Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

AN OVERVIEW OF HEMOPHILIA DIAGNOSIS AND MANAGEMENT IN CHILDREN: SIMPLE LITERATURE REVIEW

Bayan Rafat Samman[1], Eman Tawfique Alrumaih[2], Alsulaiman Lojain Abdullah A[2], Mishal Mohammed Alrsheedi[3], Maha Dham Aldhafeeri[4]*, Afnan Ahmed Alasiry[1], Khalid Saadi Alharbi[5], Bashayr Sulayyih Alosaimi[6], Noura Hamdan Alotaibi[7], Raed Abdullah Mohammed[7]

1. *Faculty of Medicine, Batterjee Medical College, Jeddah, KSA.*
2. *Faculty of Medicine, Medical University of Lodz, Lodz, Poland.*
3. *Faculty of Medicine, University of Hail, Hail, KSA.*
4. *Faculty of Medicine, Almaarefa University, Riyadh, KSA.*
5. *Faculty of Medicine, Aljouf University, Sakaka, KSA.*
6. *Faculty of Medicine, Taif University, Taif, KSA.*
7. *Faculty of Medicine, King Khalid University, Abha, KSA.*

ARTICLE INFO

Received:
29 Jul 2020
Received in revised form:
26 Nov 2020
Accepted:
01 Dec 2020
Available online:
28 Dec 2020

Keywords: Hemophilia, Coagulation cascade, Factor VIII, Bleeding disorder.

ABSTRACT.

Background: The most common severe hereditary hemorrhagic disorder is Hemophilia. Philia means Love and Hemo means blood. A and B hemophilia are the two types of hemophilia that result from factor VIII and factor IX protein deficiency, respectively. After minor trauma or sometimes even spontaneously, the features of hemophilia are prolonged and excessive bleeding. Due to deficiency of clotting factor XI, the third rare type C occurs and is common in Ashkenazi Jews. Sometimes, acquired hemophilia can be associated with age or childbirth, which usually resolves with appropriate treatment. Hemophilia A is the most common between them. It presents in 1 out of every 5,000 newborn children worldwide. Objectives: We aimed to review the literature reviewing the types of hemophilia in children, along with the etiology, clinical features, evaluation, diagnosis, and management of these types. Methodology: PubMed database was used for articles selection, papers were obtained and reviewed. Conclusion: Hemophilia is an inherited disorder of coagulation. This condition may lead to severe restrictions in everyday activity and severe complications. Proper recognition, testing, and management of individuals afflicted by this condition will greatly improve the chances of survival, improved quality of life, and reduce the risk of complications. Emerging therapies, such as gene therapy, may provide the possibility of a cure.

To Cite This Article: Bayan Rafat Samman, Eman Tawfique Alrumaih, Alsulaiman Lojain Abdullah A, Mishal Mohammed Alrsheedi, Maha Dham Aldhafeeri, Afnan Ahmed Alasiry and *et al.*, (2020), "An Overview of Hemophilia Diagnosis and Management in Children: Simple Literature Review", ***Pharmacophore, 11(6),*** *62-66.*

Introduction

Hemophilia refers to a variety of inherited and acquired conditions in which patients are at increased risk of bleeding. The inherited form of the disease is termed hemophilia A, B, and C depending on the deficiency or dysfunction of coagulation factors VIII, IX, and XI, respectively. [1] Rarely, this condition can present in a patient who did not have it before, an acquired form. Typically, the acquired form is due to the formation of autoantibodies to factor VIII, which is why it is termed acquired hemophilia A in literature. [2] This condition may present with a variety of presentations ranging from mild bleeding to a life-threatening condition. [1] In this review, we will go through the different types of hemophilias covering the clinical features, diagnosis, and management for each.

Methodology

PubMed database was used for articles selection, and the following keys used in the mesh (((Hemophilia) AND (Symptoms)) OR (Diagnosis)) OR (Management). Regarding the inclusion criteria, the articles were selected based on the

Corresponding Author: Maha Dham Aldhafeeri, Faculty of Medicine, Almaarefa University, Riyadh, KSA. Email: Maha119 @ hotmail.com

inclusion of one of the following topics; hemophilia A, hemophilia B, acquired hemophilia, diagnosis, and management. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Coagulation Cascade

The importance of the coagulation cascade is to aid the platelets in stopping and "plugging" the bleeding site. It is the sequential activation of a series of proenzymes and zymogens, inactive cursor proteins, to active enzymes, resulting in the conversion of fibrinogen into fibrin, the compound that reinforces the platelet plug. [3] We will focus our discussion on the intrinsic pathway of the coagulation system, as it is the one that is affected in hemophilia.

Initially, the intrinsic phase starts with the activation of several proteins by contact with negatively charged surfaces, which explains why this phase is called the "contact activation pathway". Those proteins include coagulation factor XII, prekallikrein, and high molecular weight kininogen (HMWK). Activated factor XII, in conjunction with HMWK, activates factor XI, which in turn activates factor IX (IXa). Coupled with factor VIII, factor IXa then activated factor X. The activated form of factor X, in addition to factor Va which is activated by factor VIIIa, can then activate thrombin. Once thrombin is activated, it can activate fibrin, which is the compound that is essential in the enhancement and enforcement of the platelet plug (Fig 1). [3] In hemophilia, there is a deficiency in some of these coagulation factors, which leads to improper activation of fibrin. This leads to unstable platelet plugs that break easily, and bleeding would not stop unless intervention is administered.

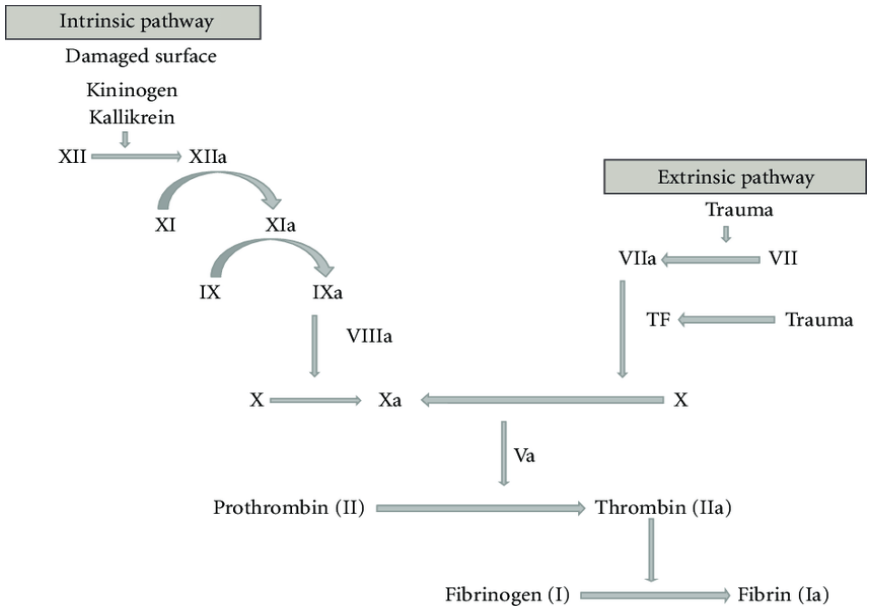

Figure 1. Coagulation Cascade. [4]

Hemophilia A

Hemophilia A is an X-linked, recessive condition that manifests as a congenital absence or deficiency of coagulation factor VIII. Since this condition has an X-linked inheritance, it affects males far more than it does females. Males affected with hemophilia A will not transmit the disease to their sons; however, their daughters will be carriers for the hemophilia gene. Factor VIII is an important factor in the coagulation cascade that leads to the activation of thrombin, leading to the activation of fibrin and formation of the primary plug. [5, 6] This condition, as stated earlier, affects males more than females. Males usually develop the severe disease in two-thirds of cases. The disease occurs in around 1 out of every 5000 male births. Female carriers may not manifest the disease, however, they may have a lower than usual amount of factor VIII. [1]

Hemophilia B

Hemophilia B is also known as Christmas disease. It is an X-linked, recessive deficiency of coagulation factor IX. Similar to hemophilia A, the disease is almost exclusive to males. Also, factor IX plays an important role, in conjunction with factor VIII, in the activation of thrombin. [7, 8] While an acquired form of the disease is acknowledged, it is very rare and happens in patients with a background of autoimmune diseases, malignancies, or chronic infections such as HIV. [9] The disease is present in about 1 out of every 40,000 male births, representing about 15% of all hemophilia cases. It is the second most common cause of hemophilia. The disease is severe in about 1/3 of cases. [10]

Hemophilia C

An autosomal recessive inherited deficiency of factor XI also termed Rosenthal syndrome. It is a rare condition, affecting 1 in every 100,000-1,000,000 births. There is no variation between males and females, unlike hemophilia A and B, since its inheritance is autosomal. This condition is common in Ashkenazi Jews. [11]

Acquired Hemophilia

In this condition, patients do not inherit the disease from their parents [12-14]. Instead, it is due to the development of autoantibodies to coagulation factors, most commonly factor VIII. Hence, this condition is termed Acquired Hemophilia A (AHA) most of the time. [2] In about half of the cases, no cause can be recognized. This condition is associated with a variety of other clinical presentation and conditions such as; immunological disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome, autoimmune thyroiditis, etc.; cancers and precancerous states that include solid tumors and leukemias; dermatological disorders like psoriasis and pemphigus; infections such as acute hepatitis B and C; secondary to medications, for instance, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), and antiarrhythmics; etc. [15-18] Acquired hemophilia is a rare condition, affecting about 1.5 per million per year. The incidence increases as people grow older, as it is affecting the elderly far more than children. Generally, females are affected more between the age brackets of 20–40 years, while males are affected more after the age of 85. [16] As this condition presents later in life, we will not discuss it further.

Clinical Manifestation

In the simplest terms, the clinical manifestation of hemophilia is that of bleeding due to impaired coagulation cascade, sequelae of bleeding, or complications from coagulation factors transfusion. It is imperative to determine the severity of the disease, as more severe disease presents with spontaneous, severe bleeding at an early age. [1, 19] Mostly, patients present with immediate or delayed bleeding after trauma. The bleeding can be profuse from the start or persists as oozing for days or weeks after trauma. Bleeding from small cuts are uncommon unless the condition is severe or concomitant platelet disorder. In contrast to severe disease, mild hemophilia may go undetected for significant periods. The disease may only become apparent when there is a significant hemostatic challenge such as the cases of trauma and surgery. [1, 19, 20] The majority of patients present with a family history of the same condition. However, this is not always true as de novo mutations are getting more common and there is also the possibility of acquired hemophilia. [19, 20]

Determining the age of the first bleed is important, as it demonstrates the severity of the condition. Most infants with a severe form of the disease present within the first year of life with easy bruising, hemarthrosis, or after an invasive procedure. Data from the CDC show that the age of the first bleed in severe, moderate, and mild hemophilia was 1 month, 8 months, and 36 months, respectively. [21] However, the age of the first presentation may vary from place to place. The site of bleeding differs between age groups. In infants, this includes the central nervous system, extracranial bleeding, and site of medical intervention like circumcision and heel stick. In children, the usual site is over the joints, especially the lower limbs, as the child begins walking. Oral injuries are also quite common. In older children, the common sites include joints, muscles, CNS, and gastrointestinal tract. [21] CNS bleeds are rarer than the other types but universally agreed to be the worst site for bleeding to occur as permanent neuronal damage may lead to the persistence of neurological manifestations after the treatment of the bleeding. Hemarthrosis, bleeding into joints, are quite common and, if not treated properly, may lead to joint space narrowing and fusion of the joint, thus leading to functional disability. [22]

Diagnosis

Hemophilia should be suspected in any male with bleeding. While positive family history is strongly suggestive, a negative family history should not be used to rule out the diagnosis. [19] Laboratory testing is similar across all types of hemophilia. Initial tests include tests of hemostasis, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count. [1, 19] If the aPTT is prolonged, a mixing test should be done. This procedure will differentiate whether the issue is due to deficiency or due to autoantibodies. If aPTT is corrected after mixing with coagulation, then the problem is due to deficiency. If the aPTT isn't corrected after mixing, then the problem is due to the presence of autoantibodies. [19, 20, 23]

If hemophilia is due to deficiency (mixing test is positive), then, the factor activity levels should be checked. The factors of interest are factors VIII, IX, and XI. The determination of which factor to be tested depends on the family history, if positive for a certain type of hemophilia, then testing should be directed towards that factor. If family history is negative, then testing of all factors is indicated. [1] In cases of negative mixing tests, the determination of autoantibody titer is needed. [15, 18] Genetic testing is appropriate in most patients, especially in female carriers as it is the first-line choice. This information is particularly important in determining the carrier status and the possibility of developing inhibitors to coagulation factors. Genetic testing is of particular importance in mild disease forms as the hemostasis testing is normal in most of those patients. [20, 24]

Management

The management of hemophilia can be divided into two forms; treatment of the acute bleeding episode and prophylaxis.

- **Acute bleeding treatment**

In hemophilia, achieving quick and aggressive hemostasis, preferably within two hours of the onset of bleeding or symptoms because of specific sites, and correction of coagulopathy is the fundamental concept of management of acute bleeding. These measures should not be delayed even if diagnostic tests are pending or if physical symptoms are not present, yet. [20, 24] All patients with acute bleeding episodes must be hospitalized. Older patients may recognize that a bleeding episode is about to

occur by the presence of a tingling sensation or an aura. However, in some cases, patients may present unconscious and quick history should be obtained from available sources. [19]

Patients should be immediately put on specific clotting factor concentrate if their deficiency is known. Otherwise, patients must receive prothrombin complex concentrate plus factor VIII concentrate. In most patients, they may require immediate surgical intervention to decompress the site of bleeding, especially in CNS or airway compromise, or may require CPR. In both of these situations, there should be no delay in the administration of coagulation factors before or during such interventions. [22] Several imaging studies can be done to determine the site of bleeding. If the bleeding stops, it is advised to continue factor replacement therapy. The factor activity level should be ordered periodically to determine whether the treatment has achieved proper control. Pain management is essential, but one must be careful that aspirin and several non-selective NSAIDs may inhibit and impair the activity and ability of platelets, leading to further bleeding. These drugs should not be used. Instead, celecoxib, a COX-2 inhibitor, can be used and, in severe cases, opioids can be used. [22]

- **Prophylaxis**

Prophylactic treatment is essential as it leads to reduced rates of admissions, reduced risk of intracranial hemorrhages and hemarthrosis, and improvement of overall quality of life. However, prophylactic treatment is expensive, reaching up to $300,000 annually, [25, 26] and it may put some burden on the life of the patient especially since most patients on prophylaxis require the placement of a central venous catheter. [22] There are three terminologies for prophylaxis; primary, secondary, and intermittent. Primary prophylaxis refers to prophylaxis in individuals who have not had a bleeding episode but are at high risk of bleeding based on severe factor deficiency. Secondary prophylaxis is for individuals who have had more than one bleeding episode. Intermittent prophylaxis is for individuals with moderate or mild factor deficiency and no prior bleeding, but due to physical activity and risk of bleeding, these patients may receive prophylaxis. [27] The choice of prophylactic agent depends largely on the factor deficient and patient's status. There are two options, factor replacement therapy, and emicizumab, an exclusive therapy to hemophilia A patients as it resembles the function of factor VIII. [22, 24] Of particular note, there have been advancements in our understanding of genes and the genes that are associated with hemophilia. This has opened the door to the possibility of gene therapy which is still undergoing heavy research in hopes of curing this condition. The main concept is to introduce exogenous DNA into the patient's cells to produce the missing proteins that are required in the coagulation cascade. [28, 29]

Complications

The complications of hemophilia include, but are not limited to, hemophilic arthropathy, infections due to repeated transfusion, and development of inhibitors. Hemophilic arthropathy refers to the persistent joint disease caused by multiple hemarthroses in a target joint. By adulthood, arthropathy may represent a major cause of morbidity and interfere with numerous activities and quality of life. Although there are protocols for transfusion of clotting factors that reduced the risk of transmission of infections, the transmission of blood-borne infections is still possible. These organisms include HIV, HCV, HBV, and parvovirus B19. The development of inhibitors is a serious complication in which patients with factor deficiency develop alloantibody to the factors that are transfused. [30, 31]

Conclusion

Hemophilia is an inherited bleeding disorder that presents with profuse external or internal bleeding into joint spaces, CNS, and other places. The condition is due to deficiency or development of inhibitors to coagulation proteins that are essential in the hemostasis of the blood. Clinical features depend on the severity of the disease, age of the first presentation, and site of the bleeding. Diagnosis is done by measuring blood hemostatic functions and factor activity. Treatment of the acute bleeding includes transfusion of deficient factors and resuscitation of the patient. Prophylaxis should not be offered to all patients and should be done individually. There are emerging therapies that may potentially cure this condition. Complications include decreased quality of life due to fused joints, risk of transmitting infections, and inhibitors' development.

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