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Basim A. Abd
Department of Medical Physiology, College of Medicine, University of Babylon, Hillah, Babylon Province, Iraq

Mohammed Ali Al-Jabory
Department of Pathology, College of Medicine, University of Babylon, Hillah, Babylon Province, Iraq

Teeb M. Jaafar Al-khafaji
Department of Pathology, College of Medicine, University of Babylon, Hillah, Babylon Province, Iraq

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REVIEW

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A Review About Hemophilia B or "Christmas Disease"

Basim A. Abd [a,*], Mohammed Ali Al-Jabory [b], Teeb M. Jaafar Al-khafaji [b]

[a] Department of Medical Physiology, College of Medicine, University of Babylon, Hillah, Babylon Province, Iraq
[b] Department of Pathology, College of Medicine, University of Babylon, Hillah, Babylon Province, Iraq

Abstract

People with hemophilia B, a genetic disorder, bleed continuously for extended periods if left untreated. Hemophiliacs bleed at the regular rate indefinitely until they receive treatment; they do not bleed more quickly than healthy people, their blood is unable to clot when they bleed in the absence of suitable treatment. The main concern while dealing with hemophilia is internal bleeding. Bleeding frequently occurs in elbows, knees, and ankles. In severe situations, this can start on its own, but it can also be induced by damage. Regretfully, hemophilia B has not garnered as much attention from researchers as other serious illnesses. The most distressing aspect of this illness is that, on occasion, even medical professionals are ignorant of its diagnosis and treatment. Depending on the hemorrhaging conditions, the only viable therapy options are the infusion of factors and certain adjuvant medicines. For the benefit of the millions of hemophilic patients, this page provides an overview of hemophilia B to draw attention from medical and pharmacy professionals.

Keywords: Hemophilia, Factor IX, Hemostasis

1. Introduction

The second most frequent kind of haemophilia is haemophilia B. Other terms for it include "Christmas disease and factor IX" deficiency. Because the disorder was first identified in a person in 1952, it was initially known as "Christmas disease." Targeted groups are not racially or economically distinct. Inherited as an X-linked recessive disorder, hemophilia B is classified generally as a rare disease. It has resulted from transmutations in the factor IX genes, affecting males and female carriers, with a 50% chance of male offspring having the disorder and their female offspring having a 50% likelihood of being carriers. Blood cannot clot correctly without factor IX which is involved in the intrinsic pathway of blood normal coagulation. The prevalence of hemophilia B is 1 in 30,000 [1, 2].

No clear approximation is found about hemophilia in all Iraqi Governorates; however, an increment is seen in Baghdadi patients with type B hemophilia in the past few years.

A study epidemiologically done by Kadhim *et al.* [3] displayed that 24.8% of Iraqi patients were encountered to have hemophilia B.

2. Historical background

In earlier times, hemophilia was believed to be present. According to the Talmud, a compilation of second-century AD Jewish rabbinical teachings, male infants should not be circumcised if two brothers have already passed away from the procedure's severe bleeding. The 12th-century Arabic physician Albucasis told of a family whose male members perished from bleeding following minor wounds. Physician John Conrad Otto of Philadelphia is credited with providing the first known description of hemophilia in his 1803 publication "An account of a hemorrhagic character existing in certain families." He was aware

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* Corresponding author.
E-mail addresses: basim6mol@gmail.com (B. A. Abd), moh.aljabory@gmail.com (M. A. Al-Jabory), dr.teebiraq@gmail.com (T. M. J. Al-khafaji).

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of a distinctive feature of hemophilia, which includes males' inherent propensity to bleed. However, Hopff from the University of Zurich wrote the initial essay in which the term "hemophilia" appeared in 1828. Hemophilia B was named "Christmas disease" after the previous term of the first kid to be diagnosed with the disease in 1952 when it was differentiated from the more prevalent hemophilia A [4, 5].

It had been believed that blood vessel fragility was the cause of hemophilia's propensity for bleeding. In the 1930s, it had been thought that the most likely cause was malfunctioning platelets. Subsequently, in 1937, Harvard's Patek and Taylor demonstrated that adding a material taken from plasma might fix the coagulation problem. It was referred to as anti-haemophilic globulin. In 1944, a scientist from Buenos Aires demonstrated that a hemophiliac's circulation may fix another hemophiliac's coagulative abnormality and vice versa. Two individuals he had come across had deficiencies in factor VIII besides factor IX, two distinct proteins. Such findings made it possible to diagnose the condition properly and laid the groundwork for currently available therapies for this hereditary hemorrhagic illness [6].

3. How does the body act to stop bleeding?

Blood vessels allow blood to move throughout the body. These vessels consist of capillaries, arteries, and veins. The blood may leak if any of these are disrupted. This can occasionally occur from injuries or abrasion on the skin. There are instances when a blood artery inside the body leaks blood. The body has to exert effort in both situations to seal the wound and prevent the blood from escaping. Hemostasis is the physiological process by which bleeding ceases. Blood clotting is regarded as a crucial phase in the hemostasis process. This is the procedure that causes a fibrin clot to form. Throughout an injury the consecutive steps that initiate the clot formation are [7]:

A. Constriction of the vessels. As a result, less blood can reach the injured area.
B. Thrombin stimulates platelets, which then clump together at the site of damage to create a transient, movable platelet plug.
C. Formation of the solid fibrin clots.

Platelet-rich plasma and vascular endothelial cells interact with a vast number of plasma glycoproteins during blood coagulation. Three mechanisms lead to the synthesis of fibrin during blood clotting (coagulation) (Fig. 1) [8].

1. A common pathway
2. The intrinsic contact activation pathway
3. The extrinsic tissue factor pathway

4. Why do subjects with hemophilia B bleed?

Factor IX normally is lacking in the hemophilia B patient. This component is necessary for factor X to become activated; if it is absent, factor X cannot get activated (Fig. 2) 7. The intrinsic pathway of blood coagulation will be inhibited in this case. In patients with hemophilia B, however, the tissue factor route (extrinsic pathway) is normal and does not rely on a

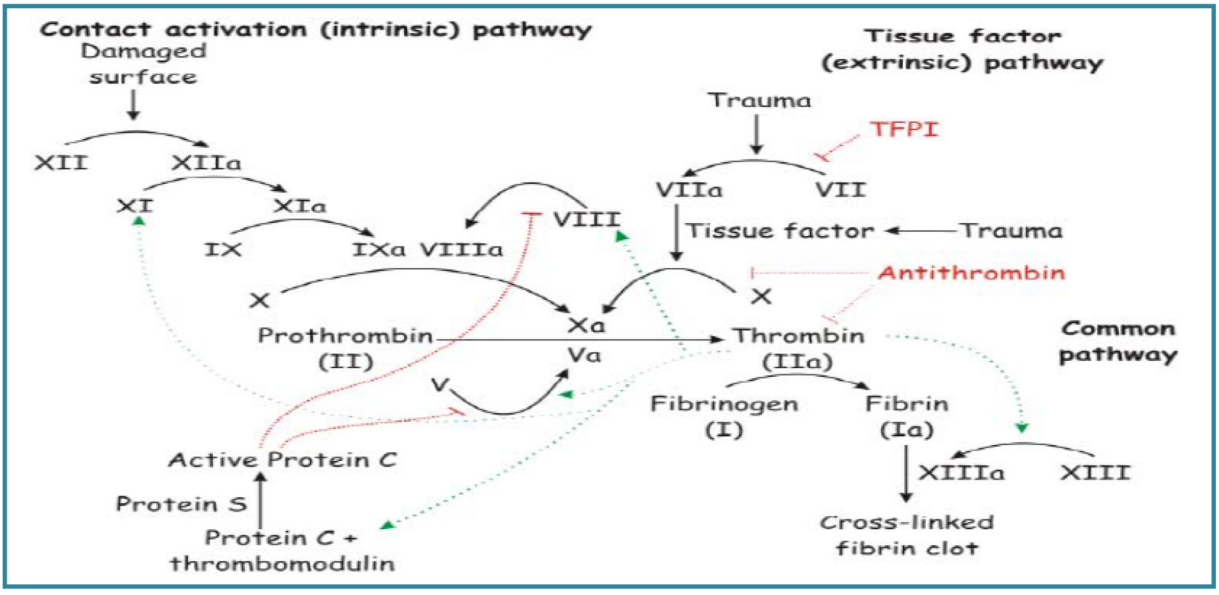

Fig. 1. The role of coagulation factors on blood clotting (The "a" with the factor indicates its activated form).

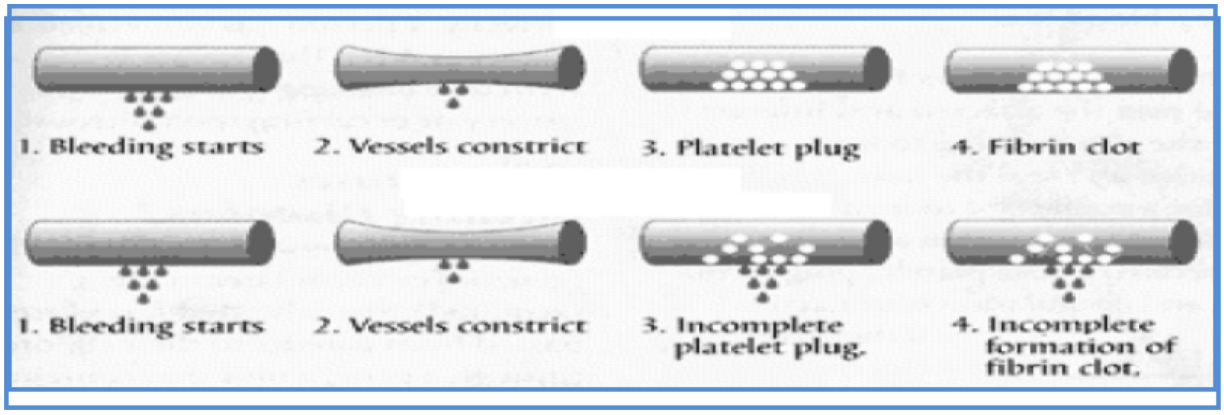

Fig. 2. Schematic representation of why the hemophilia patients bleed than the normal individuals.

combination of the previously listed factors. Consequently, it makes sense to wonder if this pathway is adequate for the development of clots [9].

Research indicates that although the initial generation of factor Xa is attributed to the factor VIIa-TF complex (extrinsic pathway), which supplies enough thrombin to trigger local platelet aggregation and activate the vital cofactors factor V and factor VIII in standard hemostasis, sustained hemostasis necessitates the continuous synthesis of supplementary factor Xa via the actions of factor IXa besides factor VIIIa because the tissue factor pathway inhibitor (TFPI) prevents the factor Xa generation by the factor VIIa-TF complex. Therefore, hemophilia B patients bleed because the Xa produced by factor VIIa-tissue factor complex and decreased by TFPI is inadequate to maintain hemostasis normally and needs to be enhanced by factor IXa and factor VIIIa. This means that to maintain hemostasis, factor IXa, and factor VIIIa have to keep generating factor Xa [9].

5. Clinical presentation

Hemophilia B manifestations and degrees of deterioration vary widely depending on the amount of factor IX present. The expression of hemophilia B can vary from mild to severe. Factor IX concentrations range from 5% to 40% of the normal in individuals with mild cases, 1%–5% of the normal in those with moderate cases, and below 1% of the normal in people with severe conditions. The levels of factor IX in the plasma and the family history determine the age at which a person learns they have hemophilia B, sometimes referred to as the age at diagnosis, and the rate of recurrence of hemorrhagic episodes. The degree of symptoms might differ, and the more severe types manifest up first [10].

The main warning sign of the illness is bleeding, which can occasionally—though not always—occur after a baby is circumcised. As soon as the baby is active, more bleeding issues typically arise. Hemorrhage into joints and accompanying discomfort and swelling, blood in the stool and urine, bruising after undue bleeding after circumcision, bleeding from the alimentary tract and genitourinary tract, nasal bleeding, continued bleeding from cuts, bleeding during dental extraction procedures, and occasionally spontaneous hemorrhage are among the symptoms. There is a partial prolonged partial thromboplastin time (PTT), normal prothrombin time (PT), normal bleeding time (BT), normal fibrinogen measures, normal levels of factor VIII, and reduced factor IX [11].

6. Affected populations

It is estimated that 1 in 25,000 new male deliveries have haemophilia B. Compared to hemophilia A, which affects about 1 in 5,000 male newborns, it is less common. While a large percentage of female hemophilia B carriers do not exhibit symptoms, between 10 and 25 percent are expected to experience mild manifestations, however, moderate to severe manifestations have also been confirmed in female carriers. Every race and ethnicity is equally impacted. People who have a moderate form of hemophilia B are characteristically identified between the ages of five and six, whereas individuals with a mild form of hemophilia B may not receive a diagnosis until much later in life or even into adulthood. People with a severe form of hemophilia B are typically detected either around birth or during the initial few years of life [12].

7. Diagnosis

Hemophilia B can be identified based on the history of bleeding, family history of hemorrhage and inheritance, and results from laboratory tests. Hemophilia B

must be confirmed by many distinct specialized tests [13].

Blood coagulation tests that assess the specific time it takes for blood to clot are used to diagnose hemophilia B in individuals. The first classical confirmatory test is activated partial thromboplastin time (aPTT). If the aPTT test results are atypical, additional targeted blood confirmatory tests need to be performed to identify if the nonstandard aPTT is caused by a hemophilia A (factor VIII), hemophilia B (factor IX), or alternative coagulation factor deficit. The degree of severity of the factor insufficiency is also ascertained by a particular factor assay. It is important to remember that the aPTT is not always accurate in identifying mild hemophilia B. Even with a normal aPTT, a particular factor IX activity level should be conducted if this diagnosis is suspected [14].

It is possible to pinpoint the precise factor IX gene variation that causes hemophilia if a person is diagnosed with hemophilia B. Finding the variation could help assess the likelihood of getting an inhibitor, which can be a major issue for people with severe hemophilia. Since factor IX levels are insufficient to establish carrier status, it is critical to identify the precise factor IX gene variant to identify female carriers within a family [15].

8. Standard care for hemophilia B

Hemophilia B is primarily treated by replacing factor IX to ensure appropriate blood coagulation and avoid any related complications of the illness. At present, recombinant clotting products or products made from human plasma or blood are commonly administrated to substitute factor IX to appropriate levels. Since recombinant factor IX contains no human blood proteins, it is favored by many doctors and voluntary health organizations. Donating human blood carries a very small risk of spreading viral illnesses like HIV and hepatitis, but because of more advanced diagnostic and therapeutic methods, this risk is now very low to undetectable [16]. Depending on their factor IX activity level, carrier females with bleeding manifestations may require factor replacement medication for several reasons, including bleeding episodes, postpartum hemorrhage after childbirth, and dental and surgical operations [17].

9. Therapeutic options

9.1. Recombinant factor IX

Products containing recombinant factor IX concentrate are readily produced in a laboratory setting. These genetically modified items are thought to be virus-free in theory because they do not originate from human blood and do not encompass any human or animal proteins. Treatment for hemophiliacs is advised to use recombinant factor IX therapy [18].

9.2. Plasma-derived concentrates of factor IX

Two primary distinct kinds of factor IX concentrate are generated from plasma: products of intermediate purity and highly purified products. Human blood or plasma donations are the source of plasma-derived products. Viral inactivation is achieved by a variety of techniques, and highly purified concentrates are virtually devoid of additional proteins of clotting factor. Although they are virally deactivated and include factor IX along with variable levels of additional clotting factor proteins, intermediate purity products are seldom used and are not recommended to treat factor IX insufficiency [19].

9.3. Fresh frozen plasma

Individuals with factor IX deficiency might only be treated with “fresh frozen plasma”, which is made from human blood if factor IX concentrates are not easily obtainable. All of the clotting factors found in circulation are present in fresh frozen plasma, which is not virus-inactivated. Furthermore, it is ineffective to elevate factor IX activities to a hemostatic rates using fresh frozen plasma [20].

10. Treatment routines

Replacement therapy may be administered to people with mild or moderate hemophilia B when necessary to stop a hemorrhagic episode. This treatment, known as “episodic infusion therapy”, is applied to halt an ongoing bleeding episode. To stop bleeding episodes, people with severe hemophilia B may need to get infusions regularly. The primary objective of this treatment, known as preventive therapy, is to stop bleeding before it starts [21]. In subjects with severe forms of hemophilia A or B, a prophylactic approach has been demonstrated to prevent several issues related to recurrent hemorrhage, including joint injury and cerebral hemorrhage. It is possible to instruct parents and impacted people to give factor IX concentrate at home [22]. Home-based medications are particularly crucial for patients suffering severe forms of hemophilia, though it’s also crucial for those with moderate to mild hemophilia because factor IX concentrate infusions work best to stop bleeding when they’re given within an hour of the start of a bleeding episode. Prophylaxis is sometimes given to patients

with moderate to mild hemophilia B to prevent bleeding during short- or long-term activities [23].

11. Perioperative management

The clinical effectiveness of hemostasis for surgical interventions or dental extraction can be assessed based on the criteria defined by the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis. This include maintaining target factor levels, administering clotting factor concentrates, administering desmopressin or anti-fibrinolytic agents and thromboembolic prophylaxis [24].

12. Conclusion

Hemophilia is a hemorrhagic disorder that is extremely difficult to manage. Given the relatively small number of people with hemophilia compared to other major illnesses like cancer, heart disease, and diabetes, hemophilia appears to be a less researched condition. As technology advances, the time when hemophilia can be easily treated and possibly completely cured is unlikely to be a distant possibility.

Ethical issue

Not applicable.

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Conflict of interest

None.

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