International Journal of
Case Reports & Short Reviews

Case Report

Hemophilia is Manifested by Frequent Bleeding -

Siniša Franjić*

Faculty of Law, International University of Brcko District, Bosnia and Herzegovina, Europe

***Address for Correspondence:** Siniša Franjić, Faculty of Law, International University of Brcko District, Brcko, Bosnia and Herzegovina, Europe, Tel: +387-49-49-0460;
Email: sinisa.franjic@gmail.com

Submitted: 22 November 2021; **Approved:** 04 December 2021; **Published:** 06 December 2021

Cite this article: Franjić S. Hemophilia is Manifested by Frequent Bleeding. Int J Case Rep Short Rev, 2021 Dec 06; 7(1): 013-017. doi: 10.37871/ijcrsr.id96

ISSN: 2638-9355

ABSTRACT

Hemophilia is most often an inherited blood clotting disorder in which the blood of patients does not clot properly, due to lack or insufficient activity of coagulation factors - proteins found in the blood and which act in a cascade, or activate each other to clot the blood. Hemophilia is manifested by frequent bleeding which occurs at the slightest injury and/or spontaneously. People with hemophilia do not bleed more than a healthy person, but bleed longer. These people also experience internal bleeding into muscles, joints and soft tissues, which can lead to permanent damage, as well as be life-threatening if they occur in vital organs, such as the brain. Repeated bleeding into the same joint can eventually lead to hemophilic arthropathy - chronic irreversible changes in that joint that result in joint deformity and dysfunction.

Keywords: Hemophilia; Signs; Pain; Diagnosis

INTRODUCTION

Hemophilia A and B are sex-linked, recessive disorders resulting in defective coagulation of factors VIII and IX, respectively [1]. Of the approximate 20,000 patients in the United States with hemophilia, 80% have factor VIII deficiency. In the general population, the range of normal factor activity varies from 50% to 200% (0.5-2.0 U/mL); the severity of hemophilia is quantified on the basis of the level of factor coagulant activity present. In all patients, 1% or less activity is considered severe, and these patients are subject to spontaneous bleeding; 1% to 5% activity represents moderate severity, with major bleeding primarily associated with trauma or surgery; and greater than 10% activity is considered mild, although bleeding after trauma and surgery similarly is noted. Bleeding may occur at multiple sites; however, recurrent hemarthroses with progressive joint destruction and intracranial bleeding remain the major causes of morbidity and mortality, respectively. Trauma remains a common and important precipitant of bleeding in all groups of patients.

A few general rules in regard to the evaluation and management of patients with hemophilia should be noted. Most patients presenting to the ED (Emergency Department) will be very familiar with their illness, including the severity of their disease (or percent factor level) and the various modalities of treatment. Many patients with moderate to severe disease will bring their own factor concentrate for replacement, and they should be allowed to use this in the ED. In all cases, immediate triage into the ED should occur, along with a very early consultation with the patient's hematologist. Intramuscular injections should be avoided; parenteral agents should be administered intravenously or subcutaneously. Ancillary studies and all invasive procedures should follow replacement therapy; replacement therapy should also be administered before transfer to another facility, if possible. Medications that interfere with coagulation or platelet aggregation should obviously be avoided. People with hemophilia A are particularly vulnerable to injury and can experience spontaneous internal bleeds (often into joints) leading to acute pain and long-term disability [2]. The most common cause of hemophilia-related deaths are due to intracranial bleeds. Hemophilia B is generally understood to be a less severe form of the disease, but for individuals with hemophilia B, spontaneous and internal bleeds can affect daily living. Treatment focuses primarily on replacing lost blood plasma and the administration of recombinant concentrates to substitute the absent clotting factor. More recently, the introduction of prophylactic IV therapies have been proven effective at preventing bleeds in those with hemophilia A. The administration of contaminated blood products to people with hemophilia throughout the 1980s, however, has also led to the development of substantial co-morbidities in older men with hemophilia (typically hepatitis B/C and HIV), as well as increased social stigma for many people living with hemophilia in the UK.

PATHOPHYSIOLOGY

Recall that many different clotting factors make up the clotting mechanism [3]. Hemophilia A accounts for 80% of all types of hemophilia and results from a def iciency of factor VIII. Hemophilia B is a factor IX deficiency; about 15% of people with hemophilia have this type. The severity and prognosis of hemophilia depend on the degree of deficiency of the specific clotting factors. Mild hemophilia has the best prognosis because it does not cause spontaneous bleeding and joint deformities like severe hemophilia can. After an injury, the person with hemophilia forms a platelet plug (which differs from a clot) at the site of an injury as would normally be expected, but the clotting factor deficiency keeps the patient from forming a stable fibrin clot. Continued bleeding washes away the platelet plug that initially formed. Contrary to popular myths, people with hemophilia do not bleed faster and are not at risk from small scratches.

Historically, treatment based on the availability of clotting factor replacement has resulted in an arcane guideline for the correction of factor deficiencies in People with Haemophilia (PwH) [4]. While all other disease entities seek to restore function to a normal level, PwH are restricted to factor nadirs still equivalent to mild or moderate disease, resulting in continued risk of bleeding. A new treatment paradigm is needed based on the defined needs of PwH. A treatment model was developed by a panel of haemophilia providers, patient advocates and health economists to establish specific treatment milestones and targeted outcomes. The panel defined a series of treatment milestones to characterize the activity and outcomes linked to level of factor deficiency correction. All agreed that the ultimate goal should be 'functional cure' and 'health equity'. Seven levels to achieving a functional cure were identified, (a) Sustain life; (b) Minimal joint impairment; (c) Freedom from any spontaneous bleeds; (d) Attainment of 'normal' mobility; (e) Able to sustain minor trauma without additional intervention; (f) Ability to sustain major surgery or trauma; and (g) Normal haemostasis. A parallel set of patient-reported outcomes to achieve health equity was identified. These guidelines are now comparable with other disorders where the goal is to replace missing proteins to attain normal activity levels. As we are no longer limited by plasma supply due to the manufacture of recombinant factors, mimetics, and the early success of gene therapy, health equity is now achievable.

Signs

Bleeding occurs as a result of injury or, in severe cases, spontaneously (unprovoked by injury) [3]. Bleeding into the muscles and joints (hemarthrosis) is common and can cause acute pain. Severe and repeated episodes of joint hemorrhage cause joint deformities, especially in the elbows, knees, and ankles, which

DOI: https://dx.doi.org/10.37871/ijcrsr.id94

decrease the patient's range of motion and ability to walk. In mild hemophilia, excessive bleeding is usually associated only with surgery or significant trauma. However, once a person with mild hemophilia begins to bleed, the bleeding can be just as serious as that of the patient with a more severe form. The patient with moderate hemophilia has an occasional bout of spontaneous bleeding. In severe hemophilia, spontaneous bleeding occurs more frequently. It would be possible for the patient to develop hemarthrosis or bleeding into the brain without any precipitating trauma. Severe episodes can produce large subcutaneous and deep intramuscular hematomas. Major trauma can cause bleeding so severe that it becomes life threatening. Another unfortunate problem related to hemophilia treatment is the frequent need to replace clotting factors and other blood products. Before 1986, blood banks and other centers did not routinely test for Human Immunodeficiency Virus (HIV) antibodies. Depending on the patient' s age and frequency of treatment, many patients may have been exposed to HIV or hepatitis. Blood banks and pharmacies have checked their blood supplies for the presence of HIV since 1986. Today, the plasma proteins are artificially created or thoroughly cleansed to prevent transmission of disease.

Symptoms

Bleeding manifestations in patients with all forms of hemophilia are directly attributable to the decreased plasma levels of either factor VIII or IX [5]. Individuals with factor levels below 1% of normal are classified as havingsevere disease, and these people will experience severe spontaneous bleeding episodes and difficult-to-control bleeding related to traumatic events. Patients with factor levels of 1.5% of normal are classified as having moderate disease; although they may bleed spontaneously, more commonly their bleeding is related to a traumatic event. Patients with factor levels of 5.50% of normal are classified as having mild disease and usually bleed only after trauma. As a result of exposure to blood products, many hemophiliacs have chronic viral hepatitis or are infected with HIV. Fortunately, as a result of newer viral inactivation procedures and recombinant technology, few seroconversions have resulted from the use of currently available factor replacement products. An interesting clinical feature is the apparent protective effect of hemophilia and for carriers of hemophilia for Coronary Heart Disease (CHD) for which studies have shown up to an 80% reduction in coronary disease related mortality.

Pain

Pain is of key important for patients with hemophilia [6]. Spontaneous joint bleeds cause the accumulation of intraarticular blood, resulting in swelling, impaired mobility, and severe acute pain. Repeated hemarthrosis progressively contribute to irreversible joint degeneration and later development of chronic hemophilic arthropathy, characterized by joint deformity, disability, and chronic pain. Pain in haemophilia can be either acute (hemarthrosis) or chronic (hemophilic arthropathy), or occur concurrently, thereby posing unique challenges to pain assessment and management. Pain is yet suboptimally treated, underlining the need to address this concern within the hemophilia comprehensive care setting. Though it is consensual that a thorough pain assessment is the basis for optimal pain management, the lack of specific and validated pain tools for hemophilia is also acknowledged, in spite of the abundance of disease-specific questionnaires for other painful conditions. Haemophilia-related pain has been assessed using distinct measures, from unidimensional Visual or Numerical Rating Scales, to multidimensional pain questionnaires like the McGill Pain Questionnaire or the Brief Pain Inventory. Efficient pain therapy is important to increase the quality of life in patients. For hemarthrosis, the following five steps are efficient to properly manage acute pain: intravenous infusion of FVIII/FIX, within 2 hours from the beginning of joint bleeding, till a plasma level not <30.50% of the insufficient factor is attained, short-run repose of the painful articulation, local cryotherapy, joint aspiration of blood, and analgesic medication. The main step is substitution therapy with the insufficient coagulation. For chronic pain, reported recommendations are separated over the ability of Acetaminophen And Nonsteroidal Anti-Inflammatory Medications (NSAIDs) as firstline pharmacologic treatment of osteoarthritis. Tramadol is more frequently used for the treatment of osteoarthritis. Thus, in contrast to NSAIDs, tramadol does not cause gastrointestinal bleeding or renal complications, and does not cause injury to the articular cartilage. Opioids can be a good alternative if patients with knee osteoarthritis have intense pain or if other analgesic medication is contraindicated. Still, the data related to their efficacy and security are inconsistent.

DIAGNOSIS

Hemophilia A (HA) and Hemophilia B (HB) are rare disorders, being caused by the total lack or under-expression of two factors from the coagulation cascade coded by genes of the X chromosome [6]. Thus, in hemophilic patients, the blood does not clot properly. This results in spontaneous bleeding episodes after an injury or surgical intervention. A patient-centered regimen is considered optimal. Age, pharmacokinetics, bleeding phenotype, joint status, adherence, physical activity, personal goals are all factors that should be considered when individualizing therapy. In the past 10 years, many innovations in the diagnostic and treatment options were presented as being either approved or in development, thus helping clinicians to improve the standard-of-care for patients with hemophilia. Recombinant factors still remain the standard of care in hemophilia, however they pose a challenge to treatment adherence because they have short halflife, which where the Extended Half-Life (EHL) factors come with the solution, increasing the half-life to 96 hours. Gene therapies have a promising future with proven beneficial effects in clinical trials. A highly specific and accurate diagnosis is essential for the optimal and efficient management of both HA and HB. Musculoskeletal complications are the most common manifestation and the main cause of the discomfort, poor quality of life, physical and mental disability. Prompt treatment of each bleeding episode can prevent joint degradation and the need for orthopedic interventions. Standard prophylaxis based on body weight should give way to cost-effective personalized therapy. Age, pharmacokinetics, bleeding phenotype, joint status, adherence, physical activity, personal goals are all factors that should be considered when individualizing therapy. For patients with/without factor VIII inhibitors, emicizumab prophylaxis maintains low bleed rates in HA patients of all ages and remains well tolerated, with no new safety concerns identified. Alternative therapies are also of good practical use, improving the quality of life in patients with HA and rare bleeding disorders. A patient-centered regimen is considered optimal. Recombinant factors still remain the standard of care in hemophilia, however they pose a challenge to treatment adherence because they have short half-life, which where the extended half-life factors come with the solution, increasing the half-life to 96 hours. Gene therapies have a promising future with proven beneficial effects in clinical trials, however, a better vector must be found since AAV has the major threat to transduce the hepatocytes and cause hepatocytolysis syndromes.

DOI: https://dx.doi.org/10.37871/ijcrsr.id94

PREGNANCY

Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) are X - linked disorders [7]. Some women have levels that are within the normal range (> 50 IU/dL), but inactivation of the normal chromosome (lyonization) may result in low factor levels. The overall frequency for these disorders is approximately 1 in 100,000 births. There is also an increased risk of primary and secondary postpartum hemorrhage in hemophilia carriers, with reported rates of 19% and 11% respectively, occurring mostly when factor levels are < 50 IU/dL. Although hemorrhage is rare in women with factor levels > 50%, severe bleeding may occur with levels between 5% and 30% after surgery or delivery. In small reports, hemophilia A and B were noted to have higher postpartum hemorrhage rates compared to women with other bleeding disorders and required up to 4 days of factor replacement. Carriers of hemophilia A generally experience a pregnancy - induced rise in factor VIII levels. However, factor IX levels are unaffected by pregnancy. Treatment is indicated for labor when factor levels are < 50 IU/dL for both types of hemophilia. DDAVP may be used or appropriate factor concentrates. If the diagnosis is not known in the face of hemorrhage, fresh frozen plasma can be used pending test results. Hemophilia A carriers synthesize normal amounts of vWF, and therefore recombinant factor VIII is effective in these patients. Affected fetuses are at risk for extra - and intracranial hemorrhage, but cesarean delivery does not reduce this risk. Fetal scalp electrodes and operative delivery should be used cautiously.

GENE THERAPY

Gene therapy has the potential to revolutionise treatment for patients with haemophilia and is close to entering clinical practice [8]. While factor concentrates have improved outcomes, individuals still face a lifetime of injections, pain, progressive joint damage, the potential for inhibitor development and impaired quality of life. Recently published studies in Adeno-Associated Viral (AAV) vector-mediated gene therapy have demonstrated improvement in endogenous factor levels over sustained periods, significant reduction in annualised bleed rates, lower exogenous factor usage and thus far a positive safety profile. In making the shared decision to proceed with gene therapy for haemophilia, physicians should make it clear that research is ongoing and that there are remaining evidence gaps, such as long-term safety profiles and duration of treatment effect. The eligibility criteria for gene therapy trials mean that key patient groups may be excluded, eg children/adolescents, those with liver or kidney dysfunction and those with a prior history of factor inhibitors or pre-existing neutralising AAV antibodies. Gene therapy offers a life-changing opportunity for patients to reduce their bleeding risk while also reducing or abrogating the need for exogenous factor administration. Given the expanding evidence base, both physicians and patients will need sources of clear and reliable information to be able to discuss and judge the risks and benefits of treatment.

TREATMENT

Hemophilia is not curable [3]. However, treatment advances have improved outcomes, and many patients can now live a normal life span. Treatment is aimed at pre venting crippling deformities and increasing life expectancy and involves stopping bleeding episodes by administering the missing clotting factors. Mild hemophilia A may be treated with injection or nasal inhalation of desmopressin (DDAVP, antidiuretic hormone), which can stimulate the body to release more clotting factors. More severe hemophilia A is treated with factor VIII; hemophilia B is treated with factor IX. Each is available in a freeze-dried powder that is reconstituted with water and administered intravenously. The newest treatment employs factors made using recombinant DNA technology without the use of any human blood products. Blood transfusions are uncommon but may be necessary after severe trauma or surgery. Complications occur when therapy is started too late. Minor trauma typically needs to be treated with at least 72 hours of added clotting factors; major traumas and sur geries may require up to 14 days of added factors to prevent sudden bleeding. Health care workers should pay careful attention to the patient who says that bleeding is starting even when no outward signs are evident. The patient usually knows from experience if bleeding is starting. If treatment is delayed at this time, the results can be disastrous. Some patients with severe disease are treated prophylactically to prevent bleeding.

The treatment of bleeding in hemophilia A involves the early and adequate administration of factor VIII as either concentrate (containing 200-1,500 U/20-mL bag-the actual number of units will be indicated on the bag) or cryoprecipitate (containing approximately 80-100 U/20-mL bag) [1]. At the current time, because concentrates can be subjected to virucidal treatments, these are considered safer and therefore preferred. It is important to remember that some patients with mild hemophilia A will respond to treatment with desmopressin (DDAVP), which is thought to act by stimulating release of factor VIII from body storage sites. Patients with factor VIII levels less than 10% are generally not considered candidates for treatment with DDAVP. DDAVP is the initial treatment of choice in patients with mild hemophilia A who have demonstrated a positive response to DDAVP infusion in the past, often via elective testing. The usual dosage of DDAVP is 0.3 mg/kg in 50 mL of normal saline administered over 30 to 40 minutes; a concentrated preparation, administered via nasal spray, is also under study. The treatment of hemophilia B requires replacement of factor IX with purified factor IX concentrates; cryoprecipitate is ineffective because of insufficient factor IX activity. Fresh frozen plasma can also sometimes be used in patients with mild factor IX deficiency associated with non–life-threatening bleeding; treatment options here are somewhat limited with fresh frozen plasma because of the low factor activity present and the consequently high volume of plasma required.The primary goal of treatment for both hemophilia A and B is to achieve sufficient coagulant activity in the plasma to control or arrest bleeding. The amount of factor required is, therefore, based on the patient's basal factor activity level, which is relatively constant, and the potential severity of the specific bleeding episode. In general, minimum acceptable hemostatic levels for factors VIII and IX are as follows: for mild bleeding, 30% for moderate bleeding, such as significant muscle or joint bleeding, 50% and for severe or life-threatening bleeding episodes, 80% to 100%. It is important to remember that each unit of factor VIII infused per kilogram of body weight will raise the plasma factor VIII level by 2% each unit of factor IX infused, because of a greater volume of distribution, will raise the plasma factor IX level by 1%. Therefore, 50 U/kg of factor VIII infused in a patient with severe hemophilia A should raise the plasma level of factor VIII to at least 100% the infusion of 100 U/kg of factor IX in a patient with severe hemophilia B should produce a similar level. In patients with life-threatening bleeding, the basal factor activity level should be considered to be 0%.

DOI: https://dx.doi.org/10.37871/ijcrsr.id94

CONCLUSION

Hemophilia is caused by several different gene abnormalities. The severity of the symptoms depends on how a particular gene abnormality impairs the activity of factors VIII and IX. When the activity is lower than 1% of normal, episodes of heavy bleeding appear and return for unclear reasons. People in whom clotting activity is 5% of normal may have only mild hemophilia. They rarely have unprovoked bleeding episodes, but surgery or injury can cause uncontrolled bleeding that can be fatal. Milder hemophilias may not be diagnosed at all, although some people with a clotting activity of 10%-25% of normal may bleed excessively after surgery, tooth extraction, or some major injury.

REFERENCES

1. DeFazio CL, Walker A, Braen GR. Initial Assessment of the Multiple Trauma Patient: Manual of Emergency Medicine, Sixth Edition. Wolters Kluwer, Lippincott Williams & Wilkins, Philadelphia, USA. 2011;33–35. https://tinyurl.com/527nnftm
2. Boardman FK, Hale R, Gohel R, Young PJ. Preventing lives affected by hemophilia: A mixed methods study of the views of adults with hemophilia and their families toward genetic screening. Mol Genet Genomic Med. 2019 May;7(5):e618. doi: 10.1002/mgg3.618. Epub 2019 Mar 5. PMID: 30838796; PMCID: PMC6503017.
3. Colo LL, Williams LS, Hopper PD: Nursing Care of Patients With Hematologic and Lymphatic Disorders: Understanding Medical Surgical Nursing, Fifth Edition: F. A. Davis Company, Philadelphia, USA. 2015;574-575. https://tinyurl.com/25yf69e3
4. Skinner MW, Nugent D, Wilton P, O'Mahony B, Dolan G, O'Hara J, Berntorp E. Achieving the unimaginable: Health equity in haemophilia: Haemophilia. 2020Jan;26(1):17-24. doi: 10.1111/hae.13862. Epub 2019 Nov; 13. PMID: 31724316; PMCID: PMC7891319.
5. Strecker-McGraw MK, Wilson MA, Stone CK, Humphries RL. Hematologic Emergencies: CURRENT Diagnosis and Treatment Emergency Medicine, Seventh Edition. The McGraw-Hill Companies, New York, USA. 2011;713. https://tinyurl.com/2yn3fdpj
6. Hotea I, Brinza M, Blag C, Zimta AA, Dirzu N, Burzo C, Rus I, Apostu D, Benea H, Marian M, Mester A, Pasca S, Iluta S, Teodorescu P, Jitaru C, Zdrenghea M, Bojan A, Torok-Vistai T, Niculescu R, Tarniceriu C, Dima D, Truica C, Serban M, Tomuleasa C, Coriu D. Current therapeutic approaches in the management of hemophilia-a consensus view by the Romanian Society of Hematology. Ann Transl Med. 2021 Jul;9(13):1091. doi: 10.21037/atm-21-747. PMID: 34423003; PMCID: PMC8339806.
7. Stafford I, Belfort MA, Dildy III GA, Belfort MA, Saade G, Foley MR, Phelan JP. Etiology and Management of Hemorrhage: Critical Care Obstetrics, Fifth Edition, Wiley-Blackwell, John Wiley & Sons, Ltd, Chichester, UK. 2010;321. doi: 10.1002/9781444316780
8. Miesbach W, O'Mahony B, Key NS, Makris M. How to discuss gene therapy for haemophilia? A patient and physician perspective: Haemophilia. 2019 Jul; 25(4):545-557. doi: 10.1111/hae.13769. Epub 2019 May;21. PMID: 31115117; PMCID: PMC6852207.

DOI: https://dx.doi.org/10.37871/ijcrsr.id94