GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY 🧬

Introduction

Red cells are continuously exposed to oxidative stress from:

- Endogenous sources (normal metabolism)
- Exogenous sources (drugs, infections, foods)

🔑 Protection against oxidative injury depends on:

- Reduced glutathione (GSH)

📌 Key concept:

Any defect in enzymes responsible for maintaining GSH leaves RBCs vulnerable to oxidative damage and hemolysis.

Genetics 🧠

- X-linked recessive
- G6PD gene located on X chromosome
- 400 variants identified
- Only a few cause clinically significant disease

📌 Most common enzymatic cause of hemolytic anemia worldwide

NORMAL ROLE OF G6PD ⚙️

Biochemical Function

- G6PD catalyzes the first step of the pentose phosphate pathway
- Generates NADPH

📌 NADPH is essential for:

- Regeneration of reduced glutathione (GSH)

Normal Protective Pathway Flowchart 🔄

- Oxidative stress (e.g., H_2 O_2) → Reduced glutathione (GSH) neutralizes oxidants → GSH becomes oxidized → NADPH (via G6PD) regenerates GSH → RBC membrane & hemoglobin protected

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PATHOGENESIS ⚠️

Core Mechanism

G6PD deficiency leads to failure of GSH regeneration, allowing oxidants to damage RBCs.

Oxidative Injury Flowchart 🔥

- Oxidant exposure (drug / infection / food) → ↓ NADPH production → ↓ Reduced glutathione (GSH) → Accumulation of oxidants → Oxidation of

hemoglobin → Denaturation of globin chains → Heinz body formation

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Heinz Body-Mediated Damage 🩸

- Heinz bodies:
  - Aggregates of denatured hemoglobin
  - Attach to inner RBC membrane

Two Possible Outcomes

1. Severe membrane damage

- RBC membrane rupture → Intravascular hemolysis

2. Partial damage

- ↓ Deformability
- Splenic macrophages remove Heinz bodies → "Bite cells" formed → RBC trapped in spleen → Extravascular hemolysis

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Heinz Body to Bite Cell Flowchart 🔄

- Heinz bodies in RBC → Splenic macrophages "pluck out" inclusions → Membrane defect created → Bite cell formation → Trapping in spleen → Phagocytic destruction

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TRIGGERS OF HEMOLYSIS ⚠️

Drugs

- Antimalarials → Primaquine
- Sulfonamides
- Nitrofurantoin
- Phenacetin
- Aspirin (high doses)
- Vitamin K derivatives

Foods

- Fava beans (Favism)

Infections (Most Common Trigger) 🦠

- Infection → Activated phagocytes → ↑ Oxidant production → RBC oxidative damage

📌 Key exam line:

Infection is the most common precipitating factor for hemolysis.

CLINICAL FEATURES 🩺

Pattern of Hemolysis

- Acute, episodic
- Usually intravascular
- Occurs 2–3 days after exposure

Severity:

- Mild → Severe
- Depends on G6PD variant

Gender Differences 🧬

Males

- All RBCs are G6PD deficient
- Uniform susceptibility
- More severe hemolysis

Females

- Heterozygous carriers
- Two RBC populations due to lyonization

📌 Unfavorable lyonization

- Majority of RBCs deficient → Clinical disease may appear

VARIANTS OF G6PD DEFICIENCY 📊

Variant	Geographic Distribution	Severity
G6PD A-	Africa (malaria endemic areas)	Mild
G6PD Mediterranean	Middle East	Severe

G6PD A- Variant 🌍

- Mild decrease in enzyme activity
- Only older RBCs affected

📌 Clinical course:

- Hemolysis initially
- Marrow compensates with young RBCs
- Hemolysis subsides even if drug continues

G6PD Mediterranean Variant ⚠️

- Marked enzyme deficiency
- All RBCs severely affected
- Hemolysis is:
    - More severe
    - More prolonged

KEY MORPHOLOGICAL FEATURES 🔬

Feature	Finding
Peripheral smear	Bite cells
Special stains	Heinz bodies
Hemolysis type	Intravascular ± extravascular
Reticulocytes	Increased

EXAM SUMMARY BOX 📌

- X-linked enzymopathy
- Defective NADPH production
- ↓ Reduced glutathione
- Oxidative damage to hemoglobin
- Heinz bodies → bite cells
- Triggered by drugs, infections, fava beans
- Episodic hemolysis

Concept 🏆

G6PD deficiency causes episodic intravascular hemolysis due to oxidative damage to hemoglobin resulting in Heinz body formation and bite cells.

-> The End <-