

Prevalence of glucose 6 phosphate dehydrogenase among Hyperbilirubinemic Neonates in Sohag Governorate, Egypt

Mostafa M Abosdera and Alzahraa E Almasry

Pediatric Department, Sohag Faculty of Medicine, Sohag, Egypt

aabosdera@yahoo.com

Abstract: Neonatal hyperbilirubinemia is a frequent problem as neonatal jaundice affects 60% of full-term infants and 80% of preterm infants in the first 3 days of life. The relationship between G-6-PD deficiency and hyperbilirubinemia in the newborn period is well recognized. Severe neonatal hyperbilirubinemia resulting in Kernicterus is the most serious complication of this enzyme deficiency in the newborn period. Pyruvate kinase (PK) deficiency is the most common enzymopathy of the glycolytic pathway in erythrocyte despite its rare occurrence. The aim of this study was to investigate the prevalence of G-6-PD deficiency and pyruvate kinase (PK) deficiency in neonatal indirect hyperbilirubinemia, and compare the clinical presentation and course of G-6-PD deficient and normal patients. This study was conducted on three hundred neonates with neonatal jaundice, 156 males and 144 females. They were selected from the NICU in Sohag University Hospital. Cases were recruited during the study period from April 2012 to March 2013.

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Key words: Neonatal hyperbilirubinemia (NH), Total serum bilirubin (TsB), Glucose 6 phosphate dehydrogenase (G6PD), Pyruvate kinase (PK), Uridine- Di phosphate- Glucuronic acid transferase-1 (UDPGT-1).

1. Introduction

Neonatal hyperbilirubinemia, (defined as a total serum bilirubin level exceeding 5 mg/dl) is a frequent problem as neonatal jaundice affects 60% of full-term infants and 80% of preterm infants in the first 3 days of life. Although it is a transient problem, the condition accounts for up to 75 % of hospital readmissions in the first week after birth (**Porter and Dennis, 2002**).

The mechanism of neonatal hyperbilirubinemia is variable including: Bilirubin overproduction which occurs in hemolytic diseases with either positive Coombs' test (ABO incompatibility, Rhesus incompatibility, and minor blood group antigens) or negative Coombs' test (red blood cell membrane defects, e.g.: spherocytosis, elliptocytosis, and/or red blood cell enzyme defects, such as glucose-6-phosphate dehydrogenase (G-6-PD) and pyruvate kinase deficiencies (**Porter and Dennis, 2002**).

Sepsis and some drugs are other examples of hemolytic diseases. Bilirubin overproduction may occur in non-hemolytic diseases, like cephalhematoma, bruising, central nervous system hemorrhage, swallowed blood, polycythemia, ileal atresia, and pyloric stenosis. Breast milk associated jaundice also is an important factor contributing to indirect neonatal hyperbilirubinemia (**Siberry and Iannone, 2000**).

Decreased bilirubin conjugation also occurs in physiological jaundice Crigler - Najjar Syndrome,

hypothyroidism, sepsis and premature newborns (**Dennery et al., 2009**).

G-6-PD is a crucial X-linked enzyme producing reduced glutathione in the erythrocyte cytoplasm for protecting hemoglobin against oxidative damage. The presence of unopposed oxidizing agents leading to oxidation of the sulfhydryl bridges between parts of the hemoglobin molecule decrease the solubility of hemoglobin, leading to precipitations called Heinz bodies (**Capellini and Fiorelli 2008**).

Icterus neonatorum in G-6-PD deficiency probably is due principally to inadequate processing of bilirubin by the immature liver of G-6-PD deficient infants, although shortening of red cell life span may play a role. Severe jaundice due to G-6-PD deficiency seems to be limited to infants who have also inherited a mutation of the Uridine - Di phospho - Glucuronic acid transferase -1 (UDPGT-1) gene promoter (**Beulter, 2008**).

G-6-PD deficiency should be considered in neonates who develop hyperbilirubinemia within the first 24 hours of life, a history of jaundice in a sibling, bilirubin levels greater than the 95th percentile, and in Asian males (**Bhutani et al., 2004**). G-6-PD deficiency and neonatal jaundice vary widely in their frequency and severity in different populations. Genetic, cultural and environmental factors such as maternal exposure to oxidant drugs, herbal remedies, or the effect of naphthalene-camphor balls that are sometimes used to preserve

baby's clothes can contribute to these differences. Neonatal jaundice is more typical and more severe in premature infants with G-6-PD deficiency than in babies born within the normal gestation period (**Cappellini and Fiorelli, 2008**).

The relationship between G-6-PD deficiency and hyperbilirubinemia in the newborn period is well recognized. Severe neonatal hyperbilirubinemia resulting in Kernicterus is the most serious complication of this enzyme deficiency in the newborn period. Thus early neonatal screening Programme should be instituted especially in countries where the prevalence of enzyme deficiency is high (**Atay et al., 2005**).

Hyperbilirubinemia in G-6-PD-deficient neonates is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin, rather than increased bilirubin production resulting from hemolysis, thus, no difference in reticulocyte count and hematocrit level between G-6-PD-deficient and normal groups (**Dhillon et al., 2003**). Pyruvate kinase deficiency is a rare cause of neonatal hemolytic jaundice, with a prevalence estimated at 1 case per 20,000 births in the United States (**Christensen et al., 2010**).

Aim of the work

To investigate the prevalence of G-6-PD deficiency and pyruvate kinase deficiency in neonatal indirect hyperbilirubinemia, and compare the clinical presentation and course of G-6-PD deficient and normal patients.

2. Patients and Methods

This study was conducted on three hundred neonates with neonatal jaundice, 156 males and 144 females. The age of neonates ranged from 2 days to 10 days. They were selected from the NICU in Sohag University Hospital. Cases were recruited during the study period from April 2012 to March 2013.

Inclusion criteria

All neonates with indirect hyperbilirubinemia that require hospitalization

Exclusion criteria

Cases with direct hyperbilirubinemia, polycythemia, sepsis, cephalhematoma, ABO and RH incompatibility, physiological jaundice were excluded

All cases were subjected to

1- Careful history taking focusing on risk factors that may lead to neonatal jaundice as:

1. Gestational age.
2. Mode of delivery & instrument use (forceps & ventose).

3. Factors that may lead to neonatal sepsis as premature rupture of membranes, maternal fever and vaginal discharge.
4. Scanty breast milk & delayed passage of meconium.
5. Family history of consanguinity and its degree, jaundice in previous siblings, RH or ABO incompatibility, family history of chronic hemolytic anaemia presenting in the neonatal period (spherocytosis & elliptocytosis) and history of G-6-PD or PK deficiency in family members.
6. Time of onset of jaundice, phototherapy duration, serum bilirubin at admission, maximum serum bilirubin level and the need for exchange transfusion.

2- Thorough clinical examination including:

1. Vital data: tachypnea, tachycardia, fever or hypothermia.
2. Complexion: Jaundice or Pallor.
3. Anthropometric measurements: weight, length, head circumference .
4. Decreased perfusion & lethargy.
5. Hepatosplenomegaly & palpable flank masses.
6. Complete systemic examination: GIT, Chest, Cardiac and Neurological.

3- Investigations

- 1) Serum bilirubin (total and direct)
- 2) Complete blood picture.
- 3) Reticulocytic count.
- 4) Coombs' test (direct).
- 5) Maternal & neonatal blood group & RH.
- 6) Serum C- reactive protein (CRP).
- 7) G-6-PD enzyme assay.
- 8) Pyruvate kinase enzyme assay.

Statistical design

The collected data were tabulated and analyzed using the suitable statistical methods.

3. Results

Our study showed that G-6-PD-deficient neonates as a cause of indirect hyperbilirubinemia, was found in 18 newborns (6 % only). No cases of pyruvate kinase deficiency were found in our study.

Our study revealed that there is no statistically significant difference could be detected between G-6-PD deficiency group regarding age of the newborn and gestational age while significant difference could be detected regarding gender as G-6-PD affect only males (Table 1).

Table (1): Comparison between G-6-PD normal and abnormal group as regard general data

Variable	Hyperbilirubinemic neonates - Total number = 300		P value
	Hyperbilirubinemic neonates without G-6-PD deficiency No=282 (94%)	Hyperbilirubinemic neonates with G-6-PD- deficiency No=18 (6%)	
Age in day Mean \pm SD	4.18 \pm 2.06	5.00 \pm 1.55	0.83
Age in day \leq 3 4-7 \geq 8	102 (36.17%) 141 (50.00%) 39 (13.83%)	3 (16.67%) 15 (83.33%) 0 (0.00%)	0.27
Gestational age Mean \pm SD	37.20 \pm 2.07	38.67 \pm 1.75	0.09
Gestational age \leq 37 >37	108 (38.30%) 174 (61.70%)	3 (16.67%) 15 (83.33%)	0.29
Gender Female Male	144 (51.06%) 138 (48.94%)	0 (0.00%) 18 (100.00%)	0.02

In the studied series there was no statistically significant difference could be detected between G-6-PD normal and abnormal groups regarding different variables of CBC while there

was statistically high significant difference could be detected regarding total bilirubin and direct bilirubin (Table 2).

Table (2): Comparison between normal and abnormal group as regard laboratory data

Variable	Hyperbilirubinemic neonates - Total number = 300		P value
	Hyperbilirubinemic neonates without G-6-PD deficiency (n=282) Mean \pm (SD)	Hyperbilirubinemic neonates with G-6-PD- deficiency (n=18) Mean \pm (SD)	
Total bilirubin	16.36 \pm (2.93)	24.17 \pm (5.24)	<0.0001
Direct bilirubin	1.12 \pm (0.49)	2.02 \pm (1.36)	0.0003
WBCs	9.87 \pm (2.61)	9.56 \pm (2.20)	0.78
Neutrophil	1.65 \pm (1.25)	1.89 \pm (0.78)	0.63
Lymphocytes	6.82 \pm (2.07)	5.75 \pm (1.80)	0.22
RBCs	3.93 \pm (0.74)	3.49 \pm (0.34)	0.14
HB	11.63 \pm (2.19)	10.24 \pm (1.19)	0.13
HCT	36.53 \pm (7.07)	31.55 \pm (4.09)	0.09
MCV	93.16 \pm (7.64)	90.48 \pm (6.66)	0.41
MCH	29.71 \pm (2.79)	29.43 \pm (2.51)	0.81
MCHC	31.88 \pm (1.09)	32.5 \pm (1.06)	0.18
PLT	350.98 \pm (118.83)	384.83 \pm (165.31)	0.51
Reticulocytes	2.72 \pm (2.66)	4.02 \pm (2.99)	0.26

In our series there was statistically significant difference could be detected between G-6-PD normal and abnormal groups regarding family history of G6PD (Table 3).

Table (3): Comparison between normal and abnormal group as regard family history of G6PD.

Variable	Hyperbilirubinemic neonates - Total number = 300		P value
	Hyperbilirubinemic neonates without G-6-PD deficiency No=282 (94%)	Hyperbilirubinemic neonates with G-6-PD- deficiency No=18 (6%)	
Family history of G6PD No Yes	258 (91.49) 24 (8.51)	6 (33.33) 12 (66.67)	0.049

4. Discussion

In the present study, the prevalence of G-6-PD deficiency among hyperbilirubinemic neonates was 6 % only as shown in table 1. This result came in agreement with **Ohkura et al. (1984)** who reported an incidence of 8.6 % of G-6-PD deficient hyperbilirubinemic neonates in Mazandaran and Gilan provinces of Iran. **Rahimia et al. (2006)** have found an approximate frequency of 5.3% in the Kurdish hyperbilirubinemic neonates of western Iran.

The prevalence of G-6-PD deficiency varies greatly in different countries and among different ethnic groups within a country. It was detected with high incidence in many studies as **Omran et al. (1999)** study in Al Houfuf area in Saudi Arabia which showed an incidence of about 30%. In addition, **El-Hazmi, (1990)** in Saudi Arabia has reported that it was in the range of 2-26%. This high incidence of G-6-PD deficiency is due to the high rate of consanguinity among Saudi population. Its prevalence in United Arab Emirates was 11% by **Bayoumi et al. (1996)**, in Kuwait 19% also by **Bayoumi et al. (1996)**. In India incidence of G-6-PD deficiency was 32% of the cases presenting with neonatal hyperbilirubinemia as reported by **Pao et al. (2005)**. Also G-6-PD deficiency was found in 38.2% of the hyperbilirubinemic neonates in Nigeria as reported by **Uko et al., (2003)**. The prevalence of G6PD deficiency among Egyptian neonates with hyperbilirubinemia is 14.4% (**Abdel Fattah M, et al., 2010**).

In our study, no cases of pyruvate kinase deficiency were detected. Pyruvate kinase (PK) deficiency is the most common enzymopathy of the glycolytic pathway in erythrocyte despite its rare occurrence. It constitutes one of the common causes of hereditary non-spherocytic hemolytic anemia; its prevalence in Indian neonatal jaundice is 3.21% (**Kedar et al., 2006**). **Abdel Fattah et al., 2010** found that the prevalence of PK deficiency among Egyptian neonates with hyperbilirubinemia is 2.8%.

Our results -as shown in table 1- show that all G-6-PD deficient newborns were males thus there is no G-6-PD deficient female neonates, this result came in agreement with those obtained by **Yu et al. (1992)**, **Huang et al. (1996)**, they reported that G-6-PD deficient females were not at increased risk in the development of neonatal hyperbilirubinemia. Similarly another study by **Weng et al. (2005)** carried out on newborns with indirect hyperbilirubinemia in Taiwan reported that the prevalence of G-6-PD deficiency was 3.54% in males and 1.57% in females. Thus the prevalence of G-6-PD deficiency in males was significantly higher than females in this study. The percentage of boys

was higher than girls in other studies as well, such as the study by **Koosha & Rafizadeh (2007)** which reported that 3.6% of males and 0.6% of females were G-6-PD-deficient. Similarly the ratio between male: female G-6-PD deficient neonate was 3: 1 in many studies as study by **Yousefi et al. (2006)** in Iran, study by **Iranqour et al. (2003)** In India also the study by **Atay et al. (2005)** in Spain and France.

However, such results were not matched with the reports obtained by some studies as that done by **Omran et al. (1999)** in Saudi Arabia which performed on neonates with indirect hyperbilirubinemia associated with G-6-PD deficiency showed higher incidence of G-6-PD deficiency in females. This may be due to the high rate of consanguinity among the Saudi population, leading to increased numbers of female homozygotes.

In the present study- as shown in table 2, no significant relationship was noted between the severity of jaundice and the hematological indices as RBCs, reticulocyte count or hemoglobin concentration. Such findings were also reported by **Kaplan et al. (1998)** and **Yu et al. (1992)** who suggested that jaundice is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin, rather than increased bilirubin production resulting from hemolysis. This is in agreement with **Abolghasemi et al. (2004)** who reported that jaundice might not necessarily be related to hemolysis, but probably to transferase activity in liver cells. This is supported by the fact that in jaundiced G-6-PD-deficient neonates there are lower levels of bilirubin diglucuronide, normal packed cell volumes (PCV), normal reticulocyte counts and insignificant rise of carboxyhemoglobin (**Murki et al., 2005**). Also **Jennifer & Frank, (2005)** study which was based on hematological indices could not demonstrate evidence of acute hemolysis in G-6-PD- deficient jaundiced cases. Also in **Jallohs (2005)** Study which was based on measuring ETCO (End-Tidal carbon monoxide) concluded that marked hemolysis and increased bilirubin production in G-6-PD-deficient Mediterranean type is not sufficient to explain hyperbilirubinemia and they reported that hemolysis is not a main determinate of neonatal jaundice in G-6-PD deficient babies. In contrary, a Nigerian study done by **Kaplan et al. (1996)** documented that the difference in the mean total Hb value of the G-6-PD-deficient group compared with controls was extremely significant.

The present study –as shown in table 2- showed that levels of total serum bilirubin was significantly higher among G-6-PD deficient group compared to non-deficient group. In agreement with the present

results, several studies as **Iranqour et al. (2003)**, **Abolghasemi et al. (2004)** and **Kaplan et al. (2004)** reported that the maximal total serum bilirubin levels was significantly higher among G-6-PD deficient jaundiced neonates when compared with G-6-PD normal icteric neonates.

On the contrary, other studies showed that there were no differences in the total peak serum bilirubin concentration between normal G-6-PD and G-6-PD-deficient newborns as results obtained by **Omran et al. (1999)**, **Atay et al. (2005)** and **Koosha and Rafizadeh (2007)** where they reported insignificant results between normal G-6-PD and G-6-PD-deficient regarding highest bilirubin concentration.

As regarding history of G-6-PD deficiency in the family in this study -as shown in table 3, there was statistically significant difference could be detected between G-6-PD-deficient neonates and history of G-6-PD deficiency in the family where it was positive in 66.67% of cases that had G-6-PD deficiency. This came on agreement with studies made by **Ahmed et al. (1995)**, **Omran et al. (1999)** and **Abolghasemi et al. (2004)**, while it disagrees with other studies made by **Yousefi et al. (2006)** and **Tan (1981)** where they reported that there was no significant relation between G-6-PD-deficient neonates and history of G-6-PD deficiency in the family.

In the current study, we demonstrated that G-6-PD deficiency by itself is a risk factor for the development of neonatal hyperbilirubinemia even without exposure to chemicals that might cause hemolysis. Our findings implied that the possible cause of neonatal hyperbilirubinemia was not directly related to hemolysis, but was secondary to reduced hepatic conjugation and excretion of bilirubin. Our results came in concordance with other studies by **Kaplan et al. (1998)**, **Edwards et al. (2002)**, **Weng et al. (2005)** and **Abolghasemi et al. (2004)**.

Conclusion

Neonatal hyperbilirubinemia is one of the most common problems and requires hospital admission for investigation and treatment. Despite a low prevalence of G-6-PD deficiency in our study (6%), we recommend that we suspect G-6-PD deficiency in full-term male neonate when we find prolonged indirect hyperbilirubinemia with high total serum bilirubin (Tsb) level and longer duration of phototherapy than usual and not associated with laboratory evidence of hemolyses specially if there is history of G-6-PD deficiency in the family, also we recommend that G-6-PD deficiency and PK deficiency tests be performed in all Egyptian and Mediterranean icteric newborns. In addition, we

recommend that measurement of the enzyme UGT be made available for the clinical use in the evaluation of neonatal hyperbilirubinemia.

Recommendation

Neonatal jaundice associated with G-6-PD deficiency can be prevented in many cases by educating the public and health workers and mothers. Pregnant women and mothers should be advised to avoid potentially hemolytic agents, as the responsible agent may be also acquired by transplacental passage or by breast-feeding or both. Some authors believe that epidemiological studies Of G-6-PD deficiency should be concentrated; on neonatal screening and obtaining results within the first few days of life, before the onset of neonatal hyperbilirubinemia.

Prevention of attacks of acute hemolysis constitutes an important therapeutic measure. In exaggerated physiological jaundice we must exclude G-6-PD deficiency.

We recommend that G-6-PD activity measurement be compulsory for every icteric newborn. This should be done in spite of laboratory findings for hemolysis as a routine test and it should be done as a screening test at birth time. Early diagnosis can reduce the number of complications in icteric neonate and prevents future acute hemolytic attacks.

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