Rare Coagulopathies

Jim Munn, RN, BS, BSN, MS

INTRODUCTION

The process of fibrin clot formation that results in resolution of bleeding is a complex but well-regulated series of reactions involving blood vessels, platelets, procoagulant plasma proteins, natural inhibitors, and fibrinolytic enzymes. Deficiencies or defects in any of these hemostatic components may result in bleeding. Although not as familiar as hemophilia or von Willebrand disease (VWD) to most practitioners, several rare coagulopathies exist that can be problematic to treat and sometimes difficult to diagnose. A nurse caring for patients with bleeding disorders must be familiar with some of these less common congenital bleeding diatheses, occasionally referred to as recessively inherited coagulation disorders. These disorders, although rare, become more prevalent in consanguineous societies or in areas of the world where marriage between close family relatives is practiced. This chapter provides an overview of selected rare coagulopathies.

Because of the rarity of some of the hereditary hemorrhagic disorders, treatment with blood products may be required. Please refer to MASAC guideline #215 for product descriptions and treatment recommendations. (1)

PROCOAGULANT PLASMA PROTEIN (FACTOR) DEFICIENCIES

FACTOR I (FIBRINOGEN) DEFICIENCY

Fibrinogen (factor I) is a hepatically-synthesized protein composed of three chains (α - alpha, β - beta, γ - gamma) that occur on two identical halves of a rather large molecule. When the alpha (fibrinopeptide A) and beta (fibrinopeptide B) chains are cleaved from fibrinogen, fibrin monomers are formed. The monomers then polymerize and are stabilized by factor XIII, leading eventually to fibrin clot formation. Fibrinogen is required for both fibrin clot formation and normal platelet aggregation. Disorders of fibrinogen may result from quantitative deficiencies of the protein (afibrinogenemia and hypofibrinogenemia), qualitative defects of the molecule (dysfibrinogenemia) or a combination of the two (hypodysfibrinogenemia).

Afibrinogenemia is the complete absence of fibrinogen protein in circulation.

Hypofibrinogenemia results when some protein with normal structure is present in circulation but is below that required for normal hemostasis (50 mg/dL). (2)

Dysfibrinogenemia results from a structurally abnormal fibrinogen molecule that is present in normal amounts in the plasma but does not work to promote a clot.

Hypodysfibrinogenemia occurs when lower amounts of an abnormal fibrinogen molecule are present in circulation.

First described in 1920, (3) afibrinogenemia is very rare, with an estimated prevalence of 1-2 cases per million of the population. (4) The factor I gene is located on the long arm of chromosome 4; several genotypes exist that can result in factor I deficiency. Fibrinogen deficiencies are autosomally inherited and occur in both males and females. Afibrinogenemia is inherited as an autosomal recessive trait, which means that both parents must pass on the defective gene to their child. Hypofibrinogenemia is essentially the heterozygous form of afibrinogenemia, meaning that the individual has one abnormal gene. On the other hand, the qualitative defects of fibrinogen, dysfibrinogenemia and hypodysfibrinogenemia, are often inherited as autosomal dominant traits.

Diagnosis

Diagnosis of fibrinogen disorders is made by clinical history, physical exam, and laboratory investigations. Because fibrinogen is a common pathway plasma protein, both the prothrombin time (PT) and activated partial thromboplastin time (aPTT) should be prolonged. The thrombin time also is prolonged when low levels of fibrinogen are suspected. A comparison of activity and antigen levels of fibrinogen will help distinguish qualitative defects from quantitative deficiencies. When the functional activity level is low but the antigen level is normal, dysfibrinogenemia or hypodysfibrinogenemia should be considered. If both the activity and antigen levels are proportionally low, a quantitative deficiency is present. Care must be taken to exclude acquired deficiencies of fibrinogen that can occur in patients with liver or kidney disease and other disorders such as macroglobulinemia and multiple myeloma.

Clinical Features

Clinically, the most common bleeding presentations in fibrinogen deficiencies are umbilical cord stump oozing and mucosal hemorrhage. (5) Menorrhagia, post-partum hemorrhage, miscarriage, gastrointestinal bleeding, and muscle hematomas may also occur. Hemarthrosis can occur in severe forms of fibrinogen defects, but joint destruction does not appear to be the same as that experienced by patients with hemophilia. Bleeding may range from mild to severe, and in patients with hypofibrinogenemia, there may be no bleeding or bleeding associated only with trauma or surgery. (6)

Dysfibrinogenemia may result in little or no bleeding, mild to severe bleeding with clinical features as described above, thrombosis, or a combination of bleeding and clotting. About half of diagnosed patients with congenital dysfibrinogenemia have no symptoms. The remaining patients show about equal proportions of bleeding, clotting or a combination of the two. (7)

Treatment

Severe or moderate bleeding in patients with quantitative deficiencies of fibrinogen (afibrinogenemia and hypofibrinogenemia) is treated with a plasma-derived, virally-inactivated, fibrinogen-rich factor concentrate. Raising the circulating fibrinogen level to >50 mg/dL is required for moderate bleeding. In severe, life- or limb-threatening hemorrhage, or patients undergoing surgery, fibrinogen should be replaced to at least 100 mg/dL. Since the plasma half-life of fibrinogen is quite long, two to four days, some patients with afibrinogenemia may treat prophylactically with weekly infusions. (8)

The current fibrinogen factor concentrate licensed in the U.S. is not approved for treatment of bleeding in patients with dysfibrinogenemia or hypodysfibrinogenemia. Bleeding in these patients is most often treated with cryoprecipitate. Fresh-frozen plasma (FFP) also has been used on occasion to treat bleeding in these patients. Fibrinogen levels of 50-100 mg/dL usually are sufficient to achieve hemostasis. In patients with thrombotic concerns, thromboprophylaxis measures, such as use of compression stockings and low-molecular weight heparin (LMWH), may be necessary as well. (4)

FACTOR II (PROTHROMBIN) DEFICIENCY

One of the vitamin K-dependent factors, factor II is synthesized in the liver. Prothrombin is the precursor to thrombin, which is necessary to aid in activation of factors I, V, VIII, XI and XIII. Factor II in its active form, thrombin, is necessary for fibrinogen to be converted to fibrin, ultimately resulting in stable clot formation. Factor II deficiency is very rare, and complete absence of the protein is considered incompatible with life. (8) Prothrombin deficiency may occur as a result of low levels of normal protein (hypoprothrombinemia) or when dysfunctional factor II molecules are present (dysprothrombinemia). Minimum hemostatic levels of 20-30% are needed for adequate hemostasis; the plasma half-life of factor II is about three to four days. (2)

The disorder was first reported by Dr. Armand Quick in 1947. (9) The incidence of prothrombin deficiency is estimated at 1 case per 2 million people in the general population. (4) The gene for prothrombin is located on chromosome 11, with several mutations described, and the disorders of prothrombin are inherited as autosomal recessive conditions; both parents must pass on the gene defect to an affected child. As can be seen in other autosomal recessive disorders, prothrombin deficiency is higher in areas of the world where consanguineous marriage is common.

Diagnosis

Prothrombin deficiency generally exhibits laboratory abnormalities in the PT and aPTT, but a normal thrombin time. Both prothrombin functional activity and antigenic levels should be drawn and compared to distinguish whether a quantitative (hypoprothrombinemia) or qualitative

(dysprothrombinemia) defect is present. Other factor levels, specifically VII, IX and X, should be drawn to rule out the possibility of a combined factor deficiency or a deficiency in another common pathway protein, such as fibrinogen or factors V and X. Other acquired conditions should be excluded as well that may result in lowered prothrombin levels such as vitamin K deficiency, presence of a lupus anticoagulant, use of vitamin K antagonist anticoagulants, or liver disease.

Clinical Features

Bleeding can be very heterogeneous for patients with prothrombin deficiency, but the most common manifestations appear to be easy bruising, mucocutaneous bleeding (epistaxis and oral mucosal bleeding), intramuscular bleeding, menorrhagia, and hemarthrosis. (10) Generally, lower prothrombin levels lead to more severe and frequent bleeding symptoms.

Treatment

No pure prothrombin concentrates are available, so treatment to control bleeding is achieved using prothrombin complex concentrates (PCCs) or FFP. The minimal hemostatic level of prothrombin is 20-40% of normal activity. (2) Replacement with PCCs is complicated by the fact that amounts of prothrombin in the commercially available products differ not only from one company to another but in each lot of concentrate produced. PCCs are labeled in factor IX units, so providers may need to call the manufacturer of the product to be used to ascertain the amount of factor II present in the lot chosen to treat a bleeding episode or to cover surgery. PCCs ordered as 20-30 units per kilogram of body weight of factor IX typically are sufficient to raise prothrombin to hemostatic levels. (11) Care also should be taken when using either PCCs or FFP because transfusion reactions, allergic manifestations, volume overload, and thrombotic complications can occur. Also, the concomitant use of antifibrinolytic agents with PCCs should be avoided given the high risk of thromboembolic complications. Prophylaxis using a PCC in a patient with severe prothrombin deficiency has been reported. (12)

FACTOR V (LABILE FACTOR, PROACCELERIN) DEFICIENCY (OWREN'S DISEASE, PARAHEMOPHILIA)

A cofactor in the conversion of prothrombin to thrombin, factor V (FV) is produced in the liver and is found in alpha granules of platelets. During fibrin clot formation, activated factor V combines with activated factor X in the presence of calcium ions to form the "prothrombinase" complex that cleaves prothrombin into thrombin. This process occurs on negatively-charged phospholipids located on a variety of plasma membranes: platelets, endothelial cells and monocytes.

The factor V molecule was first postulated in 1943 (13) with the first patient reported in the literature by Dr. Paul Owren in 1947. (14) Prevalence of the homozygous form of factor V deficiency is believed to be one per million. (4) The gene for factor V is located on chromosome

1; several molecular variants of the factor V gene have been reported. Factor V deficiency is inherited as an autosomal recessive condition, and usually only patients with severe disease (<1-10% of circulating factor V) present early in life and with more severe bleeding manifestations. The minimal hemostatic level of factor V is 15-20% of normal, and its plasma half-life is 36 hours. (2)

Diagnosis

Similar to factor II deficiency, factor V deficiency is characterized by a prolonged PT and aPTT, with a normal thrombin time. Specific assays for factor V activity and antigen levels are drawn to complete the investigation of factor V deficiency. Because factor V has 40% sequence homology to factor VIII, a factor VIII assay also should be performed to rule out a combined deficiency of factors V and VIII that has been reported. (15) Acquired forms of factor V deficiency related to liver disease, some autoimmune diseases, and bovine factor V-containing topical hemostatic agents used during surgery also must be ruled out. Another abnormality of factor V that results in thrombosis, factor V Leiden, should not be confused with factor V deficiency.

Clinical Features

Phenotypic expression of factor V deficiency can be quite variable. Generally only patients with <1% factor V appear to have the most severe bleeding, such as intracranial hemorrhage or hemarthrosis. The intra-articular bleeding seen in factor V deficiency is rare and does not occur to the same extent as one would see in severe hemophilia patients. Other common sites of bleeding in factor V deficiency include epistaxis, easy bruising, oral mucosal bleeding, menorrhagia, and bleeding resulting from trauma or surgery. Patients with factor V levels of >20% typically have no bleeding symptoms.

Treatment

At present, hemorrhage associated with factor V deficiency must be treated with a blood component such as FFP, as no commercially available factor V concentrate exists. Fluid overload may be of concern due to the large volume of plasma needed to control bleeding. In some circumstances, such as in life- and limb-threatening bleeding, or prior to surgery in severe patients (<1% factor V), plasma exchange has been used to achieve greater concentrations of factor V. Because factor V is found in alpha granules of platelets, occasionally platelet transfusions have been given with some benefit to control bleeding. Use of platelet transfusions, however, should be minimized to limit donor exposure and avoid alloantibody formation.

FACTOR VII (STABLE FACTOR, PROCONVERTIN) DEFICIENCY (ALEXANDER'S DISEASE)

Another of the vitamin K-dependent proteins produced in the liver, factor VII (FVII) is part of the clotting cascade's extrinsic pathway. Simply put, activated factor VII (FVIIa) complexes

with tissue factor (TF) that is exposed during blood vessel injury to initiate blood clotting. This complex helps convert factor X to its activated form, similar to the conversion of factor X to activated FX by the intrinsic proteins factors FIXa and FVIIIa, sometimes referred to as "tenase" complexes. As in most rare disorders, structural defects or deficiencies in the level of circulating factor VII protein may lead to bleeding.

Alexander and colleagues were the first to describe in the literature a patient with factor VII deficiency they referred to as having "congenital serum prothrombin conversion accelerator deficiency." (16) The prevalence of factor VII deficiency, considered the most common of the rare bleeding disorders, is about 1 per 300,000-500,000 in the population. (4) The FVII gene is located on chromosome 13 and is inherited as an autosomal recessive trait. Several genetic mutations have been identified that result in factor VII deficiency, missense mutations being the most common (almost 80%). (17) Clinical manifestations of factor VII deficiency can be quite variable; patients with low levels of circulating proteins may exhibit no bleeding. On the other hand, patients with levels <1% can have symptoms that mimic classic hemophilia – intramuscular, intra-articular and central nervous system bleeding. (17) Also of interest, thrombosis has been reported in patients with congenital factor VII deficiency. (18) The plasma half-life of factor VII is four to six hours, with a minimal hemostatic level thought to be 15-20%. (2)

Diagnosis

An isolated prolonged PT is the hallmark laboratory result associated with factor VII deficiency. The aPTT and thrombin time are normal. Low factor VII activity and antigen levels will help confirm a factor VII deficiency diagnosis. Acquired factor VII deficiency can be seen in patients with liver disease and vitamin K deficiency and in those taking oral anticoagulants, so care should be taken to obtain a careful history when diagnosing this defect.

Clinical Features

As mentioned earlier, clinical symptoms can be highly variable in factor VII-deficient patients. Hemarthrosis, intracranial hemorrhage (sometimes fatal), gastrointestinal bleeding, and muscle hematomas have been reported in patients with severe (<1%) factor VII deficiency. More commonly, patients will present with epistaxis, easy bruising, gum bleeding, menorrhagia, post-operative bleeding, and/or hematuria. Variability between genotype and phenotype is common in rare disorders, and factor VII deficiency is no exception. As was noted earlier, a few patients with inherited factor VII deficiency have presented with thrombosis.

Treatment

Treatment for patients with factor VII deficiency involves the use of a recombinant, activated factor VII (rFVIIa) concentrate. Although patients may be treated with FFP or other products containing factor VII (PCCs, activated prothrombin complex concentrates (aPCCs), or in Europe,

a plasma-derived factor VII concentrate), rFVIIa is the most widely used product in the United States and is considered optimal therapy for patients with factor VII deficiency. (19) Lower levels of factor VII are needed to achieve adequate hemostasis than to treat FVIII or FIX inhibitors, so rFVIIa can be dosed correspondingly. Generally, doses of 15-30 micrograms per kilogram given less frequently (every four to six hours) are sufficient to control bleeding compared to 90-120 micrograms per kilogram every two to three hours in hemophilic patients with inhibitors. (19) Prophylaxis using rFVIIa in some severe factor VII-deficient patients has been reported as well. (20)

FACTOR X (STUART-PROWER FACTOR) DEFICIENCY

Along with factors II, VII and IX, factor X (FX) is a vitamin K-dependent plasma protein. The activated form of factor X, along with activated factor V, calcium ions, and a negatively-charged phospholipid membrane, forms the "prothrombinase" complex that cleaves factor II (prothrombin) to form thrombin. Hepatic synthesis of factor X results in a two-chain molecule that itself can be cleaved into activated factor X by both the extrinsic (FVII/TF complex) and intrinsic pathways (FIXa/FVIIIa). True homozygous deficiency of the protein is thought to be incompatible with life. (21)

In the 1950s, two patients, surnames Stuart and Prower, were identified with a novel bleeding disorder that would eventually be called factor X deficiency. (22, 23) Located on chromosome 13, like the factor VII gene, factor X genetic defects are usually missense mutations. (2) Inheritance is autosomal recessive, so females and males equally are affected. The incidence of severe factor X deficiency appears to be about one per million. (4) Severity of bleeding in patients with factor X deficiency is often correlated with circulating factor X levels: the lower the plasma level, the more severe the bleeding. The plasma half-life of factor X is about 40-60 hours, with a minimal hemostatic level of about 15-20%. (2)

Diagnosis

Factor X is a part of the common coagulation pathway, so laboratory studies revealing deficiency of the protein will exhibit prolongation of both the PT and aPTT. The thrombin time will be normal. Because other factor deficiencies can show prolonged PT and aPTT, a factor X assay will help confirm the diagnosis. A factor X antigen level may help distinguish a quantitative deficiency from a qualitative defect. Liver disease and vitamin K deficiency can result in factor X deficiency. Other conditions that may lower factor X levels include amyloidosis, respiratory infections, acute myeloid leukemia, and other malignancies.

Clinical Features

Patients with factor X deficiency can present in a number of ways, umbilical cord stump bleeding often being one of the first signs. Other types of clinical bleeding reported in factor X-deficient patients include epistaxis, menorrhagia, post-partum hemorrhage, and surgical

bleeding. In patients with severe (<1%) deficiency, hemarthrosis, intracranial hemorrhage, and intramuscular bleeding can be seen. Mild patients (those with factor X levels of about 10%) may manifest easy bruising, soft tissue bleeds, menorrhagia, and bleeding with trauma or surgery.

Treatment

No purified factor X concentrate is available in the United States for patients with factor X deficiency, although one is currently in clinical trials. When bleeding warrants factor replacement, either a PCC or FFP is used. PCCs are heat-treated products that contain the vitamin K-dependent factors II, VII, IX and X in varying amounts. Viral transmission is greatly reduced with the use of these products compared to use of blood components. Dosing with PCCs is often 20-30 units per kilogram of body weight daily, which is generally sufficient to control bleeding. Note that these PCC products are dosed by Factor IX units; the quantity of Factor X varies from manufacturer and from lot to lot. For surgery or severe, life- or limb-threatening bleeding, the manufacturer can give the actual units of Factor X in a particular lot to be used. Given the long half-life of factor X, prophylaxis with PCCs has been successful in some severe factor X-deficient patients using once or twice weekly infusions to prevent bleeding. (4) Due to the long half-life of factor X, FFP can be initiated as a bolus dose of 20 milliliters per kilogram of body weight followed by repeat bolus doses of 3-6 milliliters per kilogram every 12 hours. (4)

FACTOR XI DEFICIENCY (HEMOPHILIA C, PLASMA THROMBOPLASTIN ANTECEDENT (PTA) DEFICIENCY, ROSENTHAL SYNDROME)

Once considered part of the contact pathway in coagulation, factor XI (FXI) is a plasma protein synthesized in the liver that is converted to its active form by thrombin and activated factor XII. When this occurs, engagement of the intrinsic coagulation pathway begins, and factor IX is cleaved by activated factor XI to form activated factor IX, eventually resulting in fibrin clot formation. Although patients may have extremely low levels of factor XI, the phenotypic expression in patients is highly variable. Bleeding in patients with <1% of circulating factor XI is dissimilar to that of patients with severe factor VIII or FIX deficiency; spontaneous bleeding and hemarthroses are rare in severe factor XI deficiency, and in some cases no bleeding may occur. Generally, when plasma factor XI levels fall below 20% of normal, patients are more likely to be homozygotes or compound heterozygotes that may experience bleeding manifestations. (7)

Rosenthal and colleagues first described factor XI deficiency in the literature in 1953 in patients who experienced severe bleeding after dental extractions. (24) Factor XI gene mutations occur on the long arm of chromosome 4, just like fibrinogen. The disorder is inherited in an autosomal recessive fashion, so males and females are equally affected. There are three rather well-known mutations in factor XI-deficient patients: types I, II and III. Type I mutations are splice junction defects, type II is a nonsense mutation found mainly in Ashkenazi and Iraqi Jews, and type III, another genetic defect frequently seen in Ashkenazi Jews, is a missense mutation. (4) Although

factor XI deficiency has been described in all racial groups, it appears more frequently in Ashkenazi and Iraqi Jews and may be as prevalent as 4-8% of those populations. (25) In the non-Jewish population, the incidence appears to be about one in a million. (4) Hemostasis is achieved with factor XI levels of 15-20%; the plasma half-life of the protein is about 40-70 hours. (2)

Diagnosis

An isolated prolonged aPTT, when factors VIII and IX deficiency have been ruled out, points to factor XI deficiency. Both the thrombin time and the PT will be normal. A specific factor XI assay should be performed to confirm the diagnosis. Combined coagulation protein deficiencies must be ruled out when testing for factor XI deficiency. Factor XI deficiency also has been reported in patients with Noonan Syndrome and Gaucher Disease, which necessitates ruling these conditions out before diagnosis of a heritable deficiency is made. (26)

Clinical Features

Many patients with factor XI deficiency have little or no bleeding manifestations; however, those who present with bleeding complications often do so in the setting of surgery or trauma. Bleeding appears to be mucocutaneous in nature and is associated with areas of continual fibrinolytic activity (nose, mouth, and genitourinary tract). Post-partum hemorrhage and menorrhagia may occur in female patients. One of the best predictors of bleeding in factor XI-deficient patients is personal or family history of problematic bleeding. (4)

Treatment

The absence of a licensed, commercially available factor concentrate in the United States for patients with factor XI deficiency requires treatment with FFP. FFP is typically begun as a bolus dose of 15-20 milliliters per kilogram of body weight, with subsequent doses given on alternate days or else 3-6 milliliters per kilogram every 12 hours to maintain factor XI levels above 15-20%. (2, 4) Fluid volume concerns exist with this approach, so some patients may benefit from plasma exchange therapy. Some patients undergoing surgery have been given rFVIIa outside of its licensed indication. (4)

FACTOR XII (HAGEMAN FACTOR) DEFICIENCY

Produced in the liver, Factor XII (FXII) is part of the contact pathway, which is not fully understood physiologically. The role of factor XII appears to be as a serine protease (cleaving enzyme) that, when activated (FXIIa), assists with the activation of factor XI to FXIa as well as the conversion of prekallikrein to kallikrein. Patients with low levels of factor XII do not appear to have a propensity for bleeding even when challenged surgically. Paradoxically, they may exhibit thromboembolic tendencies, but a true association between factor XII deficiency and thrombosis has not been proven. (27)

First described in the literature in 1954, (28) factor XII deficiency is often discovered during routine pre-operative evaluation when the aPTT is markedly prolonged (>100 seconds), as was the case with the proband patient, Mr. John Hageman. (29) The gene for factor XII is located on the tip of the long arm of chromosome 5. Several gene defects have been reported, and the disorder usually is inherited as an autosomal recessive trait. Normal factor XII levels appear to be lower in Asians than in other ethnic groups. (30) The true incidence of factor XII deficiency is not well-known, however, in a study looking at 300 normal blood donors, heterozygous factor XII deficiency was found in 2% of the subjects. (31) The plasma half-life of factor XII is about is about 50-70 hours. (32)

Diagnosis

Suspicion of factor XII deficiency should be high in patients with screening labs revealing an extremely prolonged aPTT (usually >100 seconds), with normal PT and thrombin time and no history of clinical bleeding. Although this scenario can be seen in patients with other contact factor deficiencies (prekallikrein, high-molecular weight kininogen), a specific assay for factor XII will help confirm the diagnosis. Other acquired conditions (liver disease, nephrotic syndrome) may result in low factor XII levels and need to be considered prior to making a diagnosis of an inherited deficiency.

Clinical Features

Patients with factor XII deficiency, even those with <1% circulating protein levels, appear to have no clinical bleeding manifestations.

Treatment

No treatment is required for factor XII-deficient patients. Remember, controversy exists about whether these patients are predisposed to thrombosis. (27)

FACTOR XIII (FIBRIN STABILIZING FACTOR) DEFICIENCY

Plasma factor XIII (FXIII) circulates as a tetramer composed of two subunits, A and B, each having two chains. In the presence of thrombin and calcium ions, factor XIII becomes activated factor XIII (FXIIIa), which helps to stabilize the cross-linkage of fibrin polymers to form an insoluble fibrin clot. (33) B subunits are manufactured in the liver, while A subunits appear to be synthesized in megakaryocytes and monocytes. (33) Typically, only patients with FXIII levels <1% present with clinical bleeding.

The existence of a "fibrin-stabilizing factor" was first postulated in 1944 (34) and confirmed in 1948, (35) and the first reported case in the literature was described in 1960 by Duckert and colleagues. (36) Two chromosomes are involved in the genetic inheritance of factor XIII: the

short arm of chromosome 6 contains the gene for the A subunit, and chromosome 1 contains the B subunit gene. Several molecular defects have been identified that result in factor XIII deficiency; these can be classified into two types, type 1 occurring in the B subunit gene, and type 2 in the A subunit gene. (33) Most patients with FXIII deficiency have gene mutations affecting the A subunit. The incidence of factor XIII deficiency has been estimated at one in 3,000,000-5,000,000 people, making it one of the rarest congenital hypocoagulopathies. (37) Only about 2-5% of factor XIII is needed for adequate hemostasis, and the plasma half-life is about 11-14 days. (2)

Diagnosis

Whenever patients present with screening labs that are normal for all tests – PT, aPTT, thrombin time – and with delayed bleeding from the umbilical cord stump or post-circumcision, poor wound healing or intracranial hemorrhage, factor XIII deficiency should be considered. A clot solubility test that looks at dissolution of a clot placed in either 5 M (molar) urea or 1% monochloroacetic acid over 24 hours may be the first test to aid diagnosis. If the clot dissolves within those 24 hours, the patient plasma is considered absent of factor XIII. Factor XIII-specific assays for activity and antigen can be performed as well. Several conditions have been associated with acquired FXIII deficiency, including patients with inflammatory bowel disease, leukemia, medication use, liver disease, and systemic lupus erythematosus, to name a few. (32, 33)

Clinical Features

Umbilical cord stump bleeding is common in factor XIII deficiency, reported in almost 80% of cases. (4) Other reported forms of bleeding in FXIII deficiency involve oral mucosal bleeds, ecchymoses, post-operative hemorrhage that can be immediate or delayed, recurrent miscarriages in women, and oligospermia and infertility in men. (32, 33) Of most concern is the patient that presents with spontaneous intracranial hemorrhage, which has been reported to have an incidence of up to 30% and is the leading cause of mortality in this patient population. (38)

Treatment

Currently only one licensed factor XIII concentrate is available in the United States. It is a virally-inactivated, plasma-derived, single-protein concentrate that is licensed for prophylactic treatment at 40 units per kilogram of body weight every 28 days to keep circulating FXIII trough levels between 5-20%. (39) The product contains both A and B subunits. Cryoprecipitate and FFP have been used for treatment of factor XIII deficiency as well but should only be used for emergencies when the licensed concentrate is not available. Cryoprecipitate usually is dosed with one bag per 10-20 kilograms of body weight every 3-4 weeks. FFP is often administered as 10 milliliters per kilogram of body weight every 4-6 weeks given the long plasma half-life of factor XIII. Of note, a recombinant factor XIII concentrate that contains only the A subunit has

been submitted for approval to the United States Food and Drug Administration. Licensure has not been granted at the time of this writing.

COMBINED FACTOR DEFICIENCIES

Several combined factor deficiencies exist, the most common being combined factors V and VIII deficiency and combined factors II, VII, IX and X deficiency (the vitamin K-dependent proteins, which also include proteins C and S). Bleeding is often noted after trauma or surgery and may be severe in some cases, especially in the combined vitamin K-dependent protein-deficient patients where umbilical cord stump bleeding and intracranial hemorrhage have been reported. (4) Diagnosis involves performing screening tests for PT, aPTT and thrombin time. In both combined scenarios the PT and aPTT will be prolonged, but the thrombin time should be normal. Treatment for bleeds must take into account the severity and location of the bleed and the baseline protein levels in the combined deficiency. Recombinant factor VIII concentrates and FFP are often administered to patients with combined FV and FVIII deficiency to arrest severe bleeding. Patients with deficiencies in the vitamin K-dependent proteins receive oral vitamin K therapy often at diagnosis. For severe bleeding episodes they may require PCCs or FFP. Caution should be taken with PCCs due to thromboembolic risk. (4, 32)

FIBRINOLYSIS INHIBITOR PROTEIN (FACTOR) DEFICIENCIES

Fibrinolysis is the body's natural response to clot formation and allows for enzymatic degradation of fibrin clots after injured blood vessels have been repaired. This process occurs mainly by the conversion of plasminogen to plasmin, which is responsible for clot lysis. Whenever plasmin production continues unregulated due to deficiencies of natural inhibitors, increased fibrinolysis may occur, leading to excessive bleeding. Two of these naturally occurring inhibitors of fibrinolysis will be discussed: α_2-antiplasmin (α_2-AP) and plasminogen activator inhibitor type 1 (PAI-1). When plasmin formation is hampered, a tendency for thrombosis exists, since fibrin clots are not properly degraded.

α_2-ANTIPLASMIN (α_2-PLASMIN INHIBITOR) DEFICIENCY

α_2-Antiplasmin (α_2-AP) is a direct inhibitor of plasmin formation. α_2-AP complexes directly with plasmin to help regulate fibrinolysis and increase the resistance of fibrin to enzymatic breakdown by plasmin by forming cross-linkages with FXIII, making the fibrin clot less susceptible to proteolysis. A third mechanism of action has been found whereby α_2-AP inhibits adsorption of plasminogen to fibrin on the surface of the formed clot, which is where fibrinolysis occurs. (40) Patients with α_2-AP levels that are undetectable (homozygous inheritance) have more pronounced bleeding than heterozygous patients. Bleeding is often delayed in patients with α_2-AP deficiency, similar to that seen in FXIII deficiency. The protein has a circulating half-life of about three days. (32)

The first case of congenital α_2-AP deficiency was described in 1969. (40) Located on chromosome 17, the gene for α_2-AP has revealed several molecular defects resulting in α_2-AP deficiency. The disorder is inherited as an autosomal recessive trait, so males and females alike are affected. The incidence of α_2-AP deficiency has not been determined.

Diagnosis

Screening lab tests used for detection of procoagulant plasma protein deficiencies, namely the PT, aPTT and thrombin time, are all normal. The euglobulin lysis time, which helps measure fibrinolysis, will be shortened, as a fibrin clot will dissolve more rapidly since plasmin production is not inhibited in patients with α_2-AP deficiency. Specific assays (activity and antigen) for α_2-AP may be run, and as is the case with most plasma protein defects, levels can be correspondingly low for both tests (quantitative deficiency), or the activity may be low with a normal antigen level (qualitative defect). Liver failure and amyloidosis may also result in low levels of α_2-AP.

Clinical Features

Patients with severe forms of α_2-AP deficiency (homozygous individuals) may have bleeding similar to that seen in other severe bleeding disorders, with umbilical cord stump bleeding, hemarthrosis, and bleeding in areas of enhanced fibrinolytic activity such as the mouth and nose. Women may have menorrhagia. Heterozygous patients generally have milder phenotypes and may have no bleeding symptoms. Surgeries, including dental procedures, and trauma may exacerbate bleeding in milder patients. Symptoms often increase with advancing age, as plasma levels tend to fall in older individuals. (40)

Treatment

Antifibrinolytic therapy is the treatment of choice for patients having enhanced fibrinolytic defects such as α_2-AP and PAI-1 deficiencies. ε-Aminocaproic acid and tranexamic acid have been used successfully in these disorders. The ε-aminocaproic acid dose is 100 milligrams per kilogram every six hours administered either orally or intravenously. Tranexamic acid is dosed intravenously at 10 milligrams per kilogram of body weight every 6-8 hours. (32, 40) The oral form has been approved in the US only for treatment of menorrhagia.

PLASMINOGEN ACTIVATOR INHIBITOR-1 DEFICIENCY

Similar to α_2-AP, plasminogen activator inhibitor-1 (PAI-1) is a protein necessary to help regulate fibrinolysis. (41) Unlike α_2-AP, PAI-1 does not inhibit plasmin formation directly but works instead on two plasminogen activators: tissue-plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Both of these proteins enhance the conversion of plasminogen to plasmin so that fibrinolysis can occur. PAI-1 inhibits the catalytic function of t-PA and u-PA, giving rise to a well-regulated "checks and balances" system within the

fibrinolytic pathway of coagulation. Generally, only patients with complete absence of PAI-1 have clinical bleeding that is usually delayed and is often the result of trauma or surgery. PAI-1 levels as low as 3% are sufficient for adequate hemostasis to occur. PAI-1 has a short plasma half-life of about ten minutes.

Schleef and colleagues in 1989 published the first account of an individual with PAI-1 deficiency and a history of clinical bleeding. (41) The gene for PAI-1 is located on chromosome 7, and the first patient with a homozygous genetic defect for PAI-1 deficiency was reported in 1992. (42) No true incidence rate has been determined. Communities displaying consanguinity due to close relative marriages show greater numbers of patients with PAI-1 deficiency, as is the case in Indiana, where a large kindred of Amish patients have been identified with the disorder, nine persons having homozygous deficiency and over 100 individuals heterozygous for the mutation. (43)

Diagnosis

Screening coagulation tests will be normal in patients with PAI-1 deficiency, and specific assays must be done to determine PAI-1 activity and antigen. Both activity and antigen levels must be essentially undetectable to diagnose homozygous PAI-1 deficiency.

Clinical Features

Delayed bleeding after surgery or trauma appears to be the hallmark of enhanced fibrinolytic disorders such as α_2-AP and PAI-1 deficiencies. Patients have been reported with trauma-induced intracranial hemorrhage, menorrhagia, and even hemarthrosis. (43) Easy bruising, epistaxis, and oral bleeding after dental work also have been reported.

Treatment

As in α_2-AP deficiency, antifibrinolytics are the treatment of choice for PAI-1 deficiency. ε-Aminocaproic acid and tranexamic acid have been used successfully in these disorders. The ε-aminocaproic acid dose is 100 milligrams per kilogram every six hours administered either orally or intravenously. The tranexamic acid dose is 7.5-10 milligrams per kilogram of body weight intravenously every 6-8 hours. (32, 40) The oral form has been approved in the US only for treatment of menorrhagia.

INHERITED PLATELET DISORDERS

Platelets play a major role in fibrin clot formation and as an initial responder to vascular damage. Mature platelets are usually small, disc-shaped cell fragments with a circulating lifespan of about 7-10 days. Whenever blood vessel injury occurs, platelets, with the assistance of von Willebrand factor (VWF), respond by lining the exposed subendothelium. Formation of a platelet plug occurs, while at the same time recruitment of other platelets and plasma proteins to the site of

injury ensues, resulting ultimately in development of an insoluble fibrin clot. Three distinct phases occur during this process: initiation, extension and cohesion. Inherited platelet defects have been identified in each of these phases. Although each inherited platelet disorder is unique in some way, similarities in approach to diagnosis, clinical features and treatment do exist. Given the numerous types of known inherited platelet function defects, only those most frequently encountered in the hematology setting will be discussed in this chapter.

Diagnosis

As with all diagnostic evaluations, a good history and physical exam must precede laboratory investigations. Once the history and physical have been completed, most platelet disorders are evaluated using several lab tests. Although previously employed as a standard screening tool for diagnosing platelet disorders, the bleeding time is rarely used anymore due to concerns related to the imprecise nature of the test. Individual bleeding times can vary in the same patient even when the same lab technician performs the test.

The complete blood count and differential and examination of a blood smear should be performed, as unique characteristics of some platelet defects may be visualized under the microscope. Platelet functional analyzer, designed to simulate primary hemostasis, has been shown to assist in diagnosing more severe forms of platelet defects, (44) however, a low sensitivity in detecting milder platelet disorders using the device has been reported. (45) Platelet aggregation and secretion studies have become very helpful in diagnosing platelet disorders. Using a light transmission approach, platelet-rich plasma is subjected to a number of exogenous platelet agonists to assess the ability of the patient's platelets to aggregate and secrete their own contents compared to known controls. Care must be taken to obviate improper results that may arise from anti-platelet medication use prior to sampling, diet-induced lipemia that may affect light transference, and mechanical testing concerns such as the size, shape, rate and type of stir bar used. Also of benefit has been the use of electron microscopy, which can evaluate platelet ultrastructure, cytoskeletal abnormalities, and platelet organelle (α- and δ-granule) absences or deficiencies.

Clinical Features

Mucocutaneous bleeding is the most frequent presentation in patients with inherited platelet function defects. Easy bruising, epistaxis, gum and oral bleeding, and petechiae may be seen in young children. In women, menorrhagia and post-partum hemorrhage can be problematic. Hematologic challenges such as trauma, surgery, and dental procedures may result in excessive bleeding in these patients. Phenotypic severity is often correlated with the severity of the inherited platelet disorder. Patients may develop iron-deficiency anemia due to repeated bleeding episodes.

Treatment

Hemorrhagic episodes in patients with heritable platelet defects are often treated based on the severity of the bleed, bleed location, and response to previous therapy. As with other congenital bleeding disorders, the goal of therapy is to minimize exposure to fresh blood components that have not been virally attenuated. Because there are no "man-made" platelet products available, patients with inherited platelet disorders may require platelet transfusions at some point in their life. Because of concerns with viral transmission, exogenous transfusion reactions, fluid volume overload, and allo-antibody formation, many clinicians prefer to use platelet transfusions as a last resort or for life- and limb-threatening bleeding.

For minor mucosal bleeding, such as epistaxis and mouth bleeds, antifibrinolytics can be used. In women with menorrhagia, hormonal suppression may be considered, both given orally and used as an intrauterine device (IUD), specifically a levonorgestrel-releasing IUD. Oral ε-aminocaproic acid and transexemic acid may also be helpful. Iron replacement may be necessary, because iron-deficiency anemia may be common in women with heavy menses associated with platelet function defects.

Other treatment modalities that have been used include DDAVP and rFVIIa, as an off-label therapy. Success of these therapies varies. DDAVP has been shown to shorten bleeding times in patients with platelet defects; since it is not blood-derived, its use eliminates viral transmission concerns and may forestall alloantibody formation. (46, 47) One concern with the use of DDAVP is dilutional hyponatremia associated with free-water retention, so fluid restriction for about 24 hours should be adhered to whenever using this medication. Use of DDAVP in children under 2 years of age should be avoided. (48) Several reports on the use of rFVIIa in patients with platelet disorders have been published, and licensure for its use in Glanzmann's thrombasthenia has been granted in Europe but not in the US. (49-51)

When needed to treat bleeding, platelet transfusions optimally should be single-donor, leukocyte-reduced or depleted, and HLA-matched. Apheresis units should be considered whenever possible to reduce multiple donor exposure. (52) In patients with severe forms of platelet function defects, hematopoietic stem cell transplantation (HSCT) has been reported to cure the disorder. (53)

Although platelet disorders have some characteristics in common, it is essential for the nurse caring for these patients to know the differences as well. Specific inherited platelet function defects will now be discussed and individual nuances highlighted.

PLATELET INITIATION (ADHESION) DEFECTS

BERNARD-SOULIER SYNDROME

Bernard-Soulier Syndrome (BSS) was first described by Doctors Jean Bernard and Jean-Pierre Soulier in 1948. (54) It is an autosomal recessive platelet function defect marked by macrothrombocytopenia (giant platelets in less than normal amounts) and mild to moderate

mucocutaneous bleeding. BSS is a platelet initiation, or adhesion, defect resulting from the absence of the membrane glycoprotein GP-Ib/IX/V receptor on platelets that allows for coupling with VWF and subsequent binding at sites of vascular damage. Besides macrothrombocytopenia seen under the microscope, BSS can be determined by platelet aggregation studies; BSS platelets show no response to ristocetin, an agonist that potentiates aggregation by stimulating VWF and platelet agglutination via the GP-Ib/IX/V receptor. Response to other agonists is normal.

PLATELET-TYPE VWD (PSEUDO-VWD OR PLT-VWD)

Defects in another platelet receptor, glycoprotein GP-Ibα (part of the GP-Ib/IX/V complex), have been identified that cause an increased affinity for VWF, leading to enhanced binding of VWF to platelets, which results in thrombocytopenia and decreased levels of circulating VWF multimers, much like VWD type 2B. This is in part attributed to the increased clearance of the VWF/platelet complex from circulation. Elevated mean platelet volume, or macrothrombocytopenia, also has been described in these patients and may be a distinguishing feature of this disorder as well. (55)

Differentiation of platelet-type VWD from VWD 2B can be achieved via low-dose ristocetin-induced platelet aggregation (RIPA) testing. Because the receptor defect is on the platelet surface rather than the VWF surface (as is the case for VWD 2B), platelet-type VWD blood samples will aggregate when challenged by low-dose ristocetin only when the patient's platelets are used during testing. Use of normal platelets during testing will show no increased affinity for VWF with low-dose ristocetin. Bleeding associated with platelet-type VWD is often mild to moderate in presentation. Of note, just as with VWD 2B, patients with platelet-type VWD should not be given DDAVP (which stimulates VWF release from endothelial cells) as a treatment modality due to the hyperaffinity between platelets and VWF, which may cause further thrombocytopenia.

PLATELET EXTENSION (SECRETION/ACTIVATION) DEFECTS

ALPHA (α)-GRANULE DEFICIENCY OR GRAY PLATELET SYNDROME

When visualized under the microscope, gray platelet syndrome (GPS) patients' platelets appear to have a grayish hue, hence the name of the disorder. It appears that α-granules are severely diminished or completely absent or else the contents of this platelet organelle are missing. Electron microscopy reveals either near absence of α-granules or their presence but an inability of their contents to be stained, most likely the result of packaging failure. (56) Macrothrombocytopenia is a hallmark of this disorder, and mucosal-type bleeding is usually mild to moderate in presentation. The disorder was first described in 1971. (57) GPS has been shown to be inherited in either an autosomal dominant or recessive fashion. (58, 59) Platelet aggregation testing typically demonstrates poor responses to several agonists: ADP, epinephrine, collagen and thrombin. (60)

DENSE GRANULE DEFICIENCY (DELTA (δ)-STORAGE POOL DISEASE)

The other major platelet organelle, the dense (or δ) granule, is the storage site of the adenosine phosphates ADP and ATP and serotonin, stimulants responsible for platelet aggregation. When these granules are absent in platelets, the result is dense granule deficiency, also referred to as δ-storage pool disease. The first case of dense granule deficiency was reported in 1972. (61) Platelet count is normal in these individuals; electron microscopy will aid in the detection of the missing dense granules. Aggregation and secretion studies demonstrate an impaired secondary wave when stimulated by ADP, epinephrine or thrombin. The disorder appears to be inherited in an autosomal dominant pattern. Bleeding is generally mild to moderate in severity and often can be treated using DDAVP, rFVIIa, or in more severe hemorrhage, with platelet transfusion.

HERMANSKY-PUDLAK SYNDROME

A second type of dense granule deficiency with other associated non-bleeding clinical symptoms is called Hermansky-Pudlak Syndrome (HPS). Frantisek Hermansky and Paulus Pudlak, two Czechoslovakian physicians, first described the condition in 1959. (62) Oculocutaneous albinism is the most common characteristic in these patients, and granulomatous colitis, pulmonary fibrosis and renal failure may occur as well. This autosomal recessive inherited disorder (gene located on chromosome 10) has two rather large patient populations: one Swiss, the other Puerto Rican. Prevalence in these populations is much higher than in the general population. (63) Interestingly, the Swiss cohort of patients shows normal life expectancy, whereas those patients from Puerto Rico exhibit a shortened life span, most likely the result of pulmonary fibrosis and renal failure. (63) Platelet count is normal, but electron microscopy reveals absence of dense granules. Platelet aggregation studies yield similar results in these patients as those with isolated dense granule deficiency. Likewise, bleeding manifestations and treatment are similar between the two disorders.

CHEDIAK-HIGASHI SYNDROME

Another disorder characterized by dense granule deficiency and oculocutaneous albinism is Chediak-Higashi Syndrome (CHS). Other clinical features in CHS patients include neutropenia and immunodeficiency that often result in pyogenic infections and lymphohistiocytic infiltrations; these lead to neurologic impairment that arises early in life and progresses with age. Most patients die of overwhelming infections or lymphoproliferative disease before their third decade of life. The disorder, first described by Cuban physician Antonio Béguez-César (1943) and German physician Walter Steinbrinck (1948), and later characterized by Alexander Moisés Chediak (1952) and Otokata Higashi (1954), is inherited as an autosomal recessive trait, and the gene is located on chromosome 1. (64) Treatment of bleeding, usually mild, is achieved using platelet transfusions. Hematopoietic stem cell transplantation (HSCT) has been successful in ameliorating the hematologic portion of the disease, however, the neurologic symptoms associated with CHS continue to progress. (65)

WISKOTT-ALDRICH SYNDROME

A third disorder in which dense granules are deficient is an X-linked condition known as Wiskott-Aldrich Syndrome (WAS). The condition was first described by Alfred Wiskott in 1937 and later shown to be X-linked in inheritance by Robert Aldrich in 1954. (66) Microthrombocytopenia (small platelets in diminished numbers) occurs in WAS, and bleeding from the disorder may be moderate to severe in nature. The condition also is associated with eczema, immunodeficiency, autoimmune hemolytic anemia and, developing later in life, lymphoma. Because thrombocytopenia can be severe in WAS patients, splenectomy has been performed, however, although the platelet count may correct, post-surgical infection can be fatal due to the underlying immunodeficiency. Allogeneic HSCT has been successful at curing the disease and should be considered given the high morbidity and mortality associated with WAS. (67)

PLATELET COHESION (AGGREGATION) DEFECTS

GLANZMANN'S THROMBASTHENIA

Eduard Glanzmann, in 1918, described one of the first inherited platelet disorders in patients suffering from mucocutaneous bleeding that he referred to as "thrombasthenie", or weak platelets. (68) The gene mutation of Glanzmann's Thrombasthenia (GT) has been identified on chromosome 17, and the defect is inherited as an autosomal recessive disorder. The functional defect occurs with the platelet membrane glycoprotein GP IIb/IIIa, which is required for platelet-platelet interaction. Fibrinogen bridging occurs in this interaction as well, and when the GP IIb/IIIa receptor is missing, bleeding can be quite severe. Although the platelet count is normal, aggregation testing shows no response to any agonists except ristocetin, as platelet initiation (adhesion) is unaffected in GT patients. Bleeding may be so severe and life-threatening, even from what may be considered benign sites such as epistaxis, that treatment may require HSCT as a cure. (53) DDAVP, rFVIIa, and platelet transfusions may be successful in treating less severe forms of bleeding.

OTHER INHERITED PLATELET DEFECTS

MAY-HEGGLIN ANOMALY

Physicians Richard May (1909) and Robert Hegglin (1945) are credited with the first descriptions of May-Hegglin Anomaly (MHA), a disorder of platelets in which macrothrombocytopenia and leukocyte inclusions (Döhle bodies) are identified under the microscope. (69, 70) Bleeding phenotype often is mild (easy bruisability, epistaxis and menorrhagia), and almost half of identified patients may have no symptoms. Treatment of severe bleeds requires platelet transfusions. The gene defect for MHA is located on chromosome 22, and autosomal dominant inheritance has been established in patients with the disorder. This gene, referred to as MYH9, has been shown to be affected in several other inherited conditions

associated with macrothrombocytopenia and varying degrees of hearing loss, nephritis and cataracts. These include Fechtner, Sebastian and Epstein Syndromes. (71)

OTHER INHERITED DISORDERS ASSOCIATED WITH BLEEDING

Bleeding, as we have seen, may result from a number of inherited conditions of procoagulant plasma proteins, fibrinolysis inhibitors, and platelets. Two disorders, one involving abnormal blood vessel formation, the other a connective tissue disorder, which may present with increased risk of bleeding, have also been identified.

HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER-WEBER-RENDU SYNDROME)

Three physicians, Henri Rendu, Sir William Osler and Frederick Weber, have been credited with discovery and description of cases of patients with Hereditary Hemorrhagic Telangiectasia (HHT). (72-74) Typically, examination of these patients reveals skin or mucosal lesions (telangiectasias) of small blood vessels; they may also have large abnormal vessels [arteriovenous malformations (AVMs)] within several organs of the body: lungs, liver, brain or spinal cord. HHT lesions do not involute naturally as infantile hemangiomas do but continue to grow as patients age, possibly the result of high levels of circulating vascular endothelial cell growth factor (VEGF). Telangiectasias occur most frequently in the nose (90-95%); skin, oral mucosa or lips (80%); and intestines (20%). (75) Bleeding from these sites can be mild to severe in presentation. AVMs occur most frequently in the following organs: lungs, liver and brain. Bleeding into any of these organs can be life-threatening. Diagnosis involves positive family history, visible findings of skin telangiectasias on examination, and imaging of affected organs. Treatment is often symptomatic and may involve the use of topical hemostatic agents, nasal cautery, embolization, hormonal suppression, and iron replacement if anemia develops. Severe bleeding may require blood transfusions as well. (76)

EHLERS-DANLOS SYNDROME

Ehlers-Danlos Syndrome (EDS) is comprised of a number of heritable connective tissue disorders manifested by joint hypermobility, skin hyperelasticity, hypertrophic scarring, and blood vessel fragility. This disorder may be inherited in both autosomal dominant and recessive fashions. EDS has been classified into six categories based on the preponderance of different symptoms. Easy bruising is the most common bleeding presentation, but patients may exhibit spontaneous joint subluxations and poor wound healing following surgery or trauma. Kyphoscoliosis, mitral valve prolapse, aortic dilatation, and arthrochalasia also may be present in different classifications of EDS. Diagnosis involves positive family history, positive physical findings, and in some cases, genetic mutation analysis. Skin biopsies that test for collagen disorders have been used. Treatment for bleeding in EDS patients includes the use of antifibrinolytics, DDAVP, and rFVIIa (off-label). (77, 78) Most treatment for EDS is geared toward prevention of problems and may include, among other things, bracing of joints, physiotherapy, rest, and avoidance of surgery where possible.

CONCLUSION

The rare coagulopathies discussed in this chapter, as you can see, pose problems for patients and healthcare professionals alike. Diagnosis, treatment, and education of rare disorders lag behind those for patients with hemophilia. Diagnosis, oftentimes difficult in the rare disorders, needs to be done sequentially and must take into account recent use of blood products, treatments or other concerns that may interfere with testing. Research and development of newer products are beginning to bridge the treatment gap, although some disorders are so rare that a recombinant therapy may never be realized. A paucity of patient educational information exists for many of the very rare disorders. Clinical research must be conducted so that comprehensive care team members can provide the same level of evidence-based service afforded to the more common hypocoagulopathies. Knowledge of the clinical features, diagnosis and treatment of rare bleeding diatheses is essential for the bleeding disorders nurse and will help lead to safe, competent and compassionate care for patients affected by these conditions.

REFERENCES

1. Medical and Scientific Advisory Council of the National Hemophilia Foundation. ***MASAC Recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders.*** **Medical and Scientific Advisory Council Recommendation #215, November 2012.**

2. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. *Blood* 2004; 104: 1243-1252.

3. Rabe F, Salomon E. Uber Faserstoffmangel im Blut bei einem Falle von Hamophilie. ***Dtsch Arch Klin Med*** 1920; 132: 240-244.

4. Bolton-Maggs PHB, Perry DJ, Chalmers A, et al. The rare coagulation disorders – Review with guidelines for management from the United Kingdom Haemophilia Centre Doctor's Organization. ***Haemophilia*** 2004; 10: 593-628.

5. Peyvandi F, Haertel S, Knaub S, Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J Thromb Haemost* 2006; 4(7): 1634-1637.

6. Acharya SS, DiMichele DM. Rare inherited disorders of fibrinogen. *Haemophilia* 2008; 14(6): 1151-1158.

7. Roberts HR, Escobar MA. Other coagulation deficiencies. In: Loscalzo J, Shafer AI, eds. *Thrombosis and Hemorrhage*. Baltimore: Williams & Wilkins; 2003: 575-598.

8. Bolton-Maggs P. The rare coagulation disorders. In: Schulman S, ed. *Treatment of Hemophilia*. Montreal: World Federation of Hemophilia 2006; 39: 1-12.

9. Quick AJ. Congenital hypoprothrombinemia and pseudohypoprothrombinemia. ***Lancet*** 1947; 2: 379-382.

10. Peyvandi F, Mannucci PM. Rare coagulation disorders. *Thromb Haemost* 1999; 82: 1207-1214.

11. Meeks SL, Abshire TC. Abnormalities of prothrombin: a review of the pathophysiology, diagnosis and treatment. *Haemophilia* 2008; 14: 1159-1163.

12. Lobel J, Majumdar S, Kovats-Bell S. Successful prophylactic treatment for bleeding in a girl with severe hereditary prothrombin deficiency using a prothrombin complex concentrate (Bebulin(R) VH). ***J Pediatr Hematol Oncol*** 2004; 26: 480-483.

13. Quick AJ. On the constitution of prothrombin. ***Am J Physiol*** 1943; 140: 212.

14. Owren PA. The coagulation of blood: Investigations on a new clotting factor. ***Acta Med Scand*** 1947; 194: 11-41.

15. Zhang B. Recent developments in the understanding of the combined deficiency of FV and FVIII. *Br J Haemotol* 2009: 145(1): 15-23.

16. Alexander B, Goldstein R, Landwehr G, Cook CD. Congenital SPCA deficiency: A hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. ***J Clin Invest*** 1951; 30: 596-606.

17. Mariani G, Bernardi F. Factor VII deficiency. ***Semin Thromb Hemost*** 2009; 35: 400-406.

18. Marty S, Barro C, Chatelain B, et al. The paradoxical association between inherited factor VII deficiency and venous thrombosis. ***Haemophilia*** 2008; 14: 564-570.

19. Mariani G, Konkle BA, Ingerslev J. Congenital factor VII deficiency: therapy with recombinant activated factor VII – a critical appraisal. ***Haemophilia*** 2006; 12: 19-27.

20. Mathijssen NCJ, Masereeuw R, Verbeek K *et al.* Prophylactic effect of recombinant factor VIIa in factor VII deficient patients. ***Br J Haematol*** 2004*;* **125***:* 494–*4*99.

21. Dewerchin M, Liang Z, Moons L, et al. Blood coagulation factor X deficiency causes partial embryonic lethality and fatal neonatal bleeding in mice. ***Thromb Haemost*** 2000; 83: 185-190.

22. Hougie C, Barrow EM, Graham JB. Stuart clotting defect I. Segregation of an hereditary hemorrhagic state from the heterogeneous group heretofore called "stable factor" (SPCA, proconvertin, factor VII) deficiency. ***J Clin Invest*** 1957; 36: 485-496.

23. Telfer TP, Denson KW, Wright DR. A "new" coagulation defect. ***Br J Haematol*** 1956; 2: 308-316.

24. Rosenthal RL, Dreskin OH, Rosenthal N. New hemophilia-like disease caused by deficiency of a third plasma thromboplastin factor. ***Proc Soc Exp Biol Med*** 1953; 82: 171-174.

25. Seligsohn U. High gene frequency of factor XI (PTA) deficiency in Ashkenazi Jews. ***Blood*** 1978; 51: 1223-1228.

26. Seligsohn U, Bolton-Maggs P. Factor XI deficiency. In: Lee CA, Berntorp EE, Hoots WK, eds. ***Textbook of Hemophilia, Second Edition.*** Oxford, UK: Wiley-Blackwell; 2010: 356-361.

27. Kitchens CS. The contact system. ***Arch Pathol Lab Med*** 2002; 126: 1382-1386.

28. Ratnoff OD, Colopy JE. A familial hemorrhagic trait associated with a deficiency of a clot-promoting fraction of plasma. ***J Clin Invest*** 1954; 34: 602-613.

29. Ratnoff OD, Margolius A. Hageman trait: an asymptomatic disorder of blood coagulation. ***Trans Assoc Am Physicians*** 1955; 68: 149–54.

30. Gordon EM, Donaldson VH, Saito H, et al. Reduced titers of Hageman factor (factor XII) in Orientals. ***Ann Intern Med*** 1981; 95: 697-700.

31. Halbmayer WM, Haushofer A, Schön R, et al. The prevalence of moderate and severe FXII (Hageman factor) deficiency among the normal population: Evaluation of the incidence of FXII deficiency among 300 healthy blood donors. ***Thromb Haemost*** 1994; 71: 68-72.

32. Roberts HR, Escobar MA. Less common congenital disorders of hemostasis. In: Kitchens CS, Alving BA, Kessler CM, eds. ***Consultative Hemostasis and Thrombosis, Second Edition***. Philadelphia: Saunders; 2007: 61-79.

33. Hsieh L, Nugent D. Factor XIII deficiency. ***Haemophilia*** 2008; 14: 1190-1200.

34. Robbins KC. A study on the conversion of fibrinogen to fibrin. ***Am J Physiol*** 1944; 142: 581-588.

35. Laki K, Lorand L. On the solubility of fibrin clots. ***Science*** 1948; 108: 280.

36. Duckert F, Jung E, Shmerling DH. A hitherto undescribed congenital haemorrhagic diathesis probably due to fibrin stabilizing factor deficiency. ***Thromb Diath Haemorrh*** 1960; 5: 179-186.

37. Board PG, Losowsky MS, Miloszewski KJA. Factor XIII: inherited and acquired deficiency. ***Blood Rev*** 1993; 7: 229-242.

38. Duckert F. Documentation of the plasma factor XIII deficiency in man. ***Ann N Y Acad Sci*** 1972; 202: 190-199.

39. CSL Behring product package insert - Corifact®.

40. Carpenter SL, Mathew P. α_2-Antiplasmin and its deficiency: fibrinolysis out of balance. ***Haemophilia*** 2008; 14: 1250-1254.

41. Schleef RR, Higgins DL, Pillemer E, Levitt LJ. Bleeding diathesis due to decreased functional activity of type 1 plasminogen activator inhibitor. ***J Clin Invest*** 1989; 83: 1747-1752.

42. Fay WP, Shapiro AD, Shih JL, et al. Brief report: complete deficiency of plasminogen-activator inhibitor type 1 due to a frame shift mutation. ***N Engl J Med*** 1992; 327: 1729-1733.

43. Mehta R, Shapiro AD. Plasminogen activator inhibitor type 1 deficiency. ***Haemophilia*** 2008; 14: 1255-1260.

44. Harrison P. The role of PFA-100 testing in the investigation and management of haemostatic defects in children and adults. ***Br J Haematol*** 2005; 130: 3-10.

45. Quiroga T, Goycoolea M, Munoz B, et al. Template bleeding time and PFA-100 have low sensitivity to screen patients with hereditary mucocutaneous hemorrhages: Comparative study in 148 patients. ***J Thromb Haemost*** 2004; 2: 892-898.

46. DiMichele DM, Hathaway WE. Use of DDAVP in inherited and acquired platelet dysfunction. ***Am J Hematol*** 1990; 33: 39.

47. Rao AK, Ghosh S, Sum L, et al. Mechanisms of platelet dysfunction and response to DDAVP in patients with congenital platelet function defects. A double-blind placebo controlled trial. ***Thromb Haemost*** 1995; 74: 1071.

48. Das P, Carcao M, Hitzler J. DDAVP-induced hyponatremia in young children**.** ***J Pediatr Hematol Oncol*** 2005; 27: 330-332.

49. Poon MC. The evidence for the use of recombinant human activated factor VII in the treatment of bleeding patients with quantitative and qualitative platelet disorders. ***Transfus Med Rev*** 2007; 3: 223-236.

50. Franchini M, Lippi G, Guidi GC. The use of recombinant activated factor VII in platelet-associated bleeding. ***Hematology*** 2008; 13: 41-45.

51. Almeida AM, Khair K, Hann I, Liesner R. The use of recombinant factor VIIa in children with inherited platelet function disorders. ***Br J Haematol*** 2003; 121: 477-481.

52. Simon D, Kunicki T, Nugent D. Platelet function defects. ***Haemophilia*** 2008; 14: 1240-1249.

53. Ishaqi MK, El-Hayek M, Gassas A, et al. Allogeneic stem cell transplantation for Glanzmann thrombasthenia. ***Ped Blood and Cancer*** 2009; 52: 682-683.

54. Bernard J, Soulier JP. Sur une nouvelle variété de dystrophie thrombocytaire-hémorragipare congénitale. ***Semin Hop Paris*** 1948; 24: 3217.

55. Nurden P, Nurden AT. Congenital disorders associated with platelet dysfunctions. ***Thromb Haemost*** 2008; 99: 253-263.

56. Gebrane-Younes J, Cramer EM, Orcel L, et al. Gray platelet syndrome: dissociation between abnormal sorting in megakaryocyte alpha-granules and normal sorting in Weibel-Palade bodies of endothelial cells. ***J Clin Invest*** 1993; 92: 3023-3028.

57. Raccuglia G. Gray platelet syndrome. A variety of qualitative platelet disorder. ***Am J Med*** 1971; 51: 818-828.

58. Mori K, Suzuki S, Sugai K. Electron microscopic and functional studies on platelets in gray platelet syndrome. ***Tohoku J Exp Med*** 1984; 143: 261-287.

59. Falik-Zaccai TC, Anikster Y, Rivera CE, et al. A new genetic isolate of gray platelet syndrome (GPS): Clinical, cellular, and hematologic characteristics. ***Mol Genet Metab*** 2001; 74: 303-313.

60. Nurden AT, Nurden P. The gray platelet syndrome: clinical spectrum of the disease. ***Blood Rev*** 2007; 21: 21-36.

61. Nieuwenhuis HK, Akkerman JW, Sixma JJ. Patients with prolonged bleeding time and normal aggregation tests may have storage pool deficiency: studies on one hundred six patients. ***Blood*** 1987; 70: 620-623.

62. Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959; 14: 162–169.

63. Schallreuter KU, Frenk E, Wolfe LS, et al. Hermansky-Pudlak syndrome in a Swiss population. ***Dermatology*** 1993; 187: 248-256.

64. Fatima S, Siddiqui WA, Ansari MA. Chediak-Higashi syndrome: a rare clinical entity revisited. ***JIACM*** 2010; 11: 144-145.

65. Tardieu M, Lacroix C, Neven B, et al. Progressive neurologic dysfunctions 20 years after allogeneic bone marrow transplantation for Chediak-Higashi syndrome. ***Blood*** 2005; 106: 40-42.

66. Burgio GR. The Wiskott-Aldrich syndrome. ***Eur J Pediatr*** 1995; 154: 261-262.

67. Ochs HD. The Wiskott-Aldrich syndrome. ***Clin Rev Allergy Immunol*** 2001; 20: 61-86.

68. Stevens RF, Meyer S. Historical review: Fanconi and Glanzmann: the men and their works. ***Br J Haematol*** 2002; 119: 901-904.

69. May R. Leukocyteneinschlüsse. Kasuistische Mitteilung. ***Deutsches Archiv für klinische Medizin, Leipzig***, 1909; 96: 1-6.

70. Hegglin R. Über eine neue Form einer konstitutionellen Leukozytenanomalie, kombiniert mit Thrombopathie. ***Schweizerische medizinische Wochenschrift, Basel***, 1945; 75: 91-92.

71. Seri M, Pecci A, Di Bari F, et al. MYH9-related disease: May-Hegglin anomaly, Sebastian syndrome, Fechtner syndrome and Epstein syndrome are not distinct entities but represent a variable expression of a single illness. ***Medicine (Baltimore)*** 2003; 82: 203-215.

72. Rendu HJ. Épistaxis répétées chez un sujet porteur de petits angiomes cutanés et muqueux. ***Gaz Hop*** 1896; 1322-1323.

73. Osler W. On a family form of recurring epistaxis, associated with multiple telangiectases of the skin and mucous membranes. ***Bull Johns Hopkins Hosp*** 1901; 12: 333-337.

74. Weber FP. Multiple hereditary developmental angiomata (telangiectases) of the skin and mucous membranes associated with recurrent haemorrhages. Lancet 1907; 2: 160-162.

75. Dupuis-Girod S, Bailly S, Plauchu H. Hereditary hemorrhagic telangiectasia (HHT): from molecular biology to patient care. ***J Thromb Haemost*** 2010; 8: 1447–1456.

76. Sabba C. A rare and misdiagnosed bleeding disorder: Hereditary hemorrhagic telangiectasia. ***J Thromb Haemost*** 2005; 3: 2201-2210.

77. Rochelson B, Caruso R, Davenport D, Kaelber A. The use of prophylactic desmopressin (DDAVP) in labor to prevent hemorrhage in a patient with Ehlers-Danlos syndrome. ***N Y State J Med*** 1991; 91: 268-269.

78. Faber P, Craig WL, Duncan JL, Holliday K. The successful use of recombinant factor VIIa in a patient with vascular-type Ehlers-Danlos syndrome. ***Acta Anaesthesiol Scand*** 2007; 9: 1277-1279.