
Inherited thrombophilia

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Inherited thrombophilia

EBM Guidelines

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Essentials

- Inherited thrombophilia increases the likelihood of venous thrombosis.
- The highest risk is associated with severe inherited thrombophilia which, if diagnosed, will often affect the duration of treatment in patients with venous thrombosis. High-risk thrombophilia is associated with
    - antithrombin deficiency
    - homozygosity for FV Leiden or prothrombin G20210A mutation
    - simultaneous heterozygosity for several gene defects (double heterozygosity)
    - protein C, and possibly protein S, deficiency.
- Solitary heterozygous FV Leiden or prothrombin mutation will increase the thrombotic risk only slightly.
- The association between inherited thrombophilia and arterial occlusion is less clearly demonstrated. In practice, arterial obstruction should only raise a suspicion of inherited thrombophilia if encountered in a young person with no known risk factors.
- Predisposition to thrombotic events may also be caused by acquired disturbances in the coagulation system, the most important of which is the presence of circulating phospholipid antibodies.

Causes of inherited thrombophilias

- Predisposition to thrombotic events due to intrinsic hereditary factors is called inherited thrombophilia.
- The thrombophilias identified so far are inherited as an autosomal dominant trait. Most patients are heterozygous. Homozygous patients are at a significantly greater risk to develop thrombosis, and homozygosity for antithrombin deficiency, for example, is likely to lead to death during foetal life.
- Inherited thrombophilia should be considered if the patient has a positive family history, thrombosis occurs at a young age and recurs frequently.
    - It should be borne in mind that even when familial predisposition to thrombotic events is clearly demonstrated, the underlying cause can be identified in only about 60% of cases with the investigation methods currently available. A number

of factors that increase the thrombotic tendency are yet to be ”identified”. Thus, if a patient with a strong family history presents with thrombosis, the treatment should be carried out as if the patient had thrombophilia even if the results from thrombophilia testing are normal.

- The prevalence of inherited predisposition to thrombotic events and the associated risk of venous thrombosis are presented in table [1] . The diagnosis of inherited thrombophilia due to FV Leiden or G20210A mutation can be based on one abnormal result. However, the diagnosis of other forms of inherited thrombophilia requires an abnormal result from two separate samples and a similar result in a first-degree relative.

Aetiology of venous thrombosis (in descending order of frequency)

1. Resistance to activated protein C (APC resistance, FV Leiden, FV R506Q, FV G1691A)
    - By far the most common gene defect behind thrombophilia
    - The defect is a mutation of the coagulation factor V (FV). The mutation alters FV and makes it more resistant to inactivation by activated protein C. The disorder is, therefore, known as APC resistance.
2. Polymorphism of the prothrombin gene G20210A (FII G20210A)
3. Protein C deficiency
    - Quantitative deficiency of protein C may be present (Type 1 deficiency) or its functional activity may be qualitatively deficient (Type 2 deficiency). Over 160 gene defects have been described 1.
4. Protein S deficiency
    - Quantitative deficiency of protein S may be present or its functional activity may be qualitatively deficient. Over 200 gene defects have been described 1.
5. Antithrombin III deficiency
    - Quantitative deficiency of antithrombin may be present (Type 1 deficiency) or its functional activity may be qualitatively deficient (Type 2 deficiency). 130 different gene defects are known. The thrombosis risk is related to the type and degree of the deficiency 1.
6. Other inherited cause of thrombophilia
    - Increased activity of coagulation factor VIII (has little clinical significance as far as treatment guidelines are concerned, not routinely included in thrombophilia testing) 1
    - Dysfibrinogenaemia (rare)
    - Inherited hyperhomocystinemia (there is no evidence of the benefit of homocysteine level measurement in patients with thrombosis) 1.
    - Disturbances in the fibrinolytic system (an association with thrombosis is unclear; there is no evidence of the benefit of investigating the fibrinolytic system in patients with thrombosis) 1

Table 1. Prevalence of coagulation factor abnormalities causing thrombophilia and the associated thrombosis risk 1

Predisposing factor	Prevalence in the western countries	Thrombosis risk as compared with general population (approximately)

Table 1. Prevalence of coagulation factor abnormalities causing thrombophilia and the associated thrombosis risk [1]

Predisposing factor	Prevalence in the western countries	Thrombosis risk as compared with general population (approximately)
Factor V Leiden, heterozygous	3–8 %	3 ×
Factor V Leiden, homozygous	< 0.2 %	> 30 ×
G20210A point mutation in the prothrombin gene, heterozygous	0.7–4 %	3 ×
G20210A point mutation in the prothrombin gene, homozygous	< 0.1 %	> 30 ×
Protein C deficiency	0.2–0.5	10 ×
Protein S deficiency	0.2–0.5	10 ×
Antithrombin deficiency	0.02–0.1 %	Great variation between families, up to > 100 ×

- The risk of thrombophilia is associated most strongly with
  - antithrombin deficiency
  - homozygosity for FV Leiden or prothrombin G20210A mutation
  - simultaneous heterozygosity for several gene defects (double heterozygosity)
  - protein C deficiency
  - possibly protein S deficiency.
- The aforementioned conditions are referred to as severe inherited thrombophilia which, if diagnosed, will often affect the duration of treatment in patients with venous thrombosis.
- However, heterozygous FV Leiden or prothrombin mutation as a solitary finding does not greatly increase the risk of recurrent thrombosis, and the presence of this mutation is considered to be of such minor clinical significance (low-risk thrombophilia) that, according to the latest guidelines, it does not usually warrant a change in the treatment of venous thrombosis [2].
- Association with pregnancy complications is multifaceted and many aspects remain unclear; the matter has been addressed in a recent recommendation [3].

Causes of acquired (non-inherited) thrombophilia

- The presence of phospholipid antibodies is an important and fairly common cause of acquired thrombophilia.
- Phospholipid antibodies, i.e. lupus anticoagulant, anticardiolipin antibodies and beta2-glycoprotein I antibodies, increase the risk of venous and arterial thrombosis and pregnancy complications.
- Phospholipid antibodies are included in the investigations of thrombophilia even though they are not associated with inherited thrombophilia.

Indications for thrombophilia screening

- There is no universal international consensus regarding the indications for thrombophilia screening.
- The principal aim of screening should be to identify patients with high-risk thrombophilia (see below, indications for screening)
- However, thrombophilia screening should only be considered in the given indications if the test results will affect the patient's management (or that of a close relative).
- Laboratory testing for inherited thrombophilia is usually not indicated if venous thrombosis has developed in the presence of a clear provoking factor, such as immobilisation, surgery or a malignant disease.

Factors suggesting high-risk thrombophilia (= indications for screening)

- Venous thrombosis associated with the following features:
    - idiopathic (no provoking factors) venous thrombosis in a patient aged less than 50 years
    - recurrent spontaneous venous thrombosis
    - unusual site of venous thrombosis (portal, mesenteric, splenic, hepatic, sinus/cerebral or renal vein).
    - unusually extensive spontaneous venous thrombosis
    - positive family history of spontaneous venous thrombosis
    - recurrent venous thrombosis during therapeutic anticoagulation therapy.
- Arterial thrombosis in a young patient without risk factors for atherosclerosis and with no potential cardiac sources of embolism.
- An asymptomatic patient with a family history of high-risk thrombophilia (antithrombin deficiency, homozygosity for FV Leiden or prothrombin G20210A mutation, simultaneous heterozygosity for several gene defects, i.e. double heterozygosity, protein C deficiency and possibly protein S deficiency) should be tested. The testing of asymptomatic family members is discretionary when only low-risk thrombophilia has been identified in the family (heterozygosity for FV Leiden or prothrombin mutation). However, the screening of young female family members should be considered even in these cases in view of hormonal contraception and pregnancy.
    - Asymptomatic family members of the patient are screened only for the specific type of inherited thrombophilia identified.
    - The diagnosis of thrombophilia in a healthy individual does not indicate the commencement of anticoagulant therapy, but prophylaxis should be enhanced in situations where the patient is predisposed to thrombosis (pregnancy, surgery).
    - An asymptomatic carrier should not be made to feel that he/she has a serious medical condition; thrombosis will only develop in a small proportion of the carriers of a gene defect.
- The association of inherited thrombophilia with miscarriages and pregnancy complications, as well as indications for screening, has been addressed in a recent recommendation by the American College of Chest Physicians (ACCP) 3.

Laboratory tests

- Blood samples should preferably be collected either before starting anticoagulant therapy or when the anticoagulant therapy has been finished. Local laboratories will give information as regards the blood collection tubes to be used, the handling of the specimens and transport requirements.
    - Warfarin interferes with laboratory tests, and the specimen is recommended not to be taken until at least 4 weeks have elapsed from the discontinuation of the anticoagulant therapy. If it is not possible to stop the anticoagulant therapy, some aspects of thrombophilia may be reliably evaluated during the therapy (FV Leiden, prothrombin gene defect, antithrombin, thrombin time, anticardiolipin antibodies and beta2-glycoprotein 1 antibodies).
    - Other anticoagulant therapies (LMWH, heparin etc.) may also interfere with some test results (e.g. antithrombin, lupus anticoagulant) and should be mentioned in the laboratory request form.
    - If an asymptomatic relative, for example, needs to be tested for solitary factor V Leiden mutation (FV Leiden, APC resistance) or prothrombin gene defect (FII G20210A), the testing can be carried out with a DNA technique using blood from an EDTA or citrate tube, which specimens can be sent by normal post.
- These tests are not routinely done in all laboratories, and local guidance should be sought.

Treatment

- Anticoagulation therapy prevents thrombotic events.
- Anticoagulation therapy is not started solely on the grounds of detected deficiency or gene mutation, but the indication for starting therapy is the presence of a thrombosis.
- The need to continue anticoagulation therapy for longer than normal is considered individually, as is the need for indefinite anticoagulation. These decisions are usually made by a specialist physician.
- According to current understanding and guidelines the duration of treatment should not be based so much on the type of thombophilia but on the clinical features of the thrombosis, including presentation (primary or recurrent event?), aetiology (provoked or idiopathic event?) and extent (below knee or proximal?) 2. However, if high-risk thrombophilia has been diagnosed, long-term or indefinite anticoagulation may be considered.
- Family history and other factors predisposing the patient to thrombosis must also be taken into account. Further information: see the ACCP treatment guideline 2008 2.
- The duration and dosage of heparin prophylaxis during pregnancy is determined not only by the type of thrombophilia identified but also by, for example, a personal history of thrombosis.
- Oestrogen-containing contraceptives are as a rule contraindicated.
- Hormone replacement therapy during menopause may be possible in selected patients.

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