Original Article

A retrospective survey of childhood glaucoma prevalence according to Childhood Glaucoma Research Network classification

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Purpose: To evaluate the Childhood Glaucoma Research Network (CGRN) classification system and describe the prevalence of each subtype according to this classification. **Materials and Methods:** Retrospectively, the medical records of 205 consecutive childhood glaucoma and glaucoma suspect patients at an urban tertiary care center were reviewed. The initial diagnosis and new diagnosis according to CGRN classification were recorded. **Results:** All patients fit one of the seven categories of the new classification. Seventy-one percent of diagnoses were changed upon reclassification. Twenty-three percent of patients had primary glaucoma (juvenile open-angle glaucoma and primary congenital glaucoma [PCG]); 36% had secondary glaucoma (glaucoma associated with nonacquired ocular anomalies; glaucoma associated with nonacquired systemic disease or syndrome; glaucoma associated with acquired condition; and glaucoma following cataract surgery); and 39% were glaucoma suspect. Of the patients diagnosed with glaucoma, PCG was the most common diagnosis, seen in 32% of patients. **Conclusion:** The CGRN classification provides a useful method of classifying childhood glaucoma.

Key words: Childhood glaucoma, glaucoma, glaucoma categorization

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Childhood glaucoma is a heterogeneous group of diseases which all share the final, common pathway of ocular hypertension, and pressure-related damage to ocular structures. Timely and correct diagnosis of glaucoma and its etiology is essential to optimize visual outcomes and guide appropriate treatment in children. Many different classification schemes have been proposed although none are widely adopted.[1-4] Some are too broad in their terminology while others are too specific to allow easy adaptation by all practitioners. Having a single, standardized classification system is important for diagnosis and management, improved physician communication, and future research.

Recently, the Childhood Glaucoma Research Network (CGRN), an International consortium of glaucoma specialists, proposed a unified classification system based on the clinical findings, timing, and context in which a diagnosis of glaucoma is made. The members aimed to create a classification that was simple and logical, so most clinicians could systematically determine where a condition should be placed.[5] This CGRN classification will be used to plan longitudinal surveys of the management and outcomes of childhood glaucoma patients.

The prevalence of each glaucoma subtype according to this classification is unknown. The purpose of this study is to apply the CGRN classification retrospectively in order to investigate the disease subtypes under the new classification. We wish to use this information to gain insight on the spread of childhood glaucoma in a tertiary childhood glaucoma referral clinic.

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Materials and Methods

Patients included in this study were seen in the pediatric glaucoma subspecialty clinics of an urban center in Miami, Florida, USA, which attracts a pediatric population from all over Florida and Caribbean Islands. Clinic rosters of these patients were reviewed, with June 2013 being the most recent clinic date, in order to identify 200 unique patients that fulfilled CGRN criteria for glaucoma or glaucoma suspect. Patients were included in the study if they were diagnosed with glaucoma or glaucoma suspect by one of four childhood glaucoma specialists. Appropriate Institutional Review Board approval was obtained for this study.

The diagnosis given by the examining clinician to each patient at their most recent clinic visit was recorded. Baseline characteristics including age at presentation and gender were recorded as well. The clinical characteristics of each of the patients were then evaluated according to the criteria proposed by the CGRN classification system.[5] Patients were given the diagnosis of glaucoma or glaucoma suspect according to the definitions listed in Table 1.[5] Of the patients diagnosed with glaucoma, further categorization was recorded according to CGRN criteria [Fig. 1].[5] Primary childhood glaucoma categories included primary congenital glaucoma (PCG) and juvenile open-angle glaucoma (JOAG). Secondary

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childhood glaucoma categories included glaucoma associated with nonacquired ocular anomalies; glaucoma associated with nonacquired systemic disease or syndrome; glaucoma associated with acquired condition; and glaucoma following cataract surgery. Of note, with the new CGRN definitions, if a child had both an underlying condition that predisposed to glaucoma and had cataract surgery, the child would be diagnosed with glaucoma following cataract surgery only if glaucoma developed following cataract surgery; otherwise, the diagnosis would be related to the child's underlying condition.

Table 1: Childhood Glaucoma Research Network definition of glaucoma and glaucoma suspect

Definition of glaucoma: 2 or more required
IOP >21 mmHg (investigator discretion if examination under anesthesia data alone)
Optic disc cupping
Progressive increase in cup-disc ratio
Cup-disc asymmetry of ≥0.2 when the discs are similar size
Focal rim thinning
Corneal findings
Haab striae
Diameter >11 mm in newborn, >12 mm in child <1 year of age >13 mm any age
Progressive myopia/myopic shift coupled with an increase in ocular dimensions out of keeping with normal growth
Reproducible visual field defect that is consistent with glaucomatous optic neuropathy with no other observable reason for the visual field defect
Definition of glaucoma suspect: At least one required
IOP >21 mmHg on two separate occasions
Suspicious optic disc appearance for glaucoma
Suspicious visual field for glaucoma
Increased corneal diameter or axial length in the setting of normal IOP

IOP: Intraocular pressure

Statistical analysis was performed using the Chi-square test for categorical data. Categorical data are presented as counts and percentages, and continuous data are presented as means and medians.

Results

A total of 205 unique patients with a diagnosis of childhood glaucoma or glaucoma suspect were included in this study. As not all patients referred to the pediatric glaucoma clinics were diagnosed with glaucoma or glaucoma suspect by the examining clinician, we reviewed 246 charts to obtain a number close to the target of 200 patients. Twenty-three percent of the patients had primary glaucoma (JOAG and PCG); 36% had secondary glaucoma (glaucoma associated with nonacquired ocular anomalies; glaucoma associated with nonacquired systemic disease or syndrome; glaucoma associated with acquired condition; and glaucoma following cataract surgery); and 39% were glaucoma suspect. Two percent were labeled as having glaucoma by the examining physician but did not fulfill CGRN criteria for glaucoma or glaucoma suspect. The distribution of diagnoses of those patients with either a primary or secondary glaucoma is depicted in Fig. 2.

For each CGRN childhood glaucoma category, baseline characteristics including the number of patients, affected eye, gender, and age are presented in Table 2. Glaucoma suspect was the most prevalent category. Laterality was only reported for those patients with a diagnosis of glaucoma (not for glaucoma suspect patients), and the majority of patients had bilateral involvement (60%, $P = 0.03$). The exception to this was patients diagnosed with glaucoma associated with nonacquired systemic disease or syndrome, where 64% of patients had disease involving their right eye. There was no significant difference in overall percentage of male or female patients with childhood glaucoma or glaucoma suspect (56% male, 44% female). However, more males than females were diagnosed with PCG (72% male, $P < 0.001$). The median age of patients included in the study was 3.72 years (mean 4.67 years).

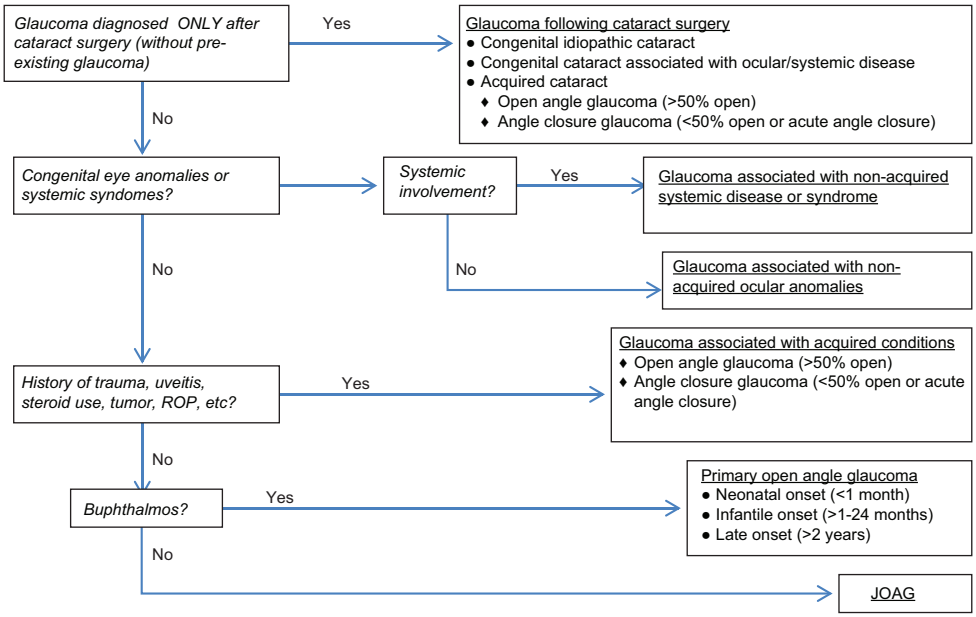

Figure 1: Brief decision tree to guide categorization according to Childhood Glaucoma Research Network classification

A slightly older age of diagnosis was seen in patients with glaucoma associated with acquired conditions (median age 7.92 years), JOAG (median age 6.58 years), and glaucoma suspect patients (median age 6.75 years).

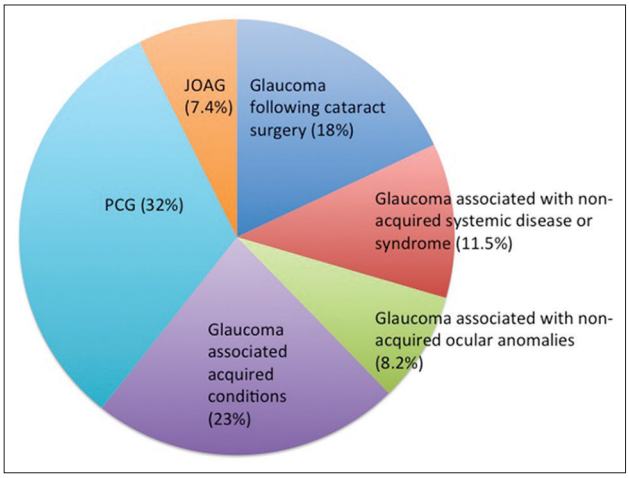

Figure 2: Percentage of the patients with a childhood glaucoma diagnosis (excluding glaucoma suspect patients) in each Childhood Glaucoma Research Network classification category

Glaucoma following cataract surgery

A total of 22 patients and 33 eyes were diagnosed with glaucoma following cataract surgery. Twenty-one patients had congenital idiopathic cataract; one patient with persistent fetal vasculature developed glaucoma following cataract extraction. Gonioscopy was recorded in 18 patients. Fourteen patients (78%) had an open angle glaucoma (>50% open); four patients (22%) had angle closure glaucoma (<50% open or acute angle closure).

The original diagnoses noted in the chart included "secondary glaucoma" in nine patients (41%), "aphakic glaucoma" in 8 patients (36%), and four distinct diagnoses including "angle closure," "JOAG," "pupillary block," and "glaucoma." Only one patient was diagnosed with "glaucoma following cataract surgery."

Glaucoma associated with nonacquired systemic disease or syndrome

Nineteen eyes of 14 patients were diagnosed with glaucoma associated with nonacquired systemic disease or syndrome.

Table 2: Baseline characteristics of all patients in the study and within each category after

	% Total (*n*)	% Laterality	% Gender	Age (years)	% Patients with change of diagnosis (*n*)*
Total	100 (205)	60 (73)† OU 25 (31) OD 15 (18) OS	56 (114) male 44 (91) female	Mean 4.67 Median 3.72	71 (145)
Glaucoma following cataract surgery	10.7 (22)	50 (11) OU 32 (7) OD 18 (4) OS	59 (13) male 41 (9) female	Mean 5.2 Median 3.1	100 (22)
Glaucoma associated with nonacquired systemic disease or syndrome	6.8 (14)	36 (5) OU 64 (9) OD 0 OS	43 (6) male 57 (8) female	Mean 2.90 Median 0.96	100 (14)
Glaucoma associated with nonacquired ocular anomalies	4.9 (10)	60 (6) OU 10 (1) OD 30 (3) OS	40 (4) male 60 (6) female	Mean 1.62 Median 0.50	100 (10)
Glaucoma associated with acquired conditions	13.7 (28)	39 (11) OU 25 (7) OD 36 (10) OS	39 (11) male 61 (17) female	Mean 7.64 Median 7.92	100 (28)
Primary congenital glaucoma	19.0 (39)	79 (31) OU 18 (7) OD 3 (1) OS	72* (28) male 28 (11) female	Mean 1.36 Median 0.25	64 (25)
JOAG	4.4 (9)	89 (8) OU 11 (1) OD 0 OS	56 (5) male 44 (4) female	Mean 6.97 Median 6.58	44 (4)
Glaucoma suspect	38.5 (79)		58 (46) male 42 (33) female	Mean 7.16 Median 6.75	48 (38)
Not glaucoma‡	1.9 (4)		25 (1) male 75 (3) female		100 (4)

*Patients in whom, after chart review, the diagnosis given by the examining physician was changed on reclassification according to CGRN, †Statistically significant within group ($P<0.05$), ‡Patients who were called glaucoma suspect by the examining physician but, on chart review, were not glaucoma or glaucoma suspect per CGRN definitions. JOAG: Juvenile open-angle glaucoma, CGRN: Childhood Glaucoma Research Network

Nine patients (64%) had a phakomatosis (4 Sturge–Weber, 2 phakomatosis pigmentovascularis, one had Klippel–Trenaunay–Weber syndrome, one had neurofibromatosis, one had cutis marmorata telangiectasia congenita); two patients (14%) had chromosome disorders (trisomy 13); one patient (7%) had a connective tissue disorder (stickler syndrome); two patients (14%) had Rubinstein–Taybi.

The initial diagnoses noted in the chart included "secondary glaucoma" in nine patients (64%; with reason for glaucoma listed alongside the diagnosis in four cases), four diagnoses of glaucoma (28%); and one patient (7%) with a diagnosis that could not be discerned based on review of the records.

Glaucoma associated with nonacquired ocular conditions

Sixteen eyes of 10 patients were given the diagnosis of glaucoma associated with nonacquired ocular anomalies. Nine patients (90%) had an open angle configuration (>50% open angle), and one had angle closure (<50% open angle). Five patients (50%) had aniridia, two patients (20%) had Axenfeld–Rieger anomaly, one (10%) patient had Peter's anomaly, one patient (10%) had congenital ectropion uveae syndrome, and one patient (10%) had persistent fetal vasculature.

Initial diagnoses for these patients included "secondary glaucoma" in six patients (60%; with etiology listed in three cases); "aniridia with glaucoma" in three patients (30%); and "congenital glaucoma" in three patient (10%).

Glaucoma associated with acquired conditions

Twenty-eight patients (39 eyes) had glaucoma associated with acquired conditions. The angle was open (>50% open) in 25 patients (89%); three patients (11%) had a closed angle (<50% closed) on presentation. Fourteen patients (50%) had uveitis; eight patients (29%) had retinopathy of prematurity; five (18%) developed glaucoma following trauma; one patient (3%) developed glaucoma following endophthalmitis.

Diagnoses recorded in the chart included "uveitic glaucoma" in 12 patients (43%); "secondary glaucoma" (with no qualifier) in eight patients (29%); "aphakic glaucoma" in three patients (11%); "traumatic glaucoma" in three patients (11%); and one patient each with diagnosis of "mixed mechanism glaucoma," and "corneal blood staining."

Primary congenital glaucoma

Thirty-nine patients and a total of 70 eyes were diagnosed with PCG in this survey. Ten of these patients (26%) had an infantile or newborn onset of disease (age 0–1 month); 24 (62%) had infantile onset PCG (>1–24 months age); five (13%) had late-onset or late-recognized disease (>2 years).

Initial diagnoses on patient examination included "primary infantile glaucoma" in 24 patients (62%), "primary congenital glaucoma" in 14 patients (36%), and "congenital glaucoma" in one patient (3%).

Juvenile open-angle glaucoma

A total of nine patients and 17 eyes were diagnosed with JOAG. Initial diagnoses listed in these patient's charts included "JOAG" in five cases (56%); "primary open angle glaucoma" in two cases (22%); and "developmental glaucoma" and "glaucoma" in one case each.

Glaucoma suspect

Seventy-nine patients were diagnosed as glaucoma suspect. Of these, 57 patients (72%) were glaucoma suspects based on their optic nerve appearance on presentation. Seventeen (22%) were glaucoma suspects based on intraocular pressure (IOP) higher than 21 mmHg on more than one clinic visit. The remaining 5 (6%) patients were glaucoma suspects based on an increased corneal diameter.

Diagnosis on presentation included "glaucoma suspect" in 44 patients (56%); ocular hypertension in 17 patients (22%); "juvenile open-angle glaucoma suspect" in 13 patients (16%); "primary open angle glaucoma suspect" in two patients (3%); and "primary congenital glaucoma suspect" in three patients (4%).

Discussion and Conclusion

Childhood glaucoma is responsible for approximately 5% of blindness in children worldwide.[6] The term childhood glaucoma encompasses a group of disorders that have serious vision-threatening implications. Although all glaucoma in children is ultimately associated with an elevated IOP leading to optic nerve damage and visual loss, the path to this common endpoint varies. Several different classification systems have been used in the past to describe patients with childhood glaucoma; however, none are widely accepted. The CGRN classification system is the first International Consensus Classification for childhood glaucoma. It provides a logical diagnostic guideline that clinicians can use to systematically and reproducibly categorize childhood glaucoma patients. Following a unified classification system will allow better standardization of communication and of future research on childhood glaucoma. To our knowledge, this is the first study to use this classification in a clinic population of childhood glaucoma and glaucoma suspect patients.

The CGRN classification proved easy to implement in our patient population, and we were able to categorize all glaucoma and glaucoma suspect patients into one of the seven categories proposed by the CGRN classification. There was no overlap; no patient fell into more than one diagnostic category. In addition, fewer distinct diagnoses were used with the new classification system, which proposes 7 possible diagnoses, compared with the 26 different diagnoses listed in the records we reviewed. In many cases, the pre-CGRN diagnosis listed in the chart did not give sufficient information about the etiology of the patient's disease. For example: Of the secondary glaucomas, "secondary glaucoma" was the most common diagnosis, listed in 43% charts. Using the CGRN classification allowed a less variable and more specific way to diagnose these patients with childhood glaucoma. It also provided more information about the type of glaucoma our patients had in comparison to the often vague diagnoses that were originally listed in the patient charts.

A review of the baseline characteristics of the patients in this study revealed no gender difference in patients with childhood glaucoma except in PCG where 72% of affected patients were male. This is consistent with previous reports in the literature of a predominance of male patients with PCG.[7,8] Although the reason for this strong gender bias is still unknown, several investigators believe a genetic basis is most likely.[9] One hypothesis is that this male predominance may be

seen only in those patients without CYP1B1 (GLC3A; On-line Mendelian Inheritance in Man reference_601771) mutations, suggesting an alternative molecular basis for this finding.[10,11] Differences in access to health care between newborn males and females may also contribute to this finding.

The majority of the patients included in this study had bilateral disease. The exception to this was patients diagnosed with glaucoma associated with nonacquired systemic disease or syndrome, where we saw a predominance of patients with disease involvement of the right eye. Because this is a new diagnostic category with a small sample size, it is difficult to compare this finding with previously published reports. However, with increased use of the CGRN classification, we can follow this trend in the future.

Our analysis was comparable to previous reports and showed that a significant majority of patients referred to our tertiary care pediatric glaucoma center were glaucoma suspects.[12,13] The majority of patients in our study were diagnosed "glaucoma suspect" due to a suspicious optic nerve appearance (72%). Fung *et al*. reported similar findings: 76% of glaucoma suspect patients in their study population had suspicious appearing optic nerves.[13] It is important to assess these patients for glaucoma, as most healthy infants and children have symmetric appearing optic nerves with a cup-disc ratio smaller than 0.3.[14] Although optic nerve cupping can be affected by optic disc size, race, and refractive error among other variables, the low incidence of optic nerve cupping in children often warrants evaluation by a glaucoma specialist.[15-17] Furthermore, in this cross-sectional study, it is not known whether any of the childhood glaucoma suspect patients eventually demonstrated progressive optic nerve or biometric changes that would later meet the criteria of childhood glaucoma.

We compared the distribution of diagnoses of patients with a type of childhood glaucoma in our clinic population with those in several previously published studies on the incidence of childhood glaucoma [Table 3].[7,12,13,18-20] Each of these investigators used different classifications for reporting the etiology of glaucoma in their patients; however, we attempted to reclassify the patients according to CGRN classification using the available information in each study. This method is exact, as slightly different criteria for diagnosing glaucoma were used by each group, and individual charts were not reviewed as they were in this study. However, it allows a comparison of overall trends in childhood glaucoma across different populations. PCG was the most common diagnosis in our patient population, and this was also the case in the majority (4 of 6) of studies we evaluated. The second most common diagnosis was glaucoma associated with acquired conditions, and this was a similar finding in 4 of the 6 additional studies. JOAG was a consistently rare diagnosis across all the studies.

One important shift that has occurred with the new CGRN classification involves the category of glaucoma following cataract surgery. It is well known that cataract surgery in infants

Table 3: Distribution of childhood glaucoma according to Childhood Glaucoma Research Network classification in this study and six previously published studies on childhood glaucoma

Study	Number of patients	Study population; location	PCG (%)	JOAG (%)	Glaucoma following cataract surgery* (%)	Glaucoma associated with nonacquired ocular disease (%)	Glaucoma associated with nonacquired systemic disease or syndrome (%)	Glaucoma associated with acquired disease (%)	Not enough information to categorize (%)
Current study	122	Tertiary childhood glaucoma clinic; Southern Florida	39 (32)	9 (7)	22 (18)	10 (8)	14 (11)	28 (23)	
Papadopoulos *et al*. 2007[18]	99	Consultant ophthalmologists; United Kingdom and Republic of Ireland	45 (45)	2 (2)	16 (16)	6 (6)	12 (12)	10 (10)	8 (8)
Aponte *et al*. 2010[12]	30	Olmstead county residents; Minnesota	1 (3)	4 (13)	6 (20)	2 (7)	4 (13)	13 (43)	-
Fung *et al*. 2013[13]	164	Tertiary referral center; Texas	46 (28)	10 (6)	30 (18)	16 (10)	18 (11)	39 (24)	5 (3)
Taylor *et al*. 1999[19]	306	Children's hospital; Toronto, Canada	117 (38)	7 (2)	61 (20)	41 (13)	34 (11)	44 (14)	2 (1)
Barsoum-Homsy and Chevrette 1986[7]	63	Pediatric glaucoma clinic; Montreal, Canada	14 (22)	0	7 (11)	24 (38)	9 (14)	9 (14)	-
Qiao *et al*. 2009[20]	1055	Hospitalized pediatric patients; Beijing China	486 (46)	63 (6)	131 (12)	59 (6)	33 (3)	211 (20)	72 (7)

Available published data was used to reclassify the patients in each of the above studies; individual charts were only reviewed in the current study. *Patients diagnosed as glaucoma associated with cataract surgery without any associated conditions (e.g., PHPV) were included in this category. Every effort was used to remove patients who acquired glaucoma from a cause other than immediate cataract surgery from this category. PCG: Primary congenital glaucoma, JOAG: Juvenile open-angle glaucoma, PHPV: Persistent hyperplastic primary vitreous

can cause glaucoma even years after uneventful surgery, with a variable incidence of 5–41% depending on age of surgery, corneal diameter, and surgical technique.[21] However, since many ocular or systemic anomalies associated with congenital cataracts as well as causes of secondary cataracts (e.g., steroid use, trauma, etc.) are independently associated with increased risk of childhood glaucoma, most diagnoses do not clearly describe the direct cause of glaucoma. For patients whose glaucoma was diagnosed only after cataract surgery, regardless of the underlying medical condition or context, glaucoma is categorized as glaucoma following cataract surgery in the CGRN classification. This approach is succinct, logical, and practical, as it emphasizes the relative importance of early lensectomy as a cause of glaucoma and removes the ambiguity present in previous studies, where the etiology of the child's glaucoma (secondary to underlying disease vs. secondary to cataract surgery) was not consistently defined.

There are several limitations to this study. The small number of patients in some of the categories of childhood glaucoma restricts us from drawing firm conclusions about specific trends in this study, including the greater percentage of patients with right eye involvement in glaucoma associated with nonacquired systemic disease or syndrome, and the frequency of open- or closed-angle configuration in patients with glaucoma following cataract surgery and glaucoma associated with acquired conditions. In addition, the follow-up period was variable among the patients, making it difficult to report useful longitudinal treatment and outcome results. In the future, a collective database where clinicians can report the diagnosis of their childhood glaucoma patients according to CGRN, as well as report therapeutic and surgical interventions and patient outcomes, will be extremely useful. A prospective database with a long follow-up period will also allow us to see how often, and in what context, a patient with a diagnosis of glaucoma suspect develops glaucoma. This will allow more exquisite management of pediatric glaucoma suspect patients. Finally, we note that the diagnosis recorded in the medical records may not necessarily reflect the language used by the International Classification of Diseases, 9th edition (ICD-9) code assigned to that particular clinical encounter, and a comparison of our cohort's CGRN diagnoses with ICD-9 codes may reflect better concordance. However, as one of the goals in the development of CGRN classification is to improve communication between providers, a comparison with the actual, recorded diagnosis seems practical.

In summary, this study shows that the CGRN classification can be reliably used to describe the etiology of a child's glaucoma and provides useful information about the clinical population of childhood glaucoma patients in a referral center. We hope that its widespread use will allow us to take better care of our patients with childhood glaucoma.

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Conflicts of interest

There are no conflicts of interest.

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