Chapter

Introductory Chapter: Hemophilia

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1. Introduction

Hemophilia disease is caused by deficiency of coagulation factors VIII and IX. Former is called hemophilia A (80–85%) whereas latter is labeled hemophilia B (10–15%). Hemophilia A and B are X-linked disorders, have common clinical presentation, with no racial predilection and are seen in all ethnic groups. The incidence is 1 in 5000 male births. A rare variety of hemophilia—hemophilia C or Rosenthal syndrome (factor XI deficiency) is seen in Jews of Ashkenazi descent. It is a milder form of hemophilia and because of autosomal transmission affects both the sexes. As per annual global surveys by WFH number of PWH (people with hemophilia) is approximately 400,000 [1].

1.1 Pathophysiology

Factors VIII and IX along with phospholipid and calcium activate factor activating complex. This factor X activating complex or factor VII in presence of tissue factor activate factor IX initiating coagulation cascade. In laboratory prothrombin time (PT) measures activation of factor X by factor VII and is therefore normal in hemophilia.

After any injury, initial hemostatic response of the human body is to form a platelet plug and formation of fibrin clot to stop bleeding. In hemophilia clot formation is delayed. The clot is soft and not robust. Bleeding in open space leads to hemorrhage and significant blood loss. Bleeding in closed joint leads to tamponade effect. When the soft clot is lysed, rebleeding can occur following minimal trauma.

1.2 Classification

Hemophilia is classified as per baseline level of factors VIII or IX in blood. One unit is defined as amount present in 1 mL of normal plasma. Severe hemophilia means that coagulation factor is <1% of normal activity, i.e., <1 U/dL of plasma. Moderate hemophilia is between 1 and 5% of normal coagulant activity, i.e., 1–5 U/dL of plasma. And mild hemophilia when coagulant activity is higher than 5% of the activity, i.e., >5–40 U/dL of plasma.

1.3 Clinical presentation

Factor VIII and IX cannot cross placenta. So a neonate can bleed at birth or even a fetus can have bleeding in utero. Thirty percent of hemophilia patients may bleed after circumcision. Up to 3% may have ICH or intracranial hemorrhage [2], and half the number getting ECH (extracranial hemorrhage). Some may get ICH as well as ECH. All efforts should be made to prevent head trauma during delivery and

discourage forceps or vacuum extraction. Mostly hemophilia is suspected at birth because of family history but in one-third, it may be due to spontaneous mutation and therefore giving no clue from family history.

When a toddler tries to cruise, he starts getting symptoms like easy bruising following minor traumas, hematomas and bleeding in to joints. In early years when child tries to stand and walk, ankle joint followed by knee joint become the target joint for bleeding and hemarthrosis becomes main symptom He may also bleed from mouth because of torn frenulum. By 1 year of age 90% hemophiliacs present with excessive bleeding [3]. In older children and adolescents hemarthrosis in knee and elbow joints becomes more common and these joints become target joints. Hinged joints like ankle knee and elbow are more often involved. In 70–80% of cases, hemarthrosis is the main presentation. Bleeding into muscles occurs in 10–20%. Less than 5% bleed in CNS. At the time of bleeding in joints, there is feeling of tingling or warmth. This is followed by increasing pain and loss of motion. In a younger child pain and swelling of the joints present earlier but as the child grows older and bleeding occurs in the joints, pain and swelling of joint decreases. The patient comes to know of bleeding earlier. They are able to tell their parents that they are bleeding in to joints and the treatment should be started. When a child continues to have repeated hemarthrosis, chronic effusion and hyperemia appears in joints. If not managed properly with coagulation factors, chronic arthropathy occurs. As the age advances more PWH (people with hemophilia) get crippled because of repeated hemarthrosis in resource restrained countries [4]. Hemophilia patients may also present with hematuria or GIT bleeding.

MUSCLES: hemophilia patients bleed deep inside muscles and these hematomas are difficult to palpate. The patient gets vague feeling of pain on movement and there is increase in circumference of the affected limb. If not managed properly it can lead to fibrosis and contractures with muscular atrophy and pseudotumor formation. Bleeding in to iliopsoas muscle is particularly notorious. Such a patient has vague pain and discomfort in lower abdomen and upper part of thigh, with internally rotated thigh. These patients may have massive internal hemorrhage in the muscles requiring urgent specific aggressive management with factors for a fortnight followed prophylaxis for several months [2].

1.4 Life-threatening hemorrhages in hemophilia

1. Bleeding in CNS.
2. Bleeding in and around airway.
3. All exsanguinating hemorrhages including bleeding in iliopsoas muscles.

Bleeding in CNS and around airway can cause pressure symptoms in vital areas and airway compression. Exsanguinating hemorrhages can also cause shock and death. Such episodes require urgent therapy on slightest suspicion.

1.5 Hemophilia in female carriers

Because of lyonization of X chromosome, some female hemophilia carriers have sufficient reduction in level of factor VIII or IX and have mild bleeding disorder. Carriers with factor level of 40–60% may have bleeding tendency [5]. Levels of factor VIII or IX should be determined in all these carriers to determine the need for treatment when they go for surgery or have bleeding episode. There is also 50% probability of birth of female hemophilia patient when a male hemophilia patient marries a female hemophilia carrier.

1.6 Laboratory evaluation

It is easy to diagnose severe hemophilia. Prothrombin time (PT) is normal and partial thromboplastin time (PTT) is 2–3 times prolonged. Mild hemophilia is difficult to diagnosis as PTT may be normal or slightly prolonged. In a newborn, PTT may be slightly prolonged due to deficiency of vitamin K dependent factor IX and raised level of factor VIII due to stress of delivery. So diagnosis of hemophilia may require repeated tests of coagulation times.

Diagnosis of factor IX deficiency is more difficult as available commercial PTT reagents are more sensitive to factor VIII deficiency. PTT may be normal even with factor IX level as low as 15–20 U/dL. So it is advisable to perform factor IX assay even when PTT is normal in suspected hemophilia B. Specific functional assays of factors VIII and IX are done by mixing studies to confirm the diagnosis of hemophilia A and B. When mixed 1:1 with normal plasma PTT becomes normal in hemophilia. If PTT is not corrected, one should suspect presence of inhibitors to factor VIII or IX. Other causes are presence of lupus inhibitor or heparin. If inhibitors are present, quantitative Bethesda assay should be performed to measure antibody titer.

Immunoassays of factors VIII and IX can also be done to identify dysfunctional proteins called cross-reacting material (CRM). Immunoassays are usually not required for management of hemophilia patients. Clot waveform analysis and thrombin generation assay are also recommended for accurate estimation of factor VIII and IX activity during management of hemophilia patients especially when the factor levels are very low [6].

1.7 Genetic testing

Both hemophilia A and B are X-linked traits, and the encoding genes F8 and F9 map to the distal portion of long arm of chromosomes [7]. Commonest genetic alteration is inversion and mostly originating in male germ cells. Family history is present in approximately two third of patients and mutations constitute one third of cases. Genetic resting is available and performed on proband first. African Americans have different haplotype and therefore have higher level of inhibitor formation. Prenatal testing can be done by amniocentesis or chorionic villous biopsy. Factor IX gene is smaller. Missense point mutation is seen in more than 60% of patients. In case genetic testing is not helping, coagulation based assay can also be used to detect carrier state and it is 90% accurate [8].

1.8 Treatment

Hallmark of treatment is prompt and appropriate management of bleeding episode; and prophylactic therapy to prevent future hemorrhages decreasing the incidence of chronic complications.

Supportive care: In general hemophilia patients should be advised to avoid trauma, but it is very difficult to advise a child in growing age of activity to completely do so. They can be advised to avoid risk prone behavior, use seat belts and bike helmets while driving. Ask them to avoid contact sports like, boxing and wrestling. They can do swimming and play table tennis, badminton, etc. In mild and moderate hemophilia these measures may help but in severe hemophilia there can be bleeding without trauma. Psychosocial counseling may help the child to achieve a balance. Hemophiliacs should be advised to avoid nonsteroidal anti-inflammatory drugs like aspirin, as these drugs interfere with platelet functions and aggregation, making him prone to bleeding. These patients should be immunized against hepatitis B and those on plasma-derived products should be screened periodically for HIV, hepatitis B and C.

Half-life of factor VIII is 8–12 h and that of factor IX is 18–24 h. In event of mild to moderate hemorrhage, level of factor VIII or IX has to be raised to hemostatic level of 35–50% range. In life threatening or severe hemorrhage, hemostatic level of factor should be raised to 100% [3].

Dose of recombinant factor VIII (rFVIII) in IU:

$$\text{Body weight (kg)} \times 0.5 \times \%\text{age of desired rise in rFVIII.} \quad (1)$$

Dose of recombinant factor IX (rFIX) in IU:

$$\text{Body weight (kg)} \times 1.4 \times \%\text{age of desired rise in rFIX.} \quad (2)$$

Endogenous factor VIII can be released by desmopressin acetate (DDAVP, 1-deamino-8-*d*-arginine vasopressin) in mild hemophilia. Intranasal preparation of concentrated preparation of desmopressin acetate 150 μg/puff is given as one puff to the patient weighing <50 kg and two puffs (300 μg) to patient >50 kg. Desmopressin is not effective in hemophilia B.

1.9 Recombinant factors

Development of recombinant factors is a major advance in treatment of hemophilia patients. Three generations—first, second and third generations are currently available [9]. First generation factor concentrates are stabilized with human albumin, second generation is stabilized with sucrose, and third generation is stabilized with/without additional human or animal plasma proteins. Efforts are still being made to get better recombinant factors with longer half-life and less immunogenicity, so that the frequency of prophylactic infusion may be further decreased [10]. With use of plasma derived factors, inhibitor formation is less, and after 150 EDs (exposure days) inhibitor formation is negligible [11]. In some centers, initial prophylaxis is given with plasma derived factors VIII and IX, and with recombinant factors after 150 EDs. Recombinant factor VIII is available in all three generations, but for factor IX, only third generation recombinant factor is available.

1.10 Adjunctive management

1. More important in resource limited conditions, when there is less availability of factor VIII and IX.

2. First aid measures are important in management of acute bleeding episode presenting as musculoskeletal hemorrhage like hemarthrosis. Protection (splint), rest, ice, compression and elevation (**PRICE**) are very useful in acute hemarthrosis [12].

3. Pain killers: NSAID drugs like aspirin should be avoided. Paracetamol is safest analgesic. Some COX-2 inhibitors can be judiciously used in arthropathy.

4. Physiotherapy/rehabilitation after pain decreases.

5. Antifibrinolytic drugs like tranexamic acid and epsilon aminocaproic acid can be used in mucosal bleeds and dental extraction.

1.11 Long-term complications

These are chronic arthropathy, development of inhibitors to factors VIII or IX and the risk of transfusion-transmitted infections.

a. Chronic arthropathy: hemarthrosis in target joints is commonest presentation in hemophilia. After every such episode, proteolytic enzymes are released by white blood cells in the joint space. Heme released from blood induces macrophage proliferation leading to synovitis. Thickened synovium develops frond like projections which on getting pinched induces further hemorrhage. Cartilaginous surface of the affected joint gets eroded and exposes bone surface leading to articular fusion and ankylosis. Because of repeated hemarthrosis, synovium gets more and more thickened leading to narrowing of joint space, little space to accommodate more blood and causing intense pain. Such patients need to be put on short-term or long-term prophylaxis to prevent progression of arthropathy.

b. Development of inhibitors: repeated infusion of factors VIII or IX may induce immune response leading to formation of inhibitor antibodies to the deficient factor. Such patients fail to respond to appropriate factor replacement after bleeding episode. Incidence of inhibitor development may be as high as 25–30% in hemophilia A and somewhat lower in hemophilia B. Risk of development of inhibitors is minimal after 150 exposure days to coagulation factors. MASAC (USA) advises inhibitor assay only up to 150 exposure days [11]. With recombinant factor VIII incidence of inhibitor development is 87% higher and 69% higher incidence of high titer inhibitor compared to plasma derived factors. Some inhibitors to factor IX may also cause anaphylaxis. Incidence of development of inhibitors is higher with recombinant factors than plasma derived factors. Such patients may lose inhibitors and respond after continued administration of factors. Some others may require desensitization by infusing higher dose of factor VIII or IX, saturating antibodies and inducing immune tolerance induction. Alternatives are rituximab, steroids and cyclophosphamide. In patients who do not respond to these agents, recombinant factor VIIa or prothrombin complex concentrate may be used to bypass factor VIII.

c. Risk of transfusion transmitted infections: in past, there had been many incidences of transmission of hepatitis B and C and even HIV when plasma derived factors VIII and IX were used. Now with advent of recombinant factors VIII and IX, such a risk is minimal but one must immunize these patients for hepatitis B and monitor immunization status of the patient.

Hemophilia A patients with inhibitors: these patients can be divided in to two types.

a. Low responding factor VIII inhibitors: inhibitor titer is <5 Bethesda units. These can be treated with factor VIII at higher doses. Continuous administration of factor VIII is more effective. For common muscle and joint hemorrhages, double dose of factor VIII is usually effective.

b. High responding factor VIII inhibitors: inhibitor titer is more than five Bethesda units. Requires management in a tertiary hemophilia care centers by hemophilia experts. Treatment is more aggressive. Alternatives are porcine factor VIII concentrates, recombinant factor VIIa, prothrombin complex concentrate or activated prothrombin complex concentrate (commercially available FEIBA or factor VIII inhibitor bypassing activity).

Hemophilia B patients with inhibitors: incidence of inhibitor formation is much lower but can cause anaphylaxis. Activated prothrombin complex concentrate and recombinant factor VII are very effective. In patients who have developed anaphylaxis,

use of activated prothrombin complex concentrate is contraindicated as this contains some factor IX, use of factor VIIa is the answer [2]. Immune tolerance is not effective as some of the patients develop nephrotic syndrome if higher dose of factor IX is given.

1.12 Hemophilia prophylaxis

Hemophilia prophylaxis is regular administration of factors VIII or IX to the patient to prevent bleeding. It was observed that mid and moderate hemophilia patients, who have coagulation factor level >1% rarely had spontaneous hemorrhage. And if we can maintain factors VIII or IX level >1%, patient will not have spontaneous hemorrhage, thereby decreasing moribund and debilitating complications with much better preservation of joint functions. Prophylaxis requires insertion of central catheter to ensure venous access, is expensive, requires more of costly factors but reduces complications and preserves joints. Hemophilia prophylaxis can be primary, secondary or tertiary [9].

a. Primary regular prophylaxis: prophylaxis treatment started regularly before second clinically relevant large joint bleed and before 3 years of age. There is no documented osteochondral joint disease on clinical and radiological examination.

b. Secondary regular prophylaxis: prophylaxis treatment after two or more joint bleeds in to large joints and before the onset of joint disease, confirmed by clinical and radiological examination.

c. Tertiary regular prophylaxis: prophylaxis treatment after onset of joint disease documented after clinical and/or plain radiograph of affected joint.

Prophylaxis can also be classified as intermittent or continuous:

a. Intermittent (Periodic): prophylactic factors given for periods not exceeding 45 weeks in a year.

b. Continuous: with an intent to treat for 52 weeks/year and for at least 45 weeks (85%) of the year under consideration.

In a patient with repeated hemarthrosis or bleeding, short-term prophylaxis for 4–8 weeks is recommended to interrupt the bleeding cycle. Whether adults require long-term prophylaxis is not yet clear. More studies are required to confirm this. Some young adults can do well off prophylaxis. Prophylaxis does not reverse the damage already done to the affected joint, but it slows the progression of arthropathy and improves quality of life. It is also cost-effective as it helps to avoid the subsequent costly management of damaged joints.

Dose schedule for prophylaxis [12]:

a. Malmo protocol: 25–40 IU/kg per dose thrice a week for hemophilia A and twice a week for hemophilia B.

b. Utrecht protocol: 15–30 IU/kg per dose thrice a week for hemophilia A and twice a week for hemophilia B.

Many countries follow different protocols. Protocol should be individualized. It is best given in the morning to cover activity of whole day.

1.13 Home therapy of hemophilia

With home therapy treatment is started earlier, so onset of complications is delayed. A certificate program shall be helpful. Family and patient need to be educated about general information and perspective of hemophilia. They need to know about first aid measures; dosage calculation, storage and administration of coagulation factors. Knowledge about aseptic technique, central catheters, proper storage and disposal of needles, record keeping and management of blood spills is mandatory. Comprehensive care team should monitor all this by making frequent follow up visits. Family members should be motivated to take care of young children. Older children and young adults can learn self-infusion and care.

1.14 Comprehensive hemophilia treatment centers (CHTC)

Hemophilia treatment centers must provide comprehensive medical care to hemophilia patients. Multiple disciplines should be involved providing state of art medical care. The center should have hematologist, pediatrician, nurses, dentist, psychologist, social worker, physical therapist and orthopedist. Even patients and their families should be part of the team. Every year the patient should be assessed for individual and potential problems, so that if required his treatment can be modified.

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