Chapter-9

Haematological Disease-III

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Abstract

Hematological diseases encompass various disorders affecting blood cells and coagulation, with hereditary acquired anemia and hemophilia being notable examples. Hereditary acquired anemia refers to anemia resulting from inherited genetic mutations that impair red blood cell production, structure, or function. These conditions include hereditary spherocytosis, G6PD deficiency, and hereditary elliptocytosis. The pathophysiology involves defects in the red blood cell membrane or enzymes, leading to hemolysis. Epidemiologically, these conditions vary in prevalence based on ethnicity and geographical regions. Symptoms include fatigue, pallor, jaundice, and splenomegaly. Diagnosis is based on family history, blood tests, and specific diagnostic assays. Treatment focuses on managing symptoms, including folic acid supplementation, blood transfusions, and sometimes splenectomy. Complications can include gallstones, severe anemia, and increased risk of infections post-splenectomy. Prevention strategies involve genetic counseling and early detection. Hemophilia is a genetic bleeding disorder caused by deficiencies in clotting factors, primarily factor VIII (hemophilia A) or factor IX (hemophilia B). The pathophysiology involves a deficiency in these clotting factors, leading to impaired blood clot formation and prolonged bleeding. Epidemiologically, hemophilia predominantly affects males and occurs worldwide, with a prevalence of about 1 in 5,000 male births for hemophilia A and 1 in 30,000 for hemophilia B. Symptoms include spontaneous bleeding, prolonged bleeding after injuries or surgery, and joint bleeds leading to arthropathy. Diagnosis is confirmed through clotting factor assays and genetic testing. Treatment involves replacement therapy with clotting factor concentrates, desmopressin for mild cases, and antifibrinolytic agents. Complications can include joint damage, development of inhibitors against clotting factors, and increased risk of bleeding. Prevention focuses on genetic counseling, early diagnosis, and prophylactic treatment to prevent bleeding episodes and improve the quality of life for affected individuals.

Hereditary Acquired Anemia

Hereditary acquired anemia refers to an anemia condition that arises from genetic or inherited factors affecting red blood cell production or function, as opposed to acquired anemia due to external factors like nutrient deficiencies or chronic diseases. Here's a detailed

look at various types of hereditary anemia, including their introduction, pathophysiology, epidemiology, symptoms, complications, diagnosis, treatment, and prevention.

1. Hereditary Anemia Overview

Introduction: Hereditary anemia encompasses various genetic disorders affecting red blood cells' production, structure, or function. These disorders are inherited in an autosomal dominant or recessive pattern and lead to chronic anemia due to abnormal red blood cell morphology or production.

2. Pathophysiology

Common Hereditary Anemias

1. **Sickle Cell Anemia**
   a. **Genetic Mutation:** Mutation in the HBB gene leads to abnormal hemoglobin S (HbS) that causes red blood cells to sickle under low oxygen conditions.
   b. **Mechanism:** Sickle-shaped cells cause vaso-occlusive crises, hemolysis, and chronic anemia.

2. **Thalassemia**
   a. **Alpha Thalassemia:** Caused by mutations in alpha-globin genes, leading to imbalanced hemoglobin production.
   b. **Beta Thalassemia:** Caused by mutations in the beta-globin gene, leading to ineffective erythropoiesis and excess alpha chains.

3. **Hereditary Spherocytosis**
   a. **Genetic Defects:** Defects in red blood cell membrane proteins (e.g., spectrin, ankyrin) lead to spherical, rigid RBCs that are prematurely destroyed.

4. **Hereditary Elliptocytosis**
   a. **Genetic Mutations:** Defects in the red blood cell membrane proteins (e.g., spectrin) cause red blood cells to assume an elliptical shape, leading to hemolysis.

5. **G6PD Deficiency**
   a. **Genetic Mutation:** Mutations in the G6PD gene impair the enzyme's function, leading to oxidative stress and hemolysis.

3. Epidemiology

a. **Sickle Cell Anemia:** Common in sub-Saharan Africa, the Middle East, Mediterranean regions, and India. Approximately 1 in 365 African-American births in the U.S.
b. **Thalassemia:** Common in the Mediterranean Basin, the Middle East, Central Asia, and parts of Africa and South Asia. Carrier rates vary by region.
c. **Hereditary Spherocytosis and Elliptocytosis:** More common in Northern European populations. Spherocytosis has a prevalence of about 1 in 2,000 individuals.
d. **G6PD Deficiency:** Common in regions with high malaria prevalence, including parts of Africa, the Middle East, and Southeast Asia. About 400 million people globally are affected.

4. Symptoms and Complications

Symptoms

a. **Sickle Cell Anemia:** Painful crises, anemia, jaundice, organ damage, and susceptibility to infections.
b. **Thalassemia:** Fatigue, pallor, bone deformities, splenomegaly, and growth retardation.
c. **Hereditary Spherocytosis:** Anemia, jaundice, splenomegaly, and gallstones.
d. **Hereditary Elliptocytosis:** Mild to moderate anemia and an increased risk of hemolysis.
e. **G6PD Deficiency:** Acute hemolytic episodes triggered by infections, certain drugs, or fava beans.

Complications

a. **Sickle Cell Anemia:** Stroke, acute chest syndrome, organ failure, and delayed growth.
b. **Thalassemia:** Iron overload, organ damage, and endocrine dysfunction.
c. **Hereditary Spherocytosis:** Splenomegaly, gallstones, and risk of anemia-related complications.
d. **Hereditary Elliptocytosis:** Chronic anemia and increased hemolysis.
e. **G6PD Deficiency:** Acute hemolysis, potential renal failure, and hemolytic anemia crisis.

5. Diagnosis

Diagnostic Tests

a. **Complete Blood Count (CBC):** Reveals anemia and abnormal red blood cell indices.
b. **Peripheral Blood Smear:** Identifies characteristic cell shapes and sizes.
c. **Hemoglobin Electrophoresis:** For diagnosing sickle cell anemia and thalassemia.
d. **Genetic Testing:** Confirms specific genetic mutations associated with various hereditary anemias.
e. **Osmotic Fragility Test:** For hereditary spherocytosis.
f. **Enzyme Assays:** For G6PD deficiency to assess enzyme activity.

Additional Tests

a. **Bone Marrow Biopsy:** In cases where anemia etiology is unclear or to assess erythropoiesis.
b. **Prenatal Testing:** Includes chorionic villus sampling or amniocentesis for at-risk pregnancies.

6. Treatment

Supportive Care

a. **Transfusions:** To manage severe anemia and complications in conditions like sickle cell anemia and thalassemia.
b. **Iron Chelation Therapy:** For patients receiving frequent transfusions to prevent iron overload.

Specific Treatments

a. **Sickle Cell Anemia**
   - **Hydroxyurea:** Increases fetal hemoglobin (HbF) levels and reduces complications.
   - **Bone Marrow Transplant:** Potentially curative for some patients.
b. **Thalassemia**
   - **Regular Blood Transfusions:** For managing severe cases.
   - **Iron Chelation:** To manage iron overload from transfusions.
   - **Bone Marrow Transplant**: Potentially curative in selected cases.
c. **Hereditary Spherocytosis and Elliptocytosis**
   - **Splenectomy:** To reduce hemolysis and improve anemia, particularly in severe cases.
d. **G6PD Deficiency**
   - **Avoidance of Triggers**: Avoidance of known oxidative stressors and certain medications.

Emerging Therapies

a. **Gene Therapy:** Research is ongoing for potential cures through gene editing and modification.
b. **New Medications:** Developing drugs to modify disease course and improve management.

7. Complications

a. **Sickle Cell Anemia:** Chronic pain, stroke, acute chest syndrome, and organ failure.
b. **Thalassemia:** Iron overload, endocrine dysfunction, and organ damage.
c. **Hereditary Spherocytosis:** Anemia-related complications and risk of gallstones.
d. **Hereditary Elliptocytosis:** Chronic anemia and hemolysis.
e. **G6PD Deficiency:** Acute hemolytic crises and potential renal issues.

8. Prevention

Primary Prevention:

a. **Genetic Counseling:** For couples with a family history or living in regions where these conditions are prevalent.
b. **Prenatal Screening:** To detect hereditary anemias early in at-risk pregnancies.

Secondary Prevention

a. **Newborn Screening:** Early detection of hereditary anemia to start management early and prevent complications.
b. **Regular Monitoring:** For individuals at risk or diagnosed with hereditary anemia to manage symptoms and prevent complications.

Tertiary Prevention:

a. **Patient Education:** Providing information on disease management, avoiding triggers, and understanding treatment options.
b. **Support Services:** Access to support groups and resources for patients and families affected by hereditary anemia.

Effective management of hereditary acquired anemia involves understanding the specific type of anemia, providing supportive and specific treatments, and implementing preventive measures to enhance quality of life and reduce complications.

Hemophilia

Introduction

Hemophilia is a group of inherited bleeding disorders characterized by the inability of blood to clot properly due to deficiencies or abnormalities in specific clotting factors. This results in prolonged bleeding or spontaneous bleeding episodes, particularly into joints and muscles.

Pathophysiology

1. **Genetic Defects**
   a. **Hemophilia A:** Caused by a deficiency or dysfunction of clotting factor VIII (FVIII), an essential protein in the blood clotting cascade.
   b. **Hemophilia B:** Caused by a deficiency or dysfunction of clotting factor IX (FIX), another crucial protein in the clotting cascade.
   c. **Hemophilia C:** Caused by a deficiency of clotting factor XI (FXI). It is less common and usually less severe than types A and B.

2. **Impaired Coagulation Cascade**
   a. **Intrinsic Pathway:** Both Hemophilia A and B affect the intrinsic pathway of the clotting cascade, leading to prolonged activated partial thromboplastin time (aPTT) but normal prothrombin time (PT).
   b. **Factor Deficiency:** The specific factor deficiency impairs the formation of fibrin clots, which are essential for stopping bleeding.

3. **Bleeding Tendency**
   a. **Spontaneous Bleeding:** Even minor injuries can lead to excessive bleeding. Internal bleeding into joints (hemarthrosis) and muscles is common.
   b. **Delayed Hemostasis:** Clotting is inefficient, leading to prolonged bleeding times and difficulty stopping bleeding.

Epidemiology

1. **Prevalence**
   a. **Hemophilia A**: Affects approximately 1 in 5,000 male births.
   b. **Hemophilia B**: Affects approximately 1 in 25,000 male births.
   c. **Hemophilia C**: Less common, with varying prevalence depending on ethnicity and geography.

2. **Inheritance Pattern**
   a. **X-Linked Recessive**: Hemophilia A and B are inherited in an X-linked recessive pattern, meaning the condition predominantly affects males, while females are carriers.
   b. **Autosomal Recessive**: Hemophilia C follows an autosomal recessive inheritance pattern and can affect both males and females.

Symptoms and Complications

Symptoms

1. **Spontaneous Bleeding:** Frequent bleeding without an obvious cause, including nosebleeds and bleeding gums.
2. **Joint Bleeding:** Pain, swelling, and limited movement due to bleeding into joints (hemarthrosis).
3. **Muscle Bleeding:** Pain, swelling, and bruising in muscles.
4. **Bleeding after Surgery or Injury:** Prolonged bleeding following medical procedures or trauma.

Complications

1. **Chronic Joint Damage:** Repeated joint bleeds can lead to hemophilic arthropathy, causing joint damage and arthritis.
2. **Inhibitors:** Some patients develop antibodies (inhibitors) against clotting factors, making treatment less effective.
3. **Internal Bleeding:** Risk of bleeding into organs or the central nervous system.
4. **Anemia:** Chronic bleeding can lead to iron deficiency anemia.

Diagnosis

Diagnostic Tests

1. **Coagulation Profile**
   a. **Activated Partial Thromboplastin Time (aPTT):** Prolonged in Hemophilia A and B.
   b. **Prothrombin Time (PT):** Normal in Hemophilia A and B; may be prolonged in Hemophilia C.
   c. **Bleeding Time:** Typically normal in hemophilia.

2. **Specific Factor Assays**
   a. **Factor VIII Assay:** Diagnoses Hemophilia A.
   b. **Factor IX Assay:** Diagnoses Hemophilia B.
   c. **Factor XI Assay:** Diagnoses Hemophilia C.

3. **Genetic Testing**
   a. **Mutation Analysis:** Identifies specific mutations in the genes coding for the clotting factors.

4. **Family History**
   a. **Pedigree Analysis:** Helps identify carriers and affected individuals in families with a history of hemophilia.

Treatment

Management Strategies

1. **Factor Replacement Therapy**
   a. **Factor VIII Concentrates:** Used for Hemophilia A.
   b. **Factor IX Concentrates:** Used for Hemophilia B.
   c. **Factor XI Concentrates:** Used for Hemophilia C in some cases.

2. **Desmopressin (DDAVP)**
   a. **Indication:** Used for mild Hemophilia A to stimulate the release of endogenous FVIII.

3. **Prophylactic Treatment**:
   a. **Regular Factor Infusions:** To prevent bleeding episodes and joint damage.

4. **Management of Inhibitors**
   a. **Immune Tolerance Induction (ITI):** For patients with inhibitors to reduce or eliminate the immune response against clotting factors.
   b. **Bypassing Agents:** Such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa) for those with inhibitors.

5. **Gene Therapy**
   a. **Emerging Treatments:** Research is ongoing into gene therapy approaches to correct the genetic defects causing hemophilia.

Emergency Management
1. **Treatment of Bleeding Episodes:** Immediate infusion of clotting factors to control bleeding.
2. **Supportive Care:** Pain management and rehabilitation for joint and muscle injuries.

Complications
1. **Joint Damage:** Chronic bleeding into joints can lead to joint deformity and arthritis.
2. **Inhibitor Development:** Development of antibodies against clotting factors can complicate treatment.
3. **Transfusion-Related Infections:** Risk of infections from blood products, although modern screening reduces this risk.
4. **Allergic Reactions:** Potential reactions to clotting factor concentrates.

Prevention

Primary Prevention
1. **Genetic Counseling:** For families with a history of hemophilia to understand inheritance patterns and risks.
2. **Prenatal Testing:** To diagnose hemophilia in at-risk pregnancies.

Secondary Prevention
1. **Early Diagnosis:** Newborn screening and early diagnosis to initiate treatment and prevent complications.

Tertiary Prevention
1. **Regular Monitoring:** Ongoing assessment and treatment adjustments to manage symptoms and prevent complications.
2. **Education and Support:** For patients and families on managing hemophilia, including recognizing bleeding symptoms and understanding treatment options.

Effective management of hemophilia involves a comprehensive approach to treat bleeding episodes, prevent complications, and improve quality of life through specialized care and ongoing monitoring. Advances in research, including gene therapy, offer hope for future improvements in treatment and potential cures.

Short Answer Type Questions (Subjective)

1. What are the primary causes of iron deficiency anemia?
2. Describe the pathophysiology of sickle cell anemia.
3. Explain the difference between acute and chronic leukemias.
4. What are the symptoms and complications of polycythemia vera?
5. Describe the symptoms and treatment of megaloblastic anemia.
6. What is the significance of Reed-Sternberg cells in diagnosing lymphoma?
7. How does hemophilia affect the blood clotting process?
8. Describe the epidemiology of beta thalassemia.
9. What are the common symptoms of iron deficiency?
10. How is Graves' disease diagnosed and treated?

Long Answer Type Questions (Subjective)

1. Discuss the pathophysiology, symptoms, diagnosis, and treatment of iron deficiency anemia.
2. Describe the genetic and molecular basis of sickle cell anemia, including its epidemiology, complications, and management strategies.
3. Explain the different types of leukemia, their pathophysiology, symptoms, diagnostic approaches, and treatment options.
4. Describe the pathophysiology, symptoms, and treatment of hemophilia, including the complications associated with this condition.