British Heart Foundation

Factfile 02/2002

THROMBOPHILIA

There is no generally agreed definition of thrombophilia but the term is used to describe patients who are at significantly increased long-term risk of venous thromboembolism (VTE), eg deep venous thrombosis or pulmonary embolism. Such individuals can be identified by clinical and/or laboratory criteria. These include a personal history of VTE which has arisen spontaneously (or after minimal provocation), has first occurred at a young age, or is recurrent. Laboratory criteria which are met in only 50% of patients are based on an identifiable abnormality of the haemostatic system associated with an increased risk of VTE. It should be recognised however that many people with a laboratory abnormality never experience a venous thrombosis.

The causes of thrombophilia

Heritable thrombophilia

Many of the causes of a long term increased risk of venous thrombosis have been associated with an heritable abnormality of one of the following plasma proteins:

	Increased risk of thrombosis	Prevalence in patients with VTE (%)	Prevalence in normal population (%)
Factor V Leiden heterozygous* (activated protein C resistance)	3-8 x	25-50	5.0
Prothrombin G20210A	3 x	6	2.0
Antithrombin deficiency	25-50 x	1	0.02
Protein C deficiency	10-15 x	3	0.3
Protein S deficiency	10 x	3	2.0
Dysfibrinogenaemia	variable	low	rare

**Factor V Leiden homozygous individuals have an 80 x risk of VTE*

Factor V Leiden mutation is due to a single base change in the gene for clotting factor V which delays its degradation, resulting in an increased persistence of the prothrombotic activated factor Va molecule. Prothrombin G20210A is due to a single base change in the 3' untranslated region of the prothrombin gene and is associated with an elevated plasma level of prothrombin. Antithrombin and Proteins C/S inactivate activated clotting factors and hence deficiencies result in persistence of activated prothombotic proteins in the blood. Dysfibrinogenaemia is rare and is usually associated with a reduced plasma fibrinogen concentration. In addition to the above single gene abnormalities, plasma factor VIII and homocysteine levels are partly regulated by heritable factors and are associated with an increased incidence of venous thrombosis.

There is increasing evidence that individuals with two or more laboratory characterisable thrombophilic abnormalities (or who are homozygous for either factor V Leiden or prothrombin G20210A) are at greater risk of venous thrombosis than those in whom there is a single abnormality.

Acquired thrombophilia

The principal acquired thrombophilic abnormality is the antiphospholipid antibody which can be associated with both venous and arterial thrombosis. The antiphospholipid antibody can be 'primary' when it is only associated with venous (or arterial) thrombosis (and is also associated with recurrent first trimester abortions). The antibody is described as 'secondary' when it is found in conjunction with other conditions eg collagenosis, SLE. This antibody is characterised either by its ability to inhibit platelet dependent coagulant reactions (when it is known as the lupus anticoagulant), or as an anti-cardiolipin antibody (detected by its binding in vitro to cardiolipin).

In addition to the above long term factors predisposing to VTE there are many other situations when there is an

14 Fitzhardinge Street, London W1H 6DH
Telephone 020 7935 0185 Website www.bhf.org.uk

Factfile *is produced by the British Heart Foundation in association with the British Cardiac Society and is compiled with the advice of a wide spectrum of doctors, including general practitioners. It reflects a consensus of opinion.*

increased risk of VTE, eg the combined contraceptive pill, HRT, obesity, malignancy and chronic inflammatory conditions. In these situations there are often several general pathological mechanisms contributing to the thrombotic tendency.

Who should be investigated for thrombophilia?
Before laboratory investigation of a patient, or family, is undertaken the following considerations need to be taken into account:

- The patient needs to appreciate the nature and limitations of the investigations. Furthermore it is important to know what advice should be given if an abnormality is identified.
- The laboratory results may be affected by other medical conditions and medication, eg, liver disease, pregnancy, the combined oral contraceptive pill or anticoagulants.
- The identification of a laboratory thrombophilic abnormality will not usually influence a patient's immediate treatment for venous thrombosis but may be of value in preventing further thrombosis and in counselling other family members so as to reduce their risk of a thrombotic episode. This is particularly applicable to women who are contemplating pregnancy so as to offer the most appropriate advice to reduce the risk of pregnancy-associated venous thromboembolism (the commonest cause of pregnancy related death).
- It must be appreciated that for an individual who has had a spontaneous DVT there may be heritable defects that have not yet been discovered: therefore a normal thrombophilia screen does not imply either a 'normal' or no increased risk of thrombosis in the future or in another family member.

Referring patients
As the clinical interpretation of a thrombophilia screen will depend upon each patient's circumstances it is sensible for patients to be referred to a specialist who has experience in counselling and testing such individuals and families (rather than just taking a blood sample and requesting thrombophilia investigations).

Patients with the following should be considered for referral:

- Spontaneous thrombosis, particularly at a young age, or associated with pregnancy.
- Thrombosis at an unusual site, eg Budd Chiari syndrome, sagittal sinus thrombosis.
- Recurrent thrombosis.
- Thrombosis in those with a VTE and a first degree relative with a history of VTE.

What further advice should be offered to patients?

- Advice should be given to reduce appropriate background 'acquired' risk factors, eg consider carefully use of the combined oral contraceptive pill or hormone replacement therapy.
- Individuals may need to take extra anti-thrombotic precautions in 'high risk' situations, eg after major surgery and during long journeys.
- Women should seek specialist advice about risks and precautions in pregnancy; if possible pre-pregnancy counselling should be offered.
- Consider which family members should be investigated and how this might be arranged.
- Patients should only be offered long-term anticoagulation or antiplatelet therapy if the benefits outweigh the potential risks of serious haemorrhage.

References:

1. Investigation and Management of Heritable Thrombophilia.
   British Journal of Haematology. 2001: 114, 512 - 528.

2. Antiphospholipid Antibody Guidelines.
   British Society of Haematology. 2000: 109, 704 - 715.

3. Antithrombotic Therapy.
   Scottish Intercollegiate Guidelines Network, SIGN Publication No 36. March 1999.

4. Prevention of Venous Thromboembolism.
   Scottish Intercollegiate Guidelines Network. March 2002.

Further Reading:

For references 1 and 2:
http://bcshguidelines.com/guidelines.asp?tf=Haemostasis+and+Thrombosis

For references 3 and 4:
http://www.sign.ac.uk