Hemophilia A: Pathophysiology and Treatment Strategies

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Hemophilia A: Pathophysiology and Treatment Strategies
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Introduction
Hemophilia is a sex-linked recessive genetic disorder that varies in severity and affects only males. The disease is caused by a deficiency in the clotting factor VIII, which is crucial for the formation of stable clots.

Pathophysiology

Signs and Symptoms

Common early manifestations are:

- Edema in the mouth
- Severe bleeding in infancy with joint swelling
- Easy bruising in infancy
- Expressing red urine or feces
- Bleeding into the brain

Newborns with severe hemophilia should be diagnosed within 24 hours of birth. The diagnosis of hemophilia A is typically confirmed by a test that measures the level of factor VIII activity in the blood.

Pathophysiologically, the first step in the coagulation cascade is the conversion of prothrombin to thrombin, which then leads to the conversion of fibrinogen to fibrin. In hemophilia A, the absence or deficiency of factor VIII leads to a failure in the formation of a stable clot.

At Risk Populations
- Men who have family history of hemophilia
- Men who have sex with men
- Men who are intravenous drug users
- Men who have a history of hematuria

Prophylactic Treatment

Patients with hemophilia A are generally prophylactically treated with intravenous factor VIII every 2-3 days to maintain factor VIII levels at approximately 50-80% of normal. This is recommended to prevent the development of inhibitors.

Acute Management of Bleeding

First line treatment of patients with hemophilia A is intravenous factor VIII replacement, and Table 4 represents the World Federation of Hemophilia’s recommended initial target factor VIII levels for specific bleeding processes.

Table 1: Signs of Bleeding from: Srivastava, A. K., Brewer, A. K., Mauser-Bunschoten, E. P., et al., 2013

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Life-Threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemarthrosis</td>
<td>Intravascular</td>
</tr>
<tr>
<td>Muscle weakness, bruising</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

Table 2: Frequency of Bleeding at Different Sites, from: Srivastava, A. K., Brewer, A. K., Mauser-Bunschoten, E. P., et al., 2013

<table>
<thead>
<tr>
<th>Site of Bleeding</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints (hemarthrosis)</td>
<td>70-80%</td>
</tr>
<tr>
<td>Muscle</td>
<td>10-20%</td>
</tr>
<tr>
<td>Central nervous system (CNS)</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 3: Relationship of Bleeding Severity to Clotting Factor Level, from: Srivastava, A. K., Brewer, A. K., Mauser-Bunschoten, E. P., et al., 2013

<table>
<thead>
<tr>
<th>Severity</th>
<th>Clotting Factor Level</th>
<th>Bleeding Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1 IU/ML (&lt;0.01% of normal)</td>
<td>Spontaneous bleeding into joints or muscles, reduced mobility, difficulty of daily activities</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5 IU/ML (0.01-0.05% of normal)</td>
<td>Occasional spontaneous bleeding, minor trauma or surgery</td>
</tr>
<tr>
<td>Mild</td>
<td>5-20 IU/ML (0.05-0.1% of normal)</td>
<td>Less severe bleeding with minor trauma or surgery</td>
</tr>
</tbody>
</table>

Significance of Pathophysiology

As is the case with many disease processes, severity of Hemophilia A can be varied due to different genetic haplotypes. As stated, factor VIII is critically important to the completion of the intrinsic coagulation pathway of hemostasis; without intrinsic activation, the remaining components of the coagulation cascade are not activated.

Underlying Pathophysiology

Hemophilia A is a sex-linked recessive disorder that affects approximately 1 in 5,000 male births in Europe and North America. The proportion of patients who are heavily symptomatic in infancy and early childhood is linked to the genotype of the affected factor VIII molecule with different factor VIII haplotypes generating different clinical phenotypes.

References

Bjørnsen, S., Sørensen, N., 2011. Diagnosis and management of inhibitors to factor VIII and IX. Treatment of Hemophilia B. Haemophilia 17(4), 2-10.