RESEARCH ARTICLE

Characteristics and long-term outcomes of childhood glaucoma: a retrospective-cohort study [version 1; peer review: 1 approved, 2 not approved]

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Abstract

Purpose: To evaluate the clinical characteristics and treatment outcomes of patients with childhood glaucoma.
Methods: We retrospectively reviewed the data of patients with childhood glaucoma who visited the glaucoma clinics at the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital between January 2008 and January 2018. The diagnosis was based on the Childhood Glaucoma Research Network classification. We recorded their clinical characteristics and requirement of any glaucoma interventions.
Results: A total of 691 eyes from 423 patients were included in this study. The patients predominantly comprised boys. The average follow-up duration was 71.3±63.8 months. The mean age at presentation was 3.9±4.4 years. Most patients presented with a high initial intraocular pressure (IOP) of 28.5±11.2 mmHg. Glaucoma associated with non-acquired ocular anomalies (22.9%) was the most common subtype, followed by primary congenital glaucoma (20.8%). We recorded a family history of glaucoma in 6.4% of patients. Most patients had bilateral glaucoma (63.4%) and required at least one intervention (51.5%). The average IOP at the latest follow-up visit was 19.1±10.8 mmHg. All glaucoma types had significantly lower IOP, compared to that at their baselines (all $p<0.001$). Moreover, most patients had an unfavourable visual acuity (49.5%) at their latest visit.
Conclusions: Secondary glaucoma associated with non-acquired ocular anomalies is the most common subtype of glaucoma. All subtypes, including primary glaucoma, were sporadic. The majority of patients had unfavourable visual outcomes. These real-world findings are fundamental to acquire a better understanding of childhood

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glaucoma.

Keywords
childhood glaucoma, congenital glaucoma, paediatric glaucoma, Childhood Glaucoma Research Network classification, retrospective cohort, paediatric eye disease

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Introduction

Childhood glaucoma is a vision-threatening disorder with an incidence of 2.29 to 5.41 per 100,000 individuals[1,2]. The diagnosis of childhood glaucoma poses some challenges. This can be attributed to the variation in clinical presentations among different age groups. Despite high intraocular pressure (IOP) being the primary cause of glaucomatous damage, an accurate IOP measurement is not always obtained in children. Angle surgery is a common therapy but it is mostly associated with unfavourable outcomes in children, compared to that in adults[3].

Childhood glaucoma encompasses several categories of glaucoma. The Childhood Glaucoma Research Network (CGRN) classification was proposed by an international consortium of glaucoma specialists in 2013 to standardise the definition of childhood glaucoma subtypes[4]. The prevalence of childhood glaucoma differs among ethnicities, ranging from 1:1,250 to 1:68,254 live births[5–12]. The incidence and clinical characteristics of childhood glaucoma in Thailand have not yet been reported. The Queen Sirikit National Institute of Child Health is one of the largest tertiary centres in Thailand. It is responsible for the treatment of a majority of the complex paediatric cases from all over the country. Paediatric glaucoma clinics have been established by the joint collaboration between the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital, a university-based hospital. These clinics aimed to treat all paediatric glaucoma cases that were referred to the aforementioned hospitals and have been operated by the same group of glaucoma specialists for more than 10 years. We aimed to describe the clinical characteristics and brief long-term treatment outcomes of the large paediatric glaucoma cohorts of the two major referral centres in Thailand.

Methods

Cohort selection

We retrospectively reviewed the medical records of all patients who had been examined at the paediatric glaucoma clinics of the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital between January 2008 and January 2018. The patient list was extracted from the hospital database to include all individuals that had at least one visit to the paediatric glaucoma clinic during the above period and/or subjects that had the ICD-10-CM diagnostic codes of Q15.0 and all H40 and H42 categories. The inclusion criteria were patients who aged <16 years at the time of the first clinic visit and met the CGRN glaucoma or glaucoma suspect definition[4]. Cases with incomplete medical record precluding the diagnosis were excluded. The CGRN definition of glaucoma and suspected glaucoma has been previously described[4].

Ethics approval

Ethical approval was obtained from the Research Ethic Committee of the Queen Sirikit National Institute of Child Health and Faculty of Medicine, Chulalongkorn University (REC.041/2562 and IRB.807/61). The requirement for written informed consent was waived due to the retrospective nature of the study.

Outcomes

We collected data for the demographic characteristics, initial clinical presentations, and diagnoses. All available clinical information was evaluated and classified according to the Childhood Glaucoma Research Network (CGRN) classification into the following seven groups: (1) primary congenital glaucoma (PCG), (2) juvenile open-angle glaucoma (JOAG), (3) secondary glaucoma following cataract surgery (SCG-C), (4) secondary glaucoma associated with non-acquired systemic disease or syndrome (SCG-S), (5) secondary glaucoma associated with non-acquired ocular anomalies (SCG-O); (6) secondary glaucoma associated with acquired conditions (SCG-A); and (7) glaucoma suspect (GS). The CGRN classification diagram has been illustrated elsewhere[4,13].

We recorded the interventions during the follow-up course and final outcomes, including visual acuity (VA) and IOP at the latest available visit in eyes with a confirmed glaucoma diagnosis (diagnosis group 1 to 6). For glaucoma interventions, we reviewed the data to determine if the subjects had received any incisional surgeries (i.e. trabeculectomy, trabeculotomy, and glaucoma drainage device implantation), cyclodestructive laser procedures (i.e. diode transscleral cyclophotocoagulation, diode laser endoscopic cyclophotocoagulation), or a combination of both at any time point of the follow-up period.

The best-corrected VAs were determined using the LEA or Snellen chart at 10 feet or 20 feet, respectively. In contrast, VA was graded by the fixation patterns using a central, steady, and maintained (CSM) technique for patients who were too young to determine the pictures or numbers[14]. The LEA chart symbols were reproduced with permission from Good-Lite Co., Elgin, IL. According to Karr *et al.*[15], the fixation pattern of CSM, CSUM, CUSUM and UCUSUM was estimated as the VA of ≥ 20/30, 20/30–20/100, ≤20/300, and ≤5/200, respectively. We extrapolated the Snellen acuity from the fixation grade with a modification from Karr *et al.*'s method and classified the VA into the following three groups: (1) favourable: best-corrected VA (BCVA) ≥20/70 or fixation grade of CSM, (2) moderately favourable: BCVA=20/70 to <20/400 or fixation grade of CSUM; and (3) unfavourable: BCVA≤20/400 or fixation grade of CUSUM or UCUSUM.

Statistical analysis

The categorical data were presented as counts and percentages. We conducted the Shapiro-Wilk test for the normality of continuous data distribution. The data were reported as means and standard deviations or medians and interquartile ranges, depending on the distribution. We used the analysis of variance to compare the initial IOP among the glaucoma subtypes and the paired t-test to compare the IOP during the initial and latest visit. Furthermore, the Stuart-Maxwell test for marginal homogeneity was used to compare the proportion of matched pairs of the VA during the initial and latest visit. Statistical analyses were performed using Stata 13.0 (Stata Corp, College Station, TX, USA). A P-value <0.05 was deemed statistically significant.

Results

The cohort comprised 423 patients (691 eyes). While 338 patients (532 eyes) were diagnosed with glaucoma, 85 patients (159 eyes) had GS. The average follow-up duration was 71.3±63.8 months (median 50; interquartile range, 22–112 months). Table 1 summarises the baseline characteristics. The average age at presentation was 3.91±4.40 years (median 1.75: interquartile range, 0.25–6.75 years). We recorded a family history of glaucoma in 15 (6.4%) patients. Furthermore, we found a statistically significant predominance of boys in all subjects (P=0.002), PCG (P=0.01), SCG-C (P=0.01), and GS (P=0.04). The mean of initial IOP was 28.5±11.2 mmHg. There was no difference in the initial IOP among the glaucoma subtypes (p=0.52). The most common presentation was cloudy eye (68.2%), which represented leukocoria or corneal haze, and megalocornea (14.5%). Table 2 demonstrates the mode of detection patterns and clinical presentations.

Most patients had bilateral glaucoma (63.4%). Among the 155 eyes of the unilateral cases, there were 72 (46.5%) and 83 (53.6%) right and left eyes, respectively. The diagnosis with significantly higher bilateral presentation included PCG (P=0.01), JOAG (P=0.03), SCG-O (P=0.03), and GS (P<0.001). SCG-S (unilateral 59.4%) and SCG-A (unilateral 53.6%) comprised a higher proportion of unilateral cases. However, the difference was statistically insignificant.

SCG-O was the most common subtype, accounting for 23% of the cohort or 29% of the glaucoma cases. In contrast, JOAG was the least common subtype. Figure 1 depicts the frequency of each glaucoma diagnosis.

The onset of PCG was neonatal (≤1 month), infantile (>1 to 24 months), and late (>2 years) in 33 (37.5%), 38 (43.2%), and two (2.3%) patients, respectively. However, the onset was undetermined in 15 (17.1%) patients with PCG. Figure 2 outlines the distribution of the anomalies associated with SCG-O, SCG-S, and SCG-A. We could obtain angle data for 56 eyes with SCG-A, of which 44 (78.6%) and 12 (21.4%) eyes had open and closed angles, respectively.

SCG-C was mostly observed following a surgery for a congenital idiopathic cataract (n=19, 57.6%), followed by congenital cataract associated with ocular anomalies or systemic diseases (n=7, 21.2%), and acquired cataract (n=3, 9.1%). There were four patients (12.1%) that the type of cataract could not be specified.

While 157 glaucomatous eyes (29.5%) underwent an incisional surgery, 68 eyes (12.8%) underwent a cyclodestructive laser surgery. In contrast, 49 (9.2%) eyes required both incisional and cyclodestructive procedures at any time point during the follow-up period. Figure 3 presents the frequency of glaucoma intervention in each glaucoma type.

SCG-A had the highest proportion of favourable VA at the initial (57.5%) and latest (53.4%) visits. However, JOAG had the highest proportion of unfavourable VA at the initial (53.9%) and latest (73.3%) visits. We observed a higher proportion of unfavourable VA at the latest visit in the overall glaucoma cases (P=0.03), compared to that at the initial visit. A worsening of the VA was primarily observed in the SCG-O group. Despite an approach in the shift, it failed to attain a statistical significance (P=0.07). Moreover, the average IOP was 19.1±10.8 mmHg at the latest visit. All glaucoma types had significantly lower IOPs, compared to the baseline values (all p<0.001). Table 3 shows a comparison of the VA and IOP between the initial and latest visits for each glaucoma type.

Conclusions/discussion

Childhood glaucoma comprises a group of eye disorders that affect children from their birth with a juvenile onset. Our study had an average follow-up of 6 years. SCG-O (22.9%) was the most common subtype, followed by PCG (20.8%) and SCG-A (18.9%). The condition mostly affected boys, with the majority being bilateral cases, similar to previously published results. Primary glaucoma, both PCG and JOAG, and SCG-O commonly require at least one type of glaucoma intervention. Following the treatment, we observed significant IOP improvements in all subtypes. Nonetheless, half of the cases demonstrated unfavourable VA at the final visit.

Existing literature has reported on a varied distribution of the subtypes[2,8–10,12]. Most researchers have found a higher prevalence of secondary glaucoma, compared to primary glaucoma. However, reports from Canada[6], Egypt[9], Great Britain and the Republic of Ireland[2], and China[7] have found that the majority of cases comprised PCG. The prevalence of secondary glaucoma depends on the prevalence of its aetiology (e.g. childhood cataract, hereditary systemic disease), which can differ among regions and ethnicities. Furthermore, this variation can be explained by the diagnostic criteria and study design. The diagnostic criteria of the studies conducted before 2013 were not based on the CGRN classification. In addition, hospital-based studies tend to have a higher proportion of complex cases, such as patients with syndromic and systemic involvement than those conducted in population-based settings. Table 4 summarises the distribution of childhood glaucoma according to the CGRN classification[1,2,5–7,9–12].

Leukocoria or corneal haze were the leading presenting symptom in PCG (46.9%) and SCG-O (77%) similar with previous studies[16–18]. Moreover, most patients with JOAG were diagnosed without any symptoms. This could partially explain the most advanced stage at the time of diagnosis and the highest proportion of unfavourable VA outcomes in the aforementioned subtype. High IOP was the leading clue for glaucoma diagnosis. Furthermore, an enlarged corneal diameter was considered an important sign of PCG[16].

We detected a family history of glaucoma in 6.4% of the 234 patients with an available family history. A study by Fung *et al.* reported on a family history of glaucoma in 17% patients with paediatric GS[5]. This high rate could be attributed to the

Table 1. Clinical and demographic characteristics of the study participants.

Characteristics	Total	PCG	JOAG	SCG-C	SCG-S	SCG-O	SCG-A	GS
Number of eyes (patients)	691 (423)	145 (88)	15 (8)	54 (33)	45 (32)	156 (97)	117 (80)	159 (85)
Gender (patients, %)								
Male	250 (59.1%)	56 (63.6%)	4 (50%)	24 (72.7%)	18 (56.3%)	53 (54.6%)	43 (53.8%)	52 (61.2%)
Female	173 (40.9%)	32 (36.4%)	4 (50%)	9 (27.3%)	14 (43.8%)	44 (45.4%)	37 (46.3%)	33 (38.8%)
Age at presentation (years)	1.6 (0.3 to 6.8)	0.4 (0.2 to 4.4)	8.4 (5.3 to 12.4)	5.6 (1.8 to 7.6)	2.1 (0.4 to 6.3)	0.3 (0 to 3.0)	6.8 (2.8 to 10.4)	2.7 (0.6 to 7.7)
Family history (patients, %) *								
Yes	15 (6.4%)	0	1 (20.0%)	1 (7.7%)	2 (13.3%)	6 (10.7%)	0	5 (8.3%)
No	219 (93.6%)	35 (100%)	4 (80.0%)	12 (92.3%)	13 (86.7%)	50 (89.3%)	50 (100%)	55 (91.7%)
Laterality (patients, %)								
Bilateral	268 (63.4%)	57 (64.8%)	7 (87.5%)	21 (63.6%)	13 (40.6%)	59 (60.8%)	37 (46.3%)	74 (87.1%)
Unilateral	155 (36.6%)	31 (35.2%)	1 (12.5%)	12 (36.4%)	19 (59.4%)	38 (39.2%)	43 (53.6%)	11 (12.9%)
Refraction (eyes, SE) †	0 (-2.00 to 1.25)	2.13 (2.13 to 2.13)	0	-2.25 (-6.63 to 5.50)	0.50 (0 to 1.25)	-2.88 (-3.25 to 3.00)	-1.25 (-2.00 to -0.25)	0.63 (-0.50 to 1.50)
Corneal diameter (eyes, mm)	11.5 (10 to 13)	12.5 (12 to 13)	10.5 (10 to 12)	10 (10 to 12)	11.5 (9 to 12.3)	11 (9 to 12.3)	11 (10 to 12)	11 (10 to 12)
Cup to disc ratio (eyes) ‡	0.6 (0.3 to 0.8)	0.8 (0.6 to 0.9)	0.9 (0.9 to 1.0)	0.4 (0.3 to 0.7)	0.5 (0.3 to 0.8)	0.3 (0.2 to 0.4)	0.4 (0.3 to 0.7)	0.6 (0.5 to 0.8)

Data shown in median (interquartile range).

* Data available in 234, 35, 5, 13, 15, 56, 50, and 60 patients for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.

† Data available in 93, 1, 2, 16, 5, 5, 19, and 45 eyes for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.

‡ Data available in 426, 71, 14, 39, 34, 41, 71, and 156 eyes for total, PCG, JOAG, SCG-C, SCG-S, SCG-O, SCG-A, and GS, respectively.

IOP, intraocular pressure; SE, spherical equivalence; PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions; GS, glaucoma suspect.

Table 2. Mode of detection patterns in eyes with a glaucoma diagnosis.

Mode of detection patterns	Total	PCG	JOAG	SCG-C	SCG-S	SCG-O	SCG-A
Presented with glaucoma-related symptoms							
Cloudy eye	230 (69.1%)	68 (57.6%)	0	7 (100.0%)	9 (40.9%)	121 (85.8%)	25 (59.5%)
Megalocornea	49 (14.7%)	27 (22.9%)	0	0	10 (45.5%)	10 (7.1%)	2 (4.8%)
Epiphora	22 (6.6%)	13 (11.0%)	0	0	2 (9.1%)	6 (4.3%)	1 (2.4%)
Red eye	14 (4.2%)	0	0	0	1 (4.5%)	4 (2.8%)	9 (21.4%)
Photophobia	13 (3.9%)	9 (7.6%)	0	0	0	0	4 (9.5%)
Blepharospasm	2 (0.6%)	1 (0.9%)	0	0	0	0	1 (2.4%)
Blurred vision	3 (0.9%)	0	3 (100.0%)	0	0	0	0
From clinical surveillance or screening (no glaucoma-specific symptoms) *	126	-	6	32	17	9	62
Unknown / missing data	73	27	6	15	6	6	13

Data shown in number of eyes (%).

* Including eyes from clinical surveillance in known systemic or ocular diseases, clinical surveillance due to family history of glaucoma and other forms of child health screening.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.

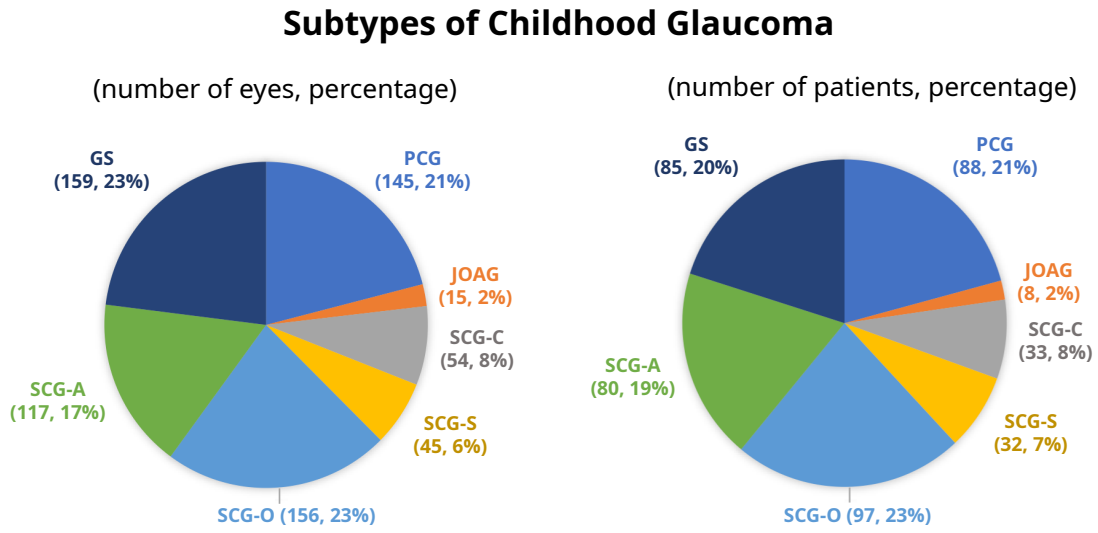

Figure 1. Subtypes of childhood glaucoma. PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions; GS, glaucoma suspect.

tendency of having the eyes checked because of a family history of glaucoma. In our study, an exclusion of the GS cases would have reduced the rate of positive family history from 6.4% to only 5.7% (10 out of 174 patients). This value was half of that reported by Papadopoulos *et al.* (11%)[2]. Despite the association of PCG and JOAG with certain mutations[19], our

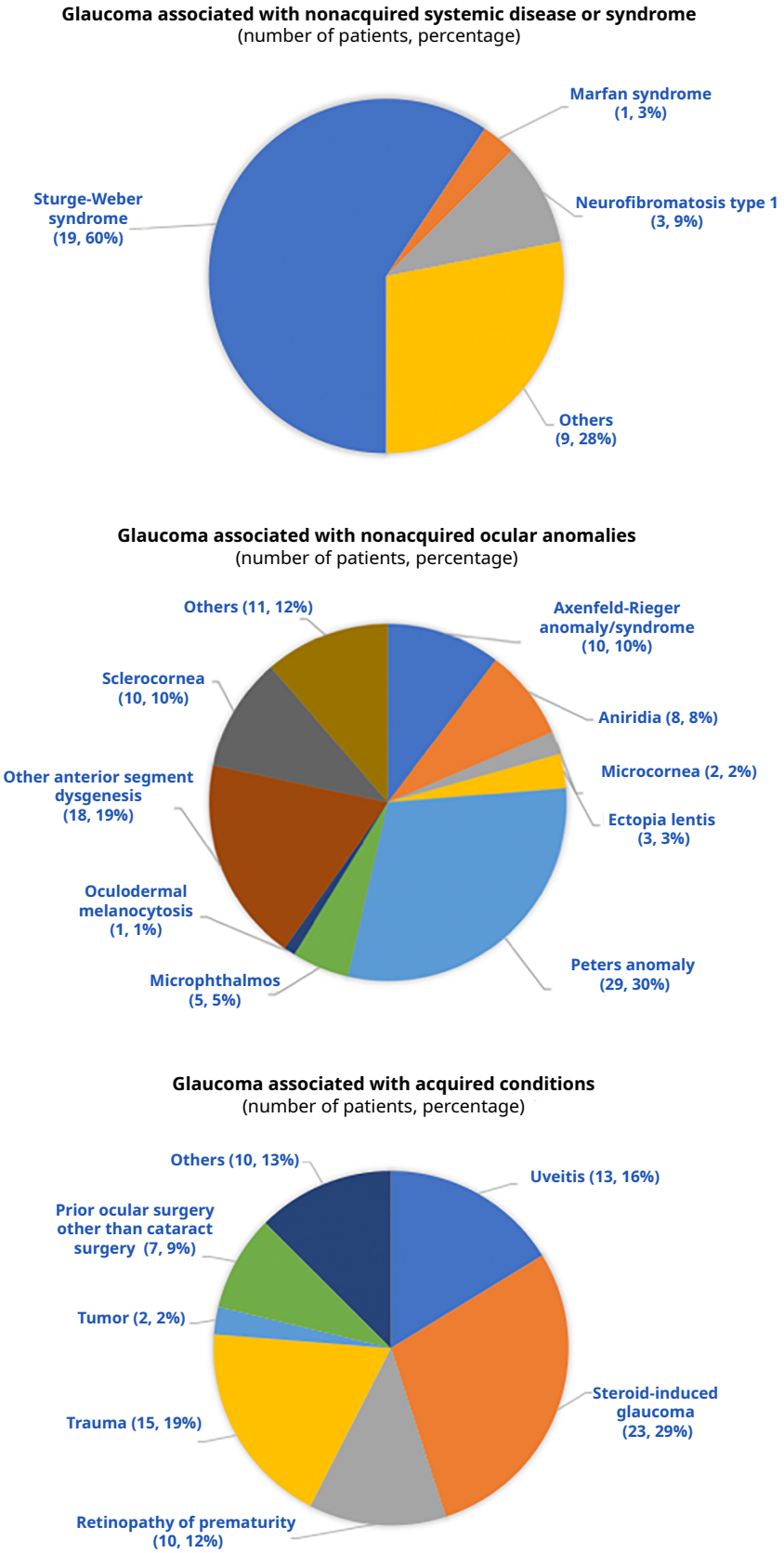

Figure 2. Causes of secondary glaucoma subtypes that are associated with non-acquired systemic disease, non-acquired ocular anomalies, and acquired conditions.

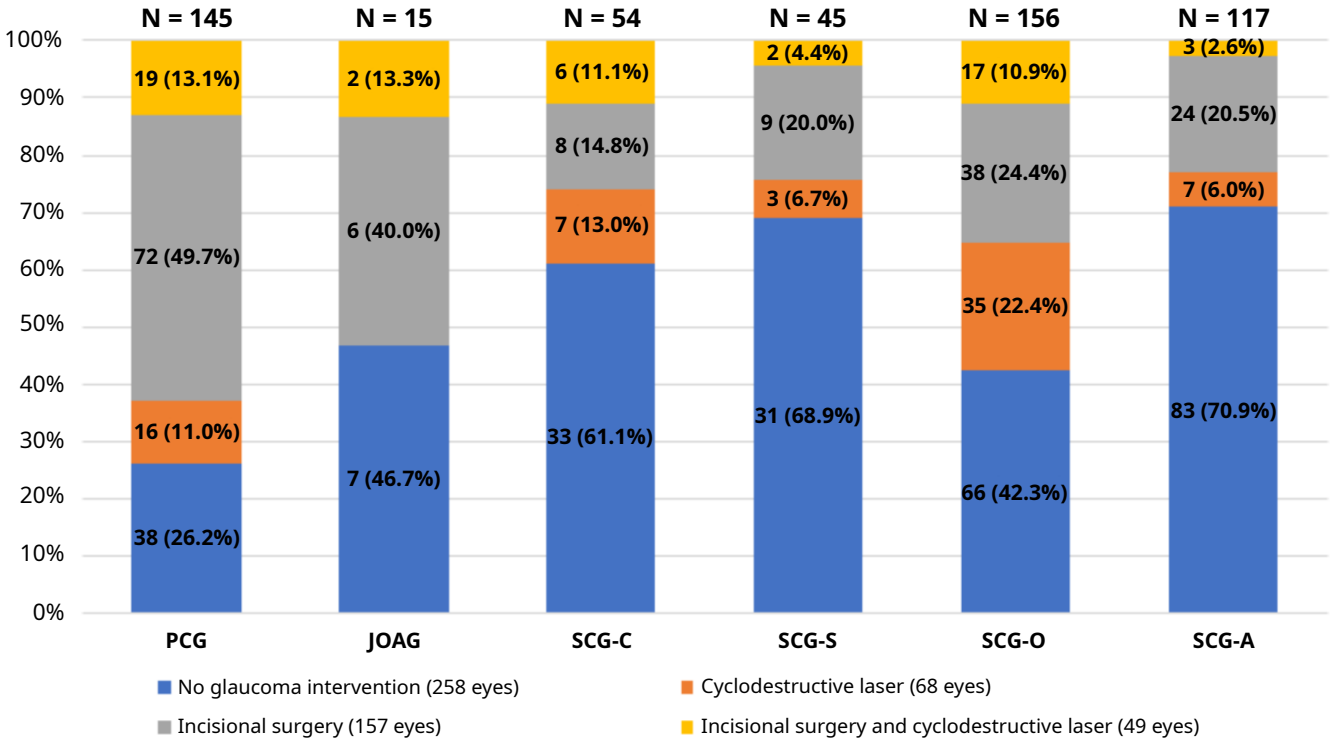

Figure 3. Type of glaucoma interventions in eyes with a glaucoma diagnosis. PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.

cohort revealed a positive family history in none of the PCG cases and in only one JOAG case. Therefore, the PCG cases in Thailand were sporadic rather than inherited.

In line with the published literature, we found that surgical interventions were mostly required in the primary type of glaucoma, both PCG and JOAG. Moreover, medication was the mainstay of treatment for most secondary glaucoma cases[2]. In addition, SCG-O cases reported a high rate of surgical intervention. The pathology of the above-mentioned subtype is related to angle dysgenesis, which usually makes it difficult to control the disease.

Ramkrishanan *et al*. reported a significant improvement of VA, which was sustained for at least four years of follow-up[20]. This was in contrast to the marginally significant worsening of VA observed in our study. This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan *et al.* The improvement of VA in their study was attributed to an improved corneal clarity following surgery.

We found that the SCG-A cases had the most favourable VA at the latest visit and the best initial VA. The majority of the cases included steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O. However, we found an overall worse VA, compared to that reported in previous publications[6,11,20]. This discrepancy could be explained by the following aspects. First, we documented a high proportion of unfavourable VA during the initial visits. Khitri *et al.* reported on an association between poor vision at diagnosis and visual impairment (<20/200)[21]. Second, our cases were diagnosed at an extremely young age, particularly in the PCG (median age 0.5 years) and SCG-O (median age 0.3 years) groups. Studies on the PCG subtype reported on final VA <20/200 in children diagnosed before the age of three months regardless of their IOP levels[22,23]. It was hypothesised that the earlier presentation reflected the poorer development of the angle. In other words, the disease was more severe. Nevertheless, the study design and definition of unfavourable VA differed among the studies.

Our study had the strength of being a large cohort study with a long follow-up duration. Our data also represents the majority of childhood glaucoma cases in Thailand. However, it had several limitations. First, there were some incomplete

Table 3. Visual acuity and intraocular pressure in eyes with a glaucoma diagnosis.

	Follow up period (months) median (IQR)	Initial visual acuity N (%)			Last visual acuity N (%)			P value*	Initial intraocular pressure (mmHg) mean (SE)	Last intraocular pressure (mmHg) mean (SE)	P value†
		Favorable	Moderately favorable	Unfavorable	Favorable	Moderately favorable	Unfavorable				
All glaucoma	60 (27 to 122)	103 (39.0%)	58 (22.0%)	103 (39.0%)	140 (34.7%)	64 (15.8%)	200 (49.5%)	0.03	28.5 (11.2)	19.1 (10.8)	<0.001
PCG	83 (36 to 134)	14 (24.6%)	14 (24.6%)	29 (50.9%)	30 (28.9%)	16 (15.4%)	58 (55.8%)	0.46	28.5 (11.0)	18.5 (12.3)	<0.001
JOAG	96 (15 to 156)	4 (30.8%)	2 (15.4%)	7 (53.9%)	3 (20.0%)	1 (6.7%)	11 (73.3%)	0.37	25.6 (14.3)	15.00 (6.8)	<0.001
SCG-C	47.5 (25 to 114)	12 (28.6%)	17 (40.5%)	13 (31.0%)	17 (34.0%)	18 (36.0%)	15 (30.0%)	0.25	27.2 (9.3)	17.2 (6.6)	<0.001
SCG-S	57 (27 to 111)	6 (30.0%)	10 (50.0%)	4 (20.0%)	13 (46.4%)	7 (25.0%)	8 (28.6%)	0.17	26.3 (9.5)	15.9 (7.6)	<0.001
SCG-O	75 (40 to 138)	17 (37.8%)	7 (15.6%)	21 (46.7%)	22 (21.2%)	16 (15.4%)	66 (63.5%)	0.07	29.9 (12.1)	21.6 (10.8)	<0.001
SCG-A	38 (16 to 81)	50 (57.5%)	8 (9.2%)	29 (33.3%)	55 (53.4%)	6 (5.8%)	42 (40.8%)	0.40	28.6 (11.1)	19.3 (11.3)	<0.001

* Calculated from the paired data of eyes with available initial visual acuity and latest visual acuity- all glaucoma 253 pairs, PCG 53 pairs, JOAG 13 pairs, SCG-C 42 pairs, SCG-S 17, SCG-O 41 pairs, and SCG-A 87 pairs.

† Calculated from the paired data of eyes with available initial intraocular pressure and latest intraocular pressure- all glaucoma 634 pairs, PCG 129 pairs, JOAG 14 pairs, SCG-C 53 pairs, SCG-S 41, SCG-O 139 pairs, and SCG-A 110 pairs.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions.

Table 4. Distribution of childhood glaucoma according to the Childhood Glaucoma Research Network classification.

Study	Number of glaucoma patients	Population	PCG	JOAG	SCG-C	SCG-S	SCG-O	SCG-A
Hospital-based setting								
Current study	338	2 Tertiary paediatric glaucoma clinics, Thailand	88 (26%)	8 (2.4%)	33 (9.8%)	32 (9.5%)	97 (28.7%)	80 (23.6%)
Senthil *et al.* 2019	275	Tertiary eye care, India	107(38.9%)	38 (13.8%)	22 (8%)	16 (5.8%)	48 (17.5%)	44 (16%)
Mokbel *et al.* 2018	207	Chief referral center, Egypt	114 (55%)	2 (1%)	15 (7.2%)	4 (2%)	11 (5.3%)	61 (29.5%)
Hoguet *et al.* 2016	122	Tertiary childhood glaucoma clinic, USA	39 (32%)	9 (7.4%)	22 (18%)	14 (11.5%)	10 (8.2%)	28 (22.9%)
Fung *et al.* 2013	152*	Dallas Glaucoma Registry, USA	46 (30.3%)	10 (6.6%)	30 (19.7%)	18 (11.8%)	16 (10.5%)	32 (21.1%)
Qiao *et al.* 2009 †	948	Hospitalized paediatric patients, Beijing, China	486 (51.3%)	63 (6.6%)	125 (13.2%)	40 (4.2%)	61 (6.4%)	173 (18.3%)
Taylor *et al.* 1999 †	296*	Hospital for sick children, Toronto, Canada	117 (39.5%)	7 (2.4%)	61 (20.6%)	32 (10.8%)	38 (12.8%)	41 (13.9%)
Barsoum-Homsy *et al.* 1986	63	Paediatric glaucoma clinic, Montreal, Canada	14 (22.2%)	0	7 (11.1%)	9 (14.2%)	24 (38%)	9 (14.2%)
Population-based setting								
Aponte *et al.* 2010 †	30	Olmstead county residents, Minnesota, USA	1 (3.3%)	4 (13.3%)	6 (20%)	4 (13.4%)	2 (6.7%)	13 (43.3%)
Papadppoulos *et al.* 2007	91*	British Ophthalmic Surveillance Unit, Great Britain and Republic of Ireland	45 (49.4%)	2 (2.2%)	16 (17.6%)	12 (13.2%)	6 (6.6%)	10 (11%)

* We excluded patients who were glaucoma suspect or had an unknown diagnosis.

† The diagnosis was reclassified from the original articles to follow the CGRN classification.

PCG, primary congenital glaucoma; JOAG, juvenile open angle glaucoma; SCG-C, secondary glaucoma following cataract surgery; SCG-S, secondary glaucoma associated with non-acquired systemic condition; SCG-O, secondary glaucoma associated with ocular anomalies; SCG-A, secondary glaucoma associated with acquired conditions

data because of the retrospective design. Moreover, information on some clinical examinations, such as VA and IOP could not always be obtained in children at every clinic visit. Second, the long follow-up period resulted in a shift in the IOP measurement methods from a handheld contact tonometer (Tono-Pen; Reichert, New York, USA) to a rebound tonometer (iCare TAO1i, Tiolat Oy, Helsinki, Finland) in extremely young or non-cooperative children. Third, there was inadequate information to clearly identify the cause of unfavourable VA outcomes. Future research should explore this underlying issue.

In conclusion, data from the referral centres in Thailand showed a higher prevalence of secondary glaucoma than primary glaucoma. Using the CGRN classification, secondary glaucoma associated with non-acquired ocular anomalies was found to be the most common subtype. All subtypes, including primary glaucoma, were sporadic. A majority of the cases had unfavourable visual outcomes. These real-world findings are fundamental data and provide a better understanding of childhood glaucoma.

Data availability

Underlying data

Harvard Dataverse: Childhood glaucoma, https://doi.org/10.7910/DVN/V3HFNF[24].

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http://www.doi.org/10.7910/DVN/V3HFNF

Open Peer Review

Current Peer Review Status: ✗ ✗ ✓

Version 1

Reviewer Report 01 April 2021

https://doi.org/10.5256/f1000research.54403.r80446

✓ **Chengguo Zuo**
State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Guangzhou, China

This interesting study analyzed the clinical characteristics and treatment results of patients with childhood glaucoma who had visited the glaucoma clinics at the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital within 10 years, and provided effective data and analysis for a better understanding of children's glaucoma in Thailand. There are several questions that need to be answered:

1. In the "Results" of the "Abstract", "Most patients presented with a high initial intraocular pressure (IOP) of 28.5±11.2 mmHg." Does the patients here refer to all patients or just for the patients with a high initial IOP?

2. In the "Results", you described that "The average age at presentation was 3.91±4.40 years (median 1.75: interquartile range, 0.25–6.75 years)." But in the "Table 1", the average age at presentation of the total patients is 1.6(0.3 to 6.8) years. Please give a more detailed explanation here or check data again.

3. In this study, the authors only collected the family history of 234 of the 423 patients, as you described that "We detected a family history of glaucoma in 6.4% of the 234 patients with an available family history." in the "Conclusions/discussion". We suggest that the description of this in the previous part "Result" that "We recorded a family history of glaucoma in 15 (6.4%) patients" need to be added the information that the data was from 234 patients, so as not to cause misleading or doubt. Besides, when analyzing the family history of patients, the author did not analyze the fact that the family history of not all the patients had been collected. This will inevitably lead to a certain degree of bias. Without analyzing this, the conclusion that" Therefore, the PCG cases in Thailand were sporadic rather than inherited." could be not that reliable.

4. There are several places in the article that need to be supported by the literature: a）：In the "Conclusion" that "The condition mostly affected boys, with the majority being bilateral cases, similar to previously published results."b）：In the "Conclusion" that "In addition, SCG-O cases reported a high rate of surgical intervention."

5. In the “Conclusion”, you described that “This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan *et al*.” Please Please provide the PCG ratio of this research and the comparison with that of your study to compare the difference between the two more intuitively.

6. In the description SCG-A had the most favourable VA at the latest visit and the best initial VA, you described that “The majority of the cases included steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O.” But from Figure 2, steroid-induced glaucoma accounts for 29%, which is not so high. Does the authors mean “The majority of the cases such as steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations…”?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Glaucoma

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 14 Dec 2021

Sunee Chansangpetch, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

This interesting study analyzed the clinical characteristics and treatment results of patients with childhood glaucoma who had visited the glaucoma clinics at the Queen Sirikit National Institute of Child Health and the King Chulalongkorn Memorial Hospital within 10 years, and

provided effective data and analysis for a better understanding of children's glaucoma in Thailand. There are several questions that need to be answered:

1. In the "Results" of the "Abstract", "Most patients presented with a high initial intraocular pressure (IOP) of 28.5±11.2 mmHg." Does the patients here refer to all patients or just for the patients with a high initial IOP?

Response: We apologize that the sentence was not clear. The IOP of 28.5±11.2 mmHg referred to all patients' IOP. We have modified the sentence as follows:
Abstract: "Most patients presented with a high initial intraocular pressure (IOP). The average initial IOP of all patients was 28.5±11.2 mmHg."

2. In the "Results", you described that "The average age at presentation was 3.91±4.40 years (median 1.75: interquartile range, 0.25–6.75 years)." But in the "Table 1", the average age at presentation of the total patients is 1.6(0.3 to 6.8) years. Please give a more detailed explanation here or check data again.

Response: Thank you very much for catching this. The median age at presentation was 1.58. We have corrected the error in the Results:
Results: "The average age at presentation was 3.91±4.40 years (median 1.58: interquartile range, 0.25–6.75 years)."

3. In this study, the authors only collected the family history of 234 of the 423 patients, as you described that "We detected a family history of glaucoma in 6.4% of the 234 patients with an available family history." in the "Conclusions/discussion". We suggest that the description of this in the previous part "Result" that "We recorded a family history of glaucoma in 15 (6.4%) patients" need to be added the information that the data was from 234 patients, so as not to cause misleading or doubt. Besides, when analyzing the family history of patients, the author did not analyze the fact that the family history of not all the patients had been collected. This will inevitably lead to a certain degree of bias. Without analyzing this, the conclusion that" Therefore, the PCG cases in Thailand were sporadic rather than inherited." could be not that reliable.

Response: We agree with the reviewer's comment. We have added that the family history data was obtained from 234 patients and removed the conclusion of the sporadic nature in the Abstract to avoid misleading. The Conclusions/Discussion section have also been modified.

Abstract - results: We recorded a family history of glaucoma in 6.4% of patients of the 234 patients with an available family history.
Conclusions/Discussion - 4th paragraph: "The true frequency of familial glaucoma, however, may be higher, as the data were available for only 55% of our patients. In addition, getting a family history without examining each family member tends to underestimate the actual occurrence of glaucoma in the family."

4. There are several places in the article that need to be supported by the literature: a）：In the "Conclusion" that "The condition mostly affected boys, with the majority being bilateral

cases, similar to previously published results."b) ：In the "Conclusion" that "In addition, SCG-O cases reported a high rate of surgical intervention."

Response: Thank you for the comment. The following references have been added.
To (a): 16. American Academy of Ophthalmology. Glaucoma in Children and Adolescents. In: Tanna AP, Lin SC, Boland MV, et al., eds. *Basic and Clinical Science Course Section 10 Glaucoma.* San Francisco: American Academy of Ophthalmology; 2020.
To (b): 5. Fung DS, Roensch MA, Kooner KS, Cavanagh HD, Whitson JT. Epidemiology and characteristics of childhood glaucoma: results from the Dallas Glaucoma Registry. *Clinical Ophthalmology.* 2013;7:1739-1746.

5. In the "Conclusion", you described that "This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan *et al*." Please Please provide the PCG ratio of this research and the comparison with that of your study to compare the difference between the two more intuitively.

Response: We appreciate the reviewer's comment. We have included the proportion of Ramkrishanan's study in comparison with our study.
Conclusions/Discussion - 7th paragraph: "This disparity could be attributed to a greater proportion of PCG cases in the study conducted by Ramkrishanan *et al.* (Ramkrishanan *et al*. 73.3% vs our study 20.8%)."

6. In the description SCG-A had the most favourable VA at the latest visit and the best initial VA, you described that "The majority of the cases included steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O." But from Figure 2, steroid-induced glaucoma accounts for 29%, which is not so high. Does the authors mean "The majority of the cases such as steroid-induced glaucoma, which might be more controllable than the subtypes related to congenital ocular malformations..."?

Response: Thank you. The sentence has been revised as suggested.
Conclusions/Discussion - 8th paragraph: "The majority of the cases included steroid-induced glaucoma, trauma and uveitis. In general, acquired conditions might be more controllable than the subtypes related to congenital ocular malformations, such as PCG and SCG-O."

Competing Interests: No competing interests to disclose

Reviewer Report 01 April 2021

https://doi.org/10.5256/f1000research.54403.r80450

Kazuhiko Mori
Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan
Hiroki Mieno
Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan

This article successfully reports the clinical characteristics and treatment outcomes of patients with childhood glaucoma from the real-world large data of 10 years in Thailand.

The statistics used are appropriate and the interpretations are consistent. Overall findings in this study are important to the field. However, there are a few points need to be fixed, and discussion needs more work to improve the interpretation of the results.

Major comments:

1. The discussion about the reason of unfavorable visual outcome is insufficient. Authors should dig much deeper into the reason of visual impairment of their patients, whether it was really unavoidable or not.
   For example, JOAG group mainly seems to have clear cornea where disc is visible (14/15) and good IOP control (25.6 to 15.0 mmHg), however, the unfavorable cases were increasing compared to the initial VA. What caused the unwilling visual outcome?
   Is it due to the corneal haziness or glaucoma progression? Inadequate orthoptic exercises? Or merely gathering of very severe cases to the tertiary hospitals?
   If there are any possible clues or suggestions to improve, it might be a good help for the readers who are struggling under the same situation.

2. As the authors mentioned, surgical interventions were mostly required in the primary type of glaucoma, both PCG and JOAG, and especially SCG-O. However, from this study, no glaucoma intervention was performed to 46.7, and 42.3% of the patients of JOAG and SCG-O, respectively. Explain the reason why almost a half of the patients did not need the surgical intervention.

Minor comments:

1. Need the details of surgical procedures.

2. Are there any relations between the laterality and visual outcome?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: glaucoma

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 14 Dec 2021

Sunee Chansangpetch, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

This article successfully reports the clinical characteristics and treatment outcomes of patients with childhood glaucoma from the real-world large data of 10 years in Thailand.

The statistics used are appropriate and the interpretations are consistent. Overall findings in this study are important to the field. However, there are a few points need to be fixed, and discussion needs more work to improve the interpretation of the results.

Response: We appreciate the reviewer's comment.

Major comments:
1. The discussion about the reason of unfavorable visual outcome is insufficient. Authors should dig much deeper into the reason of visual impairment of their patients, whether it was really unavoidable or not.

For example, JOAG group mainly seems to have clear cornea where disc is visible (14/15) and good IOP control (25.6 to 15.0 mmHg), however, the unfavorable cases were increasing compared to the initial VA. What caused the unwilling visual outcome?
Is it due to the corneal haziness or glaucoma progression? Inadequate orthoptic exercises? Or merely gathering of very severe cases to the tertiary hospitals?
If there are any possible clues or suggestions to improve, it might be a good help for the readers who are struggling under the same situation.

Response: Thank you for bringing up this important issue. As also mentioned by another reviewer, we agree that the factors associated with visual outcome would be worth exploring. The ordinal regression analysis showed that less favorable of initial visual acuity (VA) and high last IOP were significantly associated with poor visual outcome. In comparison to SCG-C, PCG, JOAG and SCG-O diagnoses were significantly associated with poor visual outcome. No significant risk of poor visual outcome was identified for SCG-S and SCG-A when compared to SCG-C.

As all patients were primarily seen by pediatric ophthalmologists (please refer to the response to reviewer 1's query No.3), we believe that inadequate orthoptic exercise and inappropriate refractive correction would be less the case. However, we could not assess the adherence to the treatment and follow-up with the pediatric ophthalmologists.

To elaborate more on the progression to unfavorable visual impairment, we further investigated the change of the VA group. Table 6 in the revised manuscript showed that most patients had no change in the VA group between the initial VA and the last VA. Most eyes with unfavorable last VA had already presented with unfavorable VA. The SCG-C tended to have an improvement of the VA. On the other hand, SCG-O had the highest proportion of worsening VA. There was no improvement in the VA group in any of the JOAG.

There were 12 eyes of SCG-O that showed worsening of the VA to the unfavourable VA at the latest visit. Almost all cases had limited visual potential due to cornea and/or anterior segment anomalies (Peters anomaly, microcornea and sclerocornea). These patients had their initial visit at a young age (all < 6 years) and the initial VA was recorded as 'fix and follow', which was classified in this study as 'favourable VA'. However, the final VA ranged from HM to FC 3 ft, which could be explained by their cornea and/or anterior segment conditions. There were 2 cases of congenital ectopia lentis. One of them underwent cataract surgery without IOL implantation. The other developed retinal detachment after trabeculectomy. Both had the final VA of hand motion.

Among the 13 JOAG with available initial visual acuity and latest visual acuity, there were 2 eyes that showed worsening of the VA group. The first case presented with a C:D ratio of 0.9 in the right eye. The contralateral eye had no light perception at the presentation. The patient had successful trabeculectomy in the right eye but lost to follow-up afterwards. She came back with the vision of PL and full disc cupping. The second case had an initial C:D ratio of 0.95 and an initial VA of 20/100. Although the patient responded well to the treatment and the IOPs were in the low teens, the VA slowly got worse. After approximately 12 years, the last VA was hand motion. Regarding 7 eyes with unfavourable final VA and unfavourable initial VA, all C:D ratios at presentation were at least 0.9.

Our data suggested that the initial VA and glaucoma stage at presentation were the main factors determining the unfavourable VA outcome. The underlying ocular abnormalities tended to limit the visual potential in SCG-O, the anterior segment dysgenesis in particular. We now mentioned this point in the 9th and 10th paragraph of the Discussion.

2. As the authors mentioned, surgical interventions were mostly required in the primary type of glaucoma, both PCG and JOAG, and especially SCG-O. However, from this study, no glaucoma intervention was performed to 46.7, and 42.3% of the patients of JOAG and SCG-O, respectively. Explain the reason why almost a half of the patients did not need the surgical intervention.

Response: We thank the reviewer for the comment. Although PCG, JOAG and SCG-O had the high rate of surgical intervention, a high proportion of eyes that had no glaucoma interventions was observed in our study. The primary reason for not receiving surgical intervention was that the IOP could be controlled with medications. All patients with evidence of high IOP were offered surgical intervention (trabeculotomy and goniotomy) for PCG. The option of surgical intervention was discussed with the families of those who had previously been treated with medication. After seeing the well-controlled IOP, some parents preferred to continue with the medication. Unlike PCG, the surgical intervention was not necessarily offered to all SCG-O and JOAG patients. The decision to perform surgery in SCG-O was mainly based on the IOP and visual prognosis. Conservative treatment with medications was preferred If there was very limited vision potential such as nystagmus or visual acuity of light perception. For JOAG, the approach was quite similar to that for adult glaucoma. The majority of cases that did not receive glaucoma intervention underwent selective laser trabeculoplasty and were able to achieve target IOPs, though with medications.

We have now explained these reasons in the 6th paragraph Discussion. Additional information of the patients that had no glaucoma intervention was listed below.

PCG: 38 eyes from 21 patients

- **9 eyes (5 patients) were lost to follow-up.**
- **2 eyes (2 patients) underwent evisceration due to severe buphthalmos. (One eye also had the ruptured globe.)**
- **1 eye (1 patient) had severe corneal ulcer and became phthisis.**
- **2 eyes (1 patient) developed late-onset infantile cataract. After lens aspiration the IOP went down to mid teen with single medication.**
- **16 eyes (8 patients) had the presenting IOP of less than 20 mmHg because they were treated with medications before the referral. The parents prefer to continue with the medication.**
- **6 eyes (3 patients) had high presenting IOP and were scheduled for the surgery. After initiating the medication during, the IOP went down to mid teen with 2-3 medications and the parents refused to have the surgery.**
- **2 eyes (1 patients) had no specified reason in the medical record.**

SCG-O: 66 eyes from 49 patients

- **4 eyes (4 patients) were lost to follow-up.**
- **1 eye (1 patient) underwent evisceration due to impending ruptured descematocele.**
- **30 eyes (17 patients) had the presenting IOP of less than 20 mmHg because they were treated with medications before the referral.**
- **8 eyes (5 patients) had high presenting IOP. After initiating the med, the IOP went down to mid teen with 2-3 medications.**
- **20 eyes (15 patients) had initial poor visual prognosis, inoperable condition (e.g. marked thin sclera) or contraindication for surgery (e.g. underlying heart disease)**

- **3 eyes (3 patients) had no specified reason in the medical record.**

JOAG: 7 eyes from 4 patients

- **2 eyes (1 patient) were lost to follow-up.**
- **3 eyes (2 patients) received selective laser trabeculoplasty.**
- **2 eyes (1 patient) had IOP lowered to teen by medications.**

Minor comments:
1. Need the details of surgical procedures.

Response: Thank you very much. We have now included a table that summarizes the type of surgical procedures for each glaucoma subtype. (new Table 3) Please note that some eyes might require more than 1 surgery, thus the overall frequency in this table may differ from that showed in Figure 3.

2. Are there any relations between the laterality and visual outcome?

Response: Thank you for the comment. The statistical analysis with chi-square test showed no association between the laterality and visual outcome (p=0.62).

Competing Interests: No competing interest to disclose

Reviewer Report 15 March 2021

https://doi.org/10.5256/f1000research.54403.r80447

Chungkwon Yoo
Department of Ophthalmology, Korea University College of Medicine, Seoul, South Korea

The authors evaluated the clinical characteristics and treatment outcomes of patients with childhood glaucoma seen in their glaucoma clinics for 10 years. This is a clinically interesting study. However, there are some issues which need to be addressed.

1. Please add the specific information on the surgical interventions used and their proportions in each glaucoma subtype: trabeculectomy, goniotomy, trabeculotomy or tube surgery?

2. Corneal diameters at initial visit?

3. Poor VA outcome may have resulted from factors other than glaucoma..e.g. inadequately corrected VA or coexisting eye problems. How many of the study eyes had been seen by pediatric ophthalmologists?

4. You may analyze the factors associated with poor visual outcome.

5. Given the fact that PCG needs surgical management, the proportion of nonsurgically managed eyes among PCG cases was unexpectedly high. What were the reasons for nonsurgical management in those patients? Please address this issue in the discussion section.

6. The authors concluded that all subtypes of glaucoma were sporadic. Although the patient-reported or family-reported 'family history of glaucoma' was uncommon, the actual familial occurrence may be more than can be assessed by history taking. Unless each family member was examined for glaucoma, you may not be certain that all subtypes of childhood glaucoma were sporadic.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: glaucoma surgery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 14 Dec 2021

Sunee Chansangpetch, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

The authors evaluated the clinical characteristics and treatment outcomes of patients with childhood glaucoma seen in their glaucoma clinics for 10 years. This is a clinically interesting study. However, there are some issues which need to be addressed.

1. Please add the specific information on the surgical interventions used and their proportions in each glaucoma subtype: trabeculectomy, goniotomy, trabeculotomy or tube surgery?Thank you very much. The table below summarizes the type of surgical procedures for each glaucoma subtype. Please note that some eyes might require more than 1 surgery, thus the overall frequency in this table may differ from the frequency shown in Figure 3.

Response: Thank you very much. We have added a table that summarizes the type of surgical procedures for each glaucoma subtype in the revised version of the manuscript. (new Table 3) Please note that some eyes might require more than 1 surgery, thus the overall frequency in this table may differ from the frequency shown in Figure 3.

2. Corneal diameters at initial visit?

Response: We apologize for the unclear description. The Refraction, Corneal diameter, Cup to disc ratio listed in Table 1 were the findings from initial visits. We have now updated the table's footnote.
Table 1 - footnote: "Refraction, corneal diameter, and cup to disc ratio were the measurements taken at first visit."

3. Poor VA outcome may have resulted from factors other than glaucoma..e.g. inadequately corrected VA or coexisting eye problems. How many of the study eyes had been seen by pediatric ophthalmologists?

Response: We absolutely agree that several factors contribute to poor VA outcome. At the Queen Sirikit National Institute of Child Health (QSNICH), all children are primarily seen by QSNICH's pediatric ophthalmologists. The patients are sent to pediatric glaucoma team for glaucoma consultation. They were still followed by pediatric ophthalmologists for other conditions such as refractive error, cataract and other coexisting eye problems. All surgical interventions except for glaucoma procedures are performed by the QSNICH's pediatric ophthalmologists. However, due to the limitations of a retrospective study, it would be difficult to clearly delineate the cause of poor visual outcome in each patient. We also acknowledge this issue in our Discussion.
Conclusions/Discussion - 10th paragraph: "It should be noted that unfavourable VA could be a result from a combination of factors other than glaucoma such as underlying ocular pathology, uncorrected refractive error or amblyopia. As all patients were concomitantly seen by pediatric ophthalmologists, we believe that inadequate orthoptic exercise and inappropriate refractive correction would be less the case. However, due to the limitations of a retrospective study, it would be difficult to clearly delineate the cause of poor visual outcome in each patient."

4. You may analyze the factors associated with poor visual outcome.

Response: Thank you for the astute comment. As suggested by the reviewer, we performed the analysis with an ordinal logistic regression to explore the factors associated with visual outcome. The complete case analysis of 219 eyes showed that

less favorable of initial visual acuity and high last IOP were significantly associated with poor visual outcome. In comparison to SCG-C, PCG, JOAG and SCG-O diagnoses were significantly associated with poor visual outcome. No significant risk of poor visual outcome was identified for the SCG-S and SCG-A groups when compared to the SCG-C group. We have updated the Methods and Results sections to include the description of the statistical analysis and the table in the revised manuscript. (new Table 5).

5. Given the fact that PCG needs surgical management, the proportion of nonsurgically managed eyes among PCG cases was unexpectedly high. What were the reasons for nonsurgical management in those patients? Please address this issue in the discussion section.

Response: Thank you for the comment. The primary reason for not receiving surgical intervention was that the IOP could be controlled with medications. All patients with evidence of high IOP were offered surgical intervention (trabeculotomy and goniotomy) for PCG. The option of surgical intervention was discussed with the families of those who had previously been treated with medication. After seeing the well-controlled IOP, some parents preferred to continue with the medication.

For additional information of the patients who did not have glaucoma intervention, please refer to the response to reviewer 2's query No.2. We have now included this explanation in the 6th paragraph of the Discussion.

6. The authors concluded that all subtypes of glaucoma were sporadic. Although the patient-reported or family-reported 'family history of glaucoma' was uncommon, the actual familial occurrence may be more than can be assessed by history taking. Unless each family member was examined for glaucoma, you may not be certain that all subtypes of childhood glaucoma were sporadic.

Response: We thank the reviewer for the insightful comment and agree with the suggestion. We have removed the conclusion in the Abstract regarding this issue and have modified the Discussion to avoid misleading.
Conclusions/Discussion - 4th paragraph: "The true frequency of familial glaucoma, however, may be higher, as the data were available for only 55% of our patients. In addition, getting a family history without examining each family member tends to underestimate the actual occurrence of glaucoma in the family."

Competing Interests: No competing interests to disclose