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THROMBOSIS RISK TESTING INFORMATION SHEET

INTRODUCTION

In recent years, an increasing number of conditions have been identified as causing thrombophilia (i.e. a predisposition to thrombosis). Numerous tests have been developed to diagnose these disorders, however, these tests are generally time-consuming and expensive, and they should not be used to 'screen' all patients with thrombosis. Instead, a careful selection of patients for thrombophilia testing is advised in order to have an acceptable cost/benefit ratio.

INDICATIONS FOR THROMBOPHILIA TESTING

A general guideline for thrombophilia testing is listed in *Table 1*. Although an early age of onset is suggestive of hereditary thrombophilia, it is known that patients with inherited genetic mutations may also present with their first thrombotic episode at an older age (>60 years). The presence of associated risk factors does not exclude the possibility of an underlying genetic defect, since thrombosis is a multifactorial disease.

Table 1. Patients for whom thrombophilia screening tests should be considered

- Family history of venous thromboembolism
- Recurrent idiopathic thrombosis
- Early age of onset (i.e. before age 45).
- Thrombosis after trivial provocation
- Association of arterial and venous thrombosis
- Association of thrombosis and fetal losses
- Thrombosis in unusual sites (e.g cerebral, portal, mesenteric)
- Warfarin-induced skin necrosis
- Neonatal purpura fulminans

Table 2. Thrombosis risk test panel (not necessarily a screening panel)

Clotting based assays:
- Protein C
- Protein S
- Antithrombin
- Activated protein C resistance
- Lupus anticoagulant
- 'Shortened' APTT

Immunological:
- Anticardiolipin antibody

DNA-based testing:
- Factor V Leiden
- Prothrombin G20210A mutation
- MTHFR C677T mutation

Others:
Homocysteine levels

A) TESTS FOR INHERITED CAUSES OF THROMBOPHILIA:

i) Activated Protein C (APC) resistance coagulation test /Factor V Leiden genetic test:

APC combines with the natural anticoagulant, protein S, to inactivate factors Va and VIIIa and limit clot formation. Most cases of APC resistance are due to a genetic mutation of the factor V molecule, known as factor V Leiden (FV Leiden), which occurs in about 5% Caucasians and is strongly associated with venous thromboembolism. Certain acquired conditions (pregnancy, oral contraceptive use, lupus anticoagulant, and elevated factor VIII levels) may also result in an APC-resistance phenotype. APC resistance is detected by specific clotting tests, and FV Leiden is detected by genetic testing.

ii) Prothrombin G20210A gene mutation:

A common genetic variation of the prothrombin gene (known as the G20210A mutation) is associated with elevated plasma levels of prothrombin, and an increased risk of venous thrombosis. This mutation is detected by genetic testing, and it appears to be the second most frequent inherited cause (following FV Leiden) of thrombosis risk, with a prevalence of about 2% in Caucasians.

iii) Assays for hyperhomocysteinaemia and methylenetetrahydrofolate reductase (MTHFR) C677T gene mutation test:

Hyperhomocysteinaemia promotes atherosclerosis as well as venous and arterial thrombosis. Plasma homocysteine levels can be measured, however fasting specimens should ideally be collected. Individuals who are homozygous for the thermolabile variant of the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), have half the activity of the normal enzyme with significantly elevated plasma homocysteine levels. However, it is unclear if homozygosity for this mutation is a risk factor for venous thrombosis. Genetic testing can detect the presence of the MTHFR mutation.

iv) Antithrombin (AT), Protein C and Protein S assays:

The association between familial deficiencies of the natural anticoagulants AT (formerly known as antithrombin III), Protein C, or Protein S and venous thromboembolism is well known. Both quantitative and qualitative deficiencies exist and specific coagulation tests and immunoassays are generally used in diagnostic testing.

B) TEST FOR ACQUIRED CAUSES OF THROMBOPHILIA:

i) Antiphospholipid antibodies (Lupus anticoagulant and anticardiolipin antibody assays):

Antiphospholipid antibodies (APA) are acquired autoantibodies directed against phospholipid-protein complexes and may be associated with venous and/or arterial thrombosis, thrombocytopaenia or recurrent miscarriage. There are two main types of APA - the lupus anticoagulant (LA) and the anticardiolipin antibody (ACL), and testing for both types should always be performed. The LA is one of the causes of a prolonged APTT. Transiently positive APA tests are not uncommon and may occur after acute infection. Thus,

it is important to confirm a positive APA test after a suitable time interval (usually more than eight weeks).

LIMITATIONS OF THROMBOPHILIA TESTING

Since such specialised testing is not performed on a daily basis, one may have to wait up to several weeks to obtain results. Most of the tests (apart from DNA analysis) are affected by the post-thrombotic phase, so they should be performed a few months after an acute episode whenever possible. Testing should only be performed in specialised laboratories, and when an abnormality is detected, the test may need to be repeated on another occasion if the diagnosis is in doubt. The existence of underlying conditions that influence normal haemostasis (such as pregnancy, liver disease, oral contraception, hormone replacement therapy) should be considered when any laboratory diagnosis for thrombophilia is performed, as they can affect the result of thrombophilia coagulation assays. The use of heparin and/or warfarin anticoagulation may affect thrombophilia testing, and if possible, it is best to wait until patients are no longer receiving anticoagulation. Specifically, AT levels are reduced by heparin, and the diagnosis of protein C or protein S deficiency is difficult and not recommended in patients receiving warfarin therapy because the results are influenced by the use of vitamin K antagonists. Diagnosis of a weak lupus anticoagulant can also be difficult in warfarinised patients.

MANAGEMENT OF THROMBOPHILIA

Since this is a rapidly evolving field, once a patient with a suspected thrombophilic risk factor has been identified, they should generally be referred to a specialist in this field of medicine for further assessment and education, and family studies if relevant. The individual patient's clinical scenario is often more important in determining management than is the result of specific thrombophilia testing. Not all patients with an underlying thrombophilia necessarily require long-term anticoagulation. Ongoing clinical trials are attempting to answer questions concerning optimal management of these patients. There are a group of patients who, from a clinical point of view, would appear to have thrombophilia, but following laboratory testing, have no identifiable thrombophilic risk factor. In general, they should also be referred to a specialist for assessment and management, as they may also require long-term anticoagulation.

CONCLUSION

There have been many advances made in thrombosis risk testing over recent years, and it is likely that new thrombophilic factors will continue to be discovered. These advances have allowed many more patients with both acquired and inherited causes of thrombophilia to be identified. Although widely available, testing should not be applied indiscriminately to all patients with thrombotic disorders. Instead, careful consideration of each individual patient (together with family history) should be made, so that the appropriate tests can be performed and a sensible approach to patient management can be made. *NOTE: Medicare rebates for thrombophilia testing are restricted to patients with a proven history of venous thrombosis and patients with a first degree relative with a proven thrombophilia defect.*