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Diversity of Retinal Vascular Anomalies in Patients with Familial Exudative Vitreoretinopathy

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Purpose: To describe the diversity of clinical findings associated with familial exudative vitreoretinopathy (FEVR) using wide-field angiography and to update the current classification system.

Design: Retrospective case series at a single tertiary referral vitreoretinal practice.

Participants: A total of 174 eyes of 87 subjects were studied.

Methods: A retrospective chart review was conducted of patients with a diagnosis of FEVR between January 2011 and January 2013 at a single tertiary care retina practice. Data were collected from patient charts, including sex, gestational age at birth, age at presentation, referring diagnosis, family history, prior ocular surgery, clinical presentation, and diagnostic imaging in each eye. Inclusion criteria included clinical diagnosis of FEVR in patients referred to our clinic for evaluation of decreased vision. Patients were excluded if a diagnosis of FEVR could not be made.

Main Outcome Measures: Clinical and angiographic findings.

Results: A total of 87 subjects met the inclusion criteria for this study. A broad spectrum of previously undescribed clinical and angiographic findings were associated with FEVR on wide-field angiography. These findings can be grossly divided into anatomic and functional changes. Anatomic changes include aberrant circumferential peripheral vessels, venous and arterial tortuosity, late-phase disc leakage, central and peripheral telangiectasias, capillary anomalies, and capillary agenesis. Functional changes include venous-venous shunting, delayed arteriovenous transit, and delayed or absent choroidal perfusion on fluorescein angiography.

Conclusions: Familial exudative vitreoretinopathy has a wide range of unrecognized or under-recognized clinical and angiographic findings that are easily identified using wide-field fluorescein angiography. These novel findings have led to an update of the original FEVR classification scheme and more complete characterization of early stages of FEVR. *Ophthalmology 2014;121:2220-2227 © 2014 by the American Academy of Ophthalmology.*

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Familial exudative vitreoretinopathy (FEVR) is a rare inheritable disorder of retinal vascular development.[1] Classically, it has been characterized by combinations of macular and vascular dragging, radial retinal folds, tractional retinal detachments, preretinal vitreous organization, vitreous hemorrhage, and subretinal exudation.[1–10] In 1976, Canny and Oliver[2] described the peripheral vascular abnormalities and nonperfusion with standard fluorescein angiography. Familial exudative vitreoretinopathy can exist as a quiescent disease in otherwise asymptomatic patients or can be associated with severe and irreversible vision loss.[3,9,11,12] The latter cases represent a potentially preventable cause of vision loss in patients younger than 30 years of age if recognized early and managed aggressively.[9,11,13]

Familial exudative vitreoretinopathy is a heterogeneous disorder with variable patterns of inheritance, expressivity, and disease course.[3,12,14–20] Mild forms of the disease often are asymptomatic and show only peripheral vascular abnormalities, such as a peripheral avascular zone, vitreoretinal adhesions, venous-venous anastomoses, and supernumerous vascular branching.[3,9,12] The vascular changes associated with FEVR are the most notable and common among these findings. We recently demonstrated that vascular changes are most easily recognized (and sometimes only recognized) using wide-field angiography.[21] More severe manifestations of FEVR occur in later stages and include neovascularization, subretinal and intraretinal hemorrhage, exudates, and vascularized preretinal membranes that can lead to retinal folds, macular ectopia, and retinal detachment due to vitreoretinal traction.[3,12] Symptoms, if present, typically take a progressive course during childhood and adolescence, with progression usually stopping by age 20 years.[9,22] However, late progression also may occur, with visually significant consequences.

In 1998, Pendergast and Trese[12] described a 5-stage FEVR classification scheme and the outcomes of treatment for the various stages, which were validated in subsequent studies.[9] Ranchod et al[9] described the clinical

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characteristics of FEVR in a retrospective review of 273 eyes of 145 patients but without the advantage of wide-field angiography. Of note, a positive family history for FEVR was obtained in 26 patients (18%), and an additional 28 patients (19%) had a family history of ocular disease not diagnosed as FEVR but potentially consistent with undiagnosed FEVR. We recently showed that up to 58% of asymptomatic family members of patients with FEVR may have subclinical findings that are largely or only apparent on wide-field fluorescein angiography.[13] Given the high rate of vascular abnormalities in asymptomatic subjects with early stage FEVR, it is reasonable to revisit the clinical findings and angiographic features that characterize the disease.

We describe the spectrum of clinical and angiographic findings associated with FEVR on wide-field angiography. These findings may have been difficult to see on clinical examination and standard fluorescein angiography in the past. We also incorporate these angiographic and clinical features in an updated FEVR classification scheme based on the original work of Pendergast and Trese.[12]

Methods

A retrospective chart review of patients with a diagnosis code for FEVR (International Classification of Diseases, 9th revision, Code 362.73) was conducted between January 2011 and January 2013 at a single tertiary care vitreoretinal practice. This date range was selected on the basis of the availability of wide-field angiography in the clinic starting in 2011. Before this date, wide-field angiography to the ora serrata was only performed in children under anesthesia using the RetCam (Clarity Medical Systems, Pleasanton, CA). Institutional review board approval for the data collection and study was granted by the Western Institutional Review Board. The study was conducted in a Health Insurance Portability and Accountability Act–compliant fashion, and research adhered to the tenets of the Declaration of Helsinki. Patients were included if a diagnosis of FEVR was given to the patient after the initial examination. To meet the diagnostic criteria for FEVR, patients had to have all 3 of the following: (1) a lack of peripheral retinal vascular development, (2) full-term or preterm birth with a disease tempo not consistent with retinopathy of prematurity, and (3) variable degrees of nonperfusion, vitreoretinal traction, subretinal exudation, or retinal neovascularization occurring at any age. Patients were excluded if a diagnosis of FEVR was confounded for any reason including if both eyes had undergone prior invasive posterior segment surgical procedures (vitrectomy or scleral buckle). Data collected from charts of patients included sex, gestational age at birth, birth weight, age at presentation, referring diagnosis (if provided), family history, prior ocular surgery, medical history, and clinical presentation in each eye. Family members were included in the study cohort if they were the full-blood relative of the patient and were willing to provide clinical history and undergo examination or diagnostic imaging as described in a recent publication.[13] The clinical cohort well described by Kashani et al[13] also was part of the clinical cohort of this current study (although 13 new patients were added to the cohort since the publication of the previous article). Tables 1 and 2 (available at www.aaojournal.org) summarize the demographic characteristics of the current cohort.

Wide-field angiography was performed using a Retcam 2 (Clarity Medical Systems) or Optos 200Tx (Optos Inc., Dunfermline, UK) imaging device. The Retcam was used for young patients requiring examination under anesthesia. Special care was taken to obtain complete views of the periphery in these cases to evaluate for peripheral retinal pathology. This was done using the standard Retcam lens and by tilting the camera angle until the ora was partly in view. In some cases, this was done with the aid of simultaneous scleral depression. In all cases, fluorescein angiography was performed during examinations done under anesthesia using a standard dose of commercially available intravenous fluorescein sodium (pediatric dose, 35 mg/10 lb). Optos imaging was performed in the clinic on patients and relatives who could tolerate both color photography and fluorescein angiography.

Patients were staged using the clinical staging criteria for FEVR described previously[12] (Table 3). This staging system was designed for classification of the clinical and angiographic features of FEVR and is reviewed briefly in this article. Stage 1 disease represents only avascular peripheral retina and is almost always an angiographic diagnosis. Stage 2 disease represents avascular retina with (2B) or without (2A) the clinical appearance of exudate or angiographic appearance of leakage in the late phase. Stage 3 disease represents macula-sparing retinal detachment that is tractional or exudative (commonly a combined mechanism). Stage 3A lacks any clinical signs of exudation, subretinal fluid, or leakage on angiography, whereas stage 3B has 1 or more of these

Table 3. Familial Exudative Vitreoretinopathy Clinical Staging System

Stage	Description
1	Avascular retinal periphery without extraretinal vascularization
2	Avascular retinal periphery with extraretinal vascularization
2A	Without exudate
2B	With exudate
3	Extramacular retinal detachment
3A	Primarily exudative
3B	Primary tractional
4	Macula-involving retinal detachment
4A	Primarily exudative
4B	Primarily tractional
5	Total retinal detachment
5A	Open funnel
5B	Closed funnel
Revised Familial Exudative Vitreoretinopathy Clinical Staging System	
1	Avascular periphery or anomalous intraretinal vascularization
1A	Without exudate or leakage
1B	With exudate or leakage*
2	Avascular retinal periphery with extraretinal vascularization
2A	Without exudate or leakage
2B	With exudate or leakage*
3	Extramacular retinal detachment
3A	Without exudate or leakage
3B	With exudate or leakage*
4	Macula-involving retinal detachment
4A	Without exudate or leakage
4B	With exudate or leakage*
5	Total retinal detachment
5A	Open funnel
5B	Closed funnel

*Indicates need for close observation or laser ablation of retinal nonperfusion and extraretinal or intraretinal vascularization as demonstrated by fluorescein angiography.