ -3.00x60°). Both pupils were pharmacologically mid-dilated with blue irides and lamellar cataracts in both eyes. He showed several hallmark signs of pigment dispersion syndrome with marked Krukenberg spindles and360 degree spoke-like transillumination defects of the iris. On gonioscopy the angles were wide open with heavy 360 degree continuous pigmentation on the trabecular meshwork; no peripheral anterior synechiae (PAS) or central posterior synechiae (CPS) were observed and the iris profile was noted to be concave. His corneal thickness was 580 microns in the right and 598 microns in the left eye and the intraocular pressures (IOP) were 25 mmHg in the right and 28 mmHg in the left eye. Fundus examination demonstrated large optic discs, measuring 2.0 mm in vertical diameter, and cup-to-disc asymmetry, the right eye having a 0.6 cup and left eye a 0.4 cup with no visible nerve fibre layer defect. Visual field analysis was bilaterally full. Anterior segment photographs and Swept-Source anterior segment OCT (SS AS-OCT) scans with three-dimensional reconstruction are shown in Fig. 1. His diagnosis was bilateral congenital cataracts and pigment dispersion syndrome (PDS) with secondary ocular hypertension. All day phasing showed the right IOP to range from 21 to 24 mmHg, with the highest measurement recorded at 9:30, and the left IOP from 22 to 25 mmHg, with highest reading at 13:00. After counselling the patient commenced treatment with Latanoprost 0.005% 1 drop at night to both eyes. Eight weeks later, the IOP was right 18 mmHg and left 17 mmHg. He was advised to carry on his topical medication and to come back in the Clinic in 6 months time for active monitoring.

DISCUSSION

The original description of a pigment spindle at the level of the endothelium dates back to 1899 in a manuscript by Krukenberg.[1] Pigmentary glaucoma was first described as a rare entity by Sugar and Barbour in 1949.[2] Prior to their manuscript both Levinsohn and Koeppe investigated the association between pigment release inside the eye and increased ocular hypertension or glaucoma.[3,4] Patients with PDS are more frequently young men with mild myopia and a posterior bowing iris profile. The rubbing between the posterior iris surface and the zonular apparatus, facilitated by a reverse papillary block mechanism, is the most accredited theory to account for the release and accumulation of iris pigment in these eyes.[5,6]

In 1981 Mühlenweg and Naumann published a case report of a 59-year-old man with congenital cataracta pulverulenta centralis who had been kept on pharmacological mydriasis for 24 years with atropine 1%, scopolamine 0.25% or tyramine hydrochloride 2.5% every day or on alternate days to improve his vision.[7] At the time of their observation the patient presented with signs typical of PDS; pigment keratic precipitates, highly pigmented trabecular meshwork, pigment deposits on the anterior iris surface and on the anterior hyaloid-capsular ligament (Egger's line). They report bilateral increased intraocular pressure without clinical sign of glaucomatous optic neuropathy. Interestingly the patient described had iris transillumination defects next to the pupillary ruff instead of the mid-iris periphery as more commonly observed in PDS patients. They interpreted that feature as the result of an excessive excursion of the pharmacologically dilated pupil on the anterior lenticular capsule causing the release of melanin pigment granules. They concluded that the patient had developed a rare form of secondary PDS, previously never described. To them the main difference from the primary form was the location of the iris chafing and therefore the position of the transillumination defects at the level of the pupillary margin, similarly to what can be sometimes found in pseudoexfolative syndrome and in senile pupillary atrophy.

The patient we describe shares several signs with the patient reported by Mühlenweg and Naumann.[7] Both cases had pigment dispersion syndrome with ocular hypertension and no evidence of glaucomatous optic neuropathy following many years of uninterrupted Atropine 1% instillation for congenital bilateral cataracts. Both cases presented with evidence of a Krukenberg spindle, increased diffuse trabecular meshwork pigmentation and iris transillumination defects. The main difference between our patient and the case reported by Mühlenweg and Naumann appears to be in the location of the iris transillumination defects. We observed them in the characteristic spoke pattern consistent with PDS; in contrast, Mühlenweg and Naumann noticed iris transillumination defects only around the pupillary ruff.

The iris profile of our patient is concave, as shown in the SS AS-OCT 3D reconstruction (Fig. 1). Although this is a common trait of PDS patients, we feel this per se may not entirely explain the clinical picture. Our patient is a 45 year-old gentleman who has been on uninterrupted treatment with Atropine 1% ointment; hence he has been for most of his life in a permanent mid-dilated pupil state, unable to accommodate and with posteriorly displaced zonular ligaments. The long standing pharmacological cyclopegia is meant to keep the ciliary muscle in a relaxed state, therefore promoting a stretching of the zonular ligaments and a posterior movement of the zonulo-lenticular complex. All these conditions should have "protected" him from developing a PDS according to the most accredited pathogenetic theory (reverse pupillary block).

It is relatively common to find myopic eyes with concave iris and yet without any of the hallmark signs of PDS. In an AS-OCT study investigating the iris configuration, Cheung et al[8] highlighted that about 13% of the 46 healthy Chinese patients with open angle had a concave iris profile in an unaccommodated state. This configuration was maintained regardless of the room illumination (from bright to dim light), although the concavity was less pronounced in the darkness. This was probably due to a reduction in the posterior chamber volume and a concomitant increase in the

posterior chamber pressure that led to a less concave profile. The subject with iris concavity were younger and had longer axial length compared to the others.

Schuster et al[9] reported that 26% of the 402 myopic eyes and 5% of the 93 emmetropic eyes investigated by means of Spectral Domain AS-OCT had a concave iris profile. Although they didn't screen for PDS signs, it is unlikely that all the subjects with concave iris had PDS. They found that concave iris configuration was associated with young age, male gender and myopia. Shah et al[10] found in a cohort of 96 school boys that 24% exhibited an iris concave profile when analysed by means of Time Domain AS-OCT. Again, this percentage seems to exceed the previously reported prevalence of PDS in Caucasians of around 2.5%.[11] Therefore iris concavity alone doesn't appear to lead necessarily to PDS; on the contrary it may be that only a small proportion of the eyes with a posterior bowing iris progresses to PDS when in the presence of other predisposing factors.

On the other hand, Liu et al[12] showed with AS-OCT imaging on 33 eyes of 20 patients with PDS that the posterior bowing iris associated with PDS was reversed after fixation of a target, which led to a planar iris configuration. After accommodation the posterior bowing was restored. This suggests that the iris concavity associated with PDS might be associated with a different mechanism (reverse pupillary block triggered by accommodation and maintained by irido-lenticular contact) compared to that commonly found in healthy young myopic people.

We speculate the long term usage of Atropine 1% may have contributed to the development of PDS in our patient. It is well known that mydriatic agents, such as cyclopentolate and phenylephrine, can cause pigment showers inside the eye, presumably due to a disruption of the pigmented cells of the posterior iris by the contraction of the dilator pupillae.[13,14] It is also been shown that atropine binds to melanin in the iris[15] and is a competitive antagonist for the cholinergic muscarinic M1-M5 receptors in cutaneous melanocytes.[16] These properties might cause, after prolonged exposure to the drug, two consequences: a greater susceptibility of the iris pigment epithelium (IPE) to physical and chemical damage and, provided that iris melanocytes share similar features with skin melanocytes, changes in the pattern and the amount of pigment distribution in the iris.

Some papers have previously described the presence of an abnormal iris IPE and a hyperplastic iris dilator muscle in PDS eyes.[17-19] The authors of those papers hypothesized that a congenital or developmental abnormality of the IPE was the main cause of PDS. The long term use of topical Atropine may have caused a similar predisposition in our patient, inducing changes at the level of the IPE and iris dilator. The IPE might become more fragile and susceptible to damage following chronic exposure to Atropine; at the same time the iris dilator might develop hyperplasia that makes the iris thicker and therefore closer to the zonular complex. The coincidental presence of a concave iris profile and a more anteriorly displaced zonular apparatus might have contributed as well to determine the onset of PDS in our patient. In the latter case, the condition could be regarded as part of an anterior segment dysgenesis case with a broader spectrum of alterations including congenital cataract and irido-zonular abnormalities.

On the other hand a poor compliance to atropine 1% ointment may have also contributed to the development of a primary PDS. However it is unlikely that our patient discontinued the medication for a prolonged time since he had a beneficial impact on his vision from the use of the drug. The patient was reassessed in several different occasions and the pupil was always found to be mid dilated with no visible activity of the pupillary sphincter muscle. It is reasonable to think that the sphincter muscle developed a certain amount of atrophic changes following years of inactivity. Also it is unlikely that, on a once every 5-day regimen of Atropine 1%, the pupil returned to an undilated state before the following instillation. This because the effect of Atropine 1% lasts for up to 2 weeks and it is certainly still considerable at day 4 after instillation.

These findings are of relevance for ophthalmologists considering long-term use of atropine to treat amblyopia or to reduce myopia progression. Even if these pigmentary changes occur in 1% or less of the patients, wide use of atropine in populations could produce a dramatic increase in pigmentary dispersion syndrome and potentially in pigmentary glaucoma. For example, in Taiwan around 50% of the myopic children receive atropine treatment to reduce myopia progression.[20] Hence we would recommend clinicians and policy makers to be cautious until more evidence supports the safe use of a chronic treatment with topical atropine.

To summarise, we describe a patient of a young male who developed PDS following many years of uninterrupted treatment with topical mydriatic agents to treat bilateral congenital cataracts. The mechanism responsible for that condition challenges the traditional theory on pigment dispersion syndrome development.

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FIGURE 1. (Left-hand side, top and bottom): anterior segment photographs clearly showing spoke-like midiris transillumination defects. (Right-hand side, top and bottom): anterior segment Swept-Source OCT scans with 3D reconstruction effectively illustrate the posterior bowing of the iris profile.