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Prevalence and Clinical Manifestation of Glucose-6-Phosphate Dehydrogenase Deficiency in Newborns with Hyperbilirubinemia in Mashhad, Iran

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Abstract

Background. Hyperbilirubinemia is a relatively common disorder among infants and one of the most common reasons is glucose- 6- phosphate dehydrogenase (G6PD) deficiency.

Aim. The aim of this study was to determine prevalence rate of enzyme deficiency in newborns with jaundice. We also compared clinical and paraclinical values among G6PD- deficient and normal G6PD infants who were admitted in the hospital due to jaundice.

Material and Methods. This prospective descriptive study has been performed on 1568 neonates, with jaundice as a chief complaint, at Ghaem hospital in Mashhad, Iran, in a six- year period. Neonates were screened for G6PD enzyme by the florescent spot method and characteristics such as birth weight, age and weight on admission, hospitalization period, need for exchange and laboratory data [Complete Blood count (CBC), reticulocyte count, indirect and direct bilirubin, coombs test and blood type] were recorded. Statistical analysis was carried out using SPSS 13.5 statistical package.

Results. The overall prevalence rate of G6PD deficiency was 5.2% (59/1139 infants) and males were predominated (88.1% vs 11.9%). Significant statistical differences between two groups of normal G6PD and G6PD deficient- neonates, were detected in the age of admission (p=0.001), hematocrit (p=0.000), hospitalization period (p=0.000) and total serum bilirubin (p=0.013). Kernicterus was reported in 6.4% of neonatal Hyperbilirubinemia.

Conclusion. G6PD deficiency is a common enzyme defect among newborns in Iran and may cause severe hyperbilirubinemia and kernicterus. By screening all infants and on-time treatment we can prevent further complications of G6PD deficiency disorder.

Introduction

Jaundice is a common clinical aspect during infancy which affects term (60%) and preterm (80%) newborns in the first week of life. The vast majority of hyperbilirubinemia is physiologic but in severe cases, complications as kernicterus, cerebral palsy and death can be occurred. Determining the cause of jaundice may improve prevention programs and treatment plans of hyperbilirubinemia [1, 2].

Glucose- 6- phosphate dehydrogenase deficiency (G6PDD) is an important detectable cause of hyperbilirubinemia. Severe neonatal hyperbilirubinemia and kernicterus is the most important complication of G6PD deficiency in newborns .G6PD deficiency is a risk factor leads to earlier blood exchange in neonates compared with normal G6PD group . It is one of the most common enzymopathies in human that affect the erythrocyte metabolism. Recent studies show more than 400 million people in worldwide are affected by this enzymopathy.

This inherited disorder in humans is X-linked; therefore boys are more affected than girls. According to WHO, Iran is located in the area with moderate to high prevalence rate for G6PD deficiency . This study determines the prevalence rate of G6PD deficiency among neonates with jaundice and compares the clinical manifestations and other risk factors between jaundice infants with normal G6PD enzyme and G6PD-deficient group.

Material and Methods

This descriptive analytic study has been done from April 2003 to September 2009 and evaluated underline disease, signs and symptoms and complications of Hyperbilirubinemia in neonates with jaundice. The ethic committee of Mashhad University of Medical Science approved this study and all patients signed informed consent. Information were collected and recorded by neonatal fellowship and neonatologist.

Clinical jaundice is determined by yellowish color of sclera, mucosal and skin. Newborns who were admitted for jaundice aged 1 to 29 days. This study has been accomplished on 1139 newborns admitted to NICU and pediatric emergency room or visited at clinic for 6 years.

Laboratory examinations were performed for two groups of infants. First, infants who were clinically jaundice to more extent of mid-abdomen with normal physical examination and second group who were defined as high risk infant (Rh or ABO incompatibility, prematurity, history of jaundice and hospitalization in prior baby and symptomatic jaundice).Maternal data like history of pregnancy and delivery, age, blood group, disease, type of delivery, duration of hospitalization after delivery, gestational order were all recorded.

Newborn's data like time of jaundice onset and discharge from hospital, signs and symptoms on admission, duration of hospitalization and treatment plan were recorded and complete physical examination was done. Finally laboratory tests were performed (CBC, indirect and direct bilirubin, coombs test, reticulocyte count, blood type, thyroid test and G6PD).

1568 neonates with chief complaint of jaundice were admitted to our neonatal ward during this study period, but only 1139 infants were evaluated for G6PD and other 429 infants had incomplete information. Several cases were excluded from study (930 out of 1139) because of jaundice due to hemolysis (187 cases with ABO and Rh isoimmunization) and non-hemolytic jaundice with definite cause (501 cases with enclosed hemorrhage, polycythemia, sepsis, hypothyroidism, and etc), 126 infants whose parents were noncompliance and 116 icteric infants who were symptomatic (respiratory distress, congenital anomaly, renal insufficiency and etc). . We finally found 59 jaundice infants with G6PD deficiency and 150 icteric infants with normal G6PD without exact reason. For a better evaluation, G6PD newborns data were compared with those of 150 newborns with idiopathic jaundice as a control group.

Blood sample was collected for each jaundice neonate into ethylondiamentetracetic acid (EDTA) anticoagulated tubes. Samples were tested by the fluorescent spot method. This semi-quantitative test is reported as sufficient or insufficient. Usually enzyme activity below 30% is determined insufficient .

Almost all the infants weighed more than 2500 grams and aged more than 48 hours were admitted with a total bilirubin of at least 17 mg/dl, for infants below 2500 gr, admission was planned for serum bilirubin higher than half of exchange limit. Blood exchange was performed for term infants with risk factors like G6PD deficiency, Rh and ABO incompatibility; septicemia and asphyxia as serum bilirubin passed 20 mg/dl and in infants without risk factor who rose over 25 mg/dl. Blood exchange was planned for preterm and neonates below 2000 gram infants whose total bilirubin (mg/dl) were increased at least 1% of their weight in gram. Admission to hospital was performed for newborns aged below 24 and 48 hours with a serum bilirubin of at least 8 mg/dl or 12 mg/dl, respectively.

Statistical analysis was carried out using SPSS 13.5 statistical package, for comparing groups. The Student T-test, Mann-Whitney and Chi-square test were performed on quantitative and qualitative variables. P-value less than 0.05, was considered statistically significant.

Results

Among 1139 admitted infants with jaundice, who were evaluated for G6PD enzyme, we found 59(5.2%) babies with G6PD deficiency and males were predominated (88.1% male, 11.9% female).Second group (neonates with jaundice and normal G6PD) include 150 infants (60% male, 40%female).

Clinical characteristics are shown in Table 1.Chi-square test determined significant statistical relationship between sex and enzyme deficiency (p= 0.001). Student

T-test did not show significant differences between two groups for variables like age, birth weight, maternal age and parity whereas a significant statistical difference for age and weight on admission and hospitalization period was recorded (Table 1).

Table 1: Clinical characteristics of participant groups.

Group / Variable	G6PD Normal Mean ± SD	G6PD Deficiency Mean ± SD	P Value
Birth weight (Kg)	2.92 ± 0.58	2.96 ± 0.48	0.64
Parity	1.84 ± 1.42	1.87 ± 1.18	0.886
Maternal age (year)	25.64 ± 5.01	26.69 ± 5.99	0.205
Admission weight (Kg)	2.77 ± 0.58	2.99 ± 0.59	0.019
Admission age (day)	6.45 ± 3.17	4.91 ± 2.31	0.001
Hospitalization period (day)	3.12 ± 1.47	4.86 ± 2.42	0.000

Laboratory characteristics have shown in figure 1.We found significant statistical differences for hematocrit and total serum bilirubin between two groups (p<0.001), (Figure 1).

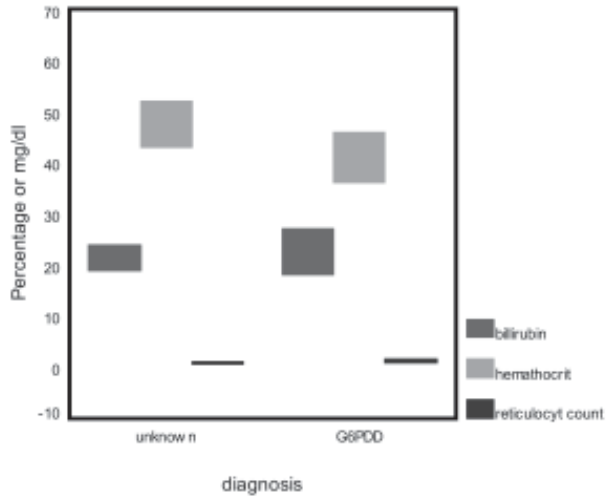

Figure 1: Biochemical values in two groups.

Almost newborns with G6PD deficiency were term (91.2%) although in group with normal G6PD, 115 neonates were term (76.7%) and 35 were preterm (23.3%).

This study did not show any significant relationship between mode of delivery, maternal and neonatal blood typing and pregnancy complication with G6PD deficiency. Sixteen patients in G6PD deficient group needed blood exchange (29.1%) whereas 28 patients in normal G6PD group were exchanged (18.7%, p: 0.361).

Kernicterus was detected in 7 infants (3 normal G6PD and 4 G6PD deficient).

Discussion

The prevalence rate of G6PD deficiency in newborns with jaundice in present study is 5.2%. Some studies in Iran reported different prevalence rate in different places, example north and south of Iran have a high rate and other parts shows a low rate. Almost results show the prevalence rate about 1.2% overall . Studies in Spain, France and Singapore gave a prevalence rate of 1.57%, 2.1% and 1.62% respectively, which is defined low. Some other countries reported a higher prevalence rate as in Saudi Arabia and Nigeria were 18%, 40% respectively.

Statistical relationship was reported between sex and enzyme deficiency (p=0.001). Significant difference for hematocrit and reticulocyte count values was determined between two groups (p: 0.000) .This difference may be explained by unknown different oxidant factors producing hemolysis and decreasing hematocrit.G6PD gene (Gd) is located on X chromosome and homozygous male infants are totally enzyme deficient and detected easily by screening test. Female neonates are usually heterozygote and show a spectrum of enzyme activity; therefore they sometimes are missed by screening test. Almost, hemolysis won't be happened in jaundice babies with G6PD deficiency, but CoHb and $ETCo_2$ values are consistently high. Although proliferation and lyses of Hem is obviously increased, but only a few numbers are affected by acute hemolysis. Measurement with HPLC detected conjugated bilirubin fraction (index of hepatic conjugation capacity) is lower in G6PD deficient babies and shows less hepatic conjugation capacity. Newborn with jaundice and G6PD deficiency and a serum bilirubin of at least 15 mg/dl, shows more total bilirubin and mono and di conjugated bilirubin compared with non-icteric G6PD-defiecient infants.

Therefore conjugation disorder may play a role in pathogenesis of hyperbilirubinemia in this group. Finally, a remarkable interaction between G6PD deficiency and Gilbert syndrome was demonstrated .The incidence of hyperbilirubinemia in G6PD deficient neonates increased from 9.7% in normal homozygotes to 31.6% in the variant UGT promoter heterozygotes to 50% in homozygotes for the variant promoter. No significant effect of the variant UGT promoter was seen in the G6PD-normal infants. Thus neither G6PD deficiency alone, nor the abnormal UGT

promoter alone (Gilbert syndrome), caused an increased incidence of hyperbilirubinemia; both factors were needed to produce a significant increase in TSB levels .

We found higher serum bilirubin in G6PD deficiency group (p: 0.013). In our study, median total bilirubin was measured 24 mg/dl among infants with G6PD deficiency.16 neonates with G6PD deficiency were in need of exchange (29.1%), same results were published before e.g. Yousefi in Iran 32%, Iraq 27%, Atay in Turkey 33.3%, Mullah in Saudi Arabia 7% and Hon in Malaysia 17% .

There was significant difference for age and weight on admission time between two groups (p=0.019). It shows admission time was earlier (4.91 ± 2.31 vs 6.45 ± 3.17). It can be explained by earlier manifestation of jaundice in neonates with G6PD deficiency. We did not find any rationale for lack of the physiologically weight loss within the first week. This report also determined different hospitalization period among 2 groups (p: 0.000) and infants with enzyme deficiency stayed longer in hospital (4.86 ± 2.42 vs 3.12 ± 1.47 day).

In this study, kernicterus was happened in 6.8% of jaundice newborns with G6PD deficiency whereas 2% of infants with idiopathic hyperbilirubinemia developed to kernicterus. The results of our study are in unanimity with other investigations, such as Atay's report, who concluded that kernicterus occurred in 4% of jaundice newborns in Turkey .

Conclusion

G6PD deficiency is relatively common among icteric infants who admitted and may lead to severe hyperbilirubinemia. Serum bilirubin and hospitalization period is increased among these infants. Early diagnosing of G6PD deficiency may reduce the complications like kernicterus. By screening all infants and starting on-time treatment we can prevent further complications of G6PD deficiency disorder.

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