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Familial Exudative Vitreoretinopathy

Spectral-Domain Optical Coherence Tomography of the Vitreoretinal Interface, Retina, and Choroid

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Purpose: The in vivo microstructural features of familial exudative vitreoretinopathy (FEVR) have not been well described. We present new anatomic features of FEVR with functional and genetic correlations.

Design: Consecutive, retrospective, observational case series.

Participants: Patients with FEVR treated from 2009 to 2014.

Methods: We identified 346 patients with FEVR. Those imaged with spectral-domain optical coherence tomography (SD OCT) with or without enhanced depth imaging (EDI) were included, and images were correlated with best-corrected visual acuity (BCVA), widefield angiography, fundus autofluorescence (AF), and *wnt* signaling pathway mutations.

Main Outcome Measures: Exploratory SD OCT findings and BCVA.

Results: A total of 225 imaging sessions were acquired in 74 eyes from 41 patients. Mean age was 19.0 years. Sixty-seven eyes (91%) had interpretable images, of which 50 (75%) had anomalous microstructural findings; all eyes with FEVR severity of stage 2 or greater had abnormalities. A broad spectrum of features were identified: various forms of posterior hyaloidal organization, vitreomacular traction (VMT), vitreopapillary traction, vitreo-fold traction, vitreo-laser scar adhesion, diminished foveal contour, persistent fetal foveal architecture, cystoid macular edema (CME), intraretinal exudates and subretinal lipid aggregation, dry or edematous radial folds, and disruption of the ellipsoid zone. Mean foveal, central macular, and choroidal thicknesses were 305±145 μm, 337±160 μm, and 216±64 μm, respectively. In stages 1 to 2, greater foveal and central macular thicknesses (*Rho* = 0.493, 0.544, respectively; both $P < 0.001$) correlated with poorer BCVA, but not choroidal thickness (*Rho* = 0.032; $P = 0.868$). Posterior hyaloidal organization ($P < 0.001$), VMT ($P < 0.001$), CME ($P < 0.001$), exudation ($P < 0.001$), and disruption of the ellipsoid zone ($P < 0.001$) were associated with poorer BCVA. Disruption of the ellipsoid zone ($\beta = 0.699$; $P < 0.001$) and posterior hyaloidal organization ($\beta = 0.289$; $P = 0.011$) retained significance in multivariate modeling ($R^2 = 0.627$; $P < 0.001$). Spectral-domain OCT detected all cases of angiographic edema and areas of outer retinal dysfunction that were hypoautofluorescent on AF. Microstructural-genetic associations were not identified.

Conclusions: Spectral-domain OCT imaging identified microstructural anomalies in the majority of patients with FEVR. *Ophthalmology 2015;122:2270-2277 © 2015 by the American Academy of Ophthalmology.*

Familial exudative vitreoretinopathy (FEVR) is a hereditary abnormality in retinal vascular development caused by *wnt* signaling defects.[1–3] Anomalous or incomplete retinal vascularization is the primary pathology, with varying degrees of secondary peripheral ischemia and subsequent complications.[4] Classic ophthalmoscopic and angiographic findings include peripheral avascular retina flanked posteriorly by abnormally branching vessels, retinal neovascularization, exudation, dragging of vasculature, hyaloidal contraction, and tractional retinal detachment.[4–6] Fluorescein angiography is critical in the diagnosis and management of FEVR, and the recent advent of widefield angiography has permitted further characterization of angiographic phenotypes. This has allowed earlier diagnosis and treatment of patients, and, in particular, their family members, many of whom demonstrate milder phenotypic variants.[7]

Identifying milder phenotypes remains a significant challenge: although index patients commonly present during childhood with advanced disease, less-advanced cases of FEVR may remain undetected in pedigrees for generations because of variable expressivity and seemingly normal gross anatomy of these mildly affected individuals.[8] Perhaps understanding the more subtle changes in these milder stages could allow for improved identification of patients, who could then benefit from widefield angiography for more definitive diagnosis.

However, the in vivo microstructural anatomy of FEVR remains largely unknown. Early histopathologic studies reported features of enucleated eyes with end-stage disease,[9–11] but histopathologic diagnosis is impractical. The advent of optical coherence tomography (OCT) allows high-resolution in vivo evaluation of posterior segment microstructures. With

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spectral-domain OCT (SD OCT) and enhanced depth imaging (EDI), our understanding and treatment paradigms for many macular diseases have been enriched. However, OCT imaging in FEVR has remained largely unexplored, presumably because of the rarity of the disease and the dominant focus of previous studies on peripheral findings.[5,7,8,12–14] We hypothesized that FEVR would be amenable to exploratory SD OCT analysis, given its known effects on the vitreoretinal interface. We also hypothesized, on the basis of our collective clinical and surgical experiences, that there are heretofore underappreciated pathologic microstructural macular features in FEVR.

We report the findings of these analyses and identify microstructural features of FEVR; their functional correlations with vision, angiographic, and autofluorescent findings; and the new implications for current and future management strategies.

Methods

This study is a single-center, retrospective, noncomparative case series of patients with a clinical or genetic diagnosis of FEVR who were treated at Associated Retinal Consultants. Participants were identified via billing codes, surgical logs, genetic databases, and image banks, during the 6-year period from January 1, 2009, to December 31, 2014. Patients who underwent SD OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) imaging with or without EDI were included. Those with only time-domain OCT were excluded, as were patients with concurrent non-FEVR vitreoretinal pathology. Institutional Review Board/Ethics Committee approval was obtained. The study complied with the Health Insurance Portability and Accountability Act of 1996 and adhered to the tenets of the Declaration of Helsinki.

Data collection included demographics, including birth history, at the first imaging session, best-corrected visual acuity (BCVA) using automated refracting Snellen acuity charts, highest FEVR staging, laser and surgical treatment history, and total number of imaging sessions. The first imaging session and BCVA were recorded, but all imaging sessions were reviewed to confirm imaging findings. Staging was determined as previously described: stage 1, avascular periphery; stage 2, avascular periphery with neovascularization; stage 3, macula-sparing retinal detachment; stage 4, macula-involving retinal detachment; stage 5, complete retinal detachment.[4,8]

Spectral-domain OCT/EDI images were analyzed for vitreoretinal interface, preretinal, intraretinal, subretinal, and choroidal abnormalities on the basis of image interpretations made during clinical encounters by the senior authors (K.A.D., M.T.T., A.C.), reviewed systematically by 1 author (Y.Y.), and examined by all authors if there were any discrepancies. Foveal thickness was measured manually from the internal limiting membrane to the outer boundary of the retinal pigment epithelium (RPE). Central macular thickness was defined as the average thickness of the 1-mm diameter circle centered on the fovea, with autosegmentations manually corrected. Subfoveal choroidal thickness in EDI images was measured from the outer border of the RPE to the choroidal-scleral junction.[15] Macular measurements were excluded for stages 3 to 5 because of poor patient fixation that often precluded macular volume scans and the unreliability of determining precise foveal centers because of dragged anatomy.

Corresponding BCVA, color photography, fluorescein angiography, and fundus autofluorescence (AF) were examined for functional correlations. Photography and fluorescein angiography during examinations under anesthesia were obtained using the RetCam II (Clarity Medical Systems, Pleasanton, CA) and the 130° widefield D1300 lens. The 200Tx (Optos, Marlborough, MA) was used for ultra-widefield (200°) photography, fluorescein angiography, and fundus AF for participants who could tolerate outpatient angiography.

Genetic sequencing is offered for our patients with suspected FEVR. The exons of *FZD4* (11q14.2) and *NDP* (Xp11.3) are initially sequenced. If mutations are not identified, *TSPAN12* (7q31.31) would be sequenced and *LRP5* (11q13.2) as needed. Detailed sequencing techniques have been published.[2,3]

Snellen BCVAs were converted to logarithm of the minimum angle of resolution units for statistical analyses. Spearman's rank correlation was used to determine the correlation coefficients of continuous variables. Analysis of variance testing was performed to identify differences in gene mutations and dichotomous independent variables. Spectral-domain OCT features associated with poorer BCVA were identified using univariate linear regression, and multivariate linear modeling was performed using variables with $P < 0.1$ during univariate analysis. Statistical tests were 2-tailed, and significance was defined as $P < 0.05$. Stata version 9.0 (StataCorp LP, College Station, TX) was used for statistical analyses.

Table 1. Demographic and Clinical Features of Patients with Familial Exudative Vitreoretinopathy undergoing Spectral Domain Optical Coherence Tomography

Feature	No. (%)
Age, yrs (n = 41 patients)	
Mean (median, range)	19.0 (15.4, 2.4–57.0)
Sex	
Male	21 (51)
Female	20 (49)
Eye imaged (n = 74 eyes)	
Right	40 (54)
Left	34 (46)
Highest FEVR staging	
Stage 1	33 (45)
Stage 2	19 (26)
Stage 3	2 (3)
Stage 4	17 (23)
Stage 5	3 (4)
Previous treatment	
None	15 (20)
Laser only	38 (51)
Laser and anti-VEGF	4 (5)
Incisional surgery	17 (23)

FEVR = familial exudative vitreoretinopathy; VEGF = vascular endothelial growth factor.

Results

A total of 346 patients with FEVR were identified during the study period. Within this cohort, 74 eyes from 41 patients (12%) underwent 225 imaging sessions with SD OCT/EDI imaging. The demographic and clinical features are summarized in Table 1. None of the patients had a history of premature birth. All patients with stage 2 or higher had prior treatment.

Interpretable SD OCT images were acquired in 67 eyes (91%). Five noninterpretable imaging sessions were for stage 4 eyes with poor vision and inability to fixate, and 2 were from a patient too young to participate fully. Of the eyes with interpretable images, abnormal findings were identified in 50 eyes (75%). All eyes