The incidence of venous thromboembolism in thrombophilic children: a prospective cohort study
Daniela Tormene, Paolo Simioni, Paolo Prandoni, Francesca Franz, Patrizia Zerbinati, Giulio Tognin, and Antonio Girolami

Antithrombin and protein C and S defects, factor V Leiden mutation, and G20210A prothrombin gene mutation are well-recognized risk factors for venous thromboembolism (VTE) in adults, especially during circumstantial situations such as trauma, immobilization, surgery, or oral contraceptive treatment. The relevance of these defects in predisposing children to VTE is still undefined. In a prospective cohort study we assessed the incidence of spontaneous and risk period–related VTE in asymptomatic children (aged 1-14 years), who were family members of a proband with an objectively diagnosed venous thromboembolic event and a documented single thrombophilic abnormality. We enrolled 143 children from 63 families. Of them, 81 (56.6%) were carriers of an inherited defect, whereas the remaining 62 were free from known genetic or acquired causes of thrombophilia. The mean observation period was 5 years (range, 1-8 years) in each group. Thirty-one risk periods occurred in the carriers group and 20 in noncarriers. Neither spontaneous nor risk period–related VTE occurred in either group during 395 and 296 observation years, respectively. However, circumstances where most of the pediatric thromboses occur (insertion of central venous lines, cancer, and cardiovascular surgery) were not encountered. In conclusion, the thrombotic risk in otherwise healthy children with a single identified thrombophilic defect appears to be very low. Common triggering conditions for VTE in thrombophilic adults do not seem to increase the thrombotic risk in children carrying the same inherited defect. Accordingly, screening for thrombophilia in otherwise healthy children younger than 15 years who belong to families with inherited defects predisposing to thrombosis seems unjustified.

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Patients and methods

Patients

Consecutive patients referring to the Thrombosis Center of the University of Padua with an episode of objectively proven deep vein thrombosis (DVT) or pulmonary embolism (PE) between 1993 and 2001 were screened for deficiencies of antithrombin and protein C or S, and the presence of factor V Leiden mutation or G20210A prothrombin mutation. All consenting family members of probands who were identified as carriers of a thrombophilic state were eligible for this investigation provided they were younger than 15 years and older than 1 year and had not experienced previous episodes of VTE. Approval was obtained from the Institutional Review Board of the University of Padua for this study. Informed consent was provided according to the Declaration of Helsinki.

Eligible patients underwent the blood determination of prothrombotic abnormalities and the bilateral compression ultrasound of the proximal vein system. Carriers of combined prothrombotic disorders were excluded from further investigation, as were subjects with vein incompressibility of either leg.

Study design

A follow-up visit was performed every 6 months. At each visit, attention was paid to risk periods for VTE (such as prolonged immobilization, recent
trauma or surgery, hormonal therapy, the insertion of a central venous line, or infectious diseases). In addition, a bilateral compression ultrason sound test of the leg venous system was performed to check the occurrence of asymptomatic thrombotic episodes.

Parents of children presenting with clinical signs or symptoms of thromboembolic events were encouraged to address our center, where proper objective tests (either compression ultrasonography or ascending phlebography in subjects with suspected DVT; either ventilation-perfusion lung scan or spiral computed tomographic scanning in case of suspected PE) were performed to confirm or rule out the clinical suspicion.

The systematic use of antithrombotic drugs was vigorously discouraged. The decision to administer thromboprophylactic drugs during periods at risk for venous thrombosis was left to the discretion of treating physicians. Children left the study when they reached the age of 15 years.

**Laboratory assays**

Laboratory tests for antithrombin and protein C and S were performed according to methods previously described. The following reference values were used: antithrombin antigen concentration, 70% to 120%; antithrombin activity, 70% to 120%; protein C antigen concentration, 65% to 130%; protein C activity, 65% to 130%; total protein S concentration, 60% to 120%; and free protein S concentration, 60% to 108%. Those subjects who were found to be deficient on 3 consecutive determinations and had at least one of the investigated relatives with the same defect were labeled as carriers of a prothrombotic state.

The DNA analysis for factor V Leiden and G20210A prothrombin variant was performed using previously described methods.

**Outcomes**

The primary outcome was the occurrence of an objectively documented thromboembolic event. Thrombotic events were categorized as spontaneous if occurring without a predisposing risk period and secondary if occurring during or within 3 months after a risk period.

**Analysis**

The incidence of thromboembolic events and its 95% CI was calculated in carrier and noncarrier groups. The relative risk (RR) for the development of both spontaneous and risk period–related VTE was calculated by dividing the incidence rate in carriers by the incidence in noncarrier family members.

### Results

**Patients**

All 143 eligible children, who were family members of 63 probands with a single recognized prothrombotic disorder, were enrolled in the current investigation. Eighty-one (56.6%) were carriers of inherited defects: 9 heterozygous carriers of antithrombin deficiency, 13 of protein C deficiency, 3 of protein S deficiency, 41 of factor V Leiden mutation (of whom 38 were heterozygous and 3 homozygous), and 15 of G20210A prothrombin mutation (of whom 2 were homozygous). The remaining 62 children were free from thrombophilia. The main characteristics of included children are shown in Table 1.

**Follow-up**

There were 395 observation-years in carriers and 296 observation-years in noncarriers. The mean observation time in each group was 5 years (range, 1-8 years), and at least 1 year of follow-up was available in all children (Table 1).

### Risk periods

Of the 81 carriers of a thrombophilic state, 21 experienced one or more risk periods of thrombosis (overall, 31 risk periods): 3 operations, 21 traumas (15 with plaster cast for 20-30 days, 6 with immobilization for more than 10 days), and 7 periods of immobilization for infections. Twenty risk periods occurred in 15 of the 62 control subjects: 4 operations, 15 traumas (13 with plaster cast for 30 days, 2 with immobilization for more than 7 days), and 1 immobilization for infection (Table 2).

Antithrombotic prophylaxis with low-molecular-weight heparin was used during 3 risk periods (traumas with plaster cast) in the carriers group: 1 in a protein C–deficient carrier, and 2 in carriers of factor V Leiden.

### Venous thromboembolic events

During the study period, 2 children presented with clinical symptoms suggestive of VTE, which was excluded in all. Therefore, no thromboembolic events (either clinically symptomatic or asymptomatic) occurred in the 2 groups, leading to an overall annual incidence of VTE of 0% (95% CI, 0.0-0.9) in the carriers group and 0% (95% C, 0.0-1.2) in noncarriers.

### Discussion

In contrast with the increasing risk of thromboembolic complications shown by adults who are carriers of a thrombophilic state, little is known about this risk in childhood. This is the first prospective cohort study designed to make an estimate of the age-related risk of both spontaneous and risk-related VTE in subjects younger than 15 years who are family members of a thrombophilic proband. During an average follow-up of 5 years, no episodes of symptomatic or asymptomatic VTE could be recorded in any of the recruited individuals. It should be noted that during the study period one or more risk factors of thrombosis were experienced by 26% of children, and that in the majority of cases no prophylactic treatment was carried out. These findings did not differ from those observed in nonthrombophilic children. Although the relatively small number of considered children precludes definite conclusions, the results of our investigation suggest that the incidence of thromboembolic complications in children who are carriers of a single prothrombotic abnormality is low enough to rule out the need for systematic thromboprophylaxis.

It is interesting to note that the absence of risk period–related complications in our cohort contrasts with the incidence reported in adults under the same circumstances.10-13 Thrombophilic adults carry a risk of venous thromboembolic events during circumanstrial risk periods (such as major trauma or surgery, immobilization,
In conclusion, otherwise healthy thrombophilic children who carry a single identified thrombophilic abnormality and are family members of a thrombophilic proband appear to be at a very low risk of both spontaneous and risk-related thromboembolic complications outside extreme circumstances such as cancer, the need for prolonged immobilization, cardiovascular surgery, or the insertion of central venous lines. Accordingly, the routine screening for thrombophilia before the age of 15 years does not seem justified. For final decisions to be made, however, a longer follow-up in a larger group of thrombophilic children observed in a wider variety of clinical situations is needed.

References


Table 2. Type and number of risk periods experienced by the children during follow-up according to their deficiency status

<table>
<thead>
<tr>
<th>Type of risk period</th>
<th>AT (2)</th>
<th>PC (4)</th>
<th>PS (11)</th>
<th>F V Leiden (2)</th>
<th>G20210A (15)</th>
<th>Noncarriers (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31[3]</td>
<td></td>
<td></td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate the number of children who experienced risk periods.
Numbers in brackets indicate the number of risk periods during which prophylaxis was given.

Hormonal therapy, pregnancy, or puerperium, which is significantly higher than that observed in noncarriers. This risk is particularly important in carriers of antithrombin and protein C and S defects, but is substantial also in subjects with factor V Leiden mutation. Accordingly, many clinicians recommend the screening for thrombophilia in adults who are asymptomatic family members of thrombophilic probands, at least in women of fertile age and in those subjects who are candidates for major risk factors for venous thrombosis. Although the small number of risk periods and the nonuniform approach concerning anticoagulant prophylaxis preclude definite conclusions, the lack of thromboembolic complications even in children who were not given prophylactic drugs following a major trauma or a surgical intervention suggests that the screening for thrombophilia might not be necessary in children who are family members of thrombophilic probands with a single identified thrombophilic defect until they are 15 years old.

We think that our results provide a reliable estimate of the thromboembolic risk of otherwise healthy children. All identified subjects were prospectively followed-up at the same study center. All episodes of clinically suspected DVT or PE were investigated with properly validated objective tests. Moreover, confounding factors were minimized by programming the exclusion from our investigation of children with a history of previous thromboembolism. Our findings should, however, be interpreted with caution. In recent years, thromboembolic events have been increasingly recognized as a major cause of morbidity and mortality in tertiary care pediatrics, especially in newborns and children with neoplastic diseases, in those requiring the placement of central venous lines or the administration of chemotherapy drugs, and in those with congenital heart disease. In addition, recent case-control studies suggest that thrombophilic children have a higher risk of stroke and other thromboembolic complications than matched control subjects without thrombophilia.


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