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The foveal depression and related factors in patients with a history of retinopathy of prematurity

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Running head: The OCT findings of patients with a history of ROP

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ABSTRACT

Purpose: This study evaluates optical coherence tomography (OCT) findings of the macula in patients with a history of retinopathy of prematurity (ROP).

Methods: We enrolled 112 patients (age: 6–15 years) and categorized them into three groups, gestational age (GA), <36 weeks with or without a history of ROP (ROP group, pre-term group) and GA, ≧37 weeks. We included one eye of each patient and measured the retinal thickness of the macula by OCT.

Results: The ROP group demonstrated the worst VA and the shallowest foveal depression. Furthermore, the foveal depression significantly correlated with the birth weight, GA, ganglion cell layer/inner plexiform layer (GCL-IPL) thickness, and a history of ROP.

Conclusions: This study established a correlation of fovea formation with premature birth, damage of GCL-IPL, and a history of ROP. The retention of the inner retina possibly contributes to abnormal foveal morphology in patients with a history of ROP.

INTRODUCTION

Retinopathy of prematurity (ROP) is a common disease that occurs in pre-term children and is characterized by retinal neovascularization because of oxidative stress [1]. The progress of retinal neovascularization required surgery or photocoagulation [2]. Even if retinopathy is regressed with appropriate treatments, various complications, such as exotropia, amblyopia, and myopia, occur in school-aged children [3].

Recently, the optical coherence tomography (OCT) devices have witnessed a significant improvement, facilitating high-quality images within a few seconds. A recent study conducted on OCT in patients with a history of ROP revealed abnormalities in foveal morphology, including the presence of the inner retinal layers and the small pit at the fovea, with retention of the inner retina as the probable cause [4,5]. However, the underlying mechanisms and the clinical significance of these abnormalities remain unclear.

This study aims to evaluate the OCT findings of the macula in eyes irrespective of ROP history and assess clinical factors related to the OCT parameters.

MATERIALS AND METHODS

This study protocol was approved by the Institutional Review Board of Kobe University Graduate School of Medicine (Kobe, Japan) and performed in accordance with the Declaration of Helsinki. We obtained written informed consent from all participants in this study. We enrolled Japanese pediatric patients from the Department of Ophthalmology at Kobe University Hospital. In addition, children aged 6–15 years were

enrolled as control subjects (full-term group) in this study. The exclusion criteria in this study were eyes with disorders, possibly affecting the visual function, eyes with a history of ocular surgery, and eyes with a dragged disc. Children with birth date less than 36 weeks were also recruited in this study and divided into two groups as follows: pre-term, with or without a history of ROP (ROP group, pre-term group). We graded ROP according to the guidelines of the International Committee for the Classification of Retinopathy of Prematurity. In addition, a history of ROP was defined as the previous history of >Stage 1. The treatment of ROP was performed according to the recommendations of the Early Treatment for ROP study. Of note, patients who received surgical treatment or intravitreal anti-vascular endothelial growth factor (VEGF) were excluded from this study.

All patients underwent comprehensive ophthalmic examination, including visual acuity measurement, slit-lamp biomicroscopy of the fundi, OCT, and measurements of axial length and corneal curvature. Patients who could not undertake ophthalmic tests were excluded. All patients underwent macular scanning using the Cirrus HD-OCT (Carl Zeiss, Dublin, CA) macula cube 200 × 200 acquisition protocol and HD 5-line Raster. In addition, we applied the ganglion cell analysis (GCA) algorithm. The depth of the foveal depression was calculated by subtracting the foveal thickness from the average of the parafoveal thickness (i.e., inner nasal, inner temporal, inner inferior, and inner superior) [6]. Scans with signal strength <6 were re-examined for better quality and excluded if not improved. If the data were obtained from both eyes of a single patient, we selected the right eye for analysis.

Statistical analyses were performed using SPSS (ver. 15.0; SPSS Inc., Chicago, IL) software. In

addition, Kruskal–Wallis tests and χ^2 tests were used where applicable. We considered $P < 0.05$ as statistically significant. We used the multivariate logistic regression analysis to analyze the association between the foveal depression and visual acuity. Furthermore, we confirmed the correlation with the Spearman's analysis.

RESULTS

Table 1 shows the demographic background the study population. Overall, we enrolled 112 subjects (ROP group, 30; pre-term group, 22; full-term group, 60; age range: 6–15 years). In the ROP group, 3 patients received no treatment and others received laser photocoagulation. We observed significant differences among the three groups in the gestational age (GA; $P < 0.0001$), birth weight (BW; $P < 0.001$), visual acuity ($P < 0.001$), refractive error ($P < 0.0001$), and average corneal curvature ($P < 0.0001$). Table 2 shows the mean values of macular parameters. A significant difference existed in the foveal thickness among groups (ROP group, 273.5 ± 21.0 μm; pre-term group, 245.7 ± 21.7 μm; full-term group, 239.5 ± 16.7 μm; $P < 0.001$). We calculated the depth of the foveal depression by subtracting the foveal thickness from the average of the parafoveal thickness (i.e., inner nasal, inner temporal, inner inferior, and inner superior). A significant difference was observed in the foveal depression among groups (ROP group, 30.6 ± 31.3 μm; pre-term group, 59.5 ± 21.9 μm; full-term group, 71.8 ± 14.9 μm; $P < 0.001$). The multivariate regression analysis revealed thin ganglion cell layer/inner plexiform layer (GCL-IPL) thickness, early GA, low BW, and a history of ROP as risk factors for a shallower foveal depression ($P < 0.01$, $P = 0.043$, $P < 0.01$, and $P < 0.01$, respectively; Table 3). After multivariate regression analysis in only ROP group,

GCL-IPL thickness was significantly associated with foveal depression (P<0.001). Figure1 shows the correlation between the foveal depression and the average thickness of GCL-IPL.

Although a significant difference existed in visual acuity among groups, we could not establish a significant association between the abnormal structure of the fovea and visual acuity. Hence, by investigating the factors related to visual acuity, we found a significant correlation between myopia with visual acuity (P = 0.006; Table 4). After multivariate regression analysis in only ROP group, refractive error was significantly associated with visual acuity (P=0.01). Patients with a history of ROP demonstrated significant myopic refraction compared to other groups (Table 1). However, a significant difference was observed in the corneal curvature (P < 0.001), but not in the axial length (P > 0.05) among groups (Table 1).

DISCUSSION

In this study, the evaluation of OCT findings of the macula in eyes with or without a history of ROP revealed a significant difference in the foveal depression among groups. A study conducted on the macula volume in pre-term children using OCT demonstrated that the central retinal region increased and that the fovea depression decreased in pre-term children compared to children born full-term [4]. In addition, the study speculated that the retention of the inner retina might contribute to the abnormal foveal morphology in patients with a history of ROP. Several studies have reported a thick fovea in premature children and have associated it with early GA and/or low BW [5,7,8]. Similarly, our study demonstrated that the eyes in the ROP group had the greatest foveal thickness among all groups. This study focused on the foveal

depression, not the foveal thickness, because the foveal thickness varies depending on the refractive status or axial length. Our results revealed the shallowest foveal depression in the eyes in the ROP group. Villegas et al. [6] demonstrated a shallow foveal depression in the eyes with a history of ROP and no significant correlation between the foveal depression and GA. However, the multivariate logistic regression analysis in this study established a significant correlation of the foveal depression with the GA, BW, a history of ROP, and GCL-IPL thickness. In the ROP group, the average GA was 26.4 weeks. Apparently, the foveal development begins at around 24–25 weeks of GA and continues throughout early childhood. [9] While the inner retina moves centrifugally, the photoreceptors move centripetally during the development process. Perhaps, the supplementation of high-concentration O_2 after birth could be accountable for the foveal development in premature children, contributing to the foveal dysplasia. Furthermore, studies have suggested that the failure of inner retinal movement resulted in a thinner GCL around the fovea. Pueyo et al. [7] demonstrated a thin GCL around the fovea in eyes with a history of treated ROP, thereby speculating that the damage by laser photocoagulation could be responsible for decrease in the GCL thickness. Notably, eyes with severe retinopathy require laser treatment. As 27 of 30 eyes in the ROP group received laser photocoagulation, either laser photocoagulation or severe retinopathy could have caused the shallow foveal depression.

In corroboration with previous reports, [5,6] the foveal depression was not found to be associated with visual acuity in this study. During the foveal development process, the outer retina begins to mature after birth and continues to develop until 4–6 years, whereas the development of the inner retina begins

133 around 24–25 weeks of GA [10]. Regarding the different timing of the development, the foveal pit
134 formation might be independent of photoreceptor development.

135 In this study, visual acuity significantly correlated with refractive error. The eyes in the ROP
136 group demonstrated worse visual acuity and a higher degree of myopic refraction. Reportedly, the severity
137 of the ROP stage correlates with severe myopia [10]. In this study, the severity of the ROP necessitated
138 laser treatment in a majority of patients in the ROP group. Recently, a study has demonstrated that children
139 treated with laser photocoagulation present a higher degree of myopia than those treated with an
140 intra-vitreous injection of bevacizumab, an anti-VEGF drug [11]. Hence, the longer the period between
141 birth and the light stimulation or laser treatment, higher the chances of developing a more acute degree of
142 myopia, resulting in worse visual acuity.

143 We observed a significant difference in the refractive error and corneal curvature
144 between the groups, but not in the axial length. Wu et al. [5] documented that myopia in premature
145 children was associated with abnormalities of the anterior segment, including the shallow anterior chamber
146 depth, lens thickness, and steep corneal curvature. Although we did not investigate the anterior chamber
147 depth or the lens thickness, our results indicated that myopia in the ROP group was refractive myopia, not
148 axial myopia.

149 This study has several limitations. First, we investigated only a small number of patients,
150 especially in the ROP group. Second, we did not investigate the effect of laser treatment on children with a
151 history of ROP. Hence, further extensive studies with a larger sample size are warranted to elucidate the

anatomic changes in children born prematurely.

In conclusion, this study demonstrated that the eyes of patients with a history of ROP had a shallow foveal depression, and the GA, BW, and GCL-IPL thickness were related to the formation of the fovea. The retention of the inner retina possibly contributes because of an abnormal foveal morphology in the eyes of patients with a history of ROP.

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