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Study of Glucose -6-Phosphate Dehydrogenase Deficiency In Neonatal Jaundice.

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Abstract: *The enzyme, Glucose-6-phosphate dehydrogenase (G6PD), deficiency leads to impaired production of reduced glutathione and predisposes the red cells to damage by oxidative metabolites, causing hemolysis. Deficient neonates may manifest clinically as hyperbilirubinemia or even kernicterus. Screening for G6PD deficiency and recognition of prevalence of the enzyme deficiency in individual communities have got definite place in the investigation of cases with neonatal jaundice. To determine the frequency and effect of G6PD deficiency the study was conducted in the Special Care Neonatal Unit of Bankura Sammilani Medical College during the period from November 2010 to December 2011. All term and preterm babies up to seventh day of age admitted with clinically evident jaundice were taken for study. Of the total 176 neonates, 24 neonates(13.63%) had G6PD deficiency, Most are males, Jaundice developed after 24 hrs of life,.The mean age of jaundice was 70.54 hrs. of age. Peak serum bilirubin was < 20 mg/dl in 33.33%, 20.1 to 25 mg/dl in 29.16%, and > 30 mg/dl in 16.66% of cases. with All babies G6PD deficiency was administered phototherapy in the study to avoid high rise in the peak bilirubin level. Out of them13(54.17%n=24) responded to phototherapy alone & 11 (45.83%) neonates in this group required double volume exchange transfusion.*

Key words*: Hemolysis, Glucose 6 phosphate Dehydrogenase, Jaundice, Phototherapy, Exchange transfusion.*

I. Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is essential to maintain stability of red blood cells [(1)]. It catalyzes the first step in the hexose monophosphate pathway of glucose metabolism and produces reduced nicotinamide adenine dinucleotide phosphate (NADPH) which is required for the maintenance of reduced glutathione (GSH). GSH is essential for protecting red cells from the oxidative damage. In G6PD deficiency the cells other than RBC do not have significant effect.

The inherited deficiency of this enzyme may manifest as congenital non spherocytic hemolytic anemia (CNSHA), drug induced hemolytic anemia (DIHA) or hemolytic disease of newborn. Deficiency of G6PD is the most common metabolic disorder of RBCs and has been estimated to affect over 400 million people worldwide [(2)]. Although global in its distribution, G6PD deficiency is encountered with greatest frequency in the tropical and subtropical zones of the eastern hemisphere. In some populations, more than 20 percent of the population may be affected by this enzyme deficiency [(3)].

In India, G6PD deficiency was first reported in 1961 by Baxi *et al* [(4)] and the prevalence rate varied from 0 - 27% in different caste, ethnic and linguistic groups [(5)].

Neonatal jaundice is the most common clinical manifestation of G6PD deficiency [(6)]. It has been reported that one third of children with G6PD deficiency develop neonatal jaundice. Severe neonatal jaundice if untreated could give rise to kernicterus, a well known cause of death [(7)] and neurodevelopmental handicap. Jaundice can occur in neonates with G6PD deficiency due to spontaneous hemolysis or hemolysis following exposure to certain oxidant drugs and infection or due to reduced glucuronidation of bilirubin in the hepatocytes. It occurs primarily in Asian and Mediterranean infants [(7)]. In India, several groups of investigators have reported neonatal jaundice due to G6PD deficiency [(8)]

The objectives of our study were:

1. To determine the frequency of G6PD deficiency in neonates admitted with clinically evident jaundice.
2. To study the effect of G6PD deficiency on the outcome of treatment of neonatal jaundice.

II. Materials and method

The study was conducted in the Special Care Neonatal Unit of Bankura Sammilani Medical College during the period from November 2010 to December 2011. All term and preterm babies upto seventh day of age admitted with clinically evident jaundice were taken for study.

2.1 Parameters studied

2.1.1 Qualitative assay of G6PD (screening test), & in screen positive (decolorisation time more than 60 minutes.) cases quantitative estimation of the enzyme has been done. The investigation has been repeated

after 3 months on outpatient basis when blood picture suggestive of acute hemolysis at the time of first investigation.

2.1.2 Complete hemogram including reticulocyte count & examination of peripheral blood smear, Serum bilirubin (total, direct, indirect), ABO grouping & Rh typing of the mother & baby, Coombs test according to situation, Random blood sugar, CRP(C reactive protein), blood culture as & when required. Serial estimation of serum bilirubin, Hemoglobin, Packed Cell Volume have been done as per guideline during treatment.Glucose-6-Phosphate Dehydrogenase:- Qualitative test for screening G6PD deficiency in erythrocytes.

2.2 Principle

Glucose-6-Phosphate-Dehydrogenase (G6PD) present in hemolysate acts on substrates, Glucose-6-Phosphate(G6PO4) & NADP, giving NADPH which in presence of (polymethyl sulphate) PMS decolorizes blue colored indophenols dye (DCPIP) leaving behind color only due to hemolysate. The rate of reaction being proportional to enzyme activity (G6PD) present, time required for decolorisation is inversely proportional to enzyme activity in the hemolysate.

2.3 Sample Collection

Whole blood has been collected using EDTA as an anticoagulant.

2.4 Preparation of working Reagent

0.5 ml of G6PD-2(Buffer) is added to the vial labeled G6PD-1(Co-enzyme substrate). Shaked well to allow complete dissolution & used immediately.

2.5 Reagent storage & stability

All reagents have been stored at 2-8^0 C . G6PD-1 has been reconstituted just before use.

2.6 Procedure

Hemoglobin content of whole blood is estimated first. If the hemoglobin content is significantly less than 15 gm/dl, Hb content has been adjusted to 15 gm/dl by proportionately increasing the aliquot of whole blood during preparation of red cell.

Preparation of Red Cell Hemolysate:

Given below is a table showing quantity of blood required for 1 ml lysing reagent corresponding to the Hemoglobin content of blood(in gram/dl).

Table:1

Hemoglobin concentration (in gram/dl)	Amount of blood to be taken (in ml)
7.0-9.5	0.04
9.6-11.5	0.03
11.6-13.5	0.025
13.6-15.0	0.02
G6PD-3(precooled lysing reagent)	1.0

Mixed well & kept it in the refrigerator (2-4^{o}C) for 10-15 minutes & used as follows:

a. The red cell hemolysate is completely transferred to the freshly prepared working reagent & shaked well.
b. 1 ml of G6PD-4 (Inert oil) is overlayed immediately.
c. The vial is sealed tightly , using the plug & cap to make it air tight & incubated at 37^{0}C.
d. The change of initial blue to brownish colour is observed at interface of hemolysate & inert oil.

2.7 Observation

First observation at 30 minute for decolorisation. If the decolorisation is incomplete, observation is done for every 5 minute, thereafter until the decolorisation is complete. In case, decolorisation takes longer than 60 min, the interval of observation is increased & followed up for 4-8 hours or more.

In G6PD deficiency the time taken for decolorisation exceed from 2 hours to 24 hours.

2.8 Interpretation

1. In normal subjects, decolorisation time is between 30-60 min.
2. In G6PD deficient subjects, (heterozygous males & homozygous females) decolorisation time is between 2 to 24 hours.

2.9 Method employed for G6PD estimation

For the G6PD assay, 1 ml of anticoagulated blood in a glass bottle was sent and analyzed in the laboratory within two hours. Determination of the activity of G6PD was done by spectrophotometry. When low G6PD levels were encountered, the test was repeated on a fresh sample to confirm the deficiency of the enzyme. This test has been repeated 3 months later also when blood picture was suggestive of acute hemolysis.

III. Results and analysis

3.1 During this period, 176 newborns who had jaundice during first week of life were subjected to different investigations of blood as already mentioned . The neonates have been categorized depending on relevant information & investigation reports in different ways as follows:

Out of a total of 176 newborns with hyperbilirubinemia, 118 (67.04% n=176) were males and 58 (32.96% n=176) were females; 150(85.23%%; n=176) were Non-tribal & 26(14.77%) were Tribal(Refer to table-2).

Table: 2 Categorization of cases according to race, sex & G6PD level

Race	Sex	Number of newborns tested	Number of G6PD deficient cases	Percentage of G6PD deficiency
	Male	100	15	15.00
Non-tribal	Female	50	3	6.00
	Combined	150	18	12.00
	Male	18	5	27.78
Tribal	Female	8	1	12.50
	Combined	26	6	23.07
	Male	118	20	16.94
Total	Female	58	4	6.89
	Combined	176	24	13.63

3.2 Overall Frequency

Twenty four newborns (13.63%; n=176) were found to have deficiency of G6PD enzyme. Out of those deficient, 20 (16.94% n=118) were males and 4 (6.89% n=58) were females. So, frequency was higher among male babies(Refer to table-2)

Racial distribution of G6PD Deficiency:

Among 150 Non-tribal newborn babies, 18(12.00%; n=150) were G6PD deficient. Out of 26 Tribal newborn babies , 6 (23.07%%; n=26) were G6PD deficient.

We infer that there was strong evidence of significant difference between frequency of G6PD deficiency in Tribal and non-tribal group of newborns with more frequency of G6PD deficiency in tribal newborns with neonatal hyperbilirubinemia. Prevalence ratios among Non-tribal and Tribal neonates were 12.00% (18 deficient out of 150) and 23.07% (6 deficient out of 26) respectively. This difference is statistically significant ($\chi 2 = 2.31$; df=1 $p < 0.05$). (Ref. to table:-2)

3.3 Distribution of G6PD deficient babies according to Birth weight.

138 newborns (78.40%; n=176) had birth weight of 2500 gm or more and 38 (21.60% n=176) were less than 2500 gm. Among those with birth weight >/=2500 gm., 19 babies (13.76%; n=138) had G6PD deficiency.

Out of 38 neonates with birth weight <2500 gm. 5 babies (13.16%; n=38) were found to have this enzyme deficiency.

Frequency of the enzyme deficiency among babies this two group was similar as because the difference between the two ratios was not statistically significant ($\chi 2 = 0.01$; df= 1, $p > 0.05$).

3.4 Distribution of cases according to gestational age:

One hundred & forty newborns (79.54%; n=176) in this study were term (GA >37wk) and 36 (20.46%) were preterm(GA <37wk). Nineteen(13.57%n=140) term & 5 preterm babies were G6PDdeficient. This difference in frequency of G6PD deficiency among term and preterm babies was not statistically significant ($\chi 2 = 0$; df=1. $p > 0.05$)

3.5 Pattern of Jaundice & treatment outcome among G6PD deficient & G6PD normal babies

3.5.1 Age at Onset of Jaundice

Out of 24 neonates with G6PD deficiency, none presented with jaundice during first 24 hours of life. Seven male babies presented on the 2nd day. Of the rest 13 male babies, 7 babies presented on 3rd day, 4 babies on 4th and one each on 5th & 6th day. Out of a total 4 female babies, 2 had onset of jaundice on 2nd day, one each on 4th day and 6th day. The mean age at onset of jaundice was 70.54 (± 23.88) hours in G6PD deficient babies.

Irrespective of sex, 9 neonates (37.50%; n=24) with G6PD deficiency had their onset of jaundice on 2nd day of life and 7 (29.16%; n=24) had onset on 3rd day & 5 (20.83% n=24) on 4th day (Refer to table-3)

Table:-3

Age at onset of jaundice (in hours)	G6PD Normal(n=152)		G6PD Deficient(n=24)	
	Male	Female	Male	Female
12-24	1	1	0	0
25-36	10	6	2	0
37-48	25	9	5	2
49-72	38	16	7	0
73-96	16	9	4	1
97-120	10	3	1	1
>120	4	4	1	0

. On the other hand, in G6PD normal (n=152) group 2 babies had appearance of jaundice on first day. Out of 104 male babies 35 had jaundice on 2nd day, 38 on 3rd day, 16 on 4th day, 10 on 5th day & 4 on 6th day. Among 48 female babies, 15 had appearance of jaundice on 2nd day, 16 on 3rd day, 9 on 4th day, 3 on 5th day & 4 presented on 6th day.

Irrespective of sex, among G6PD normal group 50(32.89% n=152) had appearance of jaundice on 2nd day, 54(35.52%) presented on 3rd day, 25(16.44% n=152) on 4th day, 13(8.55% n=152) presented on 5th day & 8(5.26% n=152) presented on 6th day (Refer to table:-3). The mean age of onset of jaundice was 67.84((±22.95) hrs.

Therefore, it can be said that most of the G6PD deficient babies had presentation of jaundice in between 2nd to 4th day.

3.5.2 Peak Serum Bilirubin

Of the 24 G6PD deficient babies, 8(33.33%, n=24) had a peak serum bilirubin level of less than 20 mg/dl. Five (20.83%; n=24) of the total deficient cases had a peak bilirubin level in the range of 20.1 to 25 mg/dl, 7(29.16%) babies had peak levels in the range of 25.1 to 30 mg/dl & 4(16.66%) had a peak serum bilirubin level more than 30 mg/dl. (Table-4)

Table:-4

Peak total serum bilirubin level (in mg/dl)	G6PD Normal(n=152)		G6PD Deficient(n=24)	
	Male	Female	Male	Female
12.1-20	80	44	5	3
20.1-25	12	4	4	1
25.1-30	5	4	6	1
>30	1	2	4	0

On the other hand, among 152 G6PD normal babies 124(81.57% n=152) had serum bilirubin level in the range of 12.1 to 20 mg/dl, 16(10.52% n=152) in between 20.1 to 25 mg/dl, 9(5.92% n=152) in the range of 25.1 to 30 mg/dl & 3(1.97% n=152) had >30 mg/dl. Mean peak serum bilirubin level in G6PD deficient & G6PD normal baby was 25.03 mg/dl & 18.03 mg/dl respectively (Table:-4).

Therefore, it is seen that in G6PD deficient babies, 12(50%n=24) had serum bilirubin level in the range of 20 to 30 mg/dl. On the other hand in G6PD normal group 124(81.57%n=152) had bilirubin level <20 mg/dl.

3.5.3 Duration of Phototherapy

All the 24 neonates with G6PD deficiency required phototherapy for a duration of more than 24 hours. Two babies(8.33%n=24) required phototherapy for a period of 24 to 48 hours. Eight (33.33%) needed phototherapy for 48 to 72 hrs. Ten (41.66%) required phototherapy for a period of 72 to 96 hrs. Only four babies required phototherapy for more than 96 hrs.

On contrary, among 152 G6PD normal babies, two (1.31% n=152) required phototherapy for less than 24 hrs, 58(38.15%) required phototherapy for 24-48 hrs, 60(39.47%) required 48-72 hrs of phototherapy, 25 required (16.44%) 72-96 hrs of phototherapy & only one baby was under phototherapy for more than 120 hrs duration. The mean duration of phototherapy of G6PD deficient & G6PD normal babies was 86(±18.17) hours & 62(±18.32) hours respectively.So, it is clear that in G6PD deficient babies 18(75%) needed phototherapy for 48 to 96 hours & in G6PD normal babies 118(77%) required phototherapy for 24 to 72 hours.

3.5.4 Requirement of Exchange Transfusion

Among 176 babies presented with early neonatal jaundice 23 required double volume exchange transfusion (one required exchange transfusion two times). 11(45.83% n=24) neonates in the G6PD deficient

group required exchange transfusion. Out of these 11 babies, 10 were male & one female. Six out of eleven were out born (5 were term & one was preterm) & presented with jaundice in advanced stage. Among five inborn babies one had associated sepsis & other one had birth asphyxia. None of the babies developed features of kernicterus.

On the other hand, out of 152 G6PD normal babies 12(5 were male & 7 were female) babies required exchange transfusion(7.89% n=152). Among these 12 babies, 7 were outborn(3 were preterm including one had early onset sepsis & one had sepsis with features of bilirubin encephalopathy,4 were term including two with associated sepsis & one with O-B incompatibility).Among 6 inborn babies, one was preterm & the rest were term. Out of 5 term babies, two had associated birth asphyxia, two had sepsis & one developed features of bilirubin encephalopathy along with sepsis. As a whole, two babies developed bilirubin encephalopathy.(Refer to Table-5)

Table:-5

Total Number of Exchange transfusion	Categorization according to G6PD level		Sex distribution		Source of patient		Associated risk factors		
	Category	Number of Cases	Male	Female	Outborn	Inborn	Birth asphyxia	Sepsis	Prematurity
23	G6PD Normal	12	5	7	7	5	2	7	4
	G6PD Deficient	11	10	1	6	5	1	1	1

IV. Discussion

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme with considerable role in the metabolism of red blood cells [(7)]. The enzyme deficiency leads to impaired production of reduced glutathione and predisposes the red cells to damage by oxidative metabolites, causing acute or chronic hemolysis. Deficient neonates may be asymptomatic or manifest clinically as hyperbilirubinemia or even kernicterus. Screening for G6PD deficiency and recognition of prevalence of the enzyme deficiency in individual communities have got definite place in the investigation of cases with neonatal jaundice.

4.1 Prevalence among neonates with hyperbilirubinemia

In the present study, the frequency of G6PD deficiency among neonates with hyperbilirubinemia has been found to be 13.63% among mixed community (i.e. overall), 12.00% among Non-tribal newborns & 23.07% among Tribal newborn as found on enzymatic assay.

4.2 Sex Distribution

In our study, a total of 24 neonates were found to have G6PD deficiency. Frequency in males and females were 16.94% (20 out of 118 male babies) and 6.89% (4 out of 58 female babies) respectively. Here also, frequency was high among males.

This male preponderance of G6PD deficiency is a well documented fact [(10)].

G6PD deficiency being an X-linked recessive disorder, the expression is greater in males as they have only one X-chromosome without ability to suppress expression of the defective gene. The heterozygous females having one defective gene and one normal gene may express as normal or mild deficiency and have the chance of escaping detection by usual screening tests or even enzyme assay.

4.3 Gestational period and Birth weight

Among those with birth weight of more than 2500 gm, 19 babies (13.76%; n=138) had G6PD deficiency. Out of 38 neonates with a birth weight of less than 2500 gm, 5 babies (13.16%; n=38) were found to have this enzyme deficiency. So, the prevalence of the enzyme deficiency among babies weighing more than 2.5 kg and those weighing less than 2.5 kg was similar ($p > 0.05$).

Nineteen (13.57%; n=140) term babies & five (13.88%; n=36) preterm babies were G6PD deficient. This difference in frequency of G6PD deficiency among term and preterm babies was not statistically significant ($p > 0.05$).

Kuruvilla et al [(11)] studied 212 neonates with hyperbilirubinemia not caused by ABO and Rh incompatibility and found similar frequency of this enzyme deficiency among babies with different birth weights and gestation.

Pattern of Jaundice:

4.4 Onset and Duration of Jaundice

Out of 24 neonates with G6PD deficiency, none presented with jaundice during first 24 hours of life. 37.50% neonates with G6PD deficiency had their onset of jaundice on 2nd day of life; in29.16% clinical jaundice was detectable on 3rd day & 20.83% had onset of jaundice on 4th day. Of those who presented on 2nd day, mostly were male. The mean age at onset of jaundice was 70.54 (± 23.88) hours.

Out of 152 neonates with normal G6PD level, two babies presented on first day of life.32.89% had onset of jaundice on 2nd day, 35.52% on 3rd day & 16.44% on 4th day of life. The mean age at the onset of jaundice was 67.84(±22.95) hours.

Capps et al (1963) [12] found that jaundice in G6PD deficient usually appeared by the 2nd to 4th day of life and disappeared at the end of first week. In the study by Kuruvilla et al [11], jaundice was not detectable within the first 24 hours in any deficient baby and the mean age of onset of jaundice was 61.4 (± 21.6) hours.

All the 24 neonates with G6PD deficiency required phototherapy for a duration of more than 24 hours. 8.33% required phototherapy for a period ranging from 24 to 48 hours, 33.33% required phototherapy for a duration of 48 to 72 hours, 41.66% required 73 to 96 hours, 12.50% required 97 to120 hours & only 4.16% required phototherapy for more than a duration of 120 hours. The mean duration of phototherapy was 86 (±18.17) hours.

Among 152 G6PD normal babies 1.31% required phototherapy for less than 24 hours,38.15% required 24 to 48 hours, 39.47% required 49 to 72 hours, 16.44% required 73 to 96 hours,3.94% required 97 to 120 hours & only 0.65% required phototherapy for a duration of more than 120 hours. The mean duration of phototherapy was 62(±18.32) hours.

Kuruvilla et al [11], in their study found mean duration of phototherapy required to be 3.4 ± 1.1 days. In another study (by Iranpour et al) [13], the duration required was 3.7 ± 1.9 days. Bora et al[14] found that G6PD deficient babies required a longer duration of phototherapy(94.60 hrs) as compared to GGPD normal babies(63.9 hrs).

4.5 Level of Jaundice

In this study, 33.33% babies with G6PD deficiency had a peak serum bilirubin level of less than 20 mg/dl, 20.83% cases had a peak bilirubin level in the range of 20.1 to 25 mg/dl, 29.16% had peak level in the range of 25.1 to 30 mg/dl & 16.66% had serum bilirubin in excess of 30 mg/dl. The mean peak total serum bilirubin level was 25.03 mg/dl.

Out of 152 G6PD normal babies, 81.57% had a peak serum bilirubin level less than 20 mg/dl, 10.52% in the range of 20.1 to 25 mg/dl, 5.52% in the range of 25.1 to 30 mg/dl & only 1.97% had peak serum bilirubin level more than 30 mg/dl. The mean peak total serum bilirubin level was 18.03 mg/dl.

Bora et al[14] showed a higher maximum average total serum bilirubin level(20.2 mg/dl) in G6PD deficient babies as compared to G6PD normal babies(16.7 mg/dl).

Iranpour et al [13], showed that mean bilirubin level in G6PD deficient group was 22.26± 8.36 mg/dl while studying 705 clinically icteric neonates who were admitted to Al-Zahra and Beheshti hospitals, two teaching hospitals in Isfahan, Iran. So, findings in our study is corroborating with the findings of the above studies.

However, 52% patients had a peak serum bilirubin level in the range of 15-20 mg/dl in the study by Kuruvilla et al[11]. Pao et al[15] showed that mean maximum serum bilirubin level in G6PD deficient babies was 17.8 mg/dl. These variations can be explained by the fact that variants of G6PD enzyme present in different ethnic groups may be different thereby causing varying degree of severity among those affected by the deficiency states.

4.6 Treatment of jaundice

with All babies G6PD deficiency was administered phototherapy in the study to avoid high rise in the peak bilirubin level. Out of them13(54.17%n=24) responded to phototherapy alone & 11 (45.83%) neonates in this group required double volume exchange transfusion.

On the contrary, out of 152 neonates with normal G6PD level 140(92.10%) responded with phototherapy alone & 12(7.89%) babies in this group required double volume exchange transfusion.

In the study by Kuruvilla et al [11], only one out of 25 G6PD deficient baby (sample size was 212) required an exchange transfusion; in all other cases jaundice improved with phototherapy alone.

Exchange transfusion was given in 1 out of 4 (Gupta et al, 1970) [10] and 11 out of 94 (Das et al, 1974) [16] cases of G6PD deficiency associated neonatal hyperbilirubinemia in absence of blood group incompatibility. In the study by Bora et al[14], 9(32%) babies required exchange transfusion out of 28 G6PD deficient & 26(14%) required exchange transfusion out of 185 G6PD normal babies.

So, like the study of Bora et al[14] in our study the rate of exchange transfusion was also high among G6PD deficient babies. This high rate of exchange transfusion in our study is attributed to late arrival of babies along with associated risk factors.

V. Conclusion

G6PD deficiency is found to be a common cause of neonatal jaundice. It is more common in tribal population. It is one important cause of jaundice developing on day two onwards. The peak serum bilirubin level is more than 20mg/dl in majority of G6PD deficiency cases. All babies require phototherapy and in 45.83% of cases require exchange transfusion.

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