Original Article

Secondary developmental glaucoma in eyes with congenital aphakia

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Purpose: To describe the clinical spectrum and management of glaucoma in congenital aphakia. **Methods:** The demographics and clinical spectrum of eyes with congenital aphakia with and without glaucoma were compared, and management outcomes of congenital aphakia cases with glaucoma were studied retrospectively between April 2000 and June 2020. **Results:** There were a total of 168 eyes (84 subjects) with a diagnosis of congenital aphakia, of which 29 eyes of 18 subjects were diagnosed with glaucoma. Corneal opacity was the presenting complaint in 26/29 eyes with glaucoma and 139/139 eyes without glaucoma. The (interquartile range (IQR)) horizontal corneal diameter was 10.5mm (IQR, 9.0-12.5) and 8mm (IQR, 5-10) in eyes with and without glaucoma (P = 0.01), respectively. The median (IQR) axial length was 17.5mm (IQR, 13.5-19.5) and 15mm (IQR, 14-16) mm in eyes with and without glaucoma (P = 0.03), respectively. Nineteen eyes with glaucoma had adequate intraocular pressure (IOP) control with one medication. Three eyes underwent transscleral diode cyclophotocoagulation and maintained IOP without medications. Three eyes underwent trabeculectomy and trabeculotomy, trabeculectomy followed by penetrating keratoplasty, and trabeculectomy, respectively, of which two eyes became phthisical. At the last follow-up, the median (IQR) IOP was 14 mm Hg (IQR, 14-17) Hg. The median (IQR) follow-up duration was 4.53 months (IQR, 2.03- 48.06). **Conclusion:** One-fifth of the eyes with congenital aphakia had secondary developmental glaucoma. The corneal diameter and axial lengths were higher in the eyes with glaucoma compared to eyes without glaucoma. Medical management is the preferred short-term mode of IOP control. Transscleral cyclophotocoagulation may be preferred over surgical intervention.

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Congenital aphakia is a rare genetic, developmental abnormality of the anterior segment that has been classified histologically into primary and secondary forms and distinguished by either the complete absence of the lens (primary) or aborted lens development (secondary) respectively during 4–5 weeks of gestation (OMIM 610256).[1,2] Congenital aphakia is caused by mutations in the forkhead box protein E3 (FOXE3) gene, a forkhead-related transcription factor involved in the lens formation. The dominant and recessive variants in FOXE3 are associated with a variable phenotype of developmental eye disorders, including anterior segment dysgenesis, microphthalmia, Peters anomaly, sclerocornea, early-onset cataract, glaucoma, and ocular coloboma.[2]

The prevalence of the disease is unknown, with a report suggesting that it occurs in 1–5/10000 live births to 1/60000 live births.[3] The clinical condition is often associated with anterior segment dysgenesis, including trabecular meshwork- Schlemm's canal maldevelopment, hypoplastic ciliary body, and vitreoretinal abnormalities.[4,5] The poorly developed or absent trabecular meshwork and Schlemm's canal predispose these eyes to glaucoma.[3,4] The association of glaucoma in congenital aphakia is only anecdotally reported.[3,4] In this report, we describe and compare the demographics and clinical spectrum in a cohort of patients with congenital aphakia with and without glaucoma and report on the outcome of glaucoma management in these eyes.

Methods

This was a retrospective chart review of cases diagnosed with congenital aphakia that presented to our institute between April 2000 and June 2020. The Institutional Ethics Committee approved the study, and the research adhered to the tenets of the Declaration of Helsinki. The history, including the age of onset, parental consanguinity, maternal history, detailed birth history, laterality, and the onset of symptoms, was noted from the clinical records. A comprehensive ocular examination was performed either in the clinic if the child was cooperative for examination or examined under anesthesia when the child was uncooperative. When an examination under anesthesia (EUA)

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was performed, all examinations except visual acuity and B-scan were performed. The review included the recording of visual acuity by using age-appropriate charts, intraocular pressure (IOP) measurement using Goldmann applanation tonometer (GAT AT900, Haag Streit, Koniz, Switzerland) in the clinic; or Perkins tonometer (Perkins; Clement-Clarke, Haag-Streit, Harlow, UK) or Icare rebound tonometer TA01i (Tiolat, Oy, Helsinki, Finland). The history, including the age of onset, parental consanguinity, maternal history, detailed birth history, laterality, and the onset of symptoms, were noted from the clinical records. Clinical records were used to distinguish whether the examination was carried out in the clinic or under anesthesia. The visual acuity, IOP, corneal clarity, the horizontal corneal diameter (HCD), fundus findings (wherever mentioned) were noted. When the visual acuity was poor and could not be recorded using age-appropriate charts, they were documented as the perception of light present or no perception of light or dazzle reflex present. Dazzle reflex was defined as the instinctive closure of the eyes to bright light.[6] The HCD was measured using calipers during EUA or using the slit lamp in the clinic. In cases where the limbus was ill-defined, corneoscleral junction or posterior limbal or blue line was used as a surrogate marker and the corneal diameter was measured. The method of IOP measurement was documented using Goldmann applanation tonometer (GAT AT900, Haag Streit, Koniz, Switzerland) or Perkins tonometer (Perkins; Clement-Clarke, Haag-Streit, Harlow, UK) or Icare rebound tonometer TA01i (Tiolat, Oy, Helsinki, Finland). The optic nerve examination was performed by indirect ophthalmoscopy whenever corneal clarity permitted and was confirmed on a B-scan. In eyes where fundus examination could not be performed due to hazy cornea, the absence or presence of cupping on B-scan was noted. The status of the lens, the axial length (AXL), and optic disc cupping were noted after reviewing the B-scan report. Axial and longitudinal B-scan was performed using the immersion technique.

The congenital aphakia diagnosis was made based on the characteristic bluish hue or silvery-white haze of the cornea,[7] microcornea, and microphthalmos and confirmed by B-scan ultrasonography by the absence of the crystalline lens in an eye that had not been subjected to any surgical intervention [Fig. 1].[4]

Glaucoma was diagnosed if any of the following were present [Fig. 2]:

1. Horizontal corneal diameter of ≥11 mm in newborn, >12 mm in child <1 year of age, >13 mm at any age, or an asymmetry of 2 mm between the eyes
2. Raised intraocular pressure (IOP) >21 mm Hg by GAT/Perkins/Icare tonometer
3. Optic disc cupping of >0.7, rim thinning or notch, optic disc cup asymmetry of >0.2 between the eyes
4. An asymmetry of >2 mm in the axial length between the eyes.

The clinical features of eyes with congenital aphakia with and without glaucoma were compared. The management of glaucoma and its outcomes were noted.

Statistical analysis

The mean ± standard deviation and median (IQR) represent the parametric and nonparametric data, respectively. Percentages were used to quantify categorical data. Comparison between the groups was performed using the Chi-square test and the unpaired *t* test. The statistical analysis was performed using software STATA v14.2 (Stata Corp, College Station, TX, USA).

Results

There were a total of 168 eyes of 84 subjects with a diagnosis of congenital aphakia, of which 29 eyes (17.2%) of 18 subjects (10 males and 8 females) were diagnosed with glaucoma. EUA was performed in 52 subjects and 32 subjects were examined in the clinic.

Demographics

There were 11 subjects with bilateral glaucoma and 7 subjects in whom only one eye was involved. Of the 7 subjects with unilateral affliction, the right eye was involved in 6 subjects and the left eye in one. Seventy-nine eyes (79/139 eyes) and 50/139 eyes with no glaucoma also had associated microcornea with microphthalmos and staphyloma, respectively. Of the 23 eyes with glaucoma, 20 had microcornea with microphthalmos and 3 had staphyloma. There were 5 eyes in the no glaucoma group and 2 eyes in the glaucoma group where an associated iris coloboma was documented. The comparison of baseline demographic and clinical features of congenital aphakia eyes with and without glaucoma is shown in Table 1.

The median (IQR) age at presentation was similar in the two groups ($P = 0.53$). Both groups' most common presenting complaint was corneal opacity (26/29 eyes with glaucoma, 139/139 eyes without glaucoma). The other presenting complaints included watering, nystagmus, and sensitivity to light. History of consanguinity was noted in 50% of the subjects with glaucoma and 43.84% of subjects without glaucoma ($P = 0.84$).

Glaucoma was diagnosed based on elevated IOP, AXL, and HCD criteria in 12 eyes, increased IOP and optic disc cupping in 12 eyes, and only optic disc cupping in 5 eyes.

The median (IQR) IOP at presentation was 28 mm Hg (IQR, 12- 38) mm Hg in eyes with glaucoma as compared to 12 mm Hg (IQR, 8-20) mm Hg in eyes without glaucoma ($P = 0.007$). In eyes with glaucoma, there were 2 eyes with no perception of light vision, 4 eyes with a perception of light, 3 eyes could appreciate hand motions, and 13 eyes fixated and followed the light. Vision could not be documented in 7 eyes due to photophobia.

Management of glaucoma

Medical management: The first line of management was glaucoma medications, which were started in all 29 eyes. In 3/29 eyes, medications were begun by the referring physician and had been stopped after intervention [Table 2]. Of the 26 eyes, 23 eyes were on one medication (beta-blocker), while 3 eyes were on two medications (beta-blockers and carbonic anhydrase inhibitor). The mean number of medications was 1.11 ± 0.33.

Laser and surgical management: We performed trabeculectomy in 1 eye and trans-scleral cyclophotocoagulation (TSCPC) in 2 eyes. The procedures and outcomes are described in Table 2. One eye developed a corneal ulcer following TSCPC and underwent a therapeutic keratoplasty. All 3 eyes that underwent laser or surgical intervention had normal IOP without any medications. Four eyes were advised laser (TSCPC) for high IOP despite medications but were lost to follow-up.

Table 1: Baseline demographic and clinical characteristics of children with congenital aphakia with and without glaucoma

Characteristics	Eyes with glaucoma	Eyes without glaucoma	*P*
Number of eyes	29 eyes of 18 subjects	139 eyes of 73 subjects	
Gender, Male:Female	10:8	43:30	1.00
Laterality, unilateral:bilateral	7:11	7:66	0.005
Parental consanguinity	9/18	32/73	0.84
Age at a presentation in months, median (IQR)	5 (0.46-23.46)	7.85 (3.0-43.67)	0.53
IOP in mm Hg, median (IQR)	28 (12-38)	12 (8-20)	0.007
Corneal diameter (mm), median (IQR)	10.5 (9-12.5)	8 (5-10)	0.01
Axial length (mm), median (IQR)	17.5 (13.5-19.5)	15 (14-16)	0.03
Associated comorbidities			
Nystagmus	6 subjects	15 subjects	
Strabismus	4 subjects	5 subjects	

Table 2: Outcomes of laser and surgical management of glaucoma

	Number of eyes (6)	Outcome
Prior surgery or laser		
Trabeculectomy with trabeculotomy	1	Phthisis
Trabeculectomy followed by penetrating keratoplasty	1	Phthisis
Cyclophotocoagulation	1	Maintained vision and IOP
Performed after referral		
Trabeculectomy	1	Maintained vision and IOP
TSCPC	1	Maintained vision and IOP
TSCPC followed by Penetrating keratoplasty	1	Developed corneal ulcer following cyclophotocoagulation. Therapeutic keratoplasty helped in maintaining vision and IOP

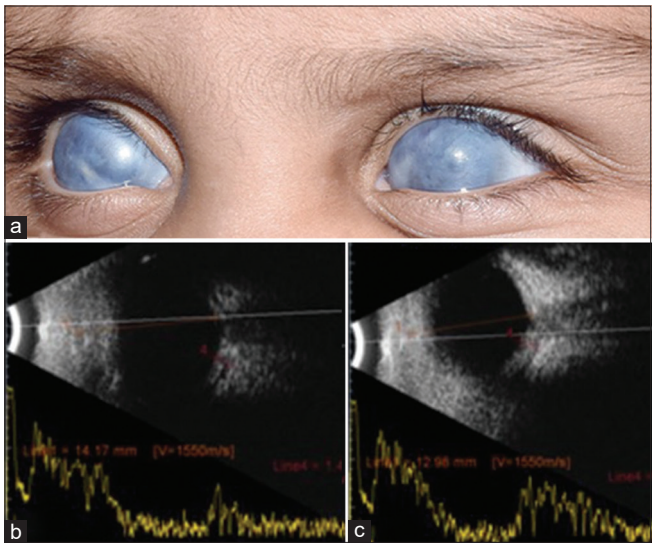

Figure 1: Characteristic bluish hue of the cornea in a child with congenital aphakia (a) and the absence of lens on B-scan in the right eye (b) and left eye (c). The IOP was 12 mm Hg in both eyes with Perkins tonometer and the axial length was 14 and 15.13 mm in the right and left eye, respectively

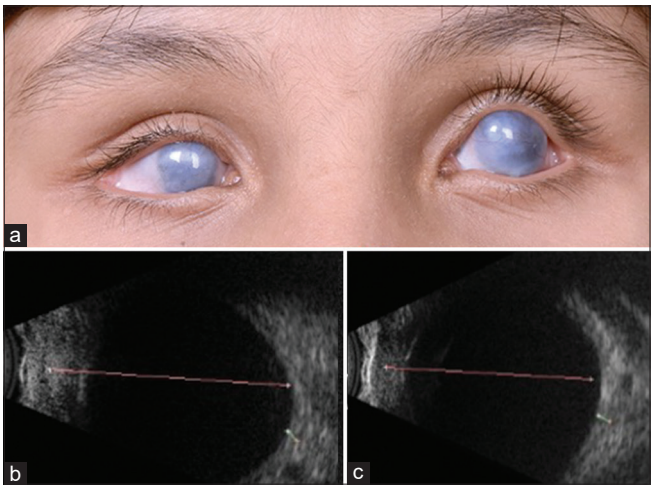

Figure 2: Note the asymmetry between the corneal diameter between the two eyes (a) and the absence of lens on B scan in RE (b) and LE (c) The HCD of the RE was 11 mm and of the left eye was 13.5 mm. The IOP was 10 mm Hg in the right eye and 24 mm Hg in the left eye with GAT. The axial length was 17 and 19 mm in the right and left eye, respectively. The left eye was diagnosed to have secondary developmental glaucoma

Surgical intervention was performed in 2 eyes, and cyclophotocoagulation was performed in 1 eye before presenting to our center. Trabeculectomy and trabeculotomy were performed in 1 eye, and trabeculectomy followed by a penetrating keratoplasty was performed in the other eye. At last follow-up, the eye that had undergone cyclophotocoagulation had normal IOP without any AGM. The 2 eyes that had undergone surgical intervention had developed phthisis bulbi after the intervention and were subsequently not on any AGM.

The median (IQR) follow-up duration was 4.53 months (IQR, 2.03- 48.46). At last follow-up, the median IOP was 14 mm Hg (IQR, 14-17) mm Hg. IOP was controlled with only medications in 19 eyes with glaucoma. One eye that underwent cyclophotocoagulation, 1 eye that underwent TSCPC, and 1 eye that underwent TSCPC followed by penetrating keratoplasty had well-controlled IOP without any medications. The mean number of glaucoma medications at final follow-up was 1.0 ± 0.43.

Discussion

This study describes the clinical and demographic features of secondary developmental glaucoma in eyes with congenital aphakia. Few investigators have described the association of glaucoma in this condition.[3,4] Our study adds additional clinical and demographic features to this rare condition and reports on how eyes with glaucoma and congenital aphakia differ from those without glaucoma. In addition, based on management outcomes, we suggest guidelines on glaucoma management in this subset of patients.

At presentation, the median (IQR) age was 5 months (IQR, 0.46- 23.46) with a range of 3 days to 33 years. An outlier, the 33-year-old with congenital aphakia, was the father of one of the subjects in whom congenital aphakia was detected on family screening.

The most common presenting complaint was corneal opacity in the eyes with and without glaucoma. Though congenital aphakia is associated with extensive anterior segment abnormalities, glaucoma was noted in only 29/168 eyes (17.2%). Moreover, congenital aphakia is more commonly bilateral; the presence of glaucoma was found to be unilateral (39%) or bilateral (61%). In eyes with unilateral glaucoma, the IOP was elevated, HCD greater, and axial length was longer than the fellow eye without glaucoma. This finding was not surprising as similar features are seen in patients with unilateral developmental glaucoma.[8,9]

Similar to childhood glaucomas or pediatric disorders with severe ocular abnormalities, vision assessment was a challenge in this condition. Out of the 29 eyes, vision could not be assessed in 7 eyes, but the presence of dazzle reflex was noted, 13 eyes could fix and freely follow the light, and 2 eyes had no light perception.

Nearly 41% (12/29) of the eyes had an increased axial length and corneal diameter along with an elevated IOP. Glaucoma was diagnosed based on elevated IOP and optic disc cupping in another 41% (12/29) of the eyes, while 18% (5/29) of eyes were diagnosed based on only optic disc cupping. In a study by Alanazi *et al*.,[10] eyes with PCG had a greater corneal diameter, a longer axial length, lesser corneal haze, and smaller C/D ratios than eyes with secondary congenital glaucomas, which had larger vertical and horizontal cup disc ratios. They hypothesized that the slow expansion of the globe in PCG eyes causes an increase in the corneal diameter but is not severe enough to cause concurrent optic disc and corneal changes. In contrast, glaucoma diagnosis in 18% of the eyes in our cohort was based only on the optic disc changes.

The median (IQR) IOP was 28 mm Hg (IQR, 12-38). The measurement of IOP was made using the GAT or Icare tonometer. As shown in studies,[4,7] the cornea in eyes with congenital aphakia is known to be thin due to little or no corneal stroma (thin pseudo-cornea-like and disorganized stromal lamellae. Thus, the accuracy of some of the IOP measurements is questionable and may account for cupping in some eyes, with other features of developmental glaucoma being absent.

We also compared clinical features of eyes with congenital aphakia with and without glaucoma. The eyes with glaucoma had a larger HCD [median (IQR): 10.5 mm (IQR, 9-12.5)] when compared to the non-glaucomatous eyes [median (IQR): 8 mm (IQR, 5-10)] eyes (P = 0.01). The axial length was also greater in eyes with glaucoma [median (IQR): 17.5mm (IQR, 13.5-19.5)] compared to the eyes without glaucoma [median (IQR): 15mm (IQR, 14- 16)] (P = 0.03). The AXL and corneal diameters were greater in eyes with glaucoma than in eyes without glaucoma, though it was just within the normal range. Coupled with inaccurate IOP measurements, glaucoma diagnosis is challenging. However, in all cases, surrogate markers of elevated IOP such as increased horizontal corneal diameter, increased axial length, and glaucomatous disc damage must be considered while diagnosing and managing glaucoma in eyes with congenital aphakia. The utility of these markers is not unique to congenital aphakia but applicable to all forms of developmental glaucoma, especially till the age of 3 years.[11]

The intraocular pressure reduction following topical glaucoma therapy was encouraging in the short term. Nineteen out of the 29 eyes had adequate IOP reduction with only one medication at the last follow-up. This contrasts with other secondary developmental glaucoma forms, where surgical intervention is often needed with guarded outcomes.[12,13]

The outcomes of surgical intervention in eyes with glaucoma and congenital aphakia were not encouraging. Two out of the 6 eyes that underwent surgery under our care or elsewhere had severe complications. The poor outcome in these eyes following a surgical intervention may be due to the formation of an unusual cicatrizing membrane[7] or the removal of an anteriorly placed secretory ciliary epithelium during penetrating keratoplasty leading to hyposecretion of aqueous humor[4,14] and eventual phthisis. In contrast, a case report described a patient with aniridia, congenital aphakia, and secondary glaucoma who underwent trabeculectomy, had well-controlled IOP, and maintained a preoperative vision of 20/400 at 6 months of follow-up.[3]

In contrast, only 1/3 eyes that underwent cyclophotocoagulation developed a corneal ulcer. The other 2 eyes had well-controlled IOP without medications at last follow-up. In our study, laser intervention such as cyclophotocoagulation had better IOP control and lesser complications than surgical intervention. Based on our experience, we strongly recommend deferring surgical intervention in these eyes due to the poor outcomes.

Apart from the limitations involving a retrospective study, there are several limitations of the study. It is possible that some cases of congenital aphakia with glaucoma may have been missed and not included in the study because of severe anterior segment dysgenesis and inability to obtain accurate IOP or corneal diameters, obtain axial length measurements, and/or inability to visualize the optic nerve. The association between high IOP and vision, and risk factors associated with the severity of the disease could not be analyzed as the

number of patients in the series was small. The median (IQR) follow-up duration was only 4.53 months (IQR, 2.03- 48.46). Follow-up of these patients is a challenge as the parents do not follow-up once the visual prognosis is explained. Lastly, the sample size was small, and our recommendations are based on short follow-up and small sample size, but the study gives us valuable information as it is a rare condition.

Conclusion

To conclude, nearly one-fifth of the congenital aphakia cohort had secondary developmental glaucoma and shared many features of eyes with other forms of secondary developmental glaucoma. However, glaucoma may be challenging to diagnose in eyes with severely malformed anterior segments. Periodic follow-up for assessment of IOP, corneal diameter changes, axial length elongation, and optic nerve head evaluation is recommended. Furthermore, conservative medical management of glaucoma appears to be the treatment of choice in the short term. In our experience, cyclophotocoagulation provided good IOP control.

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Conflicts of interest

There are no conflicts of interest.

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