Activated protein C and retinal vein occlusion

Venous thrombosis is a major medical problem which annually affects 1/1000 individuals.¹ Individual risk for venous thrombosis is increased in those with prothrombotic changes (thrombophilia) which can be genetic or acquired. Until recently few patients could be demonstrated to have genetic predisposition, the 'pick up rate' of patients with previous venous thrombotic events was less than 10%.^{2,3} The likelihood of identifying a genetic defect in patients with thrombosis changed dramatically in 1993 with the discovery of a new thrombophilic defect – activated protein C (APC) resistance.⁴

It is a reflection of the current speed of scientific advance, that less than 3 years later, a large amount is known about affected individuals, the genetic defect is known, and a reliable assay is widely available. APC resistance is due to the inability of protein C, a physiological anticoagulant, to act effectively. Protein C is a plasma protein that is converted to its active form by thrombin. It functions as an anticoagulant by inactivating factors V and VIII. However, in APC resistance a point mutation in factor V (FV:Q506 also known as factor V Leiden), renders factor V resistant to inactivation.⁵

In cohorts of patients with previous thrombosis APC resistance is found in 20–60% of patients, differences in frequency being related to the selection criteria for the population studied and differences in population prevalence of APC resistance.⁶ Heterozygosity for the factor V Leiden is associated with a 5–10-fold increased lifelong risk of thrombosis compared with a normal individual, while homozygosity is associated with a 50–100-fold increased risk.⁷ This mutation has a prevalence of about 5% in Europeans,^{5,8} thus homozygosity is expected in 0.06–0.25% of the population. It must be stated, however, that most individuals carrying the defect will never experience a thrombotic event.⁹

Central retinal vein occlusion (CRVO) has been previously associated with thrombophilic abnormalities, but the prevalence of APC resistance in this condition has not been studied. In this issue of the *BJO* two papers from Lund (p 200) and Glasgow (p 203) demonstrate that the prevalence of APC resistance is more common than any other known thrombophilic state and was present in over one third of patients younger than 45 years. This is a similar prevalence of APC resistance to that seen in other venous thrombotic states. Thus, in an ideal world, many would argue that a full thrombophilia screening should be performed in a young patient (<50 years old) after CRVO as after any other venous thrombotic event. A more cost effective approach may be to screen initially for APC resistance. If this is negative then the residual thrombophilia screen including APC resistance, lupus anticoagulant, anticardiolipin antibodies, protein C, protein S, and antithrombin III should be performed. The test for APC resistance is relatively easy to perform, provides good discrimination between normal and APC resistant subjects, and has a specificity and sensitivity of 85–90%. It is not reliable if the patient has abnormal clotting such as lupus anticoagulant or is receiving anticoagulants.⁶ The gold standard is a DNA based assay for the genetic defect but this is expensive and not widely available.

What effects will the discovery of APC resistance have on the future management of the patient with CRVO? This is not clear. The standard treatment for patients with recurrent venous thrombosis at other sites is long term warfarin. A single thrombosis is treated with a short course of anticoagulants. A single thrombosis in an individual with the antiphospholipid syndrome merits long term high dose (international normalised ratio >3) anticoagulation indefinitely.¹⁰ A single thrombosis in an individual with a genetic thrombophilic abnormality such as APC resistance is more difficult. There are not enough data, since we have not had enough time to study these individuals long term. Most haematologists would give a short course of warfarin and then follow up the individual, giving thromboprophylaxis at times of haemostatic stress such as surgery and pregnancy; some would leave patients on long term anticoagulation. Affected women should not use the combined oral contraceptive pill, for compared with women without the mutation and not using oral contraceptives, they have a 30-fold increased risk of thrombosis.¹¹

The management of patients with CRVO and APC resistance has an added complication – neovascularisation: anticoagulation and/or aspirin may contribute to the risk of intraocular haemorrhage. For the moment the risks and benefits of antithrombotic treatment in each individual must be considered carefully; a prospective study is indicated to assess the effects of long term warfarin in CRVO. Certainly the association of APC resistance with retinal vein occlusion has introduced some new management considerations in young patients with retinal vein occlusion.

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