Hemophilia

Hemophilia A and B are genetic disorders of clotting factors VIII and IX, respectively. FVIII and FIX are either defective or made in insufficient amounts, resulting in impaired secondary hemostasis. The incidence of hemophilia A and B is about 1/5000 males worldwide and affects individuals of all races and socioeconomic groups.

Classical hemophilia, hemophilia A, is estimated to account for 85% of all cases. It is a deficiency or dysfunction of FXIII. Half of cases are caused by a variety of mutations in the gene coding for FXIII, resulting in a spectrum of disease presentation. The second half of cases are due to a “flip tip” inversion in the FVIII gene resulting in misreading of a non-coding region and a shortened gene product. All individuals with this inversion have severe disease.

Hemophilia B, also known as Christmas disease, is estimated to account for 15% of hemophilia cases and is caused by a deficiency or dysfunction of FIX.

Genetics

Both genes for FVIII and FIX are located on the X chromosome. The disease primarily affects males, but female carriers may be symptomatic. Daughters of affected males are obligate carriers. Genetic counseling is recommended for families and individuals affected by hemophilia.

One third of hemophilia A is due to spontaneous mutations and affected patients have no family history. However, all cases due to FVIII inversions are inherited for a mother carrier. The risk that a mother of an affected male is a carrier of hemophilia A is about 80%.

Pathophysiology

Coagulation consists of two processes: primary and secondary hemostasis. Primary hemostasis involves the aggregation of platelets at an injury site. An initial platelet plug is established and subsequently replaced by a more stable fibrin clot through secondary hemostasis.

Secondary hemostasis involves the coagulation cascade: a sequence of reactions that ultimately leads to the formation of the stable fibrin clot. FVIII and FIX are both part of the intrinsic pathway of the coagulation cascade and are necessary to convert FX to FXa, the first step of the common pathway. A deficiency or defect in either FVIII or FIX decreases the activation FXa, impairing subsequent reactions necessary to create fibrin clots.
Clinical Presentations
There is a spectrum of disease severity among hemophiliacs. Severity is classified based on the amount of FVIII or FIX activity. The relative deficiency of activity is manifest by frequency and causes of bleeding episodes.

Clinical Classification of Hemophilia

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<thead>
<tr>
<th>Classification</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
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<tbody>
<tr>
<td>Factor VIII or IX activity</td>
<td>&lt;1%</td>
<td>1% to 5%</td>
<td>6% to 30%</td>
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<tr>
<td>Frequency of cases</td>
<td>50% to 70%</td>
<td>10%</td>
<td>30% to 40%</td>
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<td>Causes of Bleeding</td>
<td>Spontaneous</td>
<td>Minor trauma, rarely spontaneous</td>
<td>Major Trauma, surgery</td>
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<td>Frequency of Bleeding</td>
<td>2 to 4 times/month</td>
<td>4 to 6 times/year</td>
<td>Uncommon</td>
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<td>Pattern of Bleeding</td>
<td>Joint, soft tissue, bleeding after circumcision, neonatal ICH</td>
<td>Joint, soft tissues, ± bleeding after circumcision, ± neonatal ICH</td>
<td>Joint, soft tissues, ± bleeding after circumcision</td>
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Hemophilia may present differently depending on the severity of disease. Therefore severe disease is likely to present early in life, while mild and moderate disease may present later. Below is a list of possible presentations and complications of disease.

Intracranial hemorrhage (ICH)
- Occurs in 2 to 5% of individuals with hemophilia, can occur in 50% preterm infants with the disease.
- Half of If ICH cases arise spontaneously
- Leading cause of death among hemophiliacs with a 50% mortality rate

Iatrogenic causes
- Prolonged bleeding after circumcision occurs in 30% of affected neonates
- Hematomas may occur following immunizations

Oral bleeding
- Eruption of teeth may lead to anemia. Oral bleeding is not evident in infants because they swallow blood
- Delayed bleeding may occur after dental procedures or tooth loss

Soft Tissue Bleeding
- Frequent episodes of prolonged epistaxis
- Large intramuscular hematomas may occur. Muscles may become swollen, hard, and painful. May present as acute abdomen, neuropathy, or compartment syndrome
- Joint pain due to hemarthroses, can lead to hemophilic arthropathy. Patients often have a “target joint” that is site of recurrent bleeding episodes

Other presentations
- Spontaneous hematuria
- Menorrhagia
Screening & Diagnosis

Questions to ask during exam:
- Does any one in the family have a bleeding disorder?
- Did the patient have prolonged bleeding after circumcision or dental procedure?
- Is there a family history of menorrhagia?
- Does the patient have joint pain, or muscle stiffness?
- Does the patient bruise easily or excessively?
- Has the patient had episodes of spontaneous bleeding or bruising without inciting trauma?
- Is there a history of blood transfusions or iron replacement therapy?

Prenatal Genetic testing should be offered to all known carriers of hemophilia gene
- Chorionic villus sampling is offered between 9 and 11 weeks gestation
- Amniocentesis is offered between 12 and 15 weeks gestation

Neonatal factor assays should be performed on male infants with a family history of bleeding problems or prolonged bleeding after circumcision
- Hemophilia A can be diagnosed from FVIII levels in cord blood collected immediately after delivery
- Hemophilia B requires blood be taken after 6 months of age since FIX is vitamin-K dependent and all neonates have low levels of vitamin K and FIX

Other screening tests should be performed in children who present with excessive bruising or bleeding
- aPTT is prolonged
- PT is normal
- Bleeding time and PFA are normal

Diagnosis can only be made by factor assays
- Hemophilia A
  - Measure FVIII activity and level
  - Measure von Willebrand Factor to rule out von Willebrand Disease
- Hemophilia B
  - Measure FIX activity and level

Treatment
Management of hemophilia requires prevention and treatment of acute bleeding episodes. Acute bleeding episodes are treated with clotting factors. Patients often have a sense that they are bleeding. They may feel a trickling, warmth, or tingling sensation from blood accumulating in tissues. Clotting factors should be administered immediately to prevent hemarthroses, compartment syndrome, or ICH.

For patients with severe disease prophylactic replacement therapy should be implemented. Such treatment reduces episodes of bleeding and prevents the development of arthropathy and compartment syndrome. Prophylaxis involves comprehensive care teams of physician specialists, dentists, genetic counselors, physical therapists, occupational therapists, and nurse coordinators.
Team members evaluate patients regularly and help patients establish home infusion therapy of clotting factors. There are a variety of products that can be administered to treat and prevent bleeding episodes.

- Purified Plasma derived FVIII and FIX are derived from human or porcine serum.
- Recombinant FVIII and FIX are synthesized from genetically modified cells.
- Prothrombin complex concentrate contains factor II, VII, IX and X
- Recombinant FVIIa is given to patients who have developed inhibitors to other factors
- Desmopressin acetate increases the release of FVIII from endothelial cells and is useful for treating mild-to-moderate FVIII deficiency

Guidelines for clotting factor administration and maintenance are as follows:

- Patients with minor bleeding episodes should achieve factor levels of 50-60% normal
- Patients with major hemorrhage should achieve factor levels of 100%

Complications of treatment and disease

- Many patients have severe pain due to bleeding into joints and muscles. They must be treated with medications such as acetaminophen or oxycodone. Aspirin and NSAIDs must be avoided as they can exacerbate bleeding.
- Infections such as Hepatitis B, Hepatitis C, and HIV have been risks of hemophilia treatment due to the use of human clotting factor preparations. Use of purified-plasma-derived and recombinant factor concentrates has reduced the incidence of these infections in newly diagnosed hemophiliacs. Still all hemophiliacs are immunized against Hepatitis B when diagnosed.
- Inhibitors are antibodies against FVIII or FIX molecules that develop after multiple treatments with clotting factor. These inhibitors make hemostasis difficult to achieve. They are more likely to develop in patients with hemophilia A, but do occur in patients with hemophilia B as well. Patients with inhibitors have a prolonged aPTT and high titers of inhibitors. Often patients with inhibitors require treatment with FVIII bypassing products such as recombinant FVII.

Advances in Therapy

Gene therapy is currently being investigated as a treatment options for hemophiliacs. Such therapy would reduce the need for long-term IV infusions of clotting factors. In 2011, a study found adenovirus-associated virus vector expressing human factor IX gene increased FIX levels in all participants with hemophilia B. Though there results are encouraging, disease was not eliminated, but did reduce frequency of needed clotting factor transfusions.

References