Original article

Glucose 6 phosphate dehydrogenase deficiency in unexplained neonatal hyperbilirubinemia – A study in neonatal care unit of a tertiary care hospital.

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Abstract:

Background: Glucose 6 phosphate dehydrogenase (G6PD)deficiency causes impaired production of reduced glutathione and in turn exposes red blood cells to damage by oxidative metabolites with resultant hemolysis.***Objective***: To study the spectrum of neonatal hyperbilirubinemia , to investigate the relevance of G6PD deficiency in unexplained causes of neonatal hyperbilirubinemia and to look for outcome in cases of deficiency of the enzyme. ***Material & methods***: Cross sectional observational study done on 100 neonates. The inclusion criteria was babies born between 37 and 42 completed weeks of gestation with clinically evident jaundice and those of age upto seven days requiring admission in neonatal care unit .Their age, gender, religion, socioeconomic and residential status noted. History elicited from mother following informed consent and babies were examined clinically.Investigations included complete hemogram, total bilirubin with conjugated and unconjugated assay, red blood cell G6PD assay, thyroid profile and coomb's test .***Result***: The mean age (mean±s.d.) of patients was 4.5100± 1.4460 days. The study population of 100 babies included 69 males and 31 females with a male to female ratio of 2.23:1. G6PD testing showed deficiency in fifteen patients, whereas eighty five showed normal values of G6PD. All patients in the study population showed normal values of T3, T4, TSH and negative direct coomb's test. G6PD assay showed a mean value of 9.7291± 2.5480. The mean total bilirubin (mean±s.d.) of patients with deficient G6PD was 20.4533 ± 2.2853 mg/dl. G6PD deficient group showed higher serum bilirubin assay compared to non- deficient ones. ***Conclusion***: G6PD deficiency is a common enzyme defect causing severe indirect hyperbilirubinemiain neonates which can result in kernicterus with neurological damage. Early neonatal screening programmes should be implementedin areas where the deficiency is prevalent.

Keywords: Hyperbilirubinemia; G6PD;neonate; deficiency.

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Introduction:

During early weeks of life, most neonates develop visible physiological jaundice due to elevated unconjugated bilirubin in blood .Exaggerated physiological jaundice in new born is found in certain situationswhere the increased level of bilirubin with prolonged duration requires treatment.[1]Pathologica lconditions can also result in severe jaundice with serological accumulation of indirect bilirubin .[1,2]

The housekeeping enzyme Glucose 6 phosphate dehydrogenase (G6PD)is essential for maintaining the stability of red blood cells . It plays a pivotal role in the redox metabolism of allaerobic cells by oxidising glucose-6-phosphate to 6-phosphogluconolactone andsimultaneouslyreducing NADPto NADPH . Glutathioneperoxidase helps in removing peroxide

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from the erythrocytes. Reduced glutathione acts as a substratefor this enzyme.In G6PD deficient individuals, the NADPH production is diminished with simultaneous inhibition of detoxification of H_2O_2. Hydrogen peroxide damages the cell membrane by lipid peroxidation resulting in erythrocyte membrane breakdown with oxidative damage of protein and DNA .[2,3] Early diagnosis ofG6PD deficiency is considered important, as undiagnosed cases may cause severe hemolysis andanemia in the newborn. Deficiency of G6-PD is often encountered in differenttypes of neonatal jaundice .Kernicterus is one of the graveconsequence of G6PD deficiency whichcan have irreversible neurologicalsequelae if left untreated.[3,4]The frequency of healthy infants who are expected to present with idiopathic neonatal jaundice is 60%-80% . In neonates, jaundice first appear in face , proceedingdown to the trunk and then to theextremities with progressively rising bilirubin level .[4]Prevalence of newbornswith jaundice and in need for managementof hyperbilirubinaemia is five to ten percent. Birth weight, premature rupture of membrane,gestational age, maternal infectious diseases are different parameters to look for outcome of neonataljaundice.[5]

There exist some correlation between neonatal hyperbilirubinemiaand genetic variation evident from reviewing literature. Neonatalhyperbilirubinaemia and UGT1A1 gene variation can be correlated in molecular genetic studies where thedecreased enzyme activity result in accumulation of serum unconjugated bilirubin.[6,7] OATP2 gene variation also can result in severe hyperbilirubinaemiain neonates. Different variations of SLCO1B1 gene encoding the hepatic solutecarrier organic anion transporter 1B1 (bilirubin transporter) canpredispose newborns tohyperbilirubinaemia by limitinguptake of hepatic bilirubin.[6]Polymorphismsof SLCO1B3 gene can have a strong association with serum bilirubin levelscontributing to idiopathic mild unconjugated hyperbilirubinaemia in adults.[6,7]

The objectives of the present study was to visualise the spectrum of neonatal hyperbilirubinemia , to investigate the relevance of G6PD deficiency in unexplained causes of neonatal hyperbilirubinemia and to look for outcome in cases of deficiency of the enzyme.

Material & methods:

The study was a cross sectional observational study conducted in neonatal care unit of a tertiary care hospital for a time period of one year. The study population included hundred term babies. The inclusion criteria was babies born between 37 and 42 completed weeks of gestation with clinically evident jaundice and those of age upto 7 days of birth in need of admission in neonatal care unit.

The exclusion criteria was babies born before 37 and after 42 completed weeks of gestation ; those with ABO/ Rh incompatibility ; very sick babies ; with conditions that aggravate physiological jaundice; severe birth asphyxia; conjugated hyperbilirubinemia; and those with gross congenital anomaly.The study parameters comprised of age, gender, socioeconomicclass (SEC), religion, and residence.

Investigations done were complete hemogram, bilirubin estimation (total, conjugated and unconjugated) , erythrocyte G-6PD assay, thyroid profile and coomb's test. The study was conducted following approval from institutional ethics committee. Detailed history elicited from mother and relevant clinical examination carried out on babies presenting with neonatal jaundice. Complete hemogramwas done in "Sysmex" automated hematology analyser and bilirubin estimation done in a semi-autoanalyser(transasiabiochemicals make, Chem 5X).

G6PD assay done by G-Six kit – Coral Clinical Systems – Tulip Diagnostics (P) Ltd.G6PD in RBC released by a lysing agent present in thereagent. The principle of the test was catalyzingthe oxidation of Glucose 6 phosphate by G6PD with simultaneous reduction of NADP to NADPH. The rate of reduction measured as an increase in absorbance which is proportional to the G6PDH activity in the sample. Expected value of G6PDH activity was - 6.4 to 18.7 u/g Hbat 37 ^{o} C.This procedure was conducted in a semi auto analyser with 340 nm wave length at 37 ° C with light path of 1 cm. At first,1 ml of G6PD working reagent (L1) was mixed with 0.01 ml of whole blood (EDTA) and the mixture incubated for 5-10 minutes at room temperature. Then, 2 ml starter reagent added and mixed well followed by incubating the mixture for 5 mins at 37°C . Initial absorbance (A°) readand absorbance reading repeated after every 1, 2, & 3 mins. The mean absorbance change per min. (Δ A / min) calculated.

If G6PDH activity was very low then the absorbance change per minute also was very low and in such cases,first absorbance(A1) with another

absorbance(A2) after 5 minsnoted. The mean absorbance change per min then calculated as Δ A / Min = A2 –A1 /5

- G6PDH activity (U/g Hb) = ΔA × 47780/Hb g/dl) (4)

The statistical analysis done by SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data was summarized as mean, standard deviation for numerical variables andpercentages for calculating categoricalvariables. A chi-square test ($\chi 2$ test) done for statistical hypothesis where thesampling distribution of the test was in a chi-squared distribution when the null hypothesis was true. Unpaired proportions were compared by Chi-square test or Fischer's exact test, whichever wasappropriate. On determining*t* value, *p*-value was derived using table of values from Student'stdistribution.If the calculated *p*-value was below the threshold it was chosen for statisticalsignificance (usually 0.10, 0.05, or 0.01 level), then the null hypothesis got rejected infavour of the alternative hypothesis.p-valueof ≤ 0.05 was considered for statistical significance.

Ethical clearance: Permission granted by Ethical committee of institution (BMC-2888 dt. 15/12/2017)

Results: The study included 100 patients.The babies were divided into three age groups. The mean age (mean±s.d.) of patients was 4.5100± 1.4460 days. (Table:1)

TABLE : 1 : Distribution of babies according to age.

Age group	Age in days	Number of babies	Percentage
(I) 1-3 days	1	2	2
	2	4	4
	3	19	19
	Total	25	25
(II) 4-5 days	4	26	26
	5	27	27
	Total	53	53
(III) 6-7 days	6	9	9
	7	13	13
	Total	22	22
	Total	100	100

The study population included 69 males and 31 females with a male to female ratio of 2.23:1. Seventy one patients were from lower SEC, fifteen were from lower middle class and fourteen from middle class. Seventy nine patients were hinduand twenty one were muslim.

Eighty eight patients belonged to rural residential area and twelve were from urban area. (Table: 2)G6PD testing showed deficiency in fifteen patients,whereas eighty five showed normal values of G6PD. The mean red blood cell (RBC) count (mean±s.d.) of patients was 4.4800± .4207mill/mm3. The mean haemoglobin(Hb) of patients was 14.2170 ± 1.0045 gm/dl. The mean packed cell volume (PCV) of patients was 52.9100 ± 6.4230 %. The mean erythrocyte sedimentation rate (ESR) of patients was 9.2900 ± 1.3356 mm/hr.The biochemical reports revealed mean total bilirubin (TB) of patients as 20.0040 ± 2.5561 mg/dl. The mean direct bilirubin (DB) of patients was 2.0760 ± .3720 mg/dl. The mean indirect bilirubin (IB) of patients was 17.9280 ± 2.4317 mg/dl. G6PD assay showed a mean value of 9.7291± 2.5480.All patients in the study population showed adequate platelet count irrespective of G6PD status. All patients recorded normal T3, T4 and TSH values and negative coomb's test irrespective of G6PD status.

G6PD assay showed statistical significance with age where p value was 0.0367 and with residence where p value was 0.0579. The association of gender with G6PD was not statistically significant (p=0.69387). Even, the association of SEC with G6PD was found to be statistically insignificant (p= 0.6339). G6PD assay showed statistical insignificance with religion (p= 0.2033). Statistical insignificance was noted in association of G6PD with blood group of mother (p=0.8599) and with blood group of patient (p=0.8042).

TABLE:2 Comparison of epidemiological parameters in G6PD deficient and normal babies

Parameter	G6 PD Deficient group			Normal group		Total
		Number	%	Number	%	Number %
Age group	(I)	6	40	19	22.4	25
	(II)	9	60	40	47.1	49
	(III)	0	0	26	30.6	26
Gender	Male	11	73.3	58	68.2	69
	Female	4	26.7	27	31.8	31
SEC	Lower	12	80	59	69.4	71
	Lower middle	2	13.3	13	15.3	15
	Middle	1	6.7	13	15.3	14
Religion	Hindu	10	66.7	69	81.2	79
	Muslim	5	33.3	16	18.8	21

Parameter		G6 PD Deficient group		Normal group		Total
		Number	%	Number	%	Number %
Residence	Rural	11	73.3	77	90.6	88
	Urban	4	26.7	8	9.4	12
Blood group (Mother)	A(+)	7	46.7	30	35.3	37
	AB(+)	2	13.3	15	17.6	17
	O(+)	1	6.7	8	94.1	9
	B(+)	5	33.3	32	37.6	37
Blood group (Baby)	A(+)	4	26.7	29	34.1	33
	AB(+)	8	53.3	42	49.4	50
	B(+)	2	13.3	6	7.1	8
	O(+)	1	6.7	8	9.4	9

TABLE: 3: Hematological parameters in G6PD deficient and normal patients

Parameter	G6PD deficient	Normal
Mean age (in days)	3.6000±0.9103	4.6706±1.4670
Mean haemoglobin (gm/dl)	13.6733±1.1035	14.3129±0.9614
Mean packed cell volume(%)	51.8000±4.6167	53.1059±6.6940
Mean ESR (mm/hour)	9.7333±1.4376	9.2118±1.3102

The difference of mean age in two groups was found statistically significant (p=0.0075).

The difference of mean hemoglobin in two groups was also found statistically significant (p=0.0222). The difference of mean PCV in two groups was not statistically significant (p=0.4706). The difference of mean ESR in two groups was not statistically significant (p=0.1643). (Table: 3)

TABLE: 4 : Biochemical parameters in G6PD deficient and normal patients

Parameter	G6PD deficient	Normal
Total bilirubin (TB-mg/dl)	20.4533±2.2853	19.9247±2.6053
Direct bilirubin(DB-mg/dl)	2.2333±0.3811	2.0482±0.3657
Indirect bilirubin (IB-mg/dl)	18.2200±2.0484	17.8765±2.5004

The difference of mean TB in two groups was statistically significant (p=0.0430).Statistical significance was also found in the difference of mean DB in two groups (p=0.0455). However, the difference of mean IB in two groups was not statistically significant (p=0.6164). (Table-4)The mean G6PD (mean±s.d.) of patients having G6PDdeficiency was 5.2600± .1056. In patients with normalG6PD, the mean G6PD (mean±s.d.) of patients was 10.5178± 1.8584. The difference of mean G6PD in two groups was statistically significant (p<0.0001).

Discussion:

G6PD deficient group in the present study showed higher serum bilirubin assay compared to non-deficientones. Neonatal jaundice and anemia were more common in G6PD-deficient neonates. So, G6PDscreening is considered important in limiting the severity of disease. Sudden episodes of haemolysis associated with this condition increase the serum bilirubin to levels inducing neurologic damage. Mandatory routine neonatal screening for G6PD deficiency should be done in areas with prevalent G6PD deficiency.[8-14]

Comparing the prevalence of G6PD deficiency in hyperbilirubinemic neonates in present study with those available in literature ; it was found that the percentage in present study was more than Saleem MB et al and less than Badejoko BO et al[8,9](Table: 5)

(Table :5) G6PD deficiency in neonates (Comparison with studies available)[8-14]	
Badejoko BO et al[8]	20%
Saleem MB et al[9]	10.3%
Zeb Jan A et al[10]	9%
Iranpour R et al[11]	7.5%
Fu C et al[12]	7.28%
Iranpour R et al[13]	3.2%
ALSaif Set al[14]	2%
Present study	15%

Table :6 : Comparison with other studies with respect to bilirubin levels and treatment.

Parameter	Reference study	Result (Ref. Study)	(Result) Present study
Mean bilirubin level	Iranpour R et al[11]	22.26±8.36 mg/dl	20.4533 ± 2.2853 mg/dl
	Moiz B et al	16.8+/- 5.4 mg/dl	
Male/Female	Iranpour R et al[13]	84.81/15.18%	73.3/26.7%
	Iranpour R et al[11]	75.5/24.5%	
Phototherapy	Saleem MB et al[9]	85.9%	100 %
Exchange Transfusion(ET)	Iranpour R et al[11]	50.9%	6.6 %
	Saleem MB et al[9]	0%	
Mean G6PD activity indeficient group	Iranpour R et al[13]	3.22+/-1.8 U/g Hb	5.2600 ± .1056 U/g Hb

Iranpour R et al found males predominating in their study similar to present study and the mean bilirubin level was similar to present study but patients in

need for exchange transfusion in their study was too high in comparison to present study[11,12]Dhillon AS et al found G6PD deficient jaundiced neonates presentingwith severe anaemia .Alllaboratory investigations comprising blood group of mother and newborn, completeblood count with peripheral blood smear, TB, DB, coomb's test, thyroid profile, urine analysis, anderythrocyte G6PD level should be done inG6PD deficient newborns.[15]Khodashenas E et al found G6PD deficiency in 16 (3.5%) neonates in a study population of 452 neonates.No significant difference identified between normal and G6PD deficient groups interms of birth weight, weight on admission, coombs' test, hematocrit ,duration of hospital stay and total bilirubin level.[16]

But,significant difference in reticulocyte count found in the two groups.[16]All G6PD deficient babies received phototherapy for jaundice in the present study. Two babies(13.3%)received phototherapy for a period of 24 to 48 hours followed by four (26.6%) for 48 to 72 hours and eight (53.33%) for a period of 72 to 96hrs. Only one baby required phototherapy for more than 96 hrs. Onebaby required double volume exchange transfusion(ET) similar to study by Tanphaichitr VS et al .[5]Prognosis was good in G6PD deficient babies with jaundice if they received adequatetreatment with phototherapy and other medications. But those deficient babies may requiremedical attention later. (Table – 6)No case was fatal immediately and none developed kernicterus. However, present study was limited by small size of sample and tests being carried out in a single centre.

The incidence of G6PD deficient newborns was 2.1% with three-fold higher bilirubin level in them in comparison to G6PD-normal group (51% vs. 16%) in a study by Abolghasemi H et al.[17]Furthermore, Kaplan and Abramov found G6PD-deficient neonates more prone to develop neonatal indirect hyperbilirubinemia (NIH), required phototherapy and their hematocrit levels were lower in their study. Two neonates needed ET in their study group.[18]Moiz et al found significant differences in Hb level and reticulocyte counts in G6PD-deficient compared to normal newborns. [19]Weng and Chiu showed that G6PD-deficient infants had lower Hb level with evidence of hemolysis and higher serum TB level.[20]

TB level at presentation and the maximum level attained were higher in the G6PD-deficient neonates compared to normal ones in a study by Atay et al. They found no difference in hematocrit level and reticulocyte count in the two groups.[21]Ainoon et al found no significant association between level of enzyme activity and severity of NIH.[22]

Koosha and Rafizadehalso found no statistical differences in the lowest Hb level, reticulocyte count and highest TB, between G6PD-deficient and normal newborns in a study population of 376 newborns with NIH. [23]Hasan M Isa found 42% of patients with NIH to be G6PD deficient and most of them were males.[24]

Phototherapy or ET are the recommended treatment module to prevent development of severe NIH with kernicterus.[25] Despite intensive phototherapy, severe NIH may still need ET to prevent bilirubin encephalopathy. It has been proven that infants with idiopathic NIH showed unexpected rise in serum TB after ET if the donor blood was G6PD deficient.[25] Elevated serum bilirubin due to ongoing subclinical hemolysis might lead to continuation of phototherapy and possible repeat of ET.[25,26]Donor blood for ET needs screening for G6PD status in G6PD deficient prevalent regions .[25] The duration of phototherapy can be used as a surrogate marker for the severity of neonatal hyperbilubinemia but it can be shortened by ET.[25]

A protocol for assessment of neonatal hyperbilirubinemia should be established in neonatal care units. Systematic assessment for risk of severe NIH with close follow up and prompt intervention are also important to prevent complications.[27]Often, inadequate investigation in healthy neonates with severe NIHcontribute to early readmission and potential long-term complications of bilirubin-induced encephalopathy and kernicterus. Detection of newbornsathigh riskof severe NIH before discharge from hospital considered necessary to prevent complications.[25,26,27,28,29]

Conclusion:

Neonatal jaundice with higher bilirubin assay and anemiaare more common in G6PD-deficient neonates. Adequate and timely management should be doneto avoid irreversible neurological complications in them. Screening of newborns at risk is considered to be of help where early adequatetreatment with phototherapy, exchange transfusion and other medications can benefit their clinical outcomeand prevent untoward complications.

Conflict of interest : None.

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Author's contribution: Data collection, statistical analysis ,concept, study design, writing, editing, final approval and submission.

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