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Case report

A case series from a single family of familial retinal arteriolar tortuosity with common history of sudden visual loss

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ABSTRACT

Purpose: To report family members with familial retinal arteriolar tortuosity (FRAT) identified after sudden visual loss.

Observations: A 15-year-old boy had sudden visual loss in his left eye while playing on a horizontal bar. He was referred to Nagoya City University Hospital from an eye clinic. The ophthalmologic examination showed retinal hemorrhage bilaterally. His best-corrected visual acuity (BCVA) was 20/17 in the right eye and 20/67 in the left eye. Bilateral retinal arteriolar tortuosity as well as retinal hemorrhage was seen. Since his mother with 54 years of age also had a history of retinal hemorrhage that improved spontaneously, fundus examination was performed, revealing tortuosity of the retinal arterioles. Consequently, the patient and his mother were diagnosed as FRAT. He was followed without intervention. Retinal hemorrhage gradually decreased and resolved after 3 months. The BCVA of his left eye gradually improved and reached 20/20 after 1 year.

Conclusions and importance: In this case, the family history was very useful for early diagnosis. Immediate and accurate diagnosis allowed the patient to be followed without intervention and achieve subsequent resolution of retinal hemorrhage and improved vision. FRAT should be considered in cases of sub-internal limiting membrane hemorrhages in young patients even in the presence of discrete retinal arteriolar tortuosity.

1. Introduction

Familial retinal arteriolar tortuosity (FRAT) is a disorder characterized by pronounced tortuosity of the second- and third-order retinal arterioles in the macular and peripapillary areas.[1,2] Patients with FRAT are often asymptomatic, but some may experience transient visual loss due to macular hemorrhage after physical exertion or minor trauma.[2,3] The condition improves without intervention and the long-term visual prognosis is usually excellent. FRAT is inherited in an autosomal-dominant pattern[2] and has been recently reported to be caused by a missense mutation in the *COL4A1* gene, which encodes a component of type IV collagen.[4,5]

We present two cases of FRAT in one family. The case in the teenage boy was diagnosed easily based on his mother's medical history of sudden visual loss due to macular hemorrhage and examination of the mother's fundus showing tortuosity of retinal arterioles.

2. Case report

A 15-year-old boy reported sudden visual loss in his left eye while playing on a horizontal bar during a physical education class. He visited an eye clinic, where bilateral retinal hemorrhage was detected and he was referred to Nagoya City University Hospital for diagnosis.

He had a medical history of mycoplasma pneumoniae once and pyelonephritis twice. His mother also had a history of retinal disease.

At the initial visit, the best-corrected visual acuity (BCVA) was 20/17 in the right eye and 20/67 in the left eye. The intraocular pressures was 15 and 12 mmHg, respectively, in the right and left eyes. The light reflex was prompt and complete, and a relative afferent pupillary defect was not seen in both eyes. The anterior segment and optic media had no unremarkable findings.

Mydriatic fundus examination showed scattered retinal hemorrhages at the posterior pole in both eyes and sub-internal limiting membrane

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(ILM) hemorrhages at the macula of the left eye and mild tortuosity of retinal arterioles in both eyes (Fig. 1A and B). Optical coherence tomography (OCT) (Triton® Topcon Corporation; Tokyo, Japan) showed no abnormalities other than a lesion suggestive of a hemorrhage in the sub-ILM of the macula of the left eye (Fig. 1C and D); OCT angiography (OCTA) (AngioVue™, Optovue, Fremont, CA) revealed mild tortuosity of the retinal arterioles (Fig. 1E and F); fluorescein angiography (FA) (Optos® California, Nikon Co. Ltd., Tokyo, Japan) showed blocked fluorescence due to retinal hemorrhages and tortuosity of the retinal arterioles, while no other abnormalities such as fluorescence leakage or vascular occlusion were observed (Fig. 2A and B).

Examination by a pediatrician did not identify any systemic disorders that could cause retinal hemorrhages. Cranial magnetic resonance imaging and angiography showed no abnormalities. Blood tests indicated no abnormalities regarding the coagulation system and renal function. Although slight increases in creatine phosphokinase and liver enzymes in the blood and slight renal pelvic dilatation on renal ultrasonography and abdominal computed tomography were detected, the patient was followed without intervention because of the absence of clinical symptoms. Retinal hemorrhage triggered by mild exercise, mild tortuosity of the retinal arterioles in both eyes, and no other complications suggested FRAT.

His 54-year-old mother had a history of retinal hemorrhage that occurred when she was 14 years old, resembling his episode. She noticed visual loss after a mat exercise in a physical education class. Examination by an ophthalmologist identified retinal hemorrhage. Further examination in the departments of Ophthalmology and Pediatology at a general hospital could not determine the cause of retinal hemorrhage at that time. Nevertheless, retinal hemorrhage was spontaneously resolved and her BCVA returned to the baseline level before the disease onset. At this time, an ophthalmologic examination of the mother was performed, considering the possibility of FRAT. Her BCVA was 20/17 in both eyes. The anterior segment and optic media showed no remarkable findings. Fundus examination (Fig. 3A and B) and OCTA (Fig. 3C and D) showed bilateral tortuosity of the second and third arterioles, leading to the diagnosis of FRAT. Ophthalmic examination of the patient's older brother detected no abnormalities. No ophthalmic examination was performed on the patient's father.

The patient and the patient's mother were diagnosed with FRAT, based on their findings. The boy was advised not to engage in intense exercise and followed up without intervention. Two weeks after the onset, the retinal hemorrhage started to decrease (Fig. 4A and B). The BCVA in the right eye was 20/17. The BCVA in the left eye remained 20/67 due to a persistent macular hemorrhage. While most of retinal hemorrhage resolved in 1 month, the minimal sub-ILM hemorrhage remained at the macula of the left eye. The BCVA of the left eye improved to 20/40. The sub-ILM hemorrhage at the macula of the left eye was negligible after 3 months (Fig. 4C and D). The morphology of the macula almost normalized (Fig. 4E and F), and the BCVA improved to 20/29. The patient was allowed to resume exercises. One year later, the sub-ILM hemorrhage in the left eye was absorbed completely (Fig. 4G, H, I, J) the BCVA of his left eye improved to 20/20 and no retinal hemorrhage has occurred for more than 2 years since the initial episode.

During the follow-up, the patient and his mother consented to undergo a genetic analysis while collaborating with a genetics specialist. The genetic analysis was performed with the Inherited Disease Panel (Ion AmpliSeq™ Inherited Disease Panel (Life Technologies Corp., Framingham, MA)) (available at http://assets.thermofisher.com/TFS-Assets/LSG/brochures/CO25570_Ion_Inherited_Disease_GeneList_Table_CO25570.pdf) for 328 genes including *COL4A1*. However, no pathogenic variants were found. The creatine phosphokinase and liver enzymes

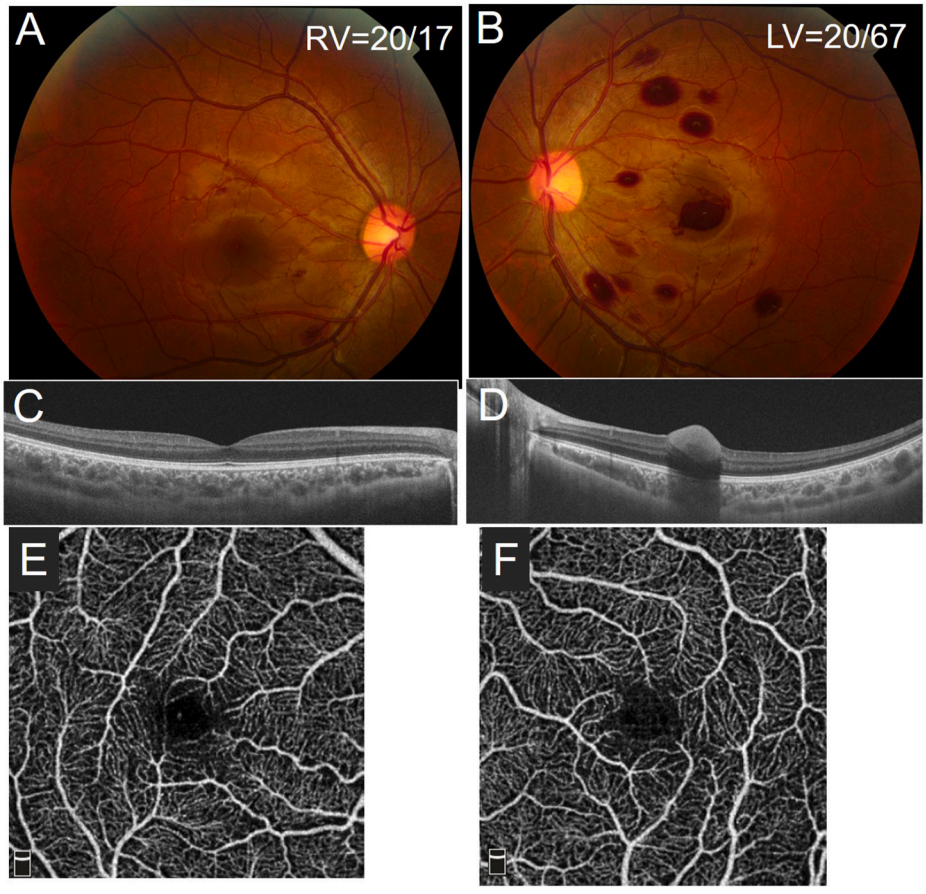

Fig. 1. Color fundus images of the right (A) and left eyes (B), optical coherence tomography images of the right (C) and left eyes (D), and optical coherence tomography angiography images of the right (E) and left eyes (F) at the initial visit. Retinal hemorrhages and mild tortuosity of retinal arterioles are seen in both eyes and a sub-internal limiting membrane hemorrhage is seen in the left eye. LV = left vision; RV = right vision. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

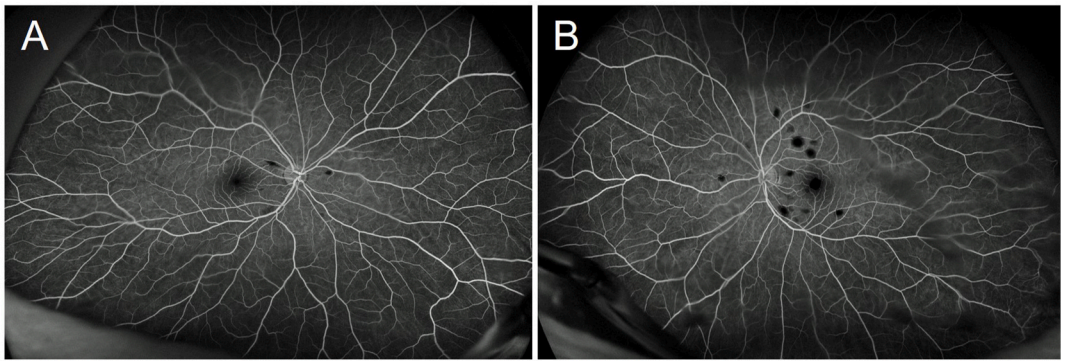

Fig. 2. Wide-field fundus fluorescein angiography images of the right (A) and left eyes (B) show blocked fluorescence due to retinal hemorrhage and tortuosity of the retinal arterioles.

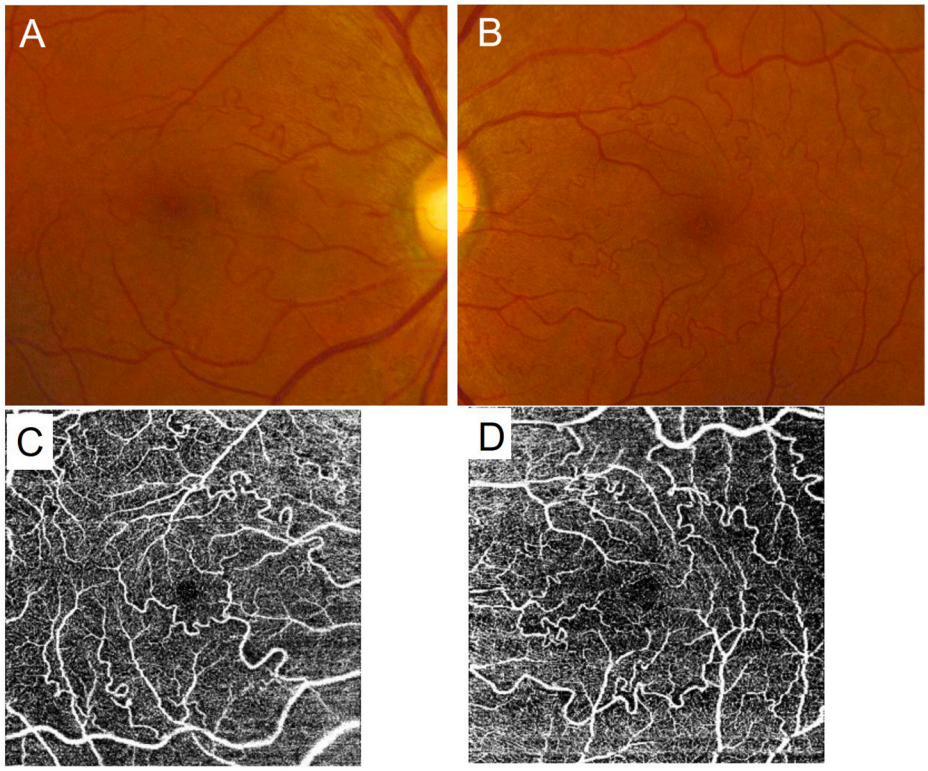

Fig. 3. The color fundus images of the right eye (A) and left eyes (B) of the patient's mother and optical coherence tomography angiography images of the right (C) and left eyes (D). Marked retinal arteriolar tortuosity is seen in both eyes. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

values normalized within 2 months and the dilation of the right pelvis gradually improved and normalized after 2 years.

3. Discussion

FRAT is a rare autosomal dominant disorder, first reported by Beyer.[6] in 1958 and followed by familial case reports from multiple countries.[3,7–10] Sutter and Helbig[2] reviewed 97 cases in 17 families and 14 sporadic cases. To the best of our knowledge, only three reports of FRAT in Japan have been published: two sporadic cases[11,12] and three generations of one family.[10]

According to previous reports, FRAT patients are often asymptomatic, while a retinal hemorrhage in the fovea sometimes causes sudden visual loss in childhood or early adulthood. A retinal hemorrhage can be triggered by mild exercise or minor trauma. In the fundus of the current patient, tortuosity of the second- and third-order retinal arteries was observed, although the first-order arteries and venous systems were normal. FA showed no leakage of tortuous arterioles or in the areas with retinal hemorrhage. The tortuosity primarily affects retinal arterioles in the macular region and retinal hemorrhage often recurs but resolves without treatment, and the long-term visual prognosis is good (Table 1).

In the current case, the patient and his mother had the same history of sudden visual loss during mild exercise. The ages at which retinal hemorrhage occurred were 15 years in the patient and 14 years in his mother. The tortuosity of the patient's retinal arterioles was not very noticeable, but the mother's retinal arterioles were markedly tortuous. While the mother was undiagnosed at the time of onset, the retinal hemorrhage resolved without intervention. These clinical findings were almost consistent with the previously reported clinical findings of FRAT and are sufficient to diagnose patients as having FRAT (Table 1), and in

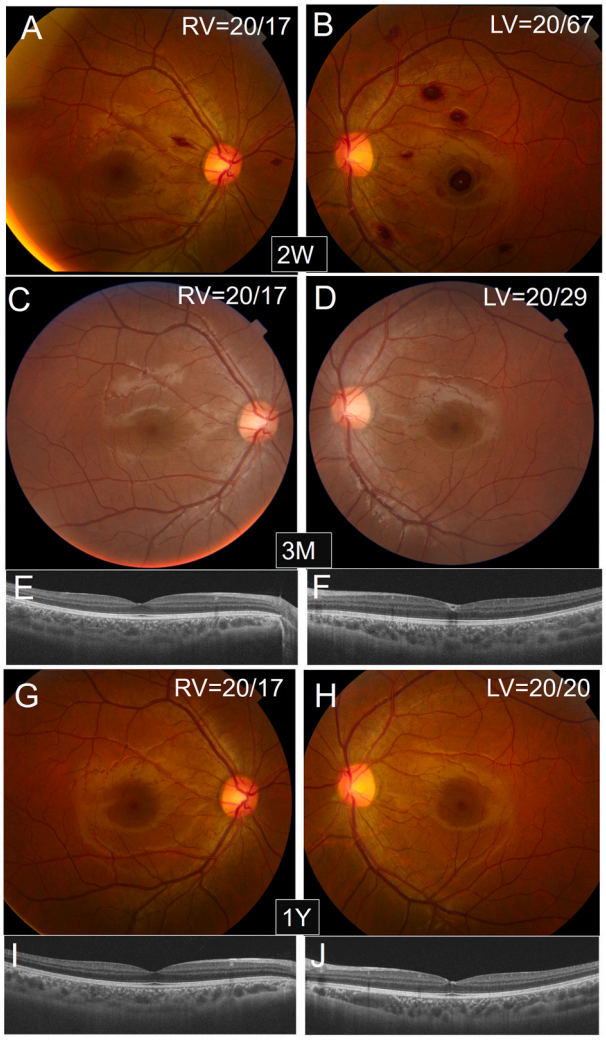

Fig. 4. Color fundus images of the right (A) and left eyes (B) 2 weeks after the initial examination. The retinal hemorrhages decreased slightly, but the macular hemorrhage remains. Color fundus images of the right (C) and left eyes (D) and optical coherence tomography (OCT) images of the right (E) and left eyes (F) 3 month later. The retinal hemorrhages resolved and the macular morphology has also almost normalized in the left eye. Color fundus images of the right (G) and left eyes (H) and OCT images of the right (I) and left eyes (J) 1 year later. The macular hemorrhage improved further and the best-corrected visual acuity of his left eye reached 20/20. LV = left vision; 2W = 2 weeks; 3 M = 3 months; 1Y = 1 year. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

fact, the retinal hemorrhage improved without intervention.

In the current report, the mother's medical history and the tortuosity of the retinal arterioles were very useful to diagnose her son. In the current case, the tortuosity of the patient's retinal arterioles was mild, but the mother's arterioles were markedly tortuous. Sutter and Helbig[2] reported that the tortuosity can progress over time while the accompanying venules remain unchanged. Therefore, the mother also may have had mild arteriolar tortuosity at the onset of the retinal hemorrhage, which may have made diagnosis difficult.

There are several recent reports on the diagnosis, treatment, and causative genes of FRAT. Saraf et al.[5] used OCTA to quantify arteriolar tortuosity in patients with FRAT and reported that they had higher retinal arteriolar tortuosity compared with controls. In the current case, we also performed OCTA for the patient and his mother. OCTA depicted the tortuosity of the mother's arterioles more clearly than fundus photography. OCTA is a non-invasive procedure and can delineate

Table 1
Clinical characteristics of familial retinal arteriolar tortuosity.

	Previous reports	Current case	
		Patient (male)	Patient's mother
Inheritance mode	Autosomal dominant	Hereditary is suggested	
Age at onset	In childhood or early adulthood	15 years old	14 years old
Symptom	Sudden visual loss	Sudden visual loss	Sudden visual loss
Trigger	Mild exercise or ocular trauma	Horizontal bar	Mat exercise
Fundus findings	Retinal hemorrhage Tortuosity of second- and third-order retinal arterioles	Retinal hemorrhage Mild tortuosity of retinal arterioles	Marked tortuosity of second- and third-order retinal arterioles
Fluorescein angiography	No leakage from tortuous arterioles and the areas with the retinal hemorrhage	Blockages due to retinal hemorrhage No leakage from tortuous arterioles	Not performed
Suggested genetic abnormalities	*COL4A1*	None	Not performed
Visual prognosis	Good	Good	Good

retinal blood vessels without using fluorescein dye. Thus, OCTA may be useful for diagnosis and further assessment of FRAT.

In patients with FRAT, the cause of visual loss is a sub-ILM hemorrhage at the macula. In most cases as in the current case, the clinical picture improves without treatment,[2,11,13,14] but if the hemorrhages are bilateral or the visual loss is severe, treatment is considered. Chen et al.[15] performed Nd:YAG laser membranotomy to treat sub-ILM hemorrhage at the macula in a patient with FRAT and reported that the treatment was effective when rapid visual recovery is needed due to bilateral sub-ILM hemorrhages at the macula.

It has been suggested recently that a variant of the *COL4A1* gene is associated with FRAT.[4,5] The *COL4A1* gene encodes the α1 (IV) subunit chain, and a variant in the gene causes basement membrane damage to the blood vessels.[16] A *COL4A1* variant has been reported in porencephaly and other cerebrovascular diseases,[16,17] and it also may be associated with hereditary angiopathy with nephropathy aneurysms and muscle cramps.[18]

Zenteno et al.[4] reported the results of exome sequencing analysis using NGS in two generations of a family with FRAT and provided evidence that a heterozygous missense variant in the *COL4A1* gene was responsible for the retinal phenotype in this pedigree. In the current report, we also performed a genetic analysis using NGS for 328 genes including *COL4A1*; however, no pathogenic variants were found including *COL4A1*. NGS technology can comprehensively analyze a large number of genes, while not all variants can be identified. First, NGS cannot identify variants in some region because it does not cover all exonic regions; the average gene coverage of the Inherited Disease Panel is 97%. Second, NGS cannot always identify mosaic variations, gross deletions, or insertions. Third, NGS cannot identify variants in transcriptional regulatory regions. In the current case, there may have been a variant of *COL4A1* that was not identified in our genetic analysis, or the patient may have a causative variant in another gene. At the moment, the current patient and his parents do not want to undergo further genetic analysis.

In conclusion, we report two members of a family with FRAT identified by sudden visual loss caused by retinal hemorrhages. In this case, the family history was very useful for early diagnosis. Early and accurate diagnosis facilitated observation of the patient, whose retinal hemorrhage and VA improved without intervention. FRAT should be considered in cases of sub-ILM hemorrhage in young patients even in the

presence of discrete retinal arteriolar tortuosity.

Patient consent

Informed consent was obtained from the patient.

Author's contributions

Tomohiro Obayashi: Investigation, Writing, Aki Kato: Investigation, Writing- Original draft preparation, Munenori Yoshida: Supervision, Yu Shibata: Investigation, Harumitsu Suzuki: Investigation, Kei Ohashi: Investigation, Writing, Yuichiro Ogura: Supervision, Tsutomu Yasukawa: Writing- Reviewing and Editing.

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Declaration of competing interest

The authors declare that they have no conflicts of interest associated with this report.

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