Clinical Aspects of Thrombophilia Testing

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Natural Anticoagulants

Rationale for Thrombophilia Testing

• Identification of a heritable thrombophilia may influence rates of venous thromboembolism (VTE) recurrence and therefore influence decisions regarding anticoagulation, especially duration of anticoagulation
• However these thrombophilias only represent part of the genetic risk for VTE

Heritable Thrombophilias Tested For

• Factor V Leiden (activated protein C resistance)
  – Heterozygotes OR ~3-5
• Prothrombin gene mutation
  – Heterozygotes OR ~2-4
• Antithrombin III deficiency
  – OR >10
• Protein C deficiency
  – OR >10
• Protein S deficiency
  – OR >10

Acquired Thrombophilias Tested For

• Anti-phospholipid syndrome (anti-cardiolipin antibodies, anti-beta 2 glycoprotein antibodies, lupus anticoagulant)
• Multiple risk factors are more than additive
Risk Factors for VTE

- Strong risk factors (odds ratio >10)
  - Fracture (hip or leg)
  - Hip or knee replacement
  - Major general surgery
  - Major trauma
  - Spinal cord injury

-Moderate risk factors (odds ratio 2-9)
  - Arthroscopic knee surgery
  - Central venous lines
  - Chemotherapy
  - CHF or respiratory failure
  - Hormone replacement therapy or oral contraceptive therapy
  - Malignancy
  - Paralytic stroke
  - Pregnancy/post-partum
  - Previous VTE
  - Inherited thrombophilia

Risk Factors for VTE

- Weak risk factors (OR <2)
  - Bed rest >3 days
  - Immobility due to sitting
  - Increasing age
  - Laparoscopic surgery
  - Obesity
  - Varicose veins

To Test or not to Test?

- Will a positive result change the decision for anticoagulation/duration of anticoagulation?

Example 1

- 30y/o man in hospital with active ulcerative colitis. Presents with above knee left leg DVT.

No – active inflammatory bowel disease is a strong risk factor for VTE

Example 2

- 30y/o lady attends GP to discuss possible pregnancy. Had previous DVT while on combined oral contraceptive pill.

No – already had oestrogen-related VTE so should have thromboprophylaxis regardless
Example 3

- 30y/o lady attends GP to discuss possible pregnancy. Mother had pregnancy-associated DVT during late pregnancy in her 2nd pregnancy.

Yes – testing is justified as if a thrombophilia is found, thromboprophylaxis would be justified, especially if same defect as mother.

Example 4

- 40y/o lady presents with large proximal DVT, unprovoked, no medical problems, no previous VTE.

Current guidelines do not recommend heritable thrombophilia testing as positive result would not significantly affect likelihood of VTE recurrence. Consider testing for antiphospholipid syndrome.

Example 5

- 60y/o man with atrial fibrillation presents with the following reaction 6 days after starting warfarin.

Yes – warfarin skin necrosis, associated with protein C/protein S deficiency (test for these). Associated with high loading doses of warfarin given without heparin cover.

Example 6

- 30y/o woman, seeing GP about wanting to go on combined oral contraceptive pill. Sister had DVT while on combined oral contraceptive pill.

No – this family history is a relative contraindication to combined oral contraceptive. Suggest alternative form of contraception.

Example 7

- 30y/o lady attends GP to discuss pregnancy. Previous DVT provoked by flight to London.

Yes – VTE provoked by minor risk factor – if thrombophilia then may need thromboprophylaxis.
Example 8

• 30y/o man with first episode of below knee DVT. Mother has had a below knee DVT, sister has had also had a below knee DVT. No previous thrombophilia testing done.

Yes – in patients with a positive family history, presence of ATIII/PC/PS deficiency associated with higher risk of VTE recurrence

Thrombophilia Testing

• In general, the presence of an inherited thrombophilia does not alter the anticoagulation management of an individual with VTE
• All patients with idiopathic VTE are at substantial risk of recurrence regardless of whether a thrombophilia is identified
• Phenotype (family history) matters

Who should be tested?

• Patients presenting with first VTE <40 years with positive family history (at least 2 first degree relatives affected)
  — Retrospective study of young patients with a family history of VTE found that deficiency of ATIII/PC/PS predicted annual risk of recurrence of 6.23% vs 2.25% for Factor V Leiden or prothrombin gene mutation (Lijfering 2009)
• Indiscriminate testing of patients presenting with first unprovoked VTE is not indicated

Who should be tested?

• Women at risk of VTE who are pregnant/considering pregnancy
  — Previous VTE due to minor risk factor
  — First degree relative with previous VTE unprovoked, or due to minor risk factor, pregnancy or COC pill
  — Most pregnant women with previous unprovoked VTE will need thromboprophylaxis regardless
  — Most pregnant women with previous VTE provoked by strong risk factor will not need thromboprophylaxis

Testing In Specific Situations

• Testing is not recommended after:
  — Upper limb thrombosis
  — Retinal vein thrombosis
• Testing has uncertain predictive value after:
  — Cerebral venous sinus thrombosis
  — Intra-abdominal thrombosis
Testing after acute VTE

- Acute thrombosis can transiently decrease the plasma concentration of antithrombin III and occasionally protein C and protein S
- However if normal AT III, protein C and protein S levels at presentation of VTE prior to anticoagulation, deficiencies of these are essentially excluded

Testing on Anticoagulants

- Heparin
  - May cause a decrease in antithrombin III levels
  - May cause false positive lupus anticoagulant
- Warfarin
  - Markedly reduces protein C and protein S functional activity
  - Less markedly reduces protein C and protein S levels
  - Occasionally causes falsely normal antithrombin III levels in patients with antithrombin III deficiency
  - May cause false negative lupus anticoagulant

Testing on Anticoagulants

- Prothrombin gene mutation, Factor V Leiden, anti-cardiolipin antibodies and anti-beta 2 glycoprotein antibodies are unaffected by anticoagulation

Testing With Oestrogen

- Pregnancy and oestrogen therapy can be associated with reduced protein S levels and may cause false positive activated protein C resistance (factor V Leiden)

Recommendations

- Ideally, perform thrombophilia screen at least 2-4 weeks after completed initial 3-6 month course of anticoagulation
- If low levels of protein C, protein S or antithrombin III, or if antiphospholipid antibodies are found, repeat testing in 12 weeks is indicated to confirm
- Ideally, test at least 1 month post-partum or off oestrogen therapy for at least 1 month (this may not be possible)

Recommendations

- Before testing, think about how management will be altered if a positive result is found
Other Things to Look For in Idiopathic VTE

• FBC
  – Evidence of myeloproliferative disorder?
    • Polycythaemia vera
    • Essential thrombocythaemia
  – Evidence of haemolysis?

• Malignancy?
  – Careful history and examination
  – Basic bloods, CXR
  – Age-appropriate cancer screening

Arterial Thrombosis

• Look for cardiac source (AF, PFO, atrial septal aneurysm etc)
• Look at FBC – ?myeloproliferative disorder
• Consider testing for antiphospholipid syndrome if it will alter management
• Don’t test for heritable thrombophilias

References