Familial exudative vitreoretinopathy (FEVR) is a hereditary disorder that was first described by Criswick and Schepens in 1969. It exhibits variable phenotypes among different individuals, patients from the same family, and even between the two eyes of one individual. Clinically, the peripheral retinal avascular zone, arteriovenous or venous-venous shunt formation, loops, vitreous adherence, retinal folds, temporal ectopia of the macula, retinal breaks, rhegmatogenous, and/or exudative retinal detachment are the most common clinical features of FEVR. Several posterior pole features have been described such as deformation of the vascular network and temporal ectopia of the macula, similar to the posterior pole in retinopathy of prematurity (ROP). Due to the slowly progressive nature of this disease, finding early stage FEVR is very important to facilitate which patients should receive timely examinations and treatments.

According to Pendergast and Trese, mild FEVR (stage I and II) are characterized by a peripheral avascular retina zone or retinal neovascularization at the junction of vascular and avascular areas. These patients were always difficult to identify due to lack of symptoms, and their posterior retinas are usually unremarkable. Thus, it is very important to find some “clues” in the easily examined posterior pole area in these patients. In recent years, some abnormalities have been reported in the posterior area of mild asymptomatic FEVR patients, such as the architecture of the vessels, and the increased distance from the macula fovea to the optic disc. However, such abnormalities are often subtle and easy to overlook by visual observation or conventional retinal image inspection. In this study, we investigated the imaging features in the posterior retinas of asymptomatic FEVR individuals with normal visual function, and compared them with those in healthy control eyes.

**MATERIALS AND METHODS**

This study was conducted in accordance with the tenets of the Declaration of Helsinki. All procedures were approved by the Investigational Review Board of Zhongshan Ophthalmic Center, Sun Yat-sen University. Informed consent was obtained after explaining the nature and the possible consequences of this study. Thirty-eight FEVR patients and 38 controls were included in this study. A standard medical investigation was performed in each subject, consisting of a general history including gestational age, birth weight, and family history. The duration of pregnancy and neonatal birth weight was determined to exclude the possible presence of ROP. The ophthalmic examination included the best corrected visual acuity (BCVA), refractive status, axial length by A scan, slit lamp examination, and a fundus examination in full mydriasis with special attention to the vascularity of the peripheral retinas.

We classified FEVR according to Pendergast and Trese’s approach. Digital fundus photography (FP; Topcon Retinal Imaging, Tokyo, Japan) was obtained using the Topcon TRC-50IIH microscope (Topcon, Tokyo, Japan). The images were digitized and saved as high-resolution color images. The images were then processed with TopCon ImageLink software (Topcon, Tokyo, Japan) to create high-quality digital images for analysis.
Camera TRC 50DX; Topcon Corp., Tokyo, Japan) and fluorescein fundus angiography (FFA; Heidelberg HRA SPECTRALIS/ HRA2; Heidelberg Engineering, Heidelberg, Germany) were performed in all FEVR individuals and controls. All clinical data were obtained by an experienced ophthalmologist. Thirty-eight mild FEVR (stages I and II) individuals, with conventional “normal-appearing” posterior poles, were included in this study. The inclusion criteria in this study were as follows:

1. All FEVR patients had a positive family history of severe FEVR with bilateral retinal folds in first degree relatives. Among them, 30 cases were parents of severe FEVR kids, two cases were sons/daughters, and two cases were siblings of severe FEVR patients.
2. All individuals with FEVR were confirmed by the presence of peripheral small vessel abnormalities, including a peripheral avascular zone with an abrupt termination of the retinal capillary network, occlusion of the capillary bed resulting in aneurysm-like capillary endings, small areas of nonperfusion, small patches of neovascular proliferations, early arteriovenous shunt formation, or diffuse leakage of dye in FFA examination (Fig. 1).
3. Best corrected visual acuity in all mild FEVR patients was 20/20 or more.

All FEVR patients with obvious macular dragging or proliferative findings, such as vitreous hemorrhage and tractional retinal detachment were excluded. In individuals with bilateral mild FEVR, considering the symmetric nature of this disease, one of the eyes was randomly selected and used in the study. Thirty-eight healthy control eyes confirmed by FFA were enrolled, including the fellow healthy eyes of 14 cases with unilateral central serious chorioretinopathy, 12 cases with idiopathic choroidal neovascularization, and 12 eyes from 12 normal individuals who received examination as parents of FEVR kids. Besides, candidates with more than −6.00 D myopia were excluded since high myopia alone may cause peripheral avascularity and a relatively tilted disc.

**Preparation of Digital Images for Analysis**

All fundus photography and FFA images were reviewed by two observers (MY, YY). For digital imaging and morphometry of the fundus, a computer workstation was used. The observers were not informed about the clinical data, group information for the patients, and the peripheral fundus photos. For each retina studied, the photograph “most centered” in the picture was chosen to ensure the best view of both the optic disc and macular area.

**Measurement of Disc Size and Disc-to-Fovea Distance**

The horizontal disc diameter ($D_h$) and vertical disc diameter ($D_v$) were measured on FP. The disc diameter (DD) is
calculated as \((D_h + D_v)/2\) (Fig. 2). The center of the disc (D) and the center of the macula (M) were identified. The disc-to-macula distance (DM) in this study was the point-to-point distance from the center of the disc to the center of the fovea, which was modified from that used in Boonstra’s study.\(^5\) The center of fovea was determined on FP and the foveal avascular zone on FFA images. The ratio of DM/DD is defined as the ratio of the disc-to-fovea distance (DM) to the average of the horizontal and vertical DDs, \((D_h + D_v)/2\), which has been shown to be a valuable tool in diagnosing mild optic nerve hypoplasia and subtle macular dragging\(^6\) (Fig. 2). All the measurements were done using the default measuring program in a commercial retinal camera (Topcon Corp.).

**Quantification of Posterior Retinal Vessels**

In our previous study (under review), we developed a quantitative method to count the posterior retinal vessels. To quantify the retinal vessels, two circles and two arcs were used in each picture, including the peripapillary inner reference circle (PIRC), peripapillary outer reference circle (PORC), peripapillary temporal inner arc (PTIA), peripapillary temporal outer arc (PTOA), shown in Figure 3. The circle diameters were based on the actual horizontal width measurement of the optic disc. The retinal vessels crossing each circle/arc were counted and recorded. The preliminary results showed excellent intra-observer and interobserver agreement in all four parameters. Moreover, values of PIRC and PORC, PTIA and PTOA were highly correlated, respectively. Thus, the inner circles and arc, PIRC and PTIA were qualified to quantify the posterior retinal vessels radiated from the optic disc, and then employed in this present study (Fig. 4).

**Intra- and Interobserver Agreement Study**

All the parameters were measured or counted twice by each observer. The intra- and interobserver agreements were high. Intraclass correlation coefficient ranged from 0.890 to 0.999, demonstrating great repeatability for both observers in the crossing vessels \(D_{h}, D_{v}\), and DM. Since all the data met normal distribution, Pearson correlation was done to identify whether the results of these two observers could make an agreement. The \(r\) value in PIRC, PTIA, \(D_{h}, D_{v}\), and DM were from 0.837 to 0.999 (\(P < 0.001\)), showing a trend toward a high interobserver agreement.

**Statistics**

The demographic features were analyzed with frequency and descriptive statistics. A \(\chi^2\) test was used to identify whether the sex and laterality were both matched between the mild FEVR individuals and the controls. The Shapiro-Wilk test was employed to verify whether the age, refractive status, axial length of the subjects, and the PIRC, PTIA, \(D_{h}, D_{v}\), DM, DD, and DM/DD results met normal distribution. An independent t-test was applied to compare the differences between the FEVR...
group and the control group when the data were normally distributed, while the Wilcoxon Rank Sum test was adopted when they were not. All data were processed and analyzed in R (version 3.1.1). A statistical value of \( P < 0.05 \) was considered statistically significant.

RESULTS

There were no statistical differences in sex (\( P = 0.250 \)); age (\( P = 0.054 \)); laterality (\( P = 0.359 \)); refractive status (\( P = 0.613 \)); and axial length (\( P = 0.195 \)) between the mild FEVR group and healthy control group. The demographic and clinical data are summarized in Table 1.

Comparison of DD, Disc-to-Macula Distance, and DM/DD Ratio

The mean optic DD was 1605.34 ± 250.60 μm in the FEVR group and 1733.39 ± 163.79 μm in the control group, respectively, with a statistically significant difference (\( P = 0.011 \)). The difference was contributed mainly by a relatively smaller horizontal DD in FEVR individuals (\( P = 0.001 \)), as the two groups’ vertical DD was similar without statistical difference (\( P = 0.214 \)). The mean DM was 5434.08 ± 824.82 μm in the FEVR group, which was obviously larger than that in the controls (\( P < 0.001 \)). Moreover, the DM/DD ratio was significantly higher in the FEVR group (\( P < 0.001 \)), due to both a smaller DD and a larger DM. The results are shown in Table 2.

Comparison of the Retinal Vessels in the Posterior Pole

The mean vessel numbers on PIRC and PTIA in the individuals with FEVR were 24.53 ± 3.10 and 10.68 ± 1.76, which were both larger than in the controls (21.39 ± 2.65 and 7.68 ± 1.61).

Since the age and the axial length of two groups as well as the refractive status of the control group met normal distribution, the mean ± SD was used, while the median, the minimum, and the maximum were employed for the refractive status of the FEVR group, which did not meet normal distribution. For comparison of the age and the axial length between two groups, an independent \( t \)-test was used. For comparison of the refractive status, the Wilcoxon Rank Sum test was applied. And for the sex and the laterality, a \( \chi^2 \) test was adopted (\( \alpha = 0.05 \)).

**TABLE 1. Demographic and Ocular Features of Mild FEVR Individuals and Controls**

<table>
<thead>
<tr>
<th>Feature</th>
<th>FEVR, ( n = 38 )</th>
<th>Control, ( n = 38 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>32.50 ± 10.12</td>
<td>37.58 ± 11.41</td>
<td>0.054</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (47.4)</td>
<td>23 (60.5)</td>
<td>0.250</td>
</tr>
<tr>
<td>Female</td>
<td>20 (52.6)</td>
<td>15 (39.3)</td>
<td></td>
</tr>
<tr>
<td>Laterality, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OD</td>
<td>17 (44.7)</td>
<td>21 (55.3)</td>
<td>0.359</td>
</tr>
<tr>
<td>OS</td>
<td>21 (55.5)</td>
<td>17 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Refractive status, ( D )</td>
<td>-0.125 (~5.75, 1.75)</td>
<td>-0.68 ± 1.61</td>
<td>0.613</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>24.21 ± 0.77</td>
<td>24.00 ± 0.66</td>
<td>0.195</td>
</tr>
</tbody>
</table>

Since the age and the axial length of two groups as well as the refractive status of the control group met normal distribution, the mean ± SD was used, while the median, the minimum, and the maximum were employed for the refractive status of the FEVR group, which did not meet normal distribution. For comparison of the age and the axial length between two groups, an independent \( t \)-test was used. For comparison of the refractive status, the Wilcoxon Rank Sum test was applied. And for the sex and the laterality, a \( \chi^2 \) test was adopted (\( \alpha = 0.05 \)).

**TABLE 2. Comparison of \( D_h \), \( D_v \), DD, DM, and DM/DD Ratios of FEVR Individuals and Controls (μm)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>FEVR, ( n = 38 )</th>
<th>Control, ( n = 38 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_h )</td>
<td>1438.21 ± 288.99</td>
<td>1630.32 ± 173.09</td>
<td>0.001</td>
</tr>
<tr>
<td>( D_v )</td>
<td>1772.03 ± 262.82</td>
<td>1836.03 ± 171.74</td>
<td>0.214</td>
</tr>
<tr>
<td>DD</td>
<td>1605.34 ± 250.60</td>
<td>1733.39 ± 163.79</td>
<td>0.011</td>
</tr>
<tr>
<td>DM</td>
<td>5434.08 ± 824.82</td>
<td>4696.29 ± 257.34</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM/DD</td>
<td>3.49 ± 0.93</td>
<td>2.73 ± 0.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( D_h \): horizontal diameter of the optic disc; \( D_v \): vertical diameter of the optic disc; DD: average diameter of the optic disc, calculated as 1/2 \( \times (D_h + D_v) \); DM: the distance from the center of the optic disc to the center of the macula fovea. For comparison of \( D_h \), \( D_v \), and DD between two groups, an independent \( t \)-test was employed, and for DM and DM/DD ratios, the Wilcoxon Rank Sum test was applied (\( \alpha = 0.05 \)).

**FIGURE 4.** Representative FA images of an asymptomatic FEVR individual (A) and a control subject (B). Yellow dots represent the counted vessel crossing the PIRC circle. For the FEVR eye, numbers of vessels crossing PIRC and PTIA were 25 and 11. For the control eye, numbers of vessels crossing PIRC and PTIA were 21 and 11.
TABLE 3. Comparison of Retinal Vessels in the Posterior Poles of FEVR Individuals and Controls

<table>
<thead>
<tr>
<th>FEVR, n = 38</th>
<th>Control, n = 38</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIRC</td>
<td>24.53 ± 5.10</td>
<td>21.39 ± 2.65</td>
</tr>
<tr>
<td>PTIA</td>
<td>10.68 ± 1.76</td>
<td>7.68 ± 1.64</td>
</tr>
</tbody>
</table>

For comparison of the vessels crossing PIRC and PTIA between two groups, an independent t-test was applied (α = 0.05).

1.64, respectively; P < 0.001). The results are summarized in Table 3. The representative fundus images of a FEVR and a control individual were shown in Figure 4.

DISCUSSION

Familial exudative vitreoretinopathy has a strikingly variable phenotype, which may range from hardly detectable peripheral vascular anomalies to neovascularization, subretinal and intraretinal hemorrhage, exudates, retinal folds, macular ectopia, and bilateral retinal detachments leading to blindness. Clinically, many mild FEVR individuals are asymptomatic with good visual function. However, FEVR in some patients is slowly progressive, and finally may lead to retinal detachment. Thus, early stage FEVR is very important to diagnose to ensure patients to receive timely treatments and lifelong monitoring. However, due to the absence of any clinical symptoms, and the normal appearance of posterior poles, mild FEVR (stage I and II patients), is not easy to detect, nor to correctly diagnose. In our study, all 38 FEVR individuals received careful examinations by our retina doctors, as they were the first-class relatives of patients. There is some subtle macular dragging, or ectopia of the macula due to the delay or absence of peripheral vascularization. In these patients, it is necessary to carefully examine the peripheral retinas to identify possible vessel abnormalities.

Finally, and most importantly, a new clinical feature of FEVR was observed in our study. We found that FEVR patients always have more retinal vessels radiating from the optic disc. To our knowledge, this is the first time the number of retinal vessels in these patients has been described and quantified. In our previous study (unpublished data), we used two circles, PIRC and PTOA, which have a diameter of two and four times that of the optic disc and are centered on the center of the optic disc, as well as PTIA and PTOA, defined as the part of the circle between the retinal temporal superior and temporal inferior branch vein, to quantify the number of vessels radiating from the optic disc. We found significantly more retinal vessels radiating from the optic disc compared to the healthy controls. The number of vessels crossing with PIRC and PTOA, especially in the temporal side (PTIA and PTOA), was higher than that in healthy controls statistically. We also found an excellent correlation between the inner circle and the outer circle, and to simplify the measurement strategy, only the inner circle was used in the present study. Interestingly, in this study, we further confirmed that more vessels radiated from the optic nerve in FEVR patients than in controls.

An early diagnosis of FEVR is important for adequate genetic counseling as well as the prevention and treatment of complications that occur, predominantly at a young age. However, it is more difficult to observe the periphery of the retina, compared with the observation of the posterior pole. Our study showed that the conventional normal appearance of the posterior retina is, in fact, not normal. The three features of the posterior retina, including a smaller optic disc, a relatively large DM/DD, and more retinal vessels radiating from the optic disc, are detectable, although subtle, with the quantitative analysis used in our study. Therefore, the finding of subtle morphometric changes in the posterior pole may be an additional sign of FEVR, and thus provide us with important clues for the diagnosis of FEVR.

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References