Pediatric Bleeding Disorders

A Clinical Casebook

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Preface

When this book was conceived, the editors were partners at Nationwide Children's Hospital in Columbus, Ohio. The editors share a lifelong passion for clinical pediatric hemostasis, along with a similar passion for mentorship and education. We also realize the value of having partners and friends who share our interests. The field of pediatric hemostasis has evolved dramatically over the last decade as new interventions such as gene therapy, antibody-based therapies, and cellular therapies become realities; significant time and effort must be dedicated to learning about how and when to use these options. In addition, hemostasis testing is evolving, and increasingly, knowledge about the power of genetic testing and global hemostatic assays is vitally important. Categorical clinical training schedules, however, have increasing demands because every aspect of hematology, oncology, and bone marrow transplant is complex and rapidly evolving. For this reason, Dr. Bryce A. Kerlin had the vision to create a fourth year hemostasis/thrombosis fellowship to meet the training needs of future generations of pediatric hemostasis physicians. The fellowship provides 1–2 years of protected time, individualized to the trainee's wants and needs. It also provides the opportunity to travel to relevant meetings such as the American Society of Hematology, Hemophilia Academy, and the Hemostasis and Thrombosis Research Society annual meetings. Our fellows have benefitted from these meetings to develop their own relationships and collaborators in the field. Fortunately, a local benefactor, Ms. Joan Wallick shared Dr. Kerlin's vision, and our fellowship is endowed

in her name. Our team has benefitted enormously from the excitement and enthusiasm of our trainees, and we have all grown because of this program. The fellows have all produced important and impactful academic works on a variety of hemostasis related projects.

As the editors planned this book, we decided to merge our passions for hemostasis and mentorship. Each editor paired with a former fellow who had completed either a categorical or fourth year fellowship with us. Each pair aimed to create clinical vignettes that would be approachable and illustrative of common scenarios encountered in pediatric hematology practice. The aim was to work through a differential diagnosis and initial treatment approach to each scenario and to offer a few clinical pearls at the end of each chapter. As so often happens in academic life, this group of collaborators no longer all work in the same city, but the collaborations, mentoring, and friendships continue despite physical distance. We dedicate this book to the generosity of Ms. Wallick, the spirit of mentorship, the patients and families who inspire us to keep learning, and all those who love the clinical conundrums associated with a vibrant pediatric hemostasis-thrombosis program.

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Contents

Part V Platelet Dysfunctions

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Part I

Hemophilia A and B

1 Management of an Infant with Hemophilia A

Surbhi Saini and Amy L. Dunn

Case Presentation You are called to the newborn nursery to consult on a 2-day-old male with circumcision-related bleeding. You find a term infant who was born by spontaneous vaginal delivery. There is no family history of bleeding disorders, and the mother was taking no medications during the pregnancy. He received vitamin K at birth. On physical examination, he is a well-developed, non-dysmorphic infant. His anterior fontanelle is flat. He has mild pallor and oozing from his circumcision site. He has no bruising or petechia. His vital signs are normal for age.

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Multiple-Choice Management Question

You suspect that this child has a congenital bleeding disorder. Do you:

A. Give fresh frozen plasma
B. Give cryoprecipitate
C. Call for a STAT hematology consult

Differential Diagnosis

The differential in this infant includes congenital factor deficiencies, severe Von Willebrand disease, hypo-/dysfibrinogenemia, thrombocytopenia, disseminated intravascular coagulation, liver disease, vitamin K deficiency, and platelet dysfunction (Fig. 1.1).

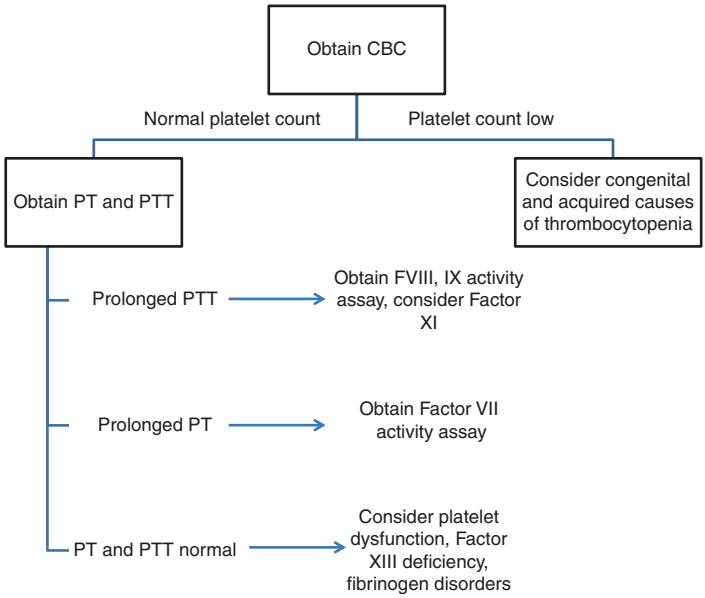

Fig. 1.1 A laboratory approach to the differential diagnosis in a healthy, male infant with prolonged bleeding from circumcision. *CBC* complete blood count, *PT* protime, *PTT* activated partial thromboplastin time

Management

Our patient has persistent, mild oozing but is clinically stable. This allows time to evaluate him and work through the differential diagnosis.

Laboratory Findings

A normal protime (PT), platelet count, fibrinogen, and thrombin time along with an elevated partial thromboplastin time (aPTT) and decreased plasma FVIII activity assay confirm the diagnosis of hemophilia A. Communication with the special coagulation laboratory is crucial to ensure timely and accurate laboratory results. The reagents necessary to perform factor VIII and FIX assays are expensive, and these assays require technical expertise. A call to the laboratory informing them of a suspected diagnosis of hemophilia will enable the laboratory to return results in the most expeditious fashion. Type 3 VWD, which can present in a similar way with elevated aPTT and decreased plasma FVIII levels, needs to be differentiated from hemophilia A. Patients with type 3 VWD will have absent multimers, along with low FVIII, VWF antigen, and ristocetin cofactor activity. VWD Normandy variant (type 2 N), which results from decreased FVIII binding to Von Willebrand factor should also be considered in the setting of moderately low FVIII levels or an autosomal inheritance pattern. This can be evaluated with a FVIII binding assay and VWD mutation analysis.

Diagnosis and Assessment

Hemophilia A, or "classic hemophilia," is a congenital bleeding disorder that results from congenital deficiency or absence of circulating factor VIII (FVIII). It is an X-linked recessive disorder with an incidence of approximately 1:5000 male births [1]. Hemophilia B is also X-linked and has an incidence of 1:20,000 male births. Hemophilia is found across the globe and affects every racial and ethnic group.

Factor VIII is a 320 kilodalton glycoprotein that is produced predominantly in the liver sinusoidal endothelial cells. Factor VIII

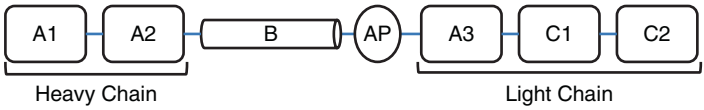

Fig. 1.2 Factor VIII consists of three A domains, one B domain, and two C domains that are linked by an activation peptide (AP)

consists of six domains, A1-A2-B-A3-C1-C2 (Fig. 1.2) with the encoding gene found on the long arm of the X chromosome (Xq28). Upon release into the circulation, FVIII is non-covalently linked to Von Willebrand factor (VWF). VWF protects FVIII from degradation and increases the circulatory half-life from approximately 2 to 12 hours. Upon activation, FVIII is released from VWF, and the activated factor VIIIa acts as a cofactor in the activation of factor X by factor IXa on the surface of activated platelets.

The most common bleeding manifestations in hemophilia A are delayed bleeding, and joint and muscle bleeding. In the newborn period, the most common symptoms are bleeding from circumcision, heel sticks, oral mucosa, and, rarely, intracranial hemorrhage [2]. Therefore, infants born to known carrier mothers should not be circumcised until FVIII or IX activity assay results rule out hemophilia. Nonetheless, lack of bleeding with circumcision does not rule out hemophilia as the incidence of circumcision-related bleeding is reported to be 23–48.2% [3, 4]. Additionally, a lack of family history does not eliminate hemophilia from consideration. There is a particularly high rate of spontaneous mutation within the *FVIII* gene, and as a result, approximately 30% of newly diagnosed patients will have a negative family history of hemophilia.

In general, the severity of bleeding in hemophilia depends upon the percentage of residual, circulating clotting factor activity (Table 1.1). Patients with levels of >5–40% are classified as having mild hemophilia, those with levels of 1–5% as moderate, and those with less than 1% activity as having severe disease. The median age of diagnosis for someone with severe hemophilia is 1 month, compared to 8 months for those with moderate disease and 36 months for those with mild disease. Commonly, patients with severe disease will suffer from spontaneous bleeding, while those with mild-moderate disease typically bleed after trauma or surgery.

Table 1.1 Incidence of hemophilia A based upon the severity of disease

Severity	Factor level (%)	Incidence (%)
Mild	<1	20
Moderate	1–5	20
Severe	>5–40	60

Table 1.2 Spectrum of hemophilia A mutations and inhibitor incidence observed in patients with varying clinical severity

	Severe		Moderate		Mild	
Mutation type	Enrolled	Inhibitor	Enrolled	Inhibitor	Enrolled	Inhibitor
	n (% of total)	*n* (% of mutation type)	*n* (% of total)	*n* (% of mutation type)	*n* (% of total)	*n* (% of mutation type)
Missense	100 (15)	9 (9)	106 (76)	11 (10)	175 (94)	13 (7)
Intron 22 inversion	283 (43)	102 (36)	6 (4)	1 (17)	1 (1)	
Frameshift	108 (16)	26 (24)	9 (6)	3 (33)		
Nonsense	79 (12)	21 (27)	2 (1)		1 (1)	
Splice site	19 (3)	8 (42)	6 (4)	1 (17)	5 (3)	
Large deletion	38 (6)	23 (61)	1 (1)			
Intron 1 inversion	10 (1)	4 (40)				
Small deletion	6 (1)				1 (1)	
Duplication	3 (1)	1 (33)	2 (1)			
None	15 (2)	4 (27)	7 (5)		4 (2)	
Total	661	198 (30)	139	16 (12)	187	13 (7)

Genetics

Many molecular defects have been described in the pathology of hemophilia A including large gene deletions, inversions, single gene rearrangements, deletions, and insertions (Table 1.2). Reported mutations leading to hemophilia A can be found at http://hadb.org.uk/ and https://www.cdc.gov/ncbddd/hemophilia/champs.html.

In our scenario, genetic testing is sent after the initial consultation and reveals a classic intron 22 inversion, which is the most common mutation seen in severe hemophilia A [5] (Fig. 1.3).

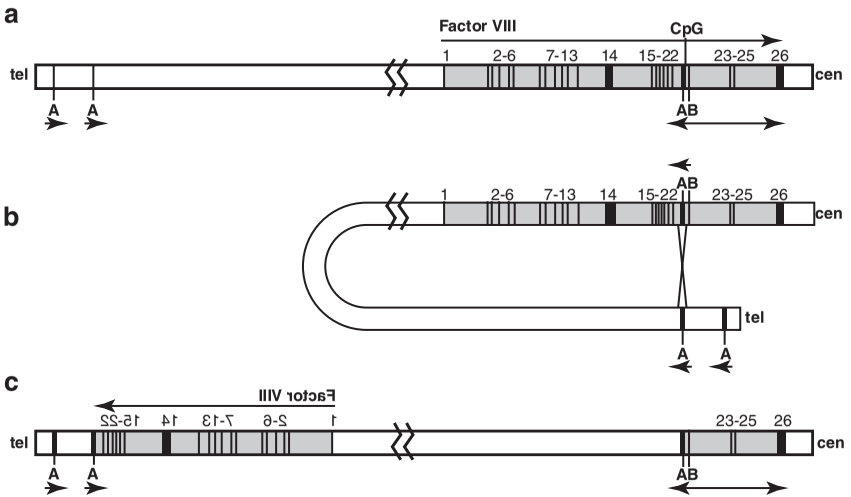

Fig. 1.3 Diagram of the factor VIII gene and illustration of the inversion model. (**a**) Region of Xq28 that includes the factor VIII gene, oriented with the telomere at the left, is depicted. Three copies of the A gene are indicated, two lying upstream of factor VIII and one inside intron 22. The location of the B transcript is also shown. The arrows indicate the direction of transcription of the factor VIII and internal A and B genes. The direction of the upstream A genes is hypothesized to be as shown. (**b**) Proposed homologous recombination between the intron 22 copy of gene A and one of the two upstream copies. A crossover between these two identical regions, oriented as shown, would result in an inversion of sequence between the two recombined A genes (**c**). A recombination could involve either of the upstream A genes, but only one is presented. The crossover could occur anywhere in the region of homology which includes the A genes. Reprinted with permission of Springer Nature. "Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A", by Delia Lakich et al, 1993, Nature Genetics

Management of Newborns with Hemophilia

Factor Concentrates

The most common treatment of HA is FVIII replacement with intravenous FVIII concentrates. Concentrates are either plasma derived, containing varying amounts of VWF, or recombinant. Both undergo multiple viral and pathogen attenuation steps. No infectious complications have been reported in decades. Whether plasma derived or recombinant, the dose of factor delivery is calculated based upon the half-life of the product, the intravascular volume of distribution (on average 1 unit of FVIII per kilogram raises the plasma concentration by 2%), and the desired clotting factor activity.

Preferred products vary by hemophilia treatment center so discussion with a hemophilia specialist is advised. Additionally, the factor formulary in each hospital is managed by the blood bank or the pharmacy, and formulary influences concentrate selection, so inclusion of the blood bank or clinical pharmacy is recommended. Factor dosing in infants is challenging due to the vial size availability. For example, to raise the factor level of the 3 kg child in our clinical scenario to 50%, the dose should be 3 kg × 25 IU = 75 IU. However, the smallest available vial size of FVIII is 250 IU, so most clinicians would infuse the entire vial.

Antifibrinolytic Agents

Antifibrinolytic therapy to stabilize the fibrin clot is particularly useful in diminishing bleeding symptoms in locations with prominent fibrinolytic activity such as the mouth, gastrointestinal tract, and uterus [6]. These agents have a wide distribution and come in IV and oral forms. Case series suggest that they can be useful adjunctive agents in circumcision-related bleeding [7].

Comprehensive Care

A series of federally funded comprehensive hemophilia treatment centers (HTCs) exist to care for persons with hemophilia. They

are typically staffed with hematologists, orthopedists, physical therapists, nurses, genetic counselors, psychologists, and social workers who specialize in the care of patients with bleeding disorders. It has been demonstrated that patients who receive their care in an HTC setting have improved outcomes and a longer life expectancy [8].

Clinical Pearls/Pitfalls

- Approximately 30% of persons with hemophilia A will have no known family history of bleeding disorders.
- Bleeding with circumcision is common in boys with hemophilia and should prompt a work-up in all cases.
- Laboratory evaluation is essential to establish the correct diagnosis, and communication with the special coagulation laboratory will facilitate expeditious results.
- Factor replacement is the preferred approach to bleeding; however, the type of product, plasma derived versus recombinant, continues to be debated due to the risk of inhibitor development.
- Communication with the blood bank or clinical pharmacy regarding available factor concentrates and vial sizes is important when dosing patients.
- Care of children with hemophilia requires consultation with a Hemophilia Treatment Center in order to obtain best patient outcomes.

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2 Clinical Care of a Child with Hemophilia A and Inhibitors

Surbhi Saini and Amy L. Dunn

Case Presentation You receive a call from the family of a 2-year-old boy with known severe hemophilia A (HA). He is on routine prophylaxis with recombinant factor VIII (rFVIII) concentrate once weekly and had his last dose yesterday. He has had 10 exposure days in total. The family reports that their son has a swollen right knee and is limping.

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Multiple-Choice Management Question

You suspect that this child may have developed an inhibitor to FVIII. Your next steps include:

A. Infuse factor VIII concentrate 50 IU/kg.
B. Inject emicizumab 3 mg/kg.
C. Perform a Bethesda assay.
D. **A and C**

Differential Diagnosis

The differential includes development of an inhibitor to FVIII, a breakthrough hemarthrosis without inhibitor formation, fracture, and non-bleeding-related soft tissue injuries.

Management

Fortunately, the patient lives close to the treatment center. After administering 50 IU/kg of rFVIII at home, the family presents to the hematology clinic. His knee is warm and has a palpable effusion but no physical findings of instability. His pain is well controlled with acetaminophen, ice, and a compression bandage. You suspect inhibitor formation. You call your coagulation lab and obtain a STAT Bethesda titer and FVIII level. The titer returns at 10 Bethesda units (BU), and the FVIII assay is <1%. This confirms presence of a high titer inhibitor.

Etiology of Inhibitor Development

Inhibitory alloantibodies to exogenous FVIII replacement concentrates, most commonly referred to as "inhibitors," occur in approximately 20–30% of patients with severe hemophilia A (HA). Inhibitor occurrence is less common in individuals with mild and moderate HA (2–3%). Inhibitors neutralize the exogenous