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CASE REPORT

Mirror image of familial exudative vitreoretinopathy in identical twins

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Abstract
Purpose To report the identical twins who had mirror fundus and angiographic images of familial exudative vitreoretinopathy (FEVR).
Case presentation A pair of 16 year old female twins presented with mirror-image asymmetry of monocular decreased vision. The twins were born full term with normal weights. Neither twin revealed any medical disorders during childhood and there was no known family history of ocular disorders. On ocular examination, the best corrected visual acuity (BCVA) was 20/20 in OD and 20/63 in OS for twin 1. For the twin 2, the BCVAs were 20/63 and 20/20 for OD and OS, respectively. Intraocular pressures were within normal limits and anterior segment examinations were unremarkable for both twins. Dilated fundus examinations and angiographic images revealed characteristics FEVR appearance with mirror image phenomenon in the twins.
Conclusion This is the first report describing identical twins with mirror images of FEVR. This report may confirm a strong underlying genetic inheritance in the pathogenesis of FEVR.

Keywords Familial exudative vitreoretinopathy · Identical twins · Mirror-image phenomenon

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Introduction

Familial exudative vitreoretinopathy (FEVR) is a rare hereditary disorder of retinal blood vessel development principally affecting retinal angiogenesis, leading to incomplete vascularization of the peripheral retina and poor vascular differentiation [1]. FEVR may be inherited in an autosomal dominant, autosomal recessive, X-linked manner, or even affect individuals with no family history [1, 2]. However, autosomal dominant inheritance as a result of haploinsufficiency is the most prominent form of FEVR. To date, six genes have been reported to associate with FEVR, including *LRP5*, *FZD4*, *TSPAN12*, *NDP*, *ZNF408*, and *KIF11* [3]. Patients with *KIF11* mutations showed typical, but variable, signs of FEVR with or without microcephaly, lymphoedema, and mental retardation [4]. FEVR is characterized with an avascular peripheral retina which causes the secondary complications of the disease. The disease can be diagnosed if there is an evidence of peripheral retinal avascularization in at

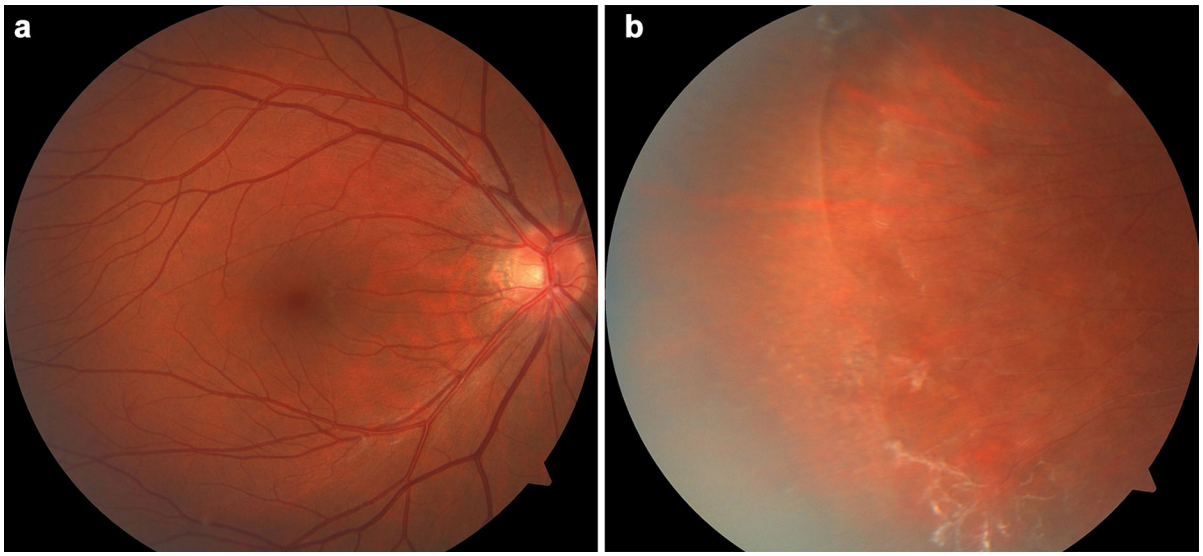

Fig. 1 Colored fundus images of the right eye show an unremarkable posterior pole with ghost vessels marking the demarcation between vascular and avascular zone in the peripheral retina for twin 1

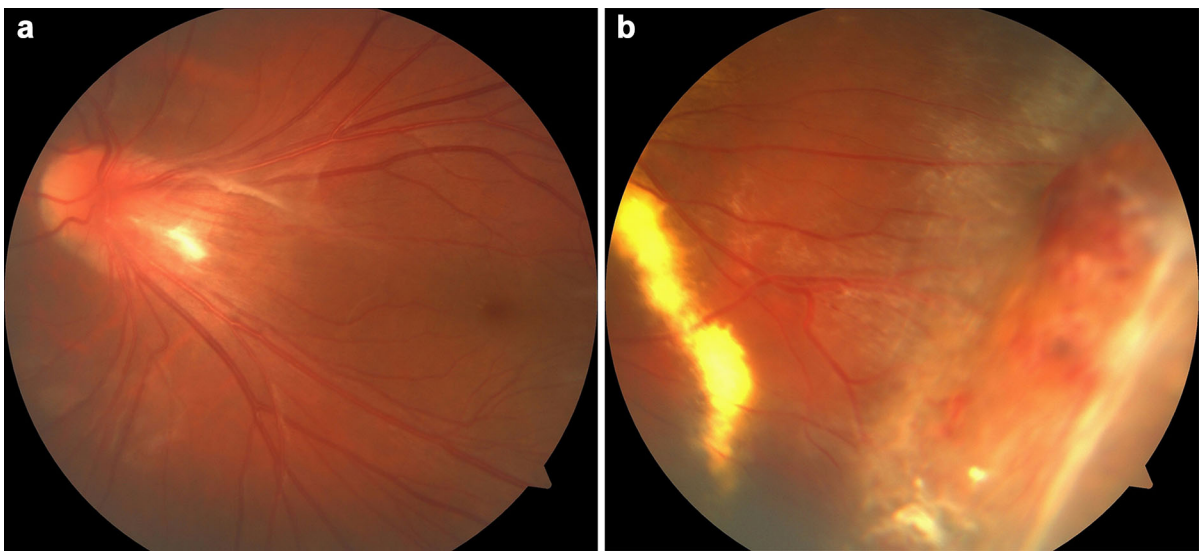

Fig. 2 Colored fundus images of the left eye show the typical FEVR appearance including macular dragging, straightening of vessels, and radial folds on macula, and retinal exudation, neovascularization with peripheral tractional detachment on the temporal peripheral retina for twin 1

least one eye in patients of any age who were born at full term, or preterm with a disease tempo not consistent with retinopathy of prematurity (ROP), or variable degrees of vitreoretinal traction, subretinal exudation, or retinal neovascularization occurring at any age [2, 5].

In monozygotic twins, the splitting of the zygote usually happens between the 8- and 16-cell stages of embryonic development and the mirror-image phenomenon (i.e., expression of features or anomalies on opposite sides) may occur in case of a possible delay in this process [6]. This phenomenon might result from genetic or environmental factors that occur before the split into two monozygotic embryos. The mirror-image twinning with inverse laterality is observed

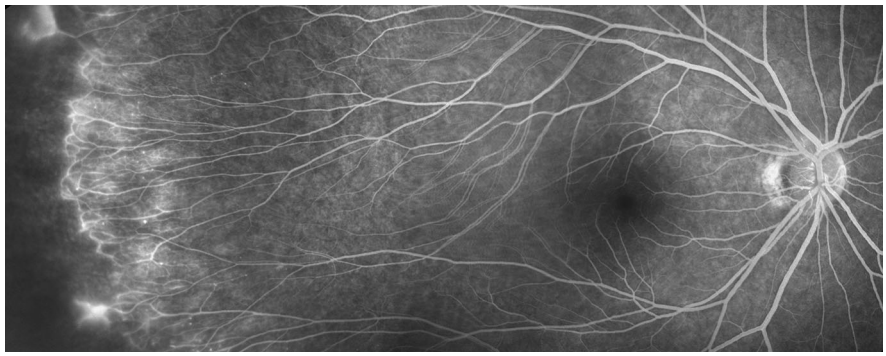

Fig. 3 Composite fundus fluorescein angiography of the right eye reveals evident peripheral avascular zone with extensive branching and anastomosis of the retinal vessels as well as leaking of new vessels on the peripheral retina for twin 1

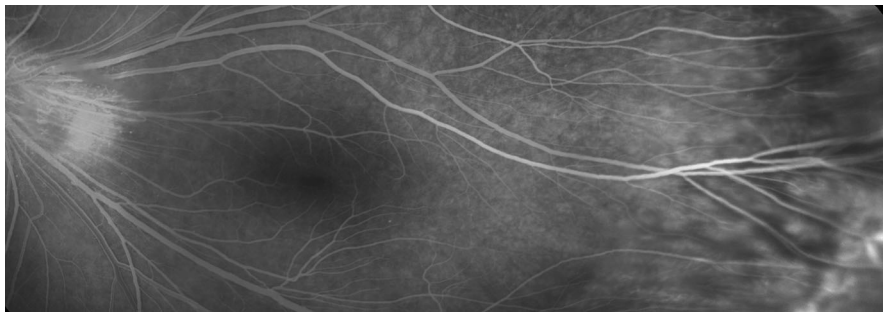

Fig. 4 Composite fundus fluorescein angiography of the left eye reveals straightening of the vessels, capillary non-perfusion areas, anastomosis of retinal vessels, and leakage in addition to staining next to temporal side of optic nerve for twin 1

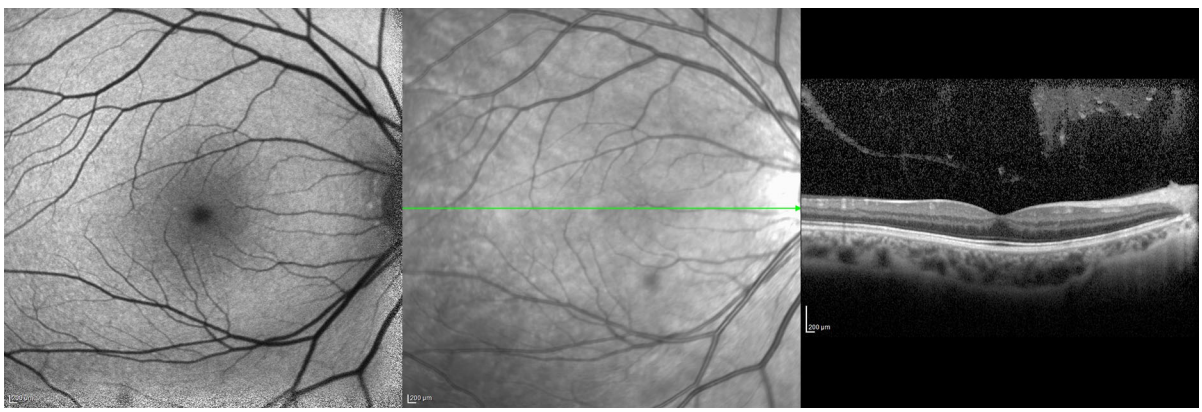

Fig. 5 Spectral domain optical coherence scans of the right eye show a normal posterior pole for twin 1

only in identical twins and in 10–15% of monozygotic twins [6].

In this presentation, we describe identical twins who had mirror fundus and angiographic images of FEVR, which is not reported before.

Case presentation

A pair of 16-year-old female twins presented with mirror-image asymmetry of monocular decreased vision. The twins were born full term with normal weights. Neither twin revealed any medical disorders during childhood, and there was no known family history of ocular disorders. They did not have any ocular treatment history. Systemic and mental examinations also showed no abnormality. On ocular examination, the best corrected visual acuity (BCVA) was 20/20 in OD and 20/63 in OS for the twin 1. For the twin 2, the BCVAs were 20/63 and 20/20 for OD and OS, respectively. Both of the twins were emmetropic. Intraocular pressures were within the

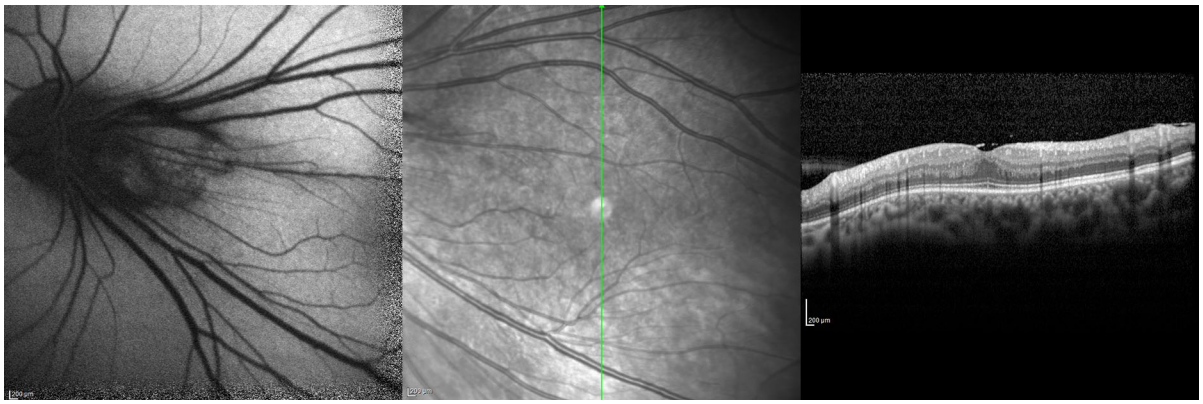

Fig. 6 Spectral domain optical coherence scans of the left eye show the macular dragging and radial folds for twin 1

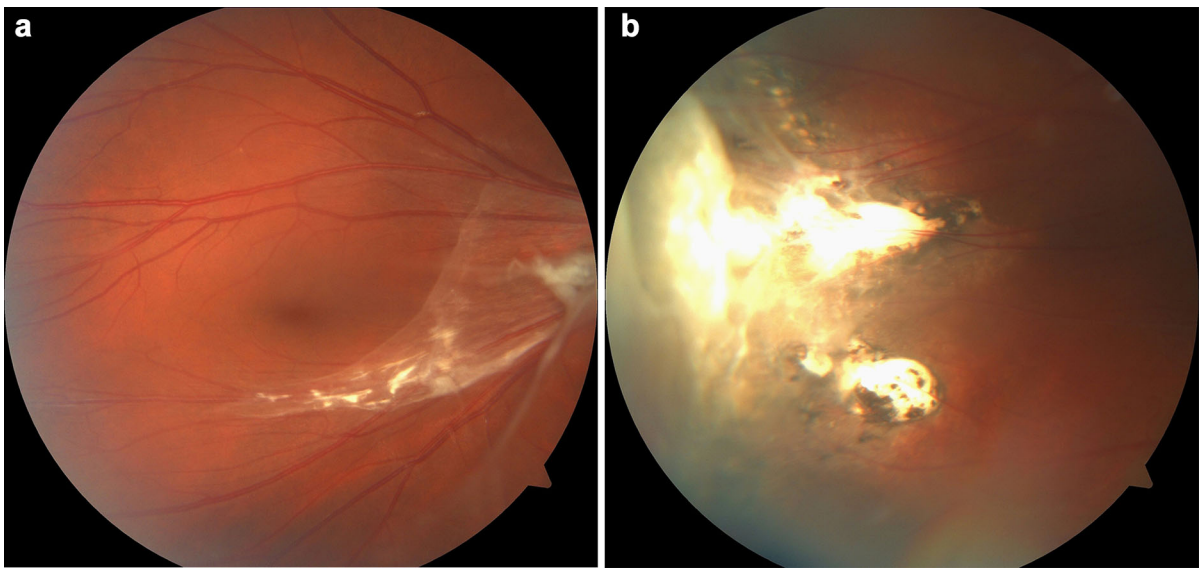

Fig. 7 Colored fundus images of the right eye demonstrate evident macular dragging, straightening of vessels, and radial folds on macula with peripheral tractional detachment, retina pigment epithelial alterations, and chorioretinal atrophy in the peripheral retina for twin 2

normal limits, and anterior segment examinations were unremarkable for both twins.

For twin 1, dilated fundus examination revealed that while the posterior pole of the right eye was normal (Fig. 1a), peripheral retina showed ghost vessels marking the demarcation between vascular and avascular zone in the right eye (Fig. 1b). For the left eye, the typical FEVR appearance including macular dragging, straightening of vessels, and radial folds on macula (Fig. 2a), and retinal exudation, neovascularization with peripheral tractional detachment on the temporal periphery was detected (Fig. 2b). Fundus fluorescein angiography (FFA) demonstrated evident peripheral avascular zone with extensive branching and anastomosis of the retinal vessels as well as leaking of new vessels in the periphery of the right eye (Fig. 3). For the periphery of the left eye, FFA revealed straightening of the vessels, capillary non-perfusion areas, anastomosis of retinal vessels, and leakage in addition to staining next to temporal side of optic nerve (Fig. 4). Spectral domain optical coherence tomography (SD-OCT) scans of the right eye revealed a normal posterior pole in the right eye (Fig. 5). For the left eye, SD-OCT scans confirmed the macular dragging and radial folds (Fig. 6).

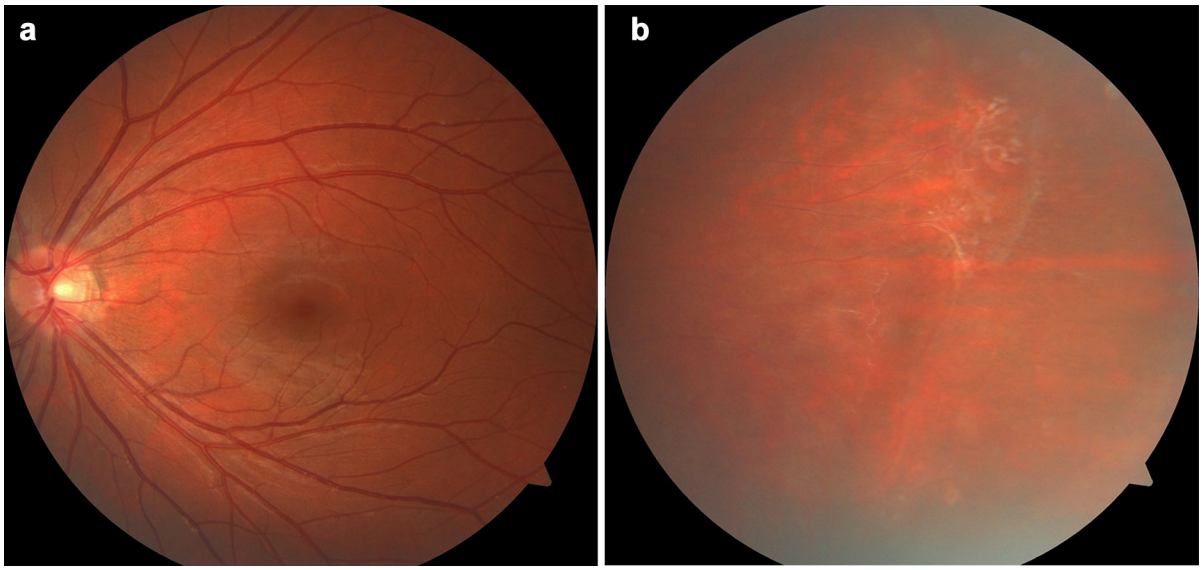

Fig. 8 Colored fundus images of the left eye demonstrate an unremarkable posterior pole with ghost vessels marking the demarcation between vascular and avascular zone in the peripheral retina for twin 2

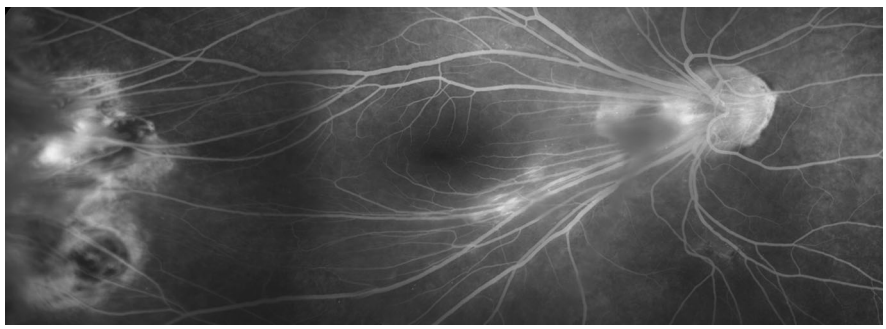

Fig. 9 Composite fundus fluorescein angiography of the right eye shows straightening of the vessels, capillary non-perfusion areas, and leakage in addition to staining next to temporal side of optic nerve for twin 2

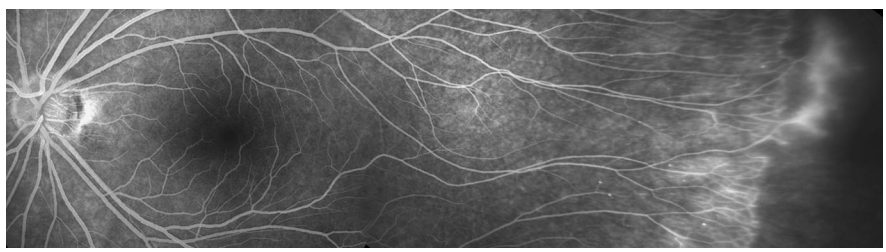

Fig. 10 Composite fundus fluorescein angiography of the left eye shows evident peripheral avascular zone with extensive branching and anastomosis of the retinal vessels as well as leaking of new vessels for twin 2

For twin 2, fundus examination demonstrated evident macular dragging, straightening of vessels, and radial folds on macula (Fig. 7a), with peripheral tractional detachment, retina pigment epithelial alterations, and chorioretinal atrophy in the periphery of the right eye (Fig. 7b). For the left eye, peripheral retina showed ghost vessels marking the demarcation between vascular and avascular zone (Fig. 8a) with a normal posterior pole (Fig. 8b). On the FFA, the right eye exhibited straightening of the vessels, capillary non-perfusion areas, and leakage in addition to staining next to temporal side of optic nerve (Fig. 9).

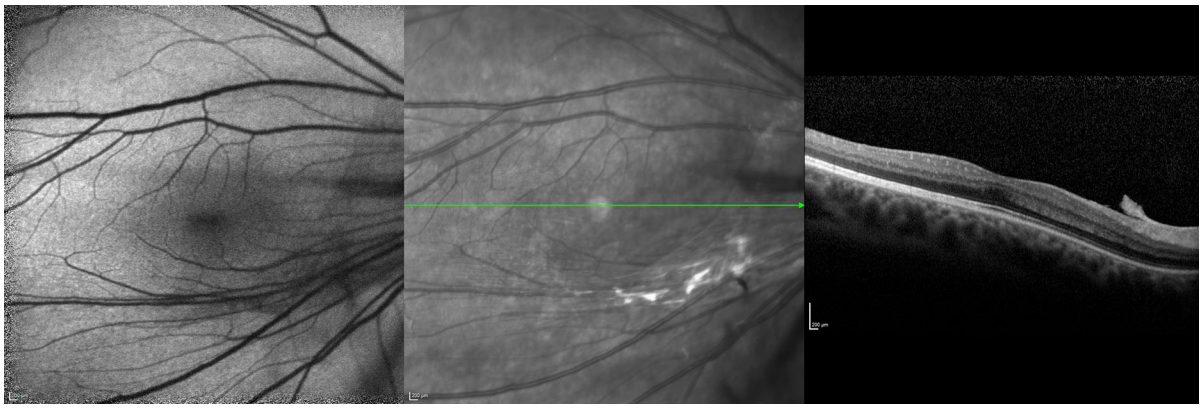

Fig. 11 Spectral domain optical coherence scans of the right eye confirm the macular dragging and radial folds for twin 2

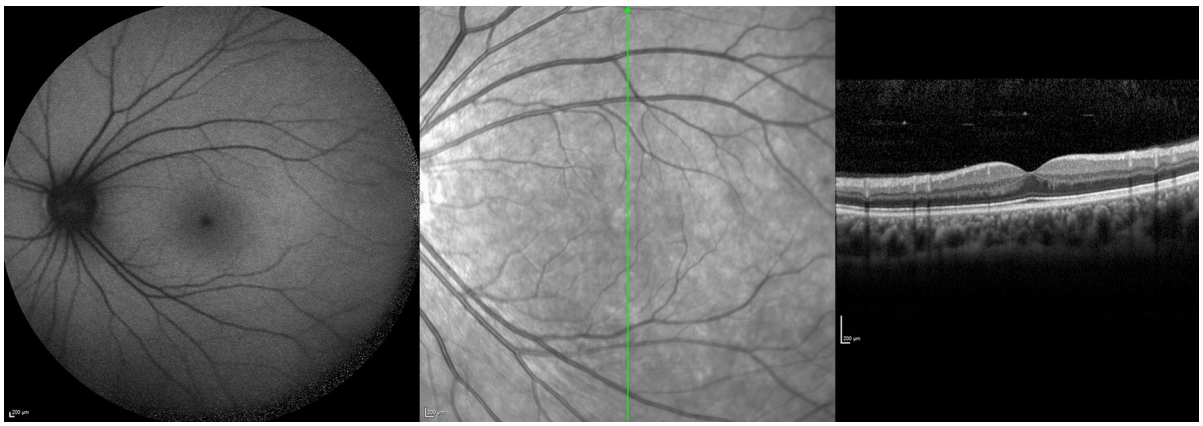

Fig. 12 Spectral domain optical coherence scans of the left eye demonstrate a normal posterior pole for twin 2

For the left eye, evident peripheral avascular zone with extensive branching and anastomosis of the retinal vessels as well as leaking of new vessels were detected on FFA (Fig. 10). SD-OCT scans of the right eye confirmed the macular dragging and radial folds on macula (Fig. 11). For the left eye, SD-OCT scans demonstrated a normal posterior pole (Fig. 12).

To confirm the genetic characteristics of twins, short tandem repeat analysis test which compares specific loci on DNA samples were performed and the results confirmed the monozygotic status.

Discussion

FEVR characterized with the premature arrest of the peripheral retinal vascularization in which expressivity can be asymmetric and highly variable, ranging from asymptomatic to severe within the same family. Additionally, between two eyes of the same individual, there may be substantial asymmetry as is seen in our twins [5, 6]. Both the genotypic and phenotypic features of the disease show a heterogeneous course, as does the clinical appearance. The changeable clinical features include avascular peripheral retina, peripheral retinal neovascularization, macular dragging, straightening of vessels, subretinal exudation, vitreoretinal tractions, and retinal detachment [1, 2, 5]. In our twins, while one eye of each one (OS for twin 1 and OD for twin 2) had classical FEVR findings such as macular dragging, straightening of vessels, and retinal detachment, fellow eyes only presented with peripheral avascular retinal appearance.

The clinical manifestations of FEVR can be nearly identical to ROP. Many clinical features associated with FEVR overlap with those found in ROP. There are several important distinctions between the clinical features of these two diseases. First, FEVR generally is occurred in subjects with no history of prematurity. Second, FEVR presents in older children and adults, whereas ROP is almost always diagnosed in the neonatal period. A third important distinction is that FEVR can have episodes of exudation and progressive traction separated by long periods of inactivity [7]. Based on these criteria, the diagnosis of our twins can be easily made as FEVR.

Treatment of FEVR could be guided by the stage of the disease. In early-staged eyes with minimal peripheral avascularity, observation is reasonable [2, 5]. In eyes with neovascularization with or without exudation, complete retinal ablation of all areas of peripheral retinal non-perfusion with laser photocoagulation is recommended. For the advanced stages of the disease, depending on the configuration and stage of the detachment, pars plana vitrectomy with or without scleral buckling might be useful [2, 5]. Another treatment option is anti-vascular endothelial growth factor therapy which can reduce the retinal exudation and neovascularization in FEVR, but the rapid resolution of exudation may stimulate worsening vitreoretinal traction that often requires surgery [5, 8]. This treatment might have a role as an adjunctive therapy before surgery [5, 8]. We also recommended laser photocoagulation treatment to ablate the peripheral avascular areas of twins.

The mirror-image phenomenon is observed only in identical twins and rarely affects ophthalmic features. Okamoto et al. [9] reported two sets of monozygotic twins with mirror-image myopic anisometropia. Park et al. [10] also described cases of mirror-image myopic anisometropia in a brother and sister pair. Similarly, Chung and Jang defined ocular myasthenia gravis in monozygotic twins with mirror-image myopic anisometropia [11]. Additionally, Kim et al. [12] reported mirror-imaged intermittent exotropia with anisometropia and infantile nystagmus with opposite abnormal head positions in pairs of monozygotic twins. They hypothesized that this symmetric mirroring phenomenon may constitute evidence that intermittent exotropia, anisometropia, and infantile nystagmus are not acquired diseases, but are genetic in origin.

In conclusion, this is the first report describing identical twins with mirror images of FEVR. This report may confirm a strong underlying genetic inheritance in the pathogenesis of FEVR.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this paper.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all participants included in the paper.

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