Familial Exudative Vitreoretinopathy

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Summary
Familial exudative vitreoretinopathy (FEVR) is a hereditary disease associated with visual loss, particularly in the pediatric group. Mutations in the NDP, FZD4, LRP5, and TSPAN12 genes have been shown to contribute to FEVR. FEVR has been reported to have X-linked recessive, autosomal dominant, and autosomal recessive inheritances. However, both the genotypic and phenotypic features are variable. Novel mutations contributing to the disease have been reported. The earliest and the most prominent finding of the disease is avascularity in the peripheral retina. As the disease progresses, retinal neovascularization, subretinal exudation, partial and total retinal detachment may occur, which may be associated with certain mutations. With early diagnosis and prompt management visual loss can be prevented with laser photocoagulation and anti-VEGF injections. In case of retinal detachment, pars plana vitrectomy alone or combined with scleral buckling should be considered. Identifying asymptomatic family members with various degrees of insidious findings is of certain importance. Wide-field imaging with fluorescein angiography is crucial in the management of this disease. The differential diagnosis includes other pediatric vitreoretinopathies such as Norrie disease, retinopathy of prematurity, and Coats’ disease.

Key Words: Familial exudative vitreoretinopathy, NDP, FZD, LRP5, TSPAN12

Introduction
Familial exudative vitreoretinopathy (FEVR) was first described by Criswick and Schepens1 in 1969. The characteristic clinical features were based on peripheral retinal vascular changes of heterogeneous severity. Those changes included avascular peripheral retina, peripheral retinal neovascularization, macular dragging, subretinal exudation, vitreoretinal traction, and retinal detachment. The vascular features were first demonstrated by fluorescein angiography (FA) by Canny and Oliver2 in 1976. In 1998, Pendergast and Trese3 described a classification scheme, which was recently updated,4 for FEVR (Table 1). Clinical presentation may vary between asymptomatic avascular peripheral retina and total retinal detachment that leads to vision loss. Although the disease is known to be familial, the phenotypic features can still be variable within families.5,6,7

Familial exudative vitreoretinopathy is a lifelong disease that can progress, resulting in blindness despite treatment. The presentation and course of the disease show variability, making the diagnosis and management challenging.3

Inheritance and Pathophysiology
A positive family history is reported to be present in approximately 20–40% of cases.8 The disease is currently known to be inherited in three forms: autosomal dominant (AD), autosomal recessive (AR), and X-linked recessive (XR), with the AD form being the most common. However, the inheritance patterns and expressivity show a heterogeneous course, as do the clinical features and prognosis of the disease.6,9

Mutations in four genes related to FEVR have been described. These gene products are Norrin Disease Protein (NDP), Frizzled-4 (FZD4), low-density lipoprotein receptor-
related protein 5 (LRP5), and tetraspanin-12 (TSPAN12). The NDP gene is located on the X chromosome (Xp11.4), FZD4 and LRP5 are located on chromosome 11 (11q14.2 and 11q13.2, respectively), and TSPAN12 is located on chromosome 7 (7q31.31). Mutations in the causative genes and the resultant diseases are as follows: NDP gene, X-linked recessive FEVR or Norrie disease; FZD4 gene, AD FEVR; LRP5 gene, both AD and AR FEVR; and TSPAN12, AD FEVR. The protein products of these genes are involved in the canonical Wnt and Norrin signaling pathways. The Wnt signaling pathway is essential for the organogenesis and angiogenesis of the mammalian eye. Norrin, which is coded by NDP, exerts a strong affinity to receptor FZD4. In this pathway, LRP5 is the co-receptor of FZD4. The complex of the ligand and the receptors is mediated by TSPAN12, an auxiliary transmembrane protein, which binds to Norrin multimers resulting in enhancement of FZD4 multimerization and clustering. Norrin-receptor complex activates the canonical Wnt pathway. In case of a blockade in the Norrin binding pathway, the signaling is disturbed, resulting in a depression in target protein production. Although the NDP mutations are involved both in Norrie disease and FEVR, most mutations are related to Norrie disease, whereas a smaller percentage of these mutations cause X-linked FEVR. Mutations in NDP were also reported to be associated with persistent fetal vasculature syndrome, Coats' disease, and retinopathy of prematurity (ROP).

Table 1. Updated clinical classification of familial exudative vitreoretinopathy

| Stage | Exudate* | Clinical features |
|-------|----------|------------------|
|       | Without  | With             |
| 1     | A        | B Avascular retinal periphery |
| 2     | A        | B Extraretinal neovascularization |
| 3     | A        | B Retinal detachment not involving macula |
| 4     | A        | B Retinal detachment involving macula |
| 5     | A (open funnel) | B (closed funnel) Total retinal detachment |

* for stages 1-4.
and pathologic vitreoretinal adhesions make the scaffold for these advanced features.

The disease does not necessarily follow the stages sequentially, and the eyes do not always present with symmetrical findings. Some features strongly indicate FEVR, such as a knife-like radial retinal fold extending from the optic nerve to even the ciliary body. However, a careful examination is mandatory. Retinoschisis is not an irrelevant finding either. Besides tractional retinal detachment (RD), rhegmatogenous RD could also complicate the clinical presentation.

A positive family history will assist making the diagnosis. However, a negative family history would not exclude FEVR, as novel mutations can also occur. On the other hand, because of the phenotypic heterogeneity, it is important to identify asymptomatic family members. Kashani et al. reported that in asymptomatic family members of FEVR patients, 58% had stage 1 and 35% had stage 2 FEVR.

Currently, for accurate diagnosis, a thorough examination combined with wide field fluorescein angiography is essential (Figures 1, 2, 3). Fluorescein angiography enhances the diagnostic sensitivity because subtle vascular changes in the periphery or even in the posterior pole can easily be overlooked by conventional funduscopy. Wide-field retinal imaging would also be helpful to detect asymptomatic family members of index patients. The incidence of the disease could be higher than expected. The determination of asymptomatic family members with the disease at child-bearing age is essential for genetic counseling and neonatal screening. The disease tends to become quiescent in the late teens or early twenties; however, later recurrences frequently occur with an unpredictable clinical course.

**Differential Diagnosis**

Distinguishing FEVR from Norrie disease, ROP and Coats’ disease may be challenging. As NDP gene mutations are implied in the pathogenesis of both diseases, FEVR must be differentiated from Norrie disease. Deletion and truncation mutations in the gene result in Norrie disease without exception. However, missense mutations cause either Norrie disease or FEVR. In Norrie disease, retinal vascular anomalies could be accompanied by mental retardation and hearing loss in approximately in a quarter of patients. Besides genetic alterations, FEVR is differentiated from Norrie disease by its slow progression. Mutations involving cysteine residues of the NDP gene resulted in Norrie disease, whereas mutations involving the non-cysteine residues were found to be associated with FEVR. As well as Norrie disease, persistent fetal vasculature syndrome, which has quite similar phenotypic features with Norrie disease without evidence of inheritance, must be considered in differential diagnosis. However, unlike FEVR, both entities lack preretinal neovascularization despite a severely avascular peripheral retina.

Unlike ROP, FEVR patients are full-term infants. ROP frequently shows spontaneous regression; although there are sequelae, late recurrences do not occur. However, there is conflicting data about the role of the NDP gene in ROP. Recently, the same FZD4 mutations were reported in both diseases, making the differential diagnosis complex. FZD4 mutations were reported to contribute to aggressive posterior ROP.

When first reported by Criswick and Schepens, the presenting features of FEVR were briefly described; however, although the authors suggested the inherited characteristics
of the disease, they could not define an inheritance pattern. As the patients to whom they referred did not have history of prematurity, the authors mainly considered Coats’ disease in the differential diagnosis and distinguished the entity from Coats’ disease by the family history, peripheral nature of the disease, and the more severe involvement of the vitreous. Unlike Coats’, male preponderance is not characteristic for FEVR.31 Recently, Robitaille et al.10 reported the disparity between Coats’ disease and FZD4 mutations.

**Treatment**

Stage 1 FEVR requires no treatment but regular follow-up. The primary treatment of FEVR is laser photocoagulation. The peripheral avascular areas should be ablated with laser in case of neovascularization demonstrating leakage in FA, which can even be performed in fractionated sessions. Successful outcome with laser treatment was reported even in stage 4 FEVR patients. Cryotherapy was used for treatment of neovascularization, particularly in patients with small, non-dilating pupils or with hazy media; however, this is no longer considered an option. In patients with RD, surgical intervention should be considered. In this case, scleral buckle alone can help in cases with limited detachment; however, more severe cases would necessitate pars plana vitrectomy (PPV). Earlier diagnosis and management would result in better prognosis.25

In a single study, based on the finding that dysregulation of the canonical Wnt pathway was associated with increased vascular endothelial growth factor (VEGF) levels, intravitreal injection of an anti-VEGF agent (pegaptanib sodium) was administered in persistent FEVR cases and reduced exudation and vascular activity were achieved.3 Recently, intravitreal bevacizumab was also reported to cause an immediate regression of neovascularization.32

In cases that undergo PPV for tractional RD, the taut nature of the posterior hyaloid must be considered. Intravitreal injection of autologous plasmin was suggested for better cleavage of the vitreomacular interface and enhanced surgical dissection of the vitreous sheets from the retinal surface in these patients.33 Although scleral buckling would help reduce traction, the main advantage of vitrectomy is removing the proliferation consisting of membranes and proliferative tissue and laser photoagulation of the avascular area can be beneficial.27

In their series, Kulaçoğlu et al.34 reported 5 cases of FEVR. All patients were presented at various stages of the disease, demonstrating asymmetric presentation. However, all 5 patients lacked a history of premature birth. Only one patient had a positive family history and all cases were late referrals with poor prognosis. In our opinion, their case series from the Turkish literature is in accordance with the reported features of the disease.

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**References**

1. Criswick VG, Schepens CL. Familial exudative vitreoretinopathy. Am J Ophthalmol. 1969;68:578-594.
2. Canny CL, Oliver GL. Fluorescein angiographic findings in familial exudative vitreoretinopathy. Arch Ophthalmol. 1976;94:1114-1120.
3. Pendergast SD, Trese MT. Familial exudative vitreoretinopathy. Results of surgical management. Ophthalmology. 1998;105:1015-1023.
4. Kashani AH, Brown KT, Chang E, Drenser KA, Capone A, Trese MT. Diversity of retinal vascular anomalies in patients with familial exudative vitreoretinopathy. Ophthalmol. 2014;121:2220-2227.
5. Quiram PA, Drenser KA, Lai MM, Capone A Jr, Trese MT. Treatment of vascularly active familial exudative vitreoretinopathy with pegaptanib sodium (Macugen). Retina. 2008;28:8-12.
6. Kashani AH, Learned D, Nudleman E, Drenser KA, Capone A, Trese MT. High prevalence of peripheral retinal vascular anomalies in family members of patients with familial exudative vitreoretinopathy. Ophthalmol. 2014;121:262-268.
7. Benson WE. Familial exudative vitreoretinopathy. Trans Am Ophthalmol Soc. 1995;93:473-521.
8. Rancho TM, Ho IY, Drenser KA, Capone A Jr, Trese MT. Clinical presentation of familial exudative vitreoretinopathy. Ophthalmol. 2011;118:2070-2075.
9. Jia LY, Li XX, Yu WZ, Zeng WT, Liang C. Novel frizzled-4 gene mutations in Chinese patients with familial exudative vitreoretinopathy. Arch Ophthalmol. 2010;128:1341-1349.
10. Robitaille J, Zheng B, Wallace K, Beis MJ, Tatidid C, Yang J, Shedow TG, Siebert L, Levin AV, Lam WC, Arthur BW, Lyons CJ, Jaakkola E, Tsioul E, Williams CA, Weaver RG Jr, Shields CL, Guernsey DL. The role of Frizzled-4 mutations in familial exudative vitreoretinopathy and Coats disease. Br J Ophthalmol. 2011;95:574-579.
11. Nikopoulos K, Venselaar H, Collin RW, Riveiro-Alvarez R, Boonstra FN, Hooyman JM, Mukhopadhyay A, Shears D, van Ben M, de Wijls JJ, van Essen AJ, Sijmons RH, Titanus MA, van Nieuwuyts CE, Ayyso C, Hoefkold LH, Cremers FP. Overview of the mutation spectrum in familial exudative vitreoretinopathy and Norrie disease with identification of 21 novel variants in FZD4, LRPS, and NDP. Hum Mutat. 2010;31:656-666.
12. Pelcastre EL, Villanueva-Mendoza C, Zenteno JC. Novel and recurrent NDP gene mutations in familial cases of Norrie disease and X-linked exudative retinopathy. Clin Exp Ophthalmol. 2010;38:367-374.
13. Boonstra FN, van Nieuwuyts CE, Schui J, de Wijls JJ, van der Donk KP, Nikopoulos K, Mukhopadhyay A, Schieffer H, Titanus MA, Cremers FP, Hoefkold LH. Clinical and molecular evaluation of probands and family members with familial exudative vitreoretinopathy. Invest Ophthalmol Vis Sci. 2009;50:4379-4385.
14. Xia CH, Liu H, Cheung D, Wang M, Cheng C, Du X, Chang B, Beutler B, Gong X. A model for familial exudative vitreoretinopathy caused by LPR3 mutations. Hum Mol Genet. 2008;17:1605-1612.
15. Poulter JA, Davidson AE, Ali M, Gilmour DF, Parry DA, Minz-Hirtner HA, Carr IM, Bottomley HM, Long VW, Downey LM, Sergouniotis PI, Wright GA, MacLaren RE, Moore AT, Webster AR, Inglehearn CF, Tomes C. Recessive mutations in TSPAN12 cause retinal dysplasia and severe familial exudative vitreoretinopathy (FEVR). Invest Ophthalmol Vis Sci. 2012;53:2873-2879.
16. Drenser KA, Dailey W, Vinekar A, Dalal K, Capone A Jr, Trese MT. Clinical presentation and genetic correlation of patients with mutations affecting the FZD4 gene. Arch Ophthalmol. 2009;127:1649-1654.

17. Kondo H, Qin M, Kuaka S, Tahira T, Hasebe H, Hayashi H, Uchio E, Hayashi K. Novel mutations in Norrie disease gene in Japanese patients with Norrie disease and familial exudative vitreoretinopathy. Invest Ophthalmol Vis Sci. 2007;48:1276-1282.

18. Yang H, Li S, Xiao X, Wang P, Guo X, Zhang Q. Identification of FZD4 and LRP5 mutations in 11 of 49 families with familial exudative vitreoretinopathy. Mol Vis. 2012;18:2438-2446.

19. Fei P, Zhang Q, Huang L, Xu Y, Zhu X, Tai Z, Gong B, Ma S, Yao Q, Li J, Zhao P, Yang Z. Identification of two novel LRP5 mutations in families with familial exudative vitreoretinopathy Mol Vis. 2014;20:395-409.

20. Kondo H, Hayashi H, Oshima K, Tahira T, Hayashi K. Frizzled 4 gene (FZD4) mutations in patients with familial exudative vitreoretinopathy with variable expressivity. Br J Ophthalmol. 2003;87:1291-1295.

21. Yang H, Xiao X, Li S, Mai G, Zhang Q. Novel TSPAN12 mutations in patients with familial exudative vitreoretinopathy and their associated phenotypes. Mol Vis. 2011;17:1128-1135.

22. Shastry BS, Trese MT. Cosegregation of two unlinked mutant alleles in some cases of autosomal dominant familial exudative vitreoretinopathy. Eur J Hum Genet 2004;12:79-82.

23. Toomes C, Bottomley HM, Scott S, Mackey DA, Craig JE, Appukuttan B, Stout JT, Flaxel CJ, Zhang K, Black GC, Fryer AD, Downey LM, Inglehearn CF. Spectrum and frequency of FZD4 mutations in familial exudative vitreoretinopathy. Invest Ophthalmol Vis Sci. 2004;45:2083-2090.

24. Toomes C, Bottomley HM, Jackson RM, Towns KV, Scott S, Mackey DA, Craig JE, Jiang L, Yang Z, Trembath R, Woodruff G, Gregory-Evans CY, Gregory-Evans K, Parker MJ, Black GC, Downey LM, Zhang K, Inglehearn CF. Mutations in LRP5 or FZD4 underlie the common familial exudative vitreoretinopathy locus on chromosome 11q. Am J Hum Genet. 2004;74:721-730.

25. Shukla D, Singh J, Sudheer G, Soman M, John RK, Ramasamy K, Perumalsamy N. Familial exudative vitreoretinopathy (FEVR). Clinical profile and management. Indian J Ophthalmol. 2003;51:325-328.

26. Miyakubo H, Hashimoro H, Miyakubo S. Retinal vascular pattern in familial exudative vitreoretinopathy. Ophthalmology 1984;91:1524-1530.

27. Ikeda T, Fujikado T, Tano Y, Tsujikawa K, Kosuzumi K, Sawa H, Yasuhara T, Maeda K, Kinoshita S. Vitrectomy for rhegmatogenous or tractional retinal detachment with familial exudative vitreoretinopathy. Ophthalmol 1999;106:1081-1085.

28. Wu WC, Drenser K, Trese M, Capone A Jr, Dailey W. Retinal phenotype-genotype correlation of pediatric patients expressing mutations in the Norrie disease gene. Arch Ophthalmol. 2007;125:225-230.

29. Walsh MK, Drenser KA, Capone A, Trese MT. Early vitrectomy effective for bilateral combined anterior and posterior persistent fetal vasculature syndrome. Retina. 2010;30:2-8.

30. Dickinson JL, Sale MM, Passmore A, FitzGerald LM, Wheatley CM, Burdon KP, Craig JE, Tengtrisorn S, Carden SM, Maclean H, Mackey DA. Mutations in the NDP gene: contribution to Norrie disease, familial exudative vitreoretinopathy and retinopathy of prematurity. Clin Experiment Ophthalmol. 2006;34:682-688.

31. Sigler E, Randolph JC, Carvajal JI, Wilson MW, Haik BG. Current management of Coats disease. Surv Ophthalmol. 2014;59:30-46.

32. Tagami M, Kusuhara S, Honda S, Tsukahara Y, Negi A. Rapid regression of retinal hemorrhage and neovascularization in a case of familial exudative vitreoretinopathy treated with intravitreal bevacizumab. Graefes Arch Clin Exp Ophthalmol. 2008;246:1787-1789.

33. Joshi MM, Ciaccia S, Trese MT, Capone A Jr. Posterior hyaloid contracture in pediatric vitreoretinopathies. Retina. 2006;26:38-41.

34. Kulaçoğlu DN, Gürelk G, Özdelen Ş, Aydin B, Hasanetoğlu B. Ailevi eksüdatif vitreoretinopatide görsel ve anatomik sonuçlar. Ret-Vit 2003;11:142-149.