Risk Factors for Blindness in Children With Primary Congenital Glaucoma—Follow-up of a Registry Cohort

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• PURPOSE: To evaluate the baseline features associated with blindness in a cohort of children with primary congenital glaucoma (PCG) from a hospital registry.
• DESIGN: Retrospective clinical cohort study.
• METHODS: SETTING: Observational cohort study. STUDY POPULATION: The registry included all children who presented to our tertiary care institute between 1995 and 2014 with a diagnosis of childhood glaucoma. OBSERVATION PROCEDURE: Baseline characteristics at initial presentation of children with PCG in the registry who were blind at the last follow-up were compared with those who were not blind, using bivariate and then multivariate regressions to account for potential confounders. MAIN OUTCOME MEASURES: Blindness was defined as a best-corrected visual acuity of 3/60 (20/400) or worse in the better eye at the final follow-up.
• RESULTS: The eligible sample consisted of 196 children with a mean age of 9.54 ± 22.44 months at presentation. After a mean ± standard deviation follow-up of 8.49 ± 3.85 years, 20 (10.2%) children were blind. The baseline demographic factors, intraocular pressure, horizontal corneal diameter, spherical equivalent, axial length, and corneal thickness, were similar for the "blind" and "not blind" groups ($P > .05$). In the multivariate regression, only the severity of corneal opacification remained significantly ($P < .001$) associated with the risk of blindness (odds ratio = 4.05; 95% confidence interval: 1.89-8.85).
• CONCLUSION: Corneal clouding is a predictor of future blindness in children with PCG. Children with severe corneal clouding may need more aggressive intraocular pressure control, closer follow-up, and earlier counseling. (Am J Ophthalmol 2021;224:238–245.

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PRIMARY CONGENITAL GLAUCOMA (PCG) IS A IMPORTant cause of childhood blindness in the Middle-East region.[1–3] Even after timely surgical intervention to control intraocular pressure (IOP), a significant proportion of children with PCG end with visual impairment.[4,5] Vision-threatening difficulties can be due to optic nerve damage, corneal opacities, cataract, and amblyopia.[6,7]

As a result of visual impairment, children with PCG are challenged with a lifelong burden emotionally and psychologically on the patient and his or her family.[8–13] Strategies for reducing the childhood burden from PCG in the Middle East include premarital screening for the disease[14] and early identification of children with a high risk of blindness.

Several studies have investigated the possible risk factors associated with poor visual outcome in PCG.[15–17] Factors that have strong evidence to be associated with poor visual outcome are unilateral disease, multiple surgeries, poor vision at diagnosis, and ocular comorbidities.[11,16] Other factors such as age at initial presentation, sex, and IOP at initial presentation have not been proven to influence the long-term visual outcome.[12,17]

The King Khaled Eye Specialist Hospital (KKESH) PCG Registry was established to provide better characterization of features of PCG in Saudi Arabia.[18] This registry contains the baseline clinical features of children with PCG who presented to KKESH, the major tertiary Government facility in the Kingdom, from 2001 to 2003. Longitudinal follow-up of children in the registry has allowed the association of baseline features with clinical outcomes.

The aim of the current study was to study and report the association of baseline clinical features at presentation and risk of blindness in the KKESH Registry cohort.

METHODS

• STUDY DESIGN: This was a cohort study with an internal control group of children in the original KKESH congenital glaucoma registry,[19] to compare the baseline characteristics at initial presentation of children who were blind at the last follow-up with those who were not blind as defined below.

The registry included all children, regardless of initial visual status, age, or diagnosis subtype who presented to our institute between 1995 and 2014 with a diagnosis of

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TABLE 1. Baseline Clinical Characteristics of Children With Primary Congenital Glaucoma Who Were *Blind* at Final Follow-up Compared With the Children Who Were *Not Blind*

	Whole Group	Blind	Not Blind	P^e
Age of presentation (mo)[a]	9.54 ± 22.44	11.65 ± 29.08	9.30 ± 21.65	.658
Sex[b]				
Male	93 (47.4)	7 (35.0)	86 (48.9)	.239
Female	103 (52.6)	13 (65.0)	90 (51.1)	
Nationality[b]				
Saudi	186 (94.9)	18 (90.0)	168 (95.5)	.293
Non-Saudi	10 (5.1)	2 (10.0)	8 (4.5)	
Geographic location[b]				
North	33 (16.8)	5 (25.0)	28 (15.9)	.457
East	13 (6.6)	0 (0.0)	13 (7.4)	
West	49 (25.0)	5 (25.0)	44 (25.0)	
South	51 (26.0)	3 (15.0)	48 (27.3)	
Central	40 (20.4)	5 (25.0)	35 (19.9)	
Family history[b]				
Positive	62 (31.6)	5 (25.0)	57 (32.4)	.672
Negative	109 (55.6)	13 (65.0)	96 (54.5)	
Unknown	25 (12.8)	2 (10.0)	23 (13.1)	
Consanguinity[b]				
First cousin	58 (29.6)	10 (50.0)	48 (27.3)	.269
Second cousin	50 (25.5)	3 (15.0)	47 (26.7)	
Distant	15 (7.7)	2 (10.0)	13 (7.4)	
Unknown	41 (20.9)	3 (15.0)	38 (21.6)	
Laterality[b]				
Bilateral	190 (96.9)	18 (90.0)	172 (97.7)	.057
Unilateral	6 (3.1)	2 (10.0)	4 (2.3)	
Previous surgery (*worst eye*)[c]				
None	174 (88.8)	16 (80.0)	158 (89.8)	.135
Trabeculectomy	10 (5.1)	2 (10.0)	8 (4.5)	
Trabeculotomy	7 (3.6)	1 (5.0)	6 (3.4)	
Trab/trab[d]	2 (1.0)	0 (0.0)	2 (1.1)	
Other	2 (1.0)	0 (0.0)	2 (1.1)	
Surgery after presentation (*worse eye*)[c]				
Trab/trab[d]	92 (46.9)	4 (20.0)	88 (50.0)	.007**
Trabeculectomy	84 (42.9)	10 (50.0)	74 (42.0)	
Deep sclerectomy	17 (8.7)	5 (25.0)	12 (6.8)	
Trabeculotomy	1 (0.5)	0 (0.0)	1 (0.6)	
Missing data	2 (1.0)	1 (5.0)	1 (0.6)	

Data are presented as n (%) unless otherwise specified. Percentages indicate row totals.
**Significant result at α = 5%.
[a]Independent Student *t* test.
[b]Pearson χ^2 test.
[c]Fisher exact test.
[d]Trab/trab = combined trabeculotomy/trabeculectomy.
[e]For comparison of the "blind" and "not blind" groups.

childhood glaucoma, including PCG and secondary forms of childhood glaucoma. Details of the registry have been previously published.[18,19]

The best-corrected visual acuity (BCVA) in each eye of all eligible children (within the last year) was retrieved from our electronic medical record system. Any children who had not had a follow-up in the last year was scheduled a clinic appointment, so that BCVA could be obtained.

Institutional review board approval was obtained, and the study followed the tenets of the Declaration of Helsinki.

TABLE 2. Clinical Features in the *Better Eye* at Baseline for Children "Blind" and "Not Blind" at the Last Follow-up

	Whole Group	Blind	Not Blind	P^a
Number of previous surgeries, mean ± SD[c]	0.10 ± 0.30	0.20 ± 0.41	0.09 ± 0.29	.260
IOP (mm Hg), mean ± SD[c]	28.75 ± 9.10	27.6 ± 7.82	28.88 ± 9.25	.552
Location of corneal opacity[d]				
Localized	129 (65.8)	13 (65.0)	116 (65.9)	.011[b]
Diffuse	17 (100.0)	5 (25.0)	12 (6.8)	
None	50 (25.5)	2 (10.0)	48 (27.3)	
Severity of corneal opacity[d]				
0	44 (22.6)	3 (15.0)	41 (23.4)	<.001[b]
1	93 (47.7)	4 (20.0)	89 (50.9)	
2	30 (15.4)	1 (5.0)	29 (16.6)	
3	28 (14.4)	12 (60.0)	16 (9.1)	
DM break[d]				
Central	34 (17.3)	1 (5.0)	33 (18.8)	.304
Peripheral	3 (100.0)	0 (0.00)	3 (1.7)	
Extensive	5 (2.8)	0 (0.0)	5 (2.6)	
None	154 (100.0)	19 (95.0)	135 (76.7)	
Horizontal corneal diameter (mm), mean ± SD[c]	12.22 ± 1.03	12.53 ± 1.35	12.19 ± 0.99	.191
Spherical equivalent refraction (D) mean ± SD[c]	−1.63 ± 2.80	−1.04 ± 3.10	−1.66 ± 2.80	.568
Axial length (mm), mean ± SD[c]	21.88 ± 14.64	21.18 ± 2.02	21.95 ± 15.43	.827
Corneal thickness (μm), mean ± SD[c]	588.13 ± 80.09	616.60 ± 70.54	585.11 ± 80.67	.148

D = diopters; DM = Descemet's membrane; IOP = intraocular pressure.
Data are presented as n (%) unless otherwise specified. Percentages indicate row totals.
[a]For comparison of the "blind" and "not blind" groups.
[b]Significant result at α = 5%.
[c]Independent Student *t* test.
[d]Fisher exact test.

• **INCLUSION AND EXCLUSION CRITERIA:** The records of all children in the registry were assessed for inclusion in the study. Exclusion criteria included those who had follow-up of less than 5 years and those with secondary forms of childhood glaucoma (eg, glaucoma after cataract surgery, glaucoma associated with ocular abnormalities, and those associated with systemic abnormalities). Any children who went blind as a result of surgical intervention from complications such as endophthalmitis and suprachoroidal haemorrhage, rather than glaucomatous disease, were also excluded from the final analysis.

• **DIAGNOSTIC CRITERIA:** For initial inclusion in the registry, the diagnosis was made in the presence of elevated IOP (>21 mm Hg) in association with at least one of the following findings: corneal haze with or without Haab striae, enlarged corneal diameter, and increased cup/disc ratio of more than 0.4 or the presence of significant cupping asymmetry between both eyes.[20]

• **DEFINITION OF BLINDNESS:** As per the WHO definition, *blindness* was defined as a BCVA of 3/60 (equivalent to 20/400 or logMAR 1.30) or worse in the better eye at the final follow-up.[21] *Blindness in at least one eye* was defined as a BCVA of 3/60 or worse in the *worse eye* and included the children who were blind in both eyes. This was used to evaluate risk factors for a lower threshold for blindness. BCVA was selected as the visual acuity with refraction or after pinhole correction. For eyes where BCVA was equal in both eyes, the better eye was selected at random (within the SPSS software) with the fellow eye selected as the worse eye.

• **DATA COLLECTION:** Data of the following parameters were collected from the patient medical records: age at presentation, sex, IOP at presentation, number and type of operations, follow-up period, BCVA at the last visit, cycloplegic refraction, corneal diameter, pachymetry, corneal clarity, axial length, and cup-to-disc ratio. IOP measurement was undertaken with pneumotonometer and/or tonopen, assessment of corneal clarity was graded from 0 to 3 ("0": crystal clear cornea; "1+": fine corneal haze where details of the iris could be easily seen; "2+": iris visible with difficulty; "3+": iris is not visible), using

a portable slit lamp.[19] The presence of Descemet breaks was classified by location as "central," "peripheral," or "extensive."[19]

• **DATA ANALYSIS:** Baseline characteristics were reported as percentages or proportions for categorical data. Continuous data were reported as means (with standard deviation). A bivariate analysis was used to compare proportions or means/medians in the "blind" group with the "not blind" group. A χ^2 test was used for categorical data and a Student *t* test used for comparing means. To account for confounding factors, a multivariable regression[22] was performed to assess the baseline factors that were independently associated with blindness. In this regression, we included age, gender, and any of the covariates from univariable regression with a *P* value equal to or less than .20. Covariates in the multivariable regression were considered significant if the *P* value was less than .05. For estimating risk factors associated with blindness, covariates were selected based on bivariate comparison of the *better eye*. The *worse eye* covariates were selected for estimating risk factors for *blindness in at least one eye*. The analysis was performed in IBM SPSS Statistics for Windows, version 24, IBM Corp, Armonk, New York, USA).

RESULTS

OF THE INITIAL 246 CHILDREN IN THE REGISTRY, 12 WITH SECondary forms of glaucoma were excluded and 38 children were excluded because of follow-up of less than 6 months; none were excluded because of blindness from surgery (no such children were identified). The eligible sample consisted of 196 children with a diagnosis of PCG.

After a mean ± standard deviation follow-up of 8.49 ± 3.85 years, 20 (10.2%) children were *blind* and 50 (25.5%) were *blind in at least one eye*. The mean age for the whole group was 9.54 ± 22.44 months, with a similar proportion of boys and girls; 190 children had bilateral disease. There was an absence of family history in over half (109/196 = 56%) of the children. Overall, 11.7% of children had surgery before presentation (Table 1).

Table 2 shows the baseline ocular parameters for the *better eye* at presentation for the blind group of children. The mean IOP at presentation was 28.75 ± 9.10 mm Hg and the mean horizontal corneal diameter 12.22 ± 1.03 mm for the whole group. The IOP, horizontal corneal diameter, spherical equivalent, axial length, and corneal thickness were similar for the "blind" and "not blind" groups (Table 2). In eyes that were blind, nearly two-thirds had grade 3 corneal clouding (12/20 = 60%). In contrast, the proportion with grade 3 corneal clouding was 6-fold lower ($P <$ .001) in the "nonblind" group (16/176 = 9.1%).

In the multivariable regression (Table 3), only the severity of corneal opacification remained significantly associated with the risk of blindness (odds ratio [OR] = 4.05; 95% confidence interval [CI]: 1.89-8.85).

TABLE 3. Multivariable Regression of Factors Associated With Blindness

Covariate	Odds Ratio	95% CI	*P*
Age at presentation	1.021	0.990-1.044	.063
Sex (male)	0.848	0.244-2.951	.796
Corneal diameter	0.781	0.383-1.594	.498
Corneal thickness	1.003	0.997-1.010	.310
Severity of CC[a]	4.053	1.856-8.852	<.001[b]
Location of CC[a]			
Localized	1.083	0.103-11.379	.947
Diffuse	2.759	0.203-37.513	.446

CC = corneal clouding; CI = confidence interval.
[a]Reference category is the absence of CC.
[b]Significant at $\alpha = 0.05$.

As a secondary analysis, risk factors for *blindness in at least one eye* were also examined. This was related to ocular features in the worse eye at presentation (Table 4). This showed the axial length ($P <$ .001), corneal diameter ($P =$ .003), the presence of Descemet breaks ($P =$ .019), and the location ($P =$ .008) and severity of corneal clouding ($P <$ .001) to be higher in the group of children with *blindness in at least one eye* compared with those without blindness. A multivariable regression relating to factors in the worse eye (Table 5) revealed that the severity of corneal clouding (OR = 8.55; 95% CI: 4.27-17.1) and axial length (OR = 1.77; 95% CI: 1.19-2.64) were significantly associated with *blindness in at least one eye*.

Of the 40 eyes (of 20 children) who were blind at the final follow-up, 8 eyes were documented clinically to have advanced glaucomatous optic neuropathy; a further 11 eyes had severe corneal clouding precluding any fundal view but were noted to have advanced optic nerve cupping on ultrasound B scan assessment. In 11 eyes with severe corneal clouding, the state of the optic nerve was unclear and not assessed with ultrasound examination. None of the children were found to have complete resolution of corneal clouding at the last follow-up.

DISCUSSION

THE MAIN AIM OF THIS STUDY WAS TO DETERMINE THE baseline risk factors associated with eventual blindness in children with PCG in this large registry-based study. Identifying such risk factors may enable early identification of children at high risk of blindness, permitting more timely treatment and closer follow-up and counseling for this group of children.

TABLE 4. Clinical Features in the *Worse Eye* at Baseline for Children With *Blindness in at Least One Eye*

	Whole Group	Blind in at Least One Eye	Not Blind	*P*[a]
Number of surgeries, mean ± SD[c]	0.11 ± 0.32	0.20 ± 0.40	0.08 ± 0.28	.06[b]
IOP (mm Hg), mean ± SD[c]	31.10 ± 8.99	32.37 ± 10.33	30.65 ± 8.48	.246
Location of CC[d]				
Localized	141 (71.9)	30 (60.0)	111 (76.0)	.008[b]
Diffuse	26 (13.3)	13 (26.0)	13 (8.9)	
None	29 (14.8)	7 (14.0)	22 (15.1)	
Severity of CC[d]				
0	17 (8.7)	2 (4.0)	15 (10.3)	<.001[b]
1	85 (43.3)	4 (8.0)	81 (55.5)	
2	44 (22.4)	3 (6.0)	41 (28.1)	
3	50 (25.5)	41 (82.0)	9 (6.2)	
DM break [e]				
Central	35 (17.9)	3 (6.0)	32 (21.9)	.019[b]
Peripheral	3 (1.5)	0 (0.00)	3 (2.1)	
Extensive	6 (3.1)	3 (6.0)	3 (2.1)	
None	152 (77.6)	44 (88.0)	108 (74.0)	
Horizontal corneal diameter (mm), mean ± SD[c]	12.55 ± 1.05	12.95 ± 1.00	12.41 ± 1.03	.003[b]
Spherical equivalent refraction (D), mean ± SD[c]	−2.35 ± 3.00	−2.81 ± 2.82	−2.29 ± 3.05	.510
Axial length (mm), mean ± SD[c]	21.28 ± 1.61	22.05 ± 1.55	21.03 ± 1.54	<.001[b]
Corneal thickness (μm), mean ± SD[c]	594.68 ± 92.90	588.63 ± 71.73	596.42 ± 98.32	.663

CC = corneal clouding; D = diopters; DM = Descemet's membrane; IOP = intraocular pressure.
Data are presented as n (%) unless otherwise specified.
[a]For comparison of "blind" and "not blind" groups.
[b]Significant result at α = 5%.
[c]Independent Student *t* test.
[d]Pearson χ^2 test.
[e]Fisher exact test.

The major finding of this study was the positive association of severity of corneal clouding with blindness. A number of factors contribute to corneal clouding in children with PCG. PCG itself can result in clouding of the cornea, which usually can be reduced by pharmacologic or surgical reduction of IOP. In addition, the CYP1B1 genetic mutation is itself associated with central corneal clouding.[23,24] We found that blind children tended to have severe but also more diffuse corneal clouding (5/20 with "diffuse" in the "blind" group compared with 12/176 in the "not blind" group, Table 2). This would be consistent with glaucoma being a major contributor to corneal status in such children rather than CYP1B1-related corneal clouding. Uncontrolled infantile glaucoma may result in stromal scarring causing permanent opacity despite adequate glaucoma control. Although corneal clouding itself is recognized as a cause of visual impairment from amblyopia in children with PCG, children with more opaque corneas are likely to have vision loss from advanced glaucomatous optic neuropathy and amblyopia.[25]

In terms of practical application, the association of corneal clouding with future blindness may influence management of children with PCG in several ways. First, it would be reasonable to assume that such children require a low target IOP to preserve both residual optic nerve and corneal clarity, and a lower threshold for operation or reoperation in such children would be reasonable. Secondly, an aggressive regimen for amblyopia therapy in children with corneal clouding, especially in children with asymmetric clouding, should be employed. Lastly, early psychological counseling, learning braille, and adoption of suitable low vision aids for such children should be considered to minimize the psychological burden of future blindness.

In our study, the proportion of children who were *blind* and *blind in at least one eye* after a mean follow-up nearly 9 years was relatively low (10.2% and 25.5%, respectively). In a South Korean study, Suh and Kee[17] found over half (61%) of the patients with PCG ended with visual impairment, despite having controlled IOP after surgical intervention. In multivariate analysis of the association of prognosis and other ocular factors, the number of surgical interventions was weakly positively correlated with a poor visual prognosis (Spearman's correlation

TABLE 5. Multivariable Regression of Factors Associated With *Blindness in at Least One Eye*

Covariate	Odds Ratio	95% CI	*P*
Age (y)	1.012	0.981-1.044	.449
Sex (male)	0.850	0.314-2.300	.749
Number of surgeries	0.977	0.240-3.983	.974
Corneal diameter	1.022	0.597-1.750	.937
Axial length	1.774	1.192-2.640	.005[b]
Severity of CC	8.549	4.265-17.134	<.001[b]
Location of CC[a]			
Localized	0.778	0.139-4.354	.775
Diffuse	2.541	0.333-19.379	.368
DM Break			
Central	0.520	0.102-2.650	.431
Peripheral	1.546	0.173-13.799	.696
Extensive	0.00	0.000	.999

CC = corneal clouding; CI = confidence interval; DM = Descemet's membrane.

[a]Absence of corneal opacity is the reference category.

[b]Significant at $P < .05$.

coefficient = 0.31, $P = .004$); we found no association between the number of procedures and visual outcome. In the same study, involvement of both eyes, age at initial presentation, sex, and IOP at initial presentation were not proven to have an influence on the long-term visual outcome, a finding that is comparable to our study.

In the original study by Barkan,[25] the primary cause of reduced vision in most cases in his study was corneal clouding followed by permanent scarring of the cornea, with associated irregular astigmatism and ensuing amblyopia of greater or less degree. Morin and Bryars[7] found poor vision in 41 of 76 eyes with PCG with glaucoma and media opacity accounting for most of the impairment. Badeeb and associates[26] found that 64% of children with congenital glaucoma (primary and secondary) were legally blind and the main cause of decreased vision was corneal scarring and haze in 47%, amblyopia in 23%, and optic nerve atrophy in 21%. Amblyopia is an important and potentially reversible cause of visual loss in children with PCG.[6,27–30] Although many have found corneal opacification to be a cause of visual loss in children with PCG, the present study provides a stronger association of corneal clouding severity with blindness by relating baseline corneal findings with subsequent blindness in a registry cohort of children selected on the basis of diagnosis.

There are several limitations of this study. First, as the proportion of children who were blind at follow-up was relatively small, the power to find a difference between the "blind" and "not blind" groups may have been limited. Although this comparison is somewhat compensated by a larger "not blind" population, parameters with significance in the bivariate analysis but not multivariate analyses should not be excluded as possible risk factors for blindness. In particular, horizontal corneal diameter (Tables 2 and 4) and the presence of Descemet's membrane breaks (Tables 2 and 4), which also relate to corneal signs of PCG, were not significant in the multivariate analysis. Axial length also showed some evidence of difference between groups for the risk of "blindness in at least one eye" (Table 4). These features are likely associated with more advanced congenital glaucoma. Even though there were only 20 children who were blind in both eyes, the severity of corneal clouding still proved to be highly significantly ($P < .001$, Table 3) associated with blindness and blindness in at least 1 eye ($P < .001$, Table 5) in both bivariate and multivariate analyses.

In children with PCG, corneal clouding can be due to corneal edema or scarring. We have not distinguished these 2 causes of corneal clouding. In our practice, we have found it rare for significant corneal scarring to develop within the first 3 months of birth. Children with PCG tend to have thicker corneas than aged-similar controls,[31] yet we did not find an association of corneal thickness with blindness in our cohort. Given that scarring tends to thin the cornea, this may indicate that many children had a degree of corneal scarring as well as edema. As a continuation of this study, a detailed study of corneal morphology of children with PCG with anterior segment ocular coherence tomography is worthwhile to further elucidate the precise corneal morphologies that are more frequent in children with PCG. A related limitation is that we did not perform a detailed assessment of corneal grading at each visit after the baseline. As such, our study cannot give conclusions regarding children who had improvements in corneal clouding but who still ended with blindness.

A second limitation is that as a tertiary care center, a few children had treatment initiated elsewhere before presenting to our facility, so that baseline clinical features are representative of those on referral rather than those at diagnosis. However, during this period the registry was initiated, our institution was performing the vast majority of procedures for PCG in the country and only a minority of children had a procedure before presenting to us (Table 1). Thirdly, some clinical features are dependent on subjective evaluation. In this regard, assessment of corneal clouding was based on clinical assessment and is subject to a degree of observer variability. However, to minimize this variability, we used an objective grading of severity of corneal clouding.

Fourthly, we did not correlate genetic findings with clinical outcome. An interesting finding from the current study was the lack of association between family history or consanguinity with the risk of blindness. Nearly all the PCG in Saudi Arabia is related to mutations of the CYP1B1 gene,[32,33] with various mutations having been described[33] and variable genotype-phenotype correlation of this gene reported.[34] Given that CYP1B1 has autosomal inheritance and also that CYP1B1 has been implicated in more severe

phenotypes,[34–36] we may have expected to find an association between family history and the risk of blindness. One possible explanation for this finding is that the incidence of CYP1B1 is relatively high, accounting for 90% of cases in the Saudi population of PCG anyway,[32] so there was no apparent difference of this gene (and family history) in the "blind" and "not blind" children with PCG in our study. A follow-on study that specifically examined the relationship between specific types of CYP1B1 mutation and phenotype correlation would be insightful in this regard.

Lastly, the findings of this study are specific to the population studied, that is, children with PCG in Saudi Arabia. The findings are likely to be applicable across the Middle East and South Asia, where the disease genotype is similar,[26,37–39] but may not be applicable to the Western populations, where PCG tends to be less frequent and a sporadic disease.

In conclusion, we found that corneal clouding at baseline is a predictor of future blindness in children with PCG. This finding may support the need for lower target IOPs in children with PCG who present with severe corneal clouding and also may allow for earlier counseling for such patients. Further work is needed to study the relative contributions of glaucoma and CYP1B1-related corneal clouding in corneal disease in these children and to evaluate the corneal clouding as a risk factor for blindness in other populations.

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REFERENCES

1. Kotb AA, Hammouda EF, Tabbara KF. Childhood blindness at a school for the blind in Riyadh, Saudi Arabia. *Ophthalmic Epidemiol* 2006;13:1–5.
2. Haddad MA, Sei M, Sampaio MW, Kara-Jose N. Causes of visual impairment in children: a study of 3,210 cases. *J Pediatr Ophthalmol Strabismus* 2007;44:232–240.
3. Steinkuller PG, Du L, Gilbert C, Foster A, Collins ML, Coats DK. Childhood blindness. *J AAPOS* 1999;3:26–32.
4. Mandal AK, Gothwal VK, Bagga H, Nutheti R, Mansoori T. Outcome of surgery on infants younger than 1 month with congenital glaucoma. *Ophthalmology* 2003;110:1909–1915.
5. Yalvac IS, Satana B, Suveren A, Eksioglu U, Duman S. Success of trabeculotomy in patients with congenital glaucoma operated on within 3 months of birth. *Eye (Lond)* 2007;21:459–464.
6. Biglan AW, Hiles DA. The visual results following infantile glaucoma surgery. *J Pediatr Ophthalmol Strabismus* 1979;16:377–381.
7. Morin JD, Bryars JH. Causes of loss of vision in congenital glaucoma. *Arch Ophthalmol* 1980;98:1575–1576.
8. Dada T, Aggarwal A, Bali SJ, Wadhwani M, Tinwala S, Sagar R. Caregiver burden assessment in primary congenital glaucoma. *Eur J Ophthalmol* 2013;23:324–328.
9. Chandna A, Gilbert C. When your eye patient is a child. *Community Eye Health* 2010;23:1–3.
10. AlQurashi M, Mocan MC, AlDarrab A, et al. Quality of life of caregivers of children with glaucoma in an Arab population: a cross-sectional study. *J Glaucoma* 2019;28:965–968.
11. Gothwal VK, Seelam B, Mandal AK. Quality of life following surgery for congenital glaucoma: findings of the LVPEI congenital glaucoma registry. *Eye (Lond)* 2019;33:659–667.
12. AlDarrab A, Al Qurashi M, Al Thiabi S, Khandekar R, Edward DP. Functional visual ability and quality of life in children with glaucoma. *Am J Ophthalmol* 2019;200:95–99.
13. Kantipuly A, Pillai MR, Shroff S, et al. Caregiver burden in primary congenital glaucoma. *Am J Ophthalmol* 2019;205:106–114.
14. Malik R, Khandekar R, Boodhna T, et al. Eradicating primary congenital glaucoma from Saudi Arabia: the case for a national screening program. *Saudi J Ophthalmol* 2017;31:247–249.
15. Yassin SA. Long-term visual outcomes in children with primary congenital glaucoma. *Eur J Ophthalmol* 2017;27:705–710.
16. Khitri MR, Mills MD, Ying GS, Davidson SL, Quinn GE. Visual acuity outcomes in pediatric glaucomas. *J AAPOS* 2012;16:376–381.
17. Suh W, Kee C. Long-term outcome of primary congenital glaucoma in South Korea. *Acta Ophthalmol* 2016;94:e162–e163.
18. Zaman B, Khandekar R, Al Shahwan S, et al. Development of a web-based glaucoma registry at King Khaled Eye Specialist Hospital, Saudi Arabia: a cost-effective methodology. *Middle East Afr J Ophthalmol* 2014;21:182–185.
19. Alanazi FF, Song JC, Mousa A, et al. Primary and secondary congenital glaucoma: baseline features from a registry at King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. *Am J Ophthalmol* 2013;155:882–889.
20. Beck AD, Chang TCP, Freedman SF. Definition, classification, differential diagnosis. In: Weinreb RN, ed. Childhood Glaucoma: Consensus Series 9. Amsterdam: Kugler; 2013.
21. WHO. Blindness and vision impairment: definitions. World Health Organisation, Geneva. Available at https://www.who.int/news-room/fact-sheets/detail/blindness-and-visual-impairment. Accessed March 1, 2020.
22. Hidalgo B, Goodman M. Multivariate or multivariable regression? *Am J Public Health* 2013;103:39–40.
23. Chavarria-Soley G, Michels-Rautenstrauss K, Caliebe A, Kautza M, Mardin C, Rautenstrauss B. Novel CYP1B1 and known PAX6 mutations in anterior segment dysgenesis (ASD). *J Glaucoma* 2006;15:499–504.
24. Kelberman D, Islam L, Jacques TS, et al. CYP1B1-related anterior segment developmental anomalies novel mutations for infantile glaucoma and von Hippel's ulcer revisited. *Ophthalmology* 2011;118:1865–1873.

25. Barkan O. Goniotomy for the relief of congenital glaucoma. *Br J Ophthalmol* 1948;32:701–728.
26. Badeeb OM, Micheal S, Koenekoop RK, den Hollander AI, Hedrawi MT. CYP1B1 mutations in patients with primary congenital glaucoma from Saudi Arabia. *BMC Med Genet* 2014;15:109.
27. Richardson KT Jr, Ferguson WJ Jr, Shaffer RN. Long-term functional results in infantile glaucoma. *Trans Am Acad Ophthalmol Otolaryngol* 1967;71:833–837.
28. Clothier CM, Rice NS, Dobinson P, Wakefield E. Amblyopia in congenital glaucoma. *Trans Ophthalmol Soc U K* 1979;99:427–431.
29. Rice NS. Management of infantile glaucoma. *Br J Ophthalmol* 1972;56:294–298.
30. Kushner BJ. Successful treatment of functional amblyopia associated with juvenile glaucoma. *Graefes Arch Clin Exp Ophthalmol* 1988;226:150–153.
31. Lopes JE, Wilson RR, Alvim HS, et al. Central corneal thickness in pediatric glaucoma. *J Pediatr Ophthalmol Strabismus* 2007;44:112–117.
32. Bejjani BA, Lewis RA, Tomey KF, et al. Mutations in CYP1B1, the gene for cytochrome P4501B1, are the predominant cause of primary congenital glaucoma in Saudi Arabia. *Am J Hum Genet* 1998;62:325–333.
33. Abu-Amero KK, Osman EA, Mousa A, et al. Screening of CYP1B1 and LTBP2 genes in Saudi families with primary congenital glaucoma: genotype-phenotype correlation. *Mol Vis* 2011;17:2911–2919.
34. de Melo MB, Mandal AK, Tavares IM, et al. Genotype-phenotype correlations in CYP1B1-associated primary congenital glaucoma patients representing two large cohorts from India and Brazil. *PLoS One* 2015;10:e0127147.
35. Hollander DA, Sarfarazi M, Stoilov I, Wood IS, Fredrick DR, Alvarado JA. Genotype and phenotype correlations in congenital glaucoma: CYP1B1 mutations, goniodysgenesis, and clinical characteristics. *Am J Ophthalmol* 2006;142:993–1004.
36. Della Paolera M, de Vasconcellos JP, Umbelino CC, et al. CYP1B1 gene analysis in primary congenital glaucoma Brazilian patients: novel mutations and association with poor prognosis. *J Glaucoma* 2010;19:176–182.
37. Kaur K, Mandal AK, Chakrabarti S. Primary congenital glaucoma and the involvement of CYP1B1. *Middle East Afr J Ophthalmol* 2011;18:7–16.
38. Jubair S, N Al-Rubae'i SH, M Al-Sharifi AN, Jabbar Suleiman AA. Investigation of *CYP1B1* gene involvement in primary congenital glaucoma in Iraqi children. *Middle East Afr J Ophthalmol* 2020;26:203–209.
39. El-Gayar S, Ganesh A, Chavarria-Soley G, et al. Molecular analysis of CYP1B1 in Omani patients with primary congenital glaucoma: a pilot study. *Mol Vis* 2009;15:1325–1331.