Macular Microvascular Findings in Familial Exudative Vitreoretinopathy on Optical Coherence Tomography Angiography

DARSI
Duke Advanced Research In SS/SDOCT Imaging

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INTRODUCTION

- Familial exudative vitreoretinopathy (FEVR):
  - Rare hereditary disorder[1]
  - Associated with genetic mutations in the Wnt signaling pathway necessary for retinal angiogenesis[2,3]
  - Characterized by incomplete and anomalous retinal vascular development
  - Abnormalities have only been reported to be in the periphery[4]
- Optical coherence tomography angiography (OCTA) can be used to noninvasively image retinal microvasculature without use of contrast dye
- OCTA provides depth-resolved images of the superficial and deep vascular complexes (SVC and DVC, respectively)[5]
- Purpose: To determine if patients with familial exudative vitreoretinopathy (FEVR) have abnormalities in the macular microvasculature

METHODS

- Study approved by IRB, adhered to HIPAA & Declaration of Helsinki; obtained parental consent for each subject
- Prospective, observational case series
- Imaged 22 eyes of 6 FEVR and 6 control patients with OCTA
  - FEVR: mean age 17.5±7.5 yrs., median 20 yrs., range 2-25 yrs.
  - Control: mean age 18.3±15.8 yrs., median 15 yrs., range 1.25-64 yrs.
  - OCTA images were obtained using the investigational Spectralis tabletop and Flex units[6] (Figure 1) in the clinic and operating room, respectively
- Masked graders analyzed the OCTA images (SVC and DVC) for abnormal vascular features (Table 1)
- Compared OCTA to fluorescein angiography (FA) findings

Figure 1. OCTA images were captured using the investigational Spectralis tabletop and portable Flex units

Abnormal Vascular Feature	Definitions/Defining Characteristics when Compared to Controls
Abnormal FAZ shape	Elongated, abnormally stretched FAZ or overall irregularity in shape
Increased or decreased vessel density	Areas of subjectively increased or decreased concentration of vessels
Disorganized vessel pattern	Deviation from expected patterns of larger caliber vessels branching into finer vessels in the SVC and a regular and uniform lacy pattern in the DVC
Vessel dilation	Any vessels of larger than expected diameter
End-bulbs	Abnormally truncated vessels that exhibited bulbous ends; stub-like terminations
Vascular curls and loops	Evidence of vascular shunting, anastomoses, or curling patterns not seen in controls
Straightened vessels	Abnormally dragged or more linear-appearing vessels than expected

Table 1. Definitions of Qualitative OCT-A Grading Characteristics in FEVR

RESULTS

OCTA of 7 of 11 eyes with FEVR displayed abnormal macular findings in the microvasculature (Table 2, Fig. 2):

- SVC: dilation, disorganization, straightening, heterogeneous vessel density, and curls
- DVC: areas of decreased density, disorganization, curls, and end-bulbs

Pt eye	FEVR Stage	Macular OCT-A findings			Fluorescein angiography findings	
		FAZ	SVC	DVC	Macula	Periphery
1, OD	2a	Normal	Normal	Normal	Mild vessel straightening	Temporal nonperfusion, leakage at the border of perfused/nonperfused retina
1, OS	2b	Normal	Normal	Normal	Normal	Temporal nonperfusion, small peripheral vascular loops, staining of prior laser
2, OD	2b	Normal	Normal	Normal	Normal	Staining of laser, leakage in inferotemporal periphery
2, OS	2a	Normal	Normal	Normal	Normal	Temporal nonperfusion, no leakage
3, OD	2b	Abnormal	Decreased density, dilated vessels	Decreased density, disorganized, end bulbs, curls	Normal	Leakage in the mid-periphery, mild peripheral nonperfusion, staining of prior laser
3, OS	2b	Abnormal	Decreased density, disorganized, dilated vessels, curls	Decreased density, disorganized, end bulbs, curls/loops	Mild vessel straightening	Staining 360-degree laser treatment
4, OD	3b	Abnormal	Disorganized, dilated, straightened vessels	Decreased, density, disorganized, end bulbs	Macular dragging and straightening, hyper-fluorescence of preretinal fibrosis	Nonperfusion in the periphery, leakage in inferotemporal periphery, hyperfluoresence of preretinal fibrosis
4, OS	2b	Abnormal	Disorganized, dilated, straightened vessels	Decreased density, disorganized, end bulbs, curls	Significant macular dragging and straightening	Peripheral nonperfusion and leakage, temporal vascular shunting
5, OD	3b	Abnormal	Decreased density, disorganized, dilated, straightened vessels, curls	Decreased density, disorganized, end bulbs, curls	Mild staining of macular pigmentary changes	Leakage in temporal periphery, staining of prior laser
5, OS	5	Not imaged due to bullous keratopathy				
6, OD	5	Abnormal	Decreased density, disorganized, dilated, straightened vessels	Decreased density, disorganized, end bulbs	Macular dragging, vessel straightening	Staining of peripheral chorioretinal scarring
6, OS	3b	Abnormal	Decreased density, disorganized, dilated, straightened vessels, curls	Decreased density, disorganized, end bulbs	Macular dragging and straightening, telangiectatic vessels and leakage	Staining of peripheral chorioretinal scarring, late peripheral leakage

Table 2. Retinal vascular features on OCTA and fluorescein angiography (FA) of patients with FEVR.

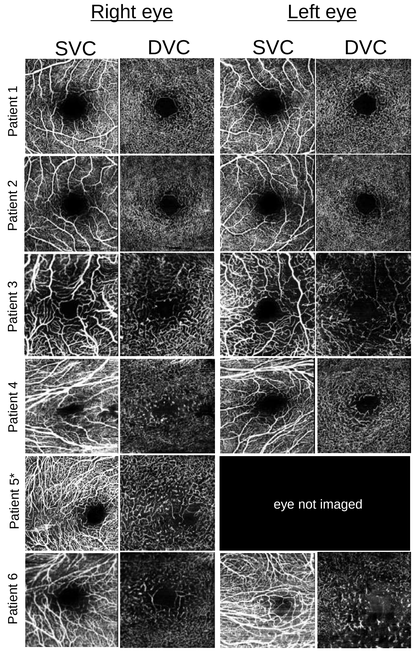

Figure 2. OCTA images of the SVC and DVC of the right and left eyes of patients with FEVR.

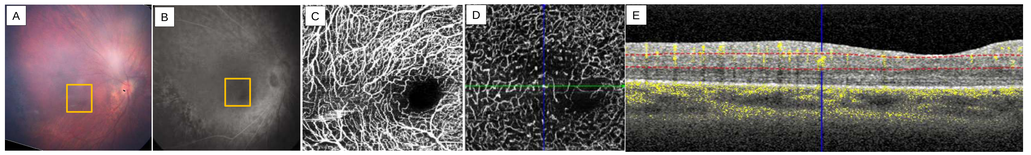

Figure 3. A patient* with FEVR and a mutation in the Wnt-pathway LRP5 gene. The right eye (A, fundus photo, and B, FA) underwent peripheral laser and cryotherapy. OCTA of the macula showed abnormalities in the SVC (C) and DVC (D). (E) OCT/OCT-A B-scan of the location of the green line in (D) is shown, with the blue cross-hair over one of the end-bulbs. The dotted red lines indicate the segmentation of the retinal layers used to form the en face OCTA image of the DVC.

DISCUSSION

- End-bulbs could correlate with vessel termination, with suspended red blood cells in motion captured on OCT-A within the stubs[7]
- Association with animal models with defective Wnt signaling
  - DVC vascular end-bulbs visible on OCT-A in humans (including one with documented LRP5 mutation) parallel mouse models of FEVR with mutations in the Wnt signaling pathway[8]
  - Mice with defective Norrin/Fzd4 signaling or LRP5 signaling demonstrate retinal hypovascularization with delayed radial migration of endothelial cells and defective arborization of deeper capillaries following the vertical endothelial innervation from the vitreal surface[9]
- Limitations
  - Small sample size
  - Cross-sectional study cannot assess longitudinal development
  - Heterogeneity of FEVR disease stages, treatment history, and clinical findings
- Next steps
  - Increase sample size of patients with FEVR
  - Correlate with histology of human retinas with FEVR

CONCLUSION

- OCTA revealed distinctive depth-resolved macular vasculature abnormalities in patients with FEVR.
- FEVR may not only be a disease of peripheral retinal but also of the macula and deep retinal vasculature
- Unique vascular patterns may assist in diagnosis and prognosis

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