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Identification of Retinal Vascular Lesions using Ultra-Wide Field Angiography in Hereditary Hemorrhagic Telangiectasia Patients

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Abstract

Purpose: To determine the presence and characterize location of retinal vascular lesions in patients with hereditary hemorrhagic telangiectasia.

Design: Prospective cross-sectional pilot descriptive study.

Participants: Eighteen patients (age 22 to 65) with a clinical diagnosis of hereditary hemorrhagic telangiectasia.

Methods: Patients completed the Visual Function Questionnaire-25 and underwent a single study visit with dilated ophthalmic examination, optical coherence tomography angiography (OCTA) and fluorescein angiography (FA) with widefield imaging.

Main Outcome Measures: Presence of retinal vascular abnormalities in 1 or more quadrants identified on widefield FA, VFQ-25 scores, retinal vessel architecture on FA and OCTA, and dilated ophthalmic exam findings.

Results: Of the 18 patients recruited, fine telangiectatic vessels with capillary dilation and tortuosity were identified in 78% by FA imaging.

Conclusions: In the first FA and OCTA analysis of the retina of unrelated HHT subjects, we found a high rate of temporal and nasal telangiectasias. These telangiectasias were more apparent

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in older patients, suggesting that they may appear in later stages of HHT development. No abnormalities of the macular vasculature and architecture were identified, explaining the generally well-preserved visual acuity. Temporal and nasal telangiectasias may have clinical significance in a patient's risk for retinal hemorrhage and likely warrant periodic surveillance by annual FA imaging.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a genetic vasculopathic syndrome with an incidence rate of 1 in 10,000 patients/year. The majority of cases are caused by an autosomal dominant mutation in one of four genes that are critical for regulating blood vessel development and response to transforming growth factor β signaling.¹ Clinically, HHT is diagnosed according to the Curacao criteria; 1) mucocutaneous telangiectasias; 2) recurrent epistaxis; 3) vascular telangiectasias in the GI tract or arteriovenous malformations in the lungs, brain, liver, or spine; and 4) a family history of affected first-degree relatives.² Due to recurrent and persistent bleeding in one or more organs and associated comorbidities, patients often benefit from care by a multidisciplinary team of providers.

Ocular manifestations among HHT patients, while not a criterion for diagnosis, have been described in as many as 45–65% of patients.^{3–5} Hemorrhagic epiphora due to conjunctival telangiectasias is the most common ophthalmologic complaint, with a prevalence of approximately 35–42%.^{3–5} A variety of retinal lesions have also been described in HHT patients, including dilation and tortuosity of veins, neovascularization, and parafoveal telangiectasias.^{6, 7}

Loss of vision secondary to retinal and vitreous hemorrhage in HHT patients with prior known retinal vascular abnormalities have additionally been reported,^{8, 9} suggesting that retinal vascular lesions among these patients may predispose to vision threatening hemorrhage.

Several prior studies have investigated the prevalence of intraocular lesions among HHT patients. Vase et al identified retinal telangiectasias in 1 of 47 (2%) patients,⁵ and a second study by Brant et al identified retinal lesions in 2 of 20 (10%) HHT patients.³ However, these studies evaluated patients on routine ophthalmologic examination with slit lamp examination and dilated fundoscopic evaluation. Only 1 of 47 patients with a suspicious finding during routine examination underwent fluorescein angiography (FA) imaging in the Vase et al study,⁵ and none underwent FA in the Brant et al study, precluding identification of subtle vascular alterations imperceptible on fundoscopy.³

FA is routinely used to detect subtle vascular abnormalities of the retina and choroid, such as diabetic retinopathy and age-related macular degeneration.¹⁰ A prior study by Rinaldi et al employed routine fluorescein angiography in the evaluation of retinal abnormalities among 8 related family members with HHT with a single mutation in the ALK1 gene and identified choriocapillaris atrophy in as many as 3/8 (38%) patients.¹¹

In this cross-sectional study, we sought to determine the prevalence retinal abnormalities detected by wide-field FA in HHT patients and to describe the distinct pattern and anatomic

location of FA- and OCT- detected retinal abnormalities, as well as to correlate these abnormalities with functional visual disturbances. Our study is unique because of the combined approach of widefield FA to examine the far peripheral retina and OCTA to examine the central macula. In addition, our cohort represents participants with active HHT who have many systemic lesions requiring therapy.

Methods

Subjects:

Individuals aged 18–65 who had previously been diagnosed with HHT by the Curacao Criteria² were recruited from the practices of two Washington University physicians (Jay Piccirillo, Murali Chakinala) specializing in treatment of HHT patients and the Cure HHT foundation. Of 128 patients identified by administrative data, 18 subjects enrolled in the study (see Figure 1) between February 2017 and May 2018. Exclusion criteria included 1) active conjunctival hemorrhage or bloody epiphora, 2) contraindications to fluorescein dye including: allergic hypersensitivity to fluorescein, pregnancy, history of severe reaction to any allergen, renal failure or on dialysis, severe asthma, or significant cardiac disease, 3) any ophthalmic pathology precluding retinal imaging (e.g. dense cataract, corneal disease). As this study was designed to be a descriptive evaluation of retinal lesions in HHT patients, no control subjects were recruited as it was deemed unethical to subject individuals without known disease or pathology to fluorescein angiography without an indication.

Procedures:

All participating subjects were evaluated at the Washington University Eye Center. The study visit included completion of Visual Function Questionnaire-25^{12, 13} an HHT severity questionnaire, and a dilated eye exam. Optical coherence tomography angiography (OCTA) images were collected on the Optovue Avanti RTVue XR machine (Optovue, Fremong, CA). Fluorescein angiography images were collected on OPTOS Ultra Wideview California AF P200DTX (Optos, Marlborough, MA, USA).

Assessment of Images:

OCTA measurements were automated using the Optovue software from six OCT images per eye (right and left), which were treated separately rather than averaged, and thus collected in an objective manner. Each data point was reviewed to evaluate for potential confounding pathology (e.g. epiretinal membrane) or data collection error (e.g. motion artifact). Data outcomes collected included measurement of foveal and parafoveal thickness; macular, foveal, and parafoveal vascular density; and foveal avascular zone (FAZ). Fluorescein angiography images were reviewed by two authors (BEO, RSA), who have significant experience with Optos imaging. Subjective information was collected on vascular changes found in HHT patients beyond normal peripheral, age-appropriate changes.

Statistical Analysis:

Basic descriptive statistics were conducted on IBM SPSS Statistics for Windows, version 24.0 (IBM Corp). OCTA data was compared to normative values available from Optovue for

foveal and parafoveal thickness and to prior research for foveal and parafoveal vessel density.^{14, 15} A 2-sided α with threshold of 0.05 was used for one sample t-test.

IRB Approval:

This study received institutional IRB approval at Washington University School of Medicine in St. Louis on February 15, 2017 (IRB ID: 201612105) and adhered to the tenets of the Declaration of Helsinki and the provisions of the Health Insurance Portability and Accountability Act.

Results

Eighteen patients were enrolled in the study. The mean age of patients was 52.3 years (range 22–65 years). Of the 18 patients, 12 (67%) were female, 1 (6%) had Type 2 diabetes mellitus, and 5 (28%) had hypertension. All patients met Curacao criteria for HHT diagnosis (Table 1): 16 (88%) had recurrent epistaxis, 13 (72%) had visceral arteriovenous malformations, 18 (100%) had telangiectasias on the lips, eyes, face, GI tract or other skin, and 17 (94 %) had a family history of the disease. This study included one mother-son pair and one set of siblings, representing 16 total families.

All patients reported symptomatic bleeding with 11 (61%) patients receiving oral or IV iron treatment, 3 (17%) requiring blood transfusions, and 10 (56%) undergoing sclerosing therapy for epistaxis. Prior complications of HHT requiring hospitalization in our study population included anemia or blood transfusion (10), hemoptysis or hemothorax (3), stroke or intracranial hemorrhage (1), seizure (1), and brain abscess (1). All patients had a history of recurrent epistaxis with 9 (56%) patients experiencing active bleeds at least daily, 8 (50%) of patients experiencing bleeds > 5 minutes, and 7 (41%) patients experiencing gushing epistaxis. At the time of the study, 7 (39%) patients had self-reported anemia.

Ophthalmic examination:

Mean best-corrected visual acuity was LogMAR=0.033 in the right eye and LogMAR=0.056 in the left eye. Two of the 18 patients reported subjective deterioration of vision over the last few years. The average composite VFQ score was 88.9 (Standard deviation: 6.8). No vascular abnormalities were noted on dilated ophthalmoscopy. Other findings of the ophthalmic exam are detailed in Table 2.

OCTA findings:

OCTA data was collected from 29 eyes from 18 patients; data from 5 eyes were omitted due to significant motion artifact interfering with accurate analysis. Mean foveal avascular area (SD) was $0.253 \pm 0.11 \text{ mm}^2$ (mean difference: -0.013 mm^2 ; 95%CI: -0.06 to 0.03 mm^2). Mean foveal vessel density was $31.96\% \pm 5.21\%$ (mean difference: 2.06% ; 95%CI: 0.15 to 3.97%); mean parafoveal density was $53.73\% \pm 3.09\%$ (mean difference: -0.47% ; 95%CI: -1.6 to 0.67). Mean foveal thickness was $258.84 \pm 24.46 \mu\text{m}$ (mean difference: $3.64 \mu\text{m}$; 95%CI: -5.33 to $12.6 \mu\text{m}$); mean parafoveal thickness was $319.26 \pm 12.25 \mu\text{m}$ (mean difference: $-0.34 \mu\text{m}$; 95%CI: -4.84 to $4.15 \mu\text{m}$).

FA findings:

Thirty of 36 eyes (83%) from 14 of 18 study subjects (78%) were found to have peripheral areas of fine telangiectasias, with capillary dilation and tortuosity upon review of FA imaging (Figure 2). Data from 6 eyes were omitted due to poor quality of images. The majority of patients had telangiectasias in either temporal or nasal retina; however, three subjects had lesions in more than one quadrant. These findings were not readily apparent on color fundus photography (Figure 2).

Discussion

Ocular involvement is not included in the clinical diagnostic criteria of HHT. However, common ocular symptoms include bloody epiphora, and conjunctival telangiectasias. Previously reported retinal abnormalities include dilation and tortuosity of retinal vessels, parafoveal telangiectasias, and neovascularization, though reporting of intraocular lesions in HHT patients is highly variable and is not accompanied with information regarding the systemic burden of HHT on patients.^{6, 7}

This study is the first in-depth vascular analysis of the peripheral retina of HHT patients using FA and OCTA. The majority of patients in our cohort (78%) were found to have peripheral telangiectasias in either the temporal or nasal retina. OCTA analysis revealed no vascular or architectural alterations within the macula, and no patient had clinically actionable lesions, which may explain the relatively well-preserved visual acuity in this cohort of study participants. Only 2 patients had subjective deterioration of visual acuity, and notably, both patients had peripheral telangiectasias temporally.

Notably, the only two subjects with no findings in either eye were younger than the mean age. It is plausible that these subjects may develop telangiectasias later in life, as nearly all patients above the mean age had peripheral telangiectasias; however this study was not designed to follow subjects longitudinally. For example, while epistaxis emerges as an early clinical finding at an average of 12 years of age among HHT patients,¹⁶ telangiectasias commonly appear 10–30 years after the onset of epistaxis, and symptomatic gastrointestinal bleeding does not present until the 5th or 6th decade.¹⁷ This suggests that retinal telangiectasias may develop as a late complication of HHT. However, the natural history of vascular malformations across the lifespan of HHT patients is not well understood.¹⁸

Prior studies have shown rates of retinal lesions varying from 0 to 10%^{3–5} in all patients, with no consistent topographic location of these lesions. Two prior case series of patients with HHT also reported fine telangiectic capillaries and tortuous arteriovenous malformations,^{19, 20} although these were found in a minority of study subjects. The authors in one of these studies³ acknowledged that subtle retinal vascular alterations may have been overlooked in the remaining subjects that did not have fundoscopic abnormalities and were consequently not examined by FA.³ Certainly, the lack of obvious findings on clinical examination in all of our study subjects would support this acknowledgement. The novel use of FA with widefield imaging likely explains the disparity in reported incidence of retinal findings in our cohort compared to those previously published. The clinical significance of these lesions may relate to the increased risk of patients with known retinal vessel

malformations developing vision-threatening hemorrhages.^{8,9} Our study shows that patients with HHT have a much higher proportion of vascular anomalies as compared to other patients with retinal vascular diseases, such as diabetes and age-related macular degeneration. However, intraocular lesions in HHT patients predominately affect the peripheral vasculature, while retinal vascular diseases typically affect the more metabolically active central vasculature of the retina.

Strengths of our study include enrollment of non-related patients, increasing generalizability to a larger spectrum of HHT patients compared to prior studies.¹¹ Additionally, we assessed patients undergoing active treatment for HHT-related multi-system pathologies, whereas prior studies have not assessed disease severity among patients.^{3,5} However, our study has its limitations. Of 118 individuals, we were only able to contact 55 individuals and recruit 18 participants, which may be reflective of the tertiary care setting. The lack of genetic testing of all our study subjects limits our ability to determine if these findings are associated with specific genotypes.

Based on these results we would recommend HHT patients follow up with an ophthalmologist or retinal specialist to obtain baseline FA with widefield imaging to document subtle, peripheral retinal vascular alterations, in addition to annual dilated exams with repeated FA to monitor for progression of disease or presence of any lesions that warrant more frequent monitoring. In addition to providing improve surveillance of any lesions that may put patients at increased risk of vision-threatening hemorrhage, increased monitoring with FA would improve our understanding of the natural history of the retinal involvement in HHT and provide longitudinal assessment of the evolution of these lesions.

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A majority of patients with hereditary hemorrhagic telangiectasia have peripheral areas of fine telangiectasis, with capillary dilation and tortuosity not appreciable on routine ophthalmoscopy, indicating a need for baseline and annual testing in these patients.

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Figure 1:
Participant Recruitment and Enrollment

Figure 2: Example widefield color fundus photographs and corresponding angiograms from study subjects with Hereditary Hemorrhagic Telangiectasia.

A. Right eye from a 52 year-old male showing temporal telangiectasias. **B.** Left eye from a 54 year-old male, showing fine telangiectasias temporally. **C.** Right eye from a 43 year-old male demonstrating peripheral telangiectasias temporally.

Table 1:

Patient characteristics

	N=18
Age (yr)	52.3 (9.7)
Average (SD)	
Years since diagnosis Average (SD)	23.2 (16.7)
Telangiectasias, N(%)	
Lips or Oral Cavity	16 (89)
Eyelid	4 (22)
Other skin	14 (78)
Intranasal	16 (89)
Gastrointestinal	5 (28)
Arterio-venous Malformations, N(%)	
Pulmonary	10 (56)
Hepatic	7 (39)
Cerebral	4 (22)
Spinal	0 (0)
Family History, N(%)	
>1 first degree relative	11(61)
1 first degree relative	6 (33)
No family history	1(6)
Chronic bleeding, N(%)	
Epistaxis	16 (89)
GI bleeding	1 (6)
Patients meeting ≥ 3 Curacao criteria, N(%)	17 (94)

Table 2:

Visual health among patients

	Mean (SD)
Best Corrected Visual acuity (LogMAR)	
Left	0.107 (0.139)
Right	0.103 (0.171)
Mean Intraocular Pressure (mmHg)	
Left	15.9 (2.7)
Right	16.3 (3.4)
Visual Functioning Questionnaire	
Driving	91.7 (9.9)
Color	98.6 (5.9)
Peripheral	91.7 (19.1)
Composite	88.9 (6.8)
Ophthalmic examination findings N (%)	
Cataracts (OU)	5 (28)
Drusen (OS/OD/OU)	5 (28)
Vitreous Syneresis	11 (61)