

# Factor VII deficiency in a patient with retinal arteriolar tortuosity syndrome

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## Abstract

**Purpose** To report a pedigree with hereditary retinal arteriolar tortuosity with macular haemorrhage and abnormality of the coagulation system.

**Methods** Case report and literature review.

**Results** A 49-year-old woman was referred due to macular haemorrhage in both eyes. Her 16-year-old son had recurrent retinal haemorrhages which presented at age 16 years and had mild retinal arteriolar tortuosity. Coagulation studies in the son revealed normal activated partial thromboplastin time (APTT), prolonged prothrombin time (PT) and 30% activity of factor VII.

**Conclusions** Factor VII deficiency may aggravate the haemorrhages in retinal arteriolar tortuosity syndrome. We therefore suggest conducting routine coagulation studies (PT, APTT) in all patients with retinal arteriolar tortuosity syndrome. Determination of factor VII activity is warranted only in patients with normal APTT and prolonged PT.

**Key words** Arteriolar tortuosity, Factor VII, Haemorrhage

Hereditary retinal arteriolar tortuosity (RAT) is a rare, well-recognised syndrome characterised by tortuosity of the retinal arterioles which increases with age.<sup>1</sup> Patients usually present with acute loss of vision from a macular haemorrhage that resolves without sequelae. The pathogenesis of the retinal arteriolar tortuosity and the spontaneous haemorrhages in the macula is not clear, and no abnormalities of the coagulation system supporting a haemorrhagic diathesis have been reported to date.

We describe two patients, a mother and son, with RAT and macular haemorrhage, where the son also had a factor VII deficiency. The relationship between the two entities is discussed.

## Case reports

### Case 1

An otherwise healthy 16-year-old boy presented in 1994 with a 2 day history of sudden visual loss in the right eye. He denied any history of trauma or bleeding tendency. Past ocular history and medical examination were unremarkable. His parents were unrelated. His best corrected visual acuity was 20/60 in the right eye and 20/20 in the left. There was no relative afferent pupillary defect. Intraocular pressure and slit-lamp examination of the anterior segment were normal bilaterally. Fundus examination of both eyes showed mild RAT (Fig. 1a,b). The venous tree was normal. The right eye had a macular haemorrhage of the subretinal limiting membrane that explained the visual loss. Prothrombin time (PT) was 18.1 s (normal 12.8–15.0 s), and the international normalised ratio (INR) was 1.85 (normal 0.9–1.15). Activated partial thromboplastin time (APTT) was normal. Factor VII activity was 30% (normal 60–120%). Other coagulation studies, including platelet count, thrombin time, bleeding time, fibrinogen and activity of factors II, V, IX and X, were normal. Haemoglobin, haematocrit, leucocyte count, liver enzymes, serum proteins and creatinine were also normal. The retinal haemorrhages resolved without treatment. During the next 4 years he had three more episodes of macular haemorrhages that also resolved spontaneously. Retinal arteriolar tortuosity increased during this 4 year period (Fig. 1c).

### Case 2

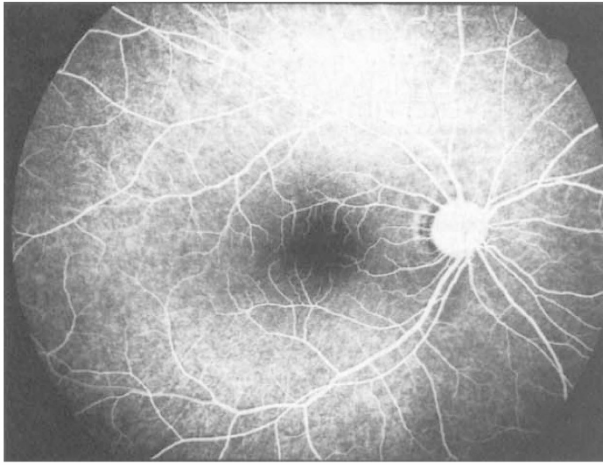
The 49-year-old mother of case 1 presented with sudden visual loss in her left eye. Her past ocular history was unremarkable. She had arterial hypertension. Her best corrected visual acuity was 20/30 in the right eye and 20/200 in the left. There was no relative afferent pupillary defect. Intraocular pressure and slit-lamp examination of the anterior segment were normal bilaterally. Fundus examination of both eyes was remarkable for RAT. The left eye had macular haemorrhages (Fig. 2). Coagulation studies were normal, including platelet count,

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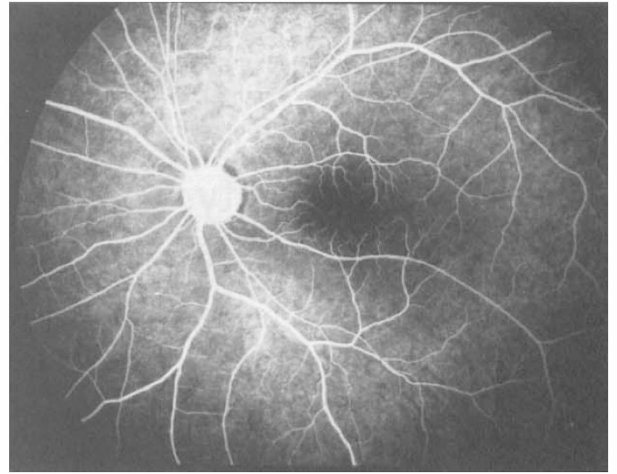
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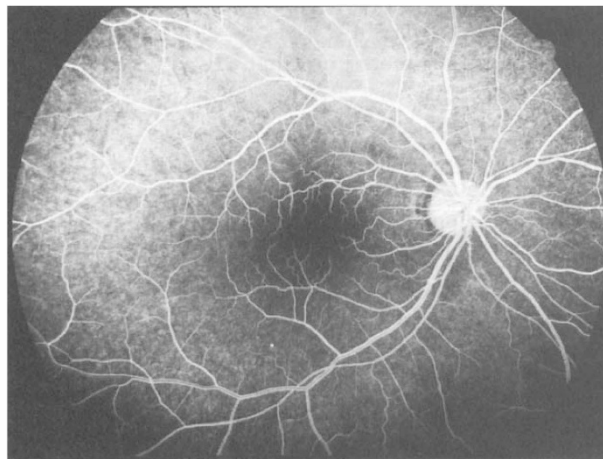
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(a)



(b)



(c)

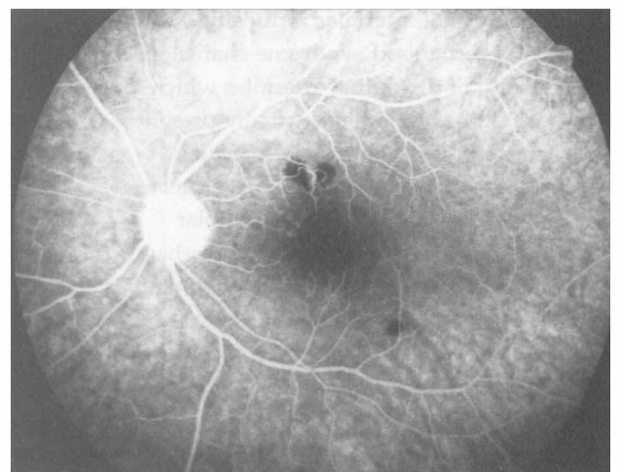
**Fig. 1.** Case 1. Fluorescein angiograms. At age 16 years mild retinal arteriolar tortuosity is present in both the right (a) and left (b) eye. No changes are apparent in the veins. At age 20 years there is increased retinal arteriolar tortuosity compared with age 16 years in the right eye (c).

PT, APTT, thrombin time, bleeding time, and activity of factors II, V, VII, IX and X. The macular haemorrhages resolved spontaneously. She experienced no additional haemorrhages during the next 2 years.

### Discussion

Familial retinal arteriolar tortuosity with retinal haemorrhages was first described by Beyer in 1958.<sup>2</sup> This syndrome is autosomal dominantly inherited, but the exact chromosomal localisation is unknown. RAT is characterised by tortuosity of the retinal arterioles, which is often subtle and easily overlooked and may increase with age to an easily discernible magnitude.<sup>1</sup> The tortuosity is more apparent in medium and small arterioles, and more prominent in macular than extramacular arterioles.<sup>1</sup> The retinal veins remain normal. Patients generally present with acute loss of vision from a macular haemorrhage that resolves without sequelae. The haemorrhages are usually small, superficial, circular or flame-shaped, and may be intraretinal or preretinal.<sup>3</sup> Retinal haemorrhages in RAT are usually spontaneous, but may be related to physical exertion, sudden elevated blood pressure or mild trauma.<sup>4,5</sup>

The pathogenesis of macular haemorrhage in patients with RAT is unclear.<sup>1</sup> A structural weakness in the perimacular vasculature was suggested, but the only abnormal histological finding of questionable significance in one patient was a focal increase in the number of endothelial cells in the retinal capillaries.<sup>3,5</sup>



**Fig. 2.** Case 2. Fluorescein angiogram of the left eye at age 49 years shows macular haemorrhages and retinal arteriolar tortuosity.

No consistent abnormalities of the coagulation system have been reported in RAT syndrome. Platelet disorder was suggested but not proved in one patient.<sup>6</sup>

The sole clinical and laboratory abnormality in our 16-year-old patient was a prolonged PT due to factor VII deficiency. This deficiency should be considered when PT is prolonged and APTT is normal.<sup>7</sup> We therefore suggest conducting routine coagulation studies (PT, APTT) in all patients with retinal arteriolar tortuosity syndrome. Determination of factor VII activity is warranted only in patients with normal APTT and prolonged PT.

Factor VII deficiency may be hereditary or acquired.<sup>8</sup> Factor VII activity of the mother was normal; the boy's father and brothers were unavailable for evaluation. The factor deficiency was considered hereditary in the boy in view of the absence of liver or biliary system disease and malabsorption, a standard diet, normal activity of other vitamin-K-dependent factors, and no drug ingestion.

Factor VII deficiency is inherited as an autosomal recessive trait. It affects males and females equally with an incidence of 1 in 500 000.<sup>9</sup> The gene for factor VII is located on chromosome 13, and most cases of factor VII deficiency are due to point mutations or partial gene deletions. The minimal haemostatic level of the factors is not clear. Generally, 15–25% of normal results in normal haemostasis.<sup>8</sup> However, there are reports of patients with factor VII activity of 20–30%, as in our patient, who developed intracranial,<sup>10</sup> subarachnoid<sup>7</sup> and postpartum haemorrhages.<sup>8</sup>

The different clinical courses of the RAT syndrome in the mother and son, in which the boy suffered more episodes of intraocular haemorrhages, together with the factor VII deficiency only in the boy, suggest a causal relationship between the factor deficiency and the propensity to the haemorrhages. The factor deficiency might have aggravated the haemorrhagic diathesis in the boy.

The retinal haemorrhages in the boy resolved spontaneously without treatment to correct the coagulation abnormality. Individuals with more severe

factor VII deficiency may require replacement with plasma or prothrombin complex to overcome the bleeding. Thus, a complete coagulation study is warranted in patients with RAT syndrome.

The genetic defect leading to RAT syndrome, and the incidence of RAT and factor VII deficiency in the same patient, are unknown. While their coexistence may be purely coincidental, it is possible that the genetic defect leading to RAT syndrome is related to that responsible for factor VII deficiency. This hypothesis requires further study.

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