Venous thromboembolism and thrombophilia testing

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Abstract

Thrombophilia testing detects those with a hereditary or acquired prothrombotic states that predispose to venous thromboembolism. If one considers Virchow's triad, thrombophilia describes the changes in blood constituents that increase the risk of venous thrombosis. Inherited and acquired risk factors for thrombosis are discussed, and an algorithm for management of acute deep venous thrombosis and pulmonary embolism presented.

Keywords DVT and PE; thrombophilia; thromboprophylaxis; thrombosis

Key points

- Around 55% of venous thromboembolism (VTE) results from hospital admission. The risk can be reduced by 50–70% with risk assessment and targeted thromboprophylaxis
- Following diagnosis, deciding whether or not an event is provoked is important when deciding on the type and duration of anticoagulation
- Direct oral anticoagulants have become first-line for treatment of VTE but they are not suitable for all patients
- It is important to look for complications of VTE, such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension

Background

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a major public health problem, with an annual incidence of more than 1 in 1000. Risk factors are diverse but can be broadly categorized into three main groups (Virchow's triad) – venous stasis (e.g. immobility, pelvic masses), hypercoagulability (e.g. pregnancy, malignancy, acquired/inherited thrombophilia) and endothelial damage (e.g. trauma, central venous access devices).

Ascertaining whether a thrombotic event is provoked or unprovoked is essential, as this is the major determinant of the duration, and sometimes the type, of anticoagulation. Taking an accurate medical (including obstetric) and family history is the most important method to clarify this. If a specific risk factor is identified as being causative, the patient only requires anticoagulant therapy for 3 months (minimum) or as long as the risk factor is present. If the risk factor is not transient, such as a severe thrombophilia, the patient may require life-long anticoagulation.

Hospital-acquired VTE (VTE up to 90 days after discharge) causes between half and two-thirds of all VTE. The risk of hospital-acquired VTE can be dramatically reduced by risk assessment and targeted thromboprophylaxis. NHS England has mandated such an approach, and the death rate from VTE has fallen. If a VTE is provoked by hospital admission, and unless the patient has cancer (which causes 10% of unprovoked VTE in those over 40 years old),[1] the risk of recurrence is low and only short-term anticoagulation of 3 months is required.

Cancer is a major cause of VTE, 10–20% of all cancer patients have a VTE during the course of their illness, and this remains the major cause of death in cancer patients after the cancer itself.

If a thrombotic event appears unprovoked, a more detailed history and examination are required to ensure that a patient does not have an underlying malignancy,[1] which is present in about 3% of cases. This should be followed by a chest X-ray, baseline blood tests (full blood count, serum calcium, liver function tests) and urinalysis. Further imaging is occasionally required depending on the patient's age and the findings from examination and baseline investigations. If a malignancy is identified, the patient should be treated with low-molecular-weight heparin for the first 6 months.

Hereditary thrombophilia testing[2] came into vogue after a number of new thrombophilias were discovered in the 1980s. However, these tests usually add little to clinical management and have fallen out of favour. Being labelled with an inherited thrombophilia adds unnecessary anxiety and medicalization, especially when most people with a state such as heterozygous factor V Leiden never have a VTE. Moreover, thrombophilia testing is of limited sensitivity: an abnormality is detected in only 50% of patients even in patients with a VTE who have a strong family history.

Recent National Institute for Health and Care Excellence guidelines have addressed the limited utility of thrombophilia screening by suggesting the following:

- Do not offer thrombophilia testing to patients who have had provoked DVT or PE.
- Do not offer thrombophilia testing to patients who are continuing anticoagulation treatment.
- Consider testing for antiphospholipid antibodies in patients who have had unprovoked DVT or PE, if there is uncertainty about continuation of anticoagulation.
- Consider testing for hereditary thrombophilia in patients who have had unprovoked DVT or PE and who have a first-degree relative who has had DVT or PE, if continuation of anticoagulation is uncertain.

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- Do not routinely offer thrombophilia testing to first-degree relatives of people with a history of DVT or PE and thrombophilia.

Hereditary thrombophilia

In those with inherited thrombophilia,[3] the VTE risk depends on their genotype. Risk is highest in individuals with defects of the natural anticoagulants (antithrombin, protein C, protein S), or with homozygosity for factor V Leiden. VTE risk is also higher if more than one inherited thrombophilia is present, and in subjects with a coexisting acquired thrombophilic risk factor, such as pregnancy, puerperium, combined oral contraceptive pill use, surgery or trauma. Patients with more severe, homozygous or multiple thrombophilic traits often present at a younger age, or have thromboses in unusual sites, recurrent VTE or a clear family history.

Inherited antithrombin, protein C and protein S deficiency

Deficiencies of these natural anticoagulants account for 10–15% of families with inherited thrombophilia and are inherited as an autosomal dominant trait. However, they are rare in the general population, with an estimated frequency of about 1 in 5000 individuals. Deficiencies can be either type 1, in which there is a parallel reduction in biochemical activity and antigen concentration, or type 2 (or functional defect), in which biochemical activity is reduced despite normal antigen concentration.

Antithrombin is the main inhibitor of thrombin. Binding to heparin or heparan sulphate dramatically enhances this inhibitory activity. With the exception of mutations affecting the heparin-binding site, homozygous antithrombin deficiency is considered incompatible with life. Heterozygous antithrombin deficiency results in a five- to 20-fold increased risk of VTE, with affected individuals typically presenting with thrombosis at an early age. As a general rule, 50% of those with antithrombin deficiency have a VTE before the age of 50, and 50% of women with antithrombin deficiency have a VTE in pregnancy if thromboprophylaxis is not used.

Protein C is a vitamin K-dependent protease, synthesized in the liver, that has an anticoagulant effect by proteolytic degradation of activated factors V and VIII. The homozygous or compound heterozygous state is either just compatible with life (protein C <0.01 U/ml), presenting with spontaneous skin necrosis in neonatal life (neonatal purpura fulminans), or produces moderately affected (protein C 0.4–0.6 U/ml) individuals with a seven- to 10-fold increased risk of VTE in later life. Individuals with protein C deficiency are at increased risk of skin necrosis during the initiation of oral anticoagulation because the half-life of protein C is shorter than that of the other vitamin K-dependent coagulation factors; this results in a temporary hypercoagulable state.

Protein S is a vitamin K-dependent protease that serves as a co-factor for the anticoagulant function of activated protein C (APC). Protein S circulates in two forms: approximately 40% as free protein S and the remainder reversibly bound to complement 4b-binding-protein. Only free protein S has co-factor activity for APC. A reduced concentration of free protein S is associated with an approximately two- to 10-fold increased risk of VTE and an increased risk of warfarin-induced skin necrosis.

Factor V Leiden

The factor V Leiden variant is a single point mutation at nucleotide position 1691 in the factor V gene that causes a substitution of arginine by glutamine. This amino acid substitution prevents APC from recognizing a cleavage site on factor V, leading to resistance to the anticoagulant action of APC.[1] Factor V Leiden is the most common cause of APC resistance. The variant is present in 5% of the Caucasian population but is rare in other ethnic groups. Heterozygosity results in a sevenfold increase in VTE risk, whereas homozygotes have a 480-fold increase in VTE.

Prothrombin G20210A variant

The prothrombin G20210A variant is a single nucleotide substitution from glutamine to arginine at position 20210 of the prothrombin gene, which results in an approximately 130% increase in prothrombin antigen or activity assays. It is present in 1–5.5% of the Caucasian population and 7% of VTE patients, so heterozygosity is associated with a two- to fivefold increase in VTE risk.

Other hereditary associations

Dysfibrinogenaemia has the unusual propensity to cause both bleeding and thrombotic episodes in the same individual. It is extremely rare (probably about 1 in a million individuals), and patients are best managed by haemostasis experts. Other inherited thrombophilias are being described in non-Caucasian populations; for example, there is a protein C variant that has a prevalence of 2% in the Chinese population that predisposes to VTE.

Acquired thrombophilia

Antiphospholipid syndrome

Antiphospholipid syndrome is the association between antiphospholipid antibodies and thrombosis and/or certain pregnancy problems. The key difference between antiphospholipid syndrome and the other thrombophilias is that they can cause thrombosis in *any* vascular bed so are an important cause of stroke in young individuals, thrombotic myocardial infarction and placental dysfunction. They can also, by immunological mechanisms, cause recurrent first-trimester loss.

To detect antiphospholipid antibodies, three laboratory tests are required, and it is important to do all three as many affected individuals are positive only for one assay. The tests are lupus anticoagulant, anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies. The tests must be repeated 12 weeks later because transient antibodies can occur.

Paroxysmal nocturnal haemoglobinuria

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare, acquired clonal disorder of the bone marrow that leads to decreased production of the of the glycosylphosphatidylinositol anchors, resulting in red cells being susceptible to complement-mediated lysis. The resulting haemolysis can lead to further complement activation, platelet activation and vascular inflammation, resulting in VTE being the most common cause of mortality in PNH.

Diagnosis and management of venous thromboembolism

The diagnosis and management[4] of DVT are covered in Figures 1 and 2.

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