Hemophilia & Acquired Hemophilia A

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Hemophilia & Acquired Hemophilia A

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Abstract

Hemophilia is a rare, usually inherited, bleeding disorder in which blood cannot clot normally at the site of a wound or injury which leads to prolonged bleeding or oozing. In severe cases of hemophilia, heavy bleeding occurs after minor trauma or even in the absence of injury. Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. Milder forms of hemophilia do not involve spontaneous bleeding. This condition is due to absence or low levels of clotting factors (f). Hemophilia is an inherited X-linked bleeding disorder resulting from a deficiency of factor (f) VIII or fIX. Hemophilia A, fVIII deficiency, occurs in 1 out of 10,000 male births, while hemophilia B, fIX deficiency, occurs in 1 out of 30,000 male births. [5] A deficiency of either f VIII or fIX results in the absence of a functioning certain blood clotting protein called factor. Coagulation factor is necessary for the clotting mechanism in our bodies to work. [1] The two main types of hemophilia are A and B. hemophilia A (also known as classic hemophilia) and hemophilia B (also known as Christmas disease). About 9 out of 10 people who have hemophilia have type A. Although the two types have very similar signs and symptoms, they are caused by mutations in different genes. Hemophilia affects males much more often than females. [1, 2, 3]

Hemophilia disorder can also be acquired later in life called as Acquired Hemophilia. Acquired hemophilia (AH) is an extremely rare condition in which body begins to produce antibodies that attack and destroy clotting Factor VIII. Induce acute and life-threatening hemorrhagic diathesis because of abnormal blood clotting. The person may bleed for no apparent reason. However unlike congenital hemophilia it is not passed on through families (because the gene is normal).

Introduction

Hemophilia is a rare, usually inherited, bleeding disorder in which blood cannot clot normally at the site of a wound or injury which leads to prolonged bleeding or oozing. In severe cases of hemophilia, heavy bleeding occurs after minor trauma or even in the absence of injury. Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. Milder forms of hemophilia do not involve spontaneous bleeding. This condition is due to absence or low levels of clotting factors (f). Hemophilia is an inherited X-linked bleeding disorder resulting from a deficiency of factor (f) VIII or fIX. Hemophilia A, fVIII deficiency, occurs in 1 out of 10,000 male births, while hemophilia B, fIX deficiency, occurs in 1 out of 30,000 male births. [5] A deficiency of either f VIII or fIX results in the absence of a functioning certain blood clotting protein called factor. Coagulation factor is necessary for the clotting mechanism in our bodies to work. [1]

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Epidemiology: Prevalence and Incidence

Congenital Hemophilia:

Hemophilia A and B incidence is the same for all populations and racial groups, estimated to be 20 per 100,000 male births. Some studies reported below average prevalence numbers in Africa and Asia. Individuals with hemophilia registered by the Hemophilia Federation of India account for only about
10% of what is expected, while hemophilia patient registry data in Malaysia and South Africa account for less than 50% of expected cases. Only five of 11 countries in Africa reported data on the number of people with hemophilia A; of those, the prevalence ranged from 1.7 to 6.5 per 100,000 males. Only four of nine countries in South America reported data; of those, the prevalence ranged from 3.0 to 9.3 per 100,000 males. Just three of 10 countries in Asia reported data; of those, prevalence ranged from 2.9 to 3.6 per 100,000 males. [37]

WFH’s global survey showed that prevalence does not remain static but instead can shift. In the early 1970s, the reported hemophilia A prevalence in the United Kingdom (UK) was approximately 10 per 100,000 males, while the U.S. reported a rate of approximately 20 per 100,000 males. Three decades later, the reported data show a near reversal: for 2006 the U.S. reported prevalence of 8 per 100,000 males, while the UK reported 20.7 per 100,000. In fact, within countries, survey data showed a clear trend of rising prevalence over time, with Canada increasing from 10.2 in 1989 to 14.2 in 2008. [37] There is increase in prevalence of hemophilia over the past 30 years; the United Kingdom had a prevalence of 9.3 per 100,000 in 1974, but it had risen to 21.6 per 100,000 by 2006. [27, 28, 37]

The incidence of hemophilia A worldwide 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 varies with the reporting country, with a range of 5.4-14.5 cases per 100,000 male individuals.[29] The prevalence of hemophilia A in high-income countries was approximately 12.8 per 100,000 males and approximately 6.6 per 100,000 males in lower-income countries. According to study by Stonebraker [27] incidence of hemophilia A or the number of people born with the condition is the same around the world so the difference in prevalence or the number of people living with the condition at any given moment appears with much higher mortality in developing countries. The prevalence of hemophilia A is 20.6 cases per 100,000 male individuals, with 60% of those having severe disease. An estimated 17,000 people were affected with hemophilia A in the United States in 2003. [29]

Alloantibodies and autoantibodies to factor VIII (FVIII inhibitors) have been reported from many parts of the world. [13] The inherited combined factor V and factor VIII deficiency has been reported in patients from Europe, Tunisia, the Middle East, Iran, China, and India.

**Acquired Hemophilia:**

Acquired hemophilia A (AHA) is a rare but life-threatening bleeding disorder, typically occurring in the elderly has a worldwide distribution with an estimated annual incidence between 1.3 and 1.5 per million per year. [30-35] Age distribution is bimodal, with a first peak occurring among young adults, due to cases in women in the postpartum period, and a second major peak in elderly patients in whom it is frequently associated with malignancy and drugs, and very difficult to manage due to the comorbidities and the fragility of the older subjects. [36]

According to recent data, the incidence in subjects aged <65 yrs is 0.28 per million per year, but increases up to 5.97 in those aged 65–85 yrs and to 16.6 in individuals older than 85 yrs. [31]

In the United Kingdom, the incidence of acquired hemophilia has been reported to be 1.48 per million persons per year. [12] There is no known association between an increased susceptibility to develop acquired auto antibodies to coagulation factors and ethnicity.

The age distribution of acquired hemophilia is typically biphasic. There is a small peak in incidence in women aged 20-30 years, and a major peak in males aged 60-80 years [8, 9] the vast majority cases of acquired hemophilia occur in older adults. The median age at presentation is between 60 and 67 years. [9, 10, 11] Acquired hemophilia has no known genetic inheritance pattern and is seen equally in men and women [10] it occurs in all racial groups.

The incidence of acquired hemophilia A in United States has been estimated to be 0.2-1.0 case per 1 million persons per year, but this figure may underestimate the true incidence of the disorder, given the difficulty in making the diagnosis. [8] In addition, some patients with acquired hemophilia and low titers of inhibitors may not be diagnosed unless they undergo surgery or trauma, which also may lead to an underestimation of the incidence of the disease. [8]

The incidence of acquired inhibitors to clotting factors other than factor VIII (FVIII) is unknown, although it is significantly lower than that reported with acquired hemophilia A.
A study of reported hemophilia A prevalence is shown in Table 1 [6] and hemophilia A prevalence is shown in Table 2 [6.1]

 Symptoms & diagnosis

The symptoms of hemophilia vary, depending on the degree of blood clotting factor (coagulation factor) deficiency and they also depend on the nature of any injury. According to the level of clotting factor amounts in the blood three levels of hemophilia are recognized.

1. Above 5%-40% (0.05-0.40)- mild hemophilia
2. 1% to 5% (0.01-0.05) - moderate hemophilia
3. Less than 1% (<0.01)- severe hemophilia [41]

The symptoms of moderate to severe hemophilia typically appear in infancy or childhood. The symptoms of milder forms of hemophilia often appear a little later in life and include symptoms associated with bleeding into the joints, muscles or soft tissues, prolonged bleeding after cuts, bites or minor surgery, bruising on the surface of the skin and blood in the urine. [39]

1. Bruising easily (for example, an infant born with hemophilia A or B may bruise simply from being lifted.)
2. Bleeding in the mouth from a cut or bite or from losing a tooth
3. Heavy nosebleeds (epistaxis) for no obvious reason
4. Heavy bleeding from a minor cut
5. Cuts that bleed again after they have already stopped for a short time
6. Blood in the urine or stool, resulting from bleeding in internal organs
7. Tightness, swelling, warmth and/or pain in the joints

Acquired hemophilia A occurs when non-hemophiliacs form antibodies against FVIII. Triggers for acquired hemophilia may include pregnancy or other medical conditions. Overdosing of anti-thrombotic medication may also lead to bleeding symptoms. [38]

Diagnosis: Nearly all patients with hemophilia have a known family history of the condition. Still, Most of the cases without a family history arise due to a spontaneous mutation in the affected gene. If family history is not known, a series of blood tests are required for diagnosis. [40, 41] Tests includes screening tests and clotting factor tests [42]

Screening tests are blood tests which include:

Complete Blood Count (CBC) will be normal in hemophilic people however the person with unusual heavy bleed may have low hemoglobin and RBC.

Activated Partial Thromboplastin Time (APTT) Test measures the clotting ability of factors VIII (8), IX (9), XI (11), and XII (12). In absence or low levels of these clotting factors lead to poor blood clot or take longer time for clotting.

Prothrombin Time (PT) Test also measures the blood clotting time. It measures primarily the clotting ability of factors I (1), II (2), V (5), VII (7), and X (10).

Fibrinogen Test is conducted either along with other blood clotting tests or when a patient has an abnormal PT or APTT test result, or both. Fibrinogen is another name for clotting factor I (1).

Clotting factor tests, also called factor assays, are required to diagnose a bleeding disorder. This blood test shows the type of hemophilia and the severity. It is important to know the type and severity in order to create the best treatment plan.

See Illustration 7

Acquired bleeding disorders affect men and women equally, and the potential for significant bleeding problems is high. [38]

Genetic testing to identify and characterize the specific mutations responsible for hemophilia is also available in specialized laboratories.

Diagnosis of acquired hemophilia can be difficult, both because the condition is rare and because the patient does not have the usual personal or family history of bleeding episodes, such as is seen in congenital hemophilia.

For Acquired Hemophilia (AHA) Activated partial thromboplastin time (aPTT) put forward the diagnosis of AHA. APTT cross-mixing tests are useful for the rapid distinction between factor deficiency and the
presence of an inhibitor. FVIII inhibitor is time and temperature-dependent; therefore, mixing tests performed immediately and after 2 hours of incubation should be compared. In some cases, all intrinsic factors are decreased, which may represent an in vitro artifact due to the depletion of FVIII in the substrate plasma by the inhibitor. Irrespective of the result of mixing tests, further investigation is required, and specific factor assays should be performed in parallel to facilitate an early diagnosis. [43, 44, 45]

In some cases, A lupus anticoagulant can also cause artefactual lowering of factor levels due to inhibition of phospholipids in the assay, and specific tests for a lupus anticoagulant should be performed. In addition, Factor assays should be repeated at higher serial dilutions of the test plasma, which will attenuate the effect of the inhibitor or LA on the factor measurement and may also distinguish between AHA and LA. And in complex cases, a FVIII antibody ELISA may be useful to distinguish between a lupus anticoagulant and an acquired FVIII inhibitor. Acquired inhibitors to FVIII often display non-linear type 2 kinetics; therefore, the inhibitor titer measured by the Bethesda assay is used to quantify FVIII alloantibodies. [43, 44, 45]

Treatment

The most important treatment for hemophilia is replacement therapy in which clotting factor VIII (for hemophilia A) or clotting factor IX (for hemophilia B) are given to the hemophilic patients which help replace the missing or low clotting factor [1]

Other Types of Treatment [1]

Desmopressin (DDAVP) is a man-made hormone used to treat people who have mild to moderate hemophilia A. DDAVP stimulates the release of stored factor VIII and von Willebrand factor.

Antifibrinolytic medicines (including tranexamic acid and aminocaproic acid) may be used with replacement therapy.

Researchers are trying to find ways to correct the faulty genes that cause hemophilia. Gene Therapy hasn’t yet developed to the point that it’s an accepted treatment for hemophilia. However, researchers continue to test gene therapy in clinical trials.

1. Treatment of a Specific Bleeding Site
2. Pain medicines, steroids, and physical therapy may be used to reduce pain and swelling in an affected joint. Talk with your doctor or pharmacist about which medicines are safe for you to take.

The management of AHA at clinical presentation is very challenging. The strategies for treatment of AHA have two major objectives. During acute bleeding episodes, effective control of bleeding manifestations is the primary objective. However, the ultimate therapeutic goal is to eliminate the inhibitor and cure the disease. The two treatment priorities are to arrest the acute bleeding and to eradicate the factor VIII autoantibody. The following are practiced for AHA treatment [46]

1. Treatment of acquired FVIII inhibitors
2. Treatment options for acquired hemophilia A
3. Treatment of acute hemorrhages
4. Bypassing agents
5. Treatments to raise FVIII levels
6. Inhibitor eradication
7. Immunosuppressive agents
8. High-dose intravenous immunoglobulin
9. Immunoabsorption
10. Immune tolerance
11. Novel eradicating therapies: rituximab

The treatment of AHA as per guidelines include, Replacement therapy with FVIII (or FIX) concentrates, plasma-derived human FVIII concentrates, recombinant human FVIII concentrates, plasma-derived human FIX concentrates, recombinant human FIX concentrate, By-pass therapy, Plasmapheresis and immunoabsorption Corticosteroids, Cyclophosphamide, Azathioprine, Ciclosporin, Human immunoglobulin for intravenous use (ivIG), Rituximab, Factor VIII concentrate.[47]

Clinical Trials

Clinical trials on Acquired Hemophilia A and All Hemophilia globally are illustrated in Figure 1 and Figure 2

Conclusion:

This Article is developed to explain what is hemophilia, (congenital & acquired) and its prevalence and incidence, disease profile and treatment throughout the world
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Illustrations

Illustration 1

Table 1: The reported hemophilia A prevalence (per 100000 males) the reported number of patients with hemophilia A in a country from 1998–2006 divided by its male population in the relevant year [6, 6.1]

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Table 1 cont
Table 2. The reported hemophilia B prevalence (per 100 000 males) from 1998 to 2006 was determined from the number of people with hemophilia B in a country reported to the World Federation of Hemophilia divided by its male population in the relevant year. [6.1]

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Illustration 4

Table 2 cont
Illustration 5

Figure 1: Worldwide all Hemophilia clinical trials

Illustration 6

Figure 2: Worldwide all Hemophilia clinical trials
Illustration 7

Table

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<th>Severity</th>
<th>Levels of Factor VIII (8) or IX (9) in the blood</th>
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<td>Normal (person who does not have hemophilia)</td>
<td>50% to 100%</td>
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<td>Mild hemophilia</td>
<td>Greater than 5% but less than 50%</td>
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<td>Moderate hemophilia</td>
<td>1% to 5%</td>
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<tr>
<td>Severe hemophilia</td>
<td>Less than 1%</td>
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</table>
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