

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%.¹⁰ In this cohort, factor V (FV) 1691G>A mutation, prothrombin 20210G>A variant, MTHFR 677C>T genotype, antithrombin, protein C, protein S, antithrombin, and lipoprotein (Lp) (a) were deter-

mined.^{11,12} Of these 103 hemophilia patients, 25 (24.3%) had tunneled subclavian CVLs in place for 12 months or more. Eight of the 25 patients with CVL (32%; inhibitor patients, n = 5; prophylaxis, n = 3) suffered at least one vascular accident (Table 1). All 8 patients developed clinical problems related to their catheter: symptoms ranged from increased resistance during use of the device to acute swelling of the arm and upper chest, followed by persistent prominence of superficial veins over the shoulder. Contrast venography confirmed DVT in all symptomatic cases; in 2 patients the CVL could not be completely removed because the catheter had welded with the vessel wall. In these 2 cases, old organized thrombotic material was considered as the pathologic background. Whereas the prevalence of prothrombotic risk factors in children with HA was no different from that which was previously reported,¹⁰⁻¹² 5 of 7 children with symptomatic vascular accidents screened for prothrombotic risk factors carried at least one genetic risk. In one other patient thrombophilia screening awaits parental consent. Similar to patient number 2 in Journeycake et al,¹ the heterozygous factor V 20210G>A mutation was present in 2 of our 7 patients. Additionally, 4 patients were treated with factor (F) VIII/vWF concentrates, and 1 child each received purified FVIII, recombinant VIIa, purified FVIII, and recombinant FVIII, respectively.

Our data and those of Journeycake et al¹ show that CVL-related vascular accidents in hemophilic patients are a common problem of multifactorial etiology. Thus in such patients, besides the duration of the CVL, the possible interaction of catheters with prothrombotic risk factors and the administration of potential thrombogenic coagulation factor concentrates without concomitant anticoagulation should be kept in mind. We would therefore recommend a general screening for prothrombotic risk factors in hemophiliacs prior to catheter implantation, continuous infusion, and immune tolerance with potential prothrombotic factor concentrates (recombinant FVIIa, FVIII/vWF).

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Table 1. Summary of patients experiencing vascular accident

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

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.

*Above 30 mg/dL.

†Catheter welded together with vessel wall and could not be completely removed.

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Response:

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.^{1,2}

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 homozygous (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.^{4,5} 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.^{6,7} 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 accession 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.

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