International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Study of Glucose-6-Phosphate Dehydrogenase Deficiency in Neonates with Jaundice

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Abstract: ***Aim: The aim of this study is early detection of G6PD deficiency in neonates with hyperbilirubinemia and association of G6PD activity with appearance and severity of jaundice in G6PD deficient neonates. Material and methods: We conducted a Prospective Analytical study on all term and preterm neonates with hyperbilrubinemia admitted to tertiary care hospital in west India for one year 2017-2018. G6PD status, hemogram, bilirubin, blood groups, need for phototherapy was compared between G6PD-deficient and G6PD-normal neonates. Result: In our study, 121 neonates with jaundice were screened for G6PD deficiency. Out of which 7 neonates showed G6PD deficiency, the incidence was 5.7%. Most common age group in G6PD deficient was 3-5 days (71.43%), mean age being 4.03 days. The male female ratio was 4.5: 1 Among the G6PD deficient neonates total serum bilirubin was higher (p=0.013), hemoglobin was lower (p=0.001), requirement of phototherapy was much higher (p=0.003) as compared to G6PD normal neonates. No statistically significant differences were observed between the two groups as per gestational age, birth weight, direct serum bilirubin and reticulocyte count. Conclusion: We recommend screening of all neonates presenting with jaundice for deficiency of G6PD enzyme as it is cost effective and easily available test. Early diagnosis may prevent adverse consequences of hyperbilirubinemia as the G6PD deficiency may lead to severe hemolysis and anemia, if undiagnosed. Therefore, routine G6PD deficiency screening should be employed to all neonates with jaundice, especially in areas where its prevalence is high***

Keywords: Glucose-6-Phosphate Dehydrogenase deficiency, Jaundice, Neonatal Hyperbiliribinemia, Phototherapy

1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a hereditary predisposition to hemolysis, is an X-linked disorder of antioxidant homeostasis that is caused by mutations in the G6PD gene 1 and estimated four hundred million people worldwide are affected[1].

Neonatal hyperbilirubinemia (defined as a total serum bilirubin level exceeding 5 mg/dl) is a frequent problem as neonatal jaundice affects 65% of full-term infants and 85% of preterm infants after 24 h of life.3G6PD is an enzyme in the pentose phosphate pathway, a metabolic pathway that supplies reducing energy to cells, in particular erythrocytes, by maintaining the level of NADPH, which in turn maintains the level of glutathione that helps protect erythrocytes against oxidative damage. In states of oxidative stress, glutathione is rapidly consumed and the buildup of oxidants can cause the red cell to lyse.[1, 4] Hence, G6PD deficiency most commonly manifests as either prolonged neonatal jaundice or acute hemolytic anemia. Extreme neonatal hyperbilirubinemia, with its severe sequelae of bilirubin neurotoxicity and the potential of death, is the most devastating manifestation of G6PD deficiency.[5, 6, 7]

Neonatal hyperbilirubinemia occurs in 2.5-6 % neonates in India. Its incidence in other parts of the world is reported to vary from 3.2-33 %. Neonatal hyperbilirubinemia has been attributed to isoimmune incompatibility, low birth weight, prematurity, abnormal parturition, G6PD deficiency, infection, liver diseases, drugs and maternal causes.[31, 32, 33]

Neonatal screening for G6PD deficiency has long been established in many countries with high disease prevalence such as in the Middle East, Eastern Europe and Southeast Asia.[1, 37, 38] Early diagnosis thereby may prevent adverse consequences of hyperbilirubinemia as the deficiency of G6PD may lead to severe hemolysis and anemia, if undiagnosed.[39, 40] The World Health Organization recommends screening all newborns in populations with a prevalence of 3-5% or more in males.[41]

In India, G6PD deficiency was first reported in 1963 by Baxi et al. and the prevalence rate varied from 0 to 27% in various geographic regions.[10] Examination of glutathione metabolism pathway within the red blood cells led to the Hexose monophosphate shunt and revealed that the abnormality was related to deficiency of red cell enzyme G6PD. With the confirmation of basic defect was a deficiency of G6PD, X-linkage was confirmed by estimation of enzyme activity.[45]

2. Material Methods

We conducted a Prospective Analytical study on all term and preterm neonates with hyperbilirubinemia admitted to the pediatric department of a tertiary care hospital in west India for one year 2017-2018. The inclusion criteria were:

a) Total serum bilirubin levels >12mg/dL in terms and

>6mg/dL in preterm infants.[24, 68]
b) Clinically visible jaundice.[69]
c) Written consent for study participation
d) No ongoing infections or acute episode of hemolysis or blood transfusion

The total number of cases included in study was 121. Written consent from the guardian of the neonate was obtained after explaining the nature and purpose of study. Relevant history like Information regarding age of neonate at the time of admission, gestational age, birth weight, family history of hemolytic event and any other relevant findings were collected and a unique identity number was allotted to each cases. Whole blood was collected using EDTA as an anticoagulant. These samples were processedwithin30 minute from the time of vene section. . The qualitative data were expressed in proportion and percentages and the quantitative data expressed as mean and standard deviations. The difference in proportion was analyzed by using chi square test and the difference in means was analyzed by using student T Test. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff values of significant variables. Significance level for tests was determined as 95% ((P< 0.05).

3. Results

In our study, 121 neonates with jaundice that were enrolled were then screened for G6PD deficiency. Out of which 7 neonates showed G6PD deficiency on qualitative examination. Complete hemogram including reticulocyte count & examination of peripheral blood smear, Serum bilirubin (total & direct), ABO grouping & Rh typing, CRP (C reactive protein). 121 neonates were included in study after fulfilling the criteria. 7 were G6PD deficient, the incidence was 5.7%. Most common age group in G6PD deficient was 3-5 days (71.43%), mean age being 4.03 days. (Table-1)

Table 1: Distribution of study population according to Age

Age (days)	Normal (N=114)		Deficient (N=7)		Total (121)	
	Number	%	Number	%	number	%
1 - 2	9	7.89	2	28.57	11	9.09
3 - 5	55	48.25	5	71.43	60	49.59
6 - 10	39	34.21	0	0.00	39	32.23
11 - 28	11	9.65	0	0.00	11	9.09
	114	100.00	7	100.00	121	100.00

Chi-square = 6.886 with 3 degrees of freedom; P = 0.099 [Not Significant]

The male female ratio of the neonates with jaundice with G6PD deficiency was 4.5: 1. (Table-2)

Table 2: Distribution of the cases according to gender

	Normal		Deficient		Total	
	Number	Percentage %	Number	Percentage %	Number	Percentage %
Female	21	18.42	1	14.29	22	18.18
Male	93	81.58	6	85.71	99	81.82
Total	114	100.00	7	100.00	121	100.00
M: F	4.43: 1		6: 1		4.5: 1	

Chi-square = 0.053 with 1 degree of freedom; P = 0.819 [Not significant]

Most of the G6PD deficient neonates with jaundice were of term pregnancy and no statistically significant difference was observed with G6PD normal neonates as per gestational age. (Table-3)

Table 3: Distribution of the cases According to Gestational Age

Gestational Age (wks)	Normal (n=114)		Deficient (n=7)		Total (n=121)	
	Number	%	Number	%	Number	%
Preterm (<37)	37	32.46	2	28.57	39	32.23
Term (37-42)	77	67.54	5	71.43	82	67.77
Total	114	100.00	7	100.00	121	100.00
Mean ± SD	37.23±1.87		36.86±1.46		37.21±1.85	

Chi-square = 0.041 with 1 degree of freedom; P = 0.839 [Not Significant]

- Out of 7 G6PD Deficient cases 71.43% were term neonates and 28.57% were of preterm neonates. Mean gestational age was 36.86±1.46 weeks
- Out of 114 G6PD normal cases 67.54% were term neonates and 32.46% were preterm neonates. Mean gestational age was 37.23±1.87 weeks
- No significant difference was observed according to Gestational age.

The birth weight of most of the G6PD deficient neonates with jaundice was between 2.5-3.5 kilograms and no statistically significant difference was observed between them and G6PD normal neonates according to birth weight of the neonate. (Table-4)

Table 4: Distribution of the cases According to Birth weight

Birth weight (kg)	Normal (N=114)		Deficient (N=7)		Total (121)	
	No	%	No	%	No	%
<2.5	11	9.64	1	14.29	12	9.91
2.5 - 3.5	101	88.59	6	85.71	107	88.42
> 3.5	02	1.75	0	0	02	1.65
Total	114	100.00	7	100.00	121	100.00

Chi-square = 0.272 with 2 degrees of freedom; P = 0.873 [Not Significant]

The mean total serum bilirubin in G6PD deficient neonates with jaundice was 19.76±4.14 mg/dl while in G6PD normal neonates with was 14.50±5.41 mg/dl. The difference was statistically significant (p=0.013). (Table-5)

Table 5: Distribution of the cases according to Total Hyperbilirubenemia in study population

Bilirubin level (mg/dl)	Normal (n=114)		Deficient (n=7)		Total (n=121)		P value LS
	Number	%	Number	%	number	%	
<12.0	42	36.84	0	0.00	42	34.71	
12-20.0	53	46.49	5	71.43	58	47.93	
20.1-25.0	14	12.28	1	14.29	15	12.40	
25.1-30.0	5	4.39	1	14.29	6	4.96	
	114	100.00	7	100.00	121	100.00	
mean±sd	14.50 ± 5.41		19.76 ± 4.14		14.80 ± 5.47		.013

Chi-square = 2.523; P = 0.013 [Significant]

The mean direct serum bilirubin in G6PD deficient neonates with jaundice was 0.44±0.26 mg/dl while in G6PD normal neonates with was 0.48±0.72 mg/dl. The difference was not statistically significant. (Table-6)

Table 6: Distribution of the cases according to Direct Hyperbilirubenemia in study population

Direct Bilirubin (mg/dl)	Normal		Deficient		Grand Total		P Value LS
	Number	%	Number	%	Number	%	
<0.4	86	75.44	5	71.43	91	75.21	0.83NS
>0.4	28	24.56	2	28.57	30	24.79	
Mean ±SD	0.48±0.72		0.44±0.26				.880NS

Chi-square = 0.045 with 1 degree of freedom; P = 0.832 [Not Significant]

The mean hemoglobin in G6PD deficient neonates with jaundice was 10.81± 3.25 gm/dl while in G6PD normal neonates with was 15.89 ± 3.57 gm/dl. The difference was statistically significant (p=0.001). (Table-7)

Table 7: Distribution of the cases according Haemoglobin

Haemoglobin (gm/dl)	Normal		Deficient		Grand Total		P value
	Number	%	Number	%	Number	%	
<13.4	24	21.05	5	71.43	29	23.97	
13.4 - 19.9	79	69.30	2	28.57	81	66.94	
>19.9	11	9.65	0	0.00	11	9.09	
Mean ± SD	15.89 ± 3.57		10.81± 3.25		15.60± 3.74		<0.001S

Chi-square = 3.670; P = <0.001 [Significant]

The mean reticulocyte count in G6PD deficient neonates with jaundice was 2.26±1.01 while in G6PD normal neonates with was 3.16±1.95. The difference was not statistically significant. (Table-8)

Table 8: Distribution of the cases According to Reticulocyte count

Reticulocyte count (%)	Normal		Deficient		Total		P Value LS
	Number	%	Number	%	Number	%	
<4.0	94	82.46	7	100.00	101	83.47	0.49NS
>4.0	20	17.54	0	0.00	20	16.53	
Total	114	100.00	7	100.00	121	100.00	
Mean ± SD	3.16±1.95		2.26±1.01		3.11±1.92		.228

Chi-square = 0.474 with 1 degree of freedom; P = 0.491

The requirement of phototherapy in G6PD deficient neonates was much higher (57.14%) than G6PD normal neonates (10.53%) There is significant difference according the phototherapy received (p=0.003). (Table-9)

Table 9: Distribution of the cases according to Phototherapy received

Phototherapy	Normal		Deficient		Grand Total	
	Number	%	Number	%	Number	%
Not Received	102	89.47	3	42.86	105	86.78
Received	12	10.53	4	57.14	16	13.22
Total	114	100.00	7	100.00	121	100.00

Chi-square = 8.758 with 1 degree of freedom; P = 0.003S

4. Discussion

In our study mean age of distribution for age of onset of jaundice in G6PD deficient neonates is 4.03 ± 3.5 days which is in concordance with most of the studies cited above. (Table-10)

Table 10: Distribution of study group according to G6PD deficiency

Study	Sample Size	Incidence	M: F	Mean age	Hemoglobin (Mg/dl)	Bilirubin (mg/dl)	Reticulocyte count %
Moiz B et al.6[4] (2009)	216	14.8%		1.6±1.3	16.5±2.5	16.7±6.0	5±2.5
Marzban A et al.6[3] (2009)	224	5.7%			16.72±1.9	19.9±1.9	2.4±1.0
Boskabadi H et al.6 (2010)	1568	5.2%		4.9±2.0		>24	
Mondal M et al.2 (2012)	176	13.6%	5: 1	2.9		12-20	
Dholokia A et al.5[9] (2012)	150	10.6%				11.8-13.7	
Munir SS et al.6[5] (2014)	163	6.7%		4.7±2.8	14.7±2	22.23±7.0	2.94
Goyal M et al.2[2] (2015)	270	4.5%	5-4: 1				
Pardhe BD et al.6[6] (2015)	100	3.0%				9.9±6.0	
Islam AKS et al.1[0] (2015)	1224	5.07%	2.5: 1	3.0±1		20.03±5.20	
Patel H et al.1[9] (2015)	170	10.6%	2: 1	2.0			
Sinha R et al.3 (2017)	400	2.5%		4±1.5	10.24	2.5 ± 5	4.15±2.0
Paneliya CB et al[34] (2016)	2400		2: 1			>15	
Thilakarajan S et al [31] (2016)	310					13.15	
Our study	121	5.79%	6: 1	4.03±3.5	10.81±3.25	19.76±4.14	2.26±1.01

In our study, the male female ratio derived is 6: 1 which is in concordance with studies cited like Mondal M et al.[2] and Goyal M et al.[22] (Table-10) Few studies show lesser male female ratio difference like Islam AKS et al.[10], Patel H et al.[19], Pardhe BD et al.[66] and Paneliya CB et al.[34]. This variation in studies may be due to difference in sample size considered for these studies.

In our study, G6PD Deficient cases 5 (71.43%) were term neonates and 2 (28.57%) were of preterm neonates. G6PD normal cases 77 (67.54%) were term neonates and 37 (32.46%) were preterm neonates. Hence, No significant difference was observed according to gestational age between G6PD normal and G6PD deficient neonates which is in concordance with the study conducted by Modal et al. (Table-10)

In our study the mean value of total bilirubin is 19.76 ± 4.14 mg/dl in G6PD deficient neonates with jaundice whereas in G6PD normal cases mean total bilirubin level was 14.50±5.41mg/dl. Significant difference was observed according to total Hyperbilirubenemia. (p=0.013). Our finding is similar to almost all studies cited above. (Table-10)

In our study the mean direct bilirubin level in G6PD deficient is 0.44±0.26mg/dl and G6PD normal neonates it is 0.48±0.72mg/dl. No significant difference was observed according to direct bilirubin level. (p=0.832). However Sinha R et al.[3] and Munir SS et al.[65] show a higher direct bilirubin level in G6PD levels which may be due to a larger sample size or ethnicity of the study population. (Table-10)

In our study the mean hemoglobin level in G6PD deficient neonates is 10.81 ± 3.25 which is similar with studies conducted by Sinha R et al.[3] and Munir SS et al.[65] However, Marzban A et al.[63] and Moiz B et al.[64] show a higher mean heamoglobin level which may be due to higher sample size and different geographic area of study. (Table-10)

The mean value of reticulocyte count is 2.26 ± 1.01 in G6PD deficient neonates and 3.16 ± 1.95 which is in concordance with Munir SS et al.[65] and Marzban A et al.[63], however Sinha R et al.[3] and Moiz B et al.[64] show a higher reticulocyte counts in G6PD deficient neonates. In our study there is no significant difference (p=0.228) in reticulocyte count between G6PD normal and G6PD deficient. (Table 10)

The requirement of phototherapy in G6PD deficient neonates was much higher (57.14%) than G6PD normal neonates (10.53%) There is significant difference according the phototherapy received (p=0.003). (Table 10)

The studies cited above shows incidence range G6PD deficient neonates from 3% to 14.8%. (Table 10) Our study shows incidence of 5.79% which falls within the range of incidence determined by various studies. The wide range of incidence rate of G6PD deficient neonates may be due to different geographic area and ethnicity of the study population.

Deficiency of this enzyme was reported from India more than 50 years back. The prevalence varies from 2.3 to 27% with an overall prevalence of 7.7% in different tribal group.[67]

Bisoiet al.[14] (2012) in their study concluded that G6PD deficiency detection by neonatal screening is feasible and cost-effective. It also allows the early preventive measures against severe hemolysis, jaundice, kernicterus, to be implemented in neonatal life, as well as other preventive measures in later life. Some practical guidance to the family members of the G6PD deficient babies regarding the food items, herbs, chemicals and drugs to be avoided will be beneficial, provided that the diagnosis is done in timely manner.

Munir SS et al.[65] (2014) state that G6PD assay should be included in all jaundiced neonates for early detection and timely prevention of complications like kernicterus.

Goyal M et al.[22] (2015) in their study found that G6PD deficiency screening test is sufficiently common, is a robust diagnostic test, if undetected can lead to adverse consequences of hemolysis and renal shut down, and can be managed with ease. The cost-effectiveness can easily be extrapolated for this disease that does not require active management in a resource-constraint setting. Regional centers, rather than multiple laboratories, across the country may serve the purpose. They emphasize the need for a newborn screening program for G6PD deficiency as an important public health perspective.

Pao M et al.[61] (2015) by their study recommended that neonatal screening for G6PD deficiency should be routinely done so that complications like acute hemolysis and hyperbilirubinemia can be managed early and kernicterus eliminated.

Paneliya CB et al.[34] (2016) by their work suggested a newborn screening program to detect G6PD deficiency to help in establishing the actual incidence of this deficiency in various parts of our country. As there was a higher frequency of neonatal jaundice amongst babies who were G6PD deficient, they recommended that clinicians ensure a strict clinical & biochemical follow to monitor jaundice in these neonates.

Chhetri N et al.[67] (2017) concluded that G6PD deficiency leading to neonatal hyperbilirubinemia is not an uncommon disorder in India as seen from several publications. Delay in recognition can lead to rapid progression of severe hyperbilirubinemia and consequently bilirubin induced neurological damage.

Sinha R et al.[3] (2017) conclude that G6PD deficiency is a common enzyme defect in Indian neonatal population (especially male) causing severe indirect hyperbilirubinemia requiring treatment; however, a larger study is required to validate the same. Early neonatal screening programs should be instituted to anticipate and institute early treatment to prevent morbidity and mortality.

Now the million dollar question that remains to answer - Shall G6PD deficiency become a mandatory investigation in all neonates with jaundice? There is a strong association between G6PD deficiency and the level of hyperbilirubinemia in neonates with jaundice. The association of G6PD was associated with higher levels of bilirubin in comparison to normal neonates with jaundice. The incidence in our study was 5.79%. Considering the cost effectiveness, availability and utility of the G6PD deficiency screening test and also early detection of G6PD deficiency in neonates with jaundice and thereby preventing the consequences of this disease by preventing the triggering factors and educating the parents, we recommend that G6PD deficiency screening test should be carried out in all neonates with jaundice. Early diagnosis may prevent adverse consequences of hyperbilirubinemia as the deficiency of G6PD may lead to severe hemolysis and anemia, if undiagnosed. Therefore routine G6PD deficiency should be employed to all neonates with jaundice, especially in areas of where its prevalence is high. The neonates that were G6PD deficient on screening test could not be confirmed by quantitative assay of the G6PD levels due to financial constrain and limited resources.

5. Limitations

Molecular studies to confirm the G6PD mutation were not performed in the G6PD deficient neonates due to unavailability at the study area. The sample size enrolled for this study was limited due to constrain of time. The exact prevalence of the G6PD deficiency in neonates in India still requires more studies with large population based cohorts. More data is needed to determine whether G6PD screening could provide additional benefit in terms of reductions in adverse outcomes over current newborn hyperbilirubinemia surveillance, discharge and follow-up practices.

6. Conclusion

We recommend screening of all neonates presenting with jaundice, for deficiency of G6PD enzyme as it is a cost effective and easily available test.

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