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Familial retinal arteriolar tortuosity and quantification of vascular tortuosity using swept-source optical coherence tomography angiography

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ABSTRACT

Purpose: Familial retinal arteriolar tortuosity (FRAT) is a rare autosomal dominant disorder that is characterized by tortuosity of the second and higher order retinal arterioles. We implement swept-source optical coherence tomography angiography (SS-OCTA) to quantify vessel tortuosity in patients with FRAT. We hypothesize that patients with FRAT will have higher retinal arteriole tortuosity when compared to controls.

Methods: Patients were scanned with a SS-OCTA device (Plex Elite 9000, Carl Zeiss Meditec, Dublin, CA). Images of a 12 × 12 mm^2 area centered on the fovea were processed, and retinal vessels > 23.5 μm in diameter were identified. An automatic tortuosity measurement program written in MATLAB was used to assess vessel tortuosity. Branch points in the vessels were detected and used to separate the vasculature into individual segments. The tortuosity was measured by calculating the arc-chord ratio of each vessel segment, where a minimum value of 1 indicated a straight vessel and higher values corresponded to increasing tortuosity.

Results: Two patients (4 eyes) with a known history of FRAT and six controls (12 eyes) were enrolled in the study. The mean tortuosity of all vessel segments (MTVS) in scans of FRAT eyes was on average 1.1244 [range: 1.1044–1.1438] while for control eyes it was 1.0818 [range: 1.0746–1.0872]. Average MTVS of FRAT eyes was significantly higher compared to control eyes ($p = 0.03$).

Conclusions and Importance: Our results are consistent with the hypothesis that patients with FRAT have higher objective measurements of tortuosity compared to controls. Broader applications of this method may be of benefit in other retinal diseases with changes in retinal vessel configuration.

1. Introduction

Familial retinal arteriolar tortuosity (FRAT) is a rare autosomal dominant disorder that affects the second and higher order retinal arterioles resulting in a characteristic fundus appearance. The condition is often asymptomatic but can be associated with recurrent vision loss due to retinal hemorrhages. The long-term visual prognosis is usually excellent. The condition has been associated with a missense mutation in the COL4A1 gene, which encodes a component of type IV collagen.[1] COL4A1 mutations have been found to cause COL4A1-related brain small-vessel disease, familial porencephaly, and hereditary angiopathy with nephropathy, aneurysms and muscle cramp (HANAC) syndrome. Mutations in COLA41 have also been associated with conditions involving anterior eye structures, the brain, musculature, vasculature, kidneys, and other sites.[1–3]

We present two cases of FRAT in one family, with one patient suffering spontaneous coronary artery dissections which may have been a systemic consequence of the COL4A1 mutation. We also apply a method to quantify the tortuosity of retinal vessels in the two described FRAT cases using optical coherence tomography angiography (OCTA). We hypothesize that patients with FRAT will have on average higher retinal arteriole tortuosity when compared to controls.

2. Case reports

2.1. Case 1

A 36-year-old woman presented with an 18-month history of progressively blurred vision in both eyes. Her past ocular history was notable for bilateral dry eyes. She had a complicated past medical history

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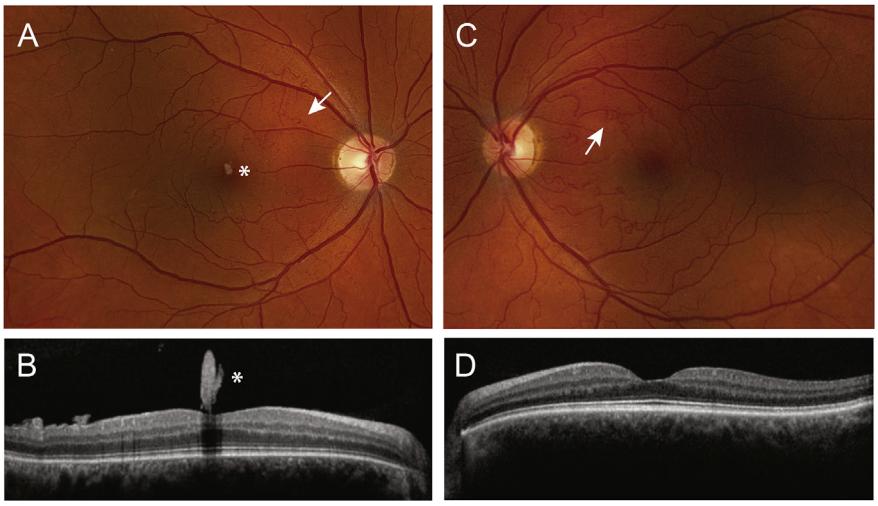

Fig. 1. Color fundus photograph of a patient with familial retinal arteriolar tortuosity (FRAT) in the right (A) and left (C) eyes. Second order arteriolar tortuosity was noted in both eyes (arrows). The patient awoke one morning and noted a new "blind spot" in the right eye. Fundus exam (A) and OCT (B, asterisk) show a white pre-retinal opacity thought to represent a spontaneously peeled epiretinal membrane occurring during a posterior vitreous detachment. OCT imaging of the left eye was unremarkable (D). The pictured pre-macular opacity eventually displaced to the nasal periphery and became less symptomatic.

including ischemic cardiomyopathy due to multiple spontaneous coronary artery dissections, ultimately necessitating a heart transplant.

At initial presentation, her best corrected visual acuity was 20/30 in the right eye and 20/20 in the left eye. Dilated fundus examination in both eyes showed tortuosity of the retinal arterioles without retinal hemorrhages, cotton wool spots, macular edema or exudates. A thin epiretinal membrane without retinal striae or macular edema was noted in the right eye. Observation was recommended.

The patient returned several months later with an acute complaint of a new central "floater" in the right eye of three weeks duration. A fixed new opacity was noted upon awakening in the central vision which had remained stable since its onset. A repeat dilated fundus examination showed a new, approximately 200-μm gray-white pre-retinal opacity near the fovea of the right eye (Fig. 1A, asterisk). Optical coherence tomography (OCT) showed a hyper-reflective preretinal opacity adherent to the inner retina with preservation of normal retinal architecture in the right eye (Fig. 1B). The left eye remained unchanged on exam and OCT (Fig. 1C and D).

On further questioning, the patient noted that she had experienced episodes of transient vision loss in the past. She also reported that her father, paternal grandmother and paternal cousins were similarly affected with episodic vision loss due to recurrent retinal hemorrhages.

Based on the appearance of the OCT before and after the formation of the opacity, it was thought the opacity was the result of an epiretinal membrane that had spontaneously peeled with the progression of a posterior vitreous detachment. However, given her family history, a localized dehemoglobinized vitreous hemorrhage was also considered in the differential. A baseline workup was undertaken to rule out any secondary causes of retinal vascular tortuosity with associated hemorrhages. A complete blood count, basic metabolic panel, and coagulation studies were normal. A serum lipid panel and hemoglobin A1c were within normal limits. Systemic blood pressure was 135/84 mmHg. Initially, the patient remained symptomatic as the opacity remained suspended in the premacular vitreous. However, after 2 years of observation, the opacity shifted to the nasal periphery and became less bothersome. Genetic testing subsequently confirmed the presence of a COL4A1 mutation in one of her alleles.

2.2. Case 2

A 62 year-old man, the father of Case 1, had previously been diagnosed with FRAT at our clinic. His clinical presentation as a child was reported over four decades ago.[4] The patient first became symptomatic with blurred vision from macular hemorrhages after performing a series of "squat jumps" at the school gym. In subsequent years, he reported periodically experiencing blurred vision from recurrent hemorrhages associated with straining or Valsalva, which he eventually learned to avoid. His hemorrhages resolved each time with observation and his vision would recover to 20/20. His medical history was significant for myocardial infarction at the age of 40, although it was unclear whether this was related to coronary artery dissection, aneurysms or embolic disease. The patient's medical history was otherwise significant for hypertension, gastric reflux, and prostate cancer in remission.

On examination, the patient was 20/20 in both eyes with normal intraocular pressures. Anterior segment exam was significant for mild nuclear sclerotic cataracts. Dilated fundus exam revealed tortuosity of second and higher order arterioles in both eyes consistent with FRAT and a flat, small choroidal nevus in the right eye (Fig. 2A and B). Comparison of current fundus photographs to those reported by Kalina et al., in 1971 shows increased tortuosity of the higher order retinal arterioles.[4] Recent genetic testing confirmed the presence of a COL4A1 mutation.

3. Materials and methods

Patients and control subjects were scanned with a swept-source OCTA device (SS-OCTA, Plex Elite 9000, Carl Zeiss Meditec, Dublin, CA) as part of a University of Washington IRB approved study. The central wavelength of the light source was 1050 nm with a bandwidth of 100 nm and a 100 kHz scanning rate. The scanning area covered a 12×12 mm^2 area centered at the fovea. Each scan acquired 500 A-scans in one B-scan. For each scanning location, two consecutive B-scans were obtained for flow signal calculation. A total of 500 transverse locations were acquired.

The 3D flow data were generated and exported from the Plex Elite device using an optical microangiography based OCTA method.[5] The flow signals of the inner retina (from inner limiting membrane to the outer boundary of outer plexiform layer) were isolated using a proprietary semi-automatic retinal layer segmentation program.[6] Maximum intensity projection was applied to the segmented inner retinal layer axially to generate the *en face* image of the blood vessels and capillaries in the inner retina for later analysis.

An automatic tortuosity measurement program, written in MATLAB, was developed to assess the tortuosity of each vessel segment. The tortuosity of vessel segment was defined as the ratio between the arc length and the chord length, i.e. the length the of vessel divided by the distance between two end points of the same vessel segment. To assess the tortuosity, Hessian filtering and thresholding were first used to extract the large retinal vessels (vessel diameter larger than 23.5 μm). Skeletonization was then applied to generate a map of the extracted vessels. The branch points of the vessels were detected and used to divide the vascular tree into individual vessel segments. The tortuosity

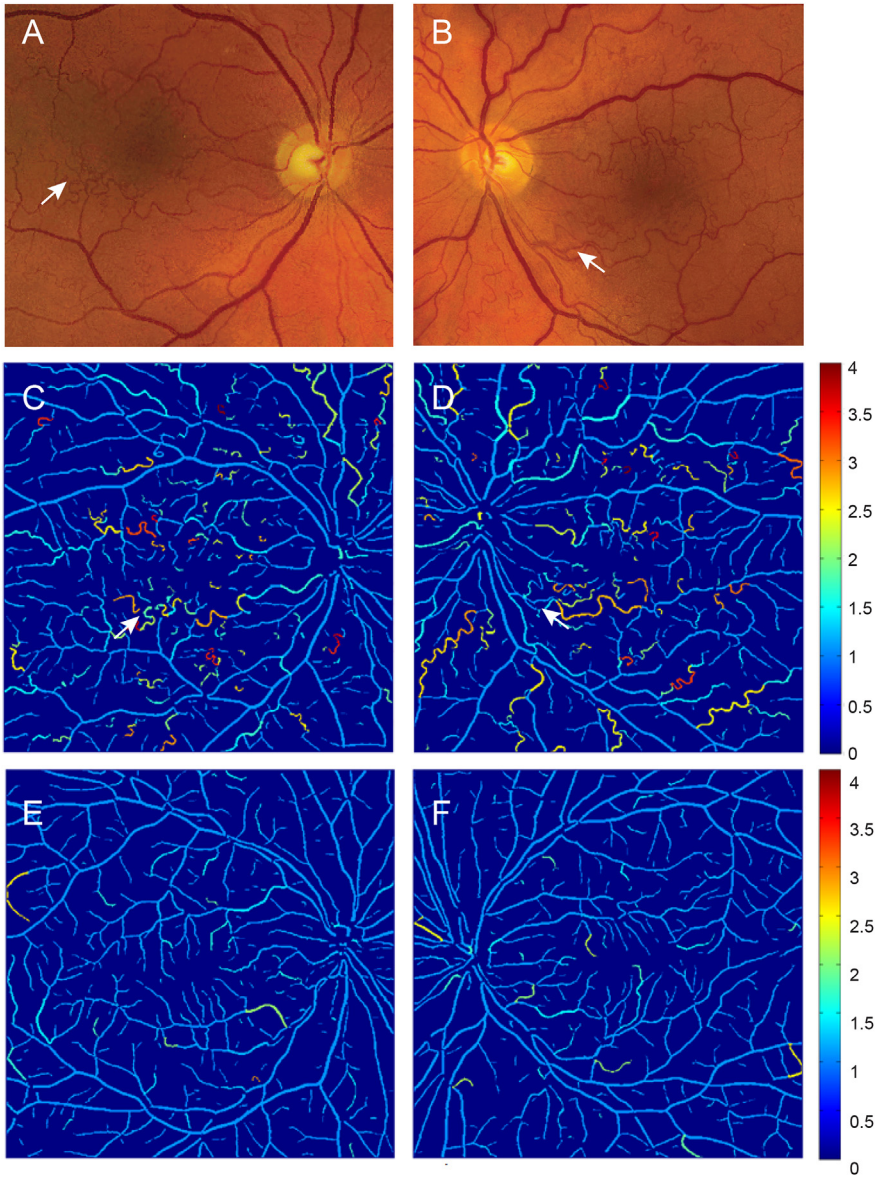

Fig. 2. Photographs show the right (A) and left (B) eyes of the father of the patient pictured in Fig. 1. Retinal vascular tortuosity can be appreciated on the fundus images and generated heat maps (C-D, arrows). (E-F) Heat map for age-matched control patient (age 60 years). En face SS-OCTA images were processed to exhibit only the retinal vasculature. The vasculature was segmented at its branch points and the arc-length ratio of each segment is shown using a color-coded scheme.

was then measured by calculating the arc-chord ratio of each vessel segment, where a minimum value of 1 indicates a straight vessel and higher values correspond to increasing tortuosity. The results were then summarized into mean, median, 75th percentile, 90th percentile, and maximal tortuosity of the entire vascular map. The results were compared with control eyes.

4. Results

Two patients (4 eyes) with a known history of FRAT and six controls (12 eyes) were included. The mean age of the controls subjects was 46.5 years (range, 22–60 years). Vascular heat maps were generated for each study participant (Fig. 2C–F).

Among FRAT eyes, the smallest mean tortuosity of all vessel segments (MTVS) was 1.1044 and the largest MTVS was 1.1438. Among control eyes, the smallest MTVS was 1.0746 and the largest MTVS was 1.0872. The average MTVS of all FRAT eyes was 1.1244 (± 0.0206 SD) compared to control eyes 1.0818 (± 0.0032 SD, p = 0.03). There was a statistically significant difference between mean, 75th percentile, and 90th percentile vessel tortuosity between FRAT and control eyes (Fig. 3). The median tortuosity of the vessel segments found in each FRAT eye was on average 1.0810 (± 0.0012 SD) compared to control eyes 1.0767 (± 0.0014 SD). The maximum tortuosity vessel segments found in each FRAT eye was on average 3.0128 (± 0.9679 SD) compared to 1.5747 in control eyes, which approached a statistically significant difference (± 0.2204 SD, p = 0.06).

5. Discussion

Familial retinal arteriolar tortuosity (FRAT) is an inherited disorder affecting the retinal vasculature. It is characterized by increased tortuosity of the second and higher order retinal arterioles in the posterior pole. The first-order arteries and venous system are usually not affected. Patients are frequently asymptomatic, but may present with recurrent, transient vision loss due to retinal hemorrhages.[2]

Inheritance for FRAT is most often autosomal dominant. It is a rare disorder, with only 16 affected families reported in the literature to date.[2,7] The arteriolar tortuosity, which develops during childhood or

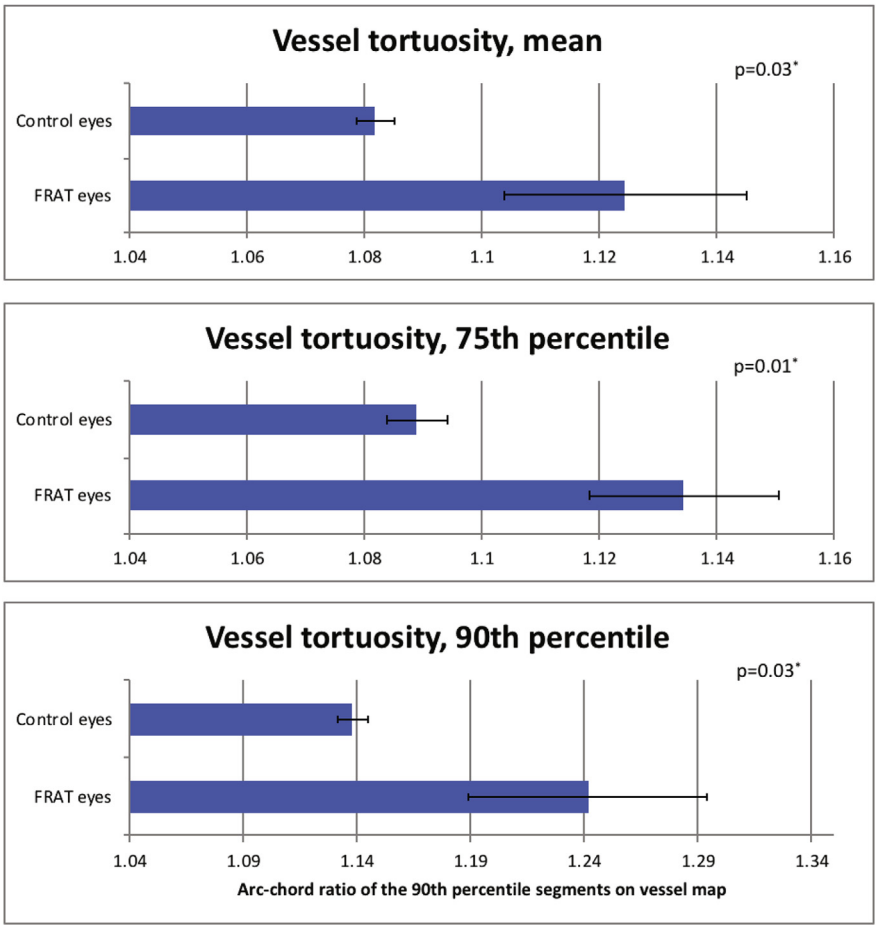

Fig. 3. Mean, 75th percentile, and 95th percentile scores of vessel tortuosity maps compared between FRAT and control eyes. Two FRAT patients (4 eyes) and 6 age-matched gender-matched controls (12 eyes) were compared. The FRAT eyes demonstrated significantly greater tortuosity compared to control eyes ($p = 0.03$) utilizing this method of quantification.

early adulthood and progresses throughout life, can be rarely associated with systemic vascular abnormalities.[2] While an exact etiology is not yet known, recent evidence suggests that a heterozygous mutation in COL4A1 may be causative in some cases of FRAT. COL4A1 has been thought to contribute to the production of collagen-based basement membrane proteins.[1] Interestingly, there are other systemic conditions due to COL4A1 mutations with retinal arteriolar tortuosity as a feature, including hereditary angiopathy with nephropathy, aneurysms, and muscle cramps (HANAC) syndrome.[3]

Diagnosis of FRAT is based on clinical findings of bilateral tortuosity of small and medium-sized arterioles in the peripapillary and macular regions. Corkscrew and spiral vessels may occur, but microaneurysms, arteriovenous shunts and other perivascular abnormalities are uncommon.[2] Fluorescein angiography may be useful to highlight the vascular tortuosity and rule out the presence of leakage, staining or hypoperfusion, which are not typical for the condition. A positive family history or fundus examination of an affected family member is supportive of the diagnosis, as was the case in our described series.

While the isolated retinal vascular tortuosity in FRAT is not by itself visually significant, patients become symptomatic from associated hemorrhages. Hemorrhages are usually preretinal or intraretinal, but subretinal and vitreous hemorrhages may occur. In FRAT, hemorrhages are often related to mild trauma or physical exertion whereby the increased fragility of the tortuous arterioles allows for breakthrough bleeding due to a Valsalva effect, consistent with the description in Case 2.[5] The risk and frequency of retinal hemorrhages does not appear to directly correlate with degree of arteriolar tortuosity.[2]

In most cases, FRAT is an isolated retinal disorder with no systemic manifestations. In rare cases, however, additional vascular malformations in other locations including nasal passage, conjunctiva and spinal cord, have been identified.[2,8] Abnormal blood coagulation studies have been reported in eight of 97 published cases, but these were weak associations and no patients had true coagulation abnormalities necessitating treatment. Systemic hypertension is reported in 10% of patients with FRAT.[2] In Case 1, the patient had significant cardiovascular disease with controlled hypertension, normal coagulation studies, and blood counts. Her coronary vascular dissections and associated ischemic cardiomyopathy, which occurred at an early age of 29, would be mechanistically consistent with abnormal collagen production related to COL4A1 mutation, though a review of literature did not reveal prior reports of coronary vascular dissection associated with this mutation. Her father's early myocardial infarction at the age of 40 years may also suggest a hereditary contribution, though it is unclear if he too suffered from coronary artery dissections. Although vascular dissections have not been widely associated with FRAT, there have been reports of FRAT and COL4A1 mutations associated with carotid aneurysms, cerebral aneurysms, and strokes.[9–11] Finally, compared to fundus photographs taken almost 50 years prior, current photographs demonstrate increased retinal arteriolar tortuosity in Case 2, which is consistent with previous reports indicating that vessel tortuosity increases with age in FRAT patients.[2]

Management of FRAT consists of observation of hemorrhage resolution over time. Prognosis is excellent and patients usually recover normal visual acuity following clearing of hemorrhages. Avoidance of straining or Valsalva likely helps to decrease the frequency of hemorrhage occurences. In some cases, however, macular pigment changes are observed which may be accompanied by mild, irreversible visual impairment.

Although FRAT is predominately a clinical diagnosis, OCTA was applied in this case to objectively demonstrate vascular tortuosity, expanding on previously reported image processing techniques.[12] OCTA is a newer imaging modality that produces *en face*, 3-dimensional images

of the retina, isolating tissues with only variable backscattering of light which in most cases represents functional blood vessels. With newer advancements such as swept-source OCTA, the speed and resolution of image acquisition is greatly advanced, rendering highly detailed images of the retinal and choroidal vasculature. Prior studies have shown novel and useful applications of this technology to detect choroidal neovascularization, neovascular growth in proliferative diabetic retinopathy, or analyze in detail choroidal architecture.[13–15]

The method described in this paper utilizes highly detailed images rendered by swept-source OCTA to objectively quantify the retinal vascular circulation. Although similar methods could be applied to fundus photographs to quantify vascular tortuosity, the application of OCTA renders more detailed maps of retinal vasculature, in particular with better rendering of deep retinal vessels. Limitations of our study include its small sample size and the use of both right and left eyes for FRAT and control patients, which may introduce bias. Nonetheless, we believe these techniques can be used to quantify retinal vascular tortuosity in a longitudinal manner that may be of use in future studies.

6. Conclusion

Our analysis demonstrates through quantitative measurements that the mean tortuosity of retinal vasculature in FRAT eyes is much higher than control eyes. Of note, the study is limited by the very small number of FRAT patients included in this report. However, broader applications of this method may be of benefit in larger studies of FRAT patients or other retinal conditions with progressive changes in retinal vessel configuration such as impending central vein occlusion, hypertensive retinopathy, or retinopathy of prematurity. Future development may allow this method to be applied in an automated manner by OCTA units, providing mean tortuosity measurements that can be compared between visits or in comparison to the fellow eye.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Conflicts of interest

None.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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Disclosures

Dr. RK Wang discloses intellectual property owned by the Oregon Health and Science University and the University of Washington related to OCT angiography, and licensed to commercial entities, which are related to the technology and analysis methods described in parts of this manuscript. Dr. RK Wang received an innovative research award from Research to Prevent Blindness. He is a consultant to Carl Zeiss Meditec, and Insight Photonic Solutions.

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