Bleeding Disorders: Insights into Aetiology, Pathogenesis, Diagnosis and Management

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Abstract **Background:** Coagulation plays an important role in haemostasis. Bleeding disorders caused by deficiency of certain coagulation factors such as hemophilia and Von Willebrand disease can affect haemostasis and may endanger life. **Aim:** To put a focus on the aetiology, pathogenesis, methods of diagnosis and lines of management of bleeding disorders. **Conclusion:** Bleeding disorders usually result from hereditary deficiency of certain coagulation factors. These disorders often affect lifestyle of the patient and may have serious complications. Further studies are needed to explore the exact pathogenesis of these disorders and new lines of management especially for gene therapy.

Cite This Article: **Ahmed M** Kabel, "Bleeding Disorders: Insights into Aetiology, Pathogenesis, Diagnosis and Management." *International Journal of Hematological Disorders*, vol. 1, no. 1 (2014): 22-26. doi: 10.12691/ijhd-1-1-4.

1. Introduction

Coagulation is the process by which blood forms clots. It is an important part of hemostasis where in a damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel. Disorders of coagulation can lead to an increased risk of bleeding or thrombosis [1]. Coagulation involves both cellular (platelets) and protein (coagulation factors) component. The system in humans has been the most extensively researched and is the best understood [2].

Bleeding disorders are often caused by failure of the blood to clot. Several conditions can affect the way the blood clots. Many causes are related to protein defects in the plasma. These proteins are directly responsible for how the blood coagulates. The majority of these defects are hereditary. However, some may develop due to other medical conditions like liver disease, vitamin K deficiency and medication side-effects. The most common coagulation defects are factor VIII, IX, XI and Von Willebrand [3].

2. Epidemiology of Bleeding Disorders

Hemophilia A is the most common X-linked genetic disease and the second most common factor deficiency after von Willebrand disease (vWD). The worldwide incidence of hemophilia A is approximately 1 case per 5000 male individuals, with approximately one third of affected individuals not having a family history. The prevalence of hemophilia A is 20.6 cases per 100,000 male individuals, with 60% of those having severe disease [4]. Hemophilia B is estimated to be approximately 1 case per 25,000-30,000 male births. The prevalence of hemophilia B is 5.3 cases per 100,000 male individuals, with 44% of those having severe disease. Hemophilia B is much less common than hemophilia A. Of all hemophilia cases, 80-85% are hemophilia A, 14% are hemophilia B, and the remainder are various other clotting abnormalities [5].

Because hemophilia is an X-linked, recessive condition, it occurs predominantly in males. Females usually are asymptomatic carriers. However, mild hemophilia may be more common in carriers than previously recognized [5]. Hemophilia C (severe form) occurs with an estimated prevalence of 1 case per 100,000 population in the United States, a rate that makes hemophilia A 10 times more common than hemophilia C. factor XI deficiency is more common than factor IX deficiency (hemophilia B) [6]. Clinically significant VWD affects approximately 125 persons per million populations, with severe disease affecting approximately 0.5-5 persons per million populations. Males and females are affected equally by VWD [7].

3. Aetiology of Bleeding Disorders

The majority of bleeding disorders are hereditary (passed from parent to child through genes). However, some may develop due to other medical conditions like liver disease, vitamin K deficiency and medication side-effects [3]. Hemophilia A is caused by an inherited or

acquired genetic mutation or an acquired factor VIII inhibitor. The defect results in insufficient generation of thrombin by the FIXa and FVIIIa complex by means of the intrinsic pathway of the coagulation cascade. This mechanism, in combination with the effect of the tissue-factor pathway inhibitor, creates an extraordinary tendency for spontaneous bleeding. This disorder is inherited in an X-linked recessive pattern [8]. The gene for FVIII is located on the long arm of the X chromosome in band q28. Numerous mutations in gene structure have been described. Genetic abnormalities include genetic deletions of variable size, abnormalities with stop codons, and frame-shift defects [1].

Hemophilia B is an X-linked recessive disease caused by an inherited or acquired mutation in the FIX gene or by an acquired factor IX inhibitor. The gene for FIX is located on the long arm of the X chromosome in band q27. Several hundred mutations with different amino acid substitutes have been described in hemophilia B [8]. These mutations include partial and total deletions, missense mutations, and others that result in the decreased or absent production of FIX or the production of an abnormal protein. The defect results in the insufficient generation of thrombin by the FIXa and FVIIIa complex by means of the intrinsic pathway of the coagulation cascade. This mechanism, in combination with the effect of the tissue-factor pathway inhibitor, creates an extraordinary tendency for spontaneous bleeding [5].

The severity of hemophilia C is based on plasma factor XI activity. Severe factor XI deficiency is present when the activity of factor XI in plasma is less than 1-15 IU/dL. Factor XI is a dimeric serine protease, which activates factor IX in the original intrinsic pathway of blood coagulation. Also, thrombin directly activates factor XI, and this direct activation may be more important than the activation due to factor XII. Recently, it has been shown that thrombin activation of factor XI is triggered by polyphosphate release from activated platelets. These molecules provide a template for assembly of factor XI and factor IX [9].

With the exception of a rare, acquired form of VWD, caused by antibodies to VWF, VWD is an inherited condition. The VWF gene is located near the tip of the short arm of chromosome 12. The gene is similar in size to the FVIII gene. Expression of the VWF gene is restricted to megakaryocytes, endothelial cells, and, possibly, placental syncytiotrophoblasts [10]. VWD type I is due to mild to moderate quantitative deficiency of vWF (20-50% of normal levels). VWD type II is due to qualitative VWF abnormalities and is subdivided into types IIA, IIB, IIN, and IIM [11]. VWD type III appears to result from the inheritance of a mutant VWF gene from both parents. VWD type I simply represents the heterozygous form of VWD type III; however, inheritance patterns indicate greater complexity [12].

4. Pathophysiology of Bleeding Disorders

Factors deficiency, factor dysfunction or factor inhibitors lead to disruption of the normal intrinsic coagulation cascade, resulting in spontaneous hemorrhage and/or excessive hemorrhage in response to trauma. Hemorrhage sites include joints, muscles, central nervous system, gastrointestinal, genitourinary, pulmonary and cardiovascular systems. Intracranial hemorrhage is most common in patients younger than 18 years and can be fatal. The gene for FVIII is located on the long arm of chromosome X. Approximately 40% of cases of severe FVIII deficiency arise from a large inversion that disrupts the FVIII gene. Deletions, insertions, and point mutations account for the remaining 50-60% of hemophilia A defects. Low FVIII levels may arise from defects outside the FVIII gene, as in type IIN von Willebrand disease, in which the molecular defect resides in the FVIII-binding domain of von Willebrand factor [13].

Mutations in the factor XI gene cause the congenital deficiency of factor XI clotting activity. The inheritance pattern of factor XI is autosomal but not completely recessive, because heterozygotes may have bleeding. The gene for factor XI is near the gene for prekallikrein on the distal arm of chromosome 4 (4q35). It is 23 kb, with 15 exons and 14 introns. Factor XI is synthesized in the liver and circulates in the plasma as a complex with high-molecular-weight kininogen. Factor XI has a half-life of about 52 hours [14].

The development of inhibitors was seen in about 30% of patients with severe haemophilia A and up to 5% of those with severe haemophilia B [15]. Clinically, FVIII and FIX inhibitors behave differently as the latter are often associated with increased frequency of allergic reactions and with development of nephrosis [16]. Factor VIII inhibitors mainly bind to the FVIII A2, A3 and C2 domains and interfere with binding of the Xase complex, to von Willebrand factor and phospholipids. Inhibitors are generally categorized according to their response type upon challenge with FVIII/IX. Most inhibitors are sustained, although they usually decrease to a lower level if the immune system is not challenged. In a few cases, the inhibitor is transient and disappears within 6 months [17]. Inhibitors may also be classified according to their kinetics: Type I with fast kinetics and strong binding; and Type II with slower kinetics and a weaker association with the FVIII molecule. The latter type is typical for acquired haemophilia but also observed in mild and moderate congenital haemophilia [18].

The risk of inhibitor development is determined by the interaction between environmental and genetic factors. The risk of inhibitor development is clearly higher in the presence of mutations that result in no or truncated protein, whereas point mutations are associated with a lower risk [19]. So, inhibitors are more prevalent in severe haemophilia compared to mild/moderate disease, where trace amounts of protein cause immune tolerization in the patient [20]. Polymorphisms in immune regulatory genes, such as interleukin-10 and TNF-α and in HLA class II genes are also associated with increased risk of, or protection against, inhibitor development [21,22].

A number of environmental factors have been proposed to be related to the risk of inhibitor development. It has been suggested that the type of replacement product used is of importance. Recombinant FVIII confers a higher risk for inhibitor development than plasma-derived VWF-containing products [23]. Another, more recent, hypothesis is the so-called 'danger theory', in which it has been suggested that the risk of inhibitor development is increased when treating patients with high doses of concentrate, especially in conjunction with inflammatory

processes [24]. So, the genetic predisposition towards inhibitor development and the complex interaction between genes and environmental factors determine whether or not an inhibitor will develop [25].

5. Clinical Presentation of Bleeding Disorders

Family history of bleeding following surgery or injury, or unexplained deaths among brothers, sisters, or other male relatives should be considered to see if bleeding disorder was a cause. A sample of blood can be drawn from the umbilical cord immediately after birth and tested to determine the level of the clotting factors [26]. About one-third of babies who are diagnosed with bleeding disorders have no other family members with the disorder. A doctor might check for bleeding disorders in a newborn if bleeding after circumcision of the penis goes on for a long time, bleeding goes on for a long time after drawing blood and heel sticks or bleeding in the head after a difficult delivery or after using special devices or instruments to help deliver the baby [27]. If a child is not diagnosed with hemophilia during neonatal period, the family might notice unusual bruising once the child begins standing or crawling. Those with severe hemophilia can have serious bleeding problems right away. Thus, they often are diagnosed during the first year of life. People with milder forms of hemophilia might not be diagnosed until later in life [28].

Depending on the level of factor activity, patients with bleeding disorders may present with easy bruising, inadequate clotting of traumatic injury or in the case of severe bleeding disorders spontaneous hemorrhage [29]. Signs of hemorrhage include general (Weakness, orthostasis, tachycardia, tachypnea), musculoskeletal (Tingling, warmth, pain, stiffness, and refusal to use joint), CNS (Headache, stiff neck, vomiting, lethargy, irritability, and spinal cord syndromes), gastrointestinal (Hematemesis, melena, frank red blood per rectum, and abdominal pain), genitourinary (Hematuria, renal colic, and post circumcision bleeding) [27]. Women can present with menorrhagia or with bleeding related to childbirth or gynecologic surgery specialy in hemophilia C [14]. There may also be signs and symptoms of infectious disease related to HIV/AIDS or hepatitis [30].

The hallmark of hemophilia is hemorrhage into the joints. This bleeding is painful and leads to long-term inflammation and deterioration of the joint (typically the ankles in children, and the ankles, knees, and elbows in adolescents and adults), resulting in permanent deformities, loss of mobility, and extremities of unequal lengths. With mild hemophilia, hemorrhage is most likely to occur with trauma or surgery. A traumatic challenge relatively late in life may have to occur before mild or moderate hemophilia is suspected [31].

6. Diagnosis of bleeding disorders

6.1. Clinical Diagnosis

Bleeding goes on for a long time, Bleeding after circumcision, Unusual raised bruises, hemorrhage into the joints mostly raise the suspicion of bleeding disorders which need more laboratory and imaging studies [7].

6.2. Laboratory Tests

Laboratory studies for suspected bleeding disorders include complete blood cell count, coagulation studies [32], screening tests for HIV and hepatitis, genetic carrier and fetal testing [29].

6.3. Imaging Studies

After initiating coagulation therapy, perform early and aggressive imaging, even when there is a low suspicion for hemorrhage. Imaging choices are guided by clinical suspicion and the anatomic location of involvement, such as head computed tomography scanning (To assess for spontaneous or traumatic intracranial hemorrhage), magnetic resonance imaging (To further evaluate hemorrhage in the head or spinal column and to assess cartilage, synovia, and joint spaces) ultrasonography (To assess joints affected by acute or chronic effusions and to assess intraperitoneal bleeding), upper and lower endoscopy in suspected gasterointestinal bleeding [28].

7. Management of Bleeding Disorders

7.1. Prophylactic Management

The immunization of patients with bleeding disorders differs from that of the normal population with respect to the risk of haematoma formation at the vaccination site and the unusual infective risks associated with the potential exposure to blood products. Most vaccinations can be given subcutaneously and this should be the preferred route. All routine childhood vaccinations should be given at the appropriate time. All patients with bleeding disorders should be vaccinated against hepatitis A and B. HIV positive patients should receive annual influenza vaccinations and should avoid the oral polio, oral typhoid, BCG and yellow fever vaccines [30]. Drugs that affect platelet function, particularly acetylsalicylic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitors, should be avoided. Paracetamol/acetaminophen is a safe alternative for analgesia [33].

7.2. Symptomatic Management

The primary aim of care is to prevent and treat bleeding with the deficient clotting factor. Whenever possible, specific factor deficiency should be treated with specific factor concentrate [5]. People with bleeding disorders are best managed in a comprehensive care centers. Acute bleeds should be treated as quickly as possible, preferably within two hours. Patients usually recognize early symptoms of bleeding even before the manifestation of physical signs. This is often described as a tingling sensation or aura [34]. During an episode of acute bleeding, an assessment should be performed to identify the site of bleeding (if not clinically obvious) and appropriate clotting factor should be administered [5]. In severe bleeding episodes that are potentially life-threatening, especially in the head, neck, chest, and gastrointestinal

tract, treatment with factor should be initiated immediately, even before diagnostic assessment is completed [3].

To facilitate appropriate management in emergency situations, all patients should carry easily accessible identification indicating the diagnosis, severity of the bleeding disorder, inhibitor status, type of treatment product used, initial dosage for treatment of severe, moderate, and mild bleeding, and contact information of treating physician. In addition to increasing factor level with clotting factor concentrates or desmopressin in mild hemophilia A (Administration of desmopressin (DDAVP) can raise FVIII level adequately to control bleeding in patients with mild, and possibly moderate, hemophilia A), protection (splint), rest, ice, compression, and elevation may be used as adjunctive management for bleeding in muscles and joints [35].

Plasma is used to correct deficiencies of clotting factors, for which a specific concentrate is not available, in patients with active bleeding. The products available are fresh-frozen plasma (FFP) that contains normal levels of the stable clotting factors, albumin and immunoglobulins. It contains at least 70% of the original coagulant factor VIII and at least similar quantities of the other labile clotting factors and natural inhibitors of coagulation. FFP for clinical use must not contain clinically significant irregular anti-erythrocyte antibodies. In order to increase its safety, FFP can be quarantined for a minimum period of 4 months [36].

Antifibrinolytic drugs (e.g. tranexamic acid, epsilon aminocaproic acid) are effective as adjunctive treatment for mucosal bleeds and dental extractions. Certain COX-2 inhibitors may be used judiciously for joint inflammation after an acute bleed and in chronic arthritis. If bleeding does not resolve despite adequate treatment, clotting factor levels should be measured. Inhibitor testing should be performed if the level is unexpectedly low. Regular exercise and other measures to stimulate normal psychomotor development should be encouraged to promote strong muscles, develop balance and coordination, and improve fitness. Good oral hygiene is essential to prevent periodontal disease and dental caries, which predispose to gum bleeding [3].

7.3. Pain Management in Patients with Bleeding Disorders

Acute and chronic pains are common in patients with hemophilia. Adequate assessment of the cause of pain is essential to guide proper management [37]. Pain caused by joint or muscle bleeding should be controlled with paracetamol, cold packs, immobilization, splints, and crutches [5]. Intramuscular injection of analgesia should be avoided. Post-operative pain should be managed in coordination with the anesthesiologist. Initially, intravenous morphine or other narcotic analgesics can be given, followed by an oral opioid such as tramadol, codeine, hydrocodone, and others [38].

7.4. Treatment of Von Willebrand Disease

Desmopressin (DDAVP) is administered by injection into a vein or, more commonly, through a nasal spray called Stimate. It's a synthetic hormone, similar to the natural hormone vasopressin, that controls bleeding by stimulating your body to release more von Willebrand

factor already stored in the lining of your blood vessels — thereby enhancing factor VIII levels. DDAVP is usually effective in people with type 1 and some subtypes of type 2 disease [35]. Replacement therapies consist of infusions of prepared doses of concentrated blood-clotting factors containing von Willebrand factor and factor VIII. They can be useful in all disease types. Contraceptives may control heavy bleeding during menstrual periods. The estrogen hormones present in birth control pills can boost levels of von Willebrand factor and factor VIII activity. Anti-fibrinolytics such as aminocaproic acid and tranexamic acid can slow down the breakdown of clotting factors. This can help keep a clot in place once it has formed, putting a stop to bleeding. Fibrin sealants are substances applied like a glue using syringes and placed directly on a cut to curtail bleeding [39].

7.5. Gene Therapy in Bleeding Disorders

Researchers made a major advance in the decades-old effort to use gene therapy to treat the bleeding disorder hemophilia B [40]. With gene therapy, scientists try to correct the problem by delivering a normal gene to the body, using what is known as a vector to insert the gene into cells usually a virus that is genetically altered to contain human DNA [41,42].

8. Conclusion

Bleeding disorders usually result from hereditary deficiency of certain coagulation factors. These disorders often affect lifestyle of the patient and may have serious complications. Further studies are needed to explore the exact pathogenesis of bleeding disorders and new lines of management especially for gene therapy which is the hope for millions of patients for complete eradication of these disorders.

Competing Interests

The author has no competing interests.

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