Session 6
Lymphatic and Haematological Disorders 4
Bioscience Department
Session Learning Outcomes

At the end of the session, student should be able to:

- Define and discuss the clinical features, pathophysiology, investigations and management of various myeloproliferative disorders including myelofibrosis, essential thrombocythaemia and polycythaemia rubra vera.
- Define and discuss the clinical features, pathophysiology, investigations and management of various bleeding disorders including haemophilia and Von Willebrand’s disease.
- Discuss the clinical features, investigations, and management of disseminated intravascular coagulation.
- Understand the haematological disorders and other factors predisposing to venous thrombosis and management of the same.
Session Plan

- Myeloproliferative Disorders:
  - Myelofibrosis
  - Essential thrombocythaemia
  - Polycythemia rubra vera

- Bleeding Disorders:
  - Disorders of primary haemostasis
  - Coagulation disorders

- Thrombotic disorders:
  - Disseminated intravascular coagulation
  - Venous thrombosis
Myeloproliferative Disorders
Myeloproliferative Disorders

Definition: A group of chronic conditions characterised by clonal proliferation of marrow erythroid precursors, megakaryocytes, or myeloid cells.

- Includes conditions like:
  - Myelofibrosis
  - Essential thrombocythaemia
  - Polycythaemia rubra vera
  - Chronic myeloid leukaemia (covered in session 5)

- Aetiology:
  - Genetic mutation on chromosome 9 that codes for JAK-2
Myelofibrosis

- **Definition:** A rare disease of the bone marrow in which there is excessive collagen fibres build up forming scar tissue inside the marrow cavity. This is due to the uncontrolled growth of fibroblasts and pluripotent stem cell. It is also known as myeloid metaplasia, leucoerythroblastosis or chronic myelosclerosis.

- **Pathophysiology:**
  Hypercellular bone marrow with an excess of abnormal megakaryocytes → release growth factors → reactive proliferation of fibroblasts → fibrosed bone marrow → blood cell maturation fails → leucoerythroblastic anaemia and giant platelets → extra medullary hematopoiesis
Myelofibrosis

- Clinical features:
  - Fatigue, Pallor, shortness of breath, palpitations
  - Fever, sweating, itching
  - Unexpected bleeding
  - Night sweat, Weight loss
  - Bone pains in the legs
  - Splenomegaly
  - Pain in the left shoulder and upper left portion of the body
Myelofibrosis

Diagnosis:
- Full blood count
- Peripheral blood smear
- Bone marrow biopsy
- Serum urate and folate
- Genetic analysis for JAK-2

Management:
- Red cell transfusions
- Folic acid supplements
- Cytotoxic therapy
- Splenectomy
- HSCT
- JAK-2 inhibitor
Myelofibrosis: Excessive collagen fibres build up forming scar tissue inside the marrow cavity due to the uncontrolled growth of fibroblasts and pluripotent stem cells.

Genetic mutation on chromosome 9 that codes for JAK-2 in 50% cases

- Uncontrolled/Clonal proliferation of blood cells.
  - Hypercellular bone marrow with an excess of abnormal megakaryocytes
    - Release growth factors
      - Reactive proliferation of fibroblasts
        - Fibroased bone marrow
          - Failure of blood cell maturation
            - Leucoerythroblastic anaemia and giant platelets
              - Extra medullary haematopoiesis

Bone pains in the legs

Symptoms of Anaemia: Fatigue, Pallor, shortness of breath, palpitations

Increased predisposition to infection: Fever, sweating

Systemic signs and symptoms: Night sweat, Weight loss

Splenomegaly, splenic infarction and perisplenitis, Pain in the left shoulder and upper left portion of the body

Diagnosis:
- FBC
- Peripheral blood smear
- Bone marrow biopsy
- Serum urate and folate
- Genetic analysis for JAK-2

Management:
- Red cell transfusions
- Folic acid supplements
- Cytotoxic therapy
- Splenectomy
- HSCT
- JAK-2 inhibitor

Colour Key:
- Definition
- Aetiology
- Pathophysiology
- Clinical features
- Diagnosis
- Management
- Complications
Essential Thrombocythaemia

- **Definition:** A disease characterised by malignant proliferation of megakaryocytes that results in a raised level of circulating platelets that are often dysfunctional leading to a tendency of bleeding and thrombotic episodes.

- **Clinical features:**
  - Bleeding from GIT, Respiratory tract and skin
  - Blood in stools
  - Easy bruising
  - Dizziness
  - Enlarged lymph nodes
  - Headaches
  - Epistaxis
  - Ulcers on the fingers and toes
  - Cerebral stroke
Essential Thrombocythaemia

- **Management:**
  - low-dose aspirin
  - Inhibitor of megakaryocyte maturation
  - Intravenous radioactive phosphorus ($^{32}$P)

- **Complications:**
  - Acute leukaemia
  - Myelofibrosis
Polycythæmia Rubra Vera

- Definition: A clonal stem cell disorder in which there is an increase in haemoglobin, PCV and red cell count.

- Clinical features:
  - Mainly in patients over the age of 40 years
  - Symptoms of hyper viscosity
  - Symptoms of peripheral arterial disease or a cerebrovascular accident
  - Venous thromboembolism
  - Peptic ulceration
  - Plethora with deep cyanosis
  - Hepatosplenomegaly and gout
  - Aquagenic pruritus
Polycythaemia Rubra Vera

Diagnosis:
- Full blood count
- Genetic analysis for JAK-2
- Absence of causes of a secondary erythrocytosis
- Bone marrow examination

Management:
- Aspirin
- Venesection
- Bone marrow suppression
- Radioactive phosphorus

Complications:
- Cerebrovascular attacks
- Coronary events
- Acute leukaemia
- Myelofibrosis
## Polycythaemia Rubra Vera

<table>
<thead>
<tr>
<th>Cause of a secondary erythrocytosis</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>High erythropoietin due to tissue hypoxia</td>
<td>High altitude Cardiorespiratory disease High-affinity haemoglobins</td>
</tr>
<tr>
<td>Inappropriately increased erythropoietin</td>
<td>Renal disease (hydronephrosis, cysts, carcinoma) Other tumours (hepatoma, bronchogenic carcinoma, uterine fibroids, phaeochromocytoma, cerebellar haemangioblastoma)</td>
</tr>
<tr>
<td>Exogenous erythropoietin administration</td>
<td>Performance-enhancing drug-taking in athletes</td>
</tr>
</tbody>
</table>
Bleeding Disorders
Bleeding Disorders

Definition: Disorders resulting from defects in any of the factors that contribute to haemostasis.

- Aetiology:
  - Platelet defects: leading to thrombocytopenia due to
    - Decreased production:
    - Increased destruction
    - Impaired function
  - Coagulation defect
  - Vascular integrity defect
# Bleeding Disorders

**Definition:** Disorders resulting from defects in any of the factors that contribute to haemostasis.

<table>
<thead>
<tr>
<th><strong>Aetiology</strong></th>
<th><strong>Conditions leading to</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased platelet production</td>
<td>Aplastic anaemia, leukaemia, Radiation therapy and cancer drugs, human immunodeficiency virus (HIV) or cytomegalovirus infection</td>
</tr>
<tr>
<td>Increased platelet destruction/consumption</td>
<td>Autoimmune, drug induced, Disseminated Intravascular Coagulation, thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>Impaired platelet function</td>
<td>von Willebrand disease, drugs, cardiopulmonary bypass, uremia</td>
</tr>
<tr>
<td>Coagulation defect</td>
<td>von Willebrand disease, haemophilia, liver disease or vitamin K deficiency</td>
</tr>
<tr>
<td>Vascular integrity defect</td>
<td>Vitamin C deficiency, excessive cortisol (Cushing disease), aging process, Hereditary haemorrhagic telangiectasia</td>
</tr>
</tbody>
</table>
**Haemophilia A**

- Definition: Haemophilia A is an X-linked recessive disorder of factor VIII deficiency that is characterised by a lifelong tendency to excessive haemorrhage and a greatly prolonged coagulation time.

Haemophilia A

- Clinical features:
  - Superficial injury presents with massive bleeding
  - Spontaneous bleeding into skin, muscle and joints
  - Typically large joints involved, especially knees, elbows, ankles and hip
  - Muscle haematomas, most commonly in the calf and psoas muscles
  - Hot, swollen and very painful joint
  - Synovial hypertrophy, destruction of the cartilage and secondary osteoarthritis
  - Retroperitoneal and intracranial bleeding
Haemophilia A

- **Diagnosis:**
  - Bleeding time (BT)
  - Prothrombin time (PT)
  - Activated Partial Thromboplastin Time (APTT)
  - Von Willebrand Factor (vWF) assays
  - Factor VIII assays

- **Management:**
  - Intravenous infusion of factor VIII concentrate
  - Vasopressin receptor agonist
Haemophilia B

- Definition: Hemophilia B, or Christmas disease, is an inherited, X-linked, recessive disorder that results in deficiency of functional plasma coagulation factor IX.

- Clinical features:
  - Similar to Haemophilia A

- Diagnosis:
  - Factor IX assays

- Management:
  - Intravenous infusion of factor IX concentrate
Revision

https://youtu.be/nkC1vZaUpxs

Click on the link to watch this video for revision (9.37 minutes)
Von Willebrand Disease

- **Definition:** Von Willebrand disease is a relatively common hereditary bleeding disorder characterized by a quantitative or qualitative deficiency of von Willebrand factor (vWF).

- **Clinical features:**
  - Superficial bruising, epistaxis, menorrhagia
  - Gastrointestinal haemorrhage
  - Bleeding episodes much less common than in severe haemophilia
  - Excessive haemorrhage may only be observed after trauma or surgery
Von Willebrand Disease

- **Diagnosis:**
  - Bleeding time (BT)
  - Prothrombin time (PT)
  - Activated Partial Thromboplastin Time (APTT)
  - Von Willebrand Factor (vWF) assays
  - Factor VIII assays

- **Management:**
  - Vasopressin receptor agonist
  - Intravenous infusion of factor VIII with vWF concentrate
Disseminated Intravascular Coagulation

- **Definition:** It is characterised by systemic activation of the pathways involved in coagulation and its regulation which may result in the generation of intravascular fibrin clots causing multi-organ failure, with simultaneous coagulation factor and platelet consumption causing bleeding.

- **Aetiology:**
  - Infection/sepsis
  - Trauma
  - Obstetric conditions
  - Severe liver failure
  - Malignancy
  - Tissue destruction
  - Vascular abnormalities
  - Toxic/immunological
Disseminated Intravascular Coagulation

- Clinical features:
  - Coagulation and formation of microemboli
  - Bleeding: petechiae, purpura, oozing from puncture sites, or severe haemorrhage
  - Tissue hypoxia and necrotic damage to vital organs
  - Renal, circulatory, or respiratory failure
  - Acute bleeding ulcers
  - Convulsions and coma
  - Haemolytic anemia
Disseminated Intravascular Coagulation

Diagnosis:
- International Society for Thrombosis and Haemostasis scoring system for diagnosis:
  - Presence of an associated disorder
  - Fibrin degradation products
  - Prothrombin time
  - Fibrinogen level
  - Platelet count

Management:
- Treatment of underlying cause
- Intensive care
- Blood component therapy
- Heparin
- Antifibrinolytic therapy is contraindicated
Revision

https://youtu.be/Gmh01S0msfY

Click on the link to watch this video for revision
(6.05 minutes)
Venous Thrombosis

- Definition: It is the most common presentation of venous thromboembolic disease.

<table>
<thead>
<tr>
<th>Factors predisposing to venous thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
</tr>
<tr>
<td><strong>Surgical conditions</strong></td>
</tr>
<tr>
<td><strong>Medical conditions</strong></td>
</tr>
<tr>
<td><strong>Haematological conditions</strong></td>
</tr>
</tbody>
</table>
Venous Thrombosis

- **Management:**
  - Elevation and analgesia
  - Thrombolysis
  - Anticoagulation with low molecular weight heparin
  - Coumarin anticoagulant, such as warfarin

- **Complications:**
  - Post-thrombotic syndrome:
    - Persistent leg swelling, heaviness and discoloration
    - Ulceration around the medial malleolus.
Readings and Resources

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