Macular Morphologic and Microvascular Analysis in Pseudophakic Children with Previous Pediatric Cataract Using Optical Coherence Tomography Angiography

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Abstract

Introduction: The macular morphologic and microvascular changes in children with pseudophakia after pediatric cataract surgery remain unknown. The aim of this study was to analyze macular morphologic and microvascular remodeling in children with pseudophakia after pediatric cataract surgery using optical coherence tomography angiography (OCTA).

Methods: Consecutive cases between December 1, 2018, and November 31, 2020 were recruited. Sixty-one participants (31 pseudophakic children and 30 healthy controls) met the inclusion criteria and were included for final analysis. OCTA was used to measure macular vascular density, the foveal avascular zone (FAZ), and macular thickness. The parameters were compared between pseudophakic and healthy eyes using binary logistic regression, with adjustment for the effect of refractive error, age, and axial length.

Results: Compared with normal eyes, a significantly reduced area of the FAZ ($p = 0.042$), increased superficial foveal vascular density ($p = 0.033$), and increased inner and outer foveal thickness ($p = 0.034$ and $0.029$, respectively) were noted in pseudophakic eyes. The deep parafoveal vascular density was generally lower in eyes with cataracts ($p \leq 0.044$). The inner foveal thickness was positively correlated with the superficial foveal vascular density ($r = 0.889$, $p < 0.001$) and negatively correlated with the area of the FAZ ($r = -0.903$, $p < 0.001$). The outer foveal thickness was positively correlated with the deep foveal vascular density ($r = 0.399$, $p = 0.002$).

Conclusions: Morphological and microvascular remodeling in children with previous pediatric cataract indicates foveal underdevelopment. The underlying mechanism requires further investigation.

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This trial was registered at NIH (clinicaltrial.gov, NCT04576884).
Introduction

Childhood cataract is one of the leading causes of treatable blindness and severe visual impairment in children and is responsible for 5–20% of pediatric blindness worldwide [1]. In children with cataracts, the presence of an opaque crystalline lens results in inadequate visual input reaching the retina. This interferes with the development of the visual system during the critical period, resulting in abnormal visual acuity (deprivation amblyopia). Structural involvement has been observed in amblyopia, presenting as shrinkage of ocular dominance columns in the visual cortex and cellular loss in the lateral geniculate nucleus [2, 3]. With advances in ophthalmic imaging technologies, there are growing structural findings at the retinal level of the visual pathway in pseudophakic children [4–6]. Although macular findings visualized by optical coherence tomography angiography (OCTA) in patients with amblyopia have been studied, these studies have been limited to strabismic or anisometropic amblyopia and have yielded inconsistent outcomes [7–9].

There is evidence that early visual deprivation has a different effect on visual development from strabismus or anisometropia [10]. It has been found that pseudophakic children are associated with a reduction in developmental deepening of the foveal pit and a lack of developmental thickening of the posterior choroid [6]. Given the close interaction between retinal neurons and vasculature during development, the microvascular changes in pseudophakic children remain unknown. The aim of this study was to explore the macular microvascular and structural changes in pseudophakic children with previous pediatric cataract.

Methods

This cross-sectional study was approved by the Wenzhou Medical University Institutional Review Board (2021-016-K-13-01) and adhered to the Declaration of Helsinki. Written informed consent was obtained from the patients and their parents.

Participants

Children aged 3–17 years who had undergone cataract surgery and healthy controls with healthy eyes, also aged 3–17 years, were recruited for this study. All participants attended the Pediatric Cataract Center of the Eye Hospital of Wenzhou Medical University, Hangzhou, China, between December 1, 2018, and November 31, 2020.

Healthy controls were required to have normal intraocular pressure and best-corrected visual acuity (BCVA) ≥20/25 if they were younger than 7 years or BCVA ≥20/20 if they were older than 7 years. Exclusion criteria for all participants included the presence of corneal opacity preventing detailed imaging, nystagmus, ocular trauma (including traumatic cataract), retinal disease, persistent fetal vasculature (PFV), intraocular inflammation, glaucoma, vitreoretinal surgery, premature birth, neurologic disease, and systemic disease that could alter microvasculature (including diabetes, cardiovascular disease, and renal disease). Patients with poor cooperation or fixation were also excluded from the study. In addition, only high-quality OCTA images with a scan quality index equal to or higher than 7 were analyzed [11], and all images were approved by an observer (Z.L.) to ensure that they were acceptable. For the bilateral cohort, one eye was randomly selected for analysis. For healthy controls, data from the right eye were selected for analysis.

Sex, age at cataract surgery, age at participation, refractive error, BCVA, intraocular pressure, and axial length (AL) measured using the IOL-Master 500 (Zeiss, Inc., Jena, Germany) were recorded. All operations were performed by the same surgeon (Y.Z.), and surgical recordings were carefully reviewed by the authors (Z.L. and Y.Z.) in order to exclude cases with PFV detected intraoperatively. Children were recruited at least 3 months after surgery. Occlusion therapy was provided by a pediatric optometrist after surgery.

OCTA Data Acquisition and Processing

OCTA scans were obtained using a spectral-domain device with software (AngioVue version 2017.1.0.155; Optovue, Inc., Fremont, CA, USA). A 3 × 3 mm cube scan centered on the fovea was acquired for both the eyes in each participant. Automated OCT segmentation was performed using software to visualize the retinal superficial capillary plexus (SCP) and deep capillary plexus (DCP). The SCP was segmented from the internal limiting membrane to 9 μm beneath the inner plexiform layer. The DCP extended from 9 μm beneath the inner plexiform layer to 9 μm above the outer plexiform layer. An updated 3D projection artifact removal algorithm (Optovue, Inc.) was applied to the updated software to remove “false” blood flow signals from the DCP.

Vascular density was defined as the percentage of the area of interest occupied by the vessel area within that region. The foveal region was a central 1 mm circle in the early treatment diabetic retinopathy study (ETDRS) grid. The parafoveal region was an annulus between the central 1 mm and 3 mm circles of the ETDRS grid, and was divided into temporal, superior, nasal, and inferior sectors. Additionally, the spectral-domain OCT tool acquired the standard structural OCT scans, and the built-in software provided the inner and outer retinal thicknesses in the five regions of the ETDRS grid. The area of the foveal avascular zone (FAZ) was automatically calculated. To eliminate the impact of the magnification error caused by AL variation, the formula proposed by Sampson et al. [12] was used to correct the FAZ outcomes.

Statistical Analysis

Statistical analyses were performed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). Snellen visual acuity was converted to the LogMAR scale for statistical analysis. The refraction data were converted into spherical equivalent (SE). The Kolmogorov–Smirnov test was used to check for a normal distribution of the variables. One-way ANOVA, Kruskal–Wallis test, or χ² test was used to compare demographic variables, SE refractive error, BCVA, and AL. Binary logistic regression was performed to com-
pare macular vascular and morphologic parameters between the pseudophakic eye group and the healthy eye group, with adjustment for the effect of refractive error, age, and AL. A partial correlation analysis was performed to evaluate the relationship between foveal parameters while adjusting for the effect of AL. A two-sided $p$ value <0.05 was considered statistically significant.

### Results

Eighty-two consecutive subjects were recruited initially, and 21 subjects were excluded because of poor image quality of OCTA result (quality index <7). Finally, 31 pseudophakic children (31 eyes) and 30 healthy controls (30 eyes) were included for further analysis. Table 1 summarizes the demographic and clinical characteristics of the patients. The median (interquartile range, range) age at cataract surgery of unilateral and bilateral pseudophakic children was 3.5 (5.0–13) years and 6.0 (2.2–10) years, respectively. There was no significant difference between the groups with regard to age and sex. The BCVA was significantly worse in pseudophakic eyes than in healthy eyes ($p = 0.003$). Significant differences in SE and AL were found between the pseudophakic and healthy eyes (both $p < 0.001$). The mean duration between the operation and the last follow-up was 4.5 ± 4.6 years, and no cases of cystoid macular edema (CME) were found.

### Macular Microvasculature Remodeling in the Pseudophakic Eyes

Table 2 summarizes the differences in macular microvascular parameters between the pseudophakic and healthy eyes.
healthy eyes. In the pseudophakic eyes, a reduced area of the FAZ ($p = 0.042$), increased foveal vascular density of the SCP ($p = 0.033$), and decreased vascular density of the DCP in the temporal ($p = 0.044$), superior ($p = 0.012$), nasal ($p = 0.005$), and inferior ($p = 0.030$) parafoveal quadrants were observed when compared to the healthy eyes.

**Macular Morphology Remodeling in the Pseudophakic Eyes**

Table 3 summarizes the comparison of macular morphological parameters between pseudophakic and healthy eyes. When compared with healthy ones, a significant increase in inner and outer retinal thickness in the fovea ($p = 0.034$ and $0.029$, respectively) was found. Significant increases in inner retinal thickness in the superior ($p = 0.032$) and inferior ($p = 0.045$) parafoveal quadrants was also observed.

**Association among Foveal Parameters**

The inner foveal thickness was positively correlated with the superficial foveal vascular density ($R^2 = 0.790$, $p < 0.001$) and negatively correlated with the area of the FAZ ($R^2 = 0.815$, $p < 0.001$). The outer foveal thickness was positively correlated with the deep foveal vascular density ($R^2 = 0.159$, $p < 0.001$, Fig. 1). We did not find significant correlation either between BCVA and macular morphology or between age at surgery and macular morphology.

**Discussion**

The principal finding of this study was that the eyes of children with previous cataracts exhibited a reduced area of the FAZ, increased superficial foveal vascular density, and increased foveal thickness. A general reduction in the deep parafoveal vascular density and increased inner parafoveal retinal thickness were also associated with previous cataract.

Premature birth has been associated with reduced foveal pit depth, increased inner retinal layer thickness, and a small or absent FAZ [13], which is similar to our observations of the foveal appearance of pseudophakic patients after cataract removal in childhood. Thus, the fovea in eyes with previous pediatric cataract seems less mature or developed than in normal eyes. Foveal development in preterm infants supports the hypothesis that the FAZ is a prerequisite for the development of a foveal pit [14, 15]. The inner retinal layers may persist in the fovea if the FAZ fails to form and the foveal pit becomes shallow. However, a significantly reduced FAZ area has not yet been reported in patients with strabismic or anisometric amblyopia [7–9]. This implies that visual deprivation may affect foveal development differently than in eyes with amblyopia arising from strabismus and anisometropia.

A model using finite element analysis demonstrated a relationship between the formation of the foveal depression and the presence of the FAZ [15]. This model suggested that the retinal stretch generated by ocular growth (axial elongation) is the major force driving postnatal re-

|                         | Pseudophakic eyes | Healthy eyes | $p$ value |
|-------------------------|-------------------|--------------|-----------|
|                         | mean   | SD     | mean   | SD     |         |
| Inner retinal thickness, µm |       |       |       |       |         |
| Foveal                  | 48.5   | 9.1   | 45.8   | 9.5   | 0.034*  |
| Temporal                | 107.0  | 6.4   | 102.9  | 4.7   | 0.063   |
| Superior                | 118.0  | 8.0   | 113.3  | 5.2   | 0.032*  |
| Nasal                   | 114.0  | 8.2   | 111.7  | 13.6  | 0.397   |
| Inferior                | 117.2  | 6.7   | 113.2  | 6.0   | 0.045*  |
| Outer retinal thickness, µm |       |       |       |       |         |
| Foveal                  | 201.7  | 13.5  | 196.4  | 10.5  | 0.029*  |
| Temporal                | 213.4  | 10.4  | 205.9  | 8.8   | 0.150   |
| Superior                | 217.6  | 10.6  | 208.2  | 8.5   | 0.091   |
| Nasal                   | 219.0  | 10.0  | 209.2  | 13.3  | 0.112   |
| Inferior                | 211.1  | 9.4   | 203.4  | 8.8   | 0.163   |

Binary logistic regression with adjustment for the effect of refractive error, age, and AL was performed. SD, standard deviation; Sig, significance. * Statistically significant ($p < 0.05$).

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modeling of the fovea [15]. Studies have consistently shown a correlation between the depth of the foveal pit and the size of the FAZ, suggesting that the size of the FAZ is related to the extent of the centrifugal displacement of the inner retinal layers [16, 17]. We also observed that the FAZ is strongly and negatively correlated with inner foveal thickness. However, further longitudinal studies are required to confirm the association between visual deprivation and foveal underdevelopment.

It could be argued that the foveal changes we observed were due to postoperative CME. Theoretically, children are believed to have a higher risk than adults for developing CME because they are more susceptible to inflammation and the routinely performed posterior capsulorhexis [18]. Nevertheless, CME is an uncommon complication after pediatric cataract surgery [6, 18]. In a longitudinal observation in the early postoperative period, CME was not observed during the 12-month follow-up and the mean macular thickness reached the presurgery level after 3 months and remained stable over the 12-month follow-up [18].

Vascular density in the deep parafoveal areas was generally reduced in the eyes with previous cataracts when compared with healthy controls. We attribute this to the effect of deprivation amblyopia caused by a history of cataract. It is widely accepted that strabismic or anisometropic amblyopia is associated with lower retinal vascular density [7–9, 19]. To the best of our knowledge, this is the first study to report this finding using OCTA in deprivation amblyopia induced by pediatric cataract.

There are some limitations to our study. First, motion artifacts might influence the quality of the OCTA images due to the weak cooperation of some children. Second, because the existence of lens opacity may prevent the current imaging system from yielding retinal images, it is difficult to explore the microvascular features in eyes with pediatric cataract. We had to include children after cataract extraction, during which retinal development had improved. Thus, an imaging technique with a faster speed and higher penetration is warranted in the future. Third, though we excluded congenital cataract caused by PFV, other causes of congenital cataract, such as anterior vitreolenticular interface dysgenesis [20], might be related to underdevelopment of ocular structures.

**Conclusion**

Eyes in pseudophakic children with previous pediatric cataracts have a reduced area of the FAZ, increased superficial foveal vascular density, and increased foveal thickness. This implies an underdevelopment of the fovea. Similar to previous findings in patients with strabismic or anisometropic amblyopia, a generally decreased vascular density in the deep parafovea was noted. Further studies are required to elucidate the underlying mechanisms.

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Statement of Ethics

The study was approved by the Review Board of the Eye Hospital of Wenzhou Medical University (approval reference number: 2021-016-K-13-01) and adhered to the tenets of the Declaration of Helsinki. Written informed consents to participate in the study were obtained from participants or participants’ parent or legal guardian.

Conflict of Interest Statement

The authors have no proprietary or commercial interest in any materials discussed in this article.

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Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.