Familial thrombophilia and retinal vein occlusion

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Abstract

Purpose To perform a pilot study on the prevalence of familial thrombophilia in all cases of retinal vein occlusion with no known risk factors.

Methods Over the 1 year study period 71 patients presented with a new diagnosis of retinal vein occlusion (age 28–90 years). Fifty-five (77%) were excluded because of local predisposing factors. The remaining 16 (23%) had a full risk factor history taken and blood investigations of rheological factors and thrombophilia including tests for the factor V Leiden mutation, prothrombin G20210A allele and hyperhomocysteinaemia.

Results Of those with no local predisposing factors, 3 patients had antiphospholipid antibodies, 3 had raised fibrinogen levels, 4 had hyperhomocysteinaemia and 1 was heterozygous for the Leiden mutation. Other lifestyle risk factors such as obesity, smoking and a positive family history of venous thrombosis were not uncommon. No patient had the prothrombin G20210A variant.

Conclusions It seems likely that several risk factors, both genetic and acquired, need to be present for thrombosis to occur. In investigating a new patient with a retinal vein occlusion one should test for hypertension, glaucoma and diabetes mellitus. Estimation of plasma viscosity and a full blood count are cheap investigations which may reveal neoplasia or vasculitis, and lipid levels should be estimated. In a young patient or one with an unexpected vein occlusion and a personal or family history of thrombosis, a hypercoagulable state may rarely be identified. This additional testing should include testing for antiphospholipid antibodies and a full thrombophilia screen including the factor V Leiden mutation, homocysteine and the prothrombin variant as part of a clinical trial. Until the role of these markers in thrombosis is better defined in relation to causation of retinal vein occlusion and treatment has been shown to improve outcome, we can not recommend them for routine testing. If a hereditary defect is found, referral should be made to a haematologist

and consideration given to anticoagulation and screening of family members to prevent further thrombotic episodes. Retinal vein occlusions are multifactorial in origin except in rare cases.

Key words Factor V Leiden, Hyperhomocysteinaemia, Management, Prothrombin, Retinal vein occlusion, Thrombophilia, Thrombosis

Venous thrombosis is a multifactorial disease. Risk factor profiles for central retinal vein occlusion (CRVO), hemiretinal vein occlusion (HRVO) and branch retinal vein occlusion (BRVO) have been well documented, with hypertension, diabetes mellitus and primary open angle glaucoma being the most frequently associated.^{1–5} Hyperviscosity and hypercoagulable states are felt to play a role in retinal vein occlusion,^{6–8} especially in patients under the age of 60 years.⁹ With the increasing recognition of hyperhomocysteinaemia, activated protein C resistance and the prothrombin allele G20210A mutation having a part in thrombosis, we undertook a prospective study to determine the prevalence of these factors in retinal vein occlusion in those patients not having hypertension, open angle glaucoma, diabetes mellitus or carcinoma.

Patients and methods

Seventy-one patients attending Bradford Royal Infirmary ophthalmic department over a 1 year period were diagnosed as having a retinal vein occlusion (40 men, 31 women; age range 28–90 years: CRVO ($n = 42$), HRVO ($n = 2$), BRVO ($n = 27$)). Fifty-five patients were excluded from the study because of local predisposing factors: hypertension ($n = 33$), diabetes mellitus ($n = 11$), primary open angle glaucoma ($n = 5$), raised lipid levels ($n = 4$) and carcinoma ($n = 2$). The remaining 16 patients (23%) were all investigated within 6 months after the occurrence of their retinal vein occlusion. All patients in this latter group were normotensive (systolic blood pressure < 160 mmHg; diastolic blood < 90 mmHg) and had no laboratory parameters suggestive of renal or hepatic

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disease. Ten were non-smokers, 2 ex-smokers (12–15 years) and 4 current smokers (2–40 cigarettes/day). Diagnosis of retinal vein occlusion was made by fundal indirect ophthalmoscopy.

Venous blood parameters measured were: full blood count, plasma viscosity, C-reactive protein, urea and electrolytes, glucose, lipid profile, thyroid function, liver function, autoantibody profile, plasma electrophoresis, homocysteine, fibrinogen, prothrombin time, activated partial thromboplastin time, factor VIII, functional and immune antithrombin III, functional and immune protein C, dilute Russell viper venom test, free protein S, activated protein C resistance (APCR) and prothrombin variant (G20210A). If APCR was found, then the factor V Leiden mutation was tested for. All tests were repeated if found to be positive.

In the study group, thrombotic associations documented were: history of smoking, obesity, age, sex, family history of thrombosis, oral contraceptive use, recent surgery, immobilisation, pregnancy/puerperium, and other medical conditions such as vasculitis.

Results

We found a strong association between retinal vein occlusion and a history of hypertension, diabetes mellitus, open angle glaucoma and carcinoma, which agrees with the findings of other studies.

Sixteen patients were negative for major risk factors (Table 1). Thirteen had non-ischæmic CRVO and 3 had non-ischæmic BRVO. All the venous occlusions were of sudden onset precipitating prompt ophthalmic opinion. Of the 3 patients with BRVO, 2 were under the age of 60 years. The youngest patient had a combination of five risk factors and the other was weakly positive for anticardiolipin antibodies. The patient over the age of 60 years had had previous vascular events, was a current smoker and had hyperhomocysteinaemia.

Of the 7 patients under the age of 60 years with CRVO, 3 had no risk factors. Two patients had weak titres of antiphospholipid antibodies, 2 had raised fibrinogen levels, 2 were obese, 2 had a strong personal or family history of thrombosis, 1 was a smoker, 1 was heterozygous for factor V Leiden mutation and 1 had hyperhomocysteinaemia. Concurrent medical problems were Raynaud’s syndrome in 1 patient.

Of the 6 patients over the age of 60 years with CRVO, 2 had hyperhomocysteinaemia, 2 had no risk factors, 1 was a smoker and 1 had a weak titre of antinuclear antibodies. No patient in the study group had any other thrombophilic markers such as protein S deficiency.

Discussion

Data from the Eye Disease Case–Control Study Group identified hypertension and primary open angle glaucoma as major risk factors for retinal vein occlusion. Also associated was diabetes mellitus, but this probably plays a lesser role in BRVO.^{1–3} The greater association of hypertension in BRVO may reflect the effect of hypertension at the crossing of the retinal artery and vein where they share a common adventitial sheath. The characteristic fundal findings occur downstream to this crossing.¹⁰

Larsson *et al.*⁹ found that 26% of patients aged under 50 years with a CRVO had APCR, but no such association was found in those over the age of 50 years.¹¹ No confirmatory test for factor V Leiden mutation was performed, though the factor V Leiden mutation has been reported to account for 94% of all APCR.¹² Such a high association of APCR and retinal vein occlusion has not been confirmed by other studies.^{13–17} This mutation is a relatively common hereditary abnormality, with a 1–8% prevalence of heterozygous carriers,^{18,19} but the prevalence is variable, being high in northern Europe (southern Sweden) and low in Italy,²⁰ Asia and Africa.²¹ In this study only 1 of the 6 patients aged under 50 years had the factor V Leiden mutation; she also suffered from

Table 1. Patient details of age, sex, type of vein occlusion and risk factors

Patient no.	Age (years)	Sex	Vein occlusion	Risk factors
1	28	F	BRVO	Homocysteine 20 (0–18 µmol/l), fibrinogen 4.2 (1.5–4 g/l), smoker, obese, FH +ve, IHD
2	74	M	CRVO	Homocysteine 24, ex-smoker for 15 years
3	74	F	CRVO	Antinuclear antibody weakly +ve, cholesterol 6.9, hypothyroid
4	76	M	CRVO	Smoker
5	49	M	CRVO	All –ve
6	43	M	BRVO	Anticardiolipin antibody weakly +ve, ex-smoker 15 years
7	52	M	CRVO	Lupus anticoagulant weakly +ve, obese, previous PE
8	43	F	CRVO	Fibrinogen 4.4, smoker, previous PE and DVT, FH +ve, DVT
9	79	M	CRVO	Homocysteine 21
10	68	M	BRVO	Homocysteine 21, smoker, previous CVA × 2 and MI
11	84	F	CRVO	All –ve
12	42	F	CRVO	Fibrinogen, anticardiolipin antibody weakly +ve, obese
13	62	F	CRVO	All –ve
14	36	F	CRVO	Factor V Leiden heterozygous, Raynaud’s syndrome
15	43	M	CRVO	All –ve
16	51	M	CRVO	All –ve

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; FH, family history; IHD, ischaemic heart disease; PE, pulmonary embolism; DVT, deep venous thrombosis; CVA, cerebrovascular accident; MI, myocardial infarction.

Raynaud's syndrome but had no other risk factors. It is important to note that most individuals carrying the defect will not experience a thrombotic event.¹²

Women taking oral contraception have a 4-fold increase in the risk of venous thrombosis, but this is increased by a multiple of 8 if they are carriers of APCR. The combined effect is that a young woman with APCR who also takes oral contraceptives has a 30-fold increase in the risk of thrombosis.²² The Leiden group concluded that routine screening prior to commencing oral contraception is not justifiable, but that it should be carried out if there is a history of thrombosis, to provide information for counselling on the choice of contraception.

It is unknown whether patients with venous thrombosis and factor V Leiden should be anticoagulated and, if so, at what dose and for how long. A calculation of the benefit to risk ratio of oral anticoagulation with a target INR of 2.5 does not support the use of long-term therapy in all patients with the factor V Leiden mutation following a first venous thrombotic event.²³ The significance of APCR in the absence of the factor V Leiden mutation remains unclear.²⁴

The G20210A prothrombin variant is another common abnormality, with a carrier prevalence of 1–4%; it is more common in southern Europe compared with the north. Like the factor V Leiden mutation it is very rare in people of Asian or African descent.²⁵ The resulting elevated plasma prothrombin levels increases the risk of venous thrombosis.^{26,27} An association of the prothrombin variant and factor V Leiden in causing arterial disease has not been demonstrated convincingly.²⁸ This variant was not found in any patient in the study group.

A variant form of the enzyme methylene tetrahydrofolate reductase is found in its homozygous form in 10% of the population and may cause raised levels of homocysteine. Hyperhomocysteinaemia predisposes the individual to arterial and venous thrombosis²⁹ and has been documented in association with retinal artery and vein occlusions.^{30,31} Increased plasma homocysteine levels may result from enzyme and vitamin deficiencies, smoking, increasing age, medical disorders such as renal failure or as an acute-phase response, and certain medications including thiazide diuretics.³² The haematological and vascular abnormalities associated with hyperhomocysteinaemia lead to a proatherogenic and prothrombotic metabolic milieu.^{33,34} Folic acid supplementation, with or without vitamin B12, lowers blood homocysteine levels but large-scale randomised trials are now needed to see whether this lowering reduces the risk of vascular disease.³⁵ There is preliminary evidence to suggest that this vitamin therapy may prevent progression of cerebral atherosclerosis.³⁶ The 4 patients in the study group with hyperhomocysteinaemia were commenced on 5 mg/day folic acid supplementation which reduced the levels of plasma homocysteine. Homocysteine potentiates other risk factors such as hypertension and hyperlipidaemia and raised levels should not be interpreted in isolation.³⁷

It is unknown whether the strong link between hyperhomocysteinaemia and cardiovascular events is actually causal.³⁸

Antiphospholipid antibodies are a heterogeneous array of antibodies directed against phospholipids. The two most commonly tested for are the anticardiolipin antibody and lupus anticoagulant. They have a paradoxical phenomenon of a thrombotic tendency *in vivo* and prolongation of coagulation *in vitro* and are associated with arterial and venous thrombosis.³⁹ Their incidence increases with age and they may be identified in 14% of healthy elderly patients.⁴⁰ Thrombotic episodes are recurrent and the site of the first thrombotic event tends to predict the site of subsequent events.⁴¹ Elevated titres of antiphospholipid antibodies in a healthy person do not warrant systemic anticoagulation,⁴² but in the symptomatic patient optimal treatment is unclear. However, it has recently been found that the combination of idiopathic antiphospholipid antibodies with the factor V Leiden mutation may further increase hypercoagulability.⁴³ As the risk of recurrent thrombosis is high, long-term anticoagulation, in which the INR is maintained at or above 3, is advisable.⁴⁴ Three patients in the study group had antiphospholipid antibodies. All were aged under 60 years and 2 of them had additional risk factors, the third being an ex-smoker for 15 years. The 2 with additional risk factors were anticoagulated with warfarin.

No abnormalities in the rarer inherited hypercoagulable states such as protein S, protein C or antithrombin III deficiency were detected in the study group, which agrees with the findings of previous studies.^{8,45} However, isolated case reports have been documented.⁴⁶

The number of risk factors required to cause thrombosis decreases with age, which itself therefore appears as a strong risk factor for thrombosis. It seems that with aging changes in the vessel wall and possible reduced mobility may all add to the risk profile, necessitating fewer additional risk factors for thrombosis to occur. In children, three or four risk factors are often required to precipitate thrombosis.⁴⁷

It seems likely that several risk factors, both genetic and acquired, need to be present for thrombosis to occur. In investigating a new patient with a retinal vein occlusion one should test for hypertension, glaucoma and diabetes mellitus. Estimation of plasma viscosity and a full blood count are cheap investigations which may reveal neoplasia or vasculitis, and lipid levels should be estimated. In a young patient, or one with an unexpected vein occlusion and a personal or family history of thrombosis, a hypercoagulable state may rarely be identified. This additional testing should include testing for antiphospholipid antibodies and a full thrombophilia screen including the factor V Leiden mutation, homocysteine and the prothrombin variant, as part of a clinical trial. Until the role of these markers in thrombosis is better defined in relation to causation of retinal vein occlusion and treatment shown to improve outcome, we can not recommend them for routine testing. If an

hereditary defect is found, referral should be made to a haematologist and consideration given to anticoagulation and screening of family members to prevent further thrombotic episodes. Retinal vein occlusions are multifactorial in origin except in rare cases.

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