

A negative correlation of axial length with aqueous humor concentration of cytokines in patients with congenital cataracts

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Purpose: To investigate the association between cytokine (and related proteins) concentrations in the aqueous humor (AH) of patients with congenital cataracts and preoperative and postoperative axial length.

Methods: Samples from the AH were collected from 25 eyes of 17 patients with congenital cataracts who underwent congenital cataract extraction and intraocular lens implantation. Multiplex enzyme-linked immunosorbent assays (ELISAs) and Luminex xMAP technology were used to assess the concentration of cytokines or chemokines, and acute phase proteins in the AH. Axial lengths were measured before surgery and at 3 months, 6 months, and 1 year after surgery.

Results: The mean protein concentrations were determined in the AH of patients with congenital cataracts. The following proteins were assessed: VEGF (9.89 ± 4.94 pg/ml), TNF- α (1.88 ± 0.12 pg/ml), TGF- β 2 (1622.88 ± 762.53 pg/ml), IL-1RA (110.78 ± 141.29 pg/ml), IL-1 β (1.85 ± 0.13 pg/ml), IL-2 (41.96 ± 14.48 pg/ml), IL-4 (9.75 ± 1.32 pg/ml), IL-5 (1.38 ± 0.09 pg/ml), IL-6 (2.31 ± 5.97 pg/ml), IL-10 (1.46 ± 0.47 pg/ml), IL-12p70 (21.50 ± 1.60 pg/ml), IL-15 (2.23 ± 0.18 pg/ml), IL-17A (1.22 ± 0.11 pg/ml), GM-CSF (2.80 ± 0.38 pg/ml), IFN- γ (9.20 ± 0.42 pg/ml), CCL2/MCP-1 (131.45 ± 90.45 pg/ml), CCL3/MIP-1 α (87.14 ± 3.83 pg/ml), CCL4/MIP-1 β (66.26 ± 2.22 pg/ml), CXCL10/IP-10 (13.99 ± 39.66 pg/ml), CCL11/eotaxin (27.17 ± 2.00 pg/ml), and PDGF-BB (0.43 ± 0.04 pg/ml). These data suggested a negative correlation between the level of VEGF in the AH and the preoperative axial length ($r^2 = 0.2615$, $p < 0.01$). Similarly, the level of GM-CSF and CCL11/eotaxin in the AH decreased with an increase in axial length ($r^2 = 0.2456$, $p = 0.01$; $r^2 = 0.1758$, $p = 0.037$). At 1 year post-surgery, a negative correlation was observed between the level of PDGF-BB and the change in the axial length ($r^2 = 0.2133$, $p = 0.02$). Axial elongation at 1 year post-surgery was 0.24 ± 0.34 mm. The predicted change in axial length at 1 year post-surgery was 1.05 ± 0.83 mm, and the actual axial elongation was statistically significantly smaller than the predicted change in healthy children (paired t test, $p < 0.01$).

Conclusions: Increased preoperative axial lengths were negatively correlated with AH levels of VEGF, GM-CSF, and CCL11/eotaxin. The level of PDGF-BB was negatively correlated with the change in axial length 1 year post-surgery. These data suggest that the concentrations of these proteins in the AH may have predictive value for changes in axial length in patients with congenital cataracts, and possibly provide a useful prognostic modality.

Congenital cataract is one of the main causes of low vision and blindness in children worldwide [1,2]. According to a World Health Organization (WHO) report, of the approximately 500,000 children who are born blind every year, 10–38% have congenital cataracts [3]. Early intervention with congenital cataract extraction and intraocular lens implantation (IOL) is critical for prevention of developing deprivation amblyopia. However, as the eye continues to grow, determining the refractive power of the IOL that should be implanted is challenging. Patients with congenital cataracts, even with surgical intervention, often suffer from high myopia as older children or adults [4,5].

Changes in axial length after cataract extraction and IOL implantation are not fully understood. Some studies suggested that cataract extraction followed by IOL implantation slightly

decreases axial elongation [6,7]. However, other studies suggested that the change in axial length from baseline is similar in pseudophakic eyes and the fellow eye [4,8]. These uncertainties make it difficult to determine the correct power of the IOL to be implanted.

Several studies in adult patients have reported an association between the aqueous humor (AH) concentration of cytokines and the axial length [9,10]. This prompted us to determine whether a similar association could be made in patients with congenital cataracts. To accomplish this, we assessed the level of cytokines in the AH in patients with congenital cataracts and sought to determine whether there was a correlation with axial length or axial elongation with the goal of developing a better strategy for predicting axial length.

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METHODS

Patients and samples: This study was an observational study that included 25 eyes of 17 patients with congenital cataracts that underwent cataract extraction with IOL implantation at the Eye Hospital of Wenzhou Medical University (Hangzhou Branch), Hangzhou, China. The mean age of the patients was 36.64 months \pm 21.95 months. Of the 25 eyes, 7 were from female patients and 18 were from male patients. The enrolled patients were healthy except for congenital cataract. All surgeries were performed by the same surgeon under general anesthesia. Surgical methods and procedures, including lensectomy combined with limited anterior vitrectomy, were approved by the Ethics Committee of Wenzhou Medical University. All patients' parents signed an informed consent form and all procedures conformed to the tenets of the Declaration of Helsinki. And the study adhered to the ARVO statement on human subjects. Approximately 0.1 ml of AH was collected under a binocular microscope by paracentesis of the anterior chamber during surgery. AH samples were stored at -80°C immediately until laboratory analysis. Patients with other congenital ophthalmic disorders, such as persistent fetal vasculature, systemic disorders (including Marfan's syndrome) were excluded. Additionally, patients with postoperative complications, such as uveitis, high intraocular pressure, or had a potential risk of glaucoma were excluded. Finally, patients that had less than 0.5ml of AH were also excluded.

Measurements: Demographic data, including gender, age at the time of surgery, and accompanying ocular anomalies, were collected. All eyes underwent a full ophthalmological examination at baseline, including best corrected visual acuity (BCVA) testing using a Teller chart, slit-lamp biomicroscopy, dilated fundus examination, and intraocular pressure (IOP) measurement via i-care tonometer (Icare pro, Icare, Vantaa, Finland). Axial length (AL) and anterior chamber depth was measured via an A-scan (Axis nano, Quantel Medical, Courron, French). AL was measured before the surgery, at three months, six months, and one year after the surgery.

The detailed procedure for the assessment of AH cytokines using Luminex xMAP technology with multi-analyte profiling beads was followed strictly (Lincoplex cytokine/chemokine multiplex kit, HCYTO- 60K; Millipore Corporation, Billerica, MA). 1. Pipet 200 μl of Lincoplex assay buffer into each well of the plate. 2. Seal and mix on a plate shaker for 10 min at room temperature ($20-25^{\circ}\text{C}$). 3. The buffer was removed by vacuum filtration. 4. A serial dilution of standards (3.2-10 000 pg/ml) was used for processing a standard curve for each cytokine. Assay Buffer should be used for 0 pg/ml

standard (Background). 5. Add 25 μl of Assay Buffer to the sample wells and 25 μl of appropriate matrix solution to the background, standards, and control wells. 6. Aqueous humor (25 μl) was added to the appropriate wells. 7. Mixed beads containing antibody-immobilized beads were added to each well and the plate was sealed with a plate sealer and covered the plate with foil, and incubated with agitation on a plate shaker for 1 h at room temperature ($20-25^{\circ}\text{C}$). 8. Gently remove well contents and wash plate 2 times with 200 μl of Lincoplex wash buffer. 9. Add 25 μl of Detection Antibodies into each well and seal, cover with foil and incubate with agitation on a plate shaker for 30 min at room temperature ($20-25^{\circ}\text{C}$). 10. Add 25 μl of streptavidin-phycoerythrin solution to each well containing the 25 μl of Lincoplex detection antibody cocktail. 11. The plate was sealed and covered with aluminum foil and incubated with agitation on a plate shaker for 30 minutes at room temperature ($20-25^{\circ}\text{C}$). 12. Gently remove well contents and wash plate 2 times with 200 μl of Lincoplex wash buffer. 13. Add 100 μl of sheath fluid to all wells. 14. The plate was covered with aluminum foil and the beads in each well were resuspended on a plate shaker for 5 min. 15. Run plate on Luminex instrument. 16. Save and analyze the Median Fluorescent Intensity (MFI) data using a 5-parameter logistic or spline curve-fitting method for calculating cytokine/chemokines concentrations in samples [9,11,12].

Fledelius et al. developed a mathematical expression to predict axial elongation in healthy children [13]. We used this expression with the patients in this study to predict within the 1st year post-surgery. The axial length growth ΔAL was analyzed with the following expression (t = age in weeks; t' = age after 1 year = $t + 52$; Figure 1).

Statistical analysis: The data were analyzed using the statistical software SPSS 21.0 (SPSS, International Business Machines Corp., New York, NY). Values were expressed as mean \pm standard deviation (SD) or median (quartile range). Fisher's exact test was used to analyze the relationship between aqueous axial length and AH concentration, and between axial elongation and AH concentration. Paired t tests were used to analyze the relationship between the actual axial elongation at 1 year post-surgery and the predicted axial elongation. For the comparisons, a p value of less than 0.05 was considered statistically significant. All reported p values were two-tailed.

RESULTS

This prospective study included 29 eyes of 20 patients with congenital cataracts. Two patients were excluded as they did not comply with the follow-up examination. One patient was

$$\begin{aligned} \Delta AL &= f(t') - f(t) \\ &= K \left[k_1(1 - e^{-\frac{t'-t_0}{T_1}}) + k_2(1 - e^{-\frac{t'-t_0}{T_2}}) \right] - K \left[k_1(1 - e^{-\frac{t-t_0}{T_1}}) + k_2(1 - e^{-\frac{t-t_0}{T_2}}) \right] \\ &= K \left[1 - k_1 e^{-\frac{t'-t_0}{T_1}} - k_2 e^{-\frac{t'-t_0}{T_2}} \right] - K \left[1 - k_1 e^{-\frac{t-t_0}{T_1}} - k_2 e^{-\frac{t-t_0}{T_2}} \right] \\ &= K \left[k_1 e^{-\frac{t-t_0}{T_1}} + k_2 e^{-\frac{t-t_0}{T_2}} - k_1 e^{-\frac{t'-t_0}{T_1}} - k_2 e^{-\frac{t'-t_0}{T_2}} \right] \end{aligned}$$

t = age in weeks; t' = Age after one year = t + 52

with the values: K = 23 mm; k₁ = 0.73; k₂ = 0.27; T₁ = 12 weeks; T₂ = 100 weeks; t₀ = 10 weeks

Figure 1. Human ocular growth prediction formula in infancy, and early childhood. We described some of the constants and variables in the formula: K is the value of the function for t going towards infinity. The actual value of 23 mm is the presumed axial measure at the age of 13 years, the end point of eye growth. T1 and T2 are time constants related to the exponential growth decay rates (12 weeks and 100 weeks, respectively). k1 (0.73) and k2 (0.27) are empirically chosen numerical weights approached to best fit.

excluded due to ocular hypertension. A total of 25 eyes of 17 patients were included in the study. There was no correlation between the changes of axial lengths in one year after operation and the preoperative axial lengths (p > 0.05).

Concentrations of cytokines: A total of 25 aqueous humor samples were collected. The mean concentrations of AH proteins were 9.89 ± 4.94 pg/ml for VEGF, 3.95 ± 0.69 pg/ml for TNF-α, 1.88 ± 0.12 pg/ml for TGF-β2, 110.78 ± 141.29 pg/ml for IL-1RA, 1.85 ± 0.13 pg/ml for IL-1β, 41.96 ± 14.48 pg/ml for IL-2, 9.75 ± 1.32 pg/ml for IL-4, 1.38 ± 0.09 pg/ml for IL-5, 2.31 ± 5.97 pg/ml for IL-6, 1.46 ± 0.47 pg/ml for IL-10, 21.50 ± 1.60 pg/ml for IL-12p70, 2.23 ± 0.18 pg/ml for IL-15, 1.22 ± 0.11 pg/ml for IL-17A, 2.80 ± 0.38 pg/ml for GM-CSF, 9.20 ± 0.42 pg/ml for IFN-γ, 131.45 ± 90.45 pg/ml for CCL2/MCP-1, 110.78 ± 141.29 pg/ml for CCL3/MIP-1α, 87.14 ± 3.83 pg/ml for CCL4/MIP-1β, 13.99 ± 39.66 pg/ml for CXCL10/IP-10, 27.17 ± 2.00 pg/ml for CCL11/eotaxin, and 0.43 ± 0.04 pg/ml for PDGF-BB.

A negative correlation between cytokines and axial length in preoperative patients: There was a negative correlation between the AH level of VEGF and the preoperative axial lengths (r² = 0.2615, p < 0.01, Pearson correlation test, y = -1.0139x + 32.653; Figure 2). Similar results were observed for the AH levels of GM-CSF and CCL11/eotaxin. Protein levels decreased with an increase in the axial length (r² = 0.2456, p = 0.01, y = -0.0754x + 4.4935; r² = 0.1758, p = 0.037, y = -0.3366x + 34.724; Figure 3 and Figure 4). There was no statistically significant correlation between the other cytokines and axial length (p > 0.05).

A negative correlation between PDGF-BB and the change in axial lengths at 1 year post-surgery: A negative correlation was observed between the level of PDGF-BB and the change in the axial length at 1 year post-surgery (r² = 0.2133, p = 0.02, y = -0.0607x + 0.4404; Figure 5). There was no statistically significant correlation between other cytokines and the change in the axial length at 1 year post-surgery (p > 0.05).

Actual axial elongation was statistically significantly smaller than the predicted change in axial length: Actual axial elongation at 1 year post-surgery was 0.24 ± 0.34 mm. The predicted axial length change according to age at 1 year was determined to be 1.05 ± 0.83 mm. Actual axial elongation was statistically significantly smaller than the predicted outcome in healthy patients (paired t test, p < 0.01).

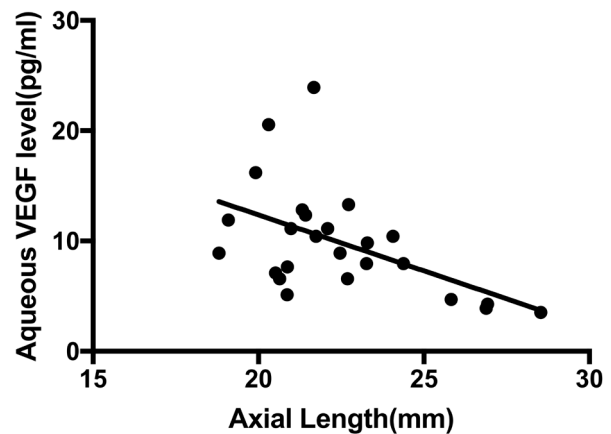


Figure 2. Axial length negatively correlates with AH VEGF.

DISCUSSION

Several studies have reported that inflammatory cytokines expressed in the anterior chamber were associated with axial length in adults. This prompted us to determine whether this was the case in pediatric patients, specifically those with congenital cataracts. As an infant's axial length is still developing, the choice of intraocular lens power selection is only often based on previous experience and the age of the child. This is often not tailored to the specific patient [14]. Some formulas used to calculate the power of intraocular lenses have a median of absolute prediction error exceeding 3.0 D [2,15]. If the axial elongation is greater than expected, the intraocular lens often needs to be replaced when the child matures. However, if the axial elongation is less than expected, children require the use of glasses or contact lenses for hyperopia [4]. This study may provide new guidelines for an individualized plan for the patient. Additionally, retinal detachment increases according to the degree of myopia, which increases according to the axial length [16,17]. For example, the incidence of peripheral retinal degeneration, such as lattice degeneration, increases with the axial length. Accurate prediction of changes in axial length may reveal potential risks of high myopia early in infancy and permit possible earlier intervention.

In the present study, we observed that the VEGF concentration in the AH was statistically significantly negatively correlated with axial length. This result is in agreement with previous studies of adults with similar cases of a decrease in intracameral protein concentration correlating with increased axial length [9,18-20]. VEGF is an angiogenic and a vasopermeable factor constitutively secreted by RPE cells [21]. Shin et al. suggested that degeneration of RPE with high myopia leads to a reduction in production of VEGF [9]. Furthermore, Chen et al. suggested that retinal hyperoxia induced by photoreceptor degeneration was another possible explanation [19]. However, retinal degeneration cannot explain the present findings in infant patients. Zhu et al. hypothesized that in highly myopic adults a larger volume and higher turnover in the vitreous lead to dilution and a faster turnover of VEGF [18]. This hypothesis somewhat helps to explain our observations; however, we suggest another. We proposed a hypothesis that a decrease in VEGF may lead to the development of increased axial length. VEGF may play a role in eye development. Similarly, the AH levels of GM-CSF and CCL11/eotaxin levels decrease with an increase in the axial length. The role of GM-CSF and CCL11/eotaxin is unknown and requires further investigation.

We also observed a negative correlation between the level of PDGF-BB and the change in axial lengths at 1 year

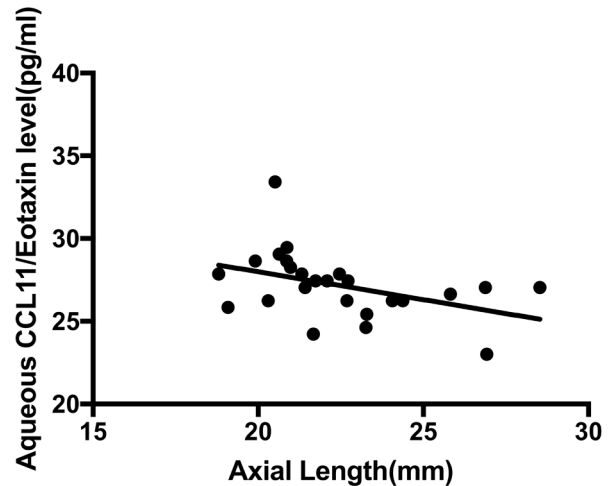


Figure 3. Axial length negatively correlates with AH CCL11/eotaxin.

post-surgery. PDGF is a dimeric protein that plays a prominent role in tissue repair and fibrotic diseases by promoting the proliferation and survival of myofibroblasts [22]. Dong et al. reported that PDGF-BB is a hypoxia-regulated gene product, which (along with VEGF-A) contributes to ocular neovascularization, and suppression of both provides an additive effect [23]. This supports the present study findings concerning VEGF and PDGF-BB. Postoperative oxidative stress status may cause corresponding changes [24]. However, what changes occur after surgery and the role they play in the growth of axial length remain unknown.

As the inflammatory cytokines related to axial lengths and axial elongation differed, no correlation between the changes in axial lengths and axial lengths were observed. We hypothesize that different mechanisms may be at play. VEGF, GM-CSF, and CCL11/eotaxin may regulate axial

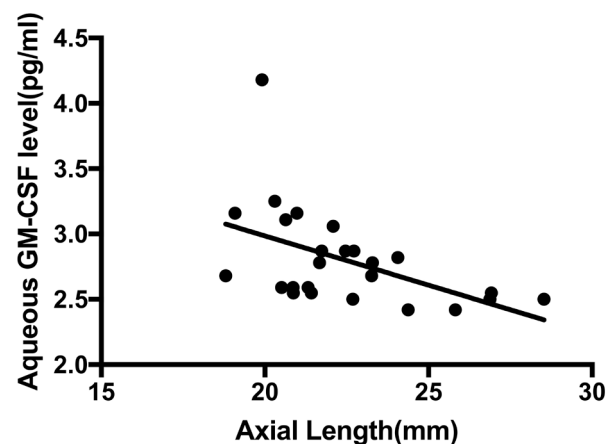


Figure 4. Axial length negatively correlates with AH GM-CSF.

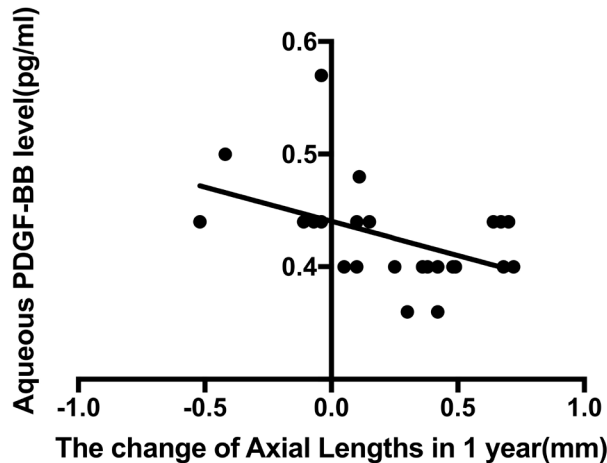


Figure 5. Axial length negatively correlates with AH PDGF-BB at 1 year post-surgery.

lengths in a healthy state, while PDGF-BB has an influence after the stress of the surgery. This may explain the different outcomes in the change in axial elongation in children who underwent previous cataract extraction and IOL implantation procedures.

We also analyzed the predicted axial elongation value in healthy children according to age as reported in a previous study [13]. However, the actual axial elongation was significantly smaller than the predicted outcome. Similarly, Lambert et al. reported that the eyes of infant patients with previous cataract surgery were shorter than the fellow eye during the first year of life [25]. These conclusions are consistent with the present results, although the mean age was different. The present results further revealed the usefulness of existing age-related axial prediction formulas in patients with congenital cataracts.

There are several potential limitations of this study. First, the number of enrolled patients was relatively small. However, the results were statistically significant, and the relatively small number of patients may only strengthen the conclusions of the study. Second, we did not adjust the axial length according to age, considering the patients were all infants and children. However, the most intensive period of bulbus oculi development is less than 1 year of age [26], and only two eyes were less than 1 year old (10 months). Third, unlike the studies in adults with high myopia that use patients with previous cataract surgery as the control group, it was hard to find an appropriate control group of infants for this study.

In summary, this study demonstrated that the AH levels of VEGF, GM-CSF, and CCL11/eotaxin are statistically significantly negatively correlated with axial lengths. A

negative correlation was found between the level of PDGF-BB and the change in axial lengths at 1 year post-surgery. Thus, these inflammatory cytokines may be a useful measurement for predicting myopia and may be of predictive value when determining the power of IOL.

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