TECHNICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Evaluating for Suspected Child Abuse: Conditions That Predispose to Bleeding

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abstract

Child abuse might be suspected when children present with cutaneous bruising, intracranial hemorrhage, or other manifestations of bleeding. In these cases, it is necessary to consider medical conditions that predispose to easy bleeding or bruising. When evaluating for the possibility of bleeding disorders and other conditions that predispose to hemorrhage, it is important for pediatricians to consider the child's presenting history, medical history, and physical examination findings before initiating a laboratory investigation. Many medical conditions can predispose to easy bleeding. Before ordering laboratory tests for a disease, it is useful to understand the biochemical basis and clinical presentation of the disorder, condition prevalence, and test characteristics. This technical report reviews the major medical conditions that predispose to bruising or bleeding and should be considered when evaluating for abusive injury.

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INTRODUCTION

In the absence of known accidental mechanisms or medical causes, children with intracranial hemorrhage (ICH), particularly subdural hemorrhage (SDH), cutaneous bruises, or other symptoms of bleeding might be suspected victims of child abuse. In such situations, physicians must often carefully evaluate for the possibility of a bleeding disorder or another medical condition as a possible cause. Family history and personal medical history have not been shown to predict the presence of bleeding disorders, although the bleeding assessment tool published by the International Society on Thrombosis and Haemostasis has improved the reliability in diagnosing bleeding disorders.[1–3] Certain bleeding disorders have higher prevalence within specific populations, which may guide testing. In addition, because of the legal proceedings associated with cases of potential abuse, physicians might feel compelled to rule out any theoretical possibility of a medical

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explanation for the child's findings, despite clinical improbability. This can result in an expensive and, in the case of young children with limited total blood volume, potentially harmful laboratory investigation of diminished clinical value. As such, it is important for physicians to fully understand the benefits and drawbacks of specific tests that may be used in evaluating for and detecting bleeding disorders.

STATEMENT OF PROBLEM

The list of congenital and acquired bleeding disorders that could potentially be confused with abusive injury is extensive: hemophilia, von Willebrand disease (VWD), disorders of fibrinogen, vitamin K deficiency, factor XIII and other factor deficiencies, thrombocytopenia, leukemia, aplastic anemia, and other bone marrow infiltrative or failure syndromes, and platelet function abnormalities, among others. Most of these conditions can present with mucosal bleeding, such as epistaxis and cutaneous bruising, but some (especially factor deficiencies) have been noted to present with isolated ICH or can increase susceptibility to severe ICH after minor trauma. Collagen vascular disorders can also predispose to easy bruising or bleeding in some circumstances. This report reviews the rationale for the consideration of bleeding disorders and collagen vascular disorders as a cause of or as contributing to ICH, bruising, or bleeding when child abuse is suspected and addresses several unsupported hypotheses related to these issues. An accompanying clinical report provides additional guidance for the pediatrician.[4]

NEW INFORMATION (FOR REVISED POLICIES)

On the basis of recent data, this technical report provides updated information regarding:

1. The overall prevalence of ICH and SDH and the specific prevalence of spontaneous and traumatic ICH and SDH in young children with deficiencies of Factor VIII or Factor IX;
2. ICH in children with VWD;
3. Prevalence and anatomic locations of ICH in patients with Factor XIII deficiency;
4. Laboratory testing modalities for bleeding disorders; and
5. Updated references and supporting details throughout the report.

CLINICAL APPROACH TO THE EVALUATION OF CONDITIONS THAT PREDISPOSE TO BLEEDING IN THE SETTING OF POSSIBLE ABUSE

In many children with bruising or bleeding concerning for abuse, the evaluation for medical conditions causing or contributing to the findings noted on the physical examination can be completed by assessing the child's presenting symptoms, trauma history, medical history, family history, and medications. Before engaging in a laboratory evaluation, it is important for physicians to consider:

1. Family history of bleeding or bruising or a history of specific coagulopathies or other conditions, along with the specific clinical characteristics of the child's findings and/or a previous history of bleeding or bruising.
2. The known presentations and prevalence of the various bleeding disorders, collagen vascular disorders, or other medical conditions under consideration.
3. The medical probability that a specific medical condition might cause or contribute to the child's bleeding or bruising.
4. The statistical characteristics of the proposed laboratory testing.
5. The history of the use of blood products or other factor replacement products that might alter laboratory test results.
6. The anticipated benefit of identifying conditions that might cause bleeding or bruising.

CLINICAL CHARACTERISTICS

Nonintracranial Bleeding

The age and developmental capabilities of the child, history of trauma, and the location and pattern of bruising often provide significant evidence in determining the presence of abusive injury.[5–10] In many cases, the constellation of findings, taken in conjunction with the clinical history, can be so strongly consistent with abusive injury that a further laboratory investigation for medical conditions is not warranted. For instance, in a verbal child with a patterned slap mark who describes being hit with an open hand at the location of the slap mark, obtaining tests to rule out a bleeding disorder is unlikely to provide useful information. However, because few data exist comparing the specific clinical presentations of bleeding disorders and abuse, in some cases, a laboratory evaluation might be necessary to minimize the chances of a misdiagnosis. The presence of a bleeding disorder or other medical condition does not rule out abuse as the etiology for bruising or bleeding.[11]

Other symptoms, such as hematemesis, hematochezia, and oronasal bleeding, can be caused by abuse or a bleeding disorder.[12–20] Evaluation for such findings includes the relative frequencies of abuse or coagulopathies presenting with these symptoms, along with the patient's history and any other medical findings, such as fractures, neglect, and other manifestations of bleeding/bruising. An increasing number of findings unrelated to bleeding disorders and consistent with abuse decrease the overall likelihood of a coagulopathy or

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other medical condition contributing to or causing bleeding or bruising.

Intracranial Hemorrhage

Multiple studies have assessed the roles of history, clinical and radiographic findings, and outcomes in making the diagnosis of abusive head trauma.[21–28] ICH was the presenting event in 19.2% of patients with bleeding disorders.[29] However, no studies have systematically compared the presentation, clinical findings, patterns of ICH, or presence of retinal hemorrhages between bleeding disorders and/or collagen vascular disorders and abusive head trauma. Therefore, for children presenting with ICH but without other findings strongly suggestive of abuse, such as fractures, significant abdominal trauma, burns, or patterned bruising, an evaluation for other medical conditions causing or contributing to the findings is necessary. Additionally, although evidence of old inflicted injury, such as healing fractures, could support the diagnosis of abuse, healing injuries may be unrelated to recent bruising or ICH.

TESTS USED TO IDENTIFY BLEEDING DISORDERS

A variety of testing modalities have been used to identify bleeding disorders. Each of these has its own limitations and strengths. This section describes a few of the more common tests used to identify inherited and acquired predisposition to bleeding and provides a framework for the interpretation of results. Diagnostic testing for each specific diagnosis will be discussed within areas of this technical report that discuss those specific diagnoses.

Laboratory Testing for Bleeding Disorders

Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been used as screening for bleeding disorders, often in a perioperative setting. The reference intervals are wide and vary between laboratories and reagents with different sensitivities. Therefore, the normal values differ depending on the laboratory in which the test is performed. The reference interval often encompasses the central 95% of the population, resulting in up to 5% of normal individuals with results that fall outside of the reference range. Most laboratory testing has a variance of 5% to 10% at baseline. There are high rates of both false-positive and false-negative results with each test. Factors that may prolong aPTT and/or PT include medications, underlying medical conditions unrelated to bleeding disorders, temperature of sample, and duration of time between sample draw and when the test is performed by the laboratory.[30] The results can be falsely prolonged from anticoagulant contamination if drawn from a line, if the ratio of plasma to sodium citrate in the collection tube is too high, if the patient has a high hematocrit, if the sample is collected in underfilled tubes, or if the sample is hemolyzed.[31]

Prothrombin Time and International Normalized Ratio

PT measures the time of clotting in response to tissue factor. It is primarily sensitive to deficiencies in the extrinsic (factor VII) and common (factors II, V, and X and fibrinogen) coagulation pathways but may miss mild factor deficiencies in the common pathway for reasons previously discussed. PT may be prolonged in children younger than 5 years, which is developmentally normal. Because local normal ranges vary, the international normalized ratio was developed by the World Health Organization to allow for comparison of results across institutions for patients taking vitamin K antagonists. The international normalized ratio is calculated as the patient's PT value divided by the normal value as determined by the local laboratory, raised to the international sensitivity index value for the reagent and analytical system used.[30]

Activated Partial Thromboplastin Time

aPTT was developed to provide a more sensitive measure of the intrinsic clotting system (factors VIII, IX, XI, and XII) by reducing the amount of tissue factor activity in the test when compared with PT. It was initially developed to identify patients with hemophilia by responding to a decrease in factor VIII.[32] Reagents used in each hospital vary, so local normal ranges determine whether the aPTT is abnormal. aPTT was designed to identify moderate or severe deficiencies in factor VIII or IX, so it may be normal with mild deficiencies.[33] aPTT may be prolonged in other factor deficiencies (see specific deficiencies, below). aPTT may also be prolonged in the setting of a lupus anticoagulant or factor XII deficiency, neither of which result in an increase in bleeding.

Platelet Function Analyzer

The platelet function analyzer (PFA-100 [Siemens Healthcare Diagnostics, Tarrytown, NY]) evaluates the adherence and aggregation of platelets under high shear stress to a membrane covered with either collagen and epinephrine or collagen and adenosine diphosphate. It is sensitive to moderate to severe platelet dysfunction as well as to von Willebrand factor (VWF) activity <30% but may miss milder platelet dysfunctions or low VWF (levels 30% to 50%). Hematocrit, low platelet count, and many medications influence the results. Results may also be influenced by age, smoking status, and pregnancy.

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It is not affected by defects in coagulation factors other than VWF or by abnormalities of fibrinogen.[34] Further discussion of the PFA-100 in screening for VWD and platelet function disorders may be found in the specific sections below.

Whole Blood Clotting Assays

The utility of whole blood clotting assays, such as the thromboelastogram, to screen for bleeding disorders has not been established.[35] These assays have primarily been used to provide guidance for choice of transfusion product in patients undergoing surgeries or who have sustained trauma. From a research perspective, whole blood clotting assays have been used to attempt to provide phenotypic characterization of people with bleeding disorders.[36] They have not been designed or studied to evaluate for bleeding disorders in the context of possible abuse.

REVIEW OF BLEEDING DISORDERS

This section describes the significant bleeding disorders that may require further evaluation in cases of suspected abuse, including their common presentations, incidence of ICH, and the method of diagnosis (Table 1).

1. Deficiency of Factor VIII or IX

Hemophilia A and B are attributable to deficiencies of factors VIII and IX, respectively. Factor VIII deficiency occurs in approximately 1 in 5000 live male births. Factor IX deficiency is rarer, occurring in 1 in 20 000 live male births. Because of the X-linked recessive inheritance pattern of these diseases, most patients affected with hemophilia are male. However, girls who are carriers can have low enough factor VIII or IX levels to present with bleeding as a result of homozygous mutations or extreme inactivation of the normal X chromosome. Rarely, a phenotypic female can have only 1×chromosome and be affected with the disease (eg, testicular feminization, Turner syndrome).[37,38] The prevalence of females with low enough factor activities to be considered to have clinical hemophilia is unknown. Although the prevalence of severe hemophilia can be expected to be lower than that of males because of the X-linked nature of the disease, the prevalence of mild to moderate hemophilia is not as easily predictable because of the influence of X-inactivation on phenotypic variability.

Major bleeding sequelae of hemophilia include bleeding into joints and soft tissues and ICH. The most common sites of the initial bleeding episode in 1 series were postcircumcision and intracranial. ICH in a child with hemophilia can occur as a result of birth trauma, in response to mild head trauma, or spontaneously. ICH is estimated to occur in 5% to 12% of patients with hemophilia throughout their lives.[29,39–41] A review of 57 episodes of ICH in 52 patients with congenital factor deficiencies showed intraparenchymal and/or intraventricular bleeding in 39 patients, subdural bleeding in 15, subarachnoid bleeding in 2, and cerebellar bleeding in 1. The majority of these patients (38) had severe hemophilia. The median age of presentation was 8 years (range, 1 month to 22 years). The overall prevalence of ICH in hemophilia patients in this study was 9.1%.[29] Another retrospective study in children younger than 4 years with bleeding disorders found that, among 3717 subjects, 6.9% had any ICH and 5.5% had atraumatic ICH. The highest prevalence of ICH was within patients with severe hemophilia A (9.1%) and B (10.7%). Of those in which the cause and location of ICH were known, 12 of 13 with spontaneous SDH had severe hemophilia. No subjects with mild or moderate hemophilia had spontaneous SDH.[42] The largest series to date of ICH in hemophilia reported a rate of 2.7% over 5 years in a cohort of 3629 patients with hemophilia, or 0.0054 cases per year. Most of the cases in this series were not the result of trauma (78.4%). The majority (69%) occurred in patients with severe hemophilia, and 18% occurred in those with mild hemophilia, in contrast to the previous study. Sites of hemorrhage were intracerebral, subdural, subarachnoid, epidural, or unspecified. Trauma was implicated in all of the epidural hemorrhages, 36% of subarachnoid hemorrhages, 10% of subdural hemorrhages, and 3% of intracerebral hemorrhages.[41] A study of hemophilia in the first 2 years of life revealed 19% of first bleeding episodes ($n = 404$) were head bleeding, of which 36.4% were ICH. Seventy-five percent of the ICH occurred in infants younger than 1 month, and most of these were associated with delivery. In contrast to the aforementioned studies, the occurrence of ICH was distributed across all severities of the disease.[39]

Approximately two thirds of patients who present with a diagnosis of hemophilia have a positive family history for the disease. The one third of patients without a known family history of hemophilia might represent new germ-line mutations, or a family history of hemophilia may just have been missed.[39,43] Diagnosis of hemophilia is established by measurement of the factor VIII or IX activity level. Hemophilia is categorized as severe if the factor level is <1%, moderate if the factor level is between 1% and 5%, and mild if the factor level is 5% to 40%. Spontaneous bleeding is more common in severe hemophilia. aPTT is prolonged in moderate and severe cases but can be normal in patients

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TABLE 1 Common Testing Strategies for Bleeding Disorders

Condition	Frequency	Inheritance	Screening Tests	Sensitivity (Sn) and Specificity (Sp), (%)	PPV and NPV, (%)	Confirmatory Test
Factor abnormalities or deficiencies						
VWD type 1	1 per 1000	AD	PFA-100[a]	Sn = 79–96[b]; Sp = 88–96[b]	PPV = 93.3; NPV = 98.2	VWantigen[b], VWF activity, vW multimer analysis, factor VIII activity
VWD type 2A	Uncommon	AD or AR	PFA-100[a]	Sn = 94–100[b]; Sp = 88–96[b]	PPV = 93.3; NPV = 98.2	VWantigen[b], VWF activity, vW multimer analysis, factor VIII activity
VWD type 2B	Uncommon	AD	PFA-100[a]	Sn = 93–96[b]; Sp = 88–96[b]	PPV = 93.3; NPV = 98.2	VWantigen[b], VWF activity, vW multimer analysis, factor VIII activity
VWD type 2M	Uncommon	AD or AR	PFA-100[a]	Sn = 94–97[b]; Sp = 88–96[b]	PPV = 93.3; NPV = 98.2	VWantigen[b], VWF activity, vW multimer analysis, factor VIII activity
VWD type 2N	Uncommon	AR, or compound heterozygote	aPTT	NA	NA	VWF-factor VIII binding assay
VWD type 3	1 per 300 000–1 000 000	AR, or compound heterozygote	PFA-100[a]	Sn = 94–100[b]; Sp = 88–96[b]	PPV = 93.3; NPV = 98.2	VWantigen[b], ristocetin cofactor, vWF multimer analysis, factor VIII activity
Factor II deficiency (prothrombin)	26 reported cases, estimated 1 per 1–2 million		aPTT, PT (may be normal)	Sn = variable	NA	Factor II activity +/− antigen levels
Factor V deficiency	1 per 1 million	AR	aPTT, PT	Sn = variable	NA	Factor V activity
Combined factor V and factor VIII deficiency	1 per 1 million	AR	aPTT > PT	Sn = variable	NA	Factor V and factor VIII activities
Factor VII deficiency	1 per 300 000–500 000	AR	PT	Sn = variable	NA	Factor VII activity
Factor VIII deficiency	1 per 5000 male births	X-linked	aPTT	Sn = variable	NA	Factor VIII activity
Factor IX deficiency	1 per 20 000 male births	X-linked	aPTT	Sn = variable	NA	Factor IX activity
Factor X deficiency	1 per 1 million	AR	aPTT, PT, RVVT	Sn = variable	NA	Factor X activity
Factor XI deficiency	1 per 100 000	AR	aPTT	Sn = variable	NA	Factor XI activity
Factor XIII deficiency	1 per 2–5 million	AR	Clot solubility	Sn = variable	NA	Factor XIII activity
Fibrinolytic defects						
α-2 antiplasmin deficiency	~40 reported cases	AR	Euglobin lysis test	Sn = variable	NA	α-2 antiplasmin activity
Plasminogen activator inhibitor-1 deficiency (PAI-1)	Very rare	AR		Sn = variable	NA	PAI -1 antigen and activity
Defects of fibrinogen						
Afibrinogenemia	1 per 500 000	AR	PT, aPTT	Sn = high	NA	Fibrinogen level
Hypofibrinogenemia	Less than afibrinogenemia		PT, aPTT	Sn = variable	NA	Thrombin time, fibrinogen activity
Dysfibrinogenemia	1 per million		Thrombin time, fibrinogen level	Sn = variable	NA	Thrombin time, fibrinogen antigen and activity level comparison, reptilase time

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TABLE 1 Continued

Condition	Frequency	Inheritance	Screening Tests	Sensitivity (Sn) and Specificity (Sp), (%)	PPV and NPV, (%)	Confirmatory Test
Platelet disorders						
ITP	Age-related	NA	CBC	Sn = high	NA	Antiplatelet Ab (rarely needed),
Glanzmann thrombasthenia	Very rare	AR	PFA-100[a]	Sn = 97–100	NA	platelet aggregation testing, flow cytometry
Bernard Soulier syndrome	Rare	AR	PFA-100[a]	Sn = 100	NA	Platelet aggregation testing, flow cytometry
Platelet release and storage disorders	Unknown, more common than other platelet function disorders	Variable	PFA-100[a]	Sn = 27–50	NA	Platelet aggregation and secretion, electron microscopy, molecular and cytogenetic testing

AD, autosomal dominant; aPTT, activated partial thromboplastin time; AR, autosomal recessive; CBC, complete blood cell (count); ITP, immune thrombocytopenia; NPV, negative predictive value; PFA-100, platelet function analyzer; PPV, positive predictive value; PT, prothrombin time; vW, von Willebrand; VWAntigen, von Willebrand antigen; VWD, von Willebrand disease; VWF, von Willebrand factor; NA, not available or not applicable; RVVT, Russell viper venom test.

[a] PFA-100 sensitivity and specificity provided for informational purposes. Testing may miss some forms of VWD and mild platelet abnormalities.

[b] Values derived from data before 2008 NIH Consensus guidelines. Sensitivity and specificity using current diagnostic cutoffs unknown but would be expected to have higher specificity with lower sensitivity.

with mild disease, depending on the laboratory reagent's sensitivity for detecting mild factor deficiencies. Factor VIII is also an acute phase reactant and can be elevated into the normal range in patients with mild disease in response to trauma or inflammation.[44]

2. Von Willebrand Disease

VWD is the most common heritable bleeding disorder, and typically presents with mild to moderate mucocutaneous bleeding. Low VWF levels (30% to 50%) may occur in up to 1% of the population, but fewer people may present with symptoms (0.01% to 0.1%). The criteria for diagnosis of VWD are VWF antigen and/or activity <30% (normal range, 50% to 150%) if not bleeding and <50% with bleeding. Individuals without bleeding symptoms who have not undergone significant bleeding challenges, such as children, and VWF levels between 30% and 50% create a diagnostic dilemma.[45] In addition, because the bleeding symptoms of VWD are generally mild, there are likely to be patients with low VWF levels who have not come to medical attention. On the basis of the number of symptomatic cases seen by hematology specialists, the prevalence has been estimated to be even lower than previously suggested (23 to 110 per million, or 0.0023% to 0.01%), suggesting that many individuals with low VWF levels might never manifest bleeding symptoms.[46]

The laboratory evaluation for, and common presentations of, the various types of VWD are variable (Tables 2 and 3). Type 1 VWD is the most common form (~ 80%) and is characterized by a normally functioning but decreased von Willebrand antigen (VWAg), resulting in low levels of both VWAg and VWF activity. Type 1 VWD has a wide range of bleeding severity and

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TABLE 2 Von Willebrand Disease Variants

Test	Type 1	Type 2A	Type 2B	PT-vWd	Type 2N	Type 2M	Type 3
vWF:Ag	Low	Low	NI/Low	Low	NI/Low	Low	Absent
vWF:Activity	Low	VWF:Act/ VWF:Ag <0.5	Low	Low	NI/Low	VWF:Act/VWF:Ag <0.5	Absent
FVIII	NI/Low	NI	NI	NI	Low	NI	Absent
RIPA	NI	Low	NI	NI	NI	Low	Absent
RIPA-LD	Absent	Absent	Increased	Increased	Absent	Absent	Absent
Frequency	70%–80%	10%–12%	3%–5%	0%–1%	1%–2%	1%–2%	1%–3%
Multimers	NI	Missing large	Missing large	Missing large	NI	NI	Absent

Adapted from US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. *The Diagnosis, Evaluation, and Management of von Willebrand Disease. Full Report.* NIH Publication No. 08-5832. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007:28. FVIII, factor VIII activity; NI, normal; PT-vWd, platelet type pseudo von Willebrand disease; RIPA, ristocetin-induced platelet aggregation; RIPA-LD, low-dose ristocetin-induced platelet aggregation; vWF:Ag, von Willebrand factor antigen; VWF:Act, von Willebrand factor activity.

variable penetration among members of the same family. Bleeding symptoms are generally worse with lower VWAg levels. Type 2 VWD subtypes are characterized by abnormally functioning von Willebrand molecules and variable bleeding severity. Type 3 VWD presents with absence of VWF and a very low but detectable factor VIII level. The bleeding in type 3 VWD can be quite severe and can also include hemarthroses resulting from low factor VIII levels (Table 3).[45]

ICH has very rarely been reported in association with VWD. In a retrospective study of more than 3700 children younger than 4 years with bleeding disorders and ICH, 11 subjects with VWD were identified to have atraumatic ICH, 8 of whom had type 1 VWD, 2 of whom had type 2 VWD, and 1 of whom had type 3. In subjects younger than 2 years in whom the cause and location of ICH were known, 2 subjects with VWD had traumatic ICH (both SDH) and 1 was reported to have a spontaneous SDH. This single subject had no long-term neurologic sequelae, and abuse was not diagnosed.[42] Labarque et al reported on 6 cases of ICH in children with VWD, 3 of whom had type 3 VWD. All 6 cases were reportedly caused by minor household falls, all subjects were symptomatic, but only 1 had a loss of consciousness. Of the 6 cases, 3 were SDH, and 1 of the SDH cases involved a child younger than 2 years. That subject was diagnosed with type 1 VWD. None of the 3 children with SDH died, and none had persistent neurologic deficits.[47] A case series detailed 4 episodes of ICH thought to have occurred spontaneously in patients with no previous history of VWD. Patient ages ranged from 18 to 65 years of age.[48] There was an additional report of ICH in a newborn infant with type 3 VWD and simultaneous sinovenous thrombosis.[49] One case report implicated type 1 VWD as a possible cause of subdural hematoma and retinal hemorrhages.[50] However, the laboratory findings in that case report did not meet the diagnostic criteria for definitive VWD,[51] and child abuse was not completely investigated because no repeat skeletal survey was performed. Large mass-effect ICH associated with minor trauma in children with VWD outside of the typical age range for abusive head injury has been reported.[52,53] The extreme rarity of

TABLE 3 Common Bleeding Symptoms of Healthy Individuals and Patients With von Willebrand Disease

Symptoms	Normals (n = 500; n = 341; n = 88; n = 60), %	All Types of VWD (n = 264; n = 1885), %	Type 1 VWD (n = 42; n = 671), %	Type 2 VWD (n = 497), %	Type 3 VWD (n = 66; n = 385), %
Epistaxis	4.6–22.7	38.1–62.5	53–61	63	66–77
Menorrhagia	23–68.4	47–60	32	32	56–69
Bleeding after dental extraction	4.8–41.9	28.6–51.5	17–31	39	53–70
Ecchymoses	11.8–50	49.2–50.4	50	NR	NR
Bleeding from minor cuts and abrasions	0.2–33.3	36	36	40	50
Gingival bleeding	7.4–47.1	26.1–34.8	29–31	35	56
Postoperative bleeding	1.4–28.2	19.5–28	20–47	23	41
Hemarthrosis	0–14.9	6.3–8.3	2–3	4	37–45
Gastrointestinal tract bleeding	0.6–27.7	14	5	8	20

Adapted from US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute. *The Diagnosis, Evaluation, and Management of von Willebrand Disease. Full Report.* NIH Publication No. 08-5832. Bethesda, MD: National Heart, Lung, and Blood Institute; 2007:21. NR, not reported; VWD, von Willebrand disease.

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this presentation and the questions surrounding the validity of a diagnosis of VWD causing ICH in some cases indicate that VWD is not a typical cause of ICH.

PT and aPTT are not effective tests to screen for VWD. Similarly, whole blood clotting assays such as the thromboelastogram or the rotational thromboelastography will not identify VWD. The PFA-100 has been used as a screening test for VWD, and results are often abnormal in patients who are known to have the disorder and have VWF levels <30%. It is superior to bleeding time because of ease of testing but does not test for blood vessel integrity and is affected by medications, platelet count, and hematocrit. Bleeding time is not recommended for bleeding disorder screening because of poor test characteristics and the invasive nature of the test.[54] The PFA-100 can be a useful tool as a preliminary screen for VWD or a platelet function defect, but if the result is normal and clinical suspicion remains high, specific testing for these disorders provides more definitive results. Abnormal results of the PFA-100 test should also prompt further testing.[45,51,55,56] It is important to realize that the PFA-100 is not a diagnostic test for bleeding disorders but rather acts as a quick screen in situations in which more specific testing is unavailable or will be delayed. If access to specific testing is available, it is appropriate to forego the PFA-100. Specific testing consists of VWAg, a test of VW activity (also referred to as ristocetin cofactor by some laboratories, although other methodologies exist), factor VIII activity, and often, von Willebrand multimer analysis.[57,58] Some practitioners also include ristocetin-induced platelet agglutination (RIPA), VWF propeptide, and/or a collagen-binding assay. Contributing to the difficulty of diagnosis, particularly for type 1 VWD, VWF levels increase in response to stress, pregnancy, and inflammation and exhibit significant variability within an individual. In addition, some patients' test results will fall below the lower limits of normal but above the current upper diagnostic cutoff (31% to 50%), creating a diagnostic dilemma.[45] Because of these issues and the lack of a single diagnostic test, the diagnosis of VWD might require repeated testing and is best accomplished by a pediatric hematologist.

Acquired von Willebrand syndrome is a rare phenomenon in pediatrics that can be associated with several clinical disorders, such as vascular anomalies, Wilms tumor and other cancers, cardiovascular lesions, hypothyroidism, lymphoproliferative or myeloproliferative disorders, storage disorders, autoimmune illnesses, monoclonal gammopathies, and certain medications. It has been estimated to occur at a prevalence of 0.04% to 0.13% in the general population, although the rate in pediatrics is likely significantly lower.[59] It is usually caused by autoimmune clearance or inhibition of VWF, increased shear stress causing consumption of VWF, or adsorption of VWF to cell surfaces. Laboratory tests used to diagnose acquired VWD are the same as those used to diagnose the congenital disorder. The addition of the von Willebrand propeptide can help to distinguish between the 2 entities.[59]

3. Factor VII Deficiency

Factor VII deficiency is the only plasma coagulation factor deficiency in which PT alone is prolonged. The incidence is estimated as 1 in 300 000 to 1 in 500 000. To date, more than 150 cases have been reported. A quantitative factor VII determination by standard factor assay methods will reveal factor VII deficiency. It is very important to use age- and gestational-related normal ranges, because factor VII is naturally low at birth and can be low in certain disease states, such as liver failure.[60] Individuals homozygous for factor VII deficiency usually have less than 10 U/dL of factor VII. Heterozygous patients usually have factor VII levels between 40 and 60 U/dL, but lower levels might be found representing single or double heterozygous abnormalities.

ICH has been reported in 4% to 6.5% of patients with factor VII deficiency and usually occurs in those with severe disease (<1% factor activity), both spontaneously and as a result of trauma.[61,62] Central nervous system (CNS) bleeding was reported in 4.4% of factor VII-deficient patients as a presenting symptom in 1 registry and was found to occur in subjects younger than 6 months.[62] Another registry including 717 subjects from Central Europe, Latin America, and the United States found an ICH prevalence of 2% in 217 symptomatic subjects. No heterozygous subject had ICH. Factor VII levels in those with ICH were <5%.[63] Bleeding symptoms can be extremely variable, and individuals can have minimal bleeding despite very low levels of factor VII. Using the most recent severity grading system, all patients with CNS bleeding have severe disease by definition.[64] Intracranial bleeding in these patients has been recorded as intraparenchymal, intraventricular, subdural, and tentorial, often accompanied with overlying cephalohematoma and usually occurring soon after birth.[61,65,66]

As mentioned earlier, it is important to rule out acquired factor VII deficiency as a result of vitamin K deficiency, liver disease, or consumptive coagulopathy. Although

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in these conditions, one would expect more extensive coagulopathy, prolongation of PT is often the only finding in the early stages of these disorders because of the short half-life of factor VII.

4. Factor XI Deficiency

Factor XI deficiency (also termed hemophilia C) has an estimated frequency in the general population of 1 in 1 million.[67,68] Factor XI deficiency occurs more frequently in the Ashkenazi Jewish population; ∼ 0.2% of Ashkenazi Jewish people are homozygous and 11% are heterozygous for this disorder.[69]

Bleeding in factor XI deficiency tends to be mild and associated with trauma or surgery. Bleeding symptoms often cannot be predicted by the factor level. Serious spontaneous hemorrhage is uncommon, including ICH, even in individuals with very low factor levels.[70] There is 1 report of subarachnoid hemorrhage in a 53-year-old male with previously undiagnosed factor XI deficiency. This patient was also found to have cerebral aneurysms.[71] In a single center retrospective review of 95 subjects with factor XI deficiency, 1 had a traumatic ICH, which resolved without specific treatment.[72]

Laboratory screening tests reveal prolonged aPTT and normal PT, although aPTT can be normal in heterozygous patients with mild deficiency. Other screening test results are normal. The specific assay for factor XI is the definitive test for this deficiency. In homozygous individuals, factor XI activity ranges from less than 1 U/dL up to 10 U/dL. Severe deficiency is defined as <15 U/dL, but genetic testing may be required because of variability of symptoms related to levels.[73] It is important to compare results with age-matched norms, because healthy ranges in infants are lower than those in adults.[74]

5. Factor XIII Deficiency

Factor XIII acts to covalently cross-link and stabilize fibrin. Because PT and aPTT measure the production of fibrin from fibrinogen and the action of factor XIII is subsequent to the initial formation of fibrin, these tests are normal in factor XIII deficiency and, therefore, cannot be used to screen for this disorder. The clot solubility test, which was the most commonly used test to screen for factor XIII deficiency, is abnormal only in very severe deficiencies of factor XIII, typically with factor XIII activities <3% of normal. A quantitative level of factor XIII is the currently recommended diagnostic test.[75,76] ICH has been reported to occur occasionally in patients with factor levels >3%, and therefore, the diagnosis can be missed if only the clot solubility test is used.[77–79] Other manifestations of factor XIII deficiency are umbilical cord bleeding, muscle hematomas, and postoperative bleeding.[80]

Deficiency of factor XIII is very rare, occurring in only approximately 1 in 2 to 5 million people. However, intracranial bleeding is a common manifestation of this disorder, occurring in up to one third of those with the deficiency.[75,80] Although it is an extremely rare condition, it is more common in certain populations with a high rate of consanguineous marriage. It is estimated that one third of the human population with severe congenital deficiency of factor XIII is in Iran.[81] Because of the rarity of the condition, few large studies of ICH in patients with factor XIII deficiency exist. A study of 38 patients with factor XIII deficiency and ICH from Iran found that in 35 of the 38 individuals, the ICH was intraparenchymal. Of the remaining 3 ICHs, 2 were subdural and 1 epidural. All subjects had factor XIII plasma levels <10%. The age at the time of ICH ranged from <1 month to 43 years, and 15 had ICH at younger than 2 years. A history of mild head trauma was present in 15 subjects (39.4%). Neurologic impairment occurred in 21 of 38 subjects.[82]

6. Other Factor Deficiencies (Factors II, V, Combined V and VIII, and X)

Prothrombin (Factor II) Deficiency

Homozygous prothrombin deficiency occurs at an estimated prevalence of 1 in 1 to 3 million. The most common bleeding presentation in homozygous and heterozygous patients is bleeding involving the skin and mucous membranes. In the North American Rare Bleeding Disorders Registry (NARBDR), 11% of the subjects with factor II deficiency suffered a CNS complication (which included both ICH and ischemic stroke). In subjects with factor II levels <0.01 U/mL, the rate of ICH was 20%.[83] Little description of these hemorrhages exists, although case reports have described subdural and epidural hematomas.[84–86] Homozygous patients can also present with surgical or trauma-induced bleeding.[87] Hemarthroses occurred in 42%, and gastrointestinal bleeding occurred in 12% of homozygous subjects in 1 registry.[88] Acquired prothrombin deficiency can occur with vitamin K deficiency, liver disease, or warfarin therapy or overdose, or in the setting of connective tissue disorders with an accompanying lupus anticoagulant.[87]

The degree to which PT and aPTT are prolonged varies from patient to patient, from a few seconds in some patients to more than 60 seconds in others, and occasionally, these screening results can be in the normal range.[60,88] The diagnosis is established with a factor assay for functional prothrombin along with an assay for antigen levels if necessary.

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Factor V Deficiency

Factor V deficiency is estimated to occur in 1 in 1 million people. It is more common in areas with a high degree of consanguinity.[83] Both homozygous and heterozygous patients with factor V deficiency typically have bleeding symptoms. Bleeding in homozygous patients tends to be spontaneous and occurs in the skin and mucous membranes, joints and muscles, genitourinary tract, gastrointestinal tract, and CNS. In the NARBDR, 8% of homozygous patients presented with intracranial bleeding.[83] Intrauterine subdural hematomas have been reported, as have spontaneous intraparenchymal hemorrhages.[89,90] Fifty percent of heterozygous patients also had bleeding. Skin and mucous membrane bleeding were the most common manifestations, and no patient experienced ICH.[83] Another study in 35 Iranian subjects with factor V deficiency found CNS bleeding in 2, both with factor V plasma levels <1%. These were described as subdural and intracerebral.[91]

Factor V can also be low in some platelet disorders because it is also present in platelet α granules. In addition, acquired factor V deficiency can occur in patients with rheumatologic disorders or malignancies, patients using antimicrobial agents, or patients using topical bovine thrombin because of antibodies to factor V.[92]

In factor V deficiency, PT and aPTT are both prolonged. Abnormal bleeding time or positive PFA-100 result is reported in approximately one third of patients, perhaps related to a deficiency of factor V in platelet α granules.[67] Other screening test results are normal. Definitive diagnosis is established with a factor V assay.

Combined Factor V and Factor VIII Deficiency

Combined deficiency of factor V and factor VIII is very rare, occurring in 1 in 1 million people, with higher frequency in populations in which consanguinity is more common. In this syndrome, factor V and factor VIII levels (both antigen and activity) range from 5% to 30% of normal.[60,93] Bleeding is usually mild to moderate. Patients typically have easy bruising, epistaxis, and gum bleeding as well as bleeding after trauma or surgery. Menorrhagia and postpartum bleeding in affected women have also been reported. Hemarthrosis can also occur. Intracranial bleeding is rare but has been reported in 1 patient out of 46 reported in the 2 largest registries of this disorder (27 and 19 subjects, respectively).[94,95]

Combined deficiency of factor V and factor VIII is passed down in an autosomal-recessive fashion and is attributable to a mutation of a protein of the endoplasmic reticulum-Golgi intermediate compartment encoded by the *LMAN1* gene. This protein has been shown to be important in facilitating protein transport from the endoplasmic reticulum to the Golgi apparatus. Thus, the decrease in factors V and VIII is attributable to defective intracellular transport and secretion unique to these 2 coagulation factors.[60] PT and aPTT are prolonged in this disorder with the prolongation of aPTT out of proportion to that of PT.

Factor X Deficiency

The prevalence of factor X deficiency is 1 in 1 million in the general population and more common in populations with higher rates of consanguinity.[60] It is passed down in an autosomal-recessive pattern. As many as 1 in 500 people might be carriers of the disorder.[96] More severe deficiency would be expected to present earlier in life. Heterozygous cases might be identified incidentally by laboratory tests performed preoperatively or for another purpose.[97]

In the NARBDR, most bleeding symptoms in factor X deficiency were mucocutaneous, including easy bruising, followed by musculoskeletal bleeding. Intracranial bleeding occurred in 15% of the homozygous cohort, of which 54% had a factor X level <0.01 U/mL. This cohort had the highest rate of ICH in the study, compared with other rare bleeding disorders. No heterozygous subjects experienced ICH.[83] Severely affected patients also present in the neonatal period with bleeding at circumcision, umbilical stump bleeding, or gastrointestinal hemorrhage.[96] The Greifswald factor X deficiency registry, which enrolls patients from Central Europe and Latin America, showed ICH in 21% of its cohort. ICH was only reported in homozygous and compound heterozygous patients.[98] In a smaller cohort of 15 subjects, 6 experienced intracranial bleeding (40%), and these occurred equally in those with <1%, 1% to 5%, and >5% factor activity. One ICH was subarachnoid, but the rest were not characterized. Certain homozygous mutations may result in increased risk of bleeding at higher factor X levels.[99]

Severe liver disease can result in deficiency of all liver-produced factors, including factor X. Acquired factor X deficiency can also occur with amyloidosis, cancer, multiple myeloma, infection, and use of sodium valproate. Acquired inhibitors to factor X have also been reported in association with upper respiratory infections and burns and usually present with active bleeding from multiple body sites.[96,98] Because of the frequency of the associated diseases, acquired factor X deficiency is actually fairly common. Although the overall rate is unknown, this disorder has been reported in up to 5% of patients with amyloidosis.[96] Therefore,

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diagnosis of inherited factor X deficiency in the face of concomitant medical diagnoses should be made carefully and ideally with the assistance of a hematologist.

Both PT and aPTT are usually prolonged. However, in 2 of the mutations, PT is prolonged and aPTT is normal, and the opposite in the case for the other variant.[100] The Russell viper venom (RVV) test is usually prolonged, although it can be normal in some variants.[67] A factor X assay is the definitive test, although it is important to compare results with normal levels for age and exclude vitamin K deficiency, and other acquired causes, before confirming the diagnosis.

7. Vitamin K Deficiency

Vitamin K is required to complete the posttranslational alteration of factors II, VII, IX, and X and proteins C and S. In the absence of vitamin K, precursor proteins are synthesized by hepatic cells, but because γ-carboxyglutamic acid residues are absent, the calcium-binding sites are nonfunctional. Deficiency of vitamin K results in induced functional deficiencies of all of these proteins. If the level of functional proteins falls below 30 U/dL, bleeding symptoms can result, and PT and/or aPTT will be prolonged.[101]

Vitamin K deficiency bleeding (VKDB) is most often seen in newborn infants in the first days of life (in infants who do not receive vitamin K at birth). Because their livers are still immature, synthesis of the vitamin K-dependent factors in newborn infants is 30% to 50% of adult levels. Almost all neonates are vitamin K deficient as a result of poor placental transmission of maternal vitamin K and the lack of colonization of the colon by vitamin K-producing bacteria in the neonate, although not all infants will go on to have VKDB without prophylaxis.[102] VKDB is divided into 3 subtypes: early, classic, and late. Early VKDB occurs primarily in infants of mothers who have been on a vitamin K-blocking medication, such as anticonvulsants, and usually occurs within hours to the first week of life. Classic-onset VKDB occurs between the first week and first month of life and is largely prevented by prophylactic vitamin K administration at birth. Late VKDB occurs from the first month to 3 months after birth.[102] This deficiency is more prevalent in breastfed babies, because human milk contains less vitamin K than does cow milk. It can be precipitated by acquired (such as a viral gastroenteritis) or inherited gastrointestinal tract disease. Infants with liver disease might also be susceptible.

Manifestations of VKDB are bleeding in the skin or from mucosal surfaces, bleeding from circumcision, generalized ecchymoses, large intramuscular hemorrhages, and intracranial bleeding (ICH). Although VKDB is rare in countries that provide prophylaxis, more than 50% of infants with late VKDB will present with ICH.[101] VKDB is prevented in the United States by encouraging administration of vitamin K to all newborn infants. Although most states have laws that require administration, some do not. Refusal of prophylactic vitamin K injections for newborn infants has led to intermittent increases in VKDB.[103] Administration of oral vitamin K prophylaxis reduces the incidence of late VKDB from 4.4 to 10.5/100 000 live births to 1.5 to 6.4/100 000 live births.[102] Intramuscular vitamin K prophylaxis prevents almost all cases of late VKDB; however, these can still occur, particularly if there is an unrecognized underlying (usually gastrointestinal) cause of vitamin K deficiency. Secondary VKDB can occur in the setting of hepatobiliary disease, antimicrobial therapy, coumadin poisoning or rat poison ingestion, biliary atresia, and chronic diarrhea. ICH in this setting is rare but does occur.[104]

Diagnosis of VKDB is the same regardless of underlying cause. Laboratory tests show prolonged PT and possibly aPTT for age. Specific factor assays for factors II, VII, IX, and X are markedly decreased. In patients who have already received vitamin K as treatment or transfusion of plasma, measurement of proteins induced by vitamin K absence (PIVKA) can confirm the diagnosis.[101,104]

Inherited combined deficiencies of vitamin K-dependent proteins occur when there is a mutation in the γ-glutamyl carboxylase or the vitamin K epoxide reductase complex. Fewer than 30 cases have been reported. Bleeding symptoms range from mild to severe, and ICH has been reported. Some patients also have dysmorphic features or skeletal defects.[105]

8. Defects of Fibrinogen

Abnormalities of fibrinogen can result in complete lack of the protein (afibrinogenemia), decreased levels (hypofibrinogenemia), or an abnormally functioning molecule (dysfibrinogenemia). Clinical presentations range from mild to severe bleeding, and some patients have an increased risk of thrombosis as well, depending on the causative mutation.[106,107] Fibrinogen deficiencies can also be acquired in other medical disorders, such as liver disease or consumptive coagulopathy.[107]

Severe disorders of fibrinogen result in prolongation of PT and aPTT, but milder disorders might be missed by these screening tests. Thrombin time tests conversion of fibrinogen to fibrin and is more sensitive to both deficiencies and abnormalities of fibrinogen than are PT and aPTT. Reptilase time is similar to thrombin

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time, except that it is not affected by heparin and might help distinguish hypofibrinogenemia from dysfibrinogenemia because of its slightly different mechanism of action. One can also measure the amount of fibrinogen antigen through a variety of methods.[107]

Most patients with dysfibrinogenemia are asymptomatic. Bleeding, when it is present, is typically mild and triggered by surgery or trauma. Additionally, they might present with thrombosis. The presence of a bleeding or thrombotic phenotype is dependent on the underlying mutation.[108] Case reports have documented a child with large, bilateral SDH with no neurologic compromise and another with ICH and cephalohematomas, each with dysfibrinogenemia.[109,110]

Overall, bleeding symptoms in afibrinogenemia are variable and can range from mild to life threatening. ICH has been reported in patients with afibrinogenemia, (5% to 10% of patients).[111,112] Up to 85% of patients present in the neonatal period with umbilical cord bleeding.[113] Patients also have an increased risk of spontaneous splenic rupture, the development of painful bone cysts, and poor wound healing.[114]

9. Defects of Fibrinolysis

Fibrinolysis refers to the breakdown of the fibrin clot and is directed by plasmin. Plasmin is generated from plasminogen by the actions of plasminogen activators. The inhibitors of this action are α-2 antiplasmin (AP [also known as α-2 plasmin inhibitor and plasmin inhibitor]), thrombin-activatable fibrinolysis inhibitor, and plasminogen activator inhibitor type 1 (PAI-1). Deficiencies in AP and PAI-1 have been described, although both are very rare.[115,116]

Patients with PAI-1 deficiency have been described as having mild to moderate bleeding symptoms, such as epistaxis, menorrhagia, and delayed bleeding after surgery or trauma. Spontaneous bleeding is rare. Diagnosis of PAI-1 deficiency can be problematic in that the laboratory assay used for diagnosis may be inaccurate at low levels. Normal ranges often are reported with the lower limit at zero, creating a large cross-over between those patients with an abnormality in PAI-1 and normal individuals. Only 2 of the reported deficiencies of PAI-1 have been correlated with an underlying genetic defect.[116] In one large kindred in whom a null mutation was identified, ICH and bleeding into joints were reported after mild trauma.[117] ICH has been reported in 2 adults in whom the only underlying coagulation abnormality identified was a low PAI-1 level. One adult also had osteogenesis imperfecta (OI).[118,119]

There have been $\sim$ 40 cases of AP deficiency reported in the literature. AP deficiency is inherited in an autosomal-recessive pattern, although heterozygous patients can also present with bleeding. Acquired deficiency has also been reported in patients with liver disease, disseminated intravascular coagulation, and acute promyelocytic leukemia. Homozygous patients tend to have severe bleeding like that seen in factor XIII deficiency, although ICH appears to occur less frequently. One episode of subarachnoid bleeding has been reported in a 6 year-old boy.[120] Heterozygous patients can have bleeding in response to trauma, surgery, or dental procedures or can be asymptomatic.[115,121] Intramedullary hematomas of long bones, which can occur without a history of trauma, are an unusual feature of homozygous AP deficiency.[122,123] Similar lesions have been seen in patients with afibrinogenemia. A shortened euglobulin lysis time can be used as a screening test for AP deficiency. Definitive diagnosis is established by measurement of AP antigen and activity.[124]

10. Congenital Platelet Abnormalities

Platelets interact with VWF to adhere to sites of vessel wall injury. Subsequent activation and aggregation of platelets, which includes the release of granular contents, leads to formation of a platelet plug. Congenital platelet disorders can result in fewer platelets, abnormal function of platelets, or a combination of the two. There is a wide range in the presenting symptoms of these disorders, from mild mucocutaneous bleeding to severe life-threatening hemorrhage.[125]

The most severe and best characterized platelet function disorders are also the rarest. These are the autosomal recessive disorders Bernard-Soulier syndrome (BSS) and Glanzmann thrombasthenia (GT). BSS results from absence or abnormal function of the GP Ib-IX-V receptor, which is responsible for platelet adhesion to VWF. Patients with BSS also commonly have mild thrombocytopenia with enlarged platelet size. In GT, the αIIβ3 platelet integrin is abnormal or missing, leading to impaired platelet aggregation, but the platelet count is normal. In both of these disorders, significant mucocutaneous bleeding and ICH have been reported, although ICH is rare, occurring in only 0.3% to 2% of patients with GT and even fewer in those with BSS.[126,127] The PFA-100 is a fairly reliable screening test for these disorders (Table 1).[125,126]

Less well characterized but more common, the disorders of platelet signaling and secretion result from a variety of defects. Platelet activation leads to a conformational change in the platelet and normally results in

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secretion of platelet granule contents, which recruits other platelets to the site of injury. Without this response, platelets are unable to recruit other platelets. This group of disorders includes Quebec platelet disorder, the MYH9 related disorders, Scott syndrome, Hermansky-Pudlak syndrome, Chediak-Higashi syndrome, and Wiskott-Aldrich syndrome. Most bleeding with these disorders is mild and manifests as excessive bruising or menorrhagia. The PFA-100 does not reliably screen for these disorders.[128] More specific platelet aggregation and secretion testing is required, and occasionally, electron microscopic examination or genetic mutation testing is necessary to confirm the diagnosis.[125] Even with appropriate platelet aggregation and secretion testing, false-positive results are common, often requiring repeat testing. All forms of genetic inheritance have been reported. Most patients with these disorders present with mucocutaneous bleeding manifestations or bleeding following surgery or trauma. Bleeding symptoms are variable and dependent on the specific defect. Joint bleeding can occur in some disorders. ICH has been reported after delivery in neonates and trauma in older individuals. Some platelet function disorders are part of syndromes with associated physical findings. Individual review of these entities is outside of the scope of this report.[129,130] Of note, a variety of medications can lead to platelet dysfunction (eg, nonsteroidal anti-inflammatory drugs, sodium valproate); therefore, it is important for physicians to obtain a careful medication history diagnosing a congenital platelet abnormality.[131] Acquired thrombocytopenia, whether from medication, immune thrombocytopenia (ITP), maternal ITP, or neonatal alloimmune thrombocytopenia, should be readily diagnosed on the basis of a complete blood cell count. The rate of ICH in patients with idiopathic ITP is <1%.[132]

11. Vascular Disorders

Certain vascular disorders can present with bruising or bleeding. Two disorders that might be confused for abuse are outlined. Discussion of all vascular disorders is outside of the scope of this report but can be found elsewhere.[133]

Ehlers-Danlos syndrome

Ehlers-Danlos syndrome (EDS) consists of a group of genetically and clinically heterogeneous connective tissue diseases that might be mistaken for child abuse.[134,135] The exact prevalence of EDS is unknown but is estimated to be 1 in 2500 to 5000.[136] There are 6 genetic subtypes, which differ in the underlying biochemical defect, inheritance pattern, and clinical symptoms[137]; however, prominent bruising and bleeding are seen in all subtypes.[138] Mutations in collagen type I, type III, type V, or the genes involved in processing type I collagen result in the majority of EDS subtypes. The tendency to bleed and/or bruise in EDS is caused by an abnormal capillary structure with deficiency of normal perivascular collagen. Cutaneous blood vessels are poorly supported and can rupture when subject to shearing forces. Tests for bleeding disorders are generally normal, except for the Hess test, which can be abnormal, indicating capillary fragility.[138,139] Clinically, the disorder manifests itself with easy bruising, bleeding gums, prolonged bleeding after surgical procedures, and menorrhagia. Skin hyperextensibility describes skin that extends easily and snaps back after release and is best tested at the volar surface of the forearm. Widened, thin scarring often occurs at knees, shins, elbows, and the forehead.[138] Joint hypermobility is also often seen.

Hypermobile EDS is generally accepted to be the most common subtype; however, the frequency and severity of bleeding and bruising symptoms, specifically in children, have not been well described. The diagnosis of hypermobile EDS is based on the clinical symptoms and physical examination findings as the specific genetic basis for this subtype is unknown. Physical examination techniques for the identification of hypermobile EDS are not valid in young children. A recent, small prospective study attempted to better quantify bleeding and bruising symptoms in children 9 to 21 years of age who met diagnostic criteria for hypermobile EDS and found that 56% of these patients (14 of 25) had a positive bleeding score using a Pediatric Bleeding Questionnaire in absence of an identified bleeding disorder.[139]

The vascular type of EDS, also known as EDS type IV, particularly might be confused with child abuse.[134] The precise prevalence is not known but has been estimated to range from 1 in 50 000 to 1 in 250 000.[140–142] Both autosomal-recessive and -dominant inheritance patterns as well as sporadic mutations have been described.[143] The clinical diagnosis is made on the basis of 4 criteria: easy bruising, skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines.[137] Major clinical diagnostic criteria include: arterial aneurysms, dissection or rupture, intestinal rupture, uterine rupture during pregnancy, and family history of EDS type IV.[144] The diagnosis is confirmed by the demonstration that cultured fibroblasts synthesize abnormal type III procollagen molecules or by the identification of a mutation in the gene for type III

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procollagen (*COL3A1*).[145] Excessive bruising is the most common presentation, but other severe complications, such as spontaneous rupture of the bowel and hemorrhagic pneumothorax, can occur. Vascular ruptures, including renal or splenic arteries; aneurysmal rupture; or stroke can also occur. ICH, including subdural hemorrhage, has only very rarely been described, and findings would likely not be confused with those commonly seen in inflicted head injury.[143,146] Severe complications are rare in childhood.[140] Joint hypermobility is often limited to the small joints of the hands. Skin hypermobility is typically not present, but the skin is often translucent, showing a visible venous pattern.[147,148] The characteristic facial appearance includes prominent eyes, pinched nose, small lips, hollow cheeks, and lobeless ears.[141,147]

If clinical suspicion exists, the diagnosis of most subtypes of EDS can be evaluated with biochemical and molecular analysis. Specific testing approaches for EDS is beyond the scope of this report and are available elsewhere.[142] Similar to previously discussed bleeding disorders, a diagnosis of EDS does not exclude the possibility of abusive injuries.

Osteogenesis Imperfecta

OI is a heterogenous group of diseases characterized by bone fragility, dentinogenesis imperfecta, and adult hearing loss.[149] OI has been associated with easy bruising and intracranial hemorrhage after minimal or no trauma.[150,151] Bleeding diathesis in OI is thought to occur as a result of platelet dysfunction and capillary fragility.[152,153]

Inheritance is generally autosomal-dominant, but autosomal-recessive inheritance and new mutations are known to occur. Most cases are the result of mutations in *COL1A1* and *COL1A2*. OI has many subtypes, and the overall prevalence is approximated at 6 to 7 in 100 000.[151]

Testing for OI using DNA sequencing or collagen analysis is available. Sensitivities and specificities vary depending on the type of OI, and testing approaches depend on the specific subtype of OI.[151] Rare case reports have attributed multiple varieties of intracranial hemorrhage, including subdural hematomas in children, to OI.[154] Additionally, 3 cases of relatively minor retinal hemorrhages coupled with subdural hematomas have been reported after trivial trauma in patients with OI type 1.[150] Despite these case reports, OI is a rare condition, and the occurrence of subdural hematomas and/or retinal hemorrhages attributable to OI is exceedingly rare. Although there have been reported associations of OI with easy bruising, no large-scale studies have characterized the frequency and nature of bruising in children with OI or compared these patterns with nonabused children without OI or abused children.

INTERPRETATION OF TESTS

Screening tests for bleeding disorders can be falsely positive or falsely negative, depending on the test and the bleeding disorder of concern. For instance, if coagulation laboratory test specimens are left to sit in a hot metal box all day, factor levels may be falsely low. In contrast, certain factors (VWF and factor VIII) are acute phase reactants and levels will be falsely elevated above baseline values if blood specimens are obtained at a time of physiologic stress. In addition, patients who suffer a traumatic brain injury often have a transient coagulopathy that does not reflect an underlying congenital disorder.[155,156]

Patients who have sustained significant trauma also might receive transfusions of blood products. Fresh-frozen plasma (FFP) is prepared by separating the liquid portion of blood from the cellular portion after the collection of whole blood or by collecting the liquid portion of blood using apheresis technique. By definition, each mL of FFP contains 1 unit of all normal coagulation factors and inhibitors of coagulation, but in general, 10 to 20 mL/kg will only raise factor levels by 15% to 25%.[157]

Cryoprecipitate is prepared by thawing FFP and refreezing the precipitate. It contains higher concentrations of fibrinogen, factor VIII, VWF, and factor XIII. Each coagulation factor has a different half-life (Table 4). Therefore, the administration of FFP or cryoprecipitate will affect the investigation for a coagulation factor deficiency differently depending on the factor being measured.

FREQUENCY OF THE CONDITION AND MEDICAL PROBABILITY

Specific data regarding the prevalence of bleeding disorders within the population of children with ICH or SDH are not available. However, there are data on the frequency of ICH as a result of specific bleeding disorders and, in the case of deficiencies of factor VIII or factor IX, the frequency of SDH in young children. If the prevalence of a condition and the frequency of a

TABLE 4 Half Lives of Coagulation Factors

Factor	Half-life Postinfusion (h)
Fibrinogen	96–150
II	60
V	24
VII	4–6
VIII	11–12
IX	22
X	35
XI	60
XIII	144–300
vWF	8–12

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particular presentation of that condition are known, a physician can construct the probability of that specific condition (bleeding disorder) resulting in the specific presentation (ICH):

$$P(B)=\text{Prev}(A) \times (B|A)$$

where B = ICH attributable to condition A, P = probability, and Prev = prevalence.

For example, factor XIII deficiency is extremely rare, occurring at an upper limit estimated population prevalence of 1 in 2 million; however, it can present with isolated intracranial bleeding in up to one third of cases. The estimated probability that factor XIII deficiency will cause an ICH in a person in the population at large is:

$$(\text{Prevalence of factor XIII deficiency}) \times (\text{Prevalence of ICH in factor XIII deficiency})$$

$$(1/2 \text{ million}) \times (1/3)=1/6 \text{ million.}$$

Table 5 contains probabilities for congenital bleeding disorders to cause ICHs in the population at large. Table 6 contains probabilities for deficiencies of factor VIII and IX to cause SDH in children <2 years of age. No calculation was made in situations in which no reliable estimates of prevalence of the condition or frequency of ICH exist. Liberal prevalence and frequency numbers were used to provide the upper limits of probability. These calculations provide broad probabilities and may be interpreted in the context of more detailed data. For instance, although deficiency of factor XIII causes ICH in approximately 1 per 6 million individuals, as previously discussed, the majority of ICH in patients with factor XIII deficiency are intraparenchymal, making factor XIII deficiency a very unlikely mimic of child abuse.

CONCLUSIONS

In cases of suspected abuse involving bruising and/or bleeding, the possibility of coagulopathies causing or contributing to the findings is a consideration. In many cases, the possible coagulopathies can be effectively evaluated by a thorough history and physical examination and possibly by the specific nature of the child's findings. However, in some cases, a laboratory evaluation for coagulopathies might be necessary. The diagnosis of a bleeding disorder does not automatically rule out the presence of child abuse. Because of the chronic nature of their disease, children with bleeding disorders may be at higher risk of abuse.[158]

Limited evidence exists comparing bruising and bleeding in children with coagulopathies with child victims of abuse. Conducting such studies would be difficult, given the overall rarity of coagulopathies. Given these limitations, existing data, including epidemiologic and clinical factors, assist in the decision-making process.

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TABLE 5 Probabilities for Congenital Coagulopathies to Cause ICH

Condition[a]	Prevalence of Condition	Prevalence of ICH	Probability[c]
VWD	1 per 1000	Extremely rare	Low[d]
Factor II deficiency	1 per 1 million	11%	1 per 10 million
Factor V deficiency	1 per 1 million	8% of homozygotes	1 per 10 million homozygotes
Combined factors V and VIII deficiencies	1 per 1 million	2%	1 per 50 million
Factor VII deficiency	1 per 300 000	4% to 6.5%	1 per 5 million
Factor VIII deficiency (all)[b]	1 per 9500 males	7.0%	1 per 140 000
Severe	1 per 20 000 males	9.1%	1 per 220 000
Moderate	1 per 40 000 males	4%	1 per 1 million
Mild	1 per 30 000 males	2.8%	1 per 1.1 million
Factor IX deficiency (all)[b]	1 per 34 000 males	7.6%	1 per 450 000
Severe	1 per 95 000 males	10.7%	1 per 885 000
Moderate	1 per 110 000 males	3.4%	1 per 3.1 million
Mild	1 per 120 000 males	8%	1 per 1.5 million
Factor X deficiency	1 per 1 million	21%	1 per 5 million
Factor XI deficiency	1 per 1 million	Extremely rare	Low[d]
Factor XIII deficiency	1 per 2 million	33%	1 per 6 million
α-2 antiplasmin deficiency	Extremely rare	Not reported	Low[d]
Plasminogen activator inhibitor-1 deficiency (PAI-1)	Extremely rare	Common	Low[d]
Afibrinogenemia	1 per 500 000	10%	1 per 5 million
Dysfibrinogenemia	1 per 1 million	Extremely rare	Low[d]

[a] The probability of having a specific bleeding disorder increases in the setting of a family history of that specific named bleeding disorder or if the patient is from an ethnicity in which a specific bleeding disorder is more common (eg, Ashkenazi Jewish people and factor XI deficiency).
[b] Age adjusted prevalence of all, severe, moderate, and mild deficiencies of factors VIII and IX were used. Probability is calculated for children <4 y of age.
[c] "Probability" indicates the probability that an individual in the general population would have the following specific coagulopathy causing an intracranial hemorrhage.
[d] It is not possible to calculate a probability based on the rarity of the occurrence.

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TABLE 6 Probabilities for Hemophilias A (Factor VIII deficiency) and B (Factor IX deficiency) to Cause SDH in Children <2 Years of Age

Condition	Prevalence of Condition	Prevalence of Traumatic SDH	Probability[a]	Prevalence of Spontaneous SDH	Probability[a]
Factor VIII deficiency (all)	1 per 9500 males	1%	1 per 1.2 million	1.1%	1 per 860 000
Severe	1 per 20 000 males	1%	1 per 2.2 million	3.4%	1 per 1.1 million
Moderate	1 per 40 000 males	1%	1 per 5.7 million	0%	Low
Mild	1 per 30 000 males	1%	1 per 3 million	0%	Low
Factor IX deficiency (all)	1 per 34 000 males	0.9%	1 per 3.8 million	0.9%	1 per 3.8 million
Severe	1 per 95 000 males	0%	Low	2%	1 per 4.8 million
Moderate	1 per 110 000 males	3%	1 per 4.4 million	0	Low
Mild	1 per 120 000 males	0%	Low	0	Low

[a] Probability indicates the probability that an individual in the general population would have the following specific coagulopathy causing an intracranial hemorrhage.

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ABBREVIATIONS

AP: α-2 antiplasmin
aPTT: activated partial thromboplastin time
BSS: Bernard-Soulier syndrome
CNS: central nervous system
EDS: Ehlers-Danlos syndrome
FFP: fresh-frozen plasma
GT: Glanzmann thrombasthenia
ICH: intracranial hemorrhage
ITP: immune thrombocytopenia
NARBDR: North American Rare Bleeding Disorders Registry
OI: osteogenesis imperfecta
PAI-1: plasminogen activator inhibitor type 1
PFA-100: platelet function analyzer
PT: prothrombin time
SDH: subdural hemorrhage
VKDB: vitamin K deficiency bleeding
VWAg: von Willebrand antigen
VWD: von Willebrand disease
VWF: von Willebrand factor

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