Rare Coagulation Factor Deficiencies: Diagnosis and Management

David Green and Axel Matzdorff

Introduction

Rare bleeding disorders are challenging because the experience of most physicians with these conditions is limited. Many of the milder disorders often go unrecognized for many years, and misdiagnosis results in inappropriate medical management. Rare bleeding disorders typically present with easy bruising, epistaxis, menorrhagia, hematoma formation after trivial trauma, and excessive bleeding following routine, minimally invasive procedures. Some patients with rare bleeding disorders might be aware of family members with unusual bleeding or bruising. The results of laboratory studies are often puzzling and are not consistent with common bleeding disorders such as hemophilia and von Willebrand disease. Arriving at the correct diagnosis generally requires a thorough knowledge of the coagulation pathways and the characteristics of the individual clotting factors. Genetic analysis to identify specific mutations can be very helpful, especially for recognizing asymptomatic family members.

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The case vignettes presented in this chapter illustrate a few acquired and congenital rare bleeding disorders (Table 1), but it must be emphasized that the clinical features of these conditions vary considerably, even in patients having the same diagnosis. Accurate diagnosis is essential, because treatment has become more focused in recent years. For example, giving fresh frozen plasma (FFP) was formerly considered adequate therapy for most coagulation factor deficiencies. However, plasma is a poor source of clotting factor; by definition, there is one unit of factor per ml of plasma, so that an adult of average weight requires at least 20 ml/kg to raise plasma levels from 1 to 50 % of normal. The plasma must be thawed and given over a relatively short interval and even in large amounts might not achieve hemostatic factor levels. In addition, patients often experience adverse effects such as volume overload and allergic reactions. Therefore, giving a specific concentrate to correct the patient's factor deficiency is the best choice. Currently, concentrates for replacement of fibrinogen and factors VII, VIII, IX, X, and XIII are approved in the USA, and concentrates of factor XI are available in other countries. Finally, rare bleeding disorders should be viewed in the context of the whole patient. In the examples included in this chapter, patients with congenital bleeding disorders have atherosclerosis, suspected cancer, or are pregnant. Readers will need to select management options for these other conditions as well as the hemorrhagic disorder.

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Table 1 Rare *coagulation* bleeding disorders discussed in this Chapter

Disorder	When to suspect	Diagnostic abnormalities	Treatment
Amyloidosis	Raccoon eyes and ecchymoses, MGUS, myeloma	Gammopathy, amyloid fibrils in tissue biopsy	Combination chemotherapy
Factor VII deficiency	Mucosal bleeding or bleeding with surgery, trauma	Prolonged PT, normal aPTT	Tranexamic acid or factor VII concentrate
Factor XI deficiency	Mucosal, surgery, trauma bleeding; Jewish descent	Prolonged aPTT, normal PT; decrease in factor XI	Tranexamic acid or FFP; inhibitor: rVIIa
Combined factor II, VII, IX, and X deficiency	Bleeding stops after treatment with vitamin K	Prolonged PT, no vitamin K deficiency or VKA	Vitamin K_1, 5–20 mg/day; no response: PCC
Combined factor V and VIII deficiency	Consanguinity; menstrual bleeding; Middle East/India	Prolonged PT and aPTT; no inhibitor	Desmopressin; factor VIII concentrate and FFP
Factor XIII deficiency	Poor wound healing, intracranial, umbilical bleeding	Normal PT and aPTT; abnormal clot solubility	Factor XIII concentrate

PT prothrombin time, *aPTT* activated partial thromboplastin time, *VKA* vitamin K antagonist, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate

Case 1

A 79-year-old man presented for the evaluation of spontaneous hematomas on his chest (*see* Fig. 1). *He had multiple medical problems including monoclonal IgM lambda gammopathy of uncertain significance* (*MGUS*), *recurrent pleural effusions*, *mild heart failure*, *and mild renal insufficiency*: *creatinine 1.8 and creatinine clearance 38 ml/min. A chest CT scan showed mediastinal lymphadenopathy. Anterior mediastinoscopy revealed several lymph nodes with amyloid deposits but no evidence of lymphoma*; *the procedure was not complicated by bleeding. The final diagnosis was AL amyloidosis causing nodular mediastinal lymphadenopathy*, *recurrent pleural effusions*, *and extensive ecchymoses.*

Question 1. Which of the following is the most common pattern of laboratory abnormalities in AL amyloidosis?

A. Normal platelet count, normal aPTT, normal PT
B. Low platelet count, normal aPTT, normal PT
C. Normal platelet count, normal aPTT, prolonged PT
D. Low platelet count, prolonged aPTT, normal PT
E. Normal platelet count, prolonged aPTT, prolonged PT

Expert Perspective In a series of 337 patients, hemorrhagic symptoms were reported in 28 % of patients with AL amyloidosis (Mumford et al. 2000). Half the patients had an abnormal coagulation screen and prolonged prothrombin times and thrombin times that were attributed to amyloid infiltration of the liver. Other hemostatic defects observed in patients with AL amyloidosis are decreased factor X, found in 15 % of patients and probably due to adsorption of the protein by amyloid fibrils; deficiencies of factors II, VII, IX, and V; enhanced fibrinolysis; and abnormal capillary fragility (Choufani et al. 2001; Neuhaus et al. 2002). Amyloid coagulopathy typically causes periorbital ecchymoses (so-called raccoon eyes), but ecchymoses of the skin of the neck, as in our patient, has also been reported (Deeren 2012). In addition, our patient's PT was mildly prolonged (18 s, normal 12–15), and his factor VII activity was 49 %. The levels of fibrinogen and factors II, IX, and X were normal.

This patient presents with two medical problems, nodular mediastinal amyloid deposition (Shaw et al. 1984; Takeshita et al. 2000) and ecchymoses of his chest wall. To further evaluate the AL amyloid disease, a bone marrow biopsy and aspirate is indicated.

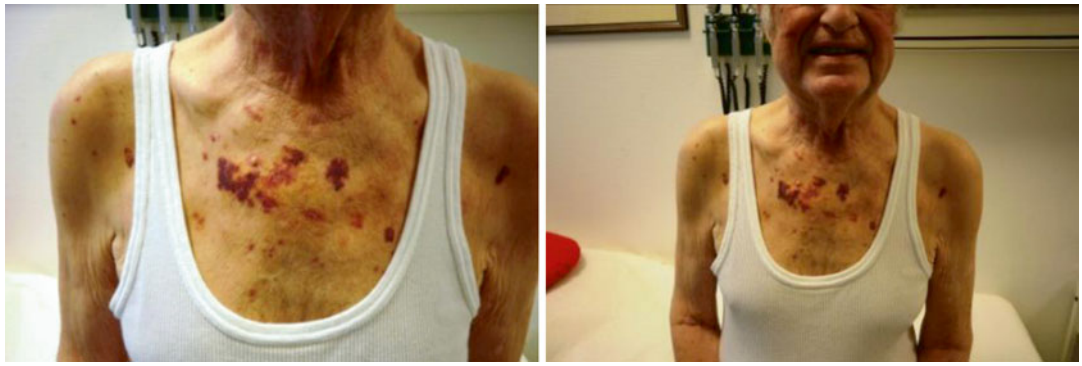


Fig. 1

Question 2. Prior to performing the bone marrow biopsy and aspirate, the patient should receive

A. No special pre-biopsy measures
B. Recombinant factor VIIa
C. Fresh frozen plasma
D. Tranexamic acid
E. Prothrombin complex concentrate

Expert Perspective Bone marrow aspiration and biopsy have no absolute contraindications. Bleeding complications are very rare (<0.1 %, Bain 2006). Biopsies are usually taken from the iliac crest where any bleeding can easily be detected and stopped by compression, and pre-biopsy hemostatic therapy is rarely indicated. It is the personal experience of the authors that even patients with severe thrombocytopenia or receiving oral vitamin K antagonist therapy do not have significant bleeding after this procedure. The situation is different with biopsies at other sites that cannot be monitored or compressed easily; for example, renal or liver biopsy.

Question 3. How best to treat the coagulopathy in this patient?

A. Low dose corticosteroids
B. Vitamin C
C. Tranexamic acid
D. Recombinant factor VIIa
E. Combination chemotherapy

Expert Perspective Because the coagulopathy is mediated by the AL amyloidosis, treatment is primarily aimed at reducing the amyloid burden (Thompson et al. 2010). In our patient, combination chemotherapy resulted in a dramatic decrease in skin hemorrhages, and the prothrombin time returned to normal. In patients with severe bleeding due to very low levels of factor X, activated prothrombin complex concentrates and activated recombinant factor VII (rVIIa) have been effective. Corticosteroids alone would be an inadequate treatment for the AL amyloidosis and might exacerbate skin bleeding. Vitamin C has little benefit for persons replete with this vitamin. Tranexamic acid, an antifibrinolytic agent, might be beneficial if excessive fibrinolysis was present, and recombinant factor VIIa would be indicated if the patient had a major hemorrhage. However, both of these agents are hazardous in elderly patients with risk factors for thrombosis; in this patient, the AL amyloidosis is a known risk factor for cardiac disease (restrictive cardiomyopathy and arrhythmias) (Falk 2005; Palladini et al. 2010).

Question 4. The hematologist had recommended treatment with melphalan, prednisone, and lenalidomide (Moreau et al. 2010) and advised that thromboprophylaxis be given. You suggest

A. Aspirin
B. Low molecular weight heparin
C. Unfractionated heparin
D. Vitamin K antagonist
E. Avoid all anticoagulants

Expert Perspective Lenalidomide, like other immunomodulatory drugs (thalidomide, pomalidomide), increases the risk for thrombosis. Guidelines recommend thromboprophylaxis with a low molecular weight heparin or aspirin (Palumbo et al. 2008). Because heparins are excreted by the kidney and this patient had evidence of renal failure, heparins might accumulate and exacerbate bleeding. A vitamin K antagonist is not appropriate for the brief period the patient will be exposed to the lenalidomide. Because treatment of the AL amyloidosis was anticipated to ameliorate the coagulopathy, aspirin was prescribed and the patient was closely monitored. Not giving antithrombotic prophylaxis would have exposed this patient to a high risk for thrombosis.

Question 5 One year later, the patient developed atrial fibrillation. You recommend

A. Aspirin, 325 mg twice daily
B. Vitamin K antagonist, target INR 1.5
C. Vitamin K antagonist, target INR 2.5
D. Fondaparinux, 2.5 mg daily
E. Avoid all anticoagulants

Expert Perspective Anticoagulant therapy is recommended for all patients with atrial fibrillation unless clearly contraindicated. Vitamin K antagonists, with a goal INR of 2–3, are preferred over aspirin or lower INRs (Hart et al. 2007). Fondaparinux has a long half-life and is entirely excreted by the kidney and therefore would be inappropriate. Because this patient has a high $CHADS_2$ score (older age, cardiovascular disease), the benefits of antithrombotic therapy exceed the risks of bleeding.

Case 2

This 82-year-old man of Jewish descent was well until age 42 when he had excessive bleeding after a wide surgical excision of a melanoma. Laboratory studies showed a factor XI <5 % and he was given FFP with resolution of the bleeding. There was no family history of a bleeding disorder. He was well for the next 20 years, but then developed hematuria and was again treated with FFP. However, the hematuria persisted and an inhibitor to factor XI was detected.

Question 6. Which combination of PT and aPTT results would you anticipate in this patient?

A. No prolongation of either PT or aPTT
B. PT prolonged, aPTT normal
C. aPTT prolonged, PT normal
D. Both PT and aPTT prolonged
E. Both PT and aPTT prolonged in a mixture of patient plasma and normal plasma

Expert Perspective The aPTT is sensitive to the levels of all clotting factors except factor VII; therefore, it will be prolonged in this patient with factor XI <5 %. The PT is sensitive to levels of factors II (prothrombin), V, VII, and X, and there is nothing in the history or physical examination to suggest that he would be deficient in these factors; therefore, the PT should be within the normal range. The inhibitor to factor XI prevents correction of the aPTT with normal plasma, but will not prolong the PT.

The hematuria eventually abated and he was well until age 75, when he experienced angina. On examination, his blood pressure was 158/88 and cardiomegaly was present. The factor XI level was 1 % and the inhibitor was just detectable at 0.6 Bethesda Units. A coronary angiogram revealed severe multivessel coronary artery disease.

Question 7. What do you recommend?

A. Aspirin, 81 mg daily
B. Vitamin K antagonist, target INR 2–3
C. Low molecular weight heparin
D. Antihypertensive agents, diuretics, and a statin
E. Diet and exercise only

Expert Perspective Aspirin, other nonsteroidal anti-inflammatory drugs, and anticoagu-

lants should be avoided in patients with congenital bleeding disorders. In this particular patient with severe, symptomatic heart disease, a trial of low-dose aspirin, 81 mg daily, was initiated but was soon discontinued because of recurrent hematuria and a large hematoma after minor trauma. Following intensive treatment with antihypertensive agents, diuretics, and statins, his episodes of angina ceased and he has been asymptomatic for more than 7 years. The take-away message is that even though bleeding might be infrequent and there appears to be a strong indication for antiplatelet therapy, these agents are poorly tolerated by patients with hemophilia and other clotting factor deficiencies and should not be prescribed. Diet and exercise, while beneficial, are inadequate treatment for symptomatic atheromatous disease.

Recently, the patient was found to have a potentially cancerous colonic polyp, and a polypectomy was strongly recommended.

Question 8. How should he be prepared for surgery?

A. No preoperative hemostatic therapy
B. Tranexamic acid given intravenously
C. Fresh frozen plasma
D. Factor XI concentrate
E. Recombinant factor VIIa and oral tranexamic acid

Expert Perspective The plasma concentration of factor XI is poorly correlated with a hemorrhagic tendency, and even those with very low levels often have only minor bleeding (Peyvandi et al. 2012a). A history of bleeding with previous surgery or trauma identifies patients likely to have excessive blood loss, so preoperative hemostatic agents will be required. Because bleeding is most often from areas rich in fibrinolytic activity such as the mouth or genitourinary tract, antifibrinolytic agents such as tranexamic acid usually suffice for dental extractions, menorrhagia, or minor surgery (Peyvandi et al. 2012b). For major surgery or extensive trauma, sufficient fresh frozen plasma is given to achieve trough levels of 45 IU/dl (Bolton-Maggs 2009). However, exposure to plasma elicits inhibitors in a third of patients homozygous for the Type II mutation of the factor XI gene, the most severe form of factor XI deficiency (Salomon et al. 2006). To diminish the frequency of inhibitor development, patients should be exposed to plasma only if there is a high risk of bleeding, and no effective alternatives are available. Patients with inhibitors are refractory to factor XI replacement therapy but satisfactory hemostasis can be obtained with low doses (15 μg/kg) of recombinant factor VIIa (rVIIa) combined with oral tranexamic acid (Livnat et al. 2009). The patient described in this vignette received rVIIa prior to the polypectomy and did not have bleeding or other complications.

Case 3

A 26-year-old woman presents in her 12th week of pregnancy for evaluation of both thrombophilia and a prolonged PT.

Her first pregnancy 2 years before had been uneventful. The patient denied a personal or family history of bleeding. Tonsillectomy and laparoscopic lysis of adhesions had been uneventful. Her first child, a boy, had no bleeding tendency. Her only medication was folic acid.

During the current pregnancy, she informed her obstetrician that her mother had been told of an increased risk of thrombosis during her pregnancy with the patient. However, her mother never had a thromboembolic event, and there was no family history of thrombosis.

The obstetrician ordered routine screening tests, including aPC resistance, protein S and protein C activity, fibrinogen, TT, PT, aPTT, AT III, and prothrombin gene mutation. Protein S activity was 45% (normal range 55–150%). The prothrombin time was 22 s (normal 12–15 s, INR 1.6) and the factor VII 53%; other clotting factors were normal. Genetic analysis showed a homozygous polymorphism in the factor VII promoter region [c1238G>A, p.Arg413Gln (Exon 8)], a mutation associated with reduced factor

VII activity (Hunault 1997). *The level of factor VII was 53 % at week 12, 85 % at week 22, and 117 % at week 32.*

This woman presents with two hemostatic problems, a mildly decreased protein S activity, and a prolonged PT with reduced factor VII activity.

Question 9. Which of the following is true about protein S?

A. It increases during pregnancy.
B. It is only active when bound to the C4B-binding protein.
C Levels of 10–20 % of normal are associated with venous thromboembolism.
D. The patient in the vignette should receive prophylactic anticoagulation.
E. It participates in the inactivation of factor Va.

Expert Perspective Protein S activity declines during pregnancy, and this patient's level is below the normal range for nonpregnant persons but within the normal range for a first trimester pregnancy (Said et al. 2010; Szecsi et al. 2010). In the circulation, about two-thirds of protein S is bound to the C4B-binding protein and is inactive; only the free protein acts as a cofactor for activated protein C in the inactivation of factors Va and VIIIa. However, moderately low levels of protein S (≥10 % of controls) do not identify patients or family members at risk for venous thrombosis (Lijfering et al. 2009; Pintao et al. 2013). Without a personal or a family history of thrombosis, the decreased protein S activity does not justify prophylactic anticoagulation.

Question 10. Which of the following is appropriate for the management of delivery in a pregnant patient with factor VII deficiency?

A. An epidural catheter is usually selected for administering anesthesia.
B. Cesarean section is preferred over vaginal delivery.
C. Factor VII concentrate should always be infused during the third stage of labor.
D. No special precautions if the factor VII increases to normal during pregnancy.
E. The infant should be delivered by forceps or vacuum method.

Expert Perspective Factor VII deficiency is an autosomal recessive disorder, and homozygous patients with severe deficiency (<10 % activity) are rare (prevalence 1:300–500,000) and have a high risk of bleeding (Mumford et al. 2014). The heterozygous condition is milder and the prevalence is 1:300–500; many patients are undetected until a mildly prolonged PT triggers further evaluation.

Regional anesthesia always carries a small but relevant risk of epidural vein injury and hematoma ("bloody tap"; Mhyre et al. 2009). Therefore, many anesthetists are hesitant to give epidural anesthesia to women with a coagulation abnormality. However, a recent study found that an epidural can be applied safely if the clotting defect has normalized during pregnancy (Chi et al. 2009) and was given to this patient without incident. Vaginal delivery is preferred over cesarean section; it avoids the risks of bleeding and infection associated with surgery. Furthermore, venous thromboembolism has been reported in 3–4 % of patients with coagulation factor deficiencies undergoing cesarean section (Ruiz-Saez 2013). This procedure should only be performed for obstetrical indications, and thromboprophylaxis is indicated after surgery in patients with moderate but not severely reduced factor VII levels.

The hemorrhagic diathesis in patients with factor VII deficiency can be highly variable and does not necessarily correlate with the level of factor VII activities (Di Minno et al. 2013; Kulkarni et al. 2006; Lapecorella et al. 2008). Although occasional patients with severe factor VII deficiency might not bleed, others with heterozygous disease can be symptomatic. The lack of correlation between factor VII level and bleeding tendency provides a challenge in determining a patient's risk of hemorrhage. The bleeding history may be helpful; the absence of

bleeding during a prior hemostatic challenge suggests a low future risk. During pregnancy, factor VII levels fail to increase in women with severe deficiencies but rise in those with milder disease and protect against bleeding (Kulkarni et al. 2006; Baumann Kreuziger et al. 2013). In the case described, no special precautions are indicated for the labor and delivery. If factor VII levels remain low during pregnancy or there is untoward bleeding, factor VII concentrate can be given at the time of delivery (Mariani et al. 2013; Peyvandi et al. 2012b). Forceps or vacuum extraction of the infant are avoided because they might provoke intracranial hemorrhage in babies inheriting the clotting factor mutations.

Case 4

This 20-year-old woman has a lifelong history of easy bruising, epistaxis, and prolonged bleeding after dental procedures. Because of excessive bleeding, transfusions were required at menarche, and she has been hospitalized three times for severe menorrhagia. Her brother had considerable bleeding after a dental extraction but is otherwise well, and physical examination of both patients is unremarkable. Coagulation studies showed that the aPTT and PT of both siblings are prolonged but are completely corrected in mixtures of patient and normal plasma. Platelet counts and fibrinogen levels are within the normal range.

Question 11. Which of the following would explain the coagulation abnormalities?

A. Factor VIII deficiency alone
B. Factor IX deficiency alone
C. Factor X deficiency alone
D. Deficiency of von Willebrand factor
E. Antiphospholipid antibody syndrome

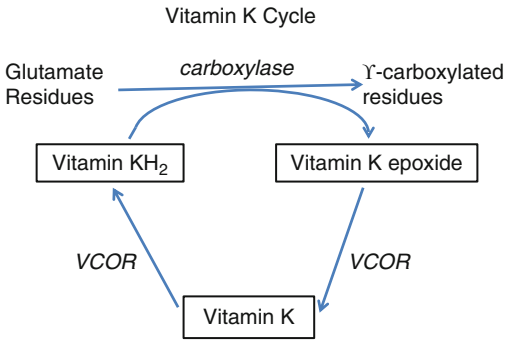
Expert Perspective Prolongation of both the aPTT and PT suggests deficiency of one or more factors in the common coagulation pathway; these include factors V, X, prothrombin, and fibrinogen. A deficiency of factor VIII, IX, XI, or XII alone would not account for the prolonged PT, and only the aPTT is prolonged in von Willebrand disease. In patients with the antiphospholipid antibody syndrome and a lupus anticoagulant, both the aPTT and PT can be prolonged, but fail to shorten with normal plasma.

Further study showed that the levels of prothrombin and factors VII, IX, and X are decreased; other factors, including factor V, are normal. Following an oral dose of vitamin K_1, the levels of the decreased clotting factors rose: prothrombin increased from 20 to 80% and factor X activity from 20 to 76%.

Question 12. What additional studies would you order for this patient?

A. Liver function tests
B. Evaluation for celiac disease
C. Serum warfarin level
D. Factor X immunoassay
E. D-dimer

Expert Perspective All the clotting factors, with the exception of factor VIII, are decreased in liver disease; the normal level of factor V makes serious liver disease unlikely. Decreases in prothrombin and factors VII, IX, and X occur with vitamin K deficiency and warfarin therapy. Malabsorption due to celiac disease or other intestinal disorders is excluded by the response to an oral dose of vitamin K. Warfarin decreases prothrombin and factors VII, IX, and X; therefore, the possibility of surreptitious ingestion of this anticoagulant should be considered. However, the fact that her brother has similar coagulation abnormalities makes this diagnosis unlikely. D-dimer is increased in patients with consumption coagulopathies; these individuals often have complex alterations in coagulation, but invariably platelets and fibrinogen as well as other clotting factors are decreased, making this diagnosis untenable.



The synthesis of factors II, VII, IX, and X requires the carboxylation of γ-glutamic acid residues on the clotting proteins (see Figure). Vitamin K in its reduced state (vitamin KH_2) is the cofactor for the carboxylase that performs this chemical synthesis, and vitamin K is reduced to KH_2 by the 2,3-epoxide reductase complex (VCOR). The response of the patient to vitamin K_1 suggests a defect in this pathway: either in the carboxylase or in VCOR. Without gamma carboxylation, the clotting factors of the prothrombin complex (prothrombin and factors VII, IX, and X) are inactive. A discrepancy between clotting factor activity and clotting factor antigen is an important clue to the diagnosis. In this patient, the prothrombin activity was 20 % but the prothrombin antigen was 80 %; factor X activity was 20 % and factor X antigen was 85 % (Goldsmith et al. 1982), confirming the diagnosis of hereditary combined vitamin K-dependent clotting factors deficiency. In addition to low levels of the prothrombin complex factors, the anticoagulant proteins C, S, and Z are decreased, as are osteocalcin and bone matrix Gla protein; deficiencies of these latter proteins may be associated with skeletal abnormalities (Napolitano et al. 2010). Most patients respond to treatment with oral or parenteral vitamin K_1 (phytomenadione); in those who fail to respond, FFP can be given for acute bleeds (Bolton-Maggs et al. 2004).

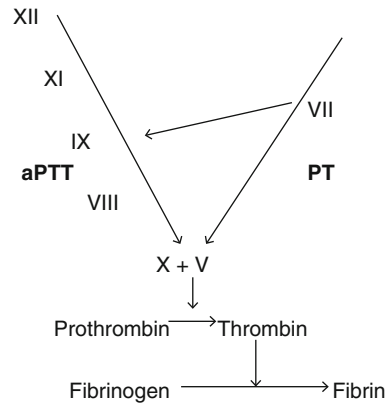
Case 5

A young man is referred to you because of prolonged bleeding after a dental extraction. He has a history of excessive bleeding after minor trauma but is otherwise well. His parents are consanguineous (first cousins). His aPTT is 70 s and his PT is 19 s; both shorten considerably after mixing with normal plasma.

Question 13. Which of the following would account for both of his abnormal clotting tests?

A. Factor VII deficiency
B. Von Willebrand disease
C. Factor IX deficiency
D. Factor XI deficiency
E. Combined factor V and factor VIII deficiency

Expert Perspective Both the aPTT and PT are prolonged with decreases in fibrinogen and factor II, V, or X (the common pathway, see Figure). Combined deficiencies of factors V and VIII or II, VII, IX, and X also prolong both tests. Heparin and direct inhibitors of factor X and thrombin, as well as the lupus anticoagulant, variably increase the aPTT and PT.



His factor V was 5 % and factor VIII was 4 %. Genetic analysis showed a missense mutation in the multiple coagulation factor deficiency 2 (MCFD2) gene (Chapin et al. 2012).

Question 14. What treatment would you recommend for major bleeding episodes or surgery?

A. Desmopressin
B. Fresh frozen plasma

C. Cryoprecipitate
D. Factor VIII concentrate
E. Fresh frozen plasma and factor VIII concentrate

Expert Perspective Patients with this rare autosomal recessive bleeding disorder (1:1,000,000) have gingival bleeding and prolonged hemorrhage after surgery or trauma (Viswabandya et al. 2010). The genetic defect affects proteins that chaperone factors V and VIII from the endoplasmic reticulum to the Golgi apparatus; the lectin mannose-binding protein 1 (LMAN1) is mutated in 70% of patients, mostly from the Middle East, and the MCFD2 mutation in persons from India and Europe (Zhang et al. 2006). Treatment with desmopressin has been effective in some patients although it does not increase factor V levels; the management of most serious bleeds requires a factor VIII concentrate as well as fresh frozen plasma to raise the levels of both factor V and factor VIII (Spreafico and Peyvandi 2009). Sufficient factor VIII should be infused to achieve concentrations of 50–70 IU/dl and repeated every 12 h; FFP is given in an initial dose of 15–20 ml/kg followed by smaller doses of 5 ml/kg every 12 h to maintain levels of 15 IU/dl (Assselta and Peyvandi 2009).

Case 6

This 30-year-old man has a history of infrequent joint bleeding as a child and repeated episodes of trauma-induced soft-tissue hematomas as an adult. At age 23 he had a spontaneous intracranial hemorrhage with residual right-sided weakness and had a second subarachnoid hemorrhage at age 27. He has no other medical problems and takes no medications. He has a healthy 6-year-old son and no other family members have a history of a bleeding disorder. Physical examination is normal and all joints are fully mobile. Laboratory studies show a hemoglobin of 15.5 g/dl, WBC 5.6×10^3/μl, and platelets 187×10^3/μl. The PTT is 31 s, PT 12 s, and factor XIII 2%.

Question 15. At this time, you would recommend

A. Wearing a helmet at all times
B. Fresh frozen plasma for future bleeding episodes
C. Weekly prophylactic infusions of cryoprecipitate
D. Monthly infusions of factor XIII concentrate
E. Observation only

Expert Perspective Congenital factor XIII deficiency is a rare autosomal recessive disorder associated with soft-tissue hemorrhages, spontaneous abortions, and impaired wound healing (Schroeder and Kohler 2013). Severe or fatal intracranial bleeding often occurs unpredictably, as in the patient described here. Therefore, prophylactic replacement therapy with a factor XIII concentrate is indicated (Bolton-Maggs et al. 2004); because the half-life of the factor is 9–14 days, doses are needed only monthly. Two factor XIII concentrates are licensed in the USA; one is plasma-derived (Corifact, CSL Behring) and the other is a recombinant factor XIII (Tretten, Novo Nordisk). They are infused intravenously in doses of 35–40 IU/kg. A clinical trial of the recombinant factor XIII showed a nearly sevenfold decrease in the annual bleeding rate, as compared with historical controls (Inbal et al. 2012). Serious adverse effects such as hypersensitivity reactions are rare, but occasional patients develop neutralizing antibodies to factor XIII (Kohler 2012).

Controversies in Rare Bleeding Disorders

- Should patients with rare bleeding disorders receive surgical thromboprophylaxis?
- Are antiplatelet agents indicated for patients with rare bleeding disorders and atherosclerotic vascular disease?
- Is treatment with recombinant factor VIIa appropriate for most patients with rare congenital bleeding disorders?

Answer

- Question 1. C
- Question 2. A
- Question 3. E
- Question 4. A
- Question 5. C
- Question 6. C
- Question 7. D
- Question 8. E
- Question 9. E
- Question 10. D
- Question 11. C
- Question 12. D
- Question 13. E
- Question 14. E
- Question 15. D

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