Delayed Bleeding in a Toddler

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A 21-month-old boy presented to the hospital with 5 days of bleeding from a scalp laceration sustained after a ground-level fall. On the day of injury, he presented to the emergency department where hemostasis was achieved and the laceration was repaired with a topical skin adhesive. Bleeding from the laceration resumed the next day after the patient had been sent home and continued for 4 more days.

The patient had an unremarkable past medical history. He had no prior episodes of spontaneous or prolonged bleeding, excessive bruising, mucocutaneous bleeding or postsurgical hemorrhage. A detailed, three-generation family history was negative for bleeding dyscrasias or thrombosis.

On examination, he was lethargic, fussy, and easily consolable. He was afebrile and tachycardic at 163 beats per minute. A left occipital hematoma with a 2-cm scalp laceration continued to bleed despite application of direct pressure. Additionally, a hematoma measuring 5 × 2 cm was seen on the left anterior proximal thigh and an area of ecchymosis measuring 2 × 2 cm was noted below the right knee.

Complete blood count showed a white blood cell count of 10.8 × 10⁹/L, hemoglobin of 6.2 g/dL, hematocrit of 18.2%, and a platelet count of 246 × 10⁹/L. Mean corpuscular volume was 76.4 fl. Prothrombin time (PT) was 13.9 seconds (normal 11.6-13.6 seconds), and activated partial thromboplastin time (aPTT) was 96.7 seconds (normal 26-36 seconds).

The scalp laceration was repaired with sutures but continued to bleed. The patient was hospitalized and hematology was consulted. Hemoglobin decreased to 4.9 g/dL within 4 hours, and he was transfused with packed red blood cells. Due to the prolonged aPTT, Factor VIII and IX activity levels were assessed and the patient was transfused with fresh frozen plasma (FFP). The wound was covered in oxidized cellulose. Additionally, the patient was given epsilon-aminocaproic acid (EACA) to reduce fibrinolysis. The bleeding ceased and his hemoglobin remained stable throughout the remainder of his 1-week hospitalization.

For diagnosis, see page e11

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
Diagnosis:
Severe Hemophilia A

On the fourth hospital day, Factor VIII activity was reported to be <1% (normal 50%-180%), confirming the diagnosis of severe hemophilia A. Factor IX activity level and von Willebrand panel were normal. An inhibitor panel was negative for antibodies against Factor VIII, thereby excluding the diagnosis of acquired hemophilia A.

**DISCUSSION**

Hemostasis occurs in two stages. Primary hemostasis is the formation of a platelet plug from platelets, von Willebrand factor, and compromised endothelium. Platelet activation initiates the coagulation cascade that leads to stabilization of the platelet plug with cross-linked fibrin in a process known as secondary hemostasis. Table 1 describes the difference in clinical presentation between primary and secondary disorders of hemostasis.

Hemophilia A results from diminished or absent Factor VIII, a crucial factor in the intrinsic pathway of the coagulation cascade. Factor VIIIa, the active form of Factor VIII, mediates Factor IXa-driven activation of Factor X. Low or absent levels of Factor VIII result in impaired generation of thrombin and fibrin, and thus impaired secondary hemostasis. Hemophilia A is inherited in an X-linked recessive manner. In most cases, there is a family history of hemophilia. However, spontaneous mutations in the mother may represent nearly half of cases. Therefore, it is important to determine whether the affected child’s mother carries the mutation; it should be noted that any further male offspring are at risk despite a negative family history.

The mean ages of diagnosis for moderate and severe hemophilia are 20 months and 9 months, respectively. Twenty percent of cases present with abnormal hemorrhage within the first 7 days of life. Up to 20% of patients present with intracranial hemorrhage or scalp bleeding as their initial presentation of hemophilia as in our patient. Interestingly, our patient did not present with abnormal hemorrhage until age 21 months despite his severe phenotype. Late onset of symptoms in severe hemophilia may be due to the presence of prothrombotic factors, such as Factor V Leiden mutation, protein C deficiency, or prothrombin G20210A mutation.

Patients presenting with excessive bleeding or bleeding into a muscle or joint should undergo further investigation for a coagulopathy. Delayed bleeding occurs in patients with hemophilia because formation of the platelet plug is intact but stabilization is impaired. The PT and aPTT tests can elucidate most disorders of secondary hemostasis. However, it is important to note that a deficiency of Factor XIII and disorders of fibrinolysis are not detected by these initial tests. Patients with hemophilia A have a prolonged aPTT and normal PT because Factor VIIIa only affects the intrinsic coagulation pathway and the extrinsic coagulation pathway is preserved (Table 2). Factor VIII activity level of >5% is classified as mild, whereas 1% to 5% is classified as moderate and <1% is classified as severe hemophilia.

The presence of heparin from a blood sample obtained from a heparin-flushed intravenous catheter can also cause prolonged aPTT with normal PT. Although heparin should theoretically cause a prolonged PT and aPTT through inhibition of thrombin (Factor II), heparin neutralizers are added to the PT assay to normalize PT and allow accurate monitoring in patients transitioning to warfarin. However, excess heparin can overcome the heparin-neutralizer effect and cause prolonged aPTT and PT.

The management of significant or life-threatening hemorrhage in a patient with a suspected but unconfirmed defect in the intrinsic coagulation pathway is not completely defined. Transfusion of FFP is effective in patients with suspected hemophilia, although risk of transmission of viral infections remains and the volume required to correct a signifi-

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**TABLE 1.** Defects in the Clinical Presentation of Primary Versus Secondary Hemostasis

<table>
<thead>
<tr>
<th>Primary Hemostasis</th>
<th>Secondary Hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucocutaneous bleeding</td>
<td>Delayed bleeding after surgery or a hemostatic insult</td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
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<tr>
<td>Menorrhagia</td>
<td>Deep tissue bleeding</td>
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<tr>
<td></td>
<td>Intramuscular hematoma</td>
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<tr>
<td></td>
<td>Hemarthrosis</td>
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<tr>
<td>Easy bruising</td>
<td></td>
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<tr>
<td>Petechiae</td>
<td></td>
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</tbody>
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*Considerable overlap exists in the clinical presentation of primary and secondary hemostasis. Adapted from Rajpurkar and Lusher.*

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cant coagulopathy may be intolerable. Recombinant Factor VIIa (rFVIIa) is an alternative option. High doses of rFVIIa can bypass defects in the intrinsic pathway through direct activation of Factor X and the common factor pathway. rFVIIa is associated with increased incidence of thromboembolism and is expensive. In our patient, the late onset of presentation suggested a mild coagulopathy, leading to the use of FFP, rFVIIa, and antifibrinolytic agents such as oxidized cellulose and EACA, which were used as adjunctive therapies.

CONCLUSION

Hemophilia A is an X-linked bleeding disorder that presents primarily in males with spontaneous, severe, and/or delayed bleeding. Although family history is often positive and can assist in making the diagnosis, up to one-half of cases are due to spontaneous mutations in the affected child’s mother. In patients presenting with bleeding and high clinical suspicion of hemophilia, empirical management with FFP, rFVIIa, and adjunctive therapies such as oxidized cellulose and EACA may be warranted while awaiting confirmation of a definitive diagnosis.

REFERENCES