SPECIALTY: HAEMATOLOGY
CLINICAL PROBLEM: THROMBOPHILIA TESTING

Inherited thrombophilic tendencies

Rationale
1. Venous thromboembolism is best thought of as a multifactorial disease, and most likely to occur when several risk factors co-exist.
2. Less than 50% of individuals/families with a strong history of VTE at a young age have an identified thrombophilic abnormality.
3. Above age 45, comorbidities such as malignancy, diabetes, chronic inflammation and vascular disease are much more potent risk factors and swamp the effect of inherited tendencies.
4. When FV Leiden was discovered nearly 20 years ago, it was thought that this would help us detect patients at risk of recurrent venous thrombo-embolism. This has not proved to be the case: FVL is a risk factor for first VTE, but the greatest risk factor for recurrence is having had a first VTE. Thrombophilic tendencies do not change this risk.
5. It has become clear that inherited thrombophilic tendencies are not implicated in arterial thromboembolism.
6. Inherited thrombophilic abnormalities do not have a high penetrance, so do not provide a strong predictor of VTE risk.
7. Inherited tendencies do not cosegregate with symptomatic VTE in families: any patient with a first degree relative with VTE is at increased risk, whether they have inherited the identified thrombophilic tendency or not.

These facts have become clear after testing many thousands of patients for inherited thrombophilias. The utility of such testing is now known to be limited. This guideline aims to set out where thrombophilia is and is not recommended as an aid to clinical management. (based on National guidelines published by the British Committee for Standards in Haematology 2010).

DVT of lower or upper limb and pulmonary embolism
Finding inherited thrombophilic tendencies does not influence intensity or duration of anticoagulation and does not predict recurrence. It therefore rarely influences the management of the patient with VTE.
In the case of FVL in the proband, studies have shown that the difference in risk of thrombosis between family members with and without FVL was not significant. It is therefore recommended not to seek cases of FVL etc in families.
In AT deficiency, the risk of provoked thrombosis is <20% per year. The risk of unprovoked thrombosis in any group is low.
It is reasonable to test for AT deficiency if a first degree relative of the proband has also had an unprovoked VTE at a young age.

Retinal vein thrombosis
The relevance of hypercoagulability is uncertain, as is the value of anticoagulation. Recurrence is rare. Testing not indicated.
**Cerebral vein (sinus) thrombosis**
It is common practice to test these patients for thrombophilia, and consider long term warfarin if a defect is detected, although this is not evidence based.

**Central venous catheter thrombosis**
Usually explained by other factors such as underlying malignancy. Testing not indicated.

**Intra-abdominal vein thrombosis**
Associated with myeloproliferative disorders, cirrhosis and abdominal surgery. Testing not indicated.

**Purpura fulminans**
Consider urgent testing for PC and PS deficiency (may be acquired as in children with chicken pox).

**Testing asymptomatic individuals**

1. **Before prescribing the COCP or HRT**
   Routine screening before prescribing the COC or HRT is not indicated.
   A first degree relative with a history of VTE is a relative contra-indication to the COC/HRT, particularly if the proband’s thrombosis was oestrogen related.
   It is unhelpful to test the asymptomatic patient.
   If the symptomatic relative has not been tested, or has a negative screen, testing the proband is unhelpful, and a non-oestrogen containing preparation should be recommended.
   If the symptomatic relative has a known inherited thrombophilic tendency, an alternative contraceptive should be recommended first, as even if the proband tests negative, they may still be at increased risk.
   If HRT is deemed essential, transdermal preparations should be used.

2. **Prevention of pregnancy associated thrombosis**
   Women with a previous unprovoked or COC or pregnancy related thrombosis will require thromboprophylaxis anyway and do not need to be tested.
   Women with a previous VTE caused by a major provoking event, eg major surgery, do not require prophylaxis during pregnancy and do not require testing.
   Women with a minor provoking event, eg air travel may benefit from testing to help make decisions.
   If there is a history of VTE in a first degree relative, the circumstances are again important. If the event was COC or pregnancy related, finding the same thrombophilia would prompt consideration of prophylaxis, especially in AT or PC deficiency.

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**Acquired thrombophilic tendencies: Antiphospholipid syndrome**

This is defined by finding persistent (ie still present after 3 months) lupus anticoagulant or anti-cardiolipin antibodies in association with clinical features of antiphospholipid syndrome. These include:
- Venous thromboembolism
- Arterial thromboembolism eg CVA
- Livedo reticularis
- Recurrent pregnancy loss (recurrent early miscarriage and mid trimester loss)
It may also be useful to test for lupus anticoagulant/ACA in:
unexplained prolonged APTT, especially with incomplete correction with normal plasma
Thrombocytopenia
In association with other autoimmune diseases such as SLE, rheumatoid where clinical
features suggest secondary APS

Summary

Full thrombophilia screen (ie inherited and acquired tendencies)
1. Unprovoked venous thromboembolism below age 40

Inherited factors only
1. Planning pregnancy, with a history of unprovoked/oestrogen related VTE in first
degree relative below age 40 (more informative if proband’s results known)
2. Children with purpura fulminans (urgent Protein C and S)
3. Adults with skin necrosis on warfarin (Protein C and S)

Lupus anticoagulant testing only
1. Arterial thromboembolism below age 35
2. Recurrent miscarriage
3. Unexplained late pregnancy loss
4. Unexplained prolonged APTT
5. ITP and other auto-immune disorders

Please discuss suspected Haemophilia with Haematologists:
St Richard’s –ext 3598
Worthing –ext 5575

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OTHERS INVOLVED: All LRMG Committee members.

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THROMBOPHILIA TESTING

(1) Inherited thrombophilic tendencies

Rationale

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12. It has become clear that inherited thrombophilic tendencies are not implicated in arterial thromboembolism.
13. Inherited thrombophilic abnormalities do not have a high penetrance, so do not provide a strong predictor of VTE risk.
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