Causal diagnosis of familial exudative vitreoretinopathy in two asymptomatic siblings. Wide-field image study of retinal abnormalities observed in the posterior pole

Diagnóstico casual de vitreorretinopatía exudativa familiar en 2 hermanos asintomáticos. Estudio de imagen de campo amplio y anormalidades retinianas objetivadas en el polo posterior

Abstract

Familial exudative vitreoretinopathy (FEVR) is a rare inherited disease classified in the group of vitreoretinal dystrophies. It is characterized by the abnormal development of peripheral retinal vessels, which can provoke pathologies ranging from mild peripheral ischemia to neovascularization, vitreous bleeding, and even retinal detachment. To overcome the difficulty of diagnosis in mild and asymptomatic cases, researchers have recently described objective signs that may be observed in the posterior pole. We present the clinical cases of two siblings diagnosed with FEVR, fortuitously, during the study of uveitis in one of them. Wide-field fluorescein angiography was of great help in the diagnosis and monitoring of this condition. Most of the new signs described in the posterior pole are present in our cases. One of the siblings, despite being asymptomatic, required laser photocoagulation of the peripheral retina. This was performed at an early stage, which enabled good anatomical and functional results to be achieved.

Key words: Familial exudative vitreoretinopathy. Dystrophy. Fluorescein angiography. Retinal photocoagulation. Retinopathy of prematurity.

Resumen

La vitreorretinopatía exudativa familiar es una enfermedad hereditaria rara encuadrable en el grupo de las distrofias vitreoretinianas. Se caracteriza por un desarrollo anormal de los vasos retinianos periféricos, lo que genera desde isquemia periférica leve hasta neovascularización, exudación e incluso desprendimiento de retina. Ante la dificultad de diagnóstico en casos leves y asintomáticos, recientemente se han descrito signos objetivables en el polo posterior que pueden facilitar un diagnóstico precoz. Presentamos los casos clínicos de 2 hermanos diagnosticados de vitreorretinopatía exudativa familiar casualmente durante el estudio de una uveítis en uno de ellos. La angiografía fluoresceínica de campo amplio resultó de gran ayuda para el diagnóstico y seguimiento. La mayoría de los nuevos signos descritos en polo posterior están presentes
Introduction

Familial exudative vitreoretinopathy (FEVR) is a rare inherited disorder described by Criswick and Schepens in 1969\(^1\). As in the case of retinopathy of prematurity (ROP), the primary disorder consists in a failure of retinal vessels to grow in the periphery, most frequently affecting the temporal artery. Secondary complications of the disease will depend on the degree of ischemia\(^2,3\). Inheritance is usually autosomal dominant, although it may be autosomal recessive or X-linked. Cases with no family history of the disease have also been described\(^2\). It is a highly penetrant disease but with variable expressivity. Its clinical features include peripheral avascular retina, neovascularization, subretinal exudation, and abnormalities in the vitreoretinal interface. In more advanced cases, falciform retinal folds, tractional detachment, and recurrent vitreous hemorrhages may appear\(^2-6\). Both eyes are usually affected, with a characteristic asymmetry. In addition, cases range from asymptomatic to severe within the same family\(^2\).

We present the cases of two brothers with signs of avascularity in the peripheral retina of both eyes.

Clinical case 1

Case 1 is a 12-year-old male who consulted for floaters in the left eye (OS) without relevant history. Family history revealed factor V Leiden thrombophilia in the father.

Best-corrected visual acuity was 20/20 and intraocular pressure was 12 mmHg in both eyes (AO).

Anterior segment examination was normal in the right eye (OD) and OS was graded with flare 1+ in anterior chamber without other findings. OD funduscopy was considered normal, whereas in OS vitreous haze 1+ was observed, papilledema with blurred optic disc margins, and mild avascularity in the peripheral temporal retina (Fig. 1).

Wide-field fluorescein angiography (WFFA) was performed, and bilateral punctate hyperfluorescence spots in the choroid were noted in the inferior hemiretina, more evident in OS, with associated papillary hyperfluorescence. A diagnosis of uveitis was made. It also revealed some capillary dilation and mild avascularity of the temporal and inferior peripheral retina (Fig. 2A and B) without signs of vasculitis, and at the time, a vitreoretinal dystrophy was not suspected. With these findings, the patient was diagnosed with posterior uveitis and began systemic workup, follow-up, and medical treatment.

Clinical case 2

Case 2 is a 9-year-old asymptomatic female and biological sister of the patient in case 1. She is brought to consultation by her adoptive parents after the diagnosis of her biological brother with posterior uveitis of unknown etiology. Relevant history included preterm labor at a gestational age of 32 weeks weighing 1.496 g without need for oxygen. No signs of ROP were observed in the evaluation performed by the children ophthalmology unit.

Best-corrected visual acuity was 20/20 and intraocular pressure was 14 mmHg OU.

Anterior segment was normal OU. OD funduscopy showed avascularity in the peripheral temporal retina. In OS, exudation was noted in the temporal peripheral retina with neovascularization and mild straightening of vessels (Fig. 3A and B).

WFFA was performed, which confirmed temporal peripheral neovascularization, revealing an intense leakage in OS. In OD, there was mild avascularity in the temporal peripheral retina (Fig. 4A and B). Given the
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history, the age of diagnosis, the findings, and the clinical asymmetry, the patient was diagnosed with FEVR.

It was decided to perform peripheral photocoagulation OU. At 3 months, a new WFFA showed persistence of neovascularization in OS (Fig. 5A and B), so photocoagulation was performed again, achieving regression of the neovessels that persisted at 9 months of follow-up (Fig. 6A and B).

In the systemic evaluation of case 1, the patient was found healthy, but he is on treatment with 17.5 mg methotrexate weekly for FEVR.

After the diagnosis of the sister and the findings described by funduscopy and WFFA, the patient was considered as having a mild case of FEVR. The patient is monitored periodically and he remained asymptomatic after 12 months of follow-up.

Discussion

FEVR is a rare entity in which a failure in retinal angiogenesis leads to an incomplete vascularization which causes ischemia that explains the clinical findings. It is usually diagnosed in childhood, although it can occur at any age, unlike ROP, which begins in early childhood. Initial presentation varies from small avascular zones in the peripheral retina to a total retinal detachment. Its evolution is unpredictable.

There are three clinical stages:

– Stage I: alterations in the vitreoretinal interface such as white with or without pressure or cystoid degeneration. Avascular areas in peripheral retina. The patients are asymptomatic.
– Stage II: neovascularization, fibrovascular proliferation, and exudates. Traction can cause macular ectopia.
– Stage III: retinal detachment, usually tractional. It can also be exudative or rhegmatogenous.

Diagnosis is usually clinical. In the fundus, the findings include avascularity of the temporal peripheral retina, neovascularization in the region between the perfused and the avascular retina, exudates, fibrosis and contraction of the peripheral retina, even serous or tractional retinal detachment. Contraction of the peripheral retina can induce stretching and dragging of the

Figure 2. A and B: Wide-field angiographies. Papillary hyperfluorescence and more intense punctate hyperfluorescent choroid spots in OS and inferior hemiretina. Slight avascularity in the temporal and inferior peripheral retina.

Figure 3. Wide-field retinographies. A: OD: Avascularity in temporal periphery. B: OS: Fibrovascular proliferation with retinal vessels stretching and neovascularization.
posterior pole, including macular ectopia, and in severe cases, the formation of retinal falciform folds. Rarely, it can lead to complete retinal dysplasia. WFFA is of great help for diagnosis and follow-up because of its ability to explore the peripheral retina. Sometimes, it facilitates finding abnormalities not easily detected by fundoscopy. It is a useful tool to diagnose familial cases with less severe phenotypes. In our cases, it allowed the detection of avascularity in the peripheral retina that was less evident by fundoscopy.

Recent studies have described microstructural anomalies in the posterior pole and alterations in the vitreoretinal interface present in asymptomatic cases. Spectral domain optical coherence tomography can detect most of these alterations in patients with FEVR, becoming a useful tool in the early diagnosis of this disease; however, more studies are needed. In our cases, macular optical coherence tomographies were normal.

Yuan et al. described several novel clinical findings that could facilitate an early diagnosis of patients with mild FEVR. According to them, the patients with Stage I or II FEVR have several abnormalities in the posterior pole compared to controls, with a significantly larger disc-to-macula (DM) distance as well as a smaller optic disc diameter (DD) with a decreased horizontal diameter. The DD is calculated as the mean between the vertical and horizontal optic DD. In our first case, DD was 1.78 mm in OD and 1.80 mm in OS. DM was 4.56 mm in OD and 5 mm in OS. In our second case, DD was 2.01 mm in OD and 2.05 mm in OS. DM was 5.18 mm in OD and 5.73 mm in OS. In both cases, DM is similar to that obtained by Yuan et al. in the group of patients with FEVR, excluding the OD of the first case that presents a normal DM. However, DD is higher in our two cases, the difference being more striking in the second case, which presents a higher DD than the control group of Yuan et al.

In addition, they describe that the number of vessels arising from the optic disc in patients with FEVR is higher compared to the healthy population. To count the vessels, they drew two circles concentric to the disc.

Figure 4. Wide-field angiographies. A: OS: Avascular peripheral retina. B: OS: Avascular peripheral retina and neovessels with intense leakage.

Figure 5. A and B: Retinography and wide-field angiography of OS. Peripheral photocoagulation and persistence of neovascularization.
and two arcs in each picture. The peripapillary inner reference circle (PIRC) has a diameter of 2 times the optic disc while the peripapillary outer reference circle has a diameter of 4 times the optic disc. The peripapillary temporal inner arc is the portion of the PIRC comprised between the superior and inferior temporal veins of the retina, whereas the peripapillary temporal outer arc would be the portion of the peripapillary temporal outer arc comprised between the superior and inferior temporal veins of the retina (Fig. 7A and B).

In the first of our cases, with clinical findings suggestive of mild FEVR, the number of vessels crossing the PIRC is 23 in OD and 17 in OS. The peripapillary inner arc is crossed by 10 vessels OU. In our second case, the number of vessels crossing the PIRC is 25 in OD and 23 in OS; and the number of vessels crossing the peripapillary inner arc is 12 in OD and 11 in OS. These results are similar to those obtained by Yuan et al. in patients with FEVR except for the number of vessels that cross the PIRC in the OS in our first case, which was lower, probably due to the mild severity of the disease in this patient.

Five genes have been identified that can produce FEVR when they undergo mutations: NDP (X-linked), FZD4 (HAD and HAR), LRP5 (HAD and HAR), TS-PAN12 (HAD and HAR), and ZNF408 (HAD). Mutations in these 5 genes account for around 50% of cases of FEVR. Some of them play a pivotal role in the signaling pathway of ligand-receptor pair Norrin/Frizzled 4, important for the embryonic development of an adequate three-dimensional structure in the retinal vascular network. Mutations in the LRP5 gene can also produce osteopenia and osteoporosis. Therefore, some authors like Gilmour state that all patients diagnosed with FEVR in which genetic tests are not available must undergo a bone densitometry. This allows early diagnosis and treatment that could prevent possible bone fractures.

On the other hand, Shastry et al. reported the case of a family with FEVR with mutation of the FZD4 gene associated with factor V Leiden mutation, suggesting a digenic inheritance of the disease in some cases. However, other authors attribute this association at random. In our cases, the biological father presented thrombophilia...
secondary to factor V Leiden mutation although no hematological alterations were found in our cases.

The treatment consists in laser photocoagulation of the ischemic retina\textsuperscript{12}. Recent studies show that intravitreal therapy with anti-VEGF drugs could be beneficial\textsuperscript{13,14}. Management in early stages is controversial. Some authors recommend assessing each case individually and treating only those in which there is a high risk of progression\textsuperscript{15}. Others, on the other hand, choose an intensive early treatment with laser or cryotherapy\textsuperscript{8}. Treatment in more severe cases with retinal detachment may require surgery with cerclage and/or vitrectomy\textsuperscript{12}.

Prognosis is a variable as a consequence of the different extension of the disease at the time of diagnosis and due to its unpredictable course. Given the severe involvement of the OS in the second case, we started treatment with peripheral photocoagulation in OU due to risk of progression. However, we decided follow-up with regular examinations in the first case. The patients younger than 3 years or those beginning with neovascularization have a worse prognosis\textsuperscript{15}.

Differential diagnosis of this disease includes:

- **ROP**: both can present with avascular periphery, neovascularization, or retinal detachment. ROP presents a steady course with neovascularization at the 37\textsuperscript{th} week of gestation and retinal detachment on the 41\textsuperscript{st} week. It does not progress or recur during the rest of childhood or adult life. Affectation is usually bilateral and symmetric. It is associated with prematurity, low weight and use of oxygen therapy after delivery.

- **Persistent fetal vasculature or persistent hyperplastic primary vitreous**: characterized by the presence of retrolental fibrovascular membranes due to non-regression of the hyaloid vasculature. It is usually unilateral and sporadic. The affected eyes are frequently microphthalmic.

- **Norrpe's disease**: it is associated with a mutation of the NPD gene. It is extremely rare and simulates a severe FEVR, except that it is quite symmetrical. It is a male disease (X-linked inheritance) and may have associated microphthalmos and corneal opacity, which helps to differentiate it from FEVR. The patients often show progressive deafness and mental retardation, whose presence supports the diagnosis.

- **Osteoporosis-pseudoglioma syndrome**: autosomal recessive disorder due to mutations of the LRP5 gene. It presents with congenital or childhood blindness and severe juvenile osteoporosis. Ocular alterations range from phthisis bulbi to less severe vitreoretinal affectations such as hyperplasia, congenital retinal falciform folds, or retinal exudation. The patients also present with short stature, microcephaly, ligamentous laxity, hypotonia, and mental retardation.

- **Incontinentia pigmenti**: it may present with avascularity of the peripheral retina and development of neovascularization during childhood or later. Like FEVR, it is usually asymmetric. It is an X-linked disease and is an intrauterine lethal disease in most males, so the described alterations are seen in women or in the few cases in which males have a 47XXY karyotype, a hypomorphic alteration with less deleterious mutations or somatic mosaicism mutation of a single chromatid. Systemic alterations are the key to diagnosis: neonatal skin lesions (transient), dental hypoplasia, and alopecia.

- **Coats disease**: it may be clinically similar but it is sporadic, idiopathic, and almost always unilateral. It consists of retinal vascular abnormalities with lipid exudates. Most patients are diagnosed before age 20 (2/3 before 10 years of age). 85% are males. It can range from asymptomatic peripheral telangiectasias to exudative total retinal detachment.

- **Toxocariasis**: it is usually unilateral and acquired. It may appear as a peripheral granuloma that can cause retinal traction and falciform folds.

- **Atypical presentations of retinoblastoma or X-linked juvenile retinoschisis** should also be considered.

### Conclusion

FEVR is a rare entity with the capacity to produce a severe deterioration of visual function in patients. Presentation can vary even within the same family. Recent studies have tried to identify microstructural alterations that may be present in the less aggressive phenotypes of the disease. In this sense, spectral domain optical coherence tomography has been used as a useful tool in several studies; however, basic diagnostic and follow-up tests continue to be funduscopic assessment and angiography. In addition, novel anatomical alterations in the posterior pole that can facilitate the early diagnosis of milder cases have been described. On the other hand, advances in genetics have allowed a better understanding of the pathogenesis of this disease and the possible associations with other systemic disorders such as osteopenia or osteoporosis.
Ethical responsibilities

Protection of human or animal subjects. The authors declare that no experiments have been conducted in humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their Institution on the publication of patient data.

Privacy rights and informed consent. The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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