Frequency, Severity & Outcome of G6PD Deficiency Among Male Newborns Presenting to Neonatal Unit of A Tertiary Care Hospital with Neonatal Jaundice

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KEYWORDS
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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common genetic disorder affecting red blood cells. It predisposes newborns to hemolysis, particularly under oxidative stress, leading to neonatal jaundice, which, if untreated, may result in severe complications like kernicterus. This study examines the frequency, severity, and outcomes of G6PD deficiency among male neonates with jaundice admitted to the neonatal unit of a tertiary care hospital.

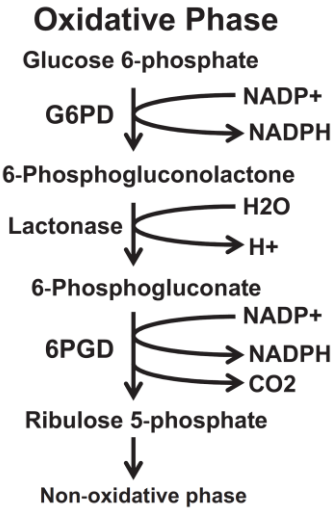
Methods: A retrospective study on a cohort of 250 male neonates, randomly selected by convenience sampling, admitted with NNJ to the neonatal unit of QHAMC Nowshera, Khyber Pakhtunkhwa, Pakistan, in the period between January 2024 to June 2024, was conducted with a focus on identifying those with G6PD deficiency and tracking their clinical outcomes. The severity of jaundice, associated hemolytic episodes, and outcomes such as treatment response and complications were analyzed.

Results: Out of 250 neonates admitted with neonatal jaundice, 42 (16.8%) were diagnosed with G6PD deficiency. The severity of jaundice ranged from mild (19.0%) to moderate (47.6%) to severe (33.4%). Phototherapy was the primary treatment in 90.5% of cases, and exchange transfusion was required in 9.5% of cases. One case (2.4%) developed kernicterus. All neonates with mild jaundice recovered fully with no long-term complications, while severe cases had extended hospital stays.

Conclusion: Results indicate that G6PD deficiency is a leading cause of neonatal jaundice, particularly in populations at higher risk due to genetic factors. Early diagnosis and treatment significantly improve outcomes, though complications such as kernicterus remain a risk in severe cases.

1. Introduction

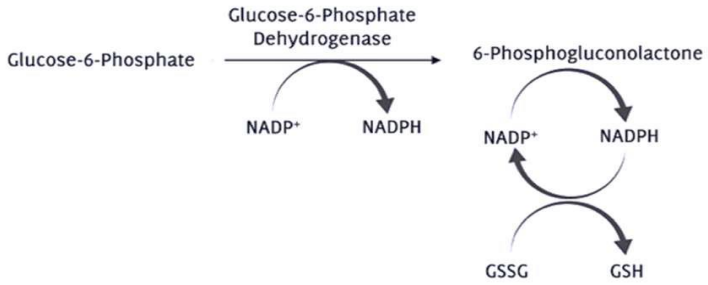
Glucose-6-phosphate dehydrogenase (G6PD) is a cytosolic NADP dependent enzyme which is found as a dimer/or tetramer[1]. It controls the entry of glucose-6-phosphate (G6P) into Hexose Monophosphate Shunt (HMP) (also called the Pentose Phosphate Pathway) (PPP), a non-energy generating pathway of glucose metabolism [2, 3].



Source: *Hecker PA, Leopold JA, Gupte SA, Recchia FA, Stanley WC. Impact of glucose-6- phosphate dehydrogenase deficiency on the pathophysiology of cardiovascular disease. Am J Physiol Heart Circ Physiol. 2013;304(4):H491-500*

G6PD is the first enzyme in the pathway which catalyzes an irreversible first step that is rate-limiting. In this reaction there is oxidation of G6P to 6-phosphogluconolactone and, in the process, Nicotinamide Adenine Dinucleotide Phosphate (NADP) is reduced to NADPH (Figure). The enzyme exhibits negative co-operativity, being inhibited readily by the product. NADPH is an agent that maintains glutathione (GSSG) in its reduced form (GSH) (Figure). By producing NADPH, the main purpose is thus provision of reductive potential [2, 3].

The reduced state of Glutathione (GSH) is important in scavenging potentially harmful free radicals & reactive oxygen species (ROS) thus protecting red cells membrane from rupturing.



Source: *Hecker PA, Leopold JA, Gupte SA, Recchia FA, Stanley WC. Impact of glucose-6- phosphate dehydrogenase deficiency on the pathophysiology of cardiovascular disease. Am J Physiol Heart Circ Physiol. 2013 Feb 15;304(4):H491-500*

PPP plays an important role in the synthesis of various molecules like nucleotides, fatty acids and cholesterol. Any kind of disruption in the pathway like decreased G6PD activity & reduced levels of NADPH, will lead to oxidative damage to RBCs due to generation of ROS, excess of which causes an increase in red cell membrane fragility, in turn causing hemolysis and jaundice[2-4].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common enzymatic disorders worldwide with a global prevalence of 4.9% [5]. 400 million people across the world are estimated to be affected, with the highest prevalence being in those of African, Asian and Mediterranean origin [6-8]. There is considerable evidence to believe that the prevalence of G6PD deficiency in Pakistan ranges from 2 to 3.8%, with highest frequency of 8.6% in Pathans [9-13].

The deficiency is caused by inheritance of any of a large number of abnormal alleles of the gene responsible for the synthesis of the G6PD protein. About 200 mutations have been described in the gene responsible for the synthesis of the G6PD protein. The normal enzyme found in most populations is designated G6PD B+. The type of mutation influences the residual enzyme activity and substrate binding depending upon which the level of disease severity varies. Common variants include G6PD A+, G6PD A- & G6PD B- (Mediterranean). Depending upon the enzyme activity, WHO has categorized the disease into five classes: Class I (very severe deficiency; <1% enzyme activity), Class II (Severe deficiency; 1-10% enzyme activity), Class III (Moderate deficiency; 10-60% enzyme activity), Class IV (Normal; 60-150% enzyme activity) & Class V (> 150% enzyme activity) [14, 15].

G6PD deficiency particularly affects males due to its X-linked recessive inheritance and is transmitted with intermediate dominance. Full expression of the trait occurs in hemizygous and homozygous females. Intermediate expression is found in heterozygous females who are carriers of the disease. Carriers are not usually affected by the condition and rarely present with symptoms[15, 16]. Female heterozygotes have been shown to have

two populations of red cells: One with normal enzyme activity and one with markedly deficient activity [15].

Primary effects of G6PD deficiency are blood related, though it affects every cell of the body. The reason is that RBCs do not have an alternate source of NADPH [15].

An important complication & one of the earliest manifestations of G6PD-deficiency is neonatal jaundice, which can occur in neonates 2 to 3 days after birth with varying severity[5, 15, 17]. It is characterized by high levels of bilirubin in blood. According to blood indices, severe hyperbilirubinemia in infants with G6PD-deficiency are not well correlated with hemolysis, though researches have shown that hemolysis plays a major role in the pathophysiology of severe hyperbilirubinemia using end tidal CO or carboxyhemoglobin. Neonatal RBCs are more susceptible to hemolysis from oxidative damage in the wake of G6PD deficiency due to their decreased lifespan and reduced levels of enzymes like carbonic anhydrase & glutathione peroxidase. Jaundice due to G6PD deficiency is also attributed to the oxidant-antioxidant imbalance and disruption in the recycling of peroxiredoxin 2 which affects bilirubin clearance[18]. In G6PD A–, spontaneous hemolysis and hyperbilirubinemia have been observed in preterm infants. If not managed adequately, in neonates with the G6PD B− variety, hyperbilirubinemia progressing to severe complications, including bilirubin encephalopathy (kernicterus), a form of severe neurological damage and even death may occur. Co-inheritance of a gene variant, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is an added risk factor in G6PD-deficient male neonates for neonatal hyperbilirubinemia [18-20].

G6PD deficiency should be considered and tested for, in any neonatal patient with hyperbilirubinemia. The diagnosis depends on direct or indirect demonstration of reduced G6PD activity in RBCs. The most widely used tests are the fluorescent spot test (FST) and the quantitative spectrophotometric assay, both of which rely on the principle of conversion of NADP+ to NADPH. Satisfactory screening tests are based on decoloration of methylene blue, reduction of methemoglobin, or fluorescence of NADPH. Identification of the genetic mutations through molecular analysis can confirm the exact underlying genetic defect [15, 21, 22].

While phototherapy remains the mainstay of treatment, the disease's clinical course can vary based on the severity of the deficiency, as well as the neonate's genetic background and health status.

In our set-up, screening for G6PD deficiency is not a routine, and it is performed only on those male neonates who present with neonatal jaundice, with or without any other risk factor for indirect hyperbilirubinemia. This study aims to determine the frequency, severity, and outcomes of G6PD deficiency among male newborns admitted with jaundice.

2. Methods:

The study included 250 male neonates, selected randomly from the available record by convenience sampling, amongst all neonates admitted with NNJ at neonatal unit of QHAMC/NMC MTI Nowshera Khyber Pakhtunkhwa Pakistan, in the period between January 2024 to June 2024; the neonates with direct hyperbilirubinemia were excluded from the study. History, examination and results of all the relevant investigations i.e., total and fractionated serum Bilirubin levels, mother's blood group (MBG) and Baby's blood group (BBG), Full Blood Count (FBC), Coombs' test (Rh-negative mother), G6PD screening test, reticulocytes count and, C-reactive protein and Blood Culture (where sepsis was suspected) were recorded on an already designed proforma.

In our setup, for detecting G6PD deficiency, qualitative test is performed. The enzyme activity is determined indirectly by measurement of the rate (time) of decolorization due to the reduction of NADP+ without using spectrophotometer. After collecting blood (1.5-2 ml) from a vein under strict hygienic condition, the blood is put into an EDTA tube and then sent to the laboratory for processing where the whole process takes 2-3 hours to get the final report. It uses the diagnostic reagent kit for the in vitro determination of the activity of the G6PD from the red cell hemolysate. G6PD in RBC is released by lysing agent of reagent kit. G6PD of red cells catalyzes the G6P with reduction of NADP to NADPH which with the help of PMS (Phenazine methosulfate) reduces blue colored 2,6 dichlorophenol indophenol into a colorless form. The rate of reduction of NADP to NADPH is measured as time taken to decolorize the coloring reagent which is proportional to the G6PD activity.

SPSS version 25.0 software package for Windows (IBM Corp., Armonk, NY, USA) was used for data evaluation and analysis. Means and standard deviations were calculated for continuous variables (e.g. bilirubin level, age of presentation). Frequencies and percentages were calculated for categorical variables (e.g., severity of jaundice, treatment outcomes). Independent t-test was used to compare mean bilirubin levels, hemoglobin

levels, and duration of hospital stay between G6PD-deficient and non-G6PD-deficient neonates. A value of $p < 0.05$ was accepted as statistically significant.

This retrospective study included male neonates presenting with jaundice due to G6PD deficiency.

Operational Definitions:

G6PD Deficiency: More than normal time (> one hour) taken in the decolorization of the color reagent (NADPH present in the RBCs hemolysate, as a reducing agent, reduces the color reagent to a colorless compound).

Frequency: The number of male neonates diagnosed with G6PD deficiency out of the total number of neonates admitted with neonatal jaundice over the study period.

Severity: The extent of jaundice measured by total serum bilirubin levels in mg/dL. Mild jaundice was defined as serum bilirubin levels between 5-12 mg/dL, moderate as 13-18 mg/dL, and severe as levels above 18 mg/dL.

Outcome: Refers to the clinical progression and resolution of jaundice, including response to treatments (e.g., phototherapy, exchange transfusion) and any long-term complications such as kernicterus. The therapy (Phototherapy or exchange transfusion) in our setup is decided & commenced by plotting the child SBR in mg/dL on a nomogram recommended by American Academy of Pediatrics Subcommittee on Hyperbilirubinemia 2004 [23].

Neonatal Jaundice: A yellowish discoloration of the skin and sclera in newborns, typically due to elevated serum bilirubin levels.

3. Results:

Out of 250 male neonates, 42 (16.8%) had G6PD deficiency. In these cases, other causes of indirect hyperbilirubinemia are also shown in Table 1. These include, Rh 28 (11.2%) & ABO incompatibilities 40 (16%), Breast milk jaundice 18 (7.2%), Prematurity 12 (4.8%), Infection 5 (2%), birth trauma 3 (1.2%) & hypothyroidism 2 (0.8%).

At presentation, mean SBR (mg/dL) of all G6PD deficient neonates with jaundice was 17.5 ± 1.6. Out of these 31 (73.8%) presented between 2nd to 5th day after birth with mean indirect SBR level of 18.2 ± 1.8 mg/dL, as shown in Table 2. Five (11.9%) neonates presented in the 1st 24 hours while 6 (14.3%) after 5th day of their life with mean indirect serum bilirubin levels (mg/dL) of 16.8 ± 1.2 & 17.0 ± 1.4 respectively.

Table 3 shows severity of jaundice in G6PD deficient neonates. 8 (19.0%) neonates had mild and 20 (47.6%) presented with moderate jaundice. 14 (33.4%) of the patient with G6PD deficiency presented with severe hyperbilirubinemia with serum bilirubin (SBR) level of greater than 18 mg/dl.

Regarding the outcome, 38 (90.5%) G6PD deficient neonates required phototherapy and 4 (9.5%) had to undergo exchange transfusion as the ultimate mode of therapy (Tables 4 & 5). All the G6PD deficient neonates recovered fully except one who developed acute bilirubin encephalopathy (Table 5).

Table 5 shows comparison of G6PD deficiency with non-G6PD deficient neonates. Prevalence of G6PD deficiency in this study was thus 16.8%, with a significant proportion of the G6PD-deficient group showing higher bilirubin levels compared to the non-deficient group (17.5±1.6 mg/dL vs. 13.2±1.4 mg/dL, $p < 0.05$). A significantly higher percentage (90.5 %) of G6PD-deficient newborns required phototherapy compared to the non-deficient group (p-value = 0.01) and exchange transfusion (9.5%) as compared to non-deficient group (1.4%) (p value = 0.05). The duration of hospital stay was longer in G6PD-deficient infants ($p < 0.01$), and the incidence of acute bilirubin encephalopathy and kernicterus was higher, though the latter did not reach statistical significance ($p = 0.15$). Hemoglobin levels were slightly lower in the G6PD-deficient group, with significant differences noted ($p = 0.03$).

Table 1: Etiologies of Hyperbilirubinemia in Neonates (n=250) with Neonatal Jaundice

Etiology/Cause	Number of Cases	Percentage (%)
G6PD Deficiency	42	16.8
ABO Incompatibility	40	16.0
Rh Incompatibility	28	11.2
Breast Milk Jaundice	18	7.2
Prematurity	12	4.8
Infection (e.g., Sepsis)	5	2.0

Cephalohematoma/Birth Trauma	3	1.2
Hypothyroidism	2	0.8
Total	250	100

Table 2: Age & Mean Serum indirect Bilirubin (SBR) Level at presentation in G6PD Deficient Neonates with Neonatal Jaundice (n=42)

Age of Presentation (Hours/Days)	Total Cases (All Neonates)	No. of G6PD Deficient Cases	(%) of G6PD Deficient Cases	Mean SBR Level ± SD (mg/dL)
1st 24 Hours	50	5	11.9%	16.8 ± 1.2
2nd to 5th Day	170	31	73.8%	18.2 ± 1.8
>5 Days	30	6	14.3%	17.0 ± 1.4
Total	250	42	100%	17.5 ± 1.6

Table 3: Severity of Jaundice in G6PD Deficient Neonates with Neonatal Jaundice (n=42)

Severity of Jaundice	Serum Bilirubin Range (mg/dL)	Number of G6PD Deficient Cases	Percentage (%)
Mild	5-12	8	19.0%
Moderate	13-18	20	47.6%
Severe	>18	14	33.4%
Total		42	100%

Table 4: Cause vs. Therapy (Outcome) in Different Etiological Causes of Neonatal Jaundice (n=250)

Etiology/Cause	Total Cases	Phototherapy No. (%)	Exchange Transfusion No. (%)
G6PD Deficiency	42	38 (90.5)	04 (9.5)
ABO Incompatibility	40	32 (80)	08 (20)
Rh Incompatibility	28	22 (78.6)	06 (21.4)
Breast Milk Jaundice	18	18 (100.0)	00
Prematurity	12	11(91.7)	01 (8.3)
Infection (e.g., Sepsis)	05	3(60.0)	02 (40)
Cephalohematoma/Birth Trauma	03	3 (100)	00
Hypothyroidism	02	2 (100)	00
Total	250	129	21 (8.4)

Table 5: Comparison of G6PD Deficient (n=42) vs. Non-G6PD Deficient Neonates (n=208) with Neonatal Jaundice (N=250)

Parameter	G6PD Deficient Cases (n=42)	Non-G6PD Deficient Cases (n=208)	p-value
Frequency (%)	16.8%	83.2%	-
Mean Bilirubin Level (mg/dL) at presentation ± SD	17.5 ± 1.6	13.2 ± 1.4	< 0.001
Phototherapy Requirement	38 (90.5%)	150 (72.1%)	0.01
Exchange Transfusion Requirement	4 (9.5%)	3 (1.4%)	0.05
Mean Duration of Hospital Stay (days)	5.5 ± 1.3	3.2 ± 0.9	< 0.01
Mean Hemoglobin Level (g/dL)	13.2 ± 1.2	14.0 ± 1.1	0.03
Development of Kernicterus	1 (2.4%)	0	0.15

4. Discussion:

G6PD deficiency was observed in 16.8% of male neonates presenting with jaundice, a rate consistent with the global prevalence in high-risk populations. The majority of the cases presented with severe jaundice, necessitating aggressive management, including exchange transfusions in about 10% of cases. The development of kernicterus in one case underscores the importance of early diagnosis and intervention. Routine screening for G6PD deficiency in populations with a high prevalence of the disorder may help prevent severe hyperbilirubinemia and its associated complications.

Previous studies have also highlighted the association between G6PD deficiency and neonatal jaundice. Kaplan et al.[24] reported a similar frequency of G6PD deficiency among jaundiced neonates, emphasizing the role of early phototherapy in preventing complications. Another study by Frank et al.[25] found that G6PD-deficient neonates have a higher risk of severe hyperbilirubinemia, further supporting the need for targeted screening and intervention.

Recent studies show that G6PD deficiency remains a significant cause of neonatal jaundice, particularly in populations where the disorder is more common [26]. In a study by Okuyan et al.[27], G6PD deficiency was highlighted as one of the main contributors to prolonged neonatal jaundice, with oxidative stress being a primary factor in hemolysis. The prevalence of G6PD deficiency among neonates with jaundice was estimated to range between 10-30% in different high-risk populations. Another study conducted in a Malaysian hospital by Lee et al [18] provided similar findings, emphasizing that G6PD deficiency is a common cause of severe neonatal

jaundice, especially among male neonates.

Phototherapy remains the mainstay of treatment for neonatal jaundice in G6PD-deficient infants[28]. In our study it was required in about 90% of cases. However, the efficacy of this intervention can vary depending on the severity of the deficiency and the rate of hemolysis. In severe cases, exchange transfusion may be required, especially when there is a risk of developing kernicterus, as reported by recent studies. Only one patient developed kernicterus in our study. In the study by Lee et al [18], despite the availability of treatments like phototherapy, a small percentage of neonates with severe G6PD deficiency developed complications due to delayed diagnosis or inadequate treatment. This finding emphasizes the need for early screening and aggressive management in neonates at risk.

New diagnostic markers like neutrophil-to-lymphocyte ratio (NLR) and systemic immune inflammation index (SII) have shown promise in early identification of neonates at risk for prolonged jaundice, suggesting that incorporating these markers into routine screening could improve outcomes. The current study also reinforces the need for more standardized guidelines in managing G6PD-deficient neonates, particularly in regions with high prevalence.

Furthermore, recent research suggests that G6PD deficiency might also affect neonatal immune function, which could have broader implications for the management of neonatal jaundice.

In conclusion, G6PD deficiency remains a significant and preventable cause of neonatal jaundice, especially in populations with a high prevalence of the disorder. Recent studies highlight the importance of early screening, particularly in male neonates, as early diagnosis can lead to more effective management and the prevention of severe complications such as kernicterus. Phototherapy is generally effective, but the introduction of novel diagnostic markers, such as NLR and SII, may improve early detection in high-risk neonates.

5. Conclusion:

G6PD deficiency is a significant cause of neonatal jaundice among male neonates in the studied population. Early identification and prompt treatment, including phototherapy and exchange transfusion, can prevent severe outcomes such as kernicterus. Routine screening for G6PD deficiency in newborns with jaundice is recommended to improve clinical outcomes.

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