

Deep vein thrombosis in children

Introduction

When compared with the adult population, deep vein thrombosis in children is a rare occurrence. However, the incidence of thrombotic events in the paediatric population is increasing (Chan et al, 2003), largely as a result of prolonged survival from childhood conditions, such as congenital heart disease and malignancy, that predispose towards venous thromboembolism. This trend, coupled with the serious complications which can occur, makes deep vein thrombosis in children an increasingly important subject.

Incidence and epidemiology

The majority of the available data on the incidence and epidemiology of deep vein thrombosis in children comes from national registries, the first of which was set up in Canada (Andrew et al, 1994) with several other countries, including Britain, adopting the concept (Chalmers, 2006).

Estimates of the incidence of deep vein thrombosis in children from these registries vary from 0.07 to 0.49 per 10 000 children per year (Goldberg and Bernard, 2010), significantly lower than adults where the rate is around 1 per 1000 per year (McManus et al, 2009). The incidence has increased over time, largely as a result of improved survival from childhood conditions that predispose to venous thromboembolism.

Importantly, however, serious complications of deep vein thrombosis are thought to occur as frequently in children as in adults, although the rate of recurrence is lower (David and Andrew, 1993; Guruge, 2009).

Incidence varies with age, showing a bimodal distribution with peaks in neonates and adolescents (Chalmers, 2006). Most registries show an equal sex

distribution and data on racial variation in incidence are lacking.

Aetiology

As in adults, a disturbance of any component of Virchow's triad can lead to thrombosis, namely changes to the vessel wall, blood flow or blood constituents. However, in contrast to adults, unprovoked deep vein thrombosis in children is rare, with over 90% of episodes of deep vein thrombosis in children occurring in the presence of a risk factor, compared with 60% in adults (Goldberg and Bernard, 2010).

The most commonly identified risk factor associated with deep vein thrombosis is the presence of a central venous line, which is implicated in >50% of cases of deep vein thrombosis in children and >90% of cases of deep vein thrombosis in neonates. Central venous lines are thought to promote thrombosis by three mechanisms:

1. Damage to vessel walls by the central venous line itself or substances given through it
2. Disruption of blood flow
3. The presence of thrombogenic materials (Chan et al, 2003).

There are several important comorbid conditions which predispose to deep vein thrombosis (Table 1), with sepsis and malignancy among the most common. Several of these risk factors may be, and often are, present simultaneously. Less commonly, an inherited or acquired thrombophilia may lead to a prothrombotic state.

There are also marked differences in the aetiology of deep vein thrombosis in inpatient and outpatient settings. In those developing a deep vein thrombosis outside

of hospital the most significant risk factors are previous thrombosis and thrombophilia. The site of deep vein thrombosis in these groups also differs, with the majority of outpatient events occurring in the lower limb (Sandoval et al, 2008), which reflects the effect of central venous line placement in the inpatient population.

Clinical features

The clinical features of deep vein thrombosis in children are similar to those seen in adults, the picture varying depending on the site of thrombosis. With deep vein thrombosis in the lower limb, localized pain and swelling predominate. In the upper limb there may be additional signs of superior vena caval obstruction, which include shortness of breath, facial swelling, flushing and headache. However, as in adults, deep vein thrombosis may be asymptomatic.

Investigations and diagnosis

The most commonly used technique is compression Doppler ultrasound which is sensitive and specific in the limbs, but when there is central venous thromboembolism or proximal extension of deep vein thrombosis contrast magnetic resonance venography is recommended. Computed tomography may be considered if magnetic resonance venography is unavailable (Chalmers et al, 2011). D-dimer measurements should not be used to exclude venous thromboembolism in children (Chalmers et al, 2011).

Before initiating treatment, baseline blood tests should be performed to assess for systemic disorders as well as renal function and coagulation status. Screening for antiphospholipid antibodies is recommended for those with unprovoked venous thromboembolism, as persistent antibodies are related to increased recurrence and are an indication for long-term anticoagulation (Chalmers et al, 2011). However, screening for inherited thrombophilia is not indicated on first presentation and should not influence treatment initiation and duration (Chalmers et al, 2011).

Management

As in the adult population the treatment of deep vein thrombosis is based on anti-

Table 1. Conditions predisposing to deep vein thrombosis

Central venous line
Sepsis
Immobility
Malignancy
Surgery
Congenital heart disease
Trauma

Dr Richard A Armstrong is Foundation Year 2 Doctor, University College London Hospitals NHS Foundation Trust, London NW1 2BU, and **Dr Jacqueline Taylor** is Consultant Paediatrician, Basildon and Chase Farm NHS Trust, Enfield

Correspondence to: Dr RA Armstrong (rarmstrong1@nhs.net)

coagulation therapy. There are two potential treatment strategies in children:

1. Warfarin with heparin (unfractionated or low molecular weight) cover for the first 5 days, or until international normalized ratio is therapeutic for 2 days, whichever is longer
2. Treatment with low molecular weight heparin throughout. This strategy may be preferable in infants under 1 year of age.

Low molecular weight heparin is more convenient to use than unfractionated heparin as administration is subcutaneous rather than intravenous. However, unfractionated heparin has the advantage of a rapid termination of its effects on cessation of treatment given its shorter half-life.

As in adults, the effects of unfractionated heparin should be monitored with activated partial thromboplastin time and those of warfarin monitored with international normalized ratio. The recommended duration of treatment varies depending on the aetiology (Table 2) (Chalmers et al, 2011).

Dosing regimens for unfractionated heparin, low molecular weight heparin and warfarin can be found in the British National Formulary for Children (Paediatric Formulary Committee, 2012) or according to local guidelines, and are both age- and weight-dependent. Target international normalized ratio is 2.5 (2.0–3.0), or 3.5 (3.0–4.0) if there are recurrent deep vein thromboses on warfarin therapy.

Non-pharmacological measures are also advised, for example thromboembolic deterrent stockings for older children or those at increased risk, adequate hydration and mobilization, and the removal of central venous lines as soon as practicable. In the case of recurrent thrombosis or if anticoagulation is contraindicated placement of intravenous filters may be considered.

Thrombolysis may be considered where thrombosis involves superior or inferior vena cava, pelvic veins or intra-cardiac

sites, and tissue plasminogen activator is the agent of choice (Chalmers et al, 2011).

Prophylaxis

There is no clear consensus on which children, if any, should receive prophylactic antithrombotics, largely because of the absence of any validated risk scoring tools in children. The typical approaches used in adults, i.e. unfractionated and low molecular weight heparins, are not licensed for use in children, but British Committee for Standards in Haematology guidelines recommend that they can be given in the presence of multiple risk factors on an individual patient basis. Furthermore, primary prophylaxis is not indicated with central venous lines (Chalmers et al, 2011). Again, doses are age- and weight-dependent.

Prognosis and complications

There is a recognized risk of mortality from childhood venous thromboembolism, underlining its importance as a diagnosis. Rates of direct mortality as a result of venous thromboembolism vary from 1.5–2.2% in the registries, with pulmonary embolism the most common cause (Chalmers, 2006). Furthermore, there is an all-cause mortality of 9–17% (Chalmers, 2006) as patients often have serious underlying conditions. Recurrent thrombosis occurs in 5.5–18.5% (Chalmers, 2006) of cases, which is lower than the rate observed in the adult population (Goldberg and Bernard, 2010).

Another serious complication is post-thrombotic syndrome, in which chronic venous insufficiency results in a clinical picture similar to varicose veins with pain and swelling of the limb, tortuous, dilated veins and skin changes including venous stasis, dermatitis and ulceration. This occurs in an estimated 33–60% of cases (Parasuraman and Goldhaber, 2006), making it at least as common in children as in adults (Chalmers, 2006). However, pulmonary embolism is a

less common complication than in the adult population (Andrew et al, 1994).

Conclusions

Deep vein thrombosis is increasingly common in paediatric patients and a working knowledge of its presentation and management is useful. There are certain patient groups at increased risk of deep vein thrombosis, especially those with central venous lines and/or malignancies. The symptoms, signs and principles of management are similar to those in adults. **BJHM**

Conflict of interest: none.

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Table 2. Recommended treatment durations based on aetiology

Aetiology	Recommended duration of anticoagulation
Provoked deep vein thrombosis*	Up to 3 months
Unprovoked deep vein thrombosis	Up to 6 months
Recurrent unprovoked deep vein thrombosis, or antiphospholipid syndrome and unprovoked deep vein thrombosis	Lifelong

*British Committee for Standards in Haematology guidelines (Chalmers et al, 2011) suggest a shorter course may be possible when deep vein thrombosis is secondary to central venous line

KEY POINTS

- Although more rare than in adults, deep vein thrombosis does occur in children.
- Disturbance of any component of Virchow's triad can lead to thrombosis.
- Major risk factors include the presence of central lines and malignancy.
- Treatment is usually with anticoagulants, as in adults.
- Complications include death, post-thrombotic syndrome and pulmonary embolism.
- Primary prophylaxis is not indicated in the majority of patients.