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Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency in Neonates Presenting with Indirect Hyperbilirubinemia in Neonatal Intensive Care Unit of Tertiary Health Care Center of Pakistan: Is the Trend Changing with Change in Consanguineous Marriages?

Shahzeen[1], Abid Ali Jamali[2]*, Aasma Kayani[3], Anam Zubair[1], Rabia Noreen[1], Sanober Fatima[3]

Abstract

Introduction: G6PD is an X-linked enzyme that catalyzes the first step in the HMP pathway to produces NADPH which is required for regeneration of the reduced form of glutathione (GSH). GSH is essential for the detoxification of hydrogen peroxide, especially in RBCs, which rely only on this pathway. There has been some declining trend in consanguineous marriages since last 3 decades in Pakistan, so we are conducting this study to find out whether this change lead to decrease in the frequency of G6PD deficiency in the country.

Materials and Methods: This was a prospective cross-sectional study, using non-probability consecutive sampling technique, conducted at the Neonatal Unit of Civil Hospital, Karachi during 2016-17, on 144 neonates with indirect hyperbilirubinemia. The study was approved by the Ethical Review Committee of the Civil Hospital, Dow University of Health Sciences Karachi.

Results: The mean age ± SD of neonates was 10.63±3.48 days and the majority were males (68%). The majority of neonates presented after the 5th day of their life i.e. 87.5%. G6PD deficiency was present in 8.3% of the neonates with indirect hyperbilirubinemia. Consanguinity was present in around 50% of the neonates who presented with neonatal jaundice. The overall mean total serum bilirubin, hemoglobin, hematocrit and reticulocyte count were 15.57±2.87 (mg/dl), 14.22±0.48 g/dl, 45.57±3.31%, and 0.84±0.32 % respectively. Most of the mothers (22.2%) have blood groups AB +ve and B +ve and the most babies (28.5%) have A +ve blood group.

Conclusion: Male gender and age 5 days or less had significantly high G6PD deficiency. Although consanguineous marriages have decreased only slightly, no significant effect on G6PD deficiency is found.

Keywords: Consanguineous Marriages; G6PD Deficiency; Hyperbilirubinemia; Neonatal Jaundice; Neonatal Indirect

Introduction

Neonatal jaundice is a common physiological occurrence and around 60-80% of otherwise healthy newborns develop jaundice in their early neonatal period [1,2]. It is a medical condition that occurs in newborns as a result of an imbalance between the production and elimination of bilirubin. Jaundice is a result of the increased breakdown of red blood cells and/or decreased hepatic excretion of bilirubin [3]. Neonatal jaundice commonly

Affiliation:

[1]Civil Hospital Karachi, Pakistan

[2]Aga Khan University hospital, Karachi, Pakistan

[3]National Institute of Child Health Karachi, Pakistan

***Corresponding author:**
Abid Ali Jamali, Aga Khan University Hospital, Pakistan.

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presents in the first week of life [4]. More than 60% of healthy newborns develop clinical jaundice associated with increased concentration of total serum bilirubin (TSB) during the first week of life. However, bilirubin (TSB) above 95th percentile for age in hours (high-risk zone) occurs in 8-9% of infants during the first week with approximately 4% affected after 72 hours [5,6]. The etiology in the majority of neonatal jaundice includes idiopathic causes, hemolytic disorders, inadequate Breastfeeding and Glucose-6-phosphate dehydrogenase (G6PD) deficiency [7]. The prevalence rate of G6PD varies from as high as 62% among Kurdish Jews to as low as 0.1% in Japan, while it ranges from 3 to 6.9% in Pakistan, Southern China and Southern Russia [4]. G6PD is a cytoplasmic enzyme that plays a pivotal role in the hexose monophosphate shunt (HMP shunt) of glucose metabolism. It catalyzes the first step in the HMP pathway i.e. conversion of Glucose-6-phosphate to 6-phosphogluconic acid. HMP shunt produces NADPH which is required for reactions of various biosynthetic pathways as well as for the stability of catalase and the preservation and regeneration of the reduced form of glutathione (GSH) [8,9]. Catalase and GSH are essential for the detoxification of hydrogen peroxide [10]. Red blood cells (RBCs) are exquisitely sensitive to oxidative damage, as other NADPH-producing enzymes are lacking within RBCs and they rely only on the HMP shunt for GSH and catalase production. G6PD deficiency is the most commonly known inherited disorder in man and is estimated to affect 400 million people worldwide. Males are more affected than females due to X-linked inheritance and the condition is common in malaria-endemic regions [11]. G6PD deficiency is genetically heterogeneous with the majority of mutations disrupting the enzyme structure, thereby reducing overall enzyme activity [12,13]. The residual enzyme activity of G6PD variants ranges from <1% to 100%. The majority of G6PD deficient individuals are asymptomatic most of the time. Symptoms are induced when red blood cells are exposed to exogenous oxidative stresses against which they cannot defend themselves, like certain drugs or infectious agents (hydrogen peroxide is generated by activated polymorphonuclear neutrophils) [14,15]. Clinically it may manifest as neonatal jaundice, acute haemolytic anaemia and drug-induced haemolysis [16]. G6PD deficiency is diagnosed on the basis of clinical history and haematological findings, including anaemia, reticulocytosis and characteristic red cell changes (for example, 'bite' cells and Heinz bodies, Assays of G6PD activity depend on measuring the rate of production of NADPH from NADP in red cells, and the assay may be performed on a sequestrene (EDTA) or heparinized blood sample. Enzyme activity declines with red cell age and is highest in reticulocytes. Assay results obtained after an acute hemolytic episode should always be confirmed during the steady-state, as reticulocytosis may rarely lead to a false-negative result. Most haematology laboratories in the UK utilize screening tests, which are rapid and can reliably distinguish between affected men and heterozygous females; formal biochemical characterization involves enzyme purification from red cells, an assay of activity by spectrophotometry and enzyme electrophoresis, and is only necessary for selected [17]. Pakistan has one of the highest reported rates of consanguineous marriages in the world. Although over the last 3 decades there has been some declining trend. Consanguineous marriage ratio decreased from over 60% before 2000 AD to slightly less than 50 % in 2017-2018 [18,19]. We are conducting this study to find out whether this change in consanguineous marriages has affected the frequency of G6PD deficiency in Pakistani children.

Materials and Methods

Study Design and Setting

This was a prospective cross-sectional study, conducted at the Neonatal Unit of the pediatric ward, Civil Hospital, Dow University of Health Sciences, Karachi, during 2016-17. The study was conducted on admitted neonates with indirect hyperbilirubinemia.

Inclusion and Exclusion Criteria (participants)

All the admitted neonates, of either gender and between 1-28days, with indirect hyperbilirubinemia of any duration (that is peak serum bilirubin more than 12mg/dl in full-term more than 15mg/dl in preterm neonates) were included in the study, and their status for G6PD deficiency was checked (The condition was characterized by abnormally low levels of glucose-6-phosphate dehydrogenase). In this study G6PD activity below 4.0 IU/gHb was considered as G6PD Deficiency. Whereas babies with conjugated hyperbilirubinemia (confirmed by direct bilirubin level that is more than 20% of total bilirubin level), neonates with sepsis (confirmed by examination i.e. poor moro and sucking reflex and by blood culture, if needed), neonates who have already received a blood transfusion and /or undergone exchanged transfusion and those neonates whose parents refused for admission or did not give consent to be enrolled in the study were excluded.

Sampling and Sample Size

Non-probability consecutive sampling technique was used for sample collection and the sample size was calculated by WHO software, by using P=16%, 5 and d=6%, was 144 neonates at 95% confidence interval.

Ethical Consideration

The study was approved by the Ethical Review Committee of the Civil Hospital, Dow University of Health Sciences Karachi, Pakistan. Written informed consent was taken from the guardian (mother or father), after explaining to them the purpose and procedure of the study in detail and ensuring their confidentiality. Patients and parents/guardians were

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given full authority to withdraw from the study at any time and they were assured that withdrawal from the study will not affect their treatment or follow-ups.

Data Collection

The neonates admitted to the neonatal intensive care unit (NICU) with indirect hyperbilirubinemia and fulfilling the inclusion criteria were enrolled in this study. The informed consent was taken with the parents. Neonate's clinical history and physical examination were done by the principal investigator. The data included the neonate's registration number, age, gender, gestational age, birth weight, and laboratory data. All the laboratory investigations were done in the laboratory of Civil Hospital Karachi. Laboratory tests for Serum Bilirubin (Direct, Indirect), Hemoglobin/Hematocrit, Reticulocyte count, Blood group of baby and mother, Coombs test and G6PD assay were done in all neonates because these tests were routinely performed in all the neonates with hyperbilirubinemia to see the rate of hemolysis and to exclude other causes of hemolysis i.e. ABO & RH incompatibility. The red cell G6PD activity, expressed as units per gram of haemoglobin (U/gHb), was determined for the quantitative determination of G6PD deficiency. Based on the frequency distribution of activity levels, the critical level for diagnosing G6PD deficiency is considered 4.0 U/gHb. Any neonate with activity below this value was diagnosed as G6PD deficient. Biasness and confounding variables were controlled by strictly following inclusion and exclusion criteria.

Data Analysis

Patients' data was compiled and analyzed through the Statistical Package for Social Sciences (SPSS) Version 21. Frequency and percentage were computed for qualitative variables like gender, G6PD deficiency and blood group. Mean±SD was calculated for quantitative variables i.e. age, hemoglobin level, serum bilirubin, and G6PD activity. The stratification was done on gender, age, consanguinity and length of hospital stay to see the effect of these modifiers on the outcome using the Chi-square test. P≤0.05 was considered significant.

Results

The mean age ± SD of neonates presenting with indirect hyperbilirubinemia was 10.63±3.48 days. Age is further stratified into two groups i.e. ≤ 5 days and > 5 days old. The detailed descriptive statistics of age are presented in I. In our study, the majority of the neonates were males (68%), with a male to female ratio of approximately 2:1. The majority of neonates presented after the 5th day of their life i.e. 87.5% as compared to only 12.5% presenting before the 5th day of life.

Table I: Detailed descriptive statistics of age (days). (n=144)

	Mean ±SD	95%CI	Median (IQR)	Range	Minimum	Maximum
Age	10.63±3.48	10.05 to 11.20	11.00 (5)	14	4	18
≤5 days (n=18)	4.55±0.51	4.30-4.80	5.00 (1)	1.00	4.00	5.00
>5days (n=126	11.50±2.79	11.00-11.99	12.00 (4)	12	6	18

Table II: Frequency and percentage of neonates presenting with indirect hyperbilirubinemia with respect to Gender, Age, Consanguinity, Length of hospital stay and coomb's test.

Variable		Frequency	Percentage
Gender	Male	98	68%
	Female	46	32%
	Total	144	100%
Age	≤ 5 days old	18	12.5%
	>5 days old	126	87.5%
	Total	144	100%
Consanguinity	Yes	71	49.3%
	No	73	50.7%
	Total	144	100%
Length of hospital stay	≤ 5 days	121	84%
	>5days	23	16%
	Total	144	100%
Coombs test	Positive	10	6.9%
	Negative	134	93.1%
	Total	144	100%

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Table III: Descriptive statistics of, hemoglobin (g/dl), hematocrit (%), reticulocyte count (%) and total serum bilirubin level (mg/dl). (n=144)

	Hemoglobin (g/dl)	Hematocrit (%)	Reticulocyte count (%)	Total serum bilirubin level (mg/dl)
Mean ±SD	14.22±0.48	45.57±3.31	0.84±0.32	15.57±2.87
95%CI	14.14-14.30	45.03-6.12	0.79-0.89	15.10-16.05
Median (IQR)	14.20 (0.90)	44.90 (2.93)	0.80 (0.30)	14.80 (3.50)
Range	1.60	12.80	1.40	10.20
Minimum	13.40	41.50	0.50	12.20
Maximum	15.00	54.30	1.90	22.40

Table IV: Frequency distribution of mother blood group and baby blood group (n=144).

Blood Group	Mother Blood Group		Baby Blood Group	
	Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
A –ve	5	3.47	6	4.17
A +ve	24	16.67	41	28.47
AB –ve	3	2.08	4	2.78
AB +ve	17	11.81	18	12.50
B –ve	7	4.86	9	6.25
B +ve	30	20.83	38	26.39
O –ve	15	10.42	8	5.56
O +ve	43	29.86	20	13.88
TOTAL	144	100%	144	100%

Table V: Descriptive statistics of hemoglobin, hematocrit, reticulocyte count and total serum bilirubin level according to G6PD deficiency. (n=144)

	Hemoglobin (g/dl)		Hematocrit (%)		Reticulocyte count (%)		Total serum bilirubin level (mg/dl)	
	G6PD deficient (n=12)	Normal G6PD (n=132)	G6PD deficient (n=12)	Normal G6PD (n=132)	G6PD deficient (n=12)	Normal G6PD (n=132)	G6PD deficient (n=12)	Normal G6PD (n=132)
Mean±SD	14.14±0.48	14.23±0.48	51.88±3.80	45.00±2.60	1.70±0.12	0.76±0.20	21.24±0.61	15.06±2.40
95%CI	13.83-14.44	14.15-14.31	49.46-54.30	44.55-45.45	1.61-1.78	0.73-0.80	20.85-21.63	14.65-15.47
Median (IQR)	14.05	14.25	53.45	44.85	1.7	0.7	21.3	14.3
	-0.88	-0.9	-2.38	-2.9	-0.18	-0.2	-1.2	-2.98
Range	1.5	1.6	11.5	12.8	0.5	1.1	1.7	10.2
Minimum	13.5	13.4	42.8	41.5	1.4	0.5	20.3	12.2
Maximum	15	15	54.3	54.3	1.9	1.6	22	22.4

Table VI: Frequency and association of G6PD deficiency according to gender, *Age*, cousin marriages and length of hospital stay. (n=144)

Variables		G6PD deficiency		Total	p-Value
		Yes (n=12)	No (n=132)		
Gender	Male	12	86	98	0.010*
	Female	0	46	46	
	Total	12	132	144	
Age	≤5 days (n=18)	10	8	18	0.000*
	>5 days (n=126)	2	124	126	
	TOTAL	12	132	144	
Consanguinity	Yes	5	66	71	0.580
	No	7	66	73	
	Total	12	132	144	
Length of hospital stay	≤5 Days (n=121)	11	110	121	0.691
	>5 Days (n=23)	1	22	23	
	Total	12	132	144	

Chi-Square Test was applied.
*P-value≤0.05 considered significant.

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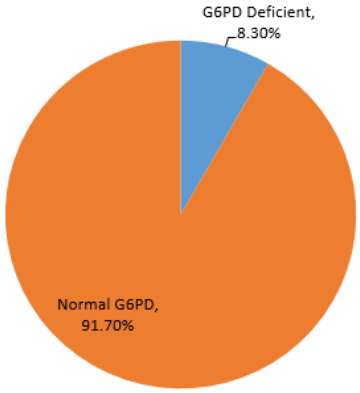

Graph I: Frequency of G6PD deficiency in neonates with indirect hyperbilirubinemia.

Consanguinity was present in around 50% of the neonates who presented with neonatal jaundice. Eighty-four per cent of the neonates were discharged within 5 days and the coombs test was positive in approximately 7% of the neonates, II. The overall mean total serum bilirubin level of our study subjects was 15.57±2.87 (mg/dl). The overall mean hemoglobin, hematocrit and reticulocyte count was 14.22±0.48 g/dl, 45.57±3.31%, and 0.84±0.32 % respectively. The detailed descriptive statistics of hemoglobin, hematocrit, reticulocyte count and total serum bilirubin level are presented in III. Most of the mothers (22.2%) have blood groups AB +ve and B +ve and most babies (28.5%) have A +ve blood group. The detailed frequency distribution of the blood group of mother and baby is presented in IV. In our study, G6PD deficiency was present in 8.3% of the neonates with indirect hyperbilirubinemia. Graph I. The descriptive statistics of mean total serum bilirubin level, hemoglobin, hematocrit and reticulocyte count in relation to G6PD activity are presented in V. Stratification with respect to gender, age, consanguinity and length of hospital stay was done to observe the effect of these modifiers on G6PD deficiency. P-value ≤0.05 was considered significant. The results showed that there was a significant association between G6PD deficiency with gender (p=0.010) and age (p=0.000) while no significant association was found with the length of hospital stay (p=0.691). Surprisingly our study did not show a significant association with consanguinity. The detailed results of associations are presented in VI.

Discussion

G6PD deficiency is an X-linked recessive condition. This deficiency makes red blood cells hypersensitive to exposure to oxidants, leading to various clinical manifestations such as neonatal jaundice [20]. Studies performed in different parts of the world have reported various prevalence rates of G6PD deficiency. The reported prevalence in Singapore, Spain, France and most of the Latin American and Caribbean countries is below 2 %, which is considerably low [21,22]. In contrast, prevalence rates across sub-Saharan Africa and the Arabian Peninsula may cross over 30% of the population [23]. In our study, the prevalence of g6pd deficiency was 8.3%. A study conducted by Kumar et al. From Pakistan reported a prevalence of 9.3% which is quite near to our results [24]. Other studies from Asia have reported different results like Khodashenas et al study from Iran, the prevalence of g6pd deficiency was estimated at 3.5%, which was lower than our study [25]. Study by Ellela et al. from Egypt reported a prevalence of 4.3% that is also lower as compared to Pakistan data [26]. This is most probably due to the lower ratio of consanguineous marriages in these countries. Consanguineous marriages in Iran are 37.4% [27] and in Egypt, it is around 40 % [28]. In our study, consanguinity was present in 49.3% of the parents of neonates who presented with indirect hyperbilirubinemia. These findings are comparable to the national demographic data conducted by NIPS [19]. G6PD deficiency is quite higher in the Arabian peninsula as well (18%) [23]. Due to the higher prevalence of cousin marriage. A recent survey conducted in Saudi Arabia showed that even educated adults were having consanguineous marriages up to 40% [29]. In our study, the most common mother blood group (MBG) was O+ve followed by B+ve and A+ve respectively. Among Rh-negative blood groups, O-ve was the most common. As compared to MBG, the most common baby blood group (BBG) was A+ve, followed by B+ve and AB+ve respectively, indicating that ABO blood group incompatibility was one of the common causes of hyperbilrubimeina in neonatal age. In our study, all G6PD deficient neonates were males and no female was found to be deficient in enzyme levels. Over 80% of the G6PD deficient neonates presented within 5 days of life. A study conducted by Akhtar et al. also reported that the majority of the G6PD deficient neonates presented on 3rd day of life [30]. Over 50% of the neonates with G6PD deficiency were the products of non-consanguineous marriages. Length of hospital stay in G6PD deficient neonates was less than 5 days in almost all of the patients. No significant difference in length of stay of neonates with or without G6PD deficiency was found. Atay et al. [31] reported similar results for length of hospital stay in their study around 15 years back.

Strengths and Limitations of the Study

This study was conducted in one of the busiest pediatric neonatology units in the city. The study center is a public health sector hospital, so almost all categories of socio-economic patients present here, ranging from very poor to upper and middle-upper class families. The main limitations of the present study include a single-center experience, low female representation and a nonrandomized study design. It was conducted with small sample size and in an urban environment therefore, the results might not be generalizable to larger populations.

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Conclusion

G6PD enzyme deficiency is common among neonates, admitted to the hospital due to jaundice. Male gender and age 5 days or less had significantly high G6PD deficiency. Although consanguineous marriages have decreased only slightly, no significant effect on G6PD deficiency is found. We need large population-based studies to find out the exact relation of G6PD with change in consanguinity.

Recommendations

G6PD deficiency can cause malignant hyperbilirubinemia, which might lead to kernicterus if not diagnosed and treated promptly. Therefore, we recommend that the establishment of an early G6PD screening program for neonates is essential. Such programs are required to prevent subsequent complications by timely diagnosis and treatment.

Declarations

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Author's contributions

SS was the lead investigator who designed this study and collected data. AJ helped in writing study protocol and analyzing the results along with writing the final manuscript. AK helped in data analysis and converting it into tabulations and graphic forms. AZ and RN both collected data and interpreted lab investigations. SF helped in manuscript writing, specially adding the references in Vancouver style.

Competing Interests

The authors declare that they have no competing interests.

Informed Consent

Informed consent is obtained from parents/guardians of the patient.

Ethical Approval

This study was approved by the Ethical Review Committee of the Civil Hospital, Dow University of Health Sciences Karachi, Pakistan

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