

G6PD Enzyme Deficiency in Neonatal Pathologic Hyperbilirubinemia in Yazd

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Abstract

Background

About 7.5% of the world population carries one or two deficient copy of glucose-6-phosphate dehydrogenase (G6PD) genes. According to WHO, its prevalence in Iran is 10 to 14.9%. This study aimed on determination of frequency of G6PD deficiency in neonates with jaundice who were hospitalized during 6 months (September 2008 to February 2009) in the city of Yazd, Iran.

Materials and Methods

In this study, 105 icteric neonates in the hospitals of Yazd were evaluated. Data was collected from hospital records, and the G6PD activity was measured by photometric biochemical assay. Statistical analysis of data was performed by the SPSS-16 software, using Student's t-test and Pearson's chi-squared test.

Results

Between all of studied neonates, 19 (18.1%) had G6PD deficiency, and consisted of 15 boys (29.4% of boys)

and 4 girls (7.4% of girls). In 100% of cases, the jaundice began in the first week after birth. The average total serum bilirubin at hospitalization was 17.22 mg/dL. In 31.5% of the G6PD-deficient neonates, exchange transfusion became necessary, which is significantly more than the rate in G6PD-sufficient (4.6%) neonates (P-value<0.05).

Conclusion

In general, the frequency of G6PD deficiency in this study seems quite high. Regarding its severity and frequent need for exchange transfusion, we recommend that all of the icteric neonates should be evaluated for G6PD activity. Also, it is better to test for G6PD deficiency in all of the neonates, to detect its presence and to prevent its complications such as favism and oxidant drug-induced hemolysis, since the test has a low cost.

Keywords

Neonatal; Jaundice; Glucosephosphate Dehydrogenase Deficiency; Bilirubin; Favism

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Introduction

The enzyme glucose-6-phosphate dehydrogenase (G6PD) is one of the most important enzymes in the human body, present in various amounts in many cells, including red blood cells (1). Deficiency of G6PD is a frequent enzyme deficiency of the human being, with estimated 400 million affected people in

the world (2). It is an inherited X-linked recessive disorder with varied clinical presentations including neonatal jaundice, hemolysis, acute icterus after exposure to chemicals and drugs, anemia, acute jaundice following consumption of fava beans (favism), and also congenital chronic non-spherocytic hemolytic anemia (3). Of these manifestations,

neonatal jaundice is the earliest one, and the most critical sign for early diagnosis of this genetic disorder (4).

Around 5% of neonates with G6PD deficiency will develop jaundice after the first 24 hours of life (in contrast to fetal erythroblastosis), and their serum indirect bilirubin reaches a peak at days 3 to 5, often more than 20 mg/dL. When jaundice becomes apparent from the end of first week, its peak may be delayed up to the 2nd week. Early diagnosis of deficiency of G6PD is quite important, because this disorder may cause severe hemolysis and anemia in the newborn, if undiagnosed. On the other hand, its detection is simple, rapid and cost-effective by the current laboratory methods. Although the current trend regarding G6PD deficiency in most countries is to determine the type of mutations and its relationship with other diseases or to try different therapeutic chemicals in these patients, but there is need for frequency determination in Iran in the light of genetic heterogeneity. So, we decided to find this in a 6 months period in Yazd city in central Iran.

Materials and Methods

In this descriptive cross-sectional study, 105 icteric newborns, who were hospitalized based on pathologic hyperbilirubinemia (defined according to criteria in textbooks of pediatrics, that is, hyperbilirubinemia at the first day, direct hyperbilirubinemia, more than 5 mg/dL/d increase in serum bilirubin, hyperbilirubinemia after the day 14, or presence of any accompanying disease) and diagnosed by pediatricians in Yazd during September 2008 to February 2009 were enrolled. The questionnaire included data about demographic parameters, clinical history and lab test results. Any ambiguous or missing data was completed by calling the parents. A venous blood sample was mixed with anticoagulant EDTA, and used for G6PD enzyme activity measurement by colorimetric assay kit from Kimiapajooohan Co., Iran. In this test, 200 μ L of whole blood was mixed with hemolyzing reagent, and the color development reagent was added to 200 μ L of the hemolyzed blood in a vial, covered with 700 μ L of liquid paraffin for inhibition of gas exchange, and incubated at 37 °C for 70 minutes. The color change in the vial was monitored continuously (at least every 15 minutes), and if this occurs before 50 minutes it was regarded as normal (adequate activity of G6PD).

Statistical Analysis

In this study Student's t-test and Pearson's chi-squared test were used for comparison of means of data, using the SPSS-16 software.

Results

The data about age of neonate at hospitalization, sex, birth weight, blood groups of neonate and mother, time of initiation of jaundice, level of total and direct serum bilirubin, and blood exchange transfusion was analyzed. The age at hospitalization was 2 to 25 days (average 14). In 100% of cases, the jaundice began in the first week after birth. Table I shows the relative frequency of G6PD deficiency in the studied neonates.

As seen from the table, of 105 newborns, 51 (48.6%) were male and 54 (51.4%) were female. Totally, 19 neonates (18.1%) had deficiency of G6PD. The male: female ratio in icteric newborns with normal G6PD activity was about 0.7, which has a significant difference ($p < 0.05$) with G6PD deficient newborns (in whom this ratio was 3.7). The mean serum total bilirubin at hospitalization of G6PD deficient and normal G6PD neonates was 18.43 and 11.86 mg/dL, respectively, reflecting a significant difference ($p < 0.05$ by t-test). The average serum total bilirubin at hospitalization in all 105 neonates was 17.2 mg/dL (range 5.2-27.5). Direct bilirubin of all icteric neonates was within reference intervals (i.e., 0 to 0.2 mg/dL) at the time of hospitalization. All of the icteric neonates received phototherapy. However, 31.5% of G6PD deficient neonates and 4.6% of neonates with normal G6PD activity underwent blood exchange, again showing a significant difference ($p < 0.05$ by chi-square test). No relationship between the relative frequency of G6PD deficiency and other assessed parameters including birth weight, gestational age, blood group of the neonate and his/her mother was found.

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at hospitalization in all 105 neonates was 17.2 mg/dL (range 5.2-27.5). Direct bilirubin of all icteric neonates was within reference intervals (i.e., 0 to 0.2 mg/dL) at the time of hospitalization. All of the icteric neonates received phototherapy. However, 31.5% of G6PD deficient neonates and 4.6% of neonates with normal G6PD activity underwent blood exchange, again showing a significant difference

Table I. Distribution of G6PD deficiency among male and female neonates.
P-value<0.05 (by chi-square test)

Sex	Normal G6PD Activity		G6PD deficiency		Total
	#	%	#	%	
Male	36	41.9	15	78.9	51
Female	50	58.1	4	21.1	54
Total	86	100	19	100	105

Discussion

In Asian and Mediterranean newborns, neonatal jaundice and kernicterus are more common than other regions (5). In the study by Marzban et al., the frequency of G6PD deficiency in 244 icteric neonates of Tehran, Iran, was found to be 5.7% (6). In similar studies in Hamadan, Iran (7) and in another center in Tehran, Iran, (8) the relative frequency was estimated at 4.4% and 7.6%, respectively. A study in India (9) reported that the relative frequency of G6PD deficiency in icteric neonates is 4.6%, while in Pakistan (10) it was 14.8% and in Egypt (11) it was found to be 14.4%. Deficiency of enzyme G6PD is more prevalent in Africa, Asia, Mediterranean region and Middle East, likely due to higher prevalence of infection with *Plasmodium falciparum* (12). Since the gene coding for this enzyme is located on chromosome X, it is much more common in boys, a fact which was also manifested in this study with M:F ratio being near 3.7. In the study performed in Sari, north of Iran (13), the above ratio was calculated as 3, and in another work (6) it was 3.6, both of them very close to our findings. In the current study, G6PD- deficient newborns had higher mean serum total bilirubin than other neonates (18.43 vs. 11.68 mg/dL). In a comparable study in Yasuj (14), west of Iran, the mean serum total bilirubin in G6PD-deficient newborns was 18.1 mg/dL, and in another study (15) at East Azerbaijan province, Northwest of Iran, it was 22.41 mg/dL. Since the severity of jaundice and other clinical manifestations of G6PD deficiency is directly related to the abnormal gene function and the race, it may be concluded that the prevalent mutant gene in those regions is the cause of

(p<0.05 by chi-square test). No relationship between the relative frequency of G6PD deficiency and other assessed parameters including birth weight, gestational age, blood group of the neonate and his/her mother was found.

more severe jaundice. The severe hyperbilirubinemia in neonates of our study justifies more prolonged hospitalization and more frequent use of exchange transfusion for them in comparison with neonates who had normal activity of G6PD.

Conclusion

In this study, G6PD enzyme deficiency in neonatal pathologic hyperbilirubinemia in Yazd was evaluated. It seems that the frequency of G6PD deficiency is quite high. Due to considerable frequency of G6PD deficiency found in this study, we suggest qualitative test of this enzyme deficiency for all icteric neonates toward early diagnosis and prevention of adverse consequences of neonatal hyperbilirubinemia, especially on brain. So, it is recommended that all of the icteric neonates should be evaluated for G6PD activity as well as to test for G6PD deficiency in all of the neonates, to detect its presence and to prevent its complications such as favism and oxidant drug-induced hemolysis, since the test has a low cost.

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Conflict of Interest

The authors have no conflict of interest.

References

1. Farhoud DD, Yazdanpanah L. Glucose-6-phosphate dehydrogenase (G6PD) deficiency. Iran J Public Health 2008; 37(4): 1-18.
2. Nouri Dalouei MR, Hejazi SH, Yousefi A, Mohammad Ganji SH, Soltanian S, Javadi KR, et al.

- Identification of mutations in G6PD gene in patients in Hormozgan province of Iran. *Med J Islam Repub Iran* Fall 2006; 17(4): 313-316.
3. Gari MA, Chaudhary AG, Al-Qahtani MH, Abuzenadah AM, Waseem A, Banni H, et al. Frequency of Mediterranean mutation among a group of Saudi G6PD patients in Western region-Jeddah. *Int J Lab Hematol* 2010; 32(1 Pt 2): 17-21.
 4. Behrman RE, Kliegman RM, Arvin AM. Jaundice and hyperbilirubinemia in the newborn. *Nelson textbook of pediatrics*, 17th Ed, Philadelphia: WB Saunders.2004: 513-17.
 5. Ebrahimi A. *Clinical explanation of laboratory tests*. 2th Ed. Tehran: Tayeb Publishing; 1390.
 6. Marzban A, Mousavinasab SNAD. Correlation between hemolysis and jaundice in glucose 6-phosphate dehydrogenase deficient neonates. *Acta Medica Iranica* 2009; 47(5): 379-82.
 7. Eghbalian F, Monsef AR. Evaluation of glucose-6-phosphate dehydrogenase deficiency without hemolysis in icteric newborns. *Iran J Ped* 2007; 17(1): 36-40.
 8. Behjati-Ardakani S, Nikkhah A, Sedaghat M. The association between G6PD deficiency and total serum bilirubin level in icteric neonates. *Acta Medica Iranica* 2007; 45(3): 233-5.
 9. Henny-Harry C, Trotman H. Epidemiology of neonatal jaundice at the University Hospital of the West Indies. *West Indian Med J* 2012; 61(1): 37-42.
 10. Moiz B, Nasir A, Khan SA, Kherani SA, Qadir M. Neonatal hyperbilirubinemia in infants with G6PD c.563C > T Variant. *BMC Pediatrics* 2012; 12: 126-133.
 11. Abdel Fattah M, Abdel Ghany E, Adel A, Mosallam D, Kamal S. Glucose-6-phosphate dehydrogenase and red cell pyruvate kinase deficiency in neonatal jaundice cases in Egypt. *Pediatr Hemat Oncol* 2010; 27(4): 262-71.
 12. Alharbi KK, Khan IA, Abed AS, Syed R. Insertion/deletion polymorphisms do play any role in G6PD deficiency individuals in the Kingdom of the Saudi Arabia. *Bioinformation* 2013; 9(1): 49-53.
 13. Ahmadi AH, Ghazizadeh Z. Evaluation of glucose-6-phosphate dehydrogenase deficiency without hemolysis in icteric newborns at Mazandaran province, Iran. *Pak J Biol Sci* 2008; 11(10): 1394-7.
 14. Nabavizadeh SH, Rezaie M, Sabzali P, Barati A, Zoladl M. Cohort study on hemolysis associated with G6PD deficiency in jaundice neonates. *Life Science Journal* 2012; 9(3): 702-5.
 15. Ghoreyshi SZAD, Soltani Ahari H, Ghoreyshi S. Glucose-6-phosphate dehydrogenase deficiency in icteric neonates admitted in Tabriz pediatric medical center. *Medical journal of Tabriz University of Medical Sciences*, Fall 2007; 29(3): 89-93.