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Elevated tissue transglutaminase levels in aqueous humor of congenital cataractous eyes with long axial length

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ABSTRACT

Objective: To investigate the distribution of axial length (AL) and posterior staphyloma (PS) in congenital cataract (CC) patients. The correlation between AL and the concentration of tissue transglutaminase (TGM2) in the aqueous humor (AH) of cataractous eyes was also evaluated.
Methods: Cross-sectional data were collected from 499 children with CC who underwent phacoemulsification, anterior vitrectomy, and IOL implantation. AL measured by IOLMaster or A-scan ultrasonography and the presence of PS examined by B-scan ultrasonography were recorded. TGM2 levels in AH of 15 CC patients with normal axial length (NAL) and 15 CC patients with PS or long axial length (LAL) were measured by enzyme-linked immunosorbent assay.
Results: The presence of PS in congenital cataractous eyes was 11.02%, and the presence of PS + LAL in congenital cataractous eyes was 29.06%. The AH levels of TGM2 in the cataractous group with NAL were lower than those in the cataractous group with PS or LAL ($P < 0.001$). The concentration of TGM2 in AH were positively correlated with AL of the patients' eyes ($P = 0.001$). Additionally, we found that TGM2 expressed in the cytoplasm of lens epithelial cells of cataractous eyes, and the expression level increased with the AL value.
Conclusions: This study begins to lay the groundwork for investigating the characteristics of PS and LAL in patients with CC. Furthermore, AL was positively correlated with AH levels of TGM2.

1. Introduction

Congenital cataract (CC) is one of the leading causes of low vision and blindness in children [1]. The reported prevalence of CC was 1.8–3.6 per 10,000 children worldwide, and the highest prevalence was in Asia [2,3]. Early diagnosis and timely surgical management of pediatric cataracts can solve the occlusion on the visual axis and restore the stimulation of the normal development of the affected eyes. However, the effect of opaque lenses on eye development remains unclear.

The preoperative condition of pediatric cataract eyes, including axial length (AL), is critical for intraocular lens (IOL) implantation

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in cataract surgery and postoperative diopter outcomes [4]. Previous studies have revealed that the occurrence of cataracts during the critical period of visual development can lead to prolonged AL and even high myopia [5]. In addition, CC has been reported to be a risk factor for posterior staphyloma (PS). Preoperative PS in pediatric cataract eyes could be an indicator of excessive postoperative axial elongation [6]. It is widely known that the elongation of AL and the occurrence of PS are considered to be typical features of high myopia in adults [7]. However, their role in pediatric cataractous eyes remains unclear. These unresolved questions add to the difficulty of determining IOL power for CC patients with features of high myopia.

Myopic eyes are characterized by scleral extracellular matrix (ECM) remodeling [8]. A study has shown that tissue transglutaminase (TGM2) plays an important role in the remodeling and stabilization of the ECM [9]. TGM2 is one of the major members of the transglutaminase family, which catalyzes Ca^{2+}-dependent protein crosslinking by forming amide bonds [10]. TGM2 protein mainly exists in the cytoplasm of cells, and some proteins can also be secreted into the ECM to perform a variety of functions. Furthermore, activation of TGM2 can induce protein aggregation by reducing protein solubility and increasing cross-link in proteins in the lens [11]. A study reported an association between the level of cytokines in aqueous humor (AH) and axial elongation in children with CC [12]. Thus, we speculated that the concentration of TGM2 in AH of CC patients had a similar relationship with AL.

To assess the correlation between TGM2 and AL in eyes with CC characterized by high myopia, we collected AH samples from these eyes and analyzed the relationship between the concentration of TGM2 and AL. In addition, we reported the preoperative eye conditions of CC patients with features of high myopia to expand our understanding of the characteristics of PS and LAL in patients with CC.

2. Methods

2.1. Patients

This study was approved by the Institutional Review Board of Eye and ENT Hospital of Fudan University, Shanghai, China. All study protocols were carried out in accordance with the tenets of Declaration of Helsinki. Written informed consent for study participation was obtained from a legal guardian of each child.

The preoperative medical records of 524 patients with CC who underwent phacoemulsification, anterior vitrectomy, and IOL implantation at the Eye and ENT Hospital of Fudan University between 2009 and 2020 were collected. We excluded patients who had other ocular diseases (including and not limited to microphthalmia, persistent fetal vasculature, corneal opacity, iris anomaly, uveitis, congenital glaucoma or trauma) or had a history of ophthalmological surgeries. Ultimately, the medical records of 499 CC patients were analyzed in this study. The right eyes of bilateral cataractous eyes and all unilateral cases were included.

We collected demographic data, including sex, laterality, age at surgery, ocular and systemic comorbidities, and preoperative intraocular pressure (IOP). All patients underwent comprehensive preoperative ophthalmological examinations. AL was measured by IOLMaster or A-scan ultrasonography. In addition, the posterior segment was examined by B-scan ultrasonography.

In this study, the criteria for long axial length of cataractous eyes was as follows: 0–6 years old $\geq$22.78 mm, 6–12 years old $\geq$23.68 mm, 12–18 years old $\geq$23.88 mm. This criterion was based on the maximum value of emmetropic eyes in the same age subgroup in the literature [13–15]. The minimal value of LAL in our study was greater than the reported emmetropic maximum value.

2.2. Sample collection

The AH samples were obtained from 30 eyes of CC patients who were divided into two groups: congenital cataractous eyes without long axial length (LAL) and PS ($n = 15$ eyes of 15 patients; serving as controls) and congenital cataractous eyes with LAL and PS ($n = 15$ eyes of 15 patients).

Approximately 150 μL of AH was collected from each patient prior to any surgical operation with a 30-gauge needle attached to a microsyringe. The needle was carefully handled to avoid contacting any intraocular tissue during AH collection. The AH samples were placed immediately into Eppendorf tubes and stored at −80 °C.

2.3. Enzyme-linked immunosorbent assay (ELISA) for TGM2

The protein concentration of TGM2 was detected using a human ELISA assay (Meilian Biotech, Shanghai). First, the AH samples were thawed and centrifuged at 4 °C. The TGM2 standard and AH samples were prepared according to the manufacturer's instructions. The concentration gradient of the standard substances used in the experiment was 1200, 600, 300, 150, 75 and 0 pg/ml. Fifty microliters of AH samples or diluted TGM2 standard substances were added to the wells and incubated at 37 °C for 30 min. Each well was washed 5 times with wash buffer, and biotinylated antibody working solution (dilution ratio 1:500) was added. After incubation, the plate was washed 5 times. Next, 100 μL of horseradish peroxidase (HRP)-labeled antibody working solution (dilution ratio 1:4000) was added to both standard and sample wells and incubated at 37 °C for 30 min. After washing 5 times, 100 μL of a color substrate solution was added to each well and incubated at 37 °C for 15 min in the dark. Reaction stop solution (50 μL) was then added to the plate, and the absorbance at 450 nm was measured.

2.4. Immunofluorescence staining

After washing three times with PBS, the anterior lens capsule samples were fixed with paraformaldehyde for 15 min. Then, the samples were permeabilized with 0.3% Triton X-100 for 10 min. After incubation for 1 h in QuickBlockTM IF blocking solution (Beyotime), the samples were treated with primary antibodies against TGM2 (1:100, Proteintech) overnight at 4 °C. The next day, the samples were incubated with fluorescein isothiocyanate (FITC)-conjugated secondary antibody (1:200, Abcam) for 2 h at room temperature in the dark. The nuclei were stained with DAPI and the slides were observed using fluorescence microscopy.

2.5. Statistical analysis

The statistical software SPSS 25.0 (International Business Machines Corp., New York) was used for data analyses. The value was expressed as the mean ± standard deviation (SD). Pearson's bivariate correlation test was used to analyze the relationship between AL and the concentration of TGM2 in the AH. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline information

In our study, we reviewed the medical records of 524 patients with CC, of which 499 cases met our criteria. All 499 patients were Chinese Han, and their ALs were collected. According to the characteristics of children's AL growth, the patients were divided into 4 age subgroups for analysis: 0–3 years old (185 cases), 3–6 years old (194 cases), 6–12 years old (110 cases) and 12–18 years old (10 cases). The mean AL of 499 cases (499 eyes) was 22.06 ± 1.74 mm (range, 16.28–32.74 mm). The mean values of AL were greater in older children (Table 1). In addition, we found that the mean AL was larger in males than in females with CC (22.25 ± 1.85 mm vs. 21.82 ± 1.57 mm, $P = 0.006$) (Table S1 in the supplementary material). Our data also show that cataractous eyes of patients with bilateral cataracts had a significantly shorter mean AL than those with unilateral cataracts (21.90 ± 1.82 mm vs. 22.28 ± 1.61 mm, $P = 0.016$) (Table S2 in the supplementary material).

3.2. The prevalence of long axial length and posterior staphyloma in cataractous eyes

In the current study, we found that 55 out of 499 cataractous eyes were identified with PS (11.02%, monocular: 28, binocular: 27). Illustrations of cataractous lens, PS, and leopard-print fundus in children with CC were shown in Fig. 1 (A-C). According to the characteristics of AL growth in children of different ages, 90 out of 499 cataractous eyes were found to have long AL (18.04%, monocular: 39, binocular: 51). In total, 145 cataractous eyes were identified with PS or LAL (29.06%, monocular: 67, binocular: 78). A total of 354 cataractous eyes had normal AL (70.94%, monocular: 144, binocular: 210).

Age at surgery and laterality were not significantly different between CC patients with normal axial length (NAL) and those with PS or LAL ($P > 0.05$, Table 2). The AL of eyes with PS or LAL (23.85 ± 1.67 mm) was found to be significantly longer than that of eyes with NAL (21.32 ± 1.13 mm, $P = 0.000$).

The mean values of AL of cataractous eyes in the NAL group were longer than those in the PS + LAL group in all age subgroups (Fig. 2). The age and AL distributions of CC children with and without PS were shown in Fig. 3. As shown, the triangles representing CC children with PS are mostly distributed in the upper part, showing a relatively longer AL than children of the same age without PS. In addition, there was a positive correlation between AL and age in patients without PS ($P = 0.000$, $y = 0.01667x + 20.98$; Fig. 3). A similar result was observed for AL and age in patients with PS ($P = 0.000$, $y = 0.04502x + 21.8$; Fig. 3).

3.3. Demographic information of patients providing aqueous humor

The mean ages of the NAL group and PS + LAL group were 62.73 ± 35.83 months (n = 15, range, 13–142 months) and 52.07 ± 23.07 months (n = 15, range, 27–95 months), respectively. Out of the 30 eyes, 11 were from males, and 19 were from females. The NAL and PS + LAL groups were well matched with respect to age (n = 15, $P = 0.341$) and sex (n = 15, $P = 1.000$) (Table S3 in supplementary materials provides the demographic information of these patients).

3.4. Concentration of TGM2 in the aqueous humor and axial length of 30 cataractous eyes

The mean AL of patients in the NAL and PS + LAL groups were 21.007 ± 0.902 and 24.497 ± 0.625 mm, respectively. The mean AL

Table 1
Axial length distribution by patient age in unilateral cases and right eyes of patients with bilateral cataracts.

Age group (years)	Patients (n)	AL (mm)	95%CI	Range
0~3	185	21.31 ± 1.59	21.08–21.54	16.28–25.63
3~6	194	22.27 ± 1.58	22.05–22.49	18.51–27.63
6~12	110	22.80 ± 1.78	22.47–23.14	19.5–32.74
12~18	10	23.61 ± 1.49	22.54–24.67	19.88–25.12
Total	499	22.06 ± 1.74	21.90–22.21	16.28–32.74

AL = axial length; CI = confidence interval.

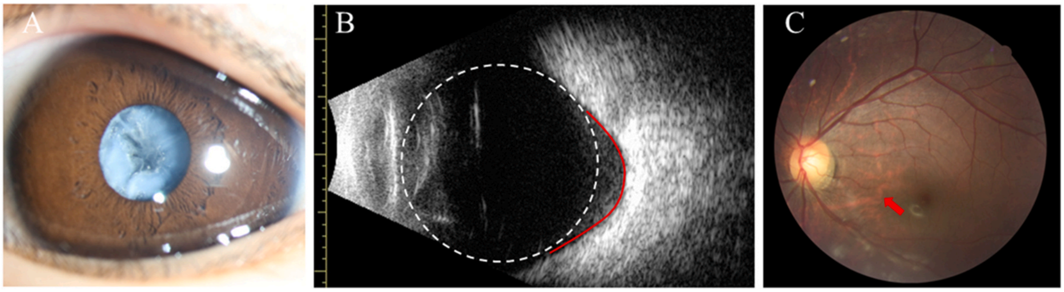

Fig. 1. Illustrations of cataractous lens, posterior staphyloma, and leopard-print fundus in children with congenital cataract. (A) Anterior segment photograph of a 3-year-old child with congenital cataract. (B) B-scan photograph of a pediatric cataractous eye showed posterior staphyloma, which was defined as a protrusion of the eye wall with a radius of curvature (red curve). (C) Fundus photograph of a pediatric cataractous eye showing leopard-print fundus, a typical feature of myopic fundus (red arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Demographic and clinical characteristics of patients with posterior staphyloma and long axial length and normal axial length subjects.

Variables	Total (%)	NAL (%)	PS + LAL (%)	*P* value
Total	499	354 (70.94)	145 (29.06)	
Male	278 (55.71)	184 (51.98)	94 (64.83)	0.009*
Female	221 (44.29)	170 (48.02)	51 (35.17)	
Age (months)	51.07 ± 36.13	50.12 ± 35.79	53.39 ± 36.98	0.359
Monocular	211 (42.28)	144 (40.68)	67 (46.21)	0.256
Binocular	288 (57.72)	210 (59.32)	78 (53.79)	
AL (mm)	22.06 ± 1.74	21.32 ± 1.13	23.85 ± 1.67	0.000*

NAL = normal axial length; PS = posterior staphyloma; LAL = long axial length.
* PS + LAL versus NAL, $P < 0.05$.

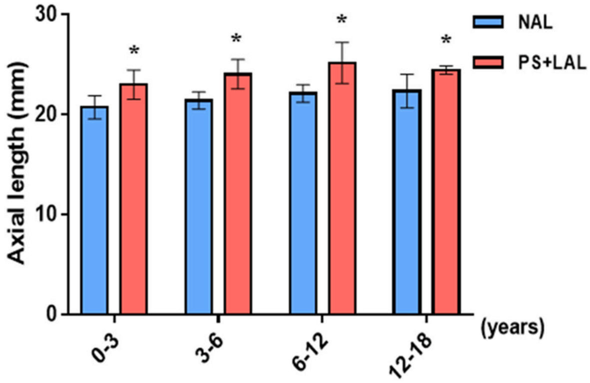

Fig. 2. The mean values of axial length of cataractous eyes in the normal axial length group and posterior staphyloma + long axial length group in all age subgroups. Data presented are means ± standard deviations (*$P < 0.001$).

of patients in the PS + LAL group was higher than that in the NAL group (n = 15, $P = 0.000$) (Fig. 4A).

The mean concentration of TGM2 protein in 30 patients was 438.375 ± 64.551 pg/ml. The mean concentration of TGM2 protein in the NAL and PS + LAL groups were 399.896 ± 52.267 and 476.855 ± 52.217 pg/ml, respectively. AH levels of TGM2 in the PS + LAL group were significantly higher than those in the NAL group (n = 15, $P = 0.000$) (Fig. 4B). Univariable analysis revealed that the concentration of TGM2 in AH (n = 30, $P = 0.001$; beta: 0.576; 95% CI: 8.598, 29.9) was significantly associated with AL of 30 cataractous eyes (Table 3).

3.5. A positive correlation between TGM2 and axial length in congenital cataract patients

Univariate analysis suggested that there was a correlation between TGM2 levels in AH and AL of CC patients. We then further explored the linear relationship between TGM2 concentration in AH and AL. As expected, the mean concentration of TGM2 protein in AH were positively correlated with AL of CC patients, and a significant correlation was found (n = 30, $P = 0.001$, y = 19.7x- 9.821;

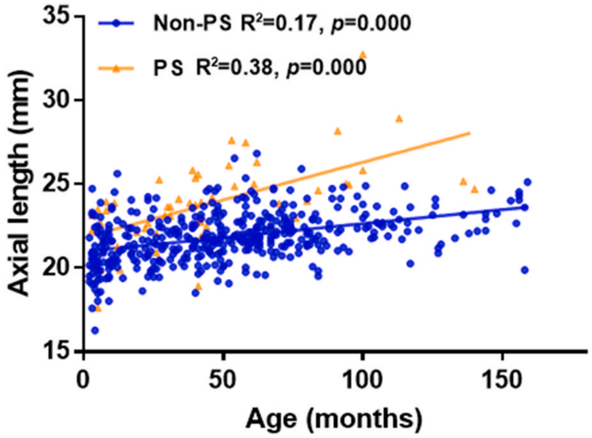

Fig. 3. Scatterplot of the axial length of pediatric cataractous patients in relation to the age at surgery.

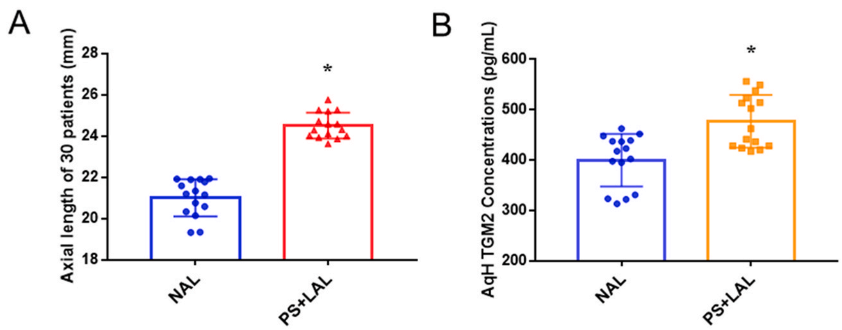

Fig. 4. Axial length and aqueous humor TGM2 levels. (A) The PS + LAL group had a higher axial length than the NAL group. (B) AH levels of TGM2 in the PS + LAL group were significantly higher than those in the NAL group. Data presented are means ± standard deviations (n = 15, **P* < 0.001).

Table 3
Univariate analysis of factors associated with TGM2 levels in aqueous humor of 30 children.

Variable	Beta coefficient (95%CI)	*P* value
Age (months)	−0.107 (-0.913, 0.454)	0.496
AL (mm)	0.576 (8.598, 29.9)	0.001*
Sex (female/male)	0.109 (-36.26, 65.094)	0.565
Eye laterality (binocular/monocular)	−0.305 (-86.326, 8.095)	0.101

AL = axial length. *$P < 0.05$.

Fig. 5).

To further clarify the expression levels of TGM2 in CC, we performed immunofluorescence staining on lens epithelial cells (LECs) under the anterior lens capsule of CC patients and normal donors. Representative images obtained by confocal immunofluorescence microscopy were shown in Fig. 6. Our data indicated that TGM2 protein levels were upregulated in the cytoplasm of LECs from patients with CC. In addition, the expression of TGM2 protein was positively correlated with AL of CC patients.

4. Discussion

In the current study, we analyzed AL values of 499 patients with congenital cataracts aged from 2 to 159 months. Consistent with previous studies, we found that the AL in the cataractous eyes of male patients was significantly longer than that in female patients [16,17]. AL was significantly longer in unilateral CC-affected eyes versus bilateral CC-affected eyes [18]. In addition, our research observed the occurrence of PS and LAL in CC-affected eyes. The presence of PS in our study was higher than that in previous studies [6]. We also observed a positive correlation between AL and age in cataractous eyes with or without PS.

Previous animal experiments suggested that the activation of TGM2 might be involved in the dissolution and aggregation of lens proteins, thus participating in the formation of cataract [11]. Notably, we assessed the intraocular concentration of TGM2 protein in human cataractous eyes. We found that TGM2 concentration in AH linearly increased with longer AL. To the best of our knowledge, the

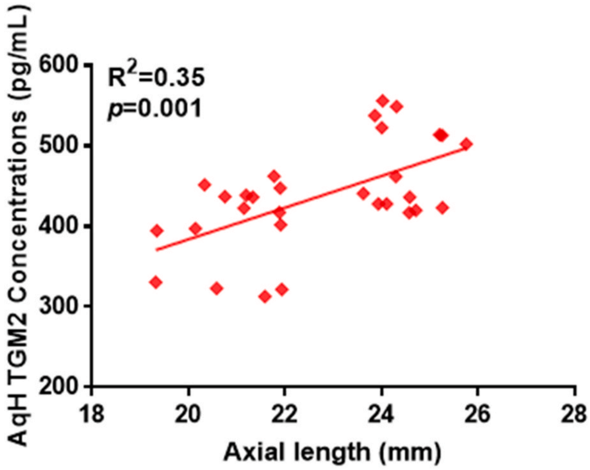

Fig. 5. Scatterplot of TGM2 concentration in the aqueous humor in relation to the axial length of pediatric cataractous eyes (n = 30).

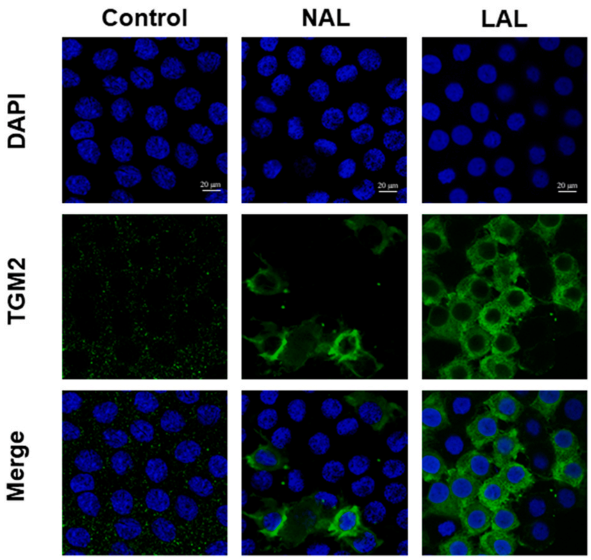

Fig. 6. Immunofluorescence image of TGM2 protein in human lens epithelial cells in the anterior lens capsule of pediatric donors and congenital cataract patients with normal axial length and long axial length. Bar = 20 μm.

current study is the first to confirm that the expression levels of TGM2 in the AH and LECs of children with CC are associated with AL, elucidating the crucial role of TGM2 in the pathogenesis of PS and LAL in CC-affected eyes.

AL is known to increase with age during eye development in healthy newborns [19]. In addition to physiological elongation, AL can be influenced by genetic and environmental factors [20]. He et al. [18] reported a mean AL of 22.03 ± 1.97 mm in the cataractous eyes of CC patients undergoing cataract surgery at 4.72 ± 3.36 years of age. Lin et al. [17] noted a mean AL of 22.90 ± 1.99 mm in the cataractous eyes of CC patients undergoing cataract extraction and IOL implantation at 81.05 ± 52.27 months of age. The mean AL of 499 cataractous eyes in our investigation was 22.06 ± 1.74 mm, which was slightly shorter than the mean AL in the above studies. This may be because the mean operative age of cataract patients enrolled in this study was 51.07 ± 36.13 months, which was younger than the mean ages reported in prior studies of Chinese patients. A study on Nepalese patients undergoing CC surgery at 92.4 ± 4.13 months of age showed a mean AL of 21.94 ± 1.94 mm, which was shorter than the AL in our research [21]. Racial differences may be relevant to these differences.

Previous studies have revealed sex-linked differences in AL in cataractous pediatric eyes [16,17]. Consistent with these findings, we found that the mean AL was larger in the cataractous eyes of males than that of females with CC. Moreover, our data also show that cataractous eyes of patients with bilateral cataracts had a significantly shorter mean AL than those of patients with unilateral cataracts, similar to reports by He et al. [18], Sahu et al. [21] and Lin et al. [17].

Moreover, previous studies have suggested that visual deprivation caused by cataracts can lead to excessive stretching of the ocular axis in pediatric eyes [16,22]. The occurrence of AL > 24 mm (31/813) and PS (40/520) in CC eyes was observed in one study [6]. However, few researchers have investigated the characteristics of high myopia in children with CC. Therefore, we are interested in exploring the impact of CC on PS and AL. Since the eyes of children are not fully developed, the definition of high myopia in adults with an axial length of ≥26 mm may not be applicable to children. Thus, we collected and analyzed axial data from all previous studies which focused on ocular biometry data in infants and children. For noncataractous pediatric eyes, Gordon et al. reported a mean AL of 22.28 ± 0.50 mm in 0- to 10-year-old patients with emmetropia. At 11–20 years of age, these mean values were 23.42 ± 0.46 mm [13]. Dogan reported noncataractous eyes with emmetropia (age, 6–10 years) as having a mean AL of 23.13 ± 0.55 mm [14]. The AL of cataractous eyes, which defined as long axial length in our study, was longer than the maximum value of emmetropic noncataractous eyes in the same age subgroup in the literature, [13–15].

The presence of PS was identified in CC eyes with AL below 22 mm, which suggested that the eyeball had been abnormally extended and that myopia already existed [6]. Similar to this finding, we also observed the occurrence of PS in the preoperative B-scan of cataractous eyes in CC children without a family history of high myopia. The prevalence of PS (55/499) in CC children in our study was higher than that in previous studies [6]. We have shown that the mean AL of pediatric cataractous eyes with PS or LAL (23.85 ± 1.67 mm) is significantly higher ($P < 0.001$) than the mean AL of pediatric cataractous eyes with NAL (21.32 ± 1.13 mm). In addition, we observed a significantly positive correlation between AL and age in patients with or without PS.

ECM remodeling is a potential mechanism of axial elongation and PS formation in myopic eyes and is regulated by TGM2 [8]. Moreover, TGM2 is one of the main members of the transglutaminase family, and its activation can increase the cross-linking between proteins in the lens and lead to the induction of protein aggregation [11]. However, the role of TGM2 in CC, especially in cataractous eyes with PS and LAL, remains to be elucidated. In this work, the AH concentration of TGM2 protein in the cataractous group with NAL were lower than those in the cataractous group with PS or LAL. Furthermore, our results showed that TGM2 protein levels in AH of cataractous eyes were positively correlated with AL. We also localized and quantified the expression of TGM2 in the anterior lens capsule of noncataractous and cataractous eyes in children. We found that TGM2 was expressed in the cytoplasm of LECs of cataractous eyes, and the expression seemed to increase with the AL value.

To the best of our knowledge, our study is the first to detect TGM2 protein expression in AH and the anterior lens capsule of pediatric cataractous eyes. Overall, these observations support the hypothesis that TGM2 is involved in growth of cataractous eyes, and at the same time, our findings suggest a possible role for TGM2 in driving axial elongation. This study has several potential limitations to consider. Firstly, the AH samples were limited. However, we observed a positive correlation between TGM2 and axial length. Further studies should be performed to confirm the results. And unlike the adult study, it was difficult to find age-matched controls for infant patients in our study. On the other hand, the specific mechanism of TGM2 in the progression of cataracts with PS and LAL needs to be further evaluated in future longitudinal studies.

5. Conclusions

We assessed the distribution of PS and LAL in pediatric cataractous eyes. Moreover, we detected TGM2 protein expression in AH samples and the anterior lens capsules of pediatric cataract patients. We found that the prevalence of PS in pediatric cataractous eyes was 11.02%. There was a significantly positive correlation between AL and age in patients with or without PS. Laboratory analysis revealed that pediatric cataractous eyes with PS and LAL had elevated levels of TGM2 protein compared to those with NAL, and the level of TGM2 protein in AH was positively correlated with AL of CC patients' cataractous eyes. These results suggest that TGM2 plays an essential role in axial elongation in CC.

Declarations

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Ethics statements

Patient consent for publication

Written informed consent from a legal guardian for study participation was obtained for all children.

Ethics approval

This study was approved by the Ethics Committee of EENT Hospital and adhered to the tenets of the Declaration of Helsinki for experiments involving human tissues.

Author contribution statement

Tianke Yang: Performed the experiments and wrote the paper.
Xiyue Zhou: Performed the experiments.

Hongzhe Li, Fan Fan, and Jianing Yang: Contributed reagents, materials, analysis tools or data.
Xiaolei Lin: Analyzed and interpreted the data.
Yi Luo and Xin Liu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional interest of any nature or kind in any product, service and/or company that could be constructed as influencing the position presented in manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2023.e18709.

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