Information sheet

Guidelines for Testing for Heritable Thrombophilia

Background

Heritable thrombophilia describes an inherited tendency to develop venous thrombosis (DVT and/or PE)[1]. Deficiencies of the naturally occurring anticoagulants antithrombin, protein C and protein S have been linked with familial venous thrombosis. The factor V Leiden (1691G>A, R506Q) and prothrombin (20210G>A) gene variants are associated with an increased risk of venous thrombosis (see Table 1 for relative risks).

When to test

Some tests for heritable thrombophilia (assays of antithrombin, protein C and protein S) are affected by the acute post-thrombotic state and by anticoagulant use[2]. Consequently, thrombophilia testing should be delayed until at least 6 weeks after cessation of anticoagulant therapy. Thrombophilia testing should be avoided during pregnancy and in patients using combined oral contraceptives or hormone replacement therapy.

Who to test

Which patients should be considered for thrombophilia testing?
Thrombophilia results are often difficult to interpret and can be misleading. Please use the contact numbers below to discuss, or consider referring the patient to the haematology clinic if appropriate.

(A) Patients with symptoms of thrombophilia

Please note: Testing for heritable thrombophilia is NOT indicated in UNSELECTED patients presenting with venous thrombosis[1].

It is recommended that thrombophilia screening should be undertaken in the following patients:

1. **Unprovoked** venous thromboembolism before the age of 40 years
2. Recurrent **unprovoked** thromboembolism
3. Thrombosis in unusual sites
4. **Unprovoked** venous thromboembolism in a patient whose first degree relative meets criteria 1-3
5. Women with unexplained late fetal loss or ≥3 spontaneous early miscarriages (it is important to exclude cardiolipin antibodies and lupus anticoagulant in these cases)
6. Unexplained skin necrosis, especially if taking vitamin K antagonists (e.g. Warfarin)
7. Children and neonates with purpura fulminans

(B) First degree relatives WITHOUT symptoms of thrombophilia

Testing asymptomatic first degree adult relatives (siblings, parents, offspring if ≥16 years) of patients with a history of venous thrombosis may be indicated in some circumstances. Identification of family members at risk for venous thrombosis may provide the opportunity for short-term targeted thrombophylaxis in periods of increased thrombotic risk (eg. surgery, trauma or immobilization).

Recommendations for testing unaffected family members[1]:

- The testing of asymptomatic relatives of patients with low risk thrombophilia (such as factor V Leiden or prothrombin gene variants) is **NOT** indicated
- The testing of asymptomatic relatives of patients with high risk thrombophilia (deficiency of antithrombin, protein C or protein S) should only be considered in selected thrombosis-prone families. Please discuss with a Consultant Haematologist before taking samples.

The absence of a proven heritable risk factor reduces the utility of thrombophilia testing and wherever possible the affected family member(s) should be tested first. If this is not possible, a

negative result in the asymptomatic relative should be interpreted with caution since it does not exclude an increased risk of venous thrombosis.

Samples for testing:
Please send 3 coagulation tubes (green topped bottles) requesting a 'Thrombophilia Screen' to the haematology laboratory. We aim to provide a customised clinical / laboratory report for every thrombophilia screen, so full clinical details are essential. Samples with insufficient clinical details or those that do not meet guidelines for testing will be stored for one month, to allow time for the requestor to supply further information or discuss the request with a Consultant Haematologist.

If you have any questions about heritable risk factors for thrombophilia please contact Dr Jason Coppell (Consultant Haematologist, email jcoppell@nhs.net, tel 01392 402468) or Professor Sian Ellard (Consultant Molecular Geneticist, email Sian.Ellard@nhs.net, tel 01392 408259). Further information is available on the Exeter laboratory website http://www.exeterlaboratory.com/genetics/heritable-thrombophilia/ .

Table 1. Frequency of thrombophilia and relative risk estimates for various clinical manifestations.[3]

	Antithrombin Deficiency	Protein C Deficiency	Protein S Deficiency	Factor V Leiden variant	Prothrombin variant
Prevalence in general population	0.02%	0.2%	0.03-0.13%	3-7%	0.7-4%
Relative risk for 1st venous thrombosis	5-10	4-6.5	1-10	3-5	2-3
Relative risk for recurrent venous thrombosis	1.9-2.6	1.4-1.8	1.0-1.4	1.4	1.4
Relative risk for arterial thrombosis	No association	No consistent association	No consistent association	1.3	0.9
Relative risk for pregnancy complications	1.3-3.6	1.3-3.6	1.3-3.6	1.0-2.6	1.1-1.2

References

[1] Baglin et al. (2009) British Committee for Standards in Haematology Guidelines: Page 1-19 (http://www.b-s-h.org.uk/)
[2] Walker et al. (2001) British Journal of Haematology, 114:512-528
[3] Middledorp and van Hylckama Vlieg (2008) British Journal of Haematology, 143:321-335

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