

**SHORT COMMUNICATION****Case report****Branch retinal vein occlusion associated with the 20210 G-to-A prothrombin variant**

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**PURPOSE.** *To describe a case of branch retinal vein occlusion (BRVO) in a patient who tested positive for the 20210 A allele of the prothrombin (PT) gene.*

**METHODS.** *A 48-year-old man had visual loss in the right eye secondary to BRVO confirmed by ophthalmoscopy and fluorescein angiography. His medical history was not remarkable for common risk factors for retinal occlusive diseases.*

**RESULTS.** *Laboratory tests for hypercoagulability were positive for PT 20210 A variant. The patient's family tested negative for the PT variant.*

**CONCLUSIONS.** *Laboratory tests for coagulopathy, including the PT 20210 A variant, should be added to the examination of patients with central or BRVO, especially if most common risk factors for thrombosis have been excluded. (Eur J Ophthalmol 2000; 10: 177-9)*

**KEY WORDS.** *Retinal vein occlusion, Clotting factors, Prothrombin 20210 A variant*

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**INTRODUCTION**

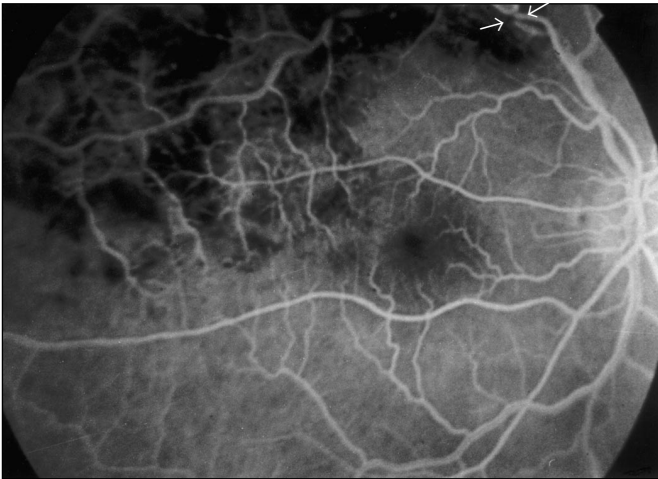
Retinal vascular occlusions are the most common secondary retinal vascular disorders after diabetic retinopathy (1). Occlusion of the central retinal vein or one of its branches is a major cause of visual impairment. In 1956, Klein and Olwin (2) postulated that mechanisms implicated in retinal vein occlusion (RVO) included: 1) external compression; 2) primary venous disease and 3) stagnation thrombosis. Several studies since then (1, 3) have provided evidence of an association between RVO and numerous systemic conditions. The risk of central and branch retinal vein occlusion (BRVO) is increased in patients with systemic hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease and elevated serum IgA levels (3).

Until recently, inherited deficiencies of antithrombin III (AT III), protein C (PC), protein S (PS) and re-

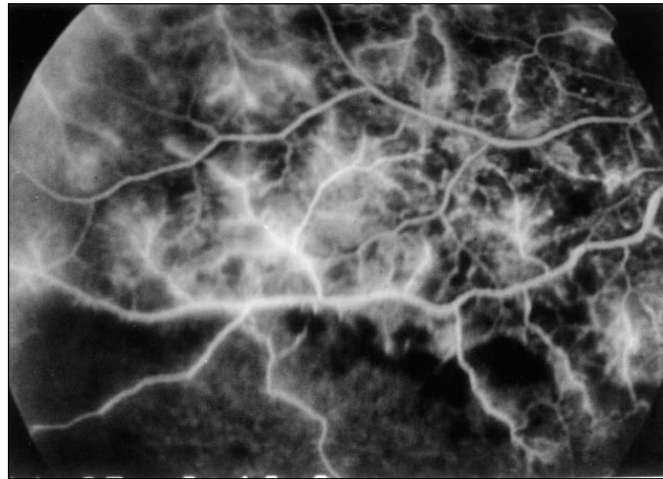
sistence to activated PC were the only single gene disorders known to be commonly associated with an increased risk of developing venous thrombosis (4). But at the end of 1996, Poort et al (5) identified a single G to A nucleotide transition at position 20210 in the 3' untranslated region of the prothrombin (PT) gene. Heterozygosity for the 20210 A allele was reported to be associated with increased PT (factor II of coagulation) and venous thromboembolism (6). We report a case of BRVO in a patient who tested positive for the clotting factor II 20210 A variant.

**Case report**

A 48-year-old Caucasian man complained of blurred vision in his right eye (RE) for three days. His ophthalmic and medical histories were unremarkable. His best-



**Fig. 1** - Fluorescein angiography of the RE showing a superotemporal branch retinal vein occlusion. The arrows indicate the site of the occlusion. Marked hypofluorescence is present secondary to the extensive hemorrhage in the distribution of the superotemporal branch vein. Vessel dilatation, tortuosity, and staining are seen in the distribution area.



**Fig. 2** - Peripheral image of the fluorescein angiography showing the same ischemic areas in the middle peripheral retina of the RE.

corrected visual acuity was 20/80 in his RE, and 20/20 in his left eye (LE). Pupillary reflexes were normal. Slit-lamp examination of both eyes was unremarkable. Applanation tonometry disclosed a pressure of RE, 15 mmHg and LE, 12 mmHg. Ophthalmoscopy of the RE showed a superotemporal RVO with flame-shaped hemorrhages in the left upper hemisphere retina. Fundus examination revealed a normal posterior pole of the LE with no signs of arterio-venous crossing. Fluorescein angiography (FA) of the RE (Figs. 1 and 2) confirmed the diagnosis and showed leakage but good perfusion; there were some retinal ischemic areas in the middle peripheral retina of the RE (Fig. 2). The occlusion was at the third superotemporal arterio-venous crossing site, with the artery anterior to the vein (Fig. 1). No macular edema was seen in the RE.

A complete medical history was obtained, looking for factors associated with an increased risk of RVO. We particularly checked for a history of diabetes mellitus, systemic hypertension, atherosclerosis, chronic open-angle glaucoma, smoking, immobilization and the use of medication, including estrogen preparations. Laboratory testing included a complete blood cell count, erythrocyte sedimentation rate, blood levels of cholesterol, triglycerides and glucose, quantitative immunoglobulins,

antinucleotide and anticardiolipin antibody titers, human immunodeficiency virus (HIV) lupus anticoagulant, treponemal antibody, common coagulation tests and studies for congenital causes of hypercoagulability, including AT III, PC, PS, resistance to activated PC deficiencies and factor V Leiden mutation. Additionally, the patient was tested for the PT 20210 A variant. Only the latter was positive for the heterozygous form of the PT 20210 A gene. Genetic analysis of the PT gene 20210 A allele was carried out by polymerase chain reaction (PCR) amplification, using one mutagenic primer which introduced a recognition site for the restriction enzyme Hind III where adenine was present at position 20210. Family history of thrombosis was negative and the patient's family tested negative for the PT variant.

Laser photocoagulation was done on the RE using an argon green laser to deliver a total of 489 burns using 0.25 W of power, 0.2-second duration, and approximately 300  $\mu\text{m}$  to 500  $\mu\text{m}$  spot size in the superior and temporal retina of the RE. Six months later the patient's visual acuity had improved to 20/30 in his RE. At a follow-up examination two years later, the patient has remained asymptomatic with no new thromboembolism.

## DISCUSSION

The pathogenesis of RVO involves a complex interaction between multiple factors affecting both the vessel wall and the blood (3). Previous reports have outlined the findings in patients with RVO (1-3). Special attention is given to identifying any signs, symptoms, or history of systemic cardiovascular disease. Now, however, inherited deficiencies of AT III, PC or PS have been recognized as being associated with an increased risk of developing venous thrombosis. Another genetic risk factor for venous thrombosis was identified in 1996 (5).

The recently described mutation in clotting factor II has been associated with a three-fold risk of deep vein thrombosis (5). This is probably due to high plasma levels of clotting factor II (6). Plasma PT is significantly higher in people with the PT 20210 A than in those without it (6). Poort et al (5) detected PT in 113 subjects without the PT mutation and eight with the allele. He obtained 1.32 U/ml (1.0 U/ml, the criteria for normal plasma) in patients with the PT variant and 1.09 U/ml in patients without.

In our patient, who tested positive for the 20210 A allele, the plasma PT level was 1.41 U/ml. Plasma PT was tested by a thromboplastin-based assay using factor II-deficient plasma (Instrumentation Laborato-

ry, UK) on a Sysmex CA coagulation analyser. In this case, although we cannot conclude that the BRVO was a direct result of the 20210. A mutation, this association was the only known risk factor for thromboembolism we found. The mechanism by which high plasma PT levels are associated with an increased risk of venous thromboembolism is unclear but probably involves enhanced activation of coagulation.

The single-base substitution (G to A) at position 20210 of the 3'-untranslated region of the PT gene was found in 18% of probands of thrombophilic families, 6% of unselected consecutive patients with deep vein thrombosis and 2% of healthy controls (5). To our knowledge, this is the first reported case of BRVO associated with the 20210 A variant.

A laboratory test for coagulopathy, including the PT 20210 A variant, should be included for patients with RVO, especially once the most commonly associated risk factors and coagulopathies have been excluded. Thus, this PT gene sequence variation adds to the list of recognized genetic risk factors for thrombophilia.

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