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RESEARCH ARTICLE

Outcome of Glucose-6-Phosphate Dehydrogenase Deficiency in Neonatal Jaundice: A report of Khyber Paktunkhawa Pakistan

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Abstract

Neonatal jaundice is a very common disease in the neonatal period. Glucose-6-phosphate dehydrogenase enzyme deficiency decrease red blood cells (RBCs) membrane defense against oxidants and makes the patients prone to hemolysis and neonatal jaundice. Therefore, we arrange a cross sectional descriptive study to determine frequency of Glucose-6-phosphate dehydrogenase deficiency in neonates with jaundice and the age of presentation of jaundice in G6PD deficient neonates presented at Department of Nursery unit Khyber Teaching Hospital Peshawar. 292 jaundiced neonates of age 0 days to 28 days with clinically diagnosed jaundice. Investigations like serum bilirubin level, direct and indirect, blood groups of baby and mother, G6PD decolorization time, were done in every neonate with jaundice. Frequency of G6PD deficiency in jaundiced neonates was determined among these jaundiced neonates. Age of the onset of jaundice in the G6PD deficient neonates was also recorded. It is concluded from the results of our study that frequency of G6PD deficiency in neonates with jaundice in this study was 16%. Avoidance of oxidant chemicals and drugs later in life will prevent chronic hemolytic anemia and acute hemolytic crisis.

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Introduction

Glucose-6-phosphate dehydrogenase deficiency is hereditary condition due to defect or defects in gene code for enzyme, Glucose-6-phosphate dehydrogenase (G6PD).[1] It is also related with neonatal jaundice, kernicterus and even death.[2] Neonatal jaundice disease is a very common in the neonatal period. Glucose-6-phosphate dehydrogenase enzyme deficiency decrease red blood cells (RBCs) membrane defense against oxidants and makes the patients prone to hemolysis and neonatal jaundice.[3,4,5] Yellowish discoloration of eyes whites, mucous membranes and skin are symptoms of neonatal jaundice which is caused by the deposition of bile salts in these tissues. Raised serum bilirubin level has many physiological and pathological reasons of which glucose-6- phosphate dehydrogenase (G6PD) enzyme deficiency is one important factor. In some cases, the neonatal jaundice is severe enough to cause death or permanent neurological damage.[6] G6PD deficiency affects all races. The highest prevalence rates, with gene frequency from 5-25%, are recorded in tropical Africa, the Middle East, tropical and subtropical Asia with some areas of the Mediterranean and Papua New Guinea.[7] The commonest clinical feature is a lack of symptoms. Most patients are asymptomatic. Neonatal jaundice usually appears by age 1-4 days at the same time as or sightly earlier than so called physiological jaundice and later than in blood group alloimmunization.[7] The data shows that jaundice in G6PD deficient neonates is because of an imbalance between production and conjugation of bilirubin with inefficient bilirubin conjugation and increased hemolysis in its pathogenesis. Borderline premature infants are at

special risk of bilirubin conjugation imbalance.[8] Deficiency of G6PD is transmitted as a sex linked recessive trait. Thus, males tend to suffer from this condition and females are carriers of the gene with a mixture of normal and G6PD lacking red blood cells in their blood. Generally, the red blood cells deficient in G6PD do not breakdown (haemolyse) spontaneously.[9] The occurrence of G6PD deficiency in newborns of Tehran is 2.1%, which is reasonably high, and also hyperbilirubinemia and jaundice are about 3-fold higher in G6PD deficient group than in the G6PD normal group (51% vs 16%). This emphasizes the need of neonatal screening on cord blood samples of both sexes for G6PD deficiency and the need to watch intently for development of hyperbilirubineumia.[10] In Pakistani newborn babies it is also one of the familiar etiologic factor for neonatal hyperbilirubinemia. However, limited data is available on the incidence of G6PD deficiency.[11] In a recent local study it was shown that in addition to other etiologic factors, G6PD deficiency was found in 25.2% of jaundiced babies.[12] Deficiency of Glucose-6-phosphate dehydrogenase is one of the important cause of neonatal jaundice. We arranged a cross sectional descriptive study to determine the frequency of Glucose-6-phosphate dehydrogenase deficiency in neonates with jaundice and the age of presentation of jaundice in G6PD deficient neonates was carried out at Department of Nursery unit Khyber Teaching Hospital Peshawar.

MATERIAL AND METHODS

Setting: The study was conducted in Nursery unit of Khyber Teaching Hospital Peshawar.
Confidence level: 95%
Anticipated population proportion: 5%
Absolute precision required: 2.5%
Sample size: 292
Sampling Technique: convenience (Non probability sampling)
Duration of Study: 4 to 6 months from the acceptance of synopsis.
Study Design: Cross sectional descriptive study
Inclusion Criteria:

1. All jaundiced neonates of age 0 days to 28 days.
2. Male and female neonates.

Exclusion Criteria:
Jaundiced neonates having other causes of jaundice e.g. Rh, ABO incompatibility. After investigation, this sample population was excluded from the undertaken study to avoid any bias factor.

DATA COLLECTION PROCEDURE:
This study was started after the approval of the institutional ethical committee.
All clinically jaundiced neonates fulfilling the inclusion criteria were included in the study. After taking informed written consent, parents were inquired about the age of presentation of jaundice, family history of glucose-6-phosphate dehydrogenase deficiency and any drug history administered to the baby. Sclerae, skin and mucous membrane were examined for jaundice and any visceromegaly was noted. Investigations i.e. serum bilirubin total, direct and indirect, blood groups of mother and baby were done in the department. Glucose-6-phosphate dehydrogenase decolorization time using sigma diagnostic G6PD reagent was also done in the same department. All information mentioned above were recorded on a proforma. All the observations were made by myself and exclusion criteria was strictly followed, so that to avoid any confounder and bias in our study.

STATISTICAL ANALYSIS:
Data analyses were done through computer software SPSS version 10.0. Frequencies and percentages were given for categorical variables like G6PD status and sex with means & standard deviation i.e. age of presentation of jaundice.

RESULTS

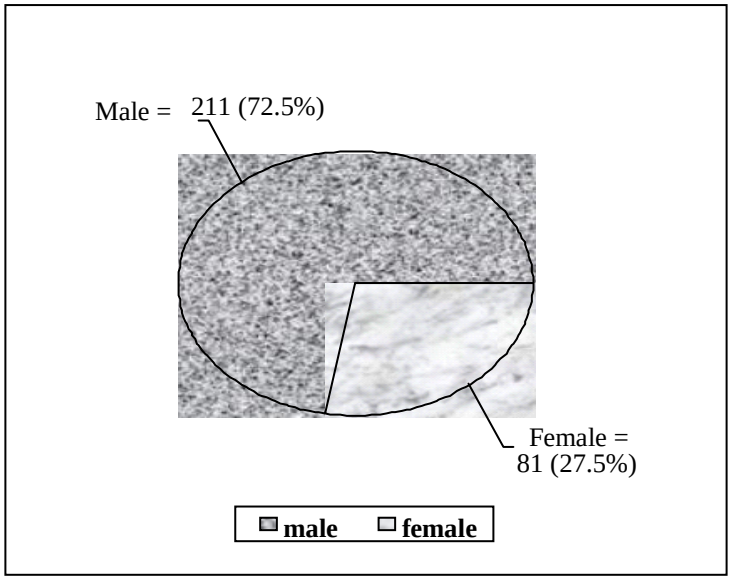
The study was conducted in Nursery unit Khyber Teaching Hospital, Peshawar. A total of 292 neonates with jaundice were included in the study. Out of these 292 neonates 211 (72.5%) were male while 81 (27.5%) were female. The overall male to female ratio was 2.63: 1 (Figure No. 1). Majority of neonates 274 (94%) age was ranged from 0-10 days, while only 17 (6%) neonates were in the age range of 11-20 days Minimum age in this study was 1 day, maximum age was 20 days with mean age of 5.46 $\pm$ standard deviation 3.07507 days (Table No. 1). Out of these 292 neonates 46(16%) were found to be G6PD deficient. Therefore, the frequency of G6PD deficient at the Nursery unit Khyber Teaching Hospital, Peshawar is 16% (Table No. 2). The most common age of appearance of jaundice in G6PD deficient babies was 3 days in 12 (28.12%) neonates, followed by 2 days in 11 (25%) neonates, 4 days in 9 (21.87%) babies. The breakup of age reveals that 34 (75%) babies developed jaundice between 2 to 4 days age. Five

days in 3 (6.25%) babies, 7 days in 3 (6.25%) babies, 1 day in 3 (6.25%) babies, 9 days and 12 days in 1 (31.25%) each baby respectively (Table No. 3). Out of 292 babies, jaundice was noticed on second day of life in majority 93 (32%) babies. In 90(31.5%) babies on 3rd postnatal day, in 35 (12%) babies on 4th day, in 35 (12%) babies on 1st day of life, in 17 (6%) on 5th day, in 6 (2%) babies on 9th postnatal day, in 4 (1.5%) neonates on 7th day, in 3 (1%) neonates on 8th postnatal day and in 1 (0.5%) baby, jaundice appeared on 6th, 10th, 11th, and 12th postnatal day respectively (Table No. 4). The neonates included in this study belonged to different districts of the province and Afghanistan refuges. Majority of these were from district Peshawar that is 128 (44%), followed by 48 (16.5%) from Charsadda, 26 (9%) from Dir, 16 (5.5%) from Nowshera, 12 (4%) from Mardan, 12 (4%) from Sawabi, 7 (2.5%) from Malakand Agency, 5 (2%) each from Afghanistan, Bajawar Agency, Khyber Agency, respectively. Four (1.5%) each from Karak, Kohat and Swat respectively.Three (1%) each from Hangu, and Mohamand Agency, respectively.One (0.5%) each from Kuram Agency, Orakzai Agency, Shangla, and Waziristan Agency, respectively (Table No. 5).In 292 neonates with jaundice, minimum weight was 1 kilogram (Kg), maximum was 4.6 kilograms (Kg) with mean weight of 2.6570 kilograms (Kg) ± standard deviation of 0.64304 Kg (Table No. 6). Past history of G6PD deficiency in other sibling of family member was positive in 7 (2.5%) babies with jaundice. While it was negative in 284 (97.5%) of neonates with jaundice. Drug history of babies showed that 3 (1%) neonates given some drugs (Table No. 7). Clinical examination revealed that yellow sclera and skin/mucousmembrane was present in all 292 (100%) neonates with jaundice. Visceromegaly was present in 12 (4%) neonates with jaundice (Table No. 8).In 292 neonates with jaundice, minimum serum bilirubin level was 6.80, maximum was 43.10 with mean serum bilirubin of 18.2750 ± standard deviation of 7.04421 (Table No. 9). G6PD decolorization time was > 60 minutes in 46 (16%) neonates with jaundice. Normal range G6PD decolorization time was noted in 245 (84%) babies. Minimum G6PD decolorization time was 25 seconds, maximum was 90 minutes with mean time of 39.6712 ± standard deviation of 14.78463 minutes (Table No. 10). Blood grouping of baby and mother showed that in majority 34 (11.5%) neonates their blood group was B^+ and their mothers was also B^+. In 32 (11%) babies their blood group was A^+ and their mothers was O^+. In 34 (11.5%) babies their blood group was B^+ and their mothers was O^+. In 28 (9.5%) babies their blood group was A^+ and their mother blood group was also A^+. In 24 (8%) babies their blood group was O^+ and their mothers blood group was also O^+. In 16 (5.5%) babies the blood group was A^+ and in their mothers blood group was A-. in 14 (5%) babies blood group was O+ and in their mothers blood group was A^+. Other

TABLES AND GRAPHS

details are shown in Table No. 11.

GRAPH NO. 1:



SEX-WISE DISTRIBUTION OF PATIENTS (n=292)

TABLE NO. 1: Male to female ratio = 3: 1, AGE-WISE DISTRIBUTION OF PATIENTS (n=292)

AGE RANGES (IN DAYS)	NO. OF CASES	PERCENTAGE
0-10 days	274	94%
11-20 days	18	6%
TOTAL	**100**	**100%**

The overall mean age of the patients was 5.46 (S.D = ±3.07) days (ranged 1 to 20 days). Minimum age was 01 day and maximum was 20 days.

TABLE NO. 2: FREQUENCY OF G6PD DEFICIENCY IN NEONATAL JAUNDICE, (n=292)

FREQUENCY	NO. OF CASES	PERCENTAGE
Normal	245	84%
G6PD deficient	46	16%
TOTAL	**292**	**100%**

TABLE NO. 3: AGE OF ONSET OF JAUNDICE IN G6PD DEFICIENT NEONATES, (n=46)

AGE OF ONSET	NO. OF CASES	PERCENTAGE
03 days	13	28.12%
02 days	11	25%
04 days	11	21.87%
05 days	03	6.25%
07 days	03	6.25%
01 day	03	6.25%
09 days	01	3.12%
12 days	01	3.12%
TOTAL	46	100%

TABLE NO. 4: AGE OF ONSET OF JAUNDICE IN ALL NEONATES WITH JAUNDICE (n=292)

AGE OF ONSET	NO. OF CASES	PERCENTAGE
2nd day	94	32%
3rd day	91	31.5%
4th day	36	12%
1st day	36	12%
5th day	19	6%
9th day	06	02%
7th day	04	1.5%
8th day	03	1%
6th day	01	0.5%
11th day	01	0.5%
12th day	01	0.5%
TOTAL	**292**	**100%**

TABLE NO. 5: AREA-WISE DISTRIBUTION OF PATIENTS (n=292)

AREA	**NO. OF CASES**	**PERCENTAGE**
Peshawar	129	44%
Charsadda	48	16.5%
Dir	26	09%
Nowshera	16	05.5%
Mardan	12	04%
Sawabi	12	04%
Malakand Agency	07	02.5%
Khyber Agency	06	02%
Afghanistan	06	02%
Bajawar Agency	06	02%
Karak	04	01.5%
Kohat	04	01.5%
Swat	04	01.5%
Hangu	03	01%
Mohmand Agency	06	02%
Kuram Agency	01	0.5%
Orakzai Agency	01	0.5%
Shangla	01	0.5%
Waziristan Agency	01	0.5%
TOTAL	**292**	**100%**

TABLE NO. 6: WEIGHT OF NEONATES WITH JAUNDICE (n=292)

MINIMUM WEIGHT	MAXIMUM WEIGHT	MEAN WEIGHT	STANDARD DEVIATION
1 Kg	4.6 Kg	2.65 Kg	± 0.64304

TABLE NO. 7: PAST HISTORY IN PATIENTS WITH JAUNDICE (n=292)

HISTORY	NO. OF CASES	PERCENTAGE
Positive past history of G6PD deficiency in other sibling of family	07	2.5%
Positive drug history given to the baby	03	1%

TABLE NO. 8: CLINICAL EXAMINATION FINDINGS IN BABIES WITH JAUNDICE (n=292)

FINDINGS	NO. OF CASES	PERCENTAGE
Yellow sclera and skin/ mucous membrane	292	100%
Visceromegaly	12	04%

TABLE NO. 9: SERUM BILIRUBIN LEVELS IN NEONATES WITH JAUNDICE (n=292)

MINIMUM SERUM BILIRUBIN LEVEL	MAXIMUM SERUM BILIRUBIN LEVEL	MEAN SERUM BILIRUBIN LEVEL	STANDARD DEVIATION
6.80 mg/dl	43.10 mg/dl	18.27 mg/dl	± 7.04421

TABLE NO. 10: G6PD DECOLORATION TIME IN NEONATES WITH JAUNDICE (n=292)

FINDINGS	**NO. OF CASES**	**PERCENTAGE**
G6PD decoloration time Of > 60 minute	46	16%
Normal G6PD decoloration time	246	84%

MINIMUM TIME	**MAXIMUM TIME**	**MEAN TIME**	**STANDARD DEVIATION**
25 seconds	90 minutes	39.6712 minutes	$\pm$ 14.78463

TABLE NO. 11: BLOOD GROUPS IN NEONATES WITH JAUNDICE AND THEIR MOTHERS (N=292)

BLOOD GROUP OF BABY AND MOTHER	**NO. OF CASES**	**PERCENTAGE**
Baby = A-	1	0.5%
Baby = A- mother = A-	3	1%
Baby = A- mother = A+	3	1%
Baby = A- mother =B-	1	0.5%
Baby =A- mother =O+	1	0.5%
Baby =A+ mother =A-	17	5.5%
Baby =A+ mother =A+	28	9.5%
Baby =A+ mother =AB+	3	1%
Baby =A+ mother =B-	3	1%
Baby =A+ mother =B+	5	1.5%
Baby =A+ mother =O+	33	11%
Baby =AB- mother =O+	1	0.5%
Baby =AB+ mother =A-	3	1%
Baby =AB+ mother =A+	5	1.5%
Baby =AB+ mother =AB-	1	0.5%
Baby =AB+ mother =AB+	1	0.5%
Baby =AB+ mother =B+	9	3%
Baby =AB+ mother =O+	3	1%
Baby =B- mother =B-	5	1.5%
Baby =B- mother =O+	1	0.5%
Baby =B+	6	2%
Baby =b+ mother =A-	1	0.5%
Baby =B+ mother =A-	1	0.5%
Baby =B+ mother =A+	1	0.5%
Baby =B+ mother =AB+	10	3.5%

Baby =B+ mother =b-	1	0.5%
Baby =B+ mother =B-	5	1.5%
Baby =b+ mother =B+	1	0.5%
Baby =B+ mother =B+	34	11.5%
Baby =B+ mother =O-	5	1.5%
Baby =B+ mother =O+	31	10.5%
Baby =O- mother =A-	1	0.5%
Baby =O- mother =O+	1	0.5%
Baby =O+	1	0.5%
Baby =O+ mother =A-	3	1%
Baby =O+ mother =A+	15	5%
Baby =O+ mother =AB+	1	0.5%
Baby =O+ mother =B-	3	1%
Baby =O+ mother =B+	12	4%
Baby =O+ mother=O-	7	2.5%
Baby =O+ mother =O+	24	8%
Mother =B+	1	0.5%
Total	**292**	**100%**

DISCUSSION

Neonatal jaundice is the most common medical problem affecting babies in the first week of life.[13-15] Jaundice in the newborn is a problem because elevation of serum bilirubin is potentially toxic to infant's developing central nervous system.[16-17]An elevation of serum bilirubin concentration is often detected during the first several days of life. Sixty five percent of newborn are clinically jaundiced. The most known pathologic causes of neonatal jaundice including G6PD deficiency, ABO incompatibility, Rh incompatibility, infections, breast milk jaundice, sepsis, hereditary spherocytosis and undetermined causes.[18] G6PD deficiency is the second most common cause of hyperbilirubinemia and hemolytic anemia in our country.[19] G6PD deficiency is the most common and clinically significant red cell enzyme defect, affecting as many as 4,500,000 newborns worldwide each year. Although known for its prevalence in the populations of the Mediterranean, Middle East, Arabian Peninsula, Southeast Asia, and Africa, G6PD has been transformed by immigrations and intermarriage into a global problem.[20-22]The children who are G6PD deficient may present in the later life with chronic hemolytic anemia or acute hemolytic crisis if they are exposed to certain oxidant drugs or chemicals. To prevent all these complications G6PD status of the person must be known.[23]In this study of 292 neonates with jaundice, the frequency of G6PD deficiency was 16%. It correlates with the studies who reported a frequency of 13% and Rehman G et al[12] reported its frequency as 14%. This figure is quite higher than the reported frequency 7.9%, Iranpur et al[24] 7.5%, whose data shows its frequency as 5.5%, while in a study conducted in Tehran the incidence of G6PD deficiency was 2.1%.[24] In another study conducted in Saudi Arabia the prevalence was found estimated to be approximately 2%[25] On the other hand, this frequency is practically lower than the frequency mentioned by Thaitumyanon et al[26] whose report is 25.5%, has reported 18.42% and Uko EK et al[27] has reported 38.2% neonates G6PD deficient. These variations may be due to demographic difference in the genetic makeup of societies, sociocultural differences, frequency of carrier individuals, sample size, method used for G6PD enzyme estimation and detection rate. G6PD deficiency is an hereditary deficiency that may be the reason for neonatal hyperbilirubinemia, since has been found in several countries and among widely different ethnic groups mainly in Mediterranean region.[28]In 292 neonates with jaundice, the age at presentation of jaundice and admission to the hospital ranged from 1 to 12 days, while the commonest age of onset of jaundice ranged from 24 to 96 hours (2-4 days) of life. Almost similar results were obtained by other worker like Ding G et al.[29] Kaplan Met al[30] mentioned in his study that the commonest age of appearance of jaundice due to G6PD deficiency is in early neonatal life.Males were affected more than females in our study. Overall 72.5% were male while 27.5% were females with male to female ratio of 2.63: 1. Kaplanet al[30] states the same figure in his study. This ratio slightly lower than the figure mentioned by Rehman G et al[12] in his study, which states it 9.5:1. This observation further supports the X-linked recessive mode of inheritance of this enzymopathy. The occurrence in female is possible due to being homozygous for G6PD deficiency.[31]Treatment of neonatal hyperbilirubinemia is usually based on the measurements of level of total serum bilirubin. Based on empirical data, it is generally recommended to begin phototherapy at minor levels in low birth weight and very low birth weight infants than in term infants, but no general agreement exists on exact limits. Treatment criteria in preterm infants do not, however, have the same empirical backing as in term infants. The

very low and extremely low birth weight infants are more susceptible to bilirubin toxicity. However, bilirubin may function as an antioxidant and enzyme inducer in this infants.[31]In 292 neonates with jaundice, mean weight was 2.6570 Kg. Mahajan G et al[31] has reported mean weight of 2264.9 grams (2.26 Kg) in his study. In our study mean serum bilirubin level was 19.14 gm/dl, while Mahajan G et al[31] has reported mean serum bilirubin level of 16.6 mg/dl in his study.

CONCLUSIONS

It is concluded from the results of our study that frequency of G6PD deficiency in neonates with jaundice was in this study was 16%.Neonatal jaundice due to G6PD deficiency mainly affects babies between age of 2 to 4 days. Males were more affected than females. Jaundice screening of newborns prior to hospital discharge is essential to identify relatively common but treatable conditions and prevent long-term morbidity and mortality. All newborns should be monitored vigilantly for the development of hyperbilirubinemia. All the neonates with jaundice must be screened for G6PD status. Early detection and prompt treatment with phototherapy and exchange transfusion will decrease the risk of acute complications. Avoidance of oxidant chemicals and drugs later in life will prevent chronic hemolytic anemia and acute hemolytic crisis.

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