Haemorrhagic Disorders

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Hemorrhagic Disorders

These include

- Disorders of platelets.
- Disorders of blood vessels.
- Disorders of coagulation & fibrinolysis.
Platelet Disorders

- Quantitative: Thrombocytopenia.
- Qualitative: Platelet defects.
Thrombocytopenia

- Thrombocytopenia exists when platelet count is less than $150 \times 10^9 /L$.
- Normal platelet count = $150 – 400 \times 10^9 /L$
- Bleeding is unusual when count is $>50 \times 10^9 /L$
- Spontaneous bleeding occurs when count is $< 20 \times 10^9 /L$
Causes of Thrombocytopenia

1. **decreased platelet production**

   Characterized by reduction of megakaryocytes in bone marrow & by small mean size of circulating platelets (Mean Platelet Volume – MPV) and association with anemia and leucopenia:
   a. Aplastic anemia.
   b. Megaloblastic anemia (decrease Vit. B12 or /and decrease folic acid).
   c. Bone marrow infiltration by neoplasms.
   d. Cytotoxic drugs (Dose Dependant).
   e. Ionizing radiation (Dose Dependant).
   f. Drugs; cause thrombocytopenia in some recipients: Methéprim, Phenyldbutazone, Gold compounds.
   g. Alcohol.
2. *Increased destruction of platelets*

Characterized by normal or increased numbers of megakaryocytes in bone marrow, circulating platelets appear larger than normal (raised MPV) and that platelets are usually only affected (no anaemia or leucopenia).
Causes of Increased Destruction of Platelets

- **hypersensitivity to drugs**
  
  Occurs suddenly following single dose drugs act as a hapten forming antigenic complex by binding to plasma protein and then antibody (usually IgG) is formed against this complex, this antigen-antibody complex then binds to platelets leading to destruction by phagocytosis usually in the spleen.

- **Drugs**: Chlorothiazides, Digoxin, Methyl-dopa, PAS (para-aminosalicylic acid), Quinine, Quinidine, Sulphonamides.
Autoimmune Thrombocytopenia

Autoantibodies usually of IgG class either as

- isolated disorder: idiopathic (immune) thrombocytopenic purpura (ITP)
- in association with other autoimmune disorders: SLE, myasthenia gravis, Evan’s syndrome (autoimmune hemolytic anemia + autoimmune thrombocytopenia), lymphoma, chronic lymphocytic leukaemia
**ITP (Idiopathic Thromocytopenic Purpura)**

Occurs chiefly in children and young adults.

<table>
<thead>
<tr>
<th>Character</th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavior (onset)</td>
<td>Acute (sudden)</td>
<td>Chronic (insidious)</td>
</tr>
<tr>
<td>Peak age incidence</td>
<td>2-8 years</td>
<td>20-40 years</td>
</tr>
<tr>
<td>Sex</td>
<td>F=M</td>
<td>3F:1M</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;6 months (usually weeks)</td>
<td>&gt; 6 months (often years)</td>
</tr>
<tr>
<td>Associated disorders</td>
<td>Preceding viral infection</td>
<td>None</td>
</tr>
</tbody>
</table>
Responsible antibody usually belongs to subclass 3 of IgG.

Clinically
- Varies from mild cutaneous bleeding to gross uterine or GIT hemorrhage.
- In severe cases it lead to intracerebral hemorrhage.

Treatment
- Steroids
- Immunosuppressive drugs
- Splenectomy
Blood: Hb – Normal
WBC – Normal

Platelet count reduced
In severe cases $20 - 50 \times 10^9/L$.
In moderate cases $(50 - 80) \times 10^9/L$.

Bleeding:
- Epistaxis
- GIT, GUT bleedings.

CNS “fatal” very rare.
3. **Hypersplenism**

Clinical syndrome:
- Enlargement of the spleen.
- Reduction in one or more of cell lines of blood (anemia, leucopenia, thrombocytopenia).
- Normal bone marrow.
- Cure after splenectomy.
4. **DIC (disseminated intravascular coagulation)**
   This causes thrombocytopenia by excessive utilization & destruction of platelets.

5. **Massive blood transfusion**
Qualitative Platelet Defects

- Platelet count is normal, but there is defect in platelet aggregation.
- e.g. Glanzmann’s disease (thrombosthenia, autosomal recessive)
Disorders of Blood Vessels
( Vascular Purpura )

**Congenital:**

Hereditary Hemorrhagic Telangiectasia
- Autosomal dominant
- Clinically: usually epistaxis, multiple telangiectatic spots in the skin & mucus membranes leading to hemorrhage & iron deficiency anemia, haemoptysis.
**Acquired:**

- Purpura simplex in women.
- Senile purpura: on the dorsum of hands & arms due to poor capillary support from collagen as also in:
  - Steroid therapy or Cushing syndrome
  - Scurvy, vit. C needed for polymerization of mucopolysaccharides necessary for collagen synthesis.
Henoch Schonlein Purpura: necrotizing vasculitis give rise to small hemorrhages especially in the skin & gut, there may be associated glomerulonephritis, usually follow streptococcal infection.

Damage to capillaries as in:
- severe acute bacterial infection: septicaemia.
- subacute bacterial endocarditis.
Disorders of Coagulation

- XII → XIIa
  - e.g. collagen fibres
- XI → Xla
- IX → IXa
- X
  - VIII, Ca++
  - Phospholipid
- Xa
  - V
    - Phospholipid
    - Ca++
    - Prothrombin (II)
      - Thrombin (IIa)
        - Fibrinogen
          - XIII (Fibrin Stabilizing Factor)
            - Fibrin
Inherited Disorders of Coagulation

Of these coagulation factors deficiencies factor VIII deficiency is important. It can lead to Haemophilia A and von Willebrand’s disease.
Structure of factor VIII

Plasma factor VIII is now considered to be a complex of two components; the larger of the two, factor VIII /von Willebrand factor (VIII R: WF) is coded by autosomal genes and is deficient in von Willebrand’s disease, it promotes primary haemostasis by interacting with platelets and also appears to function as a carrier of smaller component factor VIII coagulant (VIII C) which is coded by an X chromosome which participates directly into cascade clotting reaction & is deficient in classical haemophilia, when assayed immunologically these two components are expressed as antigen (Ag) i.e. VIII R: Ag and VIII C : Ag.
Haemophilia A

- Hereditary abnormality of coagulation.
- Sex linked: affect ♂, while ♀ are carriers.
All sons of diseased ♂ are normal.

All daughters of diseased ♂ are carriers.
50% of daughters of carrier female are carriers.
50% of sons of carrier female are diseased.
Clinically

- Male child will suffer from bleeding following circumcision, haemarthrosis usually after crawling.

- Severity of haemophilia is graded according to the level of VIII C into:
  
  i. Severe (VIII C < 1% of normal).
  
  ii. Moderate (2-3% of normal).
  
  iii. Mild (5-20% of normal).
Diagnosis

- APTT ↑
- Clotting time either normal or ↑
- Bleeding time normal
- VIII C activity ↓
- VIII C : Ag ↓
- VIII R: Ag normal
Von Willebrand’s Disease

Inherited hemorrhagic disease in which bleeding time is prolonged due to deficiency of von Willebrand’s factor (vIII R) as this factor is important for platelet adhesion to vascular subendothelium.
Comparison Between Haemophilia & von Willebrand’s Disease

<table>
<thead>
<tr>
<th>Character</th>
<th>Haemophilia A</th>
<th>Von willebrand’s disease</th>
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</thead>
<tbody>
<tr>
<td>Inheritance</td>
<td>Sex linked (♂ affected)</td>
<td>Autosomal (♂ &amp; ♀)</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Normal</td>
<td>Prolonged</td>
</tr>
<tr>
<td>VIII C</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VIII C: Ag</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VIII R</td>
<td>Normal</td>
<td>↓</td>
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Inherited disorder shows the same pattern of inheritance as haemophilia A (sex linked).

Same clinical picture but incidence of disease = 1/5th of the haemophilia A.

Treated by factor IX concentrate.
Acquired Disorders Of Coagulation

**Vitamin K deficiency**

Vitamin K is necessary for γ carboxylation of precursors of factor II (prothrombin) & some other coagulation factors. It is fat soluble, present in leaf vegetables & also synthesized by the normal intestinal flora.
Dietary deficiency of sufficient severity to produce bleeding is well recognized in:

- Neonates (Haemorrhagic Diseases of the newborn) in whom normal bacterial flora is not yet established.
- In children & adults (malnourishment).
- ↓ absorption in biliary obstruction, coeliac disease.
Liver disease

Liver is the site of synthesis of most coagulation factors.

Severe impairment of liver lead to combined factor deficiency particularly II, VII, IX, X, & I (fibrinogen).
Renal Impairment

Lead to thrombocytopenia, platelet dysfunction, (II, VII, IX, X, XIII), DIC.
**Warfarin therapy**

Control of Warfarin Therapy by

- Doing prothrombin time
- Control = seconds.
- Test = seconds.
- Test/control ratio (R) =
- INR (international normalized ratio) =
- Accepted INR = 2 - 3.5
- INR = (R)^s
- S = sensitivity index, fixed figure provided by manufacturer of the kit (e.g. S = 2)
Heparin therapy control

- Coagulation (Clotting) time
- Thrombin time
- Activated Partial Thromboplastin Time (APTT)
**Disseminated Intravascular Coagulation (DIC)**

- wide spread deposition of fibrin in the small vessels of many organs causing tissue necrosis & multiple organ dysfunction and subsequent bleeding state due to consumption of platelets & clotting factors and secondary enhancement of fibrinolytic activity. Microangiopathic haemolytic anaemia is a common accompaniment.
Causes of DIC

- Extensive burn
- Septicaemia
- Shock
- Liver disease
- Renal disease
- Complications of labour: retroplacental haemorrhage & aminotic fluid embolism.
DIC: Disseminated Intravascular Coagulation:

1) Bleeding: “Consumption coagulopathy”
   - Platelets (severe)
   - Coagulation factors (I, II, VIII, IX, X)
   - Fibrinolysis
2) Haemolytic Anemia "Microangiopathic"

- Hb
- RBC Fragmentation
- PCV
- Retic
- Indirect S. Bilirubin.
- Hburia

3) Thrombotic manifestations:

1) Acute Renal failure
2) Skin Necrosis.
3) CNS ischemia
4) Respiratory Distress.