To the editor:

Catheter-related thrombosis in children with hemophilia A: evidence of a multifactorial disease

Hemophilia A (HA) and B (HB) are X-linked genetic hemorrhagic disorders resulting from deficiencies of blood coagulation factor VIII or IX, respectively. Subjects suffering from plasma levels of factor VIII coagulant activity or factor IX below 1% of normal are classified as severe hemophiliacs. Although bleeding symptoms correlate with the levels of the remaining factor activity, it is reported that some hemophilic subjects with factor VIII levels below 1% do not all bleed with the same severity, and in rare cases of severe HA, thrombotic episodes have also been reported in childhood.1,8

Since the reported symptomatic vascular accidents in hemophiliacs are, in the majority of cases, related to central venous lines (CVLs), we have read with interest the paper by Journeycake et al.1 Their data demonstrated that hemophiliacs with tunneled subclavian CVLs in place for more than 48 months had abnormal venograms.1 In addition, 5 of 15 hemophiliacs (33.3%) had symptomatic deep venous thrombosis (DVT) related to the CVLs; 3 further patients (20%) with signs of DVT on contrast venography had no clinical problems. Because CVLs are a common adjunct to therapy of severe hemophiliacs, we would like to add some additional information on risk factors that, besides the CVLs themselves, are of importance in the development of CVL-associated vascular accidents in these patients. It has been recently suggested that the clinical phenotype of severe HA is influenced by coinheritance of prothrombotic risk factors.9 In addition, we have recently demonstrated that the first symptomatic bleeding onset in children with severe HA carrying prothrombotic risk factors is significantly later in life than in noncarriers.10

As recently described, we investigated 103 consecutively admitted pediatric previously untreated patients (PUP) patients with hemophilia with factor levels below 1%. In this cohort, factor V (FV) 1691G→A mutation, prothrombin 20210G→A mutation was present in 2 of our 7 patients. As recently described, we investigated 103 consecutively admitted pediatric previously untreated patients (PUP) patients with hemophilia with factor levels below 1%. In this cohort, factor V (FV) 1691G→A mutation, prothrombin 20210G→A mutation was present in 2 of our 7 patients. All 8 patients have hemophilia A.

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Table 1. Summary of patients experiencing vascular accident

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Factor VIII level</th>
<th>Mutation</th>
<th>Inhibitor status prior to thrombosis</th>
<th>Duration of catheter prior to thrombosis</th>
<th>Factor concentrate</th>
<th>Mode of application prior to vascular event</th>
<th>Prothrombotic risk factor</th>
<th>Exogenous trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt; 1%</td>
<td>Intron 22 2781delT (exon 14)</td>
<td>High responder Port</td>
<td>1.5 years</td>
<td>rFVIII</td>
<td>On demand</td>
<td>FV 1691G→A</td>
<td>Lp(a)*</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 1%</td>
<td>ND</td>
<td>High responder Port</td>
<td>1.8 years</td>
<td>pdFVIII</td>
<td>Prophylaxis 3/wk</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>&lt; 1%</td>
<td>ND</td>
<td>Hickman</td>
<td>4 months</td>
<td>FVIII/vWF</td>
<td>Continuous infusion: bleeding episode</td>
<td>ND</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>1.4%</td>
<td>ND</td>
<td>Port</td>
<td>1.5 years</td>
<td>FVIII/vWF</td>
<td>Prophylaxis 3/wk</td>
<td>MTHFR TT</td>
<td>Obesity</td>
</tr>
<tr>
<td>5</td>
<td>&lt; 1%†</td>
<td>Intron 22</td>
<td>Port</td>
<td>7 years</td>
<td>rFVIII</td>
<td>Prophylaxis 3/wk</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>&lt; 1%†</td>
<td>Intron 22</td>
<td>Port</td>
<td>6 years</td>
<td>FVIII/vWF</td>
<td>Prophylaxis 3/wk</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>&lt; 1%†</td>
<td>Intron 22</td>
<td>Low responder Port</td>
<td>10 years</td>
<td>pdFVIII</td>
<td>IT following prophylaxis 3/wk</td>
<td>MTHFR TT</td>
<td>None</td>
</tr>
<tr>
<td>8</td>
<td>&lt; 1%</td>
<td>Intron 22</td>
<td>High responder Port</td>
<td>7 months</td>
<td>FVIII/vWF</td>
<td>Prophylaxis 3/wk</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

All 8 patients have hemophilia A.

*F indicates factor; IT, immune tolerance therapy; Lp(a), lipoprotein (a); MTHFR TT, thermolabile methylenetetrahydrofolate reductase 677C→T genotype; ND, not determined; pdFVIII, purified factor VIII concentrate; rFVIII, recombinant factor VIII concentrate; FVIII/vWF, factor VIII/von Willebrand factor concentrate.

†Catheter welded together with vessel wall and could not be completely removed.
but they do not cause thrombosis unless associated with increased mutations being present in 5%-12% of persons studied in cohorts, tase mutations are common, with homozygous (MTHFR TT) inherited hypercoagulable disorders.1,2

states conferred by the condition itself, duration of catheter use, and caustic agents that are administered through the line, inflammatory influencing thrombotic potential of central venous catheters include variety of clinical situations, including cancer, chronic infection, We read with interest the letter by Ettingshausen et al. In-dwelling Catheter-related thrombosis in children with hemophilia A

Catheter-related thrombosis in children with hemophilia A

We read with interest the letter by Ettingshausen et al. In-dwelling catheters facilitate the long-term care of pediatric patients in a variety of clinical situations, including cancer, chronic infection, and hemophilia. But these patients are at risk of developing deep venous thrombosis (DVT) of the upper venous system. Factors influencing thrombotic potential of central venous catheters include caustic agents that are administered through the line, inflammatory states conferred by the condition itself, duration of catheter use, and inherited hypercoagulable disorders.12

The cumulative effect of these risk factors is not known. As well, we do not know which inherited factors add the greatest risk. Factor V Leiden places patients older than 15 years of age at an annual risk for DVT of 0.58%.3 Methylene tetrahydrofolate reductase mutations are common, with homozgyous (MTHFR TT) mutations being present in 5%-12% of persons studied in cohorts, but they do not cause thrombosis unless associated with increased plasma homocysteine levels.45 Prospective trials in patients who have known thrombophilia and require central lines are needed to determine the incidence of DVT related to these events.

A large percentage of patients with central venous catheters have radiographic evidence of DVT, but only a few of these patients are symptomatic.67 Acute upper venous system occlusion is associated with catheter malfunction, pulmonary embolism, extremity swelling, and superior vena cava syndrome. But long-term complications of catheter-related DVT identified by imaging studies in asymptomatic patients have yet to be defined. Ideally, catheters should be removed as early as possible prior to the development of any occlusive symptoms. Physicians should be alert to the signs of underlying DVT, including pain or difficulty with access of the catheter, swelling of the arm, or dilated superficial chest wall veins. In the event of documented DVT, inherited thrombophilia should be considered prior to the placement of a second catheter and before the continued use of agents such as recombinant factor VIIa. The efficacy and safety of DVT prophylaxis in children with catheters have not been proven. Until we have alternative therapeutic options for patients who require catheters and treatment with agents such as recombinant factor VIIa and prothrombin complex concentrates, general screening prior to catheter insertion is not practical.

Response:

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Janna M. Journeycake and George R. Buchanan

Correspondence: George R. Buchanan, Division of Hematology-Oncology, Department of Pediatrics, University of Texas, Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd, Dallas, TX 75390-9063; e-mail: george.buchanan@utsouthwestern.edu

References


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Carmen Escuriola Ettingshausen, Karin Kurnik, Rosemarie Schobess, Wolfart D. Kreuz, Susan Halimeh, Hartmut Pollman and Ulrike Nowak-Göttl