Thrombophilia in the young

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Keywords
Venous thromboembolism

Summary
Venous thromboembolism (VTE) is a rare disease that is being increasingly diagnosed and recognized in pediatrics in the past decade, usually as a secondary complication of primary severe underlying diseases. Apart from acquired thrombophilic risk factors, such as lupus anticoagulants, inherited thrombophilias (IT) have been established as risk factors for venous thromboembolic events in adults. In children with idiopathic VTE and in paediatric populations in which thromboses were associated with underlying medical diseases, IT have been described as additional prothrombotic risk factors. Follow-up data for VTE recurrence in children are available and suggest a recurrence rate of approximately 3% in neonates and 8% in other children. Here we present a review of the impact of IT on early onset of VTE and recurrence in children. Statistically significant associations between the IT traits investigated, e.g. factor V G1691A, factor II G20210A, protein C-, protein S-, antithrombin deficiency, elevated lipoprotein (a), combined IT and VTE onset were reported. In addition, statistically significant associations with recurrent VTE were calculated for protein S-, antithrombin-deficiency, and the factor II variant and combined IT. The absolute risk increase for VTE recurrence associated with IT ranged from 9.8% for children carrying the factorII variant to 26% and 29% in children with combined IT and protein S-deficiency, respectively. Data obtained gave evidence that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a paediatric thrombophilia screening program. Based on these data treatment algorithms have to be discussed.

Schlüsselwörter
Venöse Thromboembolien

Zusammenfassung

Thrombophilie bei jungen Menschen

Hämostaseologie 2008, 28: 16–20

Venous thromboembolism (VTE) is a rare disease that was increasingly diagnosed and recognized in pediatrics in the past decade (1–12), usually as a secondary complication of primary underlying diseases such as sepsis, cancer, congenital heart disease, or after therapeutic interventions such as central venous lines (Tab. 1). Paediatric VTE is a severe disease for which long-term outcomes include lack of thrombus resolution in 50% of cases and (apart from central line associated thrombosis in children with malignancy) the development of postthrombotic syndrome in greater than one third of patients (7–9).

Within the entire childhood population, neonates are at the greatest risk for VTE (5.1/100 000 live births per year in Caucasian children) (1, 2, 5, 12), with a second peak in incidence during puberty and adolescence (Fig. 1). In prospective paediatric registries in North America and Europe the annual incidence of venous events was estimated (1, 10–12) to be • 0.07 to 0.14 per 10 000 children, or • 5.3 per 10 000 hospital admissions of children and • 24 per 10 000 admissions of neonates to neonatal intensive care units.

Until today, the results of single studies on the risk of VTE onset and recurrence associated with inherited thrombophilia (IT) are contradictory or inconclusive, mainly due to lack of statistical power. Apart from acquired thrombophilic risk factors, such as lupus anticoagulants and the antiphospholipid syndrome (13–15), IT (particularly antithrombin-, protein C-, or protein S-deficiency, the mutations of coagulation factor V (G1691A) and II (G20210A), and elevated lipoprotein (a) have been established as risk factors for VTE events in adults (16–21). In children with idiopathic VTE and in paediatric populations in which thromboses were associated with underlying diseases, IT has been described as additional prothrombotic risk factor (22–56).

Follow-up data for VTE recurrence in children are available from few reports (6–9, 11, 36, 45–47, 49, 52, 54) and suggest a recurrence rate of approximately 3% in neonates and 8% in older children.
Thrombotic events in paediatric patients

Locations

The most common sites of thrombus formation in neonates are the renal veins (1, 5, 40, 47, 49), vena caval occlusion, and peripartal thromboembolic stroke (5, 11, 12). In addition, high rates of catheter-related thrombosis in neonates, infants and children have been reported (2–4, 11, 12). Central venous lines lead to thrombus formation and thrombus growth near the catheter implantation site, especially when prothrombotic risk factors are involved. Further locations of childhood thromboembolism reported are cerebral venous thrombosis (37, 39, 41, 43, 45, 54, 55), and portal or mesenteric vein thrombosis (25, 44).

Purpura fulminans is a life-threatening event characterized histologically by microvascular thrombosis in the dermis followed by perivascular haemorrhage. Haemorrhagic necrosis of the adrenal glands (Waterhouse-Friderichsen syndrome), or renal cortical necrosis may also occur. Clinically, progressive purpuric skin lesions and diffuse oozing from skin puncture sites are observed, often within hours after birth. The lesions are initially red and flat, they quickly become indurated and necrotic, and may result in gangrene formation. The known underlying causes of Purpura fulminans are disseminated intravascular coagulation (DIC), for example in response to bacterial septicaemia, e. g. B β-haemolytic streptococcal disease, Neisseria meningitides or Streptococcus pneumoniae. In addition, in neonates congenital absence of protein C or protein S, or the presence of homozygous or heterozygous factor V G1691A mutation, have been reported.

Imaging

Duplex sonography, venography, computed tomography and magnetic resonance (MR) imaging can be used to diagnose VTE in children. However, venography in combination with Doppler ultrasound is mandatory to confirm suspected thrombosis in the upper venous system (57). MR imaging and MR angiography are recommended to confirm the diagnosis of thromboembolic ischemic stroke. Ventilation/perfusion scan or MR angiography are suitable methods for diagnosing pulmonary embolism in children.

Inherited thrombophilias

Onset and recurrent VTE

The distribution of prothrombotic risk factors varies in different countries with respect to the ethnic background and the number of patient/controls investigated. Thus, to estimate the individual patient risk in paediatric patients suffering from thromboembolism, it is recommended that symptomatic patients should be investigated in comparison to age- and gender-matched healthy controls from the same geographic area.

In a recent metaanalysis including 56 studies (2560 patients) from 15 countries more than 70% of patients had at least one clinical risk factor (58). The summary odds ratios/95% confidence intervals of studies under a fixed-effects and random-effects model showed statistically significant associations between factor V G1691A, factor
II G20210A, protein C-, protein S-, or antithrombin deficiency, elevated lipoprotein (a), combined IT and VTE onset (58) (Tab. 2). For VTE recurrence, data of 1490 patients (11 studies) were available and a statistically significant association with recurrent VTE was found for protein S- or antithrombin-deficiency, the factor II variant and combined IT. Of note, the absolute risk increase for VTE recurrence associated with IT ranged from 10% for children heterozygous for the factor II variant to 26% and 29% in children with combined IT and protein S-deficiency, respectively (Tab. 2). The odds ratios reported for recurrent VTE in children are consistent with results obtained from adult cohort studies not receiving long-term anticoagulation (59–64):  
1. 4.8 (protein C),  
2. 7.7 (protein S),  
3. 4.7 (antithrombin),  
4. 1.8 (factor V),  
5. 3.7 (factor II), and  
6. 5.1 for ≥2 traits.

Data evidenced that the detection of IT is clinically meaningful in children with VTE and underlines the importance of a paediatric thrombophilia screening program. Based on these data treatment algorithms have to be discussed.

### Screening

Follow-up data for VTE recurrence in children are available from a few reports, and those suggest a recurrence rate of approximately 3% in neonates and 8% in older children. However, in the paediatric age group it still remains a controversial issue as to whether children with thrombosis or offspring from thrombosis-prone families benefit from screening for IT (65–68).

Based on the data obtained from the recent metaanalysis (58) at least the symptomatic propositus should be screened in a specialized coagulation unit for prothrombotic defects. In addition, since a second VTE after a first episode of spontaneous VTE, i.e., thrombosis in the absence of further secondary causes, has indicated a subgroup of paediatric patients suffering from combined prothrombotic risk factors (36) to be at high risk of recurrent thrombosis, a search for multiple risk factors is justified in selected patient groups.

With respect to the Mendelian laws of inheritance, approximately 50% of siblings of a symptomatic propositus suffering from a combined prothrombotic defect carry one single risk factor, while 25% carry two or more gene mutations/polymorphisms. Thus, based on the fact that an effective prophylactic anticoagulant therapy is available in risk situations, a screening IT evaluation has to be discussed also in non-symptomatic siblings and further first degree family members.

### Treatment modalities

Adult patients with a first thrombotic episode will receive oral anticoagulation (usually a vitamin K antagonist) for at least three months after venous thrombosis, six to 12 months when the deep venous thrombosis was idiopathic, and at least six to 12 months after pulmonary embolism. Decisions on extending anticoagulant therapy are individually based on the perceived risks of VTE recurrence and anticoagulant-related bleeding. Whether long-term continuation of anticoagulant treatment should be considered after a first VTE in carriers of a thrombophilic trait is still a matter of debate (69).

In children with a first VTE randomized therapeutic trials are missing and treatment guidelines are mainly adapted from adults (70). More than in adults, the prolonged use of anticoagulant treatment in a physically active age group must be weighed against the risk of bleeding. Data of the metaanalysis already mentioned (58) will help physicians to decide along with parents and patients in which cases a prolonged anti-coagulant treatment may be justified, or practically, if paediatric patients additionally carry a genetic trait with chronic conditions associated with VTE might require secondary anticoagulant in high risk situations (e.g., postoperatively, prolonged immobilization, or dehydration). The findings based on the analyses of absolute risk increase underline the hypothesis that in cases in which the temporary risk factor recur the risk of a second VTE in children is probably less likely if IT is absent (54, 58).
Until results from randomized trials are available for anticoagulant treatment and duration of symptomatic children, paediatric patients with symptomatic VTE are treated according to recommendations based on small-scale studies in children and guidelines adapted from adult patient protocols (70). The MPTS* score (Tab. 3) based on a positive or negative family history, idiopathic versus triggered VTE, results of thrombophilia testing, thrombotic locations and extension, and short-term patency rates will help physicians to classify children at risk and to estimate the duration of anticoagulant following a first event and secondary prophylactic anticoagulation in any clinical risk situations prone to thrombosis in later life. We suggest that children with:

- low-risk score (≤2) receive anticoagulation over three months,
- with a medium risk score (3–5) should be treated for 6 to 12 months, and
- high-risk score (≥6) should be treated for at least 12 months or life-long with risk adapted dosages.

In addition, there is an urgent need for each paediatric patient with an early VTE manifestation to receive secondary anticoagulation prophylaxis in clinical risk situations prone to thromboembolism, for example catheterization, dehydration, haematological malignancies, or prolonged immobilization respectively. Since randomized treatment trials are lacking doses and durations of secondary anticoagulation should be individually adapted to patient’s risk.

Conclusions

Apart from a risk stratification based on clinical acquired circumstances along with genetic thrombophilias for the onset and course of VTE diseases in children as a basic step for future evidence-based prospective anticoagulant/antithrombotic treatment trials, a world-wide paediatric expert consensus on standardized clinical outcome measurements, imaging methods to be used, and determination of follow-up intervals are urgently requested. The effective prevention of thrombosis-related complications in children will considerably reduce the burden and the costs associated with the disease.

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