Manifestations and clinical impact of pediatric inherited thrombophilia

Irene LM Klaassen¹-², C Heleen van Ommen¹, Saskia Middeldorp²

¹Department of Pediatric Hematology, Emma Children's Hospital Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands
²Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands

Short title: Pediatric thrombophilia
Journal special section designation: Blood Spotlight
Journal scientific designation: THROMBOSIS AND HEMOSTASIS
Keywords: Thrombophilia, venous thromboembolic disease, children

Corresponding author:
Saskia Middeldorp, MD, PhD
Department of Vascular Medicine
Academic Medical Center, University of Amsterdam
Meibergdreef 9
1105 AZ Amsterdam, the Netherlands
Email: s.middeldorp@amc.uva.nl
T: +31205665976
F: +31206968833
ABSTRACT

The etiology of pediatric venous thromboembolic disease (VTE) is multifactorial and in most children one or more clinical risk factors are present. In addition, inherited thrombophilic disorders contribute to the development of pediatric VTE. In this review the role of inherited thrombophilic disorders in the development of pediatric VTE as well as the benefits and limitations of thrombophilia testing will be discussed.
Introduction

Venous thromboembolic disease (VTE) is a rare disease in childhood. The reported annual incidence ranges from 0.07 to 0.14 per 10,000 children and is estimated to be 5.3 per 10,000 hospital admissions.(1-3) The incidence seems to be increasing over the past decades. Raffini et al reported a rise in the annual incidence of VTE of 70%, from 34 to 58 cases per 10,000 hospital admissions.(4) This is confirmed by Boulet et al.(5) This rise is likely caused by an increased awareness of the disease, progress in radiologic imaging and increased survival of children with previously incurable diseases due to medical and surgical improvements.

In 2008 a systematic review and meta-analysis concerning pediatric VTE and inherited thrombophilia, i.e. deficiencies of antithrombin (AT), protein C (PC) and protein S (PS), and factor V Leiden mutation (FVL) and the prothrombin mutation (PTM), showed elevated thrombotic risks in children with these defects.(6) In the current review, we discuss additional literature after 2008 in various pediatric patient groups and the usefulness of thrombophilia testing.

Methods

In- and exclusion criteria

All full-text published studies of VTE and thrombophilia in neonates and children (0-18 years) from 2008 through October 2014 were evaluated for inclusion if 1) diagnosis of VTE of any location was objectively confirmed by accepted imaging methods, 2) frequency of at least one of the inherited thrombophilic factors was assessed in a given VTE cohort or if the frequency of inherited thrombophilic factors was compared between VTE patients and controls without a history of VTE, and 3) inherited thrombophilic factors were measured in an accepted manner. Conference
abstracts, case-reports and studies with unclear methodology to differentiate
between inherited and acquired deficiencies of the natural anticoagulants were not
included.

Search strategy
A systematic search of publications listed in the electronic databases as MEDLINE,
EMBASE and The Cochrane library, from 2008 until October 2014 was conducted,
with the limits set to only articles in English language. The following key words were
used in combination both as MeSH terms and text words: “thromboembolism or deep
vein thrombosis or pulmonary embolism or venous thrombosis or anticoagulation or
antithrombotic therapy” and “thrombophilia” or “hypercoagulat” or “protein C” or
“antithrombin” or “protein S” or “(factor 5 leiden or factor v leiden or fv leiden)” or
(factor 2 mutation or factor II mutation or prothrombin mutation)” and “adolescenc or
child or infant or newborn or neonat or school child or baby or babies or toddler or
prematur or preterm or vlbw or elbw”. Citations of the searched articles were
included in the review if they were determined to be relevant. Data extraction was
performed in duplicate by two authors (I.L.M.K. and C.H.O).

Quality assessment
Quality assessment of case-control and cohort studies was performed using the
Newcastle-Ottawa Scale (NOS). (7)

Results
A total of 1014 citations were evaluated. Thirteen studies were enrolled in this review,
including three case-control studies and 10 cohort studies. The frequencies of
inherited thrombophilic factors as well as the quality assessment are shown in table 1. The studies are analysed descriptively.

Venous thrombosis and thrombophilia in neonates

Although the meta-analysis of Young et al showed that thrombophilia contributes to the development of neonatal VTE, it should be realized that neonates were underrepresented in this meta-analysis.(6) The incidence of symptomatic VTE in neonates is 5.1 per 100,000 births, and approximately 95% of neonatal VTE is associated with at least one clinical risk factor, usually a central venous catheter (CVC).(8;9) Studies concerning thrombophilia in neonates with CVC-related thrombosis are scarce. One study that was included in the meta-analysis of Young, described 10 neonates with symptomatic CVC-related thrombosis. No deficiencies of AT, PC or PS were detected. One patient was heterozygous for FVL.(10) One study was performed after 2008. It showed that thrombophilia was present in none of the 13 studied neonates with CVC-related thrombosis.(11)

Renal vein thrombosis (RVT) is the most frequent non-catheter-related VTE in neonates and its incidence was reported to be 2.2 per 100,000 births in Germany.(12) The prevalence of inherited thrombophilia seems to be higher in neonates with RVT than with catheter-related VTE, but only a few small studies have been published, all before 2008. The meta-analysis of Young included two small studies. Marks et al retrospectively identified 43 neonates with RVT between 1980 and 2001 in 4 pediatric Canadian tertiary care Centers. Twelve of the 28 neonates (43%) studied had thrombophilias.(13) A case control study by Kosch et al reported even a higher prevalence: in 40 (67.8%) of the 59 neonates, at least one thrombophilia was present compared with 14 (11.9%) of the 118 controls (odds ratio
In addition, this study confirmed that neonatal RVT is a multifactorial disease: several underlying clinical risk factors, such as asphyxia, sepsis, diabetic fetopathy, and CVCs were present.

Neonatal cerebral venous thrombosis (CVT) is a rare, but serious disease. In a multiCenter, retrospective review by Berfelo et al, two (5%) of 41 neonates tested had FVL and two (11%) of 18 neonates tested had PTM. In a retrospective nationwide population-based study, 10 infants less than 1 year of age, including 7 neonates were diagnosed with CVT. Inherited thrombophilia was present in only 1 (13%) of the 8 patients tested. Five (71%) out of 7 neonates had an underlying illness, such as asphyxia or sepsis. In 2010 a meta-analysis including both neonatal and childhood CVT showed statistically significant association between CVT and all inherited thrombophilic disorders, except PTM. In agreement, Laugesaar et al performed a meta-analysis separately for neonatal SVT, including their own study results, which showed a significant association between FVL and neonatal CVT (OR 5.5; 95% CI: 2.1-14.5), but not between PTM and neonatal CVT (OR 3.1; 95% CI: 0.8-12.4).

In conclusion, only few studies investigated the prevalence and contributing role of thrombophilia in neonatal thrombosis. Neonatal VTE is a multifactorial disease and clinical risk factors seem to play a more important role than inherited thrombophilia, especially in catheter-related VTE.

**Thrombophilia in children**

The meta-analysis by Young et al demonstrated that inherited thrombophilia contributed to the development of VTE in children. The ORs varied from 2.63 (95% CI: 1.61 to 4.29) for PTM to 9.44 (95% CI: 3.34 to 26.66) for AT deficiency. In
children with ≥ 2 genetic traits the combined OR was 8.89 (95% CI: 3.43 to 23.06).(6) The observed relative risk estimates are similar to adults.(19) Nevertheless, underlying clinical risk factors were present in a majority (>70%) of children with VTE. The most important risk factor in children is a CVC. However, other clinical risk factors, such as malignancy, cardiac disease and nephrotic syndrome, contribute to thrombotic risk as well.(2)

The presumed impact of inherited thrombophilia on the thrombotic risk of CVC-related VTE in children is challenged by results from two recent studies. Albisetti studied thrombotic events in children with malignancies and a port-a-cath by magnetic resonance venography. Only two of 45 (4%) patients with CVC-related VTE had inherited thrombophilia compared to 8 of 69 (12%) patients without VTE.(20) In addition, in the KIDs with Catheter Associated Thrombosis (KIDCAT) study, that included 90 children with heart disease requiring CVCs in the upper venous system for perioperative care, none of the thrombophilic factors showed a significant association with CVC-related VTE.(21)

VTE is one of the most serious complications in children with nephrotic syndrome, which is attributed to a net shift in the hemostatic balance toward a hypercoagulable state by selective loss of hemostatic proteins, most notably PS and AT.20 The reported incidence of VTE in children with nephrotic syndrome varies between 9 and 36% based on recent literature.(22;23) Age ≥ 12 years at onset, severe proteinuria, and history of VTE prior to diagnosis of nephrotic syndrome were significant independent predictors of VTE. The presence of thrombophilia was only evaluated in 12 of 30 VTE patients. In 4 patients (33%) FVL was identified.(22) Suri et al retrospectively reviewed the clinical profile in nephrotic children with VTE.
Hypoalbuminemia (83%) and infection (31%) were the most common predisposing factors. Two (11%) patients were diagnosed with inherited protein S deficiency and one with inherited AT deficiency (6%).(23)

In children, CVT has an annual incidence of 0.67 per 100,000.(24) In 2010, a meta-analysis of Kenet et al., including 5 cohort-studies with 297 patients with CVT found a statistically significant association between all inherited thrombophilic disorders, except PTM, and a first CVT onset in neonates and children.(17) The summary ORs varied from 2.74 (95% CI: 1.73-4.34) for FVL to 18.4 (95% CI: 3.25 to 104.3) for AT deficiency. The study of Laugesaar et al. was not included in the above mentioned meta-analysis. They performed a meta-analysis separately for childhood CVT, including their own study results, and showed a significant association between PTM and childhood CVT (OR 5.3; 95% CI: 1.4-19.8), but not between FVL and childhood CVT (OR 2.3; 95% CI: 0.8-6.3).(18) The opposite outcome compared to the meta-analysis of Kenet et al. is probably caused by the low number of patients included in both meta-analyses.

Value of thrombophilia testing

In general, thrombophilia testing should only be performed if the results would change management. As discussed in the previous paragraphs, thrombophilia contributes to VTE in neonates and children, but its extent depends on the specific patient group. Although thrombophilia testing is often performed to gain insight into the cause of VTE in a child, identification of thrombophilia should not be considered the sole cause. Almost all children have one or more clinical risk factors, and unprovoked thrombosis occurs in only 5% of the children.(2)
Unprovoked thrombosis and a family history of VTE may help to identify thrombophilia in children with VTE. Revel-Vilk et al. studied thrombophilia in 171 children with VTE. Thrombophilic disorders were present in no more than 13% of the total number of patients, but in 60% of the adolescents with unprovoked thrombosis.(25) In a prospective cohort study of 100 children with VTE, family history of VTE appeared to be the only predictor for the presence of inherited thrombophilia (OR: 14.9; 95% CI: 1.9-113) after multivariate analysis.(26) Likewise, in the cross-sectional study of Ruud et al family history of VTE increased the RR of a child having inherited thrombophilia to 2.35 (95% CI: 1.1- 5.2). (27) However, associations are not strong, and in adults, family history has a poor predictive value for the presence of inherited thrombophilia.(28)

In children with thrombosis the most important justification for thrombophilia testing would be to distinguish patients at high risk of recurrent VTE from those at low risk. Patients at high risk might benefit from long-term anticoagulation. In adults, guidelines do not recommend thrombophilia testing to guide decisions on duration of anticoagulation, as inherited thrombophilia is considered to play a minor role in recurrence risk, with relative risk estimates between 1.4 and 2.5.(19) In children, the influence of inherited thrombophilia on recurrent thrombosis is very similar. Young et al showed an association between recurrent VTE in children and all inherited thrombophilias, except FVL. The summary ORs, ranged from 1.88 (95% CI: 1.01-3.29) for PTM to 4.46 (95% CI: 2.89-6.89) for combined disorders.(6) Prospective trials studying the risks and benefits of prolonged anticoagulation treatment in pediatric thrombophilic patients have not been performed. Until now, as in adults, duration of anticoagulant therapy in children is not modified based on the presence of thrombophilia.(29)
A potential advantage of testing pediatric patients with VTE for inherited thrombophilia is the identification of asymptomatic siblings with thrombophilia. Although the incidences of VTE in carriers of AT, PC or PS deficiency are higher than in those with FVL or PTM, and clearly higher than in relatives who do not have thrombophilia, it is not generally recommended to test. However, it might be beneficial to identify carriers of high-risk thrombophilia in thrombosis-prone families. Asymptomatic relatives with deficiencies of AT, PC or PS are thought to benefit from primary prophylaxis with anticoagulants during high-risk situations, and female carriers can be counselled about the use of combined oral contraceptives and thromboprophylaxis during pregnancy and puerperium. However, in our view, negative thrombophilia testing may provide false reassurance. For example, in high-risk thrombophilia families the risk of VTE during oral contraceptive use is indeed increased in affected (4.3% per year of use), but also in unaffected relatives (0.7% per year of use) compared with the general population (0.04% per year of use). This is probably caused by the co-segregation of yet unidentified genetic variables and/or environmental risk factors.

If testing is considered, it seems rational to postpone testing asymptomatic children until they are old enough to decide for themselves after weighing the pros and cons, as the absolute incidence of VTE is very low in children with thrombophilia. Furthermore, diagnosing a true deficiency of AT, PC and PS can be challenging in young children, because of the rapidly developing haemostatic system in the first year of life, and the presence of physiological significant lower levels of certain coagulation inhibitors compared to adults until adolescence.
Conclusion

VTE in childhood is a multifactorial disease, in which underlying clinical risk factors and inherited thrombophilia contribute to the development of VTE. The presence of a thrombophilia does not change patients' treatment strategies and consequently testing is not advised routinely in all children with VTE, except for study purposes. However, asymptomatic adult relatives in families with high-risk thrombophilia may benefit from testing by offering them primary thromboprophylaxis in high-risk situations and by counselling the female carriers before the use of oral contraceptives and pregnancy, although it should be realized that negative testing may provide false reassurance. Unprovoked thrombosis and a positive family history may help to predict the presence of thrombophilia in children with VTE. As the incidence of VTE is very low in children with thrombophilia, it seems reasonable to postpone testing in asymptomatic children until they are old enough to decide for themselves in view of the pros and cons. Pre- and post-test counselling should be performed by an experienced haematologist or coagulation specialist.

AUTHORSHIP

Contribution:
I.L.M.K. and C.H.O. selected the studies after the systematic research. I.L.M.K. wrote the manuscript; and C.H.O. and S.M. edited the manuscript.

Conflict-of-interest disclosure:
The authors declares no competing financial interests.
REFERENCE LIST


Figure 1 A flowchart of the study selection

Table 1 Prevalence of thrombophilia in cohort studies and case control studies

Table 2 Estimated incidence of a first episode of venous thrombosis in carriers over the age of 15 of various thrombophilic disorders (data apply to individuals with at least one symptomatic first-degree relative) (32)
Figure 1

Potentially relevant studies identified (n=1014)

Studies excluded after title and abstract evaluation (n=897)

Papers retrieved for full-text evaluation (n=117)

Additional identified studies from references (n=8)

Studies excluded after full-text evaluation
- Inclusion criteria (n=25)
- Not in English (n=6)
- Abstracts (n=31)
- Not crucial data (n=34)

Studies included (n=13):
- Case control (n=3)
- Cohort (n=10)
<table>
<thead>
<tr>
<th>Cohort studies</th>
<th>Patients, n (male)</th>
<th>Age</th>
<th>Type patients</th>
<th>FVL</th>
<th>PTM</th>
<th>AT</th>
<th>PC</th>
<th>PS</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alioglu (2008)(35)</td>
<td>59 (31)</td>
<td>0-15 y</td>
<td>Cardiac disease</td>
<td>9/52</td>
<td>3/52</td>
<td>0/52</td>
<td>0/52</td>
<td>0/52</td>
<td>6</td>
</tr>
<tr>
<td>Demirel (2009)(11)</td>
<td>18 (10)</td>
<td>0-25 d</td>
<td>Neonates with all VTE</td>
<td>1/18</td>
<td>1/18</td>
<td>0/18</td>
<td>1/18</td>
<td>0/18</td>
<td>5</td>
</tr>
<tr>
<td>Kerlin (2009)(22)</td>
<td>30 (12)</td>
<td>1-20 y</td>
<td>VTE in NS</td>
<td>4/12</td>
<td>0/12</td>
<td>0/12</td>
<td>0/12</td>
<td>0/12</td>
<td>6</td>
</tr>
<tr>
<td>Berfelo (2010)(15)</td>
<td>52 (39)</td>
<td>0-1 mo</td>
<td>CVT</td>
<td>2/41</td>
<td>2/18</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Tuckviene (2011)(16)</td>
<td>39 (17)</td>
<td>0-18 y</td>
<td>CVT</td>
<td>4/22</td>
<td>2/18</td>
<td>0/23</td>
<td>0/24</td>
<td>0/23</td>
<td>6</td>
</tr>
<tr>
<td>Wright (2011)(36)</td>
<td>92 (44)</td>
<td>2d-20 y</td>
<td>Children with all VTE</td>
<td>2/42</td>
<td>1/35</td>
<td>1/44</td>
<td>0/49</td>
<td>0/47</td>
<td>5</td>
</tr>
<tr>
<td>Suri (2013)(23)</td>
<td>34 (22)</td>
<td>3-12 y</td>
<td>VTE in NS</td>
<td>0/18</td>
<td>0/18</td>
<td>1/18</td>
<td>0/18</td>
<td>2/18</td>
<td>5</td>
</tr>
<tr>
<td>Pillar (2013)(37)</td>
<td>26 (0)</td>
<td>12-21 y</td>
<td>Contraception associated VTE</td>
<td>4/26</td>
<td>3/26</td>
<td>0/26</td>
<td>0/26</td>
<td>1/26</td>
<td>4</td>
</tr>
<tr>
<td>Mahajerin (2014)(39)</td>
<td>239 (101)</td>
<td>0-20 y</td>
<td>Inpatients Outpatients</td>
<td>13/144</td>
<td>4/125</td>
<td>0/135</td>
<td>0/131</td>
<td>0/131</td>
<td>6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case-control studies</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Laugesaar (2009)(18)</td>
<td>Cases 75 (45)</td>
<td>0-18 y</td>
<td>CVT</td>
<td>2/7</td>
<td>2/7</td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Controls 400 (207)</td>
<td>newborn</td>
<td></td>
<td></td>
<td>12/400(3%)</td>
<td>13/400(3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albisetti (2013)(20)</td>
<td>Cases 45 (20)</td>
<td>0.3-16.4 y</td>
<td>Malignancies and PACs</td>
<td>2/45</td>
<td>0/45</td>
<td>0/45</td>
<td>0/45</td>
<td>0/45</td>
<td>7</td>
</tr>
<tr>
<td>Controls 69 (44)</td>
<td>0.3-16.2 y</td>
<td></td>
<td></td>
<td>5/69</td>
<td>3/69</td>
<td>3/69</td>
<td>3/69</td>
<td>3/69</td>
<td></td>
</tr>
<tr>
<td>Thom (2014)(21)</td>
<td>Cases 25</td>
<td>0 – 18 y</td>
<td>Cardiac disease and CVC</td>
<td>1/25</td>
<td>0/25</td>
<td>0/25</td>
<td>0/25</td>
<td>1/25</td>
<td>8</td>
</tr>
<tr>
<td>Controls 65</td>
<td>0 – 18 y</td>
<td></td>
<td></td>
<td>3/65</td>
<td>2/65</td>
<td>3/65</td>
<td>3/65</td>
<td>2/65</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: n number, y year, mo month, d day, PAC port-a-cath, CVC central venous catheter, FVL factor V mutation, PTM prothrombin mutation, AT antithrombin deficiency, PC protein C deficiency, PS protein S deficiency, NOS Newcastle Ottowa Scale, NS nephrotic syndrome, VTE venous thromboembolic disease, abd abdominal, LE lower extremity, PE pulmonary embolism, CVT cerebral venous thrombosis, * homozygous
Table 2

<table>
<thead>
<tr>
<th></th>
<th>Antithrombin, protein C, or protein S deficiency</th>
<th>Factor V Leiden mutation</th>
<th>Prothrombin mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (%/year, 95%CI)</td>
<td>1.5 (0.7-2.8)</td>
<td>0.5 (0.1-1.3)</td>
<td>0.4 (0.1-1.1)</td>
</tr>
<tr>
<td>Surgery, trauma, or immobilization (%/episode, 95%CI)</td>
<td>8.1 (4.5-13.2)</td>
<td>1.8 (0.7-4.0)</td>
<td>1.6 (0.5-3.8)</td>
</tr>
<tr>
<td>Pregnancy (%/pregnancy, 95%CI)</td>
<td>4.1 (1.7-8.3)</td>
<td>2.1 (0.7-4.9)</td>
<td>2.3 (0.8-5.3)</td>
</tr>
<tr>
<td>During pregnancy (%, 95%CI)</td>
<td>1.2 (0.3-4.2)</td>
<td>0.4 (0.1-2.4)</td>
<td>0.5 (0.1-2.6)</td>
</tr>
<tr>
<td>Postpartum period (%, 95%CI)</td>
<td>3.0 (1.3-6.7)</td>
<td>1.7 (0.7-4.3)</td>
<td>1.9 (0.7-4.7)</td>
</tr>
<tr>
<td>Oral contraceptive use (%/year of use, 95%CI)</td>
<td>4.3 (1.4-9.7)</td>
<td>0.5 (0.1-1.4)</td>
<td>0.2 (0.0-0.9)</td>
</tr>
</tbody>
</table>
Manifestations and clinical impact of pediatric inherited thrombophilia

Irene L.M. Klaassen, C. Heleen van Ommen and Saskia Middeldorp