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The other eye of previously diagnosed unilateral primary congenital glaucoma

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Short title: Previously diagnosed unilateral primary congenital glaucoma

Abstract

Purpose: to study the criteria of the fellow eye of a unilateral Primary Congenital Glaucoma (PCG) that had been previously operated and compare them to the operated glaucomatous eye and to an age matched healthy control.

Methods: This study was a comparative cross-sectional study that included all unilateral cases of PCG older than 3 years, who attended Mansoura Ophthalmic Center, Dakahlia, Egypt, during 2018–2024. The study included 3 groups. Group A: study cases which are 20 eyes that were presumed to be the healthy fellow eyes of patients diagnosed earlier with unilateral PCG. Group B: included 24 normal eyes of 12 age matched controls. Group C: included the operated 20 PCG eyes. Complete examination was done including measurement of horizontal corneal diameter, intraocular pressure, refraction, axial length and CCT. Fundus was examined in all cases and gonioscopy was done using Koeppe 14–16 mm lens with a hand-held slit-lamp.

Results: The fellow eyes of unilateral PCG patients showed statistically significant differences in corneal diameter, refraction, and IOP when compared to normal age-matched controls. Gonioscopy showed normal angle in all control eyes. Group A had normal angle in 35% of eyes, open angle with prominent iris processes in 50 % of eyes and anterior iris insertion in 15% of eyes. There was no statistically significant difference in AL, CCT and cup disc ratio between group A and B. Treated glaucomatous eyes (group C) showed lower IOP (11.95 ± 3.54) mmHg, larger corneal diameter (13.5 ± 0.91), larger axial length (23.6 ± 1.61), lower mean CCT (513.9 ±24.4), higher cup disc ratio (0.30 ± 0.04) and more myopic refraction (-4.98 ± 0.51) when compared to their fellow eyes (group A).

Conclusion: The fellow eye of a previously diagnosed unilateral PCG can have higher axial length, larger corneal diameter, more myopic refraction than normal age-matched controls. They may have abnormal angle on gonioscopy and some corneal signs of PCG.

Keywords: Primary Congenital Glaucoma, IOP, myopia, megalocornea

INTRODUCTION

Congenital glaucoma represents a serious vision threatening developmental disease that occurs due to abnormal development of trabecular meshwork (trabeculodysgenesis) and anterior chamber angle and abnormally anterior iris insertion. The disease presents before the age of three years[1].

Primary congenital glaucoma is diagnosed according to presence of many signs as megalocornea, broad limbus, Haab's stria, increase in the cup disc ratio, axial myopia, accelerated axial growth and an IOP greater than 21 mmHg. Presence of two or more of these criteria is crucial for diagnosis. Presence of at least one of these signs but not fulfilling the criteria for diagnosis is considered as primary congenital glaucoma suspect[2].

Other signs at presentation include bluish sclera secondary to scleral thinning with ocular stretching, iris atrophy, abnormally deep anterior chamber and in more advanced cases progressive glaucomatous optic atrophy may be present. In

addition, diminished vision and visual field contraction can occur and noticed in older children. If primary congenital glaucoma is left untreated, loss of vision usually occurs[3].

Surgery is the definitive treatment. If early diagnosis and treatment occur, better vision can be expected for more than 50% of patients[4].

Children older than 3 years old with signs of primary congenital glaucoma but with normal IOP and no documented progression are considered as arrested primary congenital glaucoma[5]. The exact mechanism for spontaneous resolution remains unknown but might involve continued postnatal maturation of the drainage angle. This makes the angle cope with the aqueous load leading to a reduction in IOP[6]. The Childhood Glaucoma Research Network has standardized and expanded classification of PCG as neonatal, infantile, late onset and spontaneously arrested cases with normal Intraocular pressure (IOP) but typical signs of PCG[7].

Primary congenital glaucoma is usually bilateral. Many authors report bilaterality to be more than 70-80% of cases[8-9]. Many studies compared PCG eyes to the fellow eye in unilateral PCG or to normal controls, but only few studies compared these fellow eyes to normal eyes[10-13].

Authors from the 20th century[14] and other recent studies showed special interest to these fellow eyes and whether these eyes are completely normal, present an incompletely expressed PCG or a spontaneously arrested form of PCG early in the disease process[10,15].

In this study, parameters of the fellow eye of unilateral primary congenital glaucoma were studied and compared to the operated glaucomatous eye and to an age matched healthy control to detect presence of any aberrations from normal eyes.

PATIENTS & METHODS

This study was a comparative cross-sectional study that included all unilateral cases of primary congenital glaucoma, who attended Mansoura Ophthalmic Center, Dakahlia, Egypt, during 2018–2024. The research protocol of the study was approved by the Research Local Ethical Committee (R.23.06.2205). An informed consent was taken from the parents before being enrolled in the study. The reviewed cases included 150 eyes of 85 cases diagnosed as PCG, of which only 20 cases were documented as unilateral.

Inclusion criteria: Eligible cases of unilateral PCG were diagnosed according to the diagnostic criteria defined in the last Childhood Glaucoma Research Network classification[7] in which at least two of the following criteria were required; intraocular pressure > 21 mmHg, Haab's stria, corneal edema, horizontal corneal diameter ≥11 mm in new-born, > 12 mm in children < 2 years old and > 13 mm in any age, increased (>0.3) or asymmetric (>0.2) cup–disc ratio or progressive myopia or myopic shift with increased AL. All cases were examined at age older than 3 years old as an age limit for possible development of signs of PCG as ocular stretching, megalocornea and Haab's stria. All children in this study were not using any medications that could affect IOP.

Exclusion criteria included children with history of previous ocular surgery other than glaucoma surgery or trauma, patients with recurrent glaucoma, secondary childhood glaucoma as glaucoma following cataract surgery, glaucoma associated with local ocular abnormalities or syndromes.

The unilateral PCG children were examined with special care to their fellow eye's parameters. Twenty-four normal eyes of 12 age matched controls were enrolled from uncooperative children who needed examination under general anaesthesia for fundus examination, refraction or unilateral acquired pathology. The study included 3 groups. Group A: included study cases which are 20 eyes that were presumed to be the healthy fellow eyes of patients diagnosed earlier with unilateral primary congenital glaucoma. Group B: included 24 normal eyes of 12 age matched controls. Group C: included the operated 20 PCG eyes.

Examination was done for all cases under sevoflourane inhalational anaesthesia. The documented clinical data included the patient's age at time of examination, gender, consanguinity and family history. Complete examination was done including measurement of the horizontal corneal diameter (white to white) using surgical calliper; measurement of intraocular pressure using hand-held Perkins applanation tonometry (Haag–Streit, Harlow, UK), just after the induction of general anaesthesia

when the eyes are central; the fundus was examined by binocular indirect ophthalmoscope; axial length and CCT were measured by A scan ultrasonography, refraction by Nidek handyRef-K hand-held autorefractometer and gonioscopy by Koeppe 14–16 mm lens with a hand-held slit-lamp.

Statistical Analysis

The collected data was analysed using Statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Chi-Square test was used to examine the relationship between two qualitative variables. Fisher Exact/Monte-Carlo test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. ANOVA Test was used to assess the statistical significance of the difference of parametric variable between more two study groups means, followed by post hoc test. Kruskal-Wallis Test was used to assess the statistical significance of the difference of a non-parametric variable between more than two study groups, followed by pairwise comparison. A p value is considered significant if <0.05 at confidence interval 95%.

RESULTS:

In current study, 150 eyes of 85 children older than 3 years diagnosed with PCG were reviewed to select unilateral cases, of which 20 children had been previously diagnosed till their last follow up visit as unilateral PCG representing 23.26% of all cases.

Demographic data of the study cases are shown in table 1. There were no statistically significant differences in demographic data between the PCG patients and the control group.

Table 1: Demographic data of the study patients:

	Unilateral PCG cases (N=20)	**Age-matched Control (N=12)**	**P**
Sex			
Male	14 (70%)	7 (58%)	0.5
Female	6 (30%)	5 (42%)	
Age at examination (months)			
Mean	39 ± 2.9	38.75 ± 2.9	0.74
Median (Min, Max)	38 (36, 44)	37.5 (36, 42)	
Family history			
Positive	0	—	
Negative	20 (100%)	—	
Consanguinity			
Positive	6 (30%)	3 (25%)	0.76
Negative	14 (70%)	9 (75%)	
Affected eye in PCG/ Examined eye in control group			
Right	7 (35%)	12 (50%)	0.317
Left	13 (65%)	12 (50%)	

The presumed normal fellow eyes were examined (20 eyes, Group A) and compared to 24 healthy control eyes (group B). The biometric data studied are presented in table 2. IOP, corneal diameter, refraction, presence of broad limbus and abnormal angle with gonioscopy showed statistically significant difference between both groups. Mean IOP was (15.71 ± 1.49) mmHg in group A versus (13.92 ± 1.35) in group B, mean corneal diameter was (12.5 ± 0.99) in group A versus (11.2 ± 0.33) in group B, mean refraction was more myopic in group A (-1.26 ± 0.42) versus (0.71 ± 0.07) in group B.

Gonioscopy was performed and showed normal angle in all control eyes and in 35% of fellow eyes, 50% of fellow eyes showed open angle with prominent iris processes and 15% showed anterior iris insertion. Broad limbus was noted in 35% of group A eyes and none of control eyes. (Figure 1) There was no statistically significant difference in AL, CCT and cup disc ratio between group A and B, mean axial length was (21.95 ± 0.88) in group A and (21.2 ± 1.02) in group B, mean CCT was (537.5 ± 33.7) in group A and (548.4 ± 18.9) in group B and mean cup disc ratio was (0.13 ± 0.04) in group A and (0.04 ± 0.01) in group B. (Table 2).

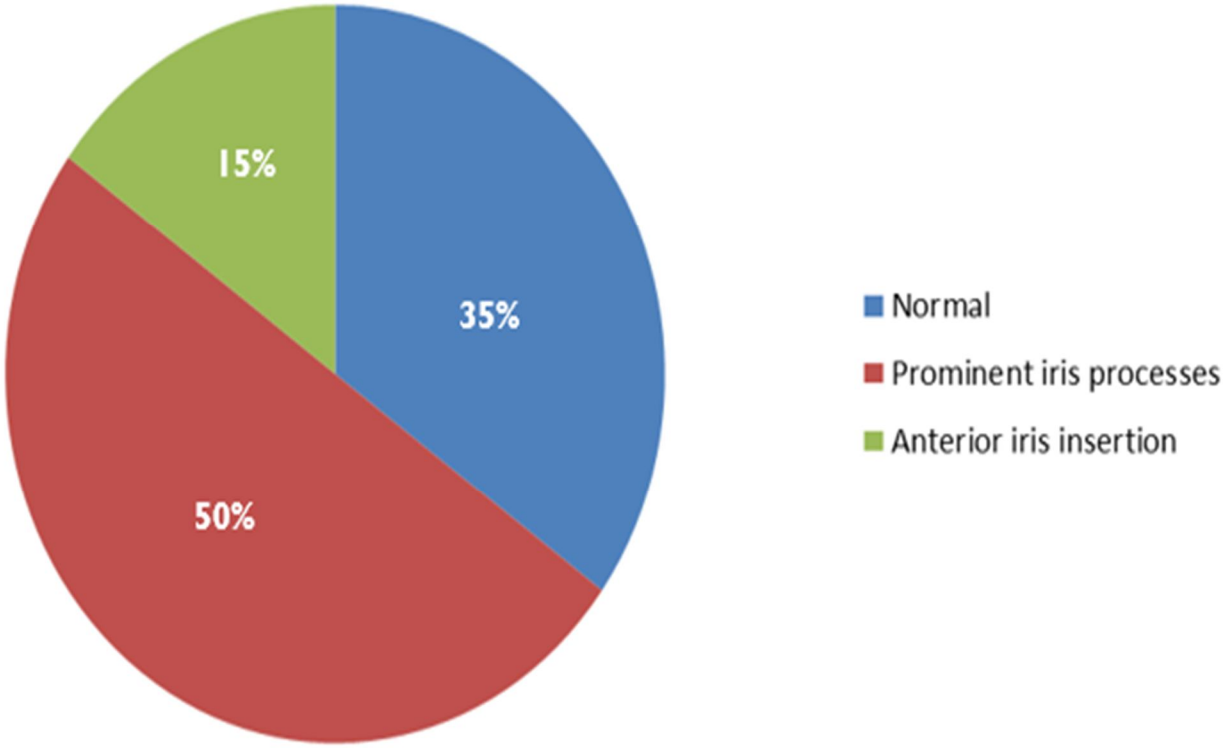

Fig. 1: Angle morphology by gonioscopy in the fellow eyes of unilateral PCG (group A)

Table 2: Comparison between the apparently healthy fellow eye of unilateral PCG and the age matched control regarding different parameters.

	Fellow eyes of unilateral PCG (group A) (N=20)	**Age-matched Control (group B) (N=24)**	**P**
IOP (in mm Hg)			
Mean ± SD.	15.71 ± 1.49	13.92 ± 1.35	0.015*
Median (Min. -Max.)	16.5 (12.2 – 16.5)	14.6 (12.2 – 16.5)	
Corneal diameter (in mm)			
Mean ± SD.	12.5 ± 0.99	11.7 ± 0.33	<0.001*
Median (Min. -Max.)	12.3 (11.0 – 13.5)	11.5 (11.0 – 12.0)	
Axial length (in mm)			
Mean ± SD.	21.95 ± 0.88	21.2 ± 1.02	0.112
Median (Min. -Max.)	21.9 (20.2 – 23.5)	21.6 (19.2 – 22.2)	
CCT (in µm)			
Mean ± SD.	537.5 ± 33.7	548.4 ± 18.9	0.13
Min. -Max.	(487 –567)	(509–578)	
Cup disc ratio			
Mean ± SE.	0.13 ± 0.04	0.04 ± 0.01	0.122
Median (Min. -Max.)	0.0 (0.0 – 0.3)	0.0 (0.0 – 0.1)	
Refraction			
Mean ± SE.	-1.26 ± 0.42	0.71 ± 0.07	0.005*
Median (Min. -Max.)	-1.5 (-4.0 – 2.0)	0.5 (0.5 – 1.5)	
Others			
Broad limbus	7 (35%)	0 (0%)	0.002*
Gonioscopy			
Normal	7 (35%)	24 (100%)	0.001*
Prominent iris processes	10 (50%)	0 (17%)	
Anterior iris insertion	3 (15%)	0	

SD.: Standard deviation, SE.: Standard error, Min.: Minimum, Max.: Maximum, *: Significant.

The fellow eyes of unilateral PCG (group A) were compared to the operated glaucomatous eyes (group C) and there was statistically significant difference in all studied parameters. Treated glaucomatous eyes showed lower IOP (11.95 ± 3.54) mmHg, higher mean corneal diameter (13.5 ± 0.91), higher mean axial length (23.6 ± 1.61), lower mean CCT (513.9 ± 24.4), higher cup disc ratio (0.30 ± 0.04) and more myopic refraction (-4.98 ± 0.51) than their fellow eyes.

(Table 3) Biometric data of seven eyes in group A with broad limbus are illustrated in table 4.

Table 3: Comparison between the apparently healthy fellow eye of unilateral PCG and the glaucomatous eye regarding different parameters:

	Fellow Eyes (group A) (N=20)	**Operated glaucomatous eyes (group C) (N=20)**	**P**
IOP (in mm Hg)			
Mean ± SD.	15.71 ± 1.49	11.95 ± 3.54	<0.001*
Median (Min. -Max.)	16.5 (12.2 – 16.5)	12.2 (7.8 – 16.5)	
Corneal diameter (in mm)			
Mean ± SD.	12.5 ± 0.99	13.5 ± 0.91	<0.001*
Median (Min. -Max.)	12.3 (11.0 – 13.5)	13.5 (11.5 – 15.0)	
Axial length (in mm)			
Mean ± SD.	21.95 ± 0.88	23.6 ± 1.61	<0.001*
Median (Min. -Max.)	21.9 (20.2 – 23.5)	23.6 (20.7 – 26.0)	
CCT (in µm)			
Mean ± SD.	537.5 ± 33.7	513.9 ±24.4	0.01*
Median (Min. -Max.)	(487 –567)	(428–541)	
Cup disc ratio			
Mean ± SE.	0.13 ± 0.04	0.30 ± 0.04	0.003*
Median (Min. -Max.)	0.0 (0.0 – 0.3)	0.3 (0.0 – 0.7)	
Refraction			
Mean ± SE.	-1.26 ± 0.42	-4.98 ± 0.51	<0.001*
Median (Min. -Max.)	-1.5 (-4.0 – 2.0)	-4.75 (-9.0 – -0.5)	
Others			
Broad limbus	7 (35%)	20 (100%)	<0.001*

Table 4: Detailed data of fellow eyes of unilateral PCG with broad limbus.

	Fellow eyes with broad limbus (N=7)
IOP (in mm Hg)	
Mean ± SD.	14.6 ±1.646
Median (Min. -Max.)	16.5 (12.2 – 16.5)
Corneal diameter (in mm)	
Mean ± SD.	13.21 ±0.26
Median (Min. -Max.)	13.3 (13.0 – 13.5)
Axial length (in mm)	
Mean ± SD.	23.28 ±0.22
Median (Min. -Max.)	23.22 (23.12 – 23.5)
CCT (in µm)	
Mean ± SD.	534.7 ± 21.8
Median (Min. -Max.)	(489 – 567)
Cup disc ratio	
Mean ± SE.	0.2 ± 0.08
Median (Min. -Max.)	0.0 (0.0 – 0.3)
Refraction	
Mean ± SE.	-2.81 ±0.93
Min. – Max.	(-2, -4)
Gonioscopy	
Normal	0
Prominent iris processes	4 (57%)
Anterior iris insertion	3 (53%)

DISCUSSION:

The current study shows that the percentage of a bilateral PCG is about 76.47%. This is relevant to other studies. Bilaterality was reported in 67.1% of PCG cases by Zagora et al, and in 74% of cases by Yassin and Al-Tamimi. Other studies from Egypt are relevant to current study; Mokbel et al reported bilateral PCG in 77.8% of cases[16], and ElSayed et al reported bilateral involvement in 78.4%[17]. Other studies reported higher rates of bilateral disease presentation as Wagdy et al, reported bilaterality to be 84%[12], Aziz et al reported bilateral disease in 99.3% of cases, Tamcelik et al reported bilaterality in 94.4% of cases, Alanazi et al reported bilateral involvement in 82.6% of cases and Taylor et al in 82% of PCG cases[18-20]. Bayoumi NH reported bilaterality to be only 58.2%[11]. The difference in bilaterality reported by many authors can be related to genetic differences according to locality, percentage of consanguineous marriage, severity of PCG and the age at which the laterality was considered final[20-22].

There was higher male preponderance in unilateral PCG cases (70%). This is relevant to that reported by Bayoumi NH where males represented 60.7% of unilateral PCG. This is relevant to the fact that PCG is more common in males[23].

In current study, mean IOP in normal age matched controls was 13.92 ± 1.35 and mean CCT was 548.4 ± 18.9 µm.

This is not relevant to another study from Egypt where they reported mean IOP in Egyptian children to be 11.5 ± 2.34 mm Hg and mean CCT to be 564.8 ± 42.72 μm[24]. This difference can be attributed to small sample size in control group in this study and that they included children aged up to 12 years old.

The cases and controls in the current study were evaluated at an age older than 3 years. Operated glaucomatous eyes had significantly lower mean IOP, CCT, larger mean corneal diameter, axial length, cup disc ratio and a more myopic refraction than both the fellow eyes and the controls. Doozandeh et al compared biometric values between operated glaucomatous eyes to their fellow eyes and to normal controls, and reported statistically significant higher axial length, but they didn't compare fellow eyes to controls in their study[12].

Fellow eyes of unilateral PCG were compared to age matched controls and showed statistically significant higher IOP (both within normal limits), larger corneal diameters and more myopic refraction. CCT values were lower in fellow eyes but the difference was not statistically significant. Gonioscopy was performed for control eyes and showed normal open angle. Gonioscopy of fellow eyes showed prominent iris processes in 50 %, anterior iris insertion in 15 % and normal open angle in 35%.

Seven eyes (35% of the fellow eyes) had broad limbus, corneal diameters between 13-13.5mm, axial length > 23.12mm and myopic refraction of > or equal to -2 (range from -2 - -4), normal intraocular pressure (without antiglaucoma medications use to these eyes or the operated eyes), normal cup to disc ratio and all exceeded the age of 3 years, that is why they were considered as an arrested form of PCG early in the disease process. These eyes represent 4.7% of PCG eyes that were reviewed in this study.

Studies dating since the 20th century have questioned this intermediate form of PCG. Shaffer and Weiss[13] have described partial expression of the infantile glaucoma angle anomaly in the "uninvolved" eye of patients with unilateral glaucoma, even in absence of other signs of the disease. Kluyskens[25-26] described two clinical presentations of PCG; complete and incomplete (or abortive) PCG and stated that patients with incomplete congenital glaucoma are likely to develop raised intraocular pressure at a later age. Belkin et al[27] have reported a case with incomplete congenital glaucoma at birth but developed raised intraocular pressure at the age of 8 years. Pollack and Oliver[25] considered presence of megalocornea, abnormal iridocorneal angle and normal IOP as "incomplete PCG". They described this iridocorneal angle abnormality to be an open angle with numerous iris processes almost covering the structures of the angle.

The variable expressivity and penetrance of genes associated with PCG can be responsible for the wide range of biometric criteria of the presumed healthy eye of unilateral PCG cases, thus they can be considered an intermediate or arrested state between normal and PCG eyes[28].

Another explanation noticed by Papadopoulos and Khaw was that in unilateral disease, the fellow eye may show typical gonioscopic findings of primary congenital glaucoma and a larger than normal corneal diameter and axial length, but with a normal optic nerve and cup disc ratio, so, this may indicate an anterior chamber angle that proceeded to maturation with *spontaneous arrest* of the disease, so, they emphasized that the fellow eye should be followed promptly for any possible chance of relapsing to PCG at any stage[29].

Gupta et al[14] with the help of anterior segment OCT, studied outflow channels of both eyes of 33 children with unilateral PCG and 30 healthy controls, and reported that hyper-reflective membrane at the angle (angle dysgenesis) was present in 63% of fellow eyes, 100% of PCG eyes and none of the control eyes. Schlemm's canal could be detected in all control eyes, 88% of fellow eyes and 24% of PCG eyes. They also detected communication between the supraciliary space and the anterior chamber in 79% of fellow eyes, and none of the PCG eyes. They postulated that fellow eyes with angle dysgenesis and/or absence of SC did not develop glaucoma due to the presence of this communication of the supraciliary space with the anterior chamber, offering an alternative pathway of aqueous outflow in these eyes preventing them from developing raised IOP.

One of the limitations in current study is absence of some data from the records, such as the difference in biometric data from first presentation and last examination to detect possible accelerated growth in interval between follow up visits.

CONCLUSION

PCG can be unilateral in around 20-30% of cases. The fellow eye of a previously diagnosed unilateral PCG can have higher axial length, larger corneal diameter, more myopic refraction than normal age-matched controls, abnormal angle on gonioscopy and some corneal signs of PCG. Scheduled follow up visits for unilateral PCG patients should be carried on to detect biometric changes in both eyes in comparison to the normal growth curve of age matched controls.

Abbreviations:

PCG: primary congenital glaucoma

IOP: intraocular pressure

CCT: central corneal thickness

AL: axial length

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Data Availability: The authors declare that all data supporting the findings of this study are available within the article.

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Conflict of interest

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