Original Article

Progression in pediatric glaucoma: Lessons learnt from 8 years' follow-up

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ABSTRACT

Background: Surgical procedures are used as 1 of the main treatment modalities for pediatric glaucoma, even though progression may occur. In this study, we aimed to investigate the risk factors affecting the progression of pediatric glaucoma.

Methods: In this retrospective cohort study, we reviewed the medical records of patients diagnosed with pediatric glaucoma between April 2009 and March 2017. Pediatric glaucoma patients who underwent regular follow-up for at least 1 year were included. Demographics, intraocular pressure (IOP), central corneal thickness (CCT), axial length (AL), cup-to-disc ratio (C/D ratio), corneal diameter, type of glaucoma, age at time of diagnosis, and age at surgery were recorded. Progression was defined as an increase in AL > 2 mm, C/D ratio > 0.2, or corneal diameter > 1 mm during 1 year of follow-up.

Results: Eighty-three eyes from 46 patients were included: 37 eyes (45%) with primary congenital glaucoma (PCG), 46 eyes (55%) with secondary glaucoma, and 27 of these 83 eyes (32.5%) showed progression. Progression was comparable between eyes with PCG and secondary glaucoma (PCG, 22%; secondary glaucoma, 41%; $P = 0.152$). Age at the time of diagnosis and age at the time of the first surgery were significantly lower in the eyes with progression ($P = 0.046$ and 0.012, respectively). The mean ± standard deviation of surgeries in progressed versus non-progressed eyes was 1.88 ± 1.1 versus 1 ± 0.8 ($P = 0.015$). The frequency of comorbid systemic disease was significantly higher in patients with glaucoma progression ($P = 0.043$). The progressed and non-progressed eyes were comparable in terms of other demographic characteristics and ocular parameters (all $P > 0.05$).

Conclusions: Pediatric glaucoma patients who were younger at the time of diagnosis and the first glaucoma surgery and those with comorbid systemic disease are at higher risk of glaucoma progression. These findings are useful for clinicians when counseling parents of children with pediatric glaucoma about disease outcomes. However, future prospective studies with larger sample sizes and longer follow-up periods are needed to confirm our findings.

KEY WORDS

pediatric glaucoma, glaucoma, surgery, progression, intraocular pressure, primary congenital glaucoma, central corneal thickness, corneal diameter, axial length, cup-to-disc ratio

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INTRODUCTION

Pediatric glaucoma is a potentially blinding ocular disease. It comprises a group of disorders with ocular damage related to intraocular pressure (IOP). The Childhood Glaucoma Research Network (CGRN) designed a new classification system to unify nomenclature in pediatric glaucoma [1]. The latest consensus by the World Glaucoma Association has classified childhood glaucoma as primary or secondary glaucoma. Primary congenital glaucoma (PCG) and juvenile open-angle glaucoma together comprise primary childhood glaucoma. The former is further subdivided by age of onset into neonatal/newborn onset PCG, with onset from birth to less than 1-month old, infantile onset (onset from 1 to 24 months), and late onset (onset after 2 years of age) [2].

The incidence of PCG varies across countries and ethnic groups [3-5]. Early diagnosis and treatment of pediatric glaucoma are crucial for minimizing visual impairment [6]. PCG is a rare type of glaucoma that occurs due to genetically determined anomalies in the trabecular meshwork and anterior chamber angle, may result in increasing IOP, with no systemic or ocular developmental anomalies [7]. The conventional triad of symptoms in PCG is photophobia, epiphora, and blepharospasm, however these could be absent in some circumstances. Other signs and symptoms include lack of eye contact, tearing, pupillary abnormalities, and nystagmus, but these may account for less than two percent of symptoms at initial presentation [3, 8]. Several risk factors have been identified that could affect glaucoma progression in pediatric patients, including race, age at the time of surgery, positive familial history, baseline corneal diameter (CD), and type of glaucoma [5 , 9]

Surgical interventions are usually considered the mainstay of treatment in PCG, and medical management may be initially used for secondary glaucoma [10, 11]. However, surgery in pediatric glaucoma is associated with a higher risk of failure or postoperative complications [12-14]. The aim of this study was to investigate the risk factors affecting the progression of pediatric glaucoma.

METHODS

In this retrospective cohort study, we reviewed the medical records of patients diagnosed with pediatric glaucoma at the Department of Ophthalmology, Imam Khomeini Hospital, Ahvaz, Iran, from April 2009 to March 2017. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (approval code IR.AJUMS.REC.1396.334).

Patients with at least 1 year of follow-up during the study period were included, and diagnosis of PCG was based on the criteria of the CGRN, which expanded and standardized the definition for PCG [1]. Patients were diagnosed with PCG when no other ocular anomaly or systemic disease was present. Eyes meeting these criteria were then subcategorized into 3 groups, based on age of onset: neonatal or newborn (onset from birth to less than 1-month old), infant (onset from 1 to 24 months), and late onset or late recognition (onset after 2 years of age) [2]. Glaucoma associated with aniridia, Axenfeld-Rieger syndrome, retinopathy of prematurity, congenital hereditary endothelial dystrophy, iris coloboma, Peter's anomaly, albinism, and glaucoma following cataract surgery were considered secondary glaucoma. The exclusion criteria were irregular follow-up and incomplete records. Loss to follow-up for > 6 months or > 1-month post-surgery were considered irregular follow-up, and these patients were excluded.

Demographic data and patient characteristics, including age at the time of glaucoma diagnosis, age at the time of first surgery, sex, IOP, central corneal thickness (CCT), C/D ratio by direct and indirect ophthalmoscopy, CD, and AL measurements were extracted from medical records. Family history of glaucoma or other ocular anomalies, type of glaucoma, type of surgery, number of surgeries, time of the last examination, final best-corrected distance visual acuity, and history of systemic pathologies or other ocular surgeries were also documented. The same technician made all paraclinical measurements throughout the study period.

IOP was measured using Tonopen (AVIA applanation tonometer, Reichert, Depew, NY, USA) under anesthesia, or using a Goldman applanation tonometer (Haag-Streit, Bern, Switzerland) in cooperative older patients. CCT was measured using ultrasound pachymetry (SP-100 Handy Pachymeter, Tomey, Nagoya, Japan). AL was determined using ultrasound biometry (Tomey Al- 3000, Tomey Inc., Nagoya, Japan). The C/D ratio was evaluated by a single ophthalmologist (F.S.) in all patients. Visual acuity was measured using the E chart at a 6-meter distance and was later converted to logarithm of the minimum angle of resolution (logMAR).

Clinical and ocular parameters were used to detect disease progression [2, 15, 16]. An increase in the C/D ratio by more than 0.2, AL by more than 2 mm (during the first 3 years of life), or CD by more than 1 mm per year during the first 3 years of life, secondary to elevated IOP, was defined as progression. Eyes that did not meet these criteria were considered to be non-progressive.

Data were collected and compared between the 2 groups to determine the risk factors for progression. Data

were analyzed using SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, III., USA). Continuous variables were analyzed using Student's *t*-test, while categorical variables were analyzed using the chi-square test. Statistical significance was set at *P*-value < 0.05.

RESULTS

Eighty-three eyes of 46 patients were included, consisting of 37 eyes (45%) with PCG and 46 eyes (55%) with secondary glaucoma. During the follow-up period, 27 eyes (32.5%) had documented progression, and 56 eyes (67.5%) did not. Progression was comparable between eyes with PCG and secondary glaucoma (PCG, 22%; secondary glaucoma, 41%; $P = 0.152$). The mean ± SD of age was 145.86 ± 62.48 months in the non-progressed and 136 ± 32.34 months in the progressed group ($P = 0.541$). Table 1 shows that the familial history of glaucoma, presence of ocular anomalies, and laterality of glaucoma were comparable between the 2 groups (all $P > 0.05$); however, the presence of systematic disease was significantly higher in the progressed versus non-progressed group ($P = 0.043$).

Table 2 shows that sex, type of glaucoma, baseline and final IOP, final best-corrected distance visual acuity, final

Table 1. Family history, systemic diseases, ocular anomalies, and involved eyes in progressed and non-progressed eyes with pediatric glaucoma

Variable		Progressive group (n = 27 eyes)	Non-progressive group (n = 56 eyes)	*P*-value*
Positive familial history, n (%)		0 (0.0)	2 (3.6)	0.204
Systemic disease, n (%)	**CP**	2 (7.4)	0 (0.0)	**0.043**
	Preterm	5 (18.5)	5 (8.9)	
Ocular anomaly, n (%)	**Albinism**	1 (3.7)	1 (1.8)	0.593
	AR syndrome	1 (3.7)	1 (1.8)	
	CHED	1 (3.7)	3 (5.4)	
	Iris Coloboma	0 (0.0)	2 (3.6)	
	Microcornea	0 (0.0)	3 (5.4)	
	Peter's anomaly	1 (3.7)	1 (1.8)	
Involved eye, n (%)	**Right**	12 (44.4)	27 (48.2)	0.463
	Left	15 (55.6)	29 (51.8)	

Abbreviations: n, number; %, percentage; CP, cerebral palsy; AR syndrome, Axenfeld-Rieger syndrome; CHED, Congenital hereditary endothelial dystrophy. *P*-value < 0.05 is shown in bold,*the Chi-square test.

Table 2. Comparison of multiple parameters between progressed and non-progressed pediatric glaucoma groups

Variable		Progressive group (n = 27 eyes)	Non-progressive group (n = 56 eyes)	*P*-value*
Age at the time of diagnosis (m), Mean ± SD		13.3 ± 24.9	36.2 ± 56.7	**0.046**
Sex	**Boys, n (%)**	15 (55.6)	30 (53.6)	0.527
	Girls, n (%)	12 (44.4)	26 (46.4)	
Type of glaucoma	**PCG, n (%)**	8 (22)	29 (78)	0.152
	SG, n (%)	19 (41)	27 (59)	
Age at time of first surgery (m) , Mean ± SD		13.8 ± 24.9	46.3 ± 61.7	**0.012**
Initial IOP (mmHg), Mean ± SD		30.4 ± 9.4	27.5 ± 10.6	0.224
Final IOP (mmHg), Mean ± SD		21.17 ± 12.82	15.93 ± 6.34	0.173
Final AL (mm), Mean ± SD		21.7 ± 2.6	20.9 ± 2.5	0.294
Final CD (mm), Mean ± SD		11.5 ± 1.4	11.3 ± 1.8	0.688
Final C/D ratio-V, Mean ± SD		0.57 ± 0.23	0.58 ± 0.26	0.925
Final C/D ratio-H, Mean ± SD		0.54 ± 0.22	0.56 ± 0.7	0.742
Final CCT(µm), Mean ± SD		649.08 ± 96.30	648.10 ± 157.42	0.984
Final BCDVA (logMAR), Mean ± SD		1.4 ± 1.5	0.91 ± 1.0	0.541

Abbreviations: n, number; %, percentage; m, months; SD, standard deviation; PCG, primary congenital glaucoma; SG, secondary glaucoma; m, months; IOP, intraocular pressure; mmHg, millimeter of mercury; mm, millimeter; AL, axial length; CD, corneal diameter; C/D ratio-V, vertical cup-to-disc ratio; C/D ratio-H, horizontal cup-to-disc ratio; CCT, central corneal thickness; µm, micrometer; BCDVA, best-corrected distance visual acuity; logMAR, logarithm of the minimum angle of resolution. *P*- value < 0.05 is shown in bold,*t-test analysis

AL, final CD, final horizontal and vertical C/D ratio, and final CCT were not statistically significant between the 2 groups (all $P > 0.05$). However, age at the time of diagnosis (mean ± SD, 13.3 ± 24.9 months in the progressive group versus 36.2 ± 56.7 months in the non-progressive group), and age at the time of first surgery (mean ± SD, 13.8 ± 24.9 months in the progressive group versus 46.3 ± 61.7 months in the non-progressive group) were significantly lower in the progressive than in the non-progressive group ($P = 0.046$ and $P = 0.012$, respectively) (Table 2). The overall mean ± SD of follow-up was 52.25 ± 37.8 months, which was 51.50 ± 43 months in the progressed and 49.55 ± 34.35 months in the non-progressed group. During the 8 years of follow-up, 32.5% of patients with pediatric glaucoma had progression.

Two of 19 eyes with secondary glaucoma that were managed with medical treatment only progressed, both of these had glaucoma following cataract surgery. The progressed group underwent significantly more glaucoma surgeries than the non-progressed group (mean ± SD, 1.88 ± 1.1 versus 1 ± 0.8, $P = 0.015$). Overall, 25 eyes (93%) in the progressed group and 39 eyes (70%) in the non-progressed group underwent surgery. A second surgery was performed on 16 and 8 eyes, and a third surgery was performed on 5 and 1 eyes in the progressed and non-progressed groups, respectively. Fourth and fifth surgeries were performed in 2 and 1 eye in the progressed group, respectively. No eye in the non-progressed group required more than 3 surgeries. Figure 1 illustrates the

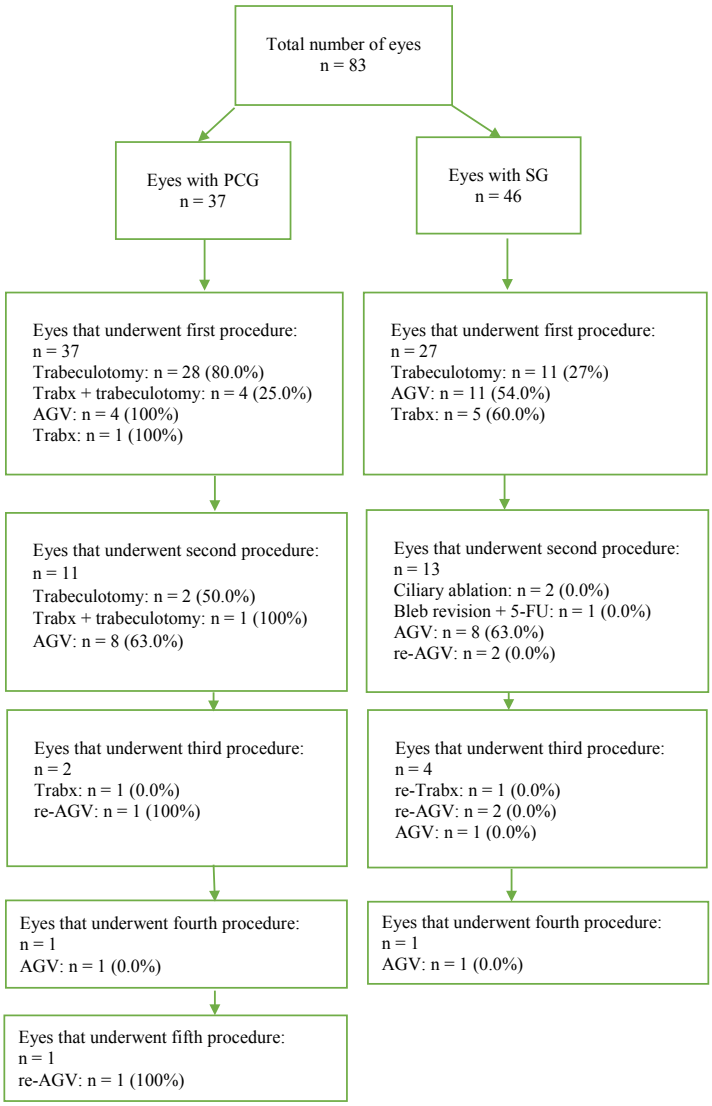

Figure 1. Surgeries in primary congenital glaucoma (PCG) and secondary glaucoma with a success rate (described as stable intraocular pressure and optic disc appearance [20]), which is given inside parentheses.

Abbreviations: PCG, primary congenital glaucoma; SG, secondary glaucoma; n, number of eyes; Trabx, trabeculectomy; AGV, Ahmed glaucoma valve; re-AGV, repeated Ahmed glaucoma valve; 5-FU, 5-fluorouracil; re-Trabx, repeated trabeculectomy.

number of surgeries performed in eyes with PCG or secondary glaucoma with the percentage of success during the study period (Figure 1).

Trabeculotomy was the most common first surgery in all patients (17 eyes in the progressed group and 22 eyes in the non-progressed group), and Ahmed glaucoma valve (AGV) implantation was the most common second surgery (6 eyes in the progressed group and 12 eyes in the non-progressed group). Trabeculotomy was the most common procedure in patients with PCG, while AGV was the most common surgery in patients with secondary glaucoma (Figure 1). Repeated AGV (re-AGV) implantation was performed in 11.1% of patients in the progressive group, as the most common third surgery.

Surgical complications occurred in 7 eyes in the progressive group (25.9%) and 6 eyes in the non-progressive group (10.7%) ($P = 0.108$). Two patients in the progressed group developed suprachoroidal hemorrhage, which finally resulted in loss of vision; these eyes had an AL of 29.32 and 29.10 mm. Among other complications, tube-corneal touch was the most frequent complication, observed in 2 patients (7.4%) in the progressive group and 1 patient in the non-progressive group (1.8%).

DISCUSSION

In this retrospective cohort of patients with pediatric glaucoma, 32.5% of eyes (22% PCG and 41% secondary glaucoma eyes) progressed over the course of the study. Patients who were younger at the time of glaucoma diagnosis and at the first glaucoma surgery were at a higher risk of progression. The progressed group underwent significantly more glaucoma surgeries. Surgical complications were comparable between the 2 groups.

Two of 19 eyes with secondary glaucoma that were managed with medical treatment only progressed, both of these had glaucoma following cataract surgery. Yu Chan et al. [3] indicated that pre-existing significant anatomical anomalies of the anterior drainage angle limit the effect of medical treatment for controlling IOP in eyes with PCG. Likewise, in the current study, all eyes with PCG underwent at least 1 angle surgery for the management of glaucoma. However, the procedures in our study were less effective than described by Yu Chan et al. [3]. Trabeculotomy was the most common surgery in eyes with PCG, while AGV was the most common procedure in eyes with secondary glaucoma. Overall, trabeculotomy was the most common first surgery, and AGV was the most common second surgery in all eyes. The re-AGV was performed in 11.1% of patients in the progressive group as the most common third surgery, and AGV was performed in the fourth and fifth surgeries in the progressive group. The complication rate did not reach statistical significance between groups, yet was clinically relevant. Two eyes with long ALs developed postoperative suprachoroidal hemorrhage and eventual loss of vision. According to a retrospective study by Zhang et al. [17], IOP ≤ 21 mmHg after trabeculotomy was achieved in 91% and 87% of patients by 1 and 3 years after surgery, respectively, which was higher than our success rate. They found a gradual decrease in the success rates of all procedures over a 9-year postoperative follow-up in patients with PCG. The successful surgical outcome correlated significantly with compliance with regular follow-up [17], which was not assessed in the current study. However, this indicates that such eyes should be treated cautiously, followed-up more regularly, and that the risks of sight-threatening complications need to be discussed thoroughly with parents before surgery.

In a retrospective evaluation of eyes with PCG, Al-Hazimi et al. [18] found clinical classification of PCG to be a supportive tool for surgical decision making. The mild form of PCG had high surgical success, irrespective of the type of procedure selected. Combined trabeculotomy-trabeculectomy with mitomycin C had the best outcomes in eyes with moderate and severe PCG [18]. In the current study, in addition to eyes with PCG, we included patients with secondary glaucoma, and we did not further subclassify eyes with PCG into mild, moderate, and severe groups. The progressed group underwent significantly more glaucoma surgeries than the non-progressed group. No eye in the non-progressed group required more than 3 surgeries. Trabeculotomy was the most common first surgery in the PCG group, with an 80% success rate.

In a study by de Silva et al. [15] on patients with pediatric glaucoma who underwent surgery in the first year, almost 9.7% of eyes progressed. However, the progression rate increased to 29.2% within 10 years. Nine eyes (30%) with PCG, during a follow-up period ranging from 22 to 59 years, showed progression in their study [15]. In our patients, we observed a 32.5% progression rate over the 8-year follow-up, which was higher than that reported by de Silva et al. [15]. The discrepancy in progression rate may arise from differences in the definition of progressive PCG: de Silva et al. considered this as a deterioration in visual acuity of > 0.2 logMAR units and/or progression of > 0.2 in C/D ratio due to increased IOP (> 21 mmHg). Furthermore, they included cases with PCG only [15], while we recruited both PCG and secondary pediatric glaucoma cases. The difference in racial background between the 2 studies might be another reason. De Silva et al. [15] found no factors associated with the good visual prognosis of PCG, but late diagnosis and treatment were highlighted as indicators of poor prognostic outcome.

Matlach et al. [19] found that short-term IOP fluctuation is associated with glaucoma progression in adult patients with glaucoma [19]. We found a significantly younger age at glaucoma diagnosis and at first surgery in the progressive group of pediatric glaucoma patients. Although the possible correlation between glaucoma progression and short-term IOP fluctuation was not investigated, baseline and final IOP values were comparable between the 2 groups. In a retrospective study of patients with pediatric glaucoma, Zagora et al. [20] reported a long-term gradual progression. They found that the success rate of angle surgery decreased from 92% in the first 2 years to 75% by 10 years. A younger age at diagnosis of PCG was associated with a worse visual prognosis, but no statistically significant relationship between age at first operation and the success or failure of angle surgery was found [20]. The differences between the report by Zagora et al. [20] and the present study might be due to their larger study population or longer mean follow-up.

In a cross-sectional study of 100 eyes of 70 patients aged > 11 years, Sinha et al. [21] found that early onset PCG at age ≤ 1 month or a high baseline preoperative IOP (> 30 mmHg) led to greater visual field loss. The visual field defects detected in PCG were similar to those reported in adults with glaucoma [21]. Similar to Sinha et al. [21], a lower age at the time of diagnosis was associated with glaucoma progression in our study. However, the current study did not find a significant difference in baseline or final IOP between the 2 groups. Papadopoulos et al. [22], in a prospective study of 99 children with newly diagnosed glaucoma, found no association between IOP control and baseline IOP, sex, ethnicity, family history, time elapsed between diagnosis and surgery, CD, age at diagnosis, and type or the total number of surgeries performed [22]. We found no significant differences in terms of sex, baseline and final IOP, family history, and final CD between the progressed and non-progressed eyes. In contrast, age at the time of diagnosis and age at the time of first surgery were significantly different between the progressive and non-progressive groups.

Currently, IOP is the only treatable risk factor for glaucoma development. In our study, baseline IOP and mean final IOP did not differ between the groups. However, we failed to assess IOP fluctuations and investigate its possible correlation with glaucoma progression in these pediatric glaucoma cases. Long-term home monitoring of IOP has also been shown to be an effective method for improving IOP control and decreasing pediatric glaucoma progression [23]. This approach is a practical measure for monitoring the progression of pediatric glaucoma. In an 8-year retrospective cohort, Erdem et al. [24] found that approximately half of the adult patients with low-pressure glaucoma showed glaucoma progression despite treatment. A significant risk factor was a high peak IOP [24]. In the context of baseline and final IOP, we did not find any significant differences. However, we did not monitor IOP fluctuations or the peak IOP, which might be another risk factor in pediatric glaucoma progression.

Beck et al. [25] compared the surgical success of aqueous shunt implantation (AGV or Baerveldt implant) and mitomycin C-augmented trabeculectomy in pediatric glaucoma in children under 2 years of age. They found excellent short-term success in patients who underwent aqueous shunt implantation (87%), as compared to trabeculectomy (36%), with a similar rate of corneal decompensation in the 2 treatment groups. However, aqueous shunt implantation led to more postoperative complications, requiring more surgical intervention than trabeculectomy. Tube cornea touch is the most common complication among patients who undergo aqueous shunt implantation [25]. Mandalos et al. [26] evaluated the 8-year outcomes and complications of glaucoma drainage device implantation (Baerveldt or Molteno) in 69 eyes with pediatric glaucoma. They found a high cumulative probability of long-term success (rates of 95.6% at 1 year and 39.7% at 8 years), associated with significant rates of complications and postoperative interventions that were managed successfully [26]. In pediatric glaucoma, the majority of eyes are responsive to the first surgery, while a few eyes might require a second or even a third surgical procedure. Tube-related complications, such as tube cornea touch, are the most common complications after AGV [13, 27]. Tube-corneal touch was the most frequent complication following AGV, in our study. Out of 83 eyes with pediatric glaucoma, 24, 6, 2, and 1 eyes underwent second, third, fourth, and fifth surgical intervention, respectively. We observed comparable surgical complications between the progressed and non-progressed groups. Two eyes with high AL in the progressed group developed suprachoroidal hemorrhage and eventual loss of vision.

High IOP in pediatric glaucoma causes corneal enlargement in children under 3 years of age and is an important marker for the diagnosis and monitoring of glaucoma progression [28]. Nevertheless, the baseline and final IOP or final CD were comparable between the 2 groups and were not risk factors for glaucoma progression in the current study. The lack of difference in final CD could be due to a significant decrease in corneal enlargement, which has been documented following successful surgical management of PCG [17]. However, assessment of CD at multiple time points in progressed versus non-progressed pediatric glaucoma eyes could provide a more robust conclusion. Matlach et al.'s study [19] in adult patients did not find any significant effect of demographic features

or ocular or general health on glaucoma progression [19]. The results of our study revealed that demographic or ocular characteristics were not risk factors for progression in our cohort of patients with pediatric glaucoma.

This study highlights the significance of a younger age at the time of diagnosis and the first surgical intervention in the prognosis of pediatric glaucoma. This further signifies the chance of requiring more surgical interventions in pediatric glaucoma with documented progression. However, our study was a retrospective study, and we did not have access to complete data on the consanguinity of patients. The other limitations of the current study were the small sample size and lack of normal controls for comparing ocular parameters in both study groups. Although Alanazi et al. [5] found a comparable mean baseline IOP, CD, and C/D ratio in eyes with primary versus secondary congenital glaucoma, our evaluation of PCG and secondary glaucoma outcomes together was not optimal in the current study. Ideally, the progression of 2 different glaucoma entities should not be analyzed in combination. Future studies should compare eyes with progressed versus non-progressed PCG or secondary glaucoma. Furthermore, multicenter prospective studies may identify more risk factors for the progression of pediatric glaucoma.

CONCLUSIONS

Pediatric glaucoma patients who are younger at the time of glaucoma diagnosis and at the first glaucoma surgery are at higher risk of glaucoma progression. Comorbid systemic disease is another risk factor for glaucoma progression. Therefore, surveillance for any systemic comorbidity is essential in children with glaucoma. In our study, eyes in the progressed group underwent significantly more surgical interventions. This information should be discussed with parents so that they can have realistic expectations and prepare for lifelong monitoring of the affected child. These findings are useful for clinicians when counseling parents of children with pediatric glaucoma about disease outcomes. However, future prospective studies with larger sample sizes and longer follow-up periods are needed to confirm our findings.

ETHICAL DECLARATION

Ethical approval: The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee of Ahvaz Jundishapur University of Medical Sciences (approval code IR.AJUMS.REC.1396.334).

Conflict of interests: None.

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