

Clinical Focus: Thromboembolic disease

CLINICAL ASPECTS OF THROMBOEMBOLIC DISEASE

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Venous thromboembolism represents a spectrum of disease that includes both deep venous thrombosis (DVT) and pulmonary embolism (PE). Embolism most commonly arises in the deep veins of the legs proximal to and including the popliteal veins. It is commonly unsuspected, undiagnosed and responsible for considerable morbidity and mortality, being directly responsible for 10% of deaths in hospital and a contributory factor in a further 10%⁽¹⁾. Although a district general hospital with a catchment population of 200,000 will diagnose around 50 cases annually it may be present in up to 1% of all hospital admissions. The mortality from untreated pulmonary embolism is up to 30%, primarily due to recurrent embolism. The death rate is reduced to 2-8% by anticoagulation treatment.

RISK FACTORS

A risk factor for thrombosis can be identified in over 80% of patients. Often multiple risk factors are present to precipitate thrombosis.

Inherited thrombophilia

This is a genetic susceptibility to recurrent thrombosis and should be suspected in young patients (<45 years) who present with thromboembolism, often recurrent, without obvious precipitant. The main defects are:

- factor V Leiden mutation
- prothrombin gene mutation
- protein S deficiency
- protein C deficiency
- antithrombin III deficiency

In a Spanish study of 2132 consecutive patients with venous thromboembolism, 12.9% had an anticoagulant protein deficiency (7.3% protein S, 3.2% protein C, 0.5% antithrombin III). A further 4.1% had antiphospholipid antibodies. The Physicians' Health Study and the Leiden Thrombophilia Study found a 12-19% incidence of heterozygosity for the factor V Leiden mutation in patients with a first DVT or PE compared to 3-6% in controls. Overall inherited thrombophilia occurs in 24-37% of patients with thromboembolism compared to 10% of controls.

Acquired hypercoagulability

The main conditions predisposing to thromboembolism are:

- malignancy
- surgery and trauma
- pregnancy
- oral contraceptives
- hormone replacement therapy

- tamoxifen
- immobilisation
- heart failure
- age
- hyperhomocysteinaemia
- antiphospholipid antibodies
- myeloproliferative disorders and proximal nocturnal haemoglobinuria
- nephrotic syndrome
- hyperviscosity
- previous thromboembolism

Cancer is associated with the production of procoagulant substances, particularly tissue factor and cancer procoagulant. Thromboembolism is the second commonest cause of death and, in patients presenting with DVT, malignancy is present in 20%. The five commonest sites of malignancy are lung (17%), pancreas (10%), colon and rectum (8%), kidney (8%) and prostate (7%). Surgery lasting more than 30 minutes performed on elderly patients for cancer and orthopedic surgery are most likely to be complicated by thromboembolic disease. Pregnancy is associated with resistance to activated protein C in the second and third trimester. The incidence of thrombosis in women taking the oral contraceptive is 1-4 per 10 000⁽²⁾ and is one per 3000-5000 patients per year in patients taking HRT⁽³⁾ (relative risk of 2.9-3.5). Tamoxifen has been associated with a trend towards more venous thrombosis in a number of trials. Immobilisation is an important risk factor for venous thrombosis though there is conflicting data for the recently publicised 'economy class syndrome'. Hyperhomocysteinaemia can be due to vitamin B6, B12 and folic acid deficiency; it can also be inherited. It is associated with increased thrombosis, particularly when factor V Leiden mutation is also present. Patients with the antiphospholipid antibody syndrome may present with venous or arterial thrombosis, thrombocytopenia or recurrent spontaneous abortion. The disorder is associated with SLE and other rheumatological conditions but may occur separately. Previous thromboembolism is a major risk factor; a previous DVT conferred a relative risk of 7.9% and in a prospective cohort study the risk of recurrence after an acute episode of DVT was 18% at two years, 25% at five years and 30% at eight years⁽⁴⁾.

DEEP VENOUS THROMBOSIS – CLINICAL FEATURES

The clinical diagnosis of DVT is notoriously unreliable but the following may be present:

- calf pain or tenderness or both

- swelling with pitting oedema
- swelling below knee in distal deep vein thrombosis and up to groin in proximal DVT
- increased skin temperature
- superficial venous dilatation
- cyanosis can occur with severe obstruction

The differential diagnosis includes

- muscle strain, tear or twisting injury to the leg – 40%
- leg swelling in a paralysed limb – 9%
- lymphangitis or lymph obstruction – 7%
- venous insufficiency – 7%
- popliteal (Bakers) cyst – 5%
- cellulitis – 3%
- knee abnormality – 2%
- unknown – 26%

PULMONARY EMBOLISM – CLINICAL FEATURES

The commonest symptoms in the PIOPED study⁽⁵⁾ were:

- dyspnoea – 73%
- pleuritic chest pain – 66%
- cough – 30%
- haemoptysis – 13%

The commonest signs were:

- tachypnoea – 70%
- rales – 51%
- tachycardia – 20%
- fourth heart sound – 24%
- accentuated P2 – 23%

Massive PE may present with severe dyspnoea or syncope accompanied by hypotension, tachycardia and acute right ventricular failure as shown by raised jugular venous pressure, a right-sided S3 and parasternal heave.

DIAGNOSIS

Diagnosis of thromboembolic disease is fraught with difficulty due to the lack of specific symptoms and signs and of a sensitive and specific test. Only about a third of patients referred to hospital with possible DVT or PE will have the disease. Although anticoagulation can be life saving in the presence of thromboembolism it is associated with significant risk of bleeding the most serious of which is cerebral haemorrhage. Accurate diagnosis is essential; the PIOPED study demonstrated the importance of combining a clinical assessment of likelihood of thromboembolism with the results of ventilation/perfusion scanning⁽⁵⁾. At Lancaster we have recently introduced a validated clinical scoring system for both DVT and PE⁽⁶⁾.

Deep venous thrombosis

Score one point for each of the following:

- active cancer
- paralysis or immobilisation of the legs
- bedridden for >3 days
- localised tenderness along the deep venous system
- entire leg swollen

- calf swelling compared to unaffected leg
- pitting oedema
- collateral superficial veins

low probability = 0

intermediate probability = 1 or 2

high probability = 3 or more

Pulmonary embolism

- clinical symptoms of DVT = 3
- no alternative diagnosis = 3
- heart rate >100 = 1.5
- immobilisation or surgery within previous 4 weeks = 1.5
- previous DVT/PE = 1.5
- haemoptysis = 1
- malignancy = 1

Score < 4 = low probability

Score 4 or more = high probability

D-dimer testing is now available in our laboratories on all sites. Use of the clinical score in combination with the D-dimer result determines whether an imaging study is necessary. In a recent audit at Lancaster no patients with a low probability of either DVT or PE based on the clinical scoring system and a negative D-dimer were found to have thromboembolic disease.

The initial investigation for patients in whom a DVT is suspected is usually a doppler ultrasound scan. If a calf vein thrombosis only is suspected a venogram may be more appropriate.

In patients with suspected PE a ventilation/perfusion (V/Q) scan is usually the first test although it is very often unhelpful in patients with an abnormal CXR due to chronic lung disease. In these patients spiral CT scanning, bilateral leg dopplers/venograms or pulmonary angiography may be required to make a diagnosis.

In only a minority of cases does the combination of V/Q scanning and clinical probability score become diagnostic of pulmonary embolism. The PIOPED study showed that a high clinical probability associated with a high probability V/Q scan was diagnostic, the presence of pulmonary embolism being confirmed by angiography. Conversely a low clinical probability combined with a low probability scan virtually excluded pulmonary embolism. All other combinations of clinical probability and V/Q scan report were found to be non-diagnostic and required further investigation. This was confirmed in the PISAPED study where perfusion scanning was shown to be as helpful as traditional ventilation/perfusion scanning⁽⁷⁾. It is most important to follow up a non-diagnostic scan with further imaging to confirm or refute the diagnosis.

COMPLICATIONS OF THROMBOEMBOLIC DISEASE

The main complications of DVT are pulmonary embolism, recurrent thrombosis and the post thrombotic syndrome. Post-thrombotic syndrome refers to persistent swelling, pain, dermatitis or ulceration of the leg. It develops due to the presence of high venous pressure in the limb due to destruction of the valves and is more commonly associated

with proximal thromboses. It complicates 50-75% of DVT's and predisposes to recurrence⁽⁸⁾. The risk of post-thrombotic syndrome can be reduced by 50% by the use of graded compression stockings and patients should be encouraged to wear them for two years after diagnosis⁽⁹⁾.

Although pulmonary emboli can be fatal most resolve completely with no longterm complications. A minority of patients go on to develop chronic thromboembolic pulmonary hypertension. This is a rare disorder and probably occurs in no more than 0.1% of survivors. Antiphospholipid antibodies occur in 10-20% of such patients. Patients usually present with worsening dyspnoea, right heart failure and hypoxaemia following an asymptomatic period. It develops without further embolic episodes and appears to result from changes in the small resistance vessels of the peripheral pulmonary vascular bed. The diagnosis can be suggested by the finding of unexplained pulmonary hypertension on echocardiography, associated with right ventricular dilatation and reduced systolic function and confirmed by right heart catheterisation and pulmonary angiography. Radionucleotide scanning can help differentiate chronic thromboembolic pulmonary hypertension from primary pulmonary hypertension. Treatment involves anticoagulation and in some cases pulmonary endarterectomy.

TREATMENT OF THROMBOEMBOLIC DISEASE

As soon as DVT or PE is suspected anticoagulation with heparin should begin. If unfractionised heparin is used, a loading dose is necessary to achieve immediate anticoagulant effect. Thereafter a continuous infusion is given to increase the APTT to 1.5 times the upper limit of the normal range. More commonly low molecular weight (LMW) heparin is used; this has the advantage of being administered as a single daily subcutaneous injection and laboratory monitoring is not required, except in pregnancy. LMW heparin has been shown to be safe and effective in the treatment of thromboembolic disease⁽¹⁰⁾. Warfarin should be prescribed as soon as heparin therapy is initiated and the INR should be within the therapeutic range (usually 2-3) for at least two days before the heparin is stopped. At least five days of heparin should be administered to reduce the risk of recurrence.

At present, the optimal duration of anticoagulation is unknown, although there are suggestions from American literature that longer treatment significantly reduces recurrence rates^(11,12). A national trial is currently taking place comparing the outcomes of three months' and six months' therapy. This trial is being coordinated by Llangough Hospital, Penarth. Morecambe Bay Hospitals have entered several patients into it.

Warfarin therapy is highly effective; in one trial of patients with proximal DVT, warfarin reduced the frequency of documented recurrent venous thromboembolism from 47% to 2%. An INR of 2-3 markedly reduces the risk of bleeding compared to more intensive regimens without reducing efficacy. In patients with known protein C deficiency warfarin must be introduced very gradually under heparin cover because of the risk of warfarin-induced skin necrosis.

In patients who have had two or more episodes of documented thromboembolism or those in whom there is

ongoing risk such as malignancy, lifelong warfarin therapy should be considered. Trials in this area are ongoing and at present the risk:benefit ratio of longterm anticoagulation should be weighed up in each patient. In patients with thrombophilia, however, anticoagulation should be continued indefinitely unless the patient is at high risk of haemorrhage.

Recent studies have shown that using self-injection of LMW heparin many patients with suspected DVT can be investigated and managed at home. Up to 80% of patients have been shown to be suitable for home management with considerable saving of hospital bed days. We plan to introduce such a scheme in the near future.

Patients who present with acute massive pulmonary embolism should be considered for thrombolysis). 250,000 IU of streptokinase over 20-30 minutes followed by 100,000 IU/hr for up to 24 hours is given. Recombinant Tissue PA can be used as an alternative. Administration via a peripheral vein or pulmonary artery catheter is equally effective. If thrombolytic therapy is contraindicated and the patient is in a cardiothoracic centre, pulmonary embolectomy is an alternative.

Inferior vena cava filters should be considered in patients at risk of further embolism who are have contraindications for anticoagulation or in those who continue to embolise despite anticoagulants. They are under utilised in the UK possibly because of cost implications and the need for a suitably skilled radiologist.

CONCLUSIONS

- Thromboembolic disease is a common cause of morbidity and mortality
- Only one third of patients referred with possible DVT or PE will have the disease
- Initial assessment should combine the clinical score with the D-dimer result
- Patients should only be further investigated if the clinical score, D-dimer or both are elevated
- Anticoagulation is highly effective treatment
- Currently patients with confirmed DVT are being entered into a clinical trial comparing 3 months and 6 months of warfarin therapy
- Home treatment of patients with DVT has been shown to be safe and effective and we plan to introduce such a scheme in the near future

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