

PERSPECTIVE

Thrombophilia: genetic polymorphisms and their association with retinal vascular occlusive disease

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Venous thrombosis affects one in 1000 individuals per year^{1 2} causing significant morbidity and mortality. Inherited thrombophilia is a genetically determined tendency to thrombosis. Dominant abnormalities or combinations of mutations of varying penetrance giving rise to less severe defects may be suspected clinically from evidence of early age of onset, frequent recurrence, or family history. Milder traits may be discovered only by laboratory investigation. In most patients, however, thrombosis is episodic, separated by long asymptomatic periods. This episodic nature indicates that there is a trigger for each event and that the inherited trait requires interaction with other factors before a clinical disorder becomes apparent.

Vascular occlusions of the eye encompass thrombosis of retinal veins, arteries, and anterior ischaemic optic neuropathy. The Eye Disease Case Control Study Group identified a number of risk factors for branch, central, and hemiretinal vein occlusions including hypertension, diabetes, a history of cardiovascular disease, an increased body mass index at 20 years of age, and patients with open angle glaucoma.³⁻⁶ Branch retinal vein occlusions were particularly linked with hypertension. This echoed the findings of earlier smaller studies.^{7 8} In addition, hyperviscosity syndromes including a raised haematocrit and elevated erythrocyte aggregation rate, as well as other prothrombotic states (for example, hypofibrinolysis, increased levels of tissue factor), induced by increased levels of lipoprotein (a), malignancy, pregnancy, oestrogen therapy, and paroxysmal nocturnal haemoglobinuria have all been associated with retinal vein occlusion.^{6 9-12}

In addition to the factors described above, there are associations between retinal vein occlusions and inherited defects in the proteins of the coagulation pathways. Hypercoagulability can be the result of deficiencies in particular elements of the coagulation cascade such as protein C, protein S, or antithrombin III. Abnormal levels of the components of the fibrinolysis pathway also occur including tissue plasminogen activator, urokinase, or increases in plasminogen activator inhibitor which inhibit resolution of a thrombus.

Risk factors for retinal artery occlusions include hypertension, diabetes, hyperlipidaemia, and smoking which all increase the likelihood of carotid artery atherosclerosis. Embolic occlusions can occur with cardiac valvular disease, long bone fractures, use of intravenous drugs, following angioplasty, and with amniotic fluid emboli. In addition, as with retinal vein occlusions, there is an association with hypercoagulability, oral contraceptive use, pregnancy, and sickle cell disease.¹³

Non-arteritic anterior ischaemic optic neuropathy (NAION) is most probably caused by local factors which compromise the short posterior ciliary arteries, the pial circulation, and the retinal circulation at the optic nerve head and are most significant in the crowded disc.¹⁴ It may

also, however, be associated with systemic factors which increase the likelihood of occlusion of these arteries. Such factors include diabetes¹⁵ (odds ratio, OR=5), increased body mass index (OR=1.07), ischaemic heart disease (OR=2.6), hypercholesterolaemia (OR=2.3), and acute events such as systemic hypotension.^{15 16}

Recently, polymorphisms in genes encoding proteins which are involved in the coagulation cascade or which can enhance coagulation have been described. This review will summarise recent literature on the role of these genetic polymorphisms as risk factors for each type of retinal vascular occlusion.

Factor V Leiden

Factor V circulates in the blood as an inactive procofactor. It is activated by thrombin producing factor Va, which serves as a cofactor for factor Xa in the conversion of prothrombin to thrombin. Factor Va is inactivated through proteolytic cleavage by activated protein C. When thrombin binds to the vascular endothelium it activates protein C into activated protein C (APC). Resistance to this cleavage by APC results in a thrombotic tendency. In 95% of cases of APC resistance, the cause is a single point mutation in the factor V gene (FV R506Q), called factor V Leiden.^{17 18} Other causes of resistance to activated protein C exist including pregnancy, surgery, oral contraceptives, lupus anticoagulant, and elevated factor VIIIa¹⁹ in plasma.

A number of previous studies have shown a positive correlation between retinal vascular occlusions and activated protein C resistance, although variations in results may be reflected by the tests used.²⁰⁻²⁵ Up to 15% of people in the white population are carriers of the factor V Leiden mutation, while it is extremely rare in non-white people.²⁶ In one study of 50 thrombosis prone families, a Kaplan-Meier analysis of thrombosis-free survival curves of normal people versus carriers of factor V Leiden disclosed that by the age of 33, 8% of normal people, 20% of heterozygotes, and 40% homozygotes will have had some sort of manifestation of venous thrombosis.¹⁹ This mutation has been implicated in venous thrombotic disease including deep vein thrombosis,²⁷ but no firm evidence exists of its association with arterial disease.¹⁸ Studies of the prevalence of factor V Leiden have demonstrated how the clinical manifestation of thrombosis often requires the presence of multiple risk factors.²⁸ The majority of both homozygotes and heterozygotes have associated risk factors such as pregnancy, trauma and surgery, and the penetrance of the gene is very variable with many carriers remaining asymptomatic.

In 1998 a case report cited the association of bilateral central retinal vein occlusion with the factor V Leiden mutation as opposed to activated protein C resistance.²² In 1999, 76 German patients with a mean age of 56 years with either retinal vein or artery occlusions were investigated. This study found that the mutation was a risk factor for retinal

vein occlusions (29% of 35 CRVO patients and 19% of 21 BRVO patients were positive for the mutation compared with 9% of their normal population), but was not a significant risk factor for retinal artery occlusions.²⁹ However, it was pointed out by Vine³⁰ that the patient group was highly selected, having been referred and hospitalised specifically for a thrombotic examination. This was also true of a study by Glueck *et al*¹¹ who found a positive correlation in a population of patients with retinal venous occlusions (mean age of 52 years) which included 24% with a history of thrombotic events. The only study not apparently biased and which found a positive correlation was a case controlled study by Albinini *et al*³¹ but this had a lower prevalence of the mutation (11.1% *v* 1% controls, compared to 18% *v* 3% controls by Glueck *et al*¹¹ and 29% *v* 9% controls by Greiner *et al*²⁹ in the affected population). Currently, most studies argue against a correlation between the R506Q mutation and retinal vein occlusions.³²⁻³⁶ Indeed, in the largest series of patients³⁷ with retinal vein occlusions (n=102) to date, no difference in the prevalence of the mutation between patients and controls was found.

Significant associations with retinal vein occlusions and the mutation have, however, been noted in ocular inflammatory disease. Behçet's disease is a chronic inflammatory multisystem disorder which affects young adults characterised in some patients by recurrent retinal vein occlusions probably due to a combination of retinal vasculitis and thrombus formation. A study of 106 Middle Eastern patients with Behçet's disease and 120 racially matched controls found that the prevalence of factor V Leiden was significantly higher among patients with ocular inflammation (OR 1.67) and was more prevalent in patients who had additionally developed retinal vascular occlusive disease³⁸ (OR 2.57). This finding supported two earlier studies of Turkish patients. In one study, 60% of patients with Behçet's disease complicated by thrombosis were heterozygous or homozygous for factor V Leiden compared to 17.9% of patients with Behçet's disease but no thrombotic history.³⁹ In the other Turkish paper, 37.5% of similar patients carried the mutation compared with 13% of controls (patients with rheumatoid arthritis).⁴⁰ Thrombosis in Behçet's disease carries a poor ocular and systemic prognosis, so the presence of an identifiable and significant risk factor could be an indicator for anticoagulant treatment in addition to an immunosuppressive regimen.

The evidence that the mutation is a risk for arterial occlusive disease is inconclusive. There have only been case reports of children and young adults with central retinal artery occlusion in association with the mutation. These cases had additional prothrombotic abnormalities such as the MTHFR mutation⁴¹ (see below) or the presence of antiphospholipid antibodies,⁴² making it difficult to interpret the isolated effect that factor V Leiden might have had in producing the thrombosis.^{43 44} A single case report⁴⁵ linked heterozygosity in a patient with NAION. However, Salomon *et al*¹⁶ did not find any increased risk conferred by the presence of the factor V mutation in 61 patients with NAION. This sparse information regarding the eye does, however, echo the findings in the more abundant studies of arterial macrovascular studies that failed to find any association between factor V Leiden and arterial occlusive disease¹⁸ elsewhere in the body.

20210A prothrombin mutation

Prothrombin is converted to thrombin by factor X in the coagulation cascade. Thrombin subsequently cleaves fibrinopeptides from fibrinogen to form insoluble fibrin. It also acts with calcium ions to activate factor VIII which stabilises the fibrin clot by cross linking the molecules. In

the untranslated portion of the gene encoding prothrombin, a guanine to adenine transition may occur at nucleotide 20210. Although the mechanism by which this mutation acts is unknown, it results in elevated levels of prothrombin (30% higher than normal) which have been found to increase the risk of deep vein thrombosis in heterozygotes (relative risk 2.6; 95% CI 1.3-5.1).⁴⁶ In white people, the prevalence of the mutation is 0.7-4%, being more common in southern Europe compared with the North, while in non-white people it is extremely rare.⁴⁷ When present in association with other risk factors such as the oral contraceptive pill, the risk for cerebral vein thrombosis is also increased (OR 149.3; 95% CI, 31.0-711.0).²⁷ However, there is no firm evidence for an increased risk of arterial thrombosis.²⁸

Isolated case reports of patients with retinal vascular occlusions and this prothrombin mutation have suggested an increased risk⁴⁸ and Albinini *et al* found a prevalence of 8.3% of the mutation compared to none in the control group in a series of 36 Italian patients with retinal vein or retinal arterial occlusions.³¹ However, a large study of 102 Israeli patients did not find an association between the polymorphism and retinal vein occlusion (2.9% patients compared to 5.7% of controls).³⁷ Likewise, both Backhouse *et al*⁴⁹ in 16 and Glueck *et al* in 14 patients with retinal vein occlusions¹¹ failed to find any association. A retrospective case controlled study of 61 patients with NAION did not find any increased prevalence of the prothrombin mutation.¹⁶

Methylenetetrahydrofolate reductase (MTHFR) mutation

Homocysteine is a highly reactive intermediate amino acid, raised levels of which have been recently associated with an increased risk of thrombosis. Hyperhomocysteinaemia refers to mild to moderately elevated levels of homocysteine which appear to predispose to premature vascular occlusion. Hyperhomocysteinaemia can be caused by smoking, increasing age, medical disorders such as renal failure, folate and vitamin B-12 deficiency, and certain medications such as thiazide diuretics.⁵⁰ Genetic causes include polymorphisms of the cystathionine β synthase gene⁵¹ and the MTHFR gene. The mutation of the gene encoding MTHFR was identified by Frosst and Blom as a C to T substitution at nucleotide 677 which converts an alanine to a valine residue.⁵² Heterozygotes carrying this thermolabile variant have a reduced enzyme activity to 65% of normal, while homozygotes have only 30% of normal activity.⁵² It is found in its homozygous form in 10% of the population⁵³ and both homozygotes and heterozygotes produce elevated levels of plasma homocysteine.

In a series of 277 patients with deep vein thrombosis, the risk of thrombosis among carriers of the 677C-T genotype was significantly increased (OR 1.6; 95% CI 1.1-2.3). Furthermore, the risk was additive as the risk with the homozygous variant was higher (OR 2.0; 95% CI 1.3-3.1) for patients with other predisposing factors such as factor V Leiden, prothrombin mutation, or acquired risk factors. The risk remained significant (OR 1.7; 95% CI 1.2-2.6) after adjusting for sex, factor V Leiden, and the prothrombin mutation.⁵⁴ This was supported by a study by Arruda *et al*⁵⁵ who found an increased prevalence of MTHFR homozygosity in patients with both arterial occlusions (OR 5.52 in the absence of diabetes, hypertension, and hyperlipidaemia) and venous occlusions (OR 2.93). The risk of venous thrombosis remained high even after other causes of hereditary thrombophilia were excluded (OR 2.63). Although Arruda used 191 patients there was no comparison with matched controls. A later case control study of 471 patients with deep

vein thrombosis did not find an increased risk in patients with the MTHFR mutation.⁵⁶ Thus, current data do not support a relation between the mutation and macrovascular occlusive risk.⁵⁷

Lowenstein *et al* first described a patient with retinal vein occlusion and the 677C-T mutation,⁵⁸ and later investigated its prevalence in a series of 59 patients with retinal vein occlusion. They found a significant number of patients carried the mutation (44% were heterozygotes and 11% homozygotes, $p=0.038$) and suggested widespread screening.⁵⁷ Likewise, a study of 102 patients found a positive correlation between MTHFR homozygosity and retinal vein occlusion (OR 1.9; 95% CI 0.95–3.81).³⁷ Conversely, Glueck *et al*¹¹ in a study of 14 patients with retinal venous occlusions could not confirm this association and a study of 116 Scandinavian patients did not find any difference in either the prevalence of the mutation or hyperhomocysteinaemia between controls and patients with central retinal vein occlusions, even if all patients over 50 were excluded.⁵⁹ Furthermore, a recent retrospective case control study of 174 Irish patients found that a homozygous MTHFR genotype did not increase the risk of retinal or arterial vein occlusion.⁶⁰ Overall, therefore, current evidence does not support a relation between the MTHFR mutation and retinal vein thrombosis.

Hyperhomocysteinaemia has been proposed as a risk factor for retinal arterial occlusion. Eight of 13 patients with central retinal artery occlusions were found to have hyperhomocysteinaemia compared with age and sex matched controls.⁶¹ In a small series of 12 non-diabetic patients under the age of 50 with NAION, plasma homocysteine was raised in two of the patients.⁶² The authors acknowledged that the study was limited given its size and the lack of controls, but suggested that hyperhomocysteinaemia might have been a contributory factor. This was supported by a subsequent study where 18 of 40 patients with NAION also had increased plasma homocysteine⁶¹ levels. In a further study, 14 patients with NAION were tested specifically for the presence of the 677C-T mutation. There was no increase in risk in patients with the mutation or hyperhomocysteinaemia.⁶³ The findings of this small study were later confirmed by a retrospective case control study of 61 patients with NAION which did not find any association between the disease and the presence of the MTHFR mutation.¹⁶

The treatment of homocysteinaemia, whatever the cause, is with small doses of folate and vitamins B-6 and B-12. This is relatively simple, inexpensive, and harmless.⁶⁵ In adults, dietary folic acid at doses of 0.5–5 mg/day lowers homocysteine concentrations by approximately 25% and additional oral vitamin B-12 results in a further 7% reduction in plasma homocysteine at a dose of 0.5 mg/day. Studies have shown that homocysteine lowering improves endothelial dilatation and serum markers of endothelial injury.⁶⁴ Levels of homocysteinaemia above 11 $\mu\text{mol/l}$ increases the risk of atherosclerosis, so it has been proposed that levels be brought down to 9–10 $\mu\text{mol/l}$.⁶⁵ This would be achieved by a daily intake of 400 μg of folic acid. It has been suggested in epidemiological studies that reductions of plasma homocysteine of 30% might reduce cardiovascular events in patients with coronary heart disease by 15–30%, but the actual results of interventional studies are still awaited. There are currently no studies of the effect of lowering plasma homocysteine on venous thrombosis.

Conclusion

In a patient presenting with a retinal vascular occlusion the clinician must identify all risk factors either from the history or by investigation in order to advise on treatment and prognosis. At this time, the investigation of such

patients in order to determine whether a thrombophilic gene polymorphism is present would seem to be only useful in a research setting. Currently, an underlying genetic defect will be discovered in 50% of selected families with a high number of unexplained thromboses, indicating that there are still undiscovered prothrombotic genetic polymorphisms.⁶⁶

In this brief review, it is evident that considerably more work is required to define the association between thrombophilic gene polymorphisms and retinal vascular occlusive disease. One of the major problems encountered with these sorts of studies is the numbers of patients required to define an association. In order to determine a significant risk for thrombosis (with an odds ratio of 3 or more) at the 5% level with a 95% power where the haplotype is unevenly distributed within the population (that is, where the mutation is present in 5%), a minimum of 120 patients will be required. Less are needed if there is a 50:50 split but this is unlikely to occur if the mutation confers a biological disadvantage. Added to this are the additional numerical problems of known confounding variables (age, sex, race, smoking, cardiovascular disease, etc) and it becomes evident that very large studies are required in order to detect even moderate associations.

Factor V Leiden is undoubtedly a risk factor for thrombosis of large veins, but not for retinal vein occlusions. Studies of retinal arterial occlusion are too few to make any definitive conclusions. At present, the associated risk is insufficient on its own to justify long term anticoagulation and the testing of all patients with retinal vascular occlusion for factor V Leiden is not recommended.

Studies analysing the presence of the MTHFR mutation and retinal venous thrombosis appear inconclusive and, again, too few studies on retinal artery occlusions have been performed to provide an answer. It is unlikely that the homocysteine levels seen in patients carrying the MTHFR mutation are adequate to cause thrombosis itself, and other risk factors or reduced vitamin B-12, B-6, or folate levels will be required. Further studies are needed to determine the association between the MTHFR mutation, environmental factors, age, and vascular disease. At this time there seems little clinical point in detecting the presence of the prothrombin gene polymorphism.

The strongest association between a thrombophilic polymorphism and retinal vascular occlusion that has been identified is in Behçet's disease in which there was a positive correlation between factor V Leiden and patients with ocular inflammatory disease, especially those with occlusion. It may be that, in the presence of infection or immune activation, where proinflammatory cytokines change the normally anticoagulant properties of the vascular endothelial surface to procoagulant ones, the additional effect of such mutations is more disastrous and this, in turn, may be an indication for long term anticoagulation.

In conclusion, none of the gene polymorphisms implicated in an increased risk of thrombosis so far tested has shown an association with vascular occlusion within the eye. However, further studies with larger groups of patients should be undertaken to identify any potential subgroup in which such polymorphisms exert an effect on the onset or subsequent severity of disease.

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