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A possible role of ocular wall stretch in offsetting intraocular pressure rise in early primary congenital glaucoma

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ABSTRACT

Aim of the study: To describe cases of primary congenital glaucoma (PCG) in patients who presented with a low intraocular pressure (IOP), which did not show a noticeable change postoperatively or during follow-up despite resolution of other PCG signs.

Material and methods: This is a retrospective clinical study. Records of infants who presented to a congenital glaucoma clinic with IOP readings ≤ 20 mmHg who were operated on by adjusted trabeculotomy were reviewed. Cases which did not demonstrate a change of more than 4 mmHg in their IOP between preoperative values and the mean IOP value of the first postoperative year, despite improvement of other signs of PCG, were further evaluated.

Results: Out of 85 eyes (54 infants) that presented with PCG with an IOP of 20 mmHg or less, 12 eyes (10 patients, age range at surgery: 0.3-22 weeks) exhibited an IOP change ≤ 4 from preoperative to postoperative values and during the follow-up course, despite regression of other PCG signs, including resolution of corneal edema, and optic disc cupping regression,

Conclusions: Due to the immaturity of collagen of the cornea and sclera in young infant eyes, ocular wall stretching seems to deflect IOP rise in some early PCG cases. These eyes respond to the impeded ocular outflow by globe enlargement, and mechanical disc cupping, rather than IOP rise. Releasing this impedance surgically leads to reduction of this stretch in the form of cupping and HCD regression, clearing of corneal cloudiness, but not a noticeable reduction in IOP.

KEY WORDS: congenital glaucoma, trabeculotomy, ocular stretch, cupping reversal.

INTRODUCTION

Cases with primary congenital glaucoma (PCG) typically present with intraocular pressure (IOP) elevation associated with some or all of the following: corneal and globe enlargement, corneal edema, and optic disc cupping. By the early 2000s, the author started to observe active cases of PCG, without a real IOP rise. Recent literature does not require a high IOP to establish the diagnosis of PCG mostly because of the potential anesthetic-induced IOP lowering effect, congruous with the use of most general anesthetic agents, and to count for arrested glaucoma cases [1-3].

Among cases presenting with no significant IOP rise, it was noted that some eyes did not demonstrate a noticeable change or lowering in IOP following surgical intervention, and throughout most of their postoperative course despite improvement in other PCG signs, such as cupping and HCD regression and resolution of corneal cloudiness.

MATERIAL AND METHODS

This is a retrospective interventional case series. Records of 54 PCG infants (85 eyes) who presented between June 2008 and December 2020 to the congenital glaucoma clinic, Research Institute of Ophthalmology, and a private practice with an IOP of ≤ 20 mmHg in one or both eyes on no medications were reviewed. All eyes underwent adjusted trabeculotomy, described by the author in detail elsewhere [4, 5]. Examples of cases which exhibited an IOP mean change ≤ 4 mmHg [3] during the first postoperative year (minimum follow-up period), despite regression of other PCG signs, are presented here. All surgical procedures and examinations were performed by the author.

IOP was measured at office (OPD) (Figure 1) when relaxed measurements were possible or during examination under sevoflurane anesthesia (EUA), when readings were taken soon after induction to get the least possible anesthetic IOP lowering effect [6]. All IOP (mmHg) measurements were

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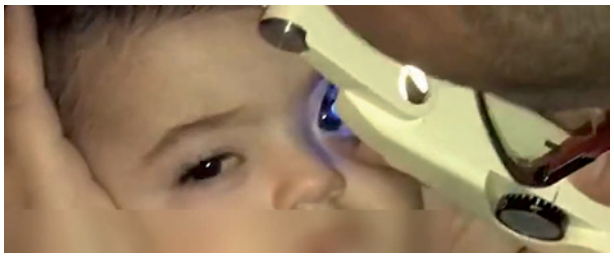

Figure 1. Relaxed office IOP measurement can be possible in some infants as early as 10-months-old

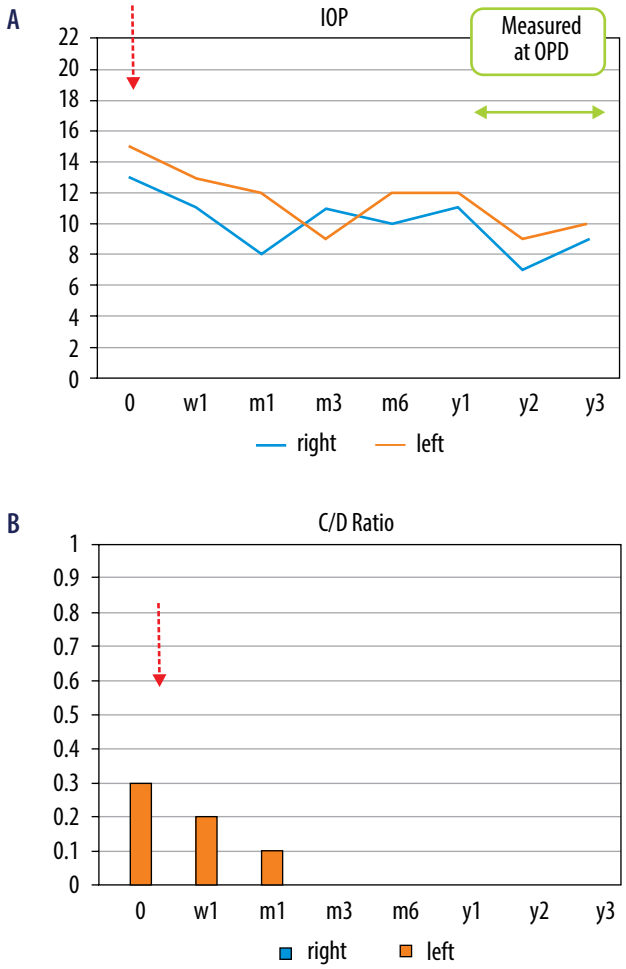

Figure 2. Case 1 IOP (A) and CDR (B) graphs; IOP lines are largely similar in the glaucomatous left (pre- and postoperative) and the healthy right eyes. Following left surgery (arrow), no significant lowering of IOP occurred, while C/D ratio started to regress to null at 3 months. By year 2, relaxed office IOP measurements were possible with little change in values compared to those during EUA

made by a Perkins Mk2 tonometer (Haag-Streit, Koeniz, Switzerland), which was calibrated prior to each use. One drop of oxybuprocaine 0.4% was applied, and lids were gently pulled open avoiding any potential pressure on the globe. At least 5 readings were taken with complete separation from the patient between readings. The mean of the middle 3 readings was used on condition that they did not differ by more than 2 mmHg. If they did, 2 more readings were taken. Cup/disc ratio (CDR) was assessed by indirect ophthalmoscopy, and horizontal corneal diameter (HCD) by caliber with masking of previous readings. CDR was graded 0.0 to 1.0 in 0.05 intervals. A 0.35 reading would imply 0.3-0.4, not exactly 0.35.

Postoperatively, IOP, CDR, corneal cloudiness and diameter were monitored. Cases were followed up at 1 week, 1, 3, 6, 12 months and yearly thereafter. Surgical success required resolution of corneal edema and CDR regression. Additional parameters were HCD reduction, and further lowering of IOP. Examinations and surgical procedures were performed by the author, who has been a dedicated pediatric glaucoma surgeon since 1999. All steps and procedures followed the guidelines of the Helsinki Declaration. The Research Institute of Ophthalmology Ethics Committee had ruled that approval was not required for the study.

RESULTS

Fifty-four infants (85 eyes, age range: 0.3-54 weeks, 28 males, 26 females) showed an IOP of 20 mmHg or less on presentation. Eyes responded to surgery by various degrees of IOP lowering. 12 eyes (10 patients, age range at surgery: 0.3-22 weeks) did not exhibit a noticeable change (> 4 mmHg) postoperatively or during the follow-up course, despite regression of other PCG signs. Their findings are represented in the following 4 cases.

Case report 1

A 3-month-old boy presented with a larger left eye, and conflicting opinions about possible glaucoma (Figure 2). He had undergone EUA twice (3-week interval) with similar findings: right and left IOP: 13, 15, CDR: 0.0, 0.3, HCD: 10.5, 11.5. Both corneas were equally clear. Based on the bigger left eye with its unilateral 0.3 CDR, it was operated on. At month 1, IOP: 8, 12, CDR: 0.0, 0.1, HCD: 10.5, 11.0. Mean left IOP during the first postoperative year: 11.6. Cupping nulled to 0.0 in the left eye within 3 months and remained 0.0 in the right. This remained throughout the follow-up period (3 years). By year 2, the child was amenable to examination at office, IOP being then 7, 9, bilateral 0.0 CDR.

Case report 2

A week-old girl was referred with some corneal cloudiness and photophobia (Figure 3A). EUA showed corneal epithelial edema, right, left IOP: 13, 11; HCD: 12, 12. The optic disc could not be seen. Because of a large (for a newborn), edematous cornea, detailed informed discussion with the parents was made. The decision of bilateral successive surgery was taken, and the right eye was operated on.

EUA a week later showed right, left IOP: 10, 11, persistent corneal cloudiness with the operated eye dubitably slightly clearer (Figure 3B), cupping: 0.3-0.4 bilaterally (seen hazily). With no significant right IOP lowering, nor significant resolution of corneal cloudiness, the surgeon deferred left eye surgery, for reevaluation in subsequent weeks. The mother was so anxious that she kept photographing her child almost daily with her phone, and sending pictures. In the course of the following 10 days, no-

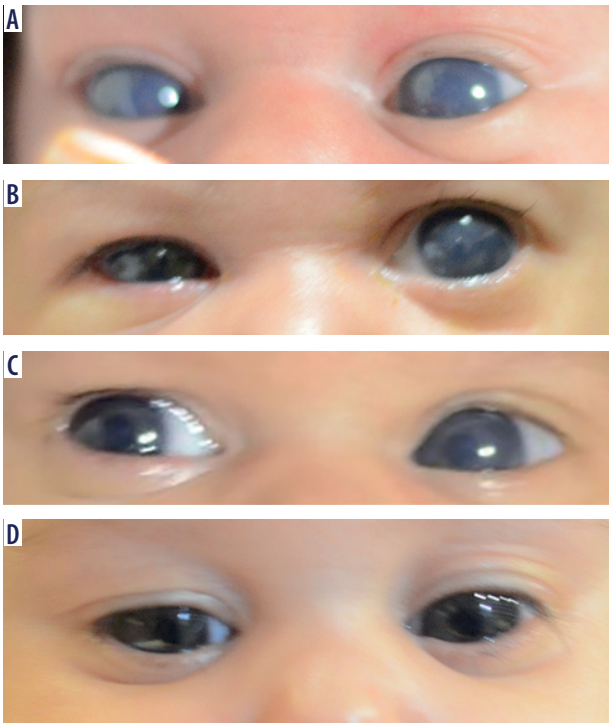

Figure 3. Daylight photos of case 2 from presentation to recovery: A) the presenting symptom of bilateral mild corneal cloudiness at the age of 6 days; B) 1 week after right operation, lids are still puffy, with no noticeable clarification of its corneal cloudiness; C) 2 weeks after right operation, right cornea clearing; D) 2 months after left operation, both corneas crystal clear to the casual observer (fine Haab's striae visible on microscopic examination)

ticeable corneal clarification in the operated eye compared to the unoperated eye was observed (Figure 3C), and the child was called for EUA.

The right cornea was almost clear, while the left remained cloudy. Right and left IOP: 7, 11; Cupping: 0.4, 0.4. With right minor IOP lowering and corneal clearing, the left eye was operated on. Its cornea started to clear postoperatively (Figure 3D). Mean IOP during the first postoperative year: 9.6, 10.3. Throughout an 8-year follow-up period, corneas have remained clear, with 0.1cupping bilaterally, and a plateau IOP of 8-11. By year 3, relaxed IOP measurements could be made in office, with no noticeable differences with previous EUA readings.

Case report 3

A 2-month-old girl presented with megalocorneas and slight left eye cloudiness. Right, left IOP: 11, 14; HCD: 11.5, 12; CDR: 0.15, 0.2. The case was considered highly suspicious of at least left PCG and put under observation. 2 months later, left eye cloudiness and photophobia persisted, with right, left IOP: 10, 11; CDR: 0.0, 0.3 (right cup nulling). Based on large and slightly increased values of parameters in the left eye, with its cloudiness and photophobia, it was operated on. 1 week postoperatively, IOP was 11, 7, with nulling of left disc cupping (Figure 4)

Five months later, the operated left eye parameters remained favorable, while the unoperated right IOP shot to 28,

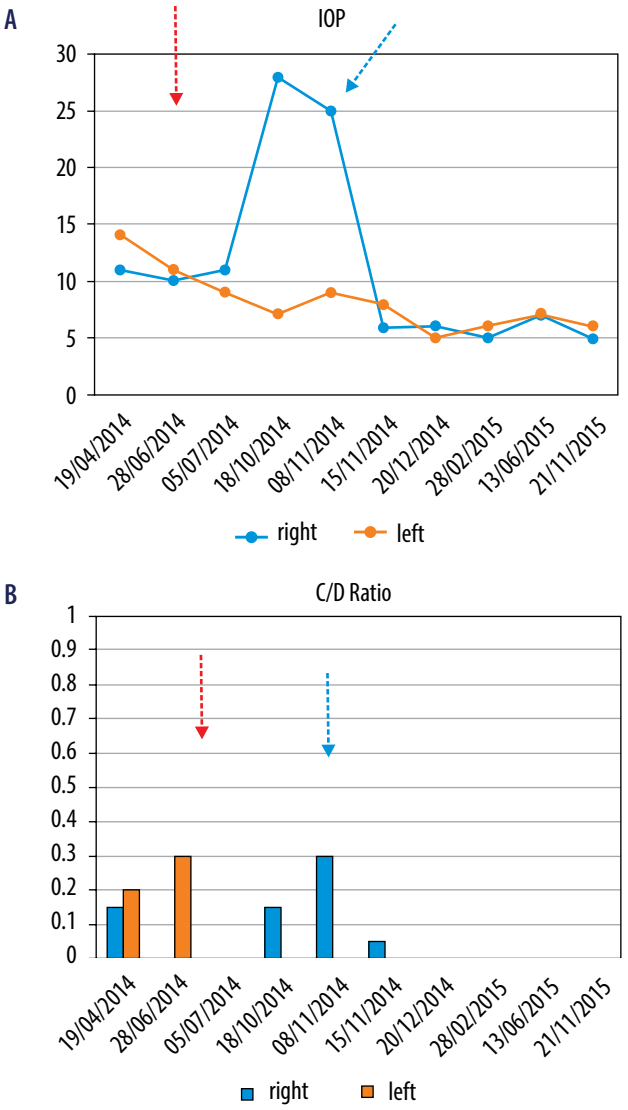

Figure 4. Case 3 IOP (A) and C/D ratio (B) graphs: While the left eye parameters improved and remained favorable following surgery, the originally milder unoperated right eye parameters shot high within few months, and remarkably improved with surgery (arrows point to surgical interference)

and its cup widened again to 0.15. Right HCD, initially less than that of left by 0.5 mm, became 0.5 mm greater than the left. It was scheduled for surgery in 2 months and put under topical timolol-carbonic anhydrase inhibitor drops. On the operation day, its IOP was 25 mmHg, and its cupping widened further to 0.3. Mean IOP during the first postoperative year: 5.8, 7.3. No cupping was observed up to the last visit 19 months after presentation.

Case report 4

A 5-month-old girl presented with a large, tearful left eye. EUA showed right and left IOP: 8, 12, CDR: 0.0, 0.3, HCD: 11, 13 with faint epithelial cloudiness in the left eye, which was operated on. Mean left IOP during the first postoperative year: 10.5. At subsequent visits up to 12 years postoperatively, IOP was almost equal in both eyes at 9-12 mmHg. Left CDR was reduced to 0.1 in the left and remained at 0 in the right.

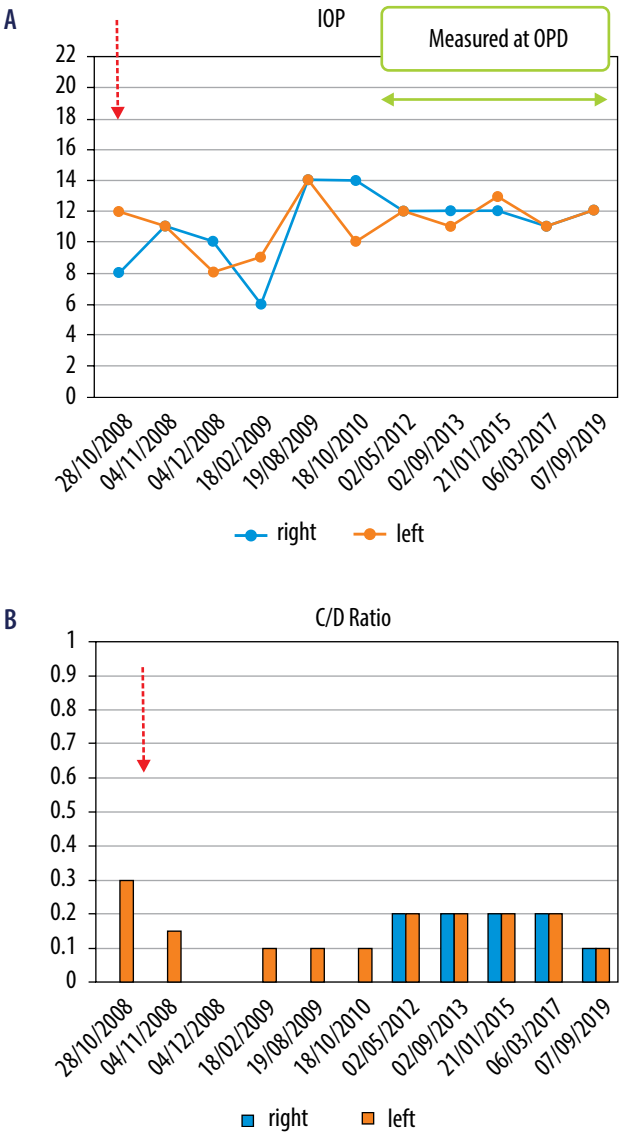

Figure 5. Case 4 IOP (A) and C/D ratio (B) graphs: surgery to the unilaterally affected left eye caused CDR regression within 2 months, with no significant IOP change. By year 4, bilateral (physiological) 0.2 cupping was evident (arrow points to surgical interference)

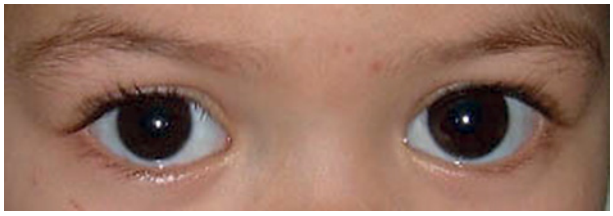

Figure 6. Case 4, Corneal diameter discrepancy remains at year 12

From year 4 onwards, CDR was equal in both eyes at 0.2. The HCD difference between left and right was reduced from 2 to 1.5 mm at week 1, and remained at this difference thence and up to the last visit at 12 years postoperatively (Figures 5, 6).

DISCUSSION

This study documents active PCG cases, with lower IOP readings, which did not show noticeable changes in their IOP postoperatively or during the follow-up despite resolution of other PCG signs. The diagnosis of PCG was established by more than one of several signs: larger for age CDR and HCD or their discrepancy, corneal cloudiness and trabeculodysgenesis. Diagnosis was confirmed further postoperatively by cupping regression, resolution of cloudiness, HCD regression, and the occasional detection of Haab's striae.

Instruments used, whether the patient is awake or asleep, and the anesthetic used are all factors that contribute to the broad range of reported (normal) IOP in children. While some authors assert that the upper limit of normal infant IOP is 21, like that in adults [7], others suggest it is lower [8, 9]. With conflicting reports, textbooks define the pressure of 20 mmHg or more in infants to be (suspicious) for glaucoma [1, 3].

Sevoflurane anesthesia is usually associated with IOP lowering [6, 10]. Anesthetic lowering did not seem to play a significant role in the low IOP readings reported here. Most readings were obtained as early as possible after induction to get the smallest IOP reduction effect. In 3 unilateral cases of this series, represented by cases 1 and 4, IOP was similarly low in the glaucomatous as well as the non-glaucomatous eye, with an asymmetry of less than 2-3 mmHg. IOP measured under the same anesthetic conditions was similarly low both pre- and postoperatively and during the follow-up, but with regression of other diagnostic parameters such as cloudiness, and cupping. If anesthesia induced significant preoperative lowering, it would be expected to cause similar lowering postoperatively, and give extremely low IOP readings, which did not happen. It is notable that on conversion from EUA to the OPD setting usually at the age of 2-3 years, no major change or rise was observed in IOP readings (Figures 2, 5).

The mathematical calculation for Goldmann applanation tonometry is based on a presumed average central corneal thickness (CCT) of 520 μm. Errors in IOP readings can occur when CCT, curvature, or biomechanical properties differ from normal values, with corneal edema underestimating the true IOP [11, 12]. In the cases reported in this study, the cloudiness caused by corneal edema observed in some of these early cases was a rather mild one, which would probably not significantly alter IOP readings. Similarly, with the mild disease described, no cases had corneal scarring that would affect IOP readings.

Trabeculodysgenesis, the main pathogenic factor in PCG [13], impedes aqueous outflow in the infant's eye, which in most cases indeed would causes IOP to rise. In younger infants, however, the immature collagen of the cornea and sclera also responds to increased IOP by stretching and globe enlargement, leading to increased HCD, Descemet's membrane cracks and increased axial length [14], and the scleral canal and lamina cribrosa widen, causing mechanical disc cupping [15, 16]. This resilience of ocular wall structures seems to offset to various degrees the rise in IOP readings. Impedance of

aqueous outflow in the mature eye of an adult with almost no resilience will directly be reflected as IOP rises, while a similar impedance in young infants' eyes would probably cause a lesser IOP rise, because of the associated ocular wall resilience deflecting to various degrees the IOP rise (balloon-like effect).

The relation between wall tension, pressure and the radius of a sphere was described more than 200 years ago by the French astronomer and mathematician Pierre de Laplace (law of Laplace), which defines the relationship between the pressure gradient across a closed elastic membrane sphere and the tension in the membrane [17]. This law is expressed by the equation $Pi\text{-}Po = 2\gamma/r$. Pi and Po are the internal and external pressures at the surface, r the radius of curvature and γ is the tension in the membrane. The internal pressure expands the sphere until it is balanced by the tension in its wall. The equation indicates that the pressure inside a spherical surface is always greater than that outside, but that the pressure increases with increase in wall tension, and decreases with its decrease. It also decreases with the increase in its radius. The resilient young infant eye is in many aspects similar to the described expansible sphere, and the scleral/corneal rigidity can translate into sphere wall tension.

This law of Laplace was previously recognized in the vascular system (albeit with some equation modification for the cylindrical vessels) [18]. Due to their distensibility, veins increase their volume with a slight change in pressure. Pressure inside arteries, with stronger and less distensible walls, is significantly greater than venous pressure.

Eyes presented in this report responded more by expansion of the immature ocular wall, rather than a noticeable IOP rise. Releasing this impedance surgically led to reduction of stretch in the form of cupping and HCD regression, clearing of corneal cloudiness, but not a true reduction in IOP (which was not truly elevated in the first place). This "balloon effect" was invaluable in the early diagnosis, management and follow-up of cases in the absence of a noticeable IOP change, and probably occurs to various extents in most young expansile eyes. Defining the amount of IOP rise vs ocular expansion will probably depend on several factors including degree of trabeculodysgenesis, ocular wall tissue maturity, and age of the infant. Stretching deflects the IOP rise in some early cases of PCG, until a certain balance is reached, following which IOP readings would rise.

The normal optic disc cup in infants is usually 0.0-0.1. Cupping larger than 0.3, especially if bilaterally asymmetric, suggests that the disc is under pressure and probably glaucomatous [19, 20]. Because of the immature collagenous structural framework of the lamina cribrosa, cupping occurs readily with even a brief IOP rise [21], and is primarily caused by posterior bowing of the lamina cribrosa, and widening of the scleral canal [16]. This accounts for cupping reversibility, reported as a favorable sign with PCG control [22]. Similarly, the normal neonatal HCD is 9.8-10.5 mm [23, 24]. An HCD of 11 or more warrants full EUA to exclude glaucoma. In this report, cupping and globe enlargement were observed before the actual IOP rise that occurred months later in some infants, and were invaluable in the early diagnosis, with increasing cupping and HCD being an indicator of ongoing disease process, and its regression a sign of control.

Case 3 represents 2 cases where one eye manifested at the age of 1 month by eye enlargement and cupping rather than IOP rise, while the contralateral eye presented at the age of 8-10 months with a cupping less than that of the first eye when presented, but with a remarkable IOP rise (28 mmHg) measured under the same anesthetic circumstances. This can be attributed to progressive collagen maturity. When seeing cases with no clear conclusion of low-grade vs self-limited, a close watch is not to be underestimated, as some might really be self-limited, but others can progress to a full blown PCG. We must remember that these eyes do have trabeculodysgenetic angles, the function of which can be compromised at one time or another.

On the other hand, cases with unilateral disease (represented by cases 1 and 4) had a minimal rise of IOP compared to the non-/mildly affected contralateral eye. Enlarged CDR regressed postoperatively to be comparable to the contralateral eye. Case 4, with the longer follow-up duration of 12 years, demonstrated bilateral reappearance of some cupping (physiological) by the age of 4 years, which probably represents normal optic disc cupping behavior in normal children. This pattern of almost plateau IOP and regressing C/D values can be observed in the graphs of cases presented.

Trabeculodysgenesis was observed in all presented cases, and looked bilaterally similar, in bilateral or unilateral cases. It seems that gonioscopic trabeculodysgenesis does not always entail infliction with frank PCG.

This work further challenges the commonly used definition of pediatric glaucoma as "a potentially blinding disease associated with elevated IOP" and demonstrates the occasional low significance that IOP readings have in PCG. An IOP below 21 mmHg, and even down to single digit numbers, is next to meaningless in its exclusion. The lack of IOP rise in early presented eyes, and its rise in later presented contralateral eyes, implies that a similar disease process can manifest with different IOP readings depending on age and maturity of corneal and scleral tissues.

No case was encountered with this preoperative/postoperative plateau IOP after the age of 5 months, which implies that this is genuine IOP behavior not related to anesthesia or other external factors. Findings in this case series shed light on the early disease process of mild PCG, with its self-limited incidents, early disease manifestations or active PCG cases despite the low IOP. What manifests in adult glaucoma as IOP fluctuation manifested in early infancy as cupping fluctuation.

To the best of our knowledge, this is the first report to document the diagnosis of active PCG associated with IOP as low as 7. When evaluating an infant for PCG, it is important to remember that a high IOP is only one of many signs to be considered. Optic disc cupping, a large cornea, its cloudiness, or a teens IOP in any newborn, should be alarming. In some cases presenting with PCG with a low IOP, further reduction of IOP is not a main criterion of postoperative re-

covery. Rather, regression of cupping, HCD, and resolution of cloudiness are more important favorable signs. Early diagnosis and prompt surgical treatment of PCG significantly influence its prognosis. This work calls for timely diagnosis of potentially missable PCG cases, and by no means encourages its over-diagnosis.

Which eyes respond more with IOP rise, and which eyes respond more by ocular expansion are questions to be answered through further studies on a larger scale on IOP behavior in different PCG cases, and its relation to age, stage of the disease, and other factors. Answers to these questions will help in understanding further the intricacies of disease development.

DISCLOSURE

The author declares no conflict of interest.

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