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Glucose-6-Phosphate Dehydrogenase Deficiency among neonates with hyperbilirubinemia in a tertiary care hospital in the north eastern region of India

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Abstract:
Background:
Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is the commonest enzyme deficiency in human. It can lead to haemolysis due to impairment in the production of reduced glutathione. In the neonates G6PD deficiency can lead to hyperbilirubinemia which can ultimately progress to the more serious condition of kernicterus if not diagnosed and treated in time.
Material and Methods:
A prospective cohort study was carried out for a period of two years. 150 newborn babies with jaundice admitted in the paediatric ward were randomly selected and included in this study. All newborns with jaundice including both term and preterm babies who were within 28 day of age were included in the study. Serum bilirubin was determined by colorimetric method. Glucose-6-phosphate dehydrogenase activity was determined by kinetic method.
Results:
The incidence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in this study was found to be 12%. Male (66%) neonates more commonly showed G6PD enzyme defect compared to female neonates (33.3%). Also among 36% preterm babies, 5.55% were G6PD deficient and among term babies, 15.6% were G6PD deficient. Among 41.3% low birth weight (LBW) babies, 11.29% were G6PD deficient and out of 51.33% normal birth weight (NBW) babies, 14.28% were G6PD deficient. G6PD deficient neonates had significantly higher total serum bilirubin level (16.94 ± 5.6508 mg/dL) than the non-G6PD deficient neonates (14.04 ± 4.28 mg/dL).
Conclusion:
It may be concluded from the present study that due to considerable incidence of G6PD deficiency found in this study (12%), it is recommended to introduce qualitative test of this enzyme deficiency as a routine laboratory investigation for all icteric neonates towards early diagnosis and prevention of adverse consequences of neonatal hyperbilirubinemia.
Key words: *Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, neonatal hyperbilirubinemia, kernicterus*

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I. Introduction:

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is the commonest enzyme deficiency in human affecting about 400 million people worldwide[(1)]. G6PD deficiency can lead to haemolysis due to impairment in the production of reduced glutathione. In the neonates G6PD deficiency can lead to hyperbilirubinemia which can ultimately progress to the more serious condition of kernicterus if not diagnosed and treated in time. High prevalence of G6PD deficiency with an overall prevalence of 7.7% is reported among the tribal population of India which are also malaria endemic area.G6PD deficiency is said to be an outcome of a balanced polymorphism, in which high rate of mortality caused by this disorder is counteracted by the protection it offers against *Plasmodium falciparum* malaria[(2)] . Alleles of the *G6PD* gene that encode the deficient enzyme is well expressed in areas where malaria is or has been endemic . It is believed that nature has selected this disorder due to malarial endemicity in many regions of the country. The study was designed to estimate prevalence of G6PD deficiency among neonates with hyperbilirubinemia in a tertiary care hospital in the north eastern region of India which is predominantly a tribal populated area with high malarial endemicity.

II. Materials And Methods :

A prospective cohort study was carried out in the Department of Biochemistry, Regional Institute of Medical Sciences (RIMS), Imphal, Manipur in collaboration with the Department of Pediatrics, RIMS, Imphal, Manipur for a period of two years (November 2012 – October 2014). Due approval was obtained from Institutional Ethical Committee, RIMS. 150 newborn babies with jaundice admitted in the Paediatric ward were randomly selected and included in this study after obtaining written informed consent from their parents. All newborns with jaundice including both term and preterm babies who were within 28 day of age were included in the study. Newborns who were above 28 days of age and having any major malformations were excluded in the study.

A detailed history of both mother and baby and meticulous physical examination of the baby was carried out. Gestational age was calculated from the 1st day of the last menstrual period of the mother. Those babies born between 37-41 weeks of gestation were classified as term babies. Those born before 37 weeks were classified as preterm babies. Babies weighing less than 2500g were defined as low birth weight babies and those weighing <1500g as very low birth weight (VLBW).[3]

Clinical assessment of neonatal jaundice was carried out at the time of collection of first blood sample, before the child was subjected to any phototherapy or exchange transfusion and at the time of discharge.During clinical examination, blood samples were also collected.Serum bilirubin was determined by colorimetric method as described by Jendrassik and Grof [4] using RX Imola automatic analyser (Randox Laboratories, USA). Both serum total and direct bilirubin were estimated. Glucose-6-phosphate dehydrogenase activity was determined by kinetic method as described by Rodak BF[5] using Eppendorf ECOM-F 6124 semi-automatic analyzer (Eppendorf Laboratories, Germany).Activity of G6PD is reported in Hb concentration. So Hb concentration was first estimated before performing G6PD assay. Hb concentration was determined by Sahli's method as described by Sood R[6] .

III. Results:

Table-I: Distribution of G6PD deficiency among male and female hyper bilirubinemic neonates.

G6PD Status	Male	Female	Total
Normal G6PD activity	72	60	132
Deficient G6PD activity	12	6	18

Table I shows that out of 18 G6PD deficient neonates, 66.6% (12) were male and 33.3% (6) were female.

Table-II: Relation of G6PD deficiency with different Socio-demographic and clinical characteristics of newborn

Characteristics		G6PD Deficiency			Chi- Square	P Value
		Present	Absent	Total		
Gender	Male	12	71	83	2.238	0.135
	Female	6	61	67		
Religion	Christian	1	15	16	0.583	0.747
	Hindu	16	109	125		
	Muslim	1	8	9		
Gestational Age	Preterm	3	51	54	3.318	0.069
	Term	15	81	96		
Birth Weight	VLBW	0	11	11	1.911	0.385
	LBW	7	55	62		
	Adequate birth weight	11	66	77		
Mode of delivery	Normal	15	111	126	0.717	0.699
	LSCS	3	17	20		
	VD	0	4	4		
Breast milk fed	Yes	13	100	113	0.107	0.744
	No	5	32	37		

Table II show that 83.33% Hindu babies, 10.7% Christian Muslim and babies were G6PD deficient. This was statistically not significant ($P > 0.05$). Maturity of the newborn was determined by its gestational age. Most (78.9%) of the babies were term babies. Among the preterm babies, 5.55% were found to be G6PD deficient, whereas it was 15.6% among the term babies. This difference of gestational age and G6PD deficiency is not statistically significant.

Table-III: Comparison between G6PD deficient & non-G6PD deficient group with regard to serum bilirubin levels

Variables	Hyperbilirubinemic neonates with G6PD deficiency(mg/dL) Mean ± SD	Hyperbilirubinemic neonates without G6PD deficiency(mg/dL) Mean ± SD	P value
Total serum bilirubin	16.94 ± 5.65	14.04 ± 4.28	0.01
Direct bilirubin	0.744 ± 1.10	0.408 ± 0.28	0.04*

*<0.05- significant

It is evident from the above Table III that G6PD deficient neonates have higher mean ± SD TSB level (16.94 ± 5.6508 mg/dL) and direct bilirubin level (0.744 ± 1.10 mg/dL) than the non-G6PD deficient neonates (TSB 14.04 ± 4.28 mg/dL and direct bilirubin 0.408 ± 0.28 mg/dL). This difference is statistically significant ($p<0.05$).

Table-IV: Distribution of G6PD deficient and normal cases requiring Phototherapy and Exchange transfusion

Treatment	G6PD Deficient (n=18)	G6PD Normal (n=132)	P value
Exchange transfusion	9	10	<0.001*
Phototherapy	7	56	0.77
Both exchange transfusion and phototherapy	2	0	0.01

*<0.001- Very highly significant

Table IV shows that 7 (38.9%) G6PD deficient neonates received phototherapy which was comparable to the 56 (42.4%) G6PD normal neonates who received phototherapy. 9 (50%) of G6PD deficient neonates and 10 (7.57%) of neonates with normal G6PD activity undergo blood exchange, showing a very highly significant difference ($p<0.001$). 2 (11.1%) G6PD deficient neonates received both PT and ET while none of the G6PD normal neonates received both treatment simultaneously ($p<0.05$).

IV. Discussion:

In the present study, the incidence of G6PD deficient neonates was found to be 12% (18 cases) out of 150 hyperbilirubinemic neonates (Tab. I). This finding was consistent with the findings of Bisoi S et al[7] who reported 16(14.68%) G6PD deficient neonates out of 109 newborns. A study conducted on the Mizo population in North-east India showed that 17.5% were G6PD deficient out of 490 study subjects.[8] These findings are much higher than the study conducted on 5140 neonates in Karnataka where they reported G6PD deficiency to be 7.8% in their study population[9]. This discrepancy maybe due to difference in the genetic make- up and or/ environmental factors. In a study conducted by Singh M A et al[10] on 303 healthy subjects of Manipur, they reported the overall incidence of G6PD deficiency to be 5.94%.

It is also evident from Table I that male (66%) neonates more commonly showed G6PD enzyme defect compared to female neonates (33.3%). This can be explained by location of gene on X chromosome, which occurs in males only in hemizygous form ,where as the female heterozygote can be protected by the other functional X chromosome of the pair. Similar observation was made by Dholakia A et al[10] and Chime HE at al.[11]However, such results did not match with the reports obtained by some studies as that done by Omranet al[9]in Saudi Arabia which studied neonates with indirect hyperbilirubinemia associated with G-6-PD deficiency.

They 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.

Table II shows that majority of neonates with G6PD deficiency were Hindus (83.33%). The reason for this might be because the study was conducted in a Hindu predominant area. The ratio between male and female was found to be 2:1. Bisoi S et al[7] in his study reported male and female ratio to be 1:1. Joshi SR et al[12] conducted a study in VataliyaPrajapati Community in Western India and found the ratio to be 3:1.

It was also observed that among 36% preterm babies, 5.55% were G6PD deficient and among term babies, 15.6% were G6PD deficient. Among 41.3% low birth weight (LBW) babies, 11.29% were G6PD deficient and out of 51.33% normal birth weight (NBW) babies, 14.28% were G6PD deficient. All these findings were found to be statistically insignificant. These results were consistent with the findings of Bisoi S et al[7] who reported that among the preterm babies in their study, 26.08% were G6PD deficient and 11.6% were G6PD deficient among term babies. Also 24.13% LBW and 11.25% NBW babies were G6PD deficient. But in a study by Mesner O et al[13] in Israel it was found that G6PD activity was higher in preterm than in term and near-term neonates, but this increase was limited to the 29– 32 weeks gestational age range.

G6PD deficient neonates (Table III) had significantly higher ($p<0.05$) mean ± SD TSB level (16.94 ± 5.6508 mg/dL) than the non-G6PD deficient neonates (TSB 14.04 ± 4.28 mg/dL). There was statistically significant difference of direct bilirubin level between G6PD deficient (0.744 ± 1.10 mg/dL) and G6PD normal (0.408 ± 0.28 mg/dL) neonates. These observations were consistent with several studies thatreported higher maximum total serum bilirubin levels in G6PD deficient jaundiced neonates compared to G6PD normal icteric neonates.[14,15]Hyperbilirubinemia in G6PD-deficient neonates is thought to be secondary to reduced hepatic conjugation and excretion of bilirubin, rather than increased bilirubin production resulting from hemolysis.[16]

Regarding treatment between G6PD deficient and G6PD normal neonates (Table IV), it was observed that number of neonates who received phototherapy were comparable between G6PD deficient (38.9%) and G6PD normal (42.4%) neonates. Significantly higher ($p<0.001$) number of G6PD deficient subjects received exchange transfusion (50%) compared to G6PD normal subjects (7.57%). 2(11.1%) neonates received both PT and ET and they were found to be G6PD deficient.These findings are consistent with the findings of El-Deen ZM et al.[14]El-Menshay et al[17] found that the frequency of using phototherapy was higher among G6PD deficient neonates and exchange transfusions was also more frequent in G6PD deficient jaundiced neonates compared to the non-deficient group, but the differences were not statistically significant.

V. Conclusion

The incidence of glucose-6-phosphate dehydrogenase deficiency in this study was found to be 12%.Male (66%) neonates more commonly showed G6PD enzyme defect compared to female neonates (33.3%). Also among 36% preterm babies, 5.55% were G6PD deficient and among term babies, 15.6% were G6PD deficient. Among 41.3% low birth weight (LBW) babies, 11.29% were G6PD deficient and out of 51.33% normal birth weight (NBW) babies, 14.28% were G6PD deficient. G6PD deficient neonates had significantly higher mean ± SD TSB level (16.94 ± 5.6508 mg/dL) than the non-G6PD deficient neonates (TSB 14.04 ± 4.28 mg/dL). Rate of exchange transfusion is much higherin G6PD deficient neonates (50%) compared to G6PD normal neonates (7.57%). Two neonates received both PT and ET and they were found to be G6PD deficient.

It may be concluded from the present study that due to considerable incidence of G6PD deficiency found in this study (12%), it is recommended to introduce qualitative test of this enzyme deficiency as a routine laboratory investigation for all icteric neonates towards early diagnosis and prevention of adverse consequences of neonatal hyperbilirubinemia.

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