Hemophilia is a long-known coagulation disorder. Symptoms often manifest early in life, therefore, the disease is usually detected in good time. The following article presents all the important facts about hemophilia—from etiology to clinical presentation to diagnosis and treatment. From the information in this article, you will be optimally prepared for your upcoming exams and clinical practice.

For a general overview of hemostaseology, we recommend that you read the article
History and Epidemiology of Hemophilia

Hemophilia: A Rare Genetic Disease

History shows that even in the distant past, people have suffered from hemophilia. Some stories about abnormally bleeding children go back to the 5th century. Especially the European royalty and many other dynasties seem to have suffered from hereditary coagulation disorders.

The reason for this might be because the familial preferences regarding marriage and procreation did not occur to anyone for a long time. Instead, hemophilia was branded as the "royal disease". The most prominent examples can be found among the British Royal family and the Russian Tsarist dynasty. The genetic bridge between these two “bleeder” families was through a granddaughter of Queen Victoria of the United Kingdom, who married Tsar Nicholas II.

There are two distinct forms of hemophilia: type A and type B. According to the World Federation of Hemophilia; 1 in 10,000 patients are affected by type A whereas only 1 in 50,000 patients suffer from type B. It is estimated that 400,000 people have hemophilia worldwide. This indicates that this disease is one of the rarer hereditary diseases.

Etiology and Pathophysiology of Hemophilia

Hemophilia as a Clotting Factor Deficiency

Hemophilia results from a type of coagulopathy that is caused by a coagulation factor deficiency. There are two main forms of hemophilia: type A and type B.

- **Hemophilia A** is a deficiency in coagulation factor VIII. Type A affects 90% of all hemophilia cases. There are different severity degrees of hemophilia, which depend on the amount of active coagulation factor present in the blood, ranging from mild to moderate and moderate to severe.
- **Hemophilia B** is caused by a deficiency in **coagulation factor IX**.

These factors are key components of the coagulation cascade. Factor VIII plays a special role: It travels in blood as a non-covalent complex which consists of two components: factor VIIIc and the von Willebrand factor (vWF). Factor VIIIc is produced in the endothelium of the liver and megakaryocytes. The vWF protects it from **proteolysis**.

**Note:** This connection is important for the differential diagnosis of hemophilia as it relates to the von Willebrand disease, which also occurs due to a coagulation factor deficiency involving factor VIII.

### Causes of Hemophilia

Hemophilia is a genetic disorder. In most cases, it is inherited as an **X-linked recessive** trait. However, in about one third of the cases, it is caused by a spontaneous mutation of the X chromosome. Below are the most important facts regarding the genetics of hemophilia:

- All male hemophiliac patients have the genetic defect.
- A male who is not hemophiliac does not have the genetic defect.
- A female who is not hemophiliac, however, can still be a heterozygous carrier of the genetic defect.
- A “true” hemophiliac female is very rare since she would have to inherit the mutated X chromosome from both mother and father.
- All daughters of a hemophiliac patient will be carriers.
- If a female carrier has a male offspring, he has a 50 % probability of being hemophiliac.
Signs and Symptoms of Hemophilia

Clinical Presentation of Hemophilia

The clinical presentation of hemophilia depends on the level of activity of the residual coagulation factors. It can range from normal bleeding patterns to very severe spontaneous bleeding.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Factor activity</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 75 %</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Subhemophilia</td>
<td>16 – 75 %</td>
<td>Mostly asymptomatic</td>
</tr>
<tr>
<td>Mild</td>
<td>6 – 15 %</td>
<td>Hematoma after severe trauma</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 – 5 %</td>
<td>Hematoma after mild trauma</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 1 %</td>
<td>Spontaneous bleeding, hemarthrosis</td>
</tr>
</tbody>
</table>

If the bleeding tends manifests early, it can be observed from umbilical cord bleeding.
Infants may experience very severe bleeding in their mouths and pharyngeal area which can cause dangerous **asphyxia**.

Intramuscular hemorrhages can remain undetected; in such cases, only a close **clinical examination** can provide the relevant indications:

- Does the patient adopt a certain posture targeted at preventing pain?
- Does the patient move their leg in an unusual way?
- Does the patient have a tendency to tuck up one leg? This could indicate an iliopsoas hemorrhage.

Later in life, signs of hemophilia include prolonged or excessive bleeding even after minor surgical procedures or trauma.

### Diagnosis of Hemophilia

#### Family History, Physical Examination, and Laboratory Testing for Hemophilia

The etiological and pathophysiological conditions of hemophilia make a thorough analysis of the patient’s family history an indispensable part of the diagnostic process. Also, the specific types of bleeding that the patient experiences have to be assessed in detail; this requires an extensive physical examination, especially of all visible skin surfaces.

**Laboratory testing** will most likely show the following typical signs of hemophilia:

- **Normal bleeding time/thrombin time, normal prothrombin time** (which excludes the differential diagnosis of von Willebrand’s disease)
- The **activated partial thromboplastin time (aPTT)** will be prolonged if coagulation factor levels are < 40 %
- **INR normal**
- With such results giving enough reason to suspect possible coagulation factor deficiency, the levels of factors VIII, IX, and vWF have to be determined.

### Treatment of Hemophilia

Treatment can best be provided through specialized **hemophilia treatment centers (HTC)**, which are well equipped to handle the complex requirements for care of hemophilic patients. The first step should comprise of comprehensive consultations with the patient, who should be informed on the hereditary implications of this disease and the necessary lifestyle changes. These changes mostly affect everyday activities and leisure activities.
Non-transfusional Treatment of Hemophilia A and B

Mild forms of hemophiliaia can be treated with desmopressin. Desmopressin is an ADH analogue. In cases of an expected high risk of bleeding (e.g., before any surgical or dental procedures), desmopressin can be administered in order to induce an increased release of stored factor VIIIc and vWF. This release is of course transient, which makes it only a temporary treatment option. Otherwise, tachyphylaxis may occur. This treatment approach is particularly suitable for children as desmopressin can be taken in form of an intranasal spray.

Factor Replacement for the Treatment of Hemophilia A and B

The basic treatment of hemophilia is the replacement of the deficient coagulation factors by infusion of factor concentrates. Indication for replacement therapy is need-based, with needs ranging from long-term preventive therapy to on-demand treatment of acute bleeding events (e.g., before surgeries). Guidelines for factor replacement recommend different doses of factor concentrates, depending on the indication or site of bleeding.

For prophylactic treatment, patients can be intravenously infused with genetically engineered, recombinant factor VIII and XI. The laboratory production of this protein which is made out of 2,200 amino acids is, however, a technical challenge because the protein cannot be stored for long in serum. Therefore, the factor concentrates are nowadays synthetically stored in powder form and mixed only on demand with the serum in a syringe immediately before infusion.

Replacement therapy is, however, not without complications. First, about 30 % of all patients who are treated with factor replacement develop inhibitors against the synthetic factor VIII protein. In addition, the factor concentrates have a rather short half-life and the body eliminates them within a short time.

For very severe cases of hemophilia, research is focused on reducing the number of infusions by enhancing the lifetime of the recombinant factors. One possibility for this is PEGylation, which enlarges the entire molecule, making it harder for it to be filtered and excreted by the kidneys. In November of 2015, the US Food and Drug Administration (FDA) approved such a PEGylated product (Adynovate) for use by adults and adolescents (age 12 and older) who suffer from hemophilia A.
Gene Therapy for Hemophilia A and B

Another possibility for treating hemophilia is gene therapy: an altered virus that produces factor VIII can be inserted into the liver. This is called an in vivo gene transfer where the virus acts as a non-pathogenic viral vector that synthesizes factor VIII inside the body. Gene therapy could create a cure for hemophilia, however it is still in preclinical trial.

Review Questions

Solutions can be found below the references.

1. Which statement about hemophilia A is incorrect?
   A. It is an X-linked recessive disease.
   B. It is a deficiency of coagulation factor 8.
   C. Examination of the intrinsic coagulation pathway is important for the diagnosis of the disease.
   D. Bleeding time is shortened.
   E. This type of hemophilia accounts for 80% of all cases.

2. Which laboratory parameters can provide the necessary information for diagnosing hemophilia?
   A. Blood count with platelet count
   B. Capillary fragility test
   C. Quick test
   D. Measurement of aPTT
   E. Platelet function test

3. Which statement about hemophilia is correct?
   A. Laboratory changes in hemophilia A cases are similar to those of vitamin K deficiency.
   B. A normal bleeding time indicates von Willebrand disease.
   C. A prolonged PTT can also be due to the prophylactic administration of a low molecular weight heparin for thrombosis prevention.
   D. Hemophilia should always be treated with generous factor replacement.
   E. Mild forms of hemophilia can be treated with an ADH analogue.

References

Herold, G. und Mitarbeiter, Innere Medizin, 2014

Immunhämatologie und klinische Transfusionsmedizin, 6. Auflage, Elsevier Urban und Fischer Verlag

Seltene Blutungsstörungen & akute Blutungen via Bayer HealthCare

Shi et al, Factor VIII ectopically targeted to platelets is therapeutic in hemophilia A with high-titer inhibitory antibodies, Journal of Clinical Investigation 2006

Leitlinien der Bundesärztekammer zur Faktorensubstitution, 4. Auflage, 2014

Correct answers: 1D, 2D, 3E