Evaluation of the Foveal Avascular Zone in Familial Exudative Vitreoretinopathy Using Optical Coherence Tomography Angiography

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Research Article

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Abstract

**Background:** To evaluate the foveal avascular zone (FAZ) and retinal structure in familial exudative vitreoretinopathy (FEVR).

**Methods:** Twenty FEVR eyes with stage 1 or 2 disease and 20 control eyes were evaluated. The central retinal thickness (CRT), inner retinal thickness (IRT), surface retinal vessel density (SRVD), and deep retinal vessel density (DRVD) were measured using optical coherence tomography. The FAZ area was calculated using ImageJ software. The equivalent spherical value (SE) and axial length (AL) were measured.

**Results:** The CRT (232±26.75 vs. 213.15 ± 16.138 μm; \(p=0.0003\)) and IRT (17.44±13.28 vs. 1.85 ± 5.696 μm; \(p=0.0005\)) were thicker in the FEVR group than in the control group. The surface FAZ area (0.26±0.1 vs. 0.33 ± 0.1 mm\(^2\); \(p=0.006\)) and the deep FAZ area (0.36±0.1 vs. 0.43 ± 0.1 mm\(^2\); \(p=0.037\)) were smaller in the FEVR group than in the control group. The SRVD values did not differ among the sectors, but the DRVD was higher in the FEVR group except for the inferior sector (superior, \(p=0.02\); inferior, \(p=0.4\); temporal, \(p=0.001\); nasal, \(p=0.02\)). The SE and AL did not differ between the two groups. There was no correlation between the surface and deep layer FAZ area and age, CRT, SE, and AL. The surface, deep FAZ area, and IRT were correlated negatively (surface, \(r = -0.57\), \(p=0.008\); deep layer FAZ area, \(r = -0.5\), \(p=0.02\)).

**Conclusion:** Eyes with FEVR has a smaller FAZ because the inner retina with the vascular structure remained in the fovea.

Background

Familial exudative vitreoretinopathy (FEVR) is a hereditary disorder first reported by Criswick and Schepens in 1969 [1]. In severe cases, FEVR causes tractional retinal detachment and/or serous retinal detachment due to exudative fibrovascular proliferation, but in mild cases, an avascular area is present in the temporal retina without fibrovascular proliferation. Such mild cases may cause breaks in the temporal retina during childhood to adulthood and then may cause rhegmatogenous retinal detachments (RRDs). In the past, retinal neovascularization, exudation, dragging of vasculature, and vitreous hemorrhage have been reported and may cause various visual impairments [2,3]. In addition, a simple stage classification was reported in 2011 [4]: stage 1, peripheral avascular retina without retinal neovascularization; stage 2, peripheral avascular retina with retinal neovascularization; stage 3, extramacular retinal detachment; stage 4, macular-involving retinal detachment or subtotal retinal detachment; and stage 5, total retinal detachment.

With recent improvements in imaging technology, optical coherence tomography angiography (OCTA) has been developed that can construct a retinal blood vessel structure without use of a contrast agent.
The foveal avascular zone (FAZ), formed by development of a ring-shaped anastomosis at the macula at the end of the artery-vein from the retinal surface, can be clearly depicted with OCTA. It has been reported that FAZ is enlarged in diabetic retinopathy [5,6]. It also has been reported that the size of the FAZ and visual acuity are inversely correlated [7,8]. Another study investigated the area of the FAZ, which is about 0.3 mm² in normal eyes, and reported that it increased with age [9].

The advantage of OCTA is that the resulting vessel density (VD) can be analyzed. A great deal of research has been done in diabetic retinopathy and reported that the VD decreases [8,10,11].

Recent reports have used OCTA examine retinopathy of prematurity (ROP) similar to FEVR. According to those reports, the macular retina was thicker and the FAZ area was smaller in ROP than in normal eyes [12-14].

The purpose of the current study was to investigate the features of FEVR using OCTA.

**Methods**

This study enrolled 20 eyes of 11 patients diagnosed with stage 1 FEVR (Fig. 1) or stage 2 FEVR and 20 eyes of 10 control patients. The controls were normal volunteers who were recruited after undergoing an ophthalmologic general examination.

FEVR was diagnosed by fluorescence fundus angiography in both eyes, and the presence or absence of avascular and neovascularization in the peripheral retina was examined. The birth weight and gestational age confirmed that the baby was not premature. We also confirmed the patient's family history.

The research was conducted according to the Declaration of Helsinki; the Institutional Review Board of the Saitama Medical Center Jichi Medical University approved the study. All participants provided informed consent after receiving an explanation of the nature of the study and the possible consequences. The exclusion criteria were a history of preterm birth, having undergone and ophthalmologic surgery, and low quality of the OCTA images. Low image quality was assumed to be less than 70% of signal strength and included projection and motion artifacts.

A retrospective review of the ophthalmologic examinations included the best-corrected visual acuity (BCVA), spherical equivalent (SE), axial length (AL), OCT, and OCTA for each patient enrolled. OCT and OCTA were performed with an DRI OCT Triton Plus (Topcon, Tokyo, Japan). The foveal structure was measured with a 5-line 9-mm cross scan. After that, the CRT and IRT were measured manually from the B-scan image. The OCTA scan size was 3 x 3 mm. FAZ data, surface retinal vascular density (SRVD), and deep retinal vascular density (DRVD) were analyzed. The SRVD and DRVD were calculated automatically by the OCT internal software. The FAZ area was calculated using ImageJ software (National Institutes of Health, Bethesda, MD, USA). When using the software, the pixel is calculated and the scale needs to be adjusted. Since OCTA is measured in 3x3-mm scan, it calculates a 3-mm pixel count. As a result of calculation using the ImageJ software, 3 mm corresponds to 320.025 pixels. The data were entered into
this data in the ImageJ set scale to calculate the area. After that, we used polygonal sections to enclose and measure the FAZ. The same method was used to calculate the surface and deep FAZ areas.

The AL was measured using the IOLMaster 500 (Carl Zeiss Meditec, Jena, Germany).

**Statistical analysis**

All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University) [15]. All data were expressed as the mean ± standard deviation.

The data from the patients with FEVR and control subjects was compared using the Mann-Whitney U-test. The correlations between continuous variables were analyzed using Pearson’s correlation analyses. *P*<0.05 was considered statistically significant.

**Results**

This study enrolled 20 eyes of 11 patients diagnosed with FEVR and 20 eyes of 10 controls. In the FEVR group, one eye was a prosthetic, and one eye was excluded from the analysis because of a previous history of surgery.

The mean ages of the FEVR and control groups, respectively, were 32.3± 17.1 years and 38.5 ± 10.8 years (*p*=0.8).

The respective mean BCVAs of the FEVR and control groups were 0.1 logarithm of the minimum angle of resolution (logMAR) and 0.0 logMAR (*p*=0.13).

The mean CRT (FEVR, 232±26.75 μm vs. control, 213.15 ± 16.138 μm; *p*=0.0003) and IRT (FEVR, 17.44±13.28 μm vs. control, 1.85 ± 5.696 μm, *p*=0.0005) were thicker than in the control group. In the FEVR group, 66.7% had a residual inner retinal layer (Fig. 2A, B).

The mean surface FAZ area (FEVR, 0.26±0.1 mm² vs. control, 0.33 ± 0.1 mm², *p*=0.006) (Fig. 3A, B, E) and deep FAZ area (FEVR, 0.36±0.1 mm² vs. control, 0.43 ± 0.1 mm²; *p*=0.037) (Fig. C, D, F) were significantly smaller in the FEVR group.

The mean foveal SRVD in the FEVR group was greater than that in the control group (FEVR, 23.37±4.0% vs. control, 20.73±3.71%; *p=0.047) (Fig. 4A, B). However, the fovea DRVD did not differ between the FEVR and control groups (FEVR, 25.91±5.2% vs. control, 22.33±4.28%; *p=0.08) (Fig. 5A, B).

The sectors of the parafoveal SRVD did not differ between the FEVR and control groups (superior, FEVR, 50.62±3.08% vs. control, 50.33±3.82%; *p=0.36, inferior, FEVR, 50.53±3.82% vs. control, 50.04±3.05%; *p=0.67, nasal, FEVR, 49.02±3.3% vs. control, 48.14±2.46%; *p=0.47, temporal, FEVR, 47.17±3.42% vs. control, 47.10±2.91%; *p=0.16) (Fig. 4A, C, D, E, F). However, each sector of the DRVD except for the inferior sector was significantly higher in the FEVR group than the control groups (inferior, FEVR, 51.75±4.45% vs.
control, 49.96±2.09\%; p=0.4) (superior, FEVR, 51.56±4.76\% vs. control, 49.59±1.9\%; p=0.02; nasal, FEVR, 50.79±5.2\% vs. control, 46.75±2.8\%; p=0.02; temporal, FEVR, 48.94±2.76\% vs. control, 47.44±2.68\%; p=0.001) (Fig. 5A, C, D, E, F). The SE (FEVR, -5.16±4.8 diopters [D] vs. control, -0.875±2.15\% ± 4.8 diopters [D]; p=0.008) and AL did not differ between the FEVR and control groups (FEVR, 26.05±1.8 mm vs. control, 24.78±1.06 mm; p=0.02).

In addition, no correlation were seen between the surface and deep FAZ areas and age (surface, r=0.25, p=0.29; deep, r=0.02, p=0.94), CRT (surface, r=-0.05, p=0.78; deep, r=0.05, p=0.75), SE (surface, r=0.36, p=0.056; deep, r=-0.03, p=0.82).

The surface, deep layer FAZ area, and IRT were correlated negatively (surface, r = −0.57, p = 0.008; deep, r = −0.5, p = 0.02) (Fig. 2C, D). No correlation was seen between the surface FAZ area and AL (r=-0.02, p=0.87), but a negative correlation was seen between the deep FAZ area and AL (r=0.43, p=0.014).

**Discussion**

The FAZ area in eyes with FEVR was reported to be small [16], as were those in ROP [12-14] and Stickler syndrome [17]. The cause of the small FAZs in the last two diseases was that the inner retinal layer remained in the fovea. In the current study, the CRT was thick because the inner retinal layer remained and was correlated negatively. Yonekawa et al. reported that 48.78% of the inner retinal layer remained [18]. The IRTs differed among the cases (17.4±13.2 μm). In previous studies, foveal development had been considered a phenomenon referred to as cone packing. Cells inside the retina move distally to form the fovea, and cone photoreceptors move centripetally to increase the concentration in the fovea [19]. If this is incomplete, the inner retinal layer may remain in the fovea or the foveal bulge may not be observed in the OCT images. It is thought that such macular hypoplasia occurs in FEVR.

Genetic variations may affect the phenotypes in FEVR. Six genes involved in FEVR have been identified, i.e., low-density lipoprotein receptor-related 5 (LRP5) [20], frizzled-4 (FZD4) [21], tetraspanin-12 (TSPAN12) [22], Norrie disease gene (NDP) [23], zinc finger protein 408 (ZNF408) [24], and kinesin family member 11 (KIF11) [25]. These are involved in the Wnt/Norrin signaling pathway and are important for retinal vascular development. Previous studies have reported that the foveal structure is established in the case of LRP5 mutations, but the CRT is significantly thicker in the presence of FZD4 and TSPAN12 mutations [16].

To the best of our knowledge, this report is the first to investigate parafoveal vessel density in each sector. In this study, the foveal SRVD was higher in FEVR, but there was no significant difference in the foveal DRVD compared with the controls. The parafoveal SRVD in each sector did not differ significantly between the FEVR and control groups, but the parafoveal DRVD was higher in the FEVR group, with the exception of the inferior sector. Previous studies have reported that eyes with FEVR had a significantly lower density of fovea and parafoveal SRVD, and the DRVD did not differ significantly [16] and was a contrasting result. Manami et al. [12] and Nonobe et al. [14] examined the surface vessel density in ROP and reported that it was significantly lower in the parafovea. In contrast, Chen et al. [13] reported that the
foveal vessel density in ROP was high in both the surface and deep layers. Since the methods of analysis differed depending on the OCT model, it is difficult to compare with other reports. Although there was a significant difference in the foveal SRVD, it is doubtful that the vascular structure of the inner retina is reflected in the analysis.

Canny and Oliver first reported abnormalities in the peripheral blood vessels using fluorescein angiography [26], and Miyakubo et al. also reported that the avascular area exhibited characteristic V-shaped blood vessels. Further, the abnormality suggested the possibility of spreading 360 degrees [27]. Although it was predicted that the higher detection rate of the temporal vessel density would be affected, in fact, there was a significant difference in the area excluding the inferior sector. We speculated that it increases the DRVD and compensates for the peripheral vascular abnormalities.

The current study had limitations. At first, we calculated the data manually. Some OCT models automatically calculate data, but there was no such model used this time. It is also possible that the examiner subjectivity had an effect. Second, OCTA images are not averaged. In the past, Uji et al. reported that averaging multiple front OCTA images improves image quality and has a major impact on the quantitative measurements [28]. Averaging may change the analysis results. Third, the study included a small number of cases. Although FEVR is rare, the number of cases should be increased and the reproducibility of the results should be examined in the future. Fourth, there is no genetic test for FEVR. Previous reports have examined the characteristics between genes, but the number of samples was small and no significant difference [16] was found. If it becomes possible to examine the characteristics among gene, we may be able to differentiate the genetic characteristics.

**Conclusion**

The current study provided some new observations in the retinal structure of patients with FEVR, i.e., the FAZ was small, the CRT was thick due to the effect of the residual inner retinal layer, the foveal SRVD was high, and the parafoveal DRVD was higher in the FEVR group except for inferiorly. The FAZ in FEVR is small because the inner retinal layer with retinal vasculature remains in the macula. In the future, to confirm the vascular changes found in the current study, we should investigate many more cases of FEVR.

**Abbreviations**

AL: axial length; BCVA: best-corrected visual acuity; CRT: central retinal thickness; DRVD: deep retinal vessel density; FAZ: foveal avascular zone; FEVR: familial exudative vitreoretinopathy; FZD4: frizzled-4; IRT: inner retinal thickness; KIF11: kinesin family member 11; logMAR: logarithm of the minimum angle of resolution; LRP5: lipoprotein receptor-related 5; NDP: Norrie disease gene; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; ROP: retinopathy of prematurity; RRD: rhegmatogenous retinal detachment; SE: spherical value; SRVD: surface retinal vessel density; TSPAN12: tetraspanin-12; VD: vessel density; ZNF408: zinc finger protein 408
Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Saitama Medical Center Jichi Medical University approved the study. All participants provided informed consent after receiving an explanation of the nature of the study and the possible consequences. Informed consent was obtained from parent and/or legal guardian of participants under 18.

Consent for publication

All patients provided written and verbal consent to publish this report.

Availability of data and materials

All data and materials associated with this article are available for review. The datasets for the analysis of the current study are readily available from the corresponding author upon reasonable request.

Competing interests

The authors have no competing interests related to this report.

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Authors’ contributions

TH was a major contributor in the drafting of the manuscript. MH, CK, and AY acquired the clinical data. YT and RT analyzed and interpreted the patients’ ophthalmologic data. AK and TK reviewed and edited the manuscript. All named authors take responsibility for the integrity of the work as a whole and have given their approval for this version to be published.

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