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GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY IN NEONATES: CLINICAL IMPLICATIONS, SCREENING TRATEGIES, AND MANAGEMENT

[1]Ananya Chandra ,MSc Botany II year,Mahatma Gandhi College, Thiruvananthapuram,Kerala,India

Abstract: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent enzymatic disorder of red blood cells worldwide, affecting approximately 400 million individuals. The condition assumes particular clinical significance during the neonatal period because it is a major cause of severe neonatal hyperbilirubinemia, hemolytic anemia, kernicterus, and, in extreme cases, neonatal mortality. G6PD deficiency is inherited as an X-linked recessive disorder caused by mutations in the G6PD gene, resulting in reduced enzyme activity and increased susceptibility of erythrocytes to oxidative stress. Neonates with G6PD deficiency often appear healthy at birth but may rapidly develop jaundice within the first few days of life. Early diagnosis through neonatal screening programs and prompt management are crucial for preventing irreversible neurological damage. This review examines the genetic basis, pathophysiology, epidemiology, clinical manifestations, diagnostic approaches, neonatal screening strategies, and current management practices associated with G6PD deficiency in neonates. The paper also highlights the importance of universal newborn screening in regions with high disease prevalence and discusses future perspectives in precision neonatal care.

Index Terms - G6PD deficiency, neonate, neonatal jaundice, hyperbilirubinemia, hemolytic anemia, newborn screening, kernicterus.

I. INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common inherited enzymatic disorders affecting human red blood cells. The enzyme G6PD plays a critical role in protecting erythrocytes from oxidative injury through the production of nicotinamide adenine dinucleotide phosphate (NADPH) in the pentose phosphate pathway. Deficiency of this enzyme compromises cellular antioxidant defense mechanisms, rendering red blood cells vulnerable to oxidative stress and premature destruction.

According to the World Health Organization (WHO), G6PD deficiency affects nearly 5% of the global population, with a particularly high prevalence in Africa, the Mediterranean region, the Middle East, and South and Southeast Asia. Neonates constitute a highly vulnerable group because G6PD deficiency is strongly associated with severe neonatal jaundice and hyperbilirubinemia. If left untreated, excessive bilirubin accumulation can lead to kernicterus, permanent neurological impairment, or death.

As noted by Frank (2005), “G6PD deficiency remains one of the leading inherited causes of hemolytic anemia and neonatal hyperbilirubinemia worldwide.” This observation underscores the continued importance of early detection and preventive management.

The increasing emphasis on neonatal screening programs has significantly improved early diagnosis and intervention. However, variations in screening policies and healthcare access continue to influence disease outcomes across different populations.

2. Historical Background

The modern understanding of G6PD deficiency emerged during investigations into hemolytic reactions associated with primaquine administration among military personnel during the mid-twentieth century. Researchers observed that certain individuals developed acute hemolytic anemia following primaquine exposure, whereas others remained unaffected.

Subsequent studies demonstrated that the susceptibility was attributable to an intrinsic erythrocyte enzymatic defect, eventually identified as G6PD deficiency. These discoveries marked a milestone in molecular hematology and contributed substantially to the understanding of inherited red blood cell disorders.

3. Genetics and Inheritance

G6PD deficiency results from mutations in the **G6PD gene**, located on the long arm of the X chromosome (Xq28). More than 230 genetic variants have been identified, leading to varying levels of enzyme activity and clinical severity.

The disorder follows an **X-linked recessive inheritance pattern**, explaining its higher prevalence among males. Since males possess only one X chromosome, a single defective allele is sufficient to manifest the disease. Females may be heterozygous carriers or, less commonly, homozygous affected individuals.

The inheritance pattern has important implications for genetic counseling and family screening. Fathers cannot transmit the disorder directly to their sons, but carrier mothers can pass the defective gene to both sons and daughters.

4. Pathophysiology

The principal function of G6PD is to catalyze the first step of the pentose phosphate pathway, generating NADPH. NADPH is essential for maintaining glutathione in its reduced form, thereby protecting red blood cells against oxidative damage.

In G6PD-deficient individuals, inadequate NADPH production results in:

- Accumulation of reactive oxygen species (ROS)
- Oxidative damage to hemoglobin
- Formation of Heinz bodies
- Membrane instability
- Premature erythrocyte destruction

Because mature erythrocytes lack mitochondria and depend entirely on the pentose phosphate pathway for antioxidant defense, they are particularly susceptible to oxidative stress.

5. Epidemiology

The prevalence of G6PD deficiency varies significantly among ethnic populations.

High-prevalence regions include:

- Sub-Saharan Africa
- Mediterranean countries
- Middle East
- India
- Southeast Asia
- China

India exhibits considerable regional variation, with prevalence rates ranging from 0% to over 27% in certain tribal populations. Several studies have highlighted the burden of neonatal G6PD deficiency in North Indian and South Indian populations.

Interestingly, the distribution of G6PD deficiency overlaps geographically with malaria-endemic regions. This pattern supports the hypothesis that G6PD deficiency confers partial protection against severe malaria, representing a classic example of balanced polymorphism.

6. Clinical Manifestations in Neonates

6.1 Neonatal Jaundice

Neonatal jaundice is the most common manifestation of G6PD deficiency.

Affected neonates may develop:

- Early-onset jaundice
- Rapidly rising bilirubin levels
- Indirect hyperbilirubinemia
- Prolonged jaundice

Jaundice often appears within the first 24–72 hours after birth and may progress rapidly.

6.2 Acute Hemolytic Episodes

Hemolysis may be triggered by:

- Bacterial infections
- Viral infections
- Certain medications
- Naphthalene exposure
- Maternal ingestion of oxidative substances

Clinical findings include:

- Pallor
- Dark urine
- Tachycardia
- Splenomegaly

- Hemoglobinuria

6.3 Kernicterus

Severe hyperbilirubinemia may lead to bilirubin deposition in the basal ganglia, resulting in kernicterus.

Manifestations include:

- Hypotonia
- High-pitched crying
- Seizures
- Developmental delay
- Sensorineural hearing loss

As Kaplan and Hammerman (2011) observed, "G6PD deficiency remains a significant and preventable cause of kernicterus in many developing countries."

7. Diagnostic Approaches

7.1 Laboratory Evaluation

Diagnostic investigations include:

Hematological Tests

- Complete blood count (CBC)
- Reticulocyte count
- Peripheral blood smear
- Serum bilirubin levels

Enzyme Assays

The gold standard for diagnosis is quantitative measurement of G6PD enzyme activity.

Common screening methods include:

- Fluorescent spot test
- Spectrophotometric assay
- Rapid diagnostic tests

Molecular Analysis

Polymerase chain reaction (PCR)-based methods enable:

- Identification of specific mutations
- Population screening
- Prenatal diagnosis
- Family studies

8. Neonatal Screening Programs

Universal neonatal screening has emerged as a highly effective strategy for reducing G6PD-related morbidity.

The objectives of screening include:

1. Early identification of affected infants
2. Prevention of severe hyperbilirubinemia
3. Reduction of kernicterus
4. Parent education regarding triggers

Several countries, including Singapore, Taiwan, Saudi Arabia, and parts of India, have successfully implemented neonatal G6PD screening programs.

Goyal et al. demonstrated that systematic newborn screening facilitates early diagnosis and improves neonatal outcomes through timely intervention.

9. Management and Treatment

9.1 Prevention

Prevention remains the cornerstone of management.

Parents should be educated regarding:

- Oxidative medications
- Fava beans
- Naphthalene-containing mothballs
- Certain herbal preparations

9.2 Management of Hyperbilirubinemia

Treatment options include:

Phototherapy

Phototherapy is the first-line treatment for neonatal hyperbilirubinemia.

Exchange Transfusion

Exchange transfusion is indicated when bilirubin levels reach dangerous thresholds despite intensive phototherapy.

Supportive Care

Supportive management includes:

- Adequate hydration
- Monitoring hemoglobin levels
- Treatment of infections

9.3 Blood Transfusion

Severe hemolytic episodes may require packed red cell transfusions to restore oxygen-carrying capacity.

10. Public Health Significance

G6PD deficiency represents a substantial public health challenge in low- and middle-income countries.

The disease contributes significantly to:

- Neonatal hospital admissions
- Hyperbilirubinemia-related morbidity
- Preventable neurological disability

- Healthcare expenditure

Universal newborn screening, public awareness programs, and physician education can substantially reduce disease burden.

WHO recommends targeted neonatal screening in populations where prevalence exceeds 3–5%.

11. Future Perspectives

Recent advances in molecular diagnostics and genomics are improving the detection of G6PD variants and facilitating personalized healthcare approaches.

Future priorities include:

- Universal neonatal screening
- Point-of-care diagnostic technologies
- Genetic counseling services
- Population-specific mutation databases
- Integration of genomic medicine into neonatal care

Emerging molecular approaches may further enhance risk prediction and individualized treatment strategies.

12. Conclusion

Glucose-6-phosphate dehydrogenase deficiency is a major inherited enzymatic disorder with profound implications during the neonatal period. While many affected newborns remain asymptomatic initially, they are at increased risk of severe hyperbilirubinemia, hemolytic anemia, kernicterus, and long-term neurological complications. Early diagnosis through newborn screening, vigilant monitoring, parental education, and timely therapeutic interventions remain essential components of neonatal care. Strengthening universal screening programs and improving awareness among healthcare professionals and families can significantly reduce morbidity and mortality associated with this preventable condition.

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