

From strabismus to pseudo-strabismus and familial exudative vitreoretinopathy, a clinical journey of phenotypically identic twins with symmetric ocular features

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ABSTRACT

Familial Exudative Vitreoretinopathy (FEVR) is a rare genetic condition and several genes have been identified. Clinically, it can cause macular dragging and therefore pseudo-strabismus or exudative or tractional retinal detachment leading to loss of vision in severe cases. Other symptoms including refractive error, cataract and glaucoma have been documented. The main differential diagnosis remains retinopathy of prematurity. We report two phenotypically identic twins that were seen in a lower level hospital and diagnosed with strabismus presumed to be secondary to myopia. A multidisciplinary team including optometrist, paediatric and vitreo-retinal ophthalmologists re-examined the twins and found eccentric fixation and features of FEVR on fundoscopy and angiography. There was a high chance that the twins would have been managed only with spectacles missing the opportunity to be followed up for a more severe vitreoretinal proliferative disease. This case report underlines the genetic basis of the disease with symmetrical and equally distributed myopia, macular dragging and subsequent pseudo-strabismus and FEVR angiographic features. A multidisciplinary team-work was of utmost importance. Beside refractive error correction, the twins also benefited from laser photocoagulation to the avascular retinae to prevent further progress of the proliferative vitreoretinopathy. A good clinical history is enough to rule out retinopathy of prematurity and focus on other causes of retinal fibrovascular membranes in the pediatric population. The fluorescein angiography can be decisive in the clinical setting while genotyping is essential for genetic counseling. Clinicians in low income countries may depend solely on a good clinical history and examination but a high index of suspicion in presence of clinical features of FEVR is key.

INTRODUCTION

Familial Exudative Vitreoretinopathy (FEVR) is a rare, genetic condition described for the first time by Criswick and Schepens in 1968¹. Key features include peripheral avascularity, ectopic macula, tractional bands also described as macular tags, subretinal exudation, retinal ischemia, new vessels proliferation, vitreous haemorrhage and retinal detachment in late stage.

FEVR, unlike its main differential diagnosis that is retinopathy of prematurity, can exhibit a slow and progressive development at any age of life^{1,2}.

FEVR in homozygous twins has been previously reported but, to our best knowledge, this is the first report a combination of pseudo-strabismus, myopia and symmetric images of FEVR in twins is reported.

CASE REPORT

Two phenotypically identic twins were referred to a tertiary level eye hospital in Bangladesh for assessment of their vision. The father reported their family had not previously noted any eye nor vision abnormality until the teacher sent them an alert over their children visual difficulties with subsequent learning problems. They then started realizing their twins had eye deviation problems and decided to seek for medical attention.

The twins were born at term with no perinatal morbidity, they had no history of signs of poor vision and had never been examined by an eye health professional. There was no history of strabismus or loss of vision in their family. At presentation, the pair of male twins were seven years old and in apparent fair general health and growth for the age. The physical examination is presented separately for each of the twins.

Twin A

Presenting visual acuity was 3/60 OD and 6/60 OS and the best corrected visual acuity was 6/36 OD and 6/18 OS. The cycloplegic retinoscopy was -5.00DS/-0.50DCx 90° OD and -3.50DS/-0.50DCx90° OS.

The orthoptic assessment found a free and full ocular motility in all gazes, no nystagmus was noted. Corneal light reflex assessment showed a nasal displacement in the right eye whereas it was on the temporal side of the left eye. On prism cover test, there was no deviation and the absence of binocular single vision subsequently confirmed by the Titmus test.

The anterior segment had no particularity. The fundoscopy of the right eye found a peripheral temporal 'V' shaped avascular zone with straitened vessels proximally. There were no fibrovascular bands. For the left eye, there was a fibrovascular band starting at the disc

and extending towards the foveal area without a clear involvement of the late. The far temporal periphery was quite avascular.

Twin S

Presenting visual acuity was 6/60 OD and 6/36 OS and the best corrected visual acuity was 6/24 OD and 6/18 OS. The cycloplegic retinoscopy was -5.00DS/-0.50DCx 90° OD and -1.0DS/-0.50DCx 80° OS.

The orthoptic assessment found a free and full ocular motility in all gazes and no nystagmus. The corneal light

reflex was displaced nasally in the left eye and temporally in the right eye. However, as observed in twin A, there was no deviation noted when the prism cover test was performed, likewise, the binocular single vision was absent. The anterior segment had no particularity. The fundoscopy found images similar to those of twin A. For the right eye, the macula was apparently free, and no obvious peripheral avascularity unlike the left eye that exhibited fibrovascular bands originating from the disc without involving the fovea itself and a peripheral temporal avascular zone.

Table 1: Summary of clinical features

	Laterality	Corneal light reflex displacement	Refraction	Macular tagging	Presenting visual acuity
Twin A	OD	Nasally	-5.00DS/-0.50DCx 90°	Absent	3/60
	OS	Temporally	-3.50DS/-0.50DCx 90°	Present	6/60
Twin S	OD	Nasally	-5.00DS/-0.50DCx 90°	Absent	6/60
	OS	Temporally	-1.0DS/-0.50DCx 80°	Present	6/36
Symmetry	Symmetric	Symmetric	Symmetric	Symmetric	

Investigations

Colour fundus photo picked areas of avascularity that were subsequently confirmed on fluorescein angiography (Figures 1 and 3).

For twin A, areas of vascular straightening and areas of hypoperfusion were noted in the peripheral temporal quadrants, leakage was also noted in the late phase in

the transitional zone between perfused and non-perfused areas (Figure 2).

Twin S had also vascular straightening and peripheral avascular zones in the temporal and inferior far periphery. In the left eye, mild leakage was noted as opposed to right eye (Figure 4). Genetic testing was not possible in a context of limited resources.

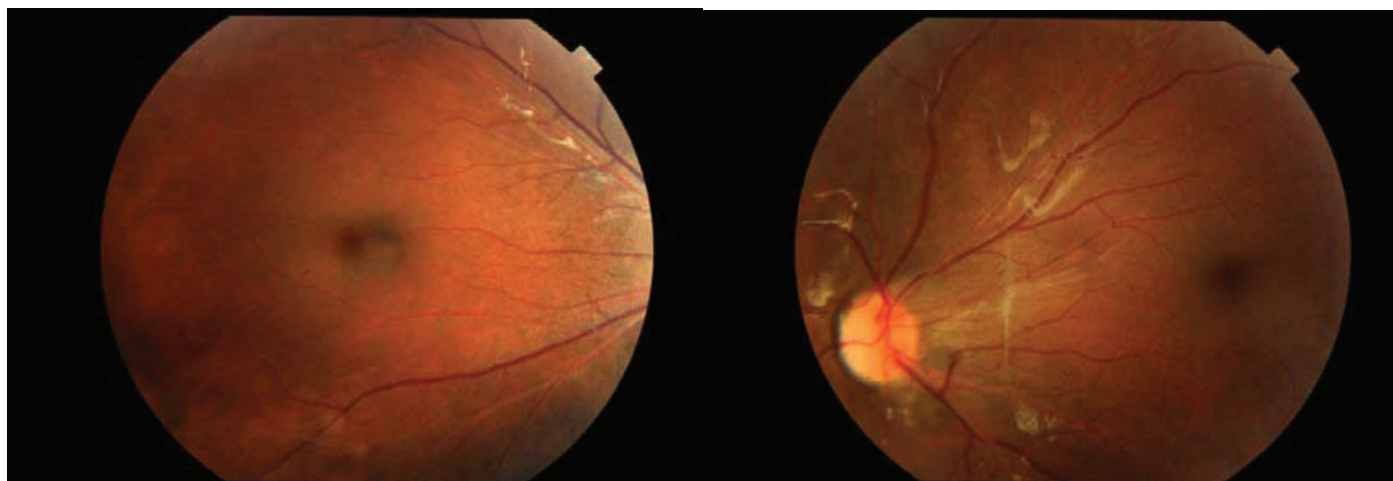


Figure 1: Colour fundus photos show bilateral vessels straightening and left disc dragging

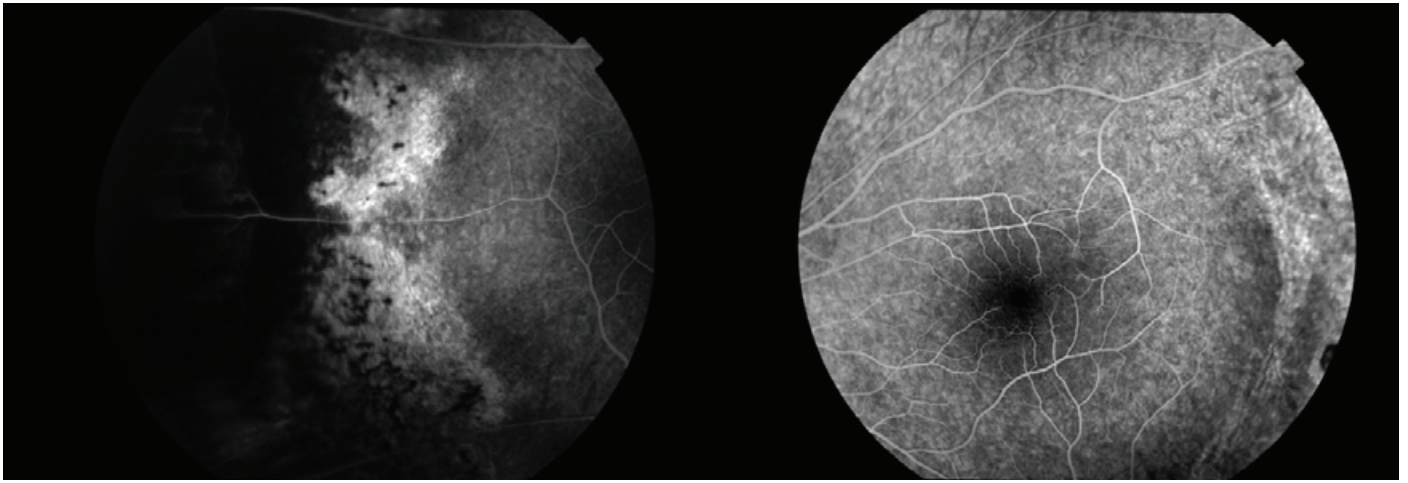


Figure 2: Fluorescein angiography images confirm temporal periphery avascularity and late leakage

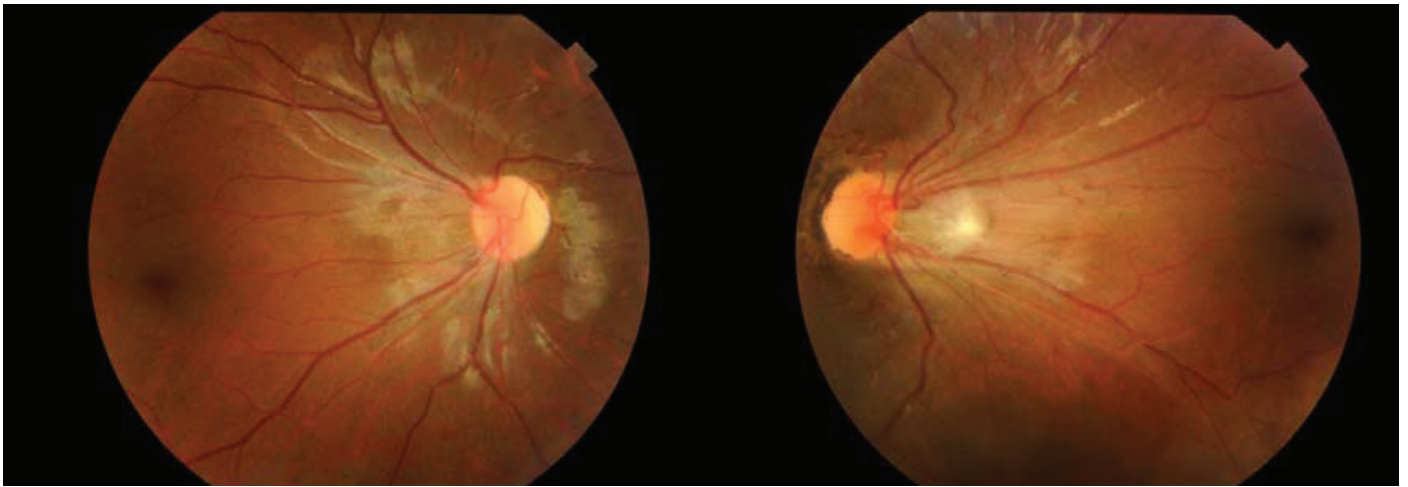


Figure 3: Colour fundus photo with bilateral vessels straightening and left disc dragging

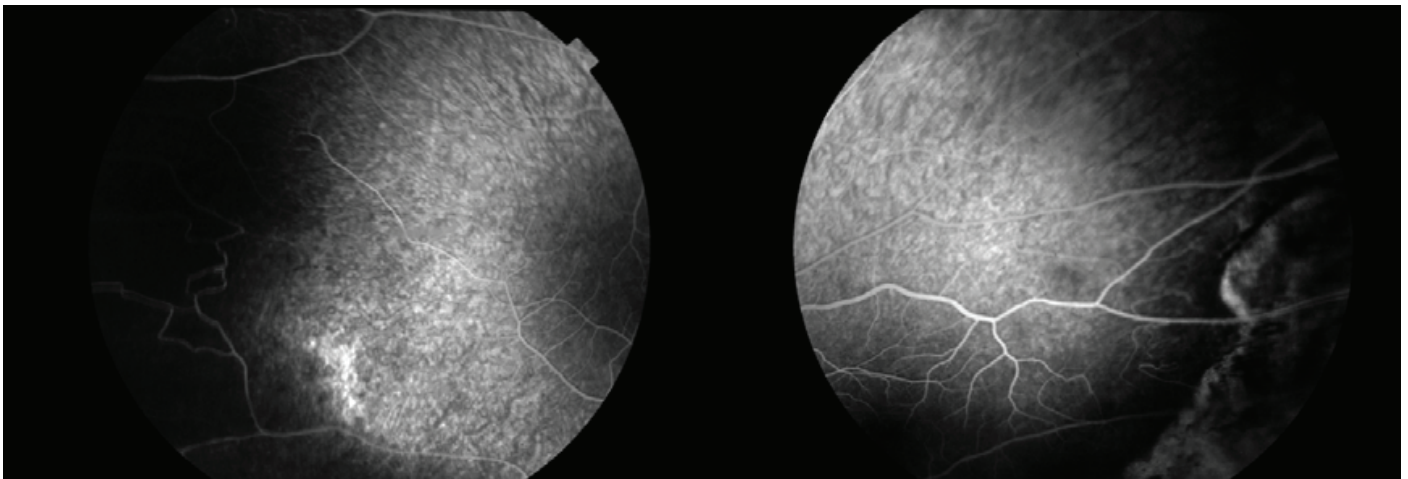


Figure 4: Fluorescein angiography images confirm peripheral temporal avascularity and late leakage

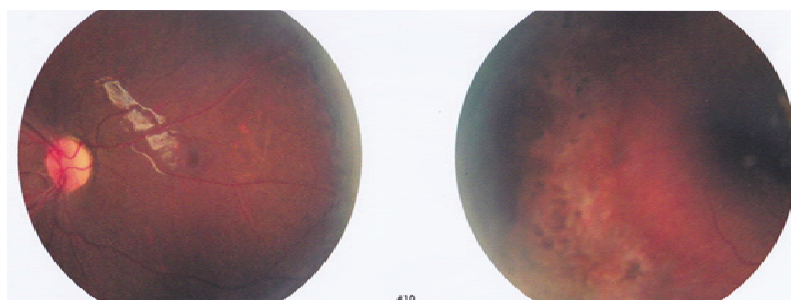


Figure 5: Twin A fundus photos after laser photocoagulation, note laser marks in the periphery

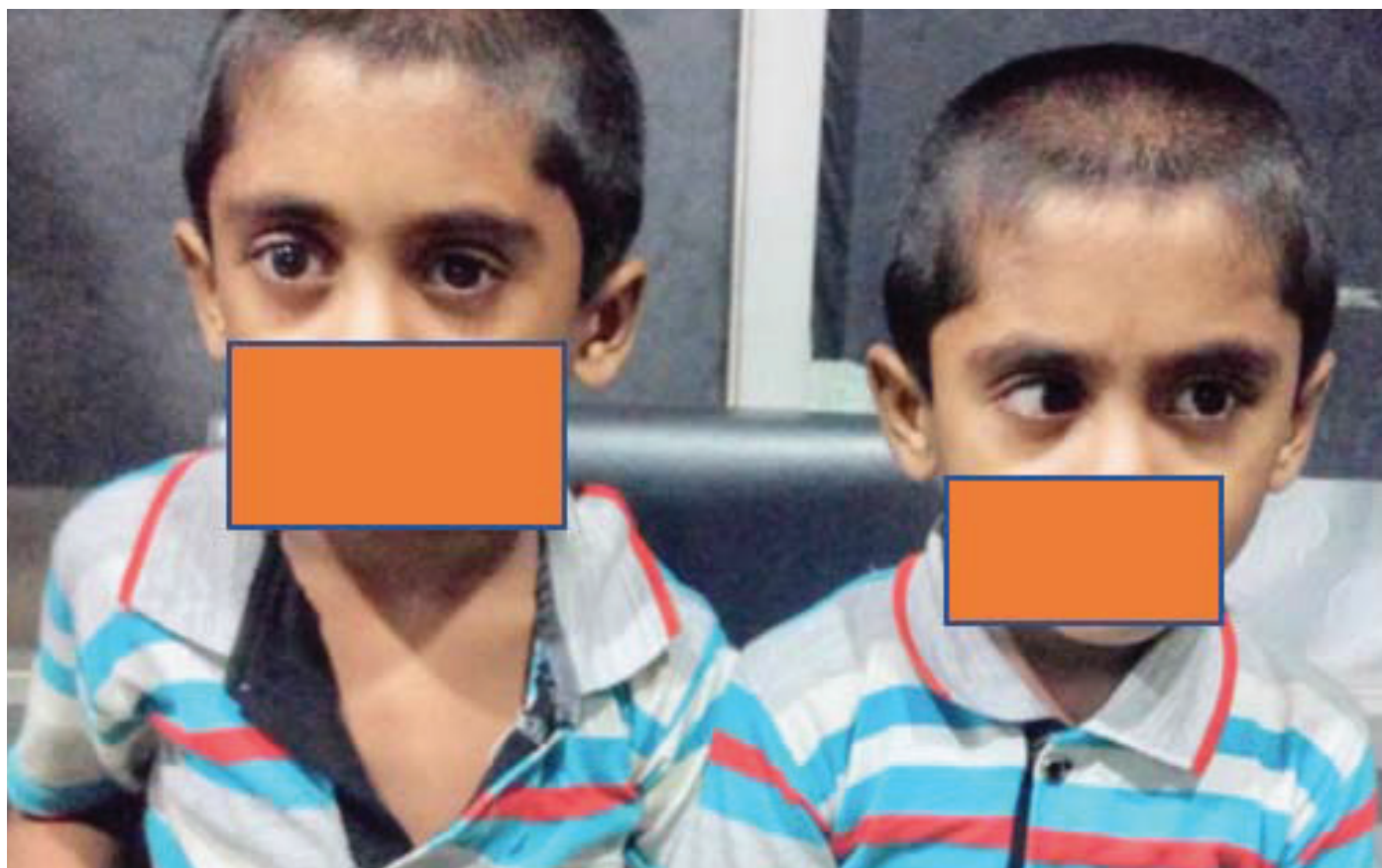


Figure 6: The corneal light reflexes showing the pseudo strabismus in both twins

Outcome and follow-up

The twins will be followed up regularly by both the paediatric ophthalmologists and vitreoretinal surgeons to assess the long-term progress of the disease.

DISCUSSION

FEVR is a rare condition and has been reported in various ways, each author trying to bridge the gap in the better understanding of the condition. The pathogenesis of the disease is now very clear, four genes mutations have been clearly linked to the disease although genetic penetrance and clinical phenotypes have been found to be variable even within the same family and between eyes of the same patient. The disease is genetically transmitted in three ways: autosomal dominant (most common), autosomal recessive and x-linked recessive. The mutations causing FEVR were identified to occur in Norrie Disease Protein (NDP), Frizzled-4 (FZD4), Low-density Lipoprotein Receptor- Related Protein 5 (LRP5), and tetraspanin-12 (TSPAN12)⁹⁻¹². Although genetic studies were not available in our twins' study, the symmetric images found in these identical boys enhance the inherited mode of the disease as previously stated by other authors.

FEVR patients were extensively studied but the pattern and pathophysiology of strabismus remains poorly understood to date. Strabismus and pseudo-strabismus are both reported in conditions affecting the macular anatomy. In 2012, Exotropia was also reported by Natung *et al*¹³. In a study conducted among babies

diagnosed with ROP, both myopia and strabismus were present. The mean spherical equivalent was $-2.4 \pm 4.4D$ and 41.1% of babies presented with strabismus (26.8% esotropia and 14.3% exotropia)¹⁴. Esotropia has also been reported in FEVR. In two articles, the FEVR was unilateral and the same eye developed esotropia^{15,16}. However other researchers supported that strabismus in FEVR was an effect of macular ectopia secondary to the dragging effect¹⁷. In our twins, since the macular ectopia was temporal, one would expect an exotropia secondary to efforts to re-center fixation on target. Conversely, orthoptic assessment found rather eccentric fixation than a squint.

It is possible to hypothesize the genetic pathogenesis of FEVR in our twins based on the symmetrical presentation of the ocular findings. In 1950, Waardenburg used the same principle stipulating: "If for a given trait, uni-ovular twins differ much less than bin-ovular twins, the trait may be accepted as essentially hereditary. If they differ just as much, the trait is mainly environmental"¹⁸.

Extensive research has been conducted by various authorities to establish the genetic myopiagenesis as well and up to 200 genetic loci were identified. It is worth noting that a lot needs to be done to understand the phenotypic variance and to discern the molecular signaling cascade of myopia¹⁹.

Since esotropia and exotropia are both described, it would be very important to study in a large cohort study the type of macular eccentricity and the type of tropias. Most cases of FEVR may be asymptomatic and may not need any treatment and several authorities have advocated for treatment of cases that have documented progression¹.

Regularity of follow-ups is a key player to track the progression if any and institute the treatment timely otherwise genetic counseling may help to tell who else in the family is at risk. Correction of the refractive error may help to achieve some useful vision.

CONCLUSIONS

Although rare, FEVR should be suspected and ruled out in all patients with atypical late onset strabismus or pseudo-strabismus. FEVR signs and symptoms may develop slowly from early childhood to adulthood. There is a risk that optometrists may associate the strabismus to the refractive error but a careful bilateral fundus examination by an ophthalmologist is a must as findings may only be evident in the peripheral retina. Fluorescein angiography is the investigation of choice that confirms the peripheral retina avascularity and guide the laser treatment before serious complications set in.

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