IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

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OUTLINE

• Introduction
• Epidemiology
• Classification
• Aetiology
• Pathophysiology
• Clinical features
• Diagnosis
• Management
• Conclusion
INTRODUCTION

• Immune Thrombocytopenic purpura (ITP) is an autoimmune disorder, also known as Autoimmune Thrombocytopenic purpura, formerly known as Idiopathic thrombocytopenic purpura.

• Is an autoimmune bleeding disorder characterized by isolated thrombocytopenia with no clinical associated conditions or other causes of thrombocytopenia.
INTRODUCTION

- May be acute (usually in children, 2 weeks after infection with sudden self-limiting purpura) or chronic (usually in women within 15-50 years).

- Salient points in diagnosis:
  - Decreased platelets count confirmed on blood film.
  - Exclusion of other causes of thrombocytopenia - Normal or increased marrow megakaryocytes are found in majority.
EPIDEMIOLOGY

- Is a rare condition, there are fewer than 100 cases in Nigeria yearly.

- It can occur both in adults and children.

- Incidence:
  - Children: 5 per 100,000
  - Adults: 2 per 100,000

- Age: Can affect individuals of any age;
  - Peak incidence occurs in children 2-5 years of age and adults 15-50 years of age, reports suggest an increasing incidence with age.

- Gender
  - Children: males and females affected equally.
  - Adults: females affected more often than males (3:1).
CLASSIFICATION

1. Based on presence or absence of other diseases:
   - **Primary ITP** - absence of other disease or with an unknown cause affecting both adults and children.
   - There is no underlying disorder in this condition.
   - Is characterized by a platelet count of 10-100 x 10^9/L.
   - **Secondary ITP** - presence of other disease
   - Maybe associated with autoimmune diseases, collagen vascular diseases, malignancy and chronic infections

2. Based on age:
   - Adult ITP: peak at 15-50 years
   - Childhood ITP: peak at 2-5 years

3. Based on Disease phase:
   - Newly diagnosed: after diagnosis to 3 months
   - Persistent: >3months-12months
   - Chronic: >12months
   - Refractory: treatment failure of splenectomy
# Differences between childhood ITP and Adult ITP

<table>
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<tr>
<th></th>
<th>Childhood ITP</th>
<th>Adult ITP</th>
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<tbody>
<tr>
<td><strong>onset</strong></td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td><strong>age</strong></td>
<td>A peak incidence between 2 and 5 years</td>
<td>More frequent in adolescents and young adults. 15 -50 years</td>
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<tr>
<td><strong>M:F ratio</strong></td>
<td>Boys = girls</td>
<td>Female &gt; males {3&gt;1}</td>
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<tr>
<td><strong>course of disease</strong></td>
<td>&lt; 6 months</td>
<td>&gt; 6 months</td>
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<tr>
<td><strong>platelet count</strong></td>
<td>&lt; 20 x 10⁹/ L</td>
<td>30- 80 x 10⁹/ L</td>
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<td><strong>Numbers of megakaryocytes of bone marrow</strong></td>
<td>Normal or increased</td>
<td>Increased markedly</td>
</tr>
<tr>
<td><strong>spleen</strong></td>
<td>Palpable</td>
<td>Non palpable</td>
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<tr>
<td><strong>Resolves</strong></td>
<td>Spontaneously within weeks - 6 month</td>
<td>Rarely resolves spontaneously.</td>
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<td><strong>Aetiology</strong></td>
<td>Usually follows a viral infection or vaccination</td>
<td>No specific causes.</td>
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<td><strong>CURRENT CHANGES</strong></td>
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<td><strong>Terminology</strong></td>
<td>previously</td>
<td>currently</td>
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<td></td>
<td>Idiopathic</td>
<td>Primary or Autoimmune</td>
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<td></td>
<td>Acute/chronic</td>
<td>newly diagnosed, persistent, chronic</td>
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<tr>
<td><strong>Pathogenesis</strong></td>
<td>Platelet destruction alone</td>
<td>platelet destruction and reduced production</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>150 x10⁹/L</td>
<td>100 x 10⁹/L</td>
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AETIOLOGY

- **Primary ITP**: Idiopathic.
- **Secondary ITP**: Caused by an underlying condition. Could be:
  - Autoimmune disorders: Systemic Lupus Erythematosus (SLE)
  - Viral infection: Human Immunodeficiency Virus, Hepatitis C Virus
  - Sepsis
  - Drugs: gold, heparin, quinidine, penicillin.
  - Lymphoproliferative disorders: Chronic Lymphocytic Leukemia, Hodgkin's lymphoma.
  - Myelodysplasia
  - Agammaglobulinemia: IgA deficiency
  - Measles Mumps Rubella vaccination side effect
  - Bone marrow transplantation side effect.
PATHOPHYSIOLOGY

Main theory:
(Proven by Harrington Hollisworth experiment)

- IgG autoantibodies produced against the membrane glycoproteins (mainly GP IIb/IIIa and Ib/IX)
- Splenic sequestration and phagocytosis by mononuclear macrophages
- Reduction in lifespan of circulating platelets and
- Inadequate compensation by bone marrow megakaryocytes.
PATHOPHYSIOLOGY

Contributing factors/theories

- IgG autoantibodies attack megakaryocytes
- Impaired production of thrombopoietin
- Direct lysis of platelets by T cells
- Molecular mimicry and immune complex formation
ITP (Pathophysiology) (cont.)

Antiplatelet autoantibodies → Sensitized platelet → Fc portion of antibody → Fc receptor → Destruction in reticuloendothelial system (spleen, liver) → Macrophage

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PATHOPHYSIOLOGY

Antibody → Platelets → Bone marrow where platelets are produced

Increased platelet destruction & Inadequate platelet production
CLINICAL FEATURES

• Petechiae
• Purpura
• Ecchymoses
• Easy bruising
• Persistent bleeding from venipuncture site
• Menorrhagia
• Mucosal bleeding-epistaxis, gingival and gastrointestinal bleeding
• Haemorrhagic Bullae
• Retinal haemorrhage
• Intracranial haemorrhage
Picture illustrating Petechiae and Purpura

Picture illustrating Ecchymoses
Endoscopic image illustrating Gastrointestinal bleeding

Picture illustrating Haemorrhagic Bullae on mucous membrane of the tongue
Opthalmoscopic photograph illustrating Retinal haemorrhage

Computed Tomography (CT) scan illustrating Intracranial haemorrhage
DIAGNOSIS

• Diagnosis of exclusion
• History
• Physical examination
• Investigations
  ➢ Peripheral blood smear
  ➢ Complete blood count
  ➢ Bone marrow aspiration and biopsy
  ➢ Antiplatelet antibody testing
• Response to therapy
PERIPHERAL BLOOD SMEAR OF A PATIENT WITH IMMUNE THROMBOCYTOPENIC PURPURA
BONE MARROW CYTOLOGY OF A PATIENT WITH IMMUNE THROMBOCYTOPENIC PURPURA
MANAGEMENT

• Goal is not **cure** but **haemostatic control**: Aim not normalising platelet count but rather attaining ‘safe’ platelet count

• Safe platelet count depend on
  - Patient age and activity level/life style
  - Haemostatic challenge

• Approach to treatment include:
  - Emergency
  - Short term
  - Long term

• Combination/monotherapy
GOALS OF TREATMENT

• Obtain a hemostatic platelet count to prevent bleeding
  – Individualized to the patient

• Minimizing toxicity associated with treatment

• Induce long-term remission
TREATMENT OPTIONS

1st line: work fairly quickly (24-48 hr) and have efficacy rates of around 70-80%.

- Corticosteroids Oral prednisone, Intravenous methylprednisolone
  - Intravenous immunoglobulins (IVIG)
  - IV Rho immunoglobulin (RhIG): For Rh(D)-positive patients with intact spleens, offers comparable efficacy, less toxicity, greater ease of administration, and a lower cost than IVIG

- 2nd Line
  - Splenectomy
  - Thrombopoietin Receptor Agonists (licensed)
  - Rituximab

- 3rd Line Other immunosuppressive agents, (not licensed)
MAIN POINTS IN MANAGEMENT

• Determine if treatment is necessary
• If needed, what approach:
  - emergency
  - short term
  - Long term
• For how long?
• **American Society of Hematology (ASH) suggests:**
  – Platelet counts > 30 x 10⁹/L usually have few or no symptoms and require no treatment
  – Avoid treatment in patients with mild, asymptomatic disease

• Platelet counts < 30 x 10⁹/L have treatment recommendations based on the presence and severity of associated bleeding symptoms

• Hospitalization and emergency treatment is indicated if:
  - Severe bleeding occurs, regardless of platelet count
  – Platelet count < 20 x 10⁹/L and signs/symptoms of mucocutaneous bleeding is present
APPROACH: EMERGENCY

- IV. Methylprednisone (30 mg/Kg/d; max 1 gr/d for 2-3 days) / 20-30min

- IVIG (1 gr/kg/d for 2-3 days)

- Infusion of platelets that is 2-3 times the usual amount infused
SHORT TERM

- Refers to treatment lasting 2 weeks or more
- Indication:
  - Sudden drop in platelet count to unacceptable level
  - During haemostatic challenge, e.g. Planned surgery or high risk activity
- Treatment started 1-2 weeks prior to event and stopped shortly after event
- Drugs: first line drugs e.g. corticosteroids
LONG TERM

• Indications:
  - Unsupported platelet count too low for normal day to day activity
  - Have failed other therapy
  - Require unacceptable high doses to maintain a safe count

• Aim of Treatment is to move platelet to a ‘safe’ zone

• Modalities:
  - Surgical- splenectomy
  - Medical: second line drugs, combination therapies
REFRACTORY ITP

- Poses a great challenge

- Rituximab
  - Arnold et al data suggest that 60% will respond, 40% complete remission
  - Bimodal response: early 1-2 weeks, second 6-8 weeks
  - Response last for 2 months to 5 years

- Combination therapy
ITP IN PREGNANCY

• If the platelet count is >50 X 109/L, the risk of serious hemorrhage is low.

• But beginning oral prednisone a week before delivery is a reasonable precaution.

• If the platelet count is <50 X 109/L before delivery, treatment with oral prednisone and IVIG is recommended.

• Avoid the use of IV RhIG in this situation until safety data are available.

• Rarely, splenectomy may be required to manage acute hemorrhage.

• Monitor neonatal thrombocytopenia
TREATMENT OPTIONS: Corticosteroids

Prednisone

Mechanism of Action:
- Impair clearance of platelets in the bone marrow and peripherally.
- Reduce antibody production

- Dose: 1 – 2 mg/kg/day PO as single or divided doses
- Usually responds within 2 - 3 weeks Response rate: 50 – 75%

- Taper over 4 – 6 weeks following platelet response
- Side effects: numerous
TREATMENT OPTIONS: IVIG

IVIG

• Mechanism of action: Undefined and potentially multifactorial

• Randomized clinical trials have demonstrated that therapy with IVIG shortens the duration of severe thrombocytopenia (platelet < 20,000/mm3).

• Dose: Variable regimen

• Standard dose: 1 g/kg/day x 1 – 2 days

• Side effects:
  ➢ hypersensitivity - headache
  ➢ renal failure - nausea/vomiting
  ➢ alloimmune hemolysis - pulmonary edema
TREATMENT OPTIONS:
Splenectomy

• Mechanism of action:
  ➢ Removes a primary site of platelet destruction and increases platelet count
  ➢ Possible site of autoantibody production

• Side effects: increase risk of infection, thrombosis, pulmonary hypertension

• Vaccination recommended HBV, pneumococcal, and meningococcal
TREATMENT OPTIONS:

Rituximab

• Rituximab (Rituxan®)

• Mechanism of action: Hypothesis-driven use B-cell depletion: decreased antiplatelet antibodies

• Dose: Most effective dose/schedule not known, not FDA-approved for ITP

• Usual dosage: 375 mg/m2 IV once weekly x 4 weeks

• Response rate: 40% at 1 year, 20 – 25% at 5 years

• Side effects:
  - Infusion reaction
  - Tumor lysis syndrome
  - Pulmonary toxicity
  - Hepatitis B reactivation
THROMBOPOETIN RECEPTOR AGONISTS

- Romiplostim (Nplate®)

- Mechanism of action: Analog of thrombopoietin which increases the production of platelets.

- Dose: 1 – 10 mcg/kg SubQ weekly.
  - Increase dose by 1 mcg/kg qweek to effect (Plts ≥ 50 x 109/L)

- Side effects:
  - Headache
  - Paresthesia
  - Myelodysplastic Syndrome
  - Mylagia
  - Insomnia
  - Pain in extremity

- Monitor: CBC with differential and platelets continually
CONCLUSION

• Immune Thrombocytopenic purpura is an autoimmune bleeding disorder characterized by isolated thrombocytopenia with no clinical associated conditions or other causes of thrombocytopenia.

• It is a disorder of exclusion.

• It is often acute in children and chronic in adults.

• The goal of treatment is to prevent complications
THANK YOU FOR
LISTENING