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A comparative study between glucose 6-phosphate dehydrogenase deficient and normal term neonates with indirect hyperbilirubinemia in a rural tertiary care hospital of Eastern India

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an important cause of neonatal indirect hyperbilirubinemia or even kernicterus leading to long-term neurological sequelae specially in countries like India where G6PD deficiency is quite prevalent. **Aims and Objectives:** We have planned this study to know the prevalence of G6PD deficiency among cases of neonatal jaundice and also to evaluate the difference between G6PD deficient and normal neonates with indirect hyperbilirubinemia in terms of laboratory parameters and need of phototherapy or exchange transfusion. **Materials and Methods:** This observational and cross-sectional study was done for a period of 1 year in the SNCU and NICU of a district Medical College of West Bengal among 200 term neonates presented with indirect hyperbilirubinemia. Birth weight, sex, hemoglobin, G6PD level, serum bilirubin at admission, phototherapy duration, and need for exchange transfusion were recorded along with other necessary parameters. **Results:** We found G6PD deficiency in 24 neonates (12%) out of 200 cases of neonatal jaundice, 20 of whom were male. There is a statistically significant difference in hemoglobin and serum bilirubin level between two groups. Difference in early presentation of jaundice within 24–48 h (66.7% vs. 34.1%) and need of prolonged phototherapy 72–96 h (45.83% vs. 7.4%) between G6PD deficient and normal group were statistically significant. Difference in requirement of exchange transfusion is not statistically significant. **Conclusion:** Early screening for G6PD deficiency should be considered in every neonates of G6PD deficient endemic countries so that we can predict the natural course of the jaundice in those G6PD deficient neonate and prevent complication by early initiation of phototherapy or exchange transfusion.

Key words: Glucose-6-phosphate dehydrogenase; Hyperbilirubinemia; Jaundice; Neonates

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INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited red cell enzymopathy affecting an estimated 400 million people globally.[1] It is an X-linked enzymopathy affecting hemizygous males, homozygous females, and also a subset of heterozygous females through chromosome X inactivation. Its global prevalence rate is about 4.9% with highest incidence in the tropical and sub-tropical countries including India.[2] In India, its prevalence ranges from 2.35 to 27% and varies between population with highest reported cases among tribal (10–15% among tribal population of West Bengal).[3,4] The Indian variant is also the most severe with the highest relative risk of hemolysis.[5] Neonatal indirect hyperbilirubinemia (NIH) and the resultant bilirubin encephalopathy leading

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to kernicterus are a severe manifestation of G6PD deficiency causing neonatal morbidity and mortality As hyperbilirubinemia due to G6PD deficiency may be evident even from the 1st day of life, so early screening of this enzyme deficiency is necessary to prevent serious neurologic complications. Timely intervention with phototherapy or exchange transfusion is the key to prevent neonatal morbidity and mortality. With this background, we have initiated this study in a medical college of Eastern India to know the prevalence of G6PD deficiency and treatment related factors among term neonates with indirect hyperbilirubinemia.

Aims and objectives

The aim of the study is to know about the prevalence of G6PD deficiency in term NIH and to compare laboratory parameters and management protocol among G6PD deficient and G6PD normal term neonates with NIH in a rural tertiary care hospital.

MATERIALS AND METHODS

This hospital-based observational and cross-sectional study was conducted in the SNCU and NICU of Department of Paediatrics, Burdwan Medical College and Hospital for a period of 1 year in term neonates getting admitted with indirect hyperbilirubinemia. Total cases of neonatal jaundice admitted in SNCU of our hospital are around 1600 in a year (as per www.sncuindiaonline.org). Among these, 49% are inborn out of which term neonates account for 60%of cases. Out of total inborn term neonates, 70% cases account for NIH. Taking 95% confidence interval and 4% sampling error, and as per the inclusion and exclusion criteria, total sample size is 200 (calculated with the formula n=4pq/d2). Cases were selected from inborn term neonates admitted in our hospital for neonatal jaundice by simple random sampling with the following inclusion criterion: (1) Term neonates assessed by new Ballard's scoring system and (2) neonates delivered in Burdwan Medical College and Hospital and admitted in SNCU and NICU with indirect hyperbilirubinemia, that is, serum bilirubin more than 12 mg% with transcutaneous bilirubinometer and conjugated bilirubin <20% of total bilirubin at 24–72 h of age. Exclusion criterion were: (1) Out born babies, (2) prematurity, (3) direct hyperbilirubinemia, (4) babies with other comorbidities like birth asphyxia, sepsis, (5) babies with major congenital anomalies, and (6) babies whose parents refused to give consent to participate in the study.

Data collection and laboratory procedures were started after receiving Ethical Clearance Certificate from the Institutional Ethics Committee of our college and written informed consent from parents of each neonate. Detailed antenatal, natal, and postnatal history were obtained from mother. Neonatal jaundice was examined by clinical methods and initial bilirubin estimation was done by transcutaneous bilirubinometer. Total serum bilirubin (TSB) estimation (both unconjugated and conjugated) was done for patients with values >12 mg/dl by transcutaneous bilirubinometer. G6PD estimation was done in term neonates with indirect hyperbilirubinemia by ultraviolet kinetic method. Other relevant investigations such as ABO and Rh grouping and typing of mother and baby, Coomb's test – indirect and direct, hemoglobin (Hb) percentage (Sahli's method), peripheral blood smear, reticulocyte count, and thyroid profile were done.

Statistical analysis

The collected data are entered in Microsoft Excel worksheet (Microsoft, Redwoods, WA, USA) and appropriate statistical tests are used for analysis such as Chi-square and Student's t-test. All the statistical analyses are done in SPSS software, version 21.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA) and the data are assessed for statistical significance at P<0.05.

RESULTS

Out of 200 neonates with hyperbilirubinemia, 24 (12%) were found to be G6PD deficient with rest 176 (88%) that had normal G6PD values. Among other important causes of indirect hyperbilirubinemia, 30% (60 out of 200) neonates have ABO incompatibility, 11% (22 out of 200) have Rh incompatibility, and 6% (12/200) have hypothyroidism without any concomitant G6PD deficiency. We found that G6PD deficiency was more prevalent in male sex with 20 out of 120 male babies and four out of 80 female babies being G6PD deficient. Male female ratio among 24 G6PD deficient neonate was 5:1.

From Table 1, it is seen that 20 out of 24 G6PD deficient neonates were male and the difference between two groups is statistically significant (P=0.012). The mean Hb level is lower in G6PD deficient group and is statistically significant (P=0.001). The mean TSB level is higher in G6PD deficient group than normal group and the difference between two groups is statistically significant (P=0.0366). Furthermore, the mean indirect serum bilirubin levels are higher in G6PD deficient group and are statistically significant (P=0.045). The mean G6PD value is lower (5.27) in deficient group in comparison to normal group (10.62) and the difference is statistically significant (P<0.00001).

From Table 2, it is seen that the majority (66.7%) of the G6PD deficient neonates with hyperbilirubinemia presented within 24–48 h of birth and the difference

between two groups is statistically significant (P=0.002). On the other hand, the majority (65.9%) of the G6PD normal neonates presented late after 48–72 h.

From Table 3, it is seen that all the 24 babies with G6PD deficiency required phototherapy for a duration of more than 24 h. Four babies (16.7%) required phototherapy for a period of 24–48 h. Eight (33.33%) needed phototherapy for 48–72 h. Eleven babies (45.83%) needed phototherapy for a period of 72–96 h and 1 baby (4.165%) required phototherapy for more than 96 h. On the contrary, among 176 G6PD normal babies, 30 (17.04%) required phototherapy for <24 h. Seventy three (41.5%) required phototherapy for 24–48 h, 60 (34.1%) required phototherapy for 48–72 h. Thirteen (7.4%) required 72–96 h of phototherapy. There is a statistically significant difference in number of neonates required phototherapy for 72–96 h (P<0.0001) between two groups.

From Table 4, we can see that out of total 200 neonates with hyperbilirubinemia, 169 baby needed only phototherapy and 31 needed phototherapy and exchange transfusion both. Among the G6PD deficient neonates with hyperbilirubinemia, 25% (6 out of 24) required exchange transfusion, whereas only 14.2% (25 out of 176) neonates with hyperbilirubinemia required exchange transfusion in the G6PD normal group (majority with Rh incompatibility). However, the difference was statistically insignificant (P=0.170).

DISCUSSION

G6PD deficiency is an X-linked hereditary enzyme deficiency with the full expression occurring mainly in hemizygous males and homozygous females where X-chromosomes carry a mutant gene. It is the most common disorder related to hexose monophosphate pathway. G6PD catalyzes the conversion of glucose-6-phosphate to glucose-6-phosphogluconate. This reaction produces NADPH which maintains glutathione in the reduced functional form thereby preventing damage of RBC membrane or precipitation of Hb during oxidative stress. The World Health Organization classifies G6PD genetic variants into five classes, the first three of which are deficiency states.[6]

Table 1: Comparison of G6PD deficient and G6PD normal neonates with indirect hyperbilirubinemia

Variables	G6PD status (N=200)		P value
	Normal (N=176)	Deficient (N=24)	
Male sex	100 (56.8%)	20 (83.3%)	0.012
Hemoglobin (g/dL)	14.3±0.9	13.7±1.1	0.001
Total serum bilirubin (mg/dl)	19.9±2.6	20.3±2.3	0.036
Indirect bilirubin (mg/dL)	17.3±2.5	18.2±2.0	0.045
G6PD level (unit/g Hb)	10.62±1.86	5.27±0.16	<0.00001

Table 2: Comparison of normal and G6PD deficient group in terms of timings of presentation of jaundice

	Total neonate with hyperbilirubinemia (N=200)	Presented early within 24–48 h		Presented late after 48–72 h	
		No.	Percentage	No.	Percentage
G6PD deficient	24	16	66.7%	8	33.3%
G6PD normal	176	60	34.1%	116	65.9%

Table 3: Comparison of normal and G6PD deficient neonates in terms of duration of phototherapy

	Total neonate with hyperbilirubinemia (N=200)	No of neonates with duration of phototherapy for				
		<24 h	24–48 h	48–72 h	72–96 h	>96 h
G6PD deficient	24	0	4	8	11	1
G6PD normal	176	30	73	60	13	0

Table 4: Comparison of normal and G6PD deficient group in terms of requirement of phototherapy and exchange transfusion

	Total neonate with hyperbilirubinemia (N=200)	Required Only phototherapy (N=169)	Required phototherapy and exchange transfusion (N=31)	Percentage of exchange transfusion
G6PD deficient	24	18	6	25%
G6PD normal	176	151	25	14.2%

- Class I: Severe deficiency (<10% activity) with chronic (non-spherocytic) hemolytic anemia
- Class II: Severe deficiency (<10% activity), with intermittent hemolysis
- Class III: Moderate deficiency (10–60% activity), hemolysis with stressors only
- Class IV: Non-deficient variant, no clinical sequelae
- Class V: Increased enzyme activity, no clinical sequelae

In a G6PD deficient neonates, oxidative stress such as perinatal insults, infection, or some drugs can lead to intravascular hemolysis. Neonatal jaundice is a severe manifestation of G6PD deficiency and is a major cause of morbidity and mortality from kernicterus especially in association with prematurity, sepsis, and environmental factors such as naphthalene balls used in the storage of neonates bedding and clothing.[7,8] Indirect hyperbilirubinemia is seen in one-third of the male neonates with G6PD deficiency. The jaundice probably starts in utero in the perinatal period but the clinical problem generally becomes apparent only about the 2nd or 3rd day of life.[4] It is seldom associated with mortality if closely monitored and phototherapy or exchange transfusion may be required to prevent long-term neurological sequelae.

In our study, we have found that the number of patients having G6PD deficiency was 24, that is, the prevalence of G6PD deficiency was 12%. Atay et al., conducted a study in 2006 including 624 term neonates with indirect hyperbilirubinemia where they found 24 neonates with G6PD deficiency.[9] Sinha et al., in their study with 400 neonates with indirect hyperbilirubinemia found 2.5% neonates with G6PD deficient.[10] Jan et al., (2013) conducted a study where out of the total 1695 patients admitted for neonatal jaundice, 152 (9%) babies were found to be G6PD deficient.[11] As India is among the countries where prevalence of G6PD deficiency is high, so 12% prevalence in our study is not surprising.

Iranpour et al., found that frequency of G6PD deficiency in male population was 5.1 % (67 out of 1307 male neonates) and in female population was 1% (12 out of 1194 female neonates).[12] The male: female ratio was 5:1 which is similar to our study findings, where male sex predominates among the G6PD deficient neonates.

Due to the increased amount of hemolysis, Hb is expected to be on the lower side in G6PD deficient neonates.[13] In our study, also we found that the mean Hb (gm/dl) in G6PD deficient group was lower (13.68±1.12) than that in normal group (14.32±0.97) and the difference in mean Hb levels was statistically significant (P=0.001). The study by the Korean Paediatric Society also found that G6PD deficient neonates had lower Hb levels (P<0.0001) than normal neonate.[14] Badejoko et al., (2014) found that G6PD-deficient and intermediate infants had higher declines in hematocrit than G6PD-normal infants (P<0.001).[15] However, Moiz et al., (2012) found no statistically significant difference in mean Hb level between the two groups.[16]

We found higher TSB and mean indirect bilirubin values in G6PD deficient group in comparison to G6PD normal group with statistically significant difference. There are other studies with similar findings. Iranpour et al., (2003) found that the mean bilirubin level in G6PD deficient and G6PD normal groups was 22.26±8.36 and 18.14±3.85 mg/dl, respectively (P=0.001).[12] Badejoko et al., (2014) study reported that the mean peak TSB levels were 14.1 (9.48), 10.2 (3.8), and 6.9 (3.3) mg/dL for G6PD-deficient, G6PD-intermediate, and G6PD-normal neonates, respectively.[15]

The mean G6PD activity in the deficient group was 5.270±0.115 whereas 10.617±1.86 in normal group which was a statistically significant with P<0.00001. Iranpour et al., (2008) also found that the mean enzyme activity in deficient patients was quite low similar to our result (male deficient group; 3.17±1.74 U/gHb and female deficient group; 3.49±2.17 U/gHb).[17]

In our study, we found that about two-third of the G6PD deficient neonates with indirect hyperbilirubinemia were presented early within 24–48 h, whereas G6PD normal neonates presented late with jaundice. This is in accordance with other studies which states that though the presentation of jaundice common in 2nd or 3rd day but it may present as early as in first 24 h.[18] This is probably due to the ongoing hemolysis in the fetus due to perinatal stress factors in G6PD deficient babies.

In terms of treatment, 18 (75%) of the total 24 G6PD deficient cases required only phototherapy and 6 (25%) of them required exchange transfusion along with phototherapy. On the other hand, out of 176 G6PD normal babies, only 25 babies (14.2%) required exchange transfusion. Although it was seen that G6PD deficiency was an important isolated cause requiring exchange transfusion for indirect hyperbilirubinemia, the difference is not statistically significant between normal and G6PD deficiency group. Isa et al., found that more G6PD-deficient patients needed exchange transfusion (P<0.0001).[14] Atay et al., found that the need for exchange transfusion was higher in G6PD-deficient group.[9] Iranpour et al., (2003) in his study found that 27 out of 53 (50.9%) G6PD deficient infants required exchange transfusion.[12] Hence, one important difference between other studies is rate of exchange transfusion between two groups that is statistically insignificant and that may be due to early detection and initiation of extensive phototherapy to the

G6PD deficient jaundiced neonates in this study. Even the neonate who does not required exchange transfusion needed phototherapy for prolonged duration in the G6PD deficient group in our study. About 45.83% neonates needed phototherapy for a period of 72–96 h in G6PD deficient group in comparison to only 7.4% G6PD normal neonatal jaundice who required phototherapy for 72–96 h with statistically significant difference. Hence, from this study, we can say that in areas where G6PD deficiency is prevalent, it is one of the most common risk factor for indirect hyperbilirubinemia, and early initiation of extensive phototherapy may reduce the need for exchange transfusion. Routine neonatal screening for G6PD deficiency should be initiated in such areas in neonates with indirect hyperbilirubinemia for early initiation of treatment and prevention of the neurological complications as shown by other studies.[19,20]

Limitations of the study

As this study was done in a single tertiary care center, so generalization of the result is not possible without doing more extensive multi-center study. Moreover this study was done in such an area where tribal population with predisposition to G6PD deficiency is more and so further studies need to be conducted in other ethnic groups as well before recommending routine G6PD deficiency screening among every neonates.

CONCLUSION

Prevalence of G6PD deficiency among neonatal jaundice is quite high in our study. They are more prevalent in male neonates and presented with clinical jaundice early within 24–48 h of birth, have higher level of serum bilirubin, and require phototherapy for a longer duration with statistically significant difference. Rate of exchange transfusion is high but not statistically significant among G6PD deficient and G6PD normal neonatal jaundice cases in our study, thus signifying the importance of early initiation of extensive phototherapy to reduce the need for exchange transfusion. In countries where G6PD deficiency is prevalent, there should be a protocol for early screening of G6PD deficiency among neonates. Early detection should alert the treating pediatrician about the need of phototherapy or exchange transfusion early in neonates with indirect hyperbilirubinemia thus decreasing the possibility of long-term neurological sequel resulting from bilirubin encephalopathy in G6PD deficient neonates.

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KLB- Critical revision of the manuscript; **PKS-** Concept and design of the study and review of literature; **SP and SM-** Data acquisition and statistical analysis; and **SL-** Manuscript writing and manuscript editing.

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