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Evaluation of Neonatal Hyperbilirubinemia at Mazandaran Province of Iran in 2004-2007: Prevalence of Glucose-6-Phosphate Dehydrogenase Deficiency

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Abstract: The purpose of this study is to evaluate the etiology of hyperbilirubinemia and the Prevalence of Glucose-6-phosphate Dehydrogenase (G6PD) deficiency in newborns who were admitted to Boali Hospital in Sari City during the period, 2004-2007. This prospective descriptive study has been conducted on 1018 icteric newborns. The dataset included: age, sex, total and direct bilirubin, hemoglobin, hematocryte, reticulocyte count, direct Coombs, G6PD level and the type of treatment. All data was analyzed by using statistical method. The prevalence of sepsis, ABO incompatibility, G6PD deficiency and Undetermined (Exaggerated physiological jaundice, prematurity, breast feeding jaundice, unknown) was 2.7% (27 neonates), 2.9% (30 neonates), 13.6% (138 neonates) and 80.1% (815 neonates), respectively. Those with severe jaundice and hyperbilirubinemia were hospitalized and treated with phototherapy or exchange transfusion. Despite a high prevalence of G6PD deficiency in our study, we recommend that G6PD deficiency tests be performed in all Iranian and Mediterranean icteric newborns.

Key words: Neontal hyperbilirubinimia, prevalence, dehydrogenase, glucose-6-phosphate

INTRODUCTION

An inherited deficiency of enzyme glucose-6-phosphate dehydrogenase (G6PD) was first discovered in 1956 (Carson *et al*., 1956). G6PD deficiency is the most common red cell enzyme abnormality associated with hemolysis (Beutler, 1978). G6PD catalyzes the first step in the hexose-monophosphate pathway in Glucose metabolism and it produces NADPH wich keeps glutathione in its reduced form. Glutathione Protects Red Blood Cells (RBCs) from oxidative damage. G6PD deficiency is clinically manifested as acute hemolytic anemia, chronic non-spherocytic hemolytic anemia and neonatal hyperbilirubinemia, wich is of hemolytic origin by agents cousing destruction of the (RBCs) (Dennery *et al*., 2001). Being an X-linked condition, the prevalence of G6PD deficiency in any given population is determined by the number of deficient males. However, deficient females are also at risk of hemolysis and jaundice (Miller, 1995). According to the report of World Health Organization (WHO), 7.5% of the world's population carry one or two genes for G6PD deficiency and 2.9% are G6PD-deficient (WHO Working Group, 1989). Although, most affected individuals are asymptomatic, there is a risk of neonatal jaundice or Favism (occurrence of an acute hemolysis and hemoglobinuria in G6PD-deficient individuals following the ingestion of fava beans, which most frequently occurs in children) (Valaes, 1994; Meloni *et al*., 1992; Piomelli, 1986). Certain drugs or infections can also lead to acute hemolytic reactions and hemoglobinuria in patients with G6PD deficiency. However, even by exclusion of all known triggers, G6PD-deficient neonates are prone to hyperbilirubinemia (Cipollina *et al*., 1999). Neonatal hyperbilirubinemia, defined as a total serum bilirubin level exceeding 5 mg dL^{-1}, is a frequent problem (Segel, 2004). Neonatal jaundice affects 60% of full-term infants and 80% of preterm infants in the first 3 days of life (Halmaek *et al*., 2002). The pathogenesis of neonatal hyperbilirubinemia has not been completely defined in G6PD-deficient newborns and hemolysis alone is not sufficient to explain hyperbilirubinemia (Cipollina *et al*., 1999). Severe complications of neonatal hyperbilirubinemia such as kernicterus have been reported from countries such as Nigeria, Greece, Saudi Arabia and the United States (Kaplan *et al*., 1997; Porter and Dennis, 2002; Melton *et al*., 1999; Shusher *et al*., 1995). In a population with a high prevalence rate, early detection of the enzyme deficiency by neonatal screening is desirable in order to take appropriate measures to prevent the complications of hemolysis and jaundice (Doxiadis *et al*., 1964).

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The early diagnosis of G6PD activity may provide an etiological diagnosis for neonatal jaundice. The WHO recommends neonatal screening on cord blood samples in populations where G6PD deficiency is common. This can help in monitoring affected children, prevent acute hemolysis and help in advising parents not to feed fava beans to their affected young children (WHO Working Group, 1989). Phototherapy is one of the most effective and successful methods in the control of jaundice, especially when it is started very early (Yaish *et al*., 1991; Mc Donald, 1995). The initial laboratory evaluation of jaundice depends on the age of the newborn and the kind of hyperbilirubinemia. Hemoglobin, hematrocryte, reticulocyte count, peripheral blood smear, ABO blood group typing, Rhesus typing and nonagglutinating antibody level (Coombs test) should be determined in indirect hyperbilirubinemia (Halmaek *et al*., 2002; Mallouh *et al*., 1992). Evaluation of G6PD deficiency and pyruvate kinase deficiency should be considered, especially for infants who are older than 4 days, have a positive family history, or are of East Asian, Greek, Mediterranean, or African descent (Halmaek *et al*., 2002). According to a WHO report, Iran is in a moderately high incidence area for G6PD deficiency (WHO Working Group, 1989). Favism is also common in some provinces of Iran, where fava beans are a common food.

The objectives of this prospective study were to estimate the incidence of G6PD deficiency in newborns of Mazandaran province (north of Iran), to establish its relationship with hyperbilirubinemia and determining the severity of icterus in the hospitalized newborns in our hospital. Efficacy of treatment with phototherapy and exchange transfusion was also evaluated.

MATERIALS AND METHODS

The research team reviewed the medical records of all the newborns who had been admitted to the neonatal ward or neonatal intensive care unit (NICU) in Boali-Sina Hospital, with the diagnosis of neonatal hyperbilirubinemia, from, 2004 through, 2007. The diagnosis was based on the International Classification of Diseases (Ahmed *et al*., 1999). according to the final diagnosis written by the treating pediatrician. This hospital is the paediatric residency teaching hospital of Mazandaran University of Medical Sciences in Sari City, with a neonatal ward and NICU. Sari City is in the centre of Mazandaran Province, which is located in the north of Islamic Republic of Iran. Newborns (less than 30 days old) with pathological hyperbilirubinemia were admitted to this hospital for evaluation (clinical and laboratory) and treatment (phototherapy and/or exchange transfusion), according to the criteria mentioned in Nelson Textbook of Pediatrics (Mallouh *et al*., 1992). Some of the criteria for pathological hyperbilirubinemia were jaundice appearing in the first 24-36 h of life, the total serum bilirubin level rising at a rate faster than 5 mg^{-1} dL day^{-1}, jaundice persisting after 14 days of life, jaundice associated with pallor, hepatomegaly, splenomegaly, symptoms and signs of sepsis, abnormal vital signs and signs of kernicterus, and serum bilirubin level greater than 12 mg dL^{-1} in full-term (especially in the absence of risk factors) or 14 mg dL^{-1} in premature infants. The main inclusion criterion was the presence of the G6PD activity test (normal or deficient) in the medical records. Medical records were reviewed precisely and deliberately for pallor, cephalhaematoma, skin bruising, hepatomegaly, splenomegaly, signs and symptoms of sepsis, hypothyroidism, CNS haemorrhage, type of treatment, maternal and neonatal blood groups, direct antibody test (Coombs test), serum levels of total and direct bilirubin concentration, hemoglobin and hematocrit levels, reticulocyte count, peripheral blood smear, G6PD test and results of blood, cerebrospinal fluid, urine and fecal cultures, as well as other tests and X-rays. It is important to mention that maternal and neonatal blood groups, Coombs test, hemoglobin and hematocryte levels, reticulocyte count, peripheral blood smear and G6PD activity test were performed routinely for all the newborns admitted for the management of neonatal hyperbilirubinemia, but if there were clinical manifestations of hypothyroidism (or jaundice persisting beyond 14 days) or sepsis, clinicians attending to the infants would request the measurement of thyroxine and thyroid stimulating hormones and order sepsis work-up, respectively. All necessary information had been recorded on standardised questionnaires. In the absence of other causes, etiology of sepsis was ascribed to newborns with positive blood cultures and/or features of infection necessitate antibiotics therapy for 7 or more days. In this study, an undetermined etiology included:

- Exaggerated physiological jaundice (jaundice occurring after the 3rd day of life in healthy, full-term newborns).
- Prematurity-associated jaundice (exaggerated physiological jaundice occuring in newborns less than 37 weeks of gestational age).
- Breast feeding jaundice (breast feeding newborns who had no identifiable risk factor for jaundice and which settled by 10-14 days of age).
- Unknown causes which included:
    - Hemolysis with positive Coombs test and/or abnormal peripheral smear and/or elevated reticulocyte count that were neither ABO/Rhesus incompatible nor G6PD deficient.

- Maternal blood swallowed during labour without bloody vomiting.
- CNS haemorrhage with normal clinical manifestations (so imaging studies were not done)
- No identifiable etiology was found.

The statistical Package for Social Sciences (SPSS; version 14) was used for the statistical analysis. Results were shown as frequency,%, median, range, minimum and maximum. For continuous variables, Student's t-test was used to compare data that did not have a normal distribution. $p \leq 0.05$ was considered statistically significant. The G6PD level was measured with a G6PD enzyme assay kit, spot test of qualitative method manufactored by Saba lab. The study was approved by the research committee of Mazandaran University of Medical Sciences.

RESULTS

The study included 1018 newborns, 572 (56.2%) of them were boys and 446 (43.8%) were girls. The prevalence of sepsis, ABO incompatibility, G6PD deficiency was 2.7% (27 neonates), 2.9% (30 neonates) and 13.6% (138 neonates), respectively (Table 1). We did not find any cases of CNS haemorrhage, intestinal atresia or stenosis, delayed meconium passage and trauma from instrumented delivery.

In 57 of the G6PD-deficient infants (41.3%), the onset of jaundice was on the 1-4th day of life (Table 2).

Among G6PD deficient newborns, 104 (10.2%) were boys and 34 (3.4%) was a girl. The median, range, minimum and maximum of the highest total bilirubin concentration (mg dL^{-1}), reticulocyte count (percent) and the lowest hemoglobin level (g dL^{-1}) of normal G6PD and G6PD-deficient newborns are shown in (Table 3). The results of our study did not show any positive Coombs test in the all group. Pre-exchange serum bilirubin levels for these babies were above 20 mg dL^{-1} and post-exchange serum bilirubin levels were approximately less than 50% of pre-exchange levels. Phototherapy was considered for all of these babies before exchange transfusion. Kernicterus was associated with G6PD deficiency (one infant), sepsis (one infant) and unknown cause (one infant). In these newborns, peak unconjugated bilirubin concentrations measured 20-35 mg dL^{-1}.

Table 1: The causes of jaundice

Causes	Number	(%)
Undetermined (Exaggerated physiological jaundice, prematurity, breast feeding jaundice, unknown)	815	80.1
G6PD	138	13.6
ABO	30	2.9
Sepsis	27	2.7
RH	1	0.1
Thrombocytopenia	1	0.1
G6PD+ABO	3	0.3
G6PD+Sepsis	3	0.3
Total	1018	100.0

Table 2: The age at onset of jaundice in G6PD-deficient infants

Age in days	Male	Female	Total (%)
1-4	47	10	57(41.3)
5-8	32	13	45(32.6)
9-12	15	7	22(15.9)
13-16	5	1	6(4.3)
17-20	3	2	5(3.6)
21-24	1	0	1(0.7)
25-28	1	1	2(1.4)
Total	104	34	138

Table 3: The highest total bilirubin concentration, lowest haemoglobin level and the reticulocyte count in normal G6PD and G6PD-deficient newborns

Variable	Normal G6PD (n = 880)	G6PD-deficient (n = 138)
Highest bilirubin concentration (mg/dL)		
Median	15.94	17.19
Std. Deviation	4.07	4.22
Range	25.10	27.90
Minimum	4.90	2.10
Maximum	30.00	30.00
Lowest hemoglobin level (g dL^{-1})		
Median	14.57	15.11
Std. Deviation	2.26	2.23
Range	15.00	18.20
Minimum	5.20	4.20
Maximum	20.20	22.40
Reticulocyte count (%)		
Median	1.97	1.70
Std. Deviation	1.32	1.18
Range	8.40	9.40
Minimum	0.10	0.10
Maximum	8.50	9.50

DISCUSSION

In this study, the cause of jaundice could not be determined in 80.1% of the newborns. Undetermined etiology was higher in our study in relation to other investigations (Melton *et al*.., 1999; Al-Omran *et al*.., 1999). It may be due to:

- Lack of symptoms, signs and laboratory evidences of CNS haemorrhage, polycythemia, intestinal atresia or stenosis, delayed meconium passage and hypothyroidism.
- Different classifications of the causes of neonatal hyperbilirubinemia. We categorised exaggerated physiological jaundice, prematurity and breast feeding jaundice under the title of undetermined etiology. The etiology of extreme hyperbilirubinemia in newborns admitted to an NICU in southern Turkey shas been idiopathic in 65.6% of cases. The Turkish

classification included isoimmunisation (presumed ABO incompatibility), increased hemolysis (no sepsis or G6PD deficiency), G6PD deficiency, sepsis, hypothyroidism and idiopathic (Tiker *et al*., 2006). Some investigators agree that in up to 50% of infants with severe jaundice, breast feeding and prematurity are the main causes identified despite extensive work-ups. In such cases, laboratory evaluation is suggested to be fairly minimal because test results are often not revealing and helpful, even in the presence of hemolysis (Melton *et al*., 1999). There is no data available on the sensitivity and specificity of routine testing for hyperbilirubinemia (Melton *et al*., 1999).

- Incapability to confirm decreased bilirubin conjugation or to measure the activity of Uridine diphosphoglucuronic acid Glucuronosyl Transferase (UGT). Physiological and breast milk jaundice are usually due to decreased bilirubin conjugation (Stoll anb Kliegman, 2000). Incomplete maturation of UGT 1A1 enzyme in premature infants may result in diminished bilirubin conjugation, placing these neonates at especial risk of hyperbilirubinemia (Kaplan *et al*., 2005). Some investigators believe that diminished bilirubin conjugation is another mechanism of jaundice in the G6PD-deficient newborns (Kaplan *et al*., 1997, 2005; Frank, 2005).
- In patients with acute haemolysis, the result of G6PD deficiency test may be falsely negative because immediately after haemolytic episode, reticulocytes and young erythrocytes predominate. Reticulocytes and young erythrocytes have normal or near-normal enzyme activity (Frank, 2005).

Statistical analyses of our results showed that there was differences in the highest total bilirubin concentration ($p<0.05$) and there were no differences in the reticulocyte count ($p>0.05$) and the lowest hemoglobin level ($p>0.05$) between normal G6PD and G6PD-deficient newborns. In the present study, 34 girls were G6PD-deficient. They may be a G6PD-deficient homozygote or heterozygote. The gene for G6PD deficiency is transmitted as a sex-linked trait with severe enzyme deficiency, occurring only in hemizygote males and homozygote females. Heterozygous females often have normal G6PD activity, but some may have intermediate activity and others may have low activity (Hassan *et al*., 2003). Random X-chromosome inactivation results in 2 RBC populations in female heterozygotes. One population consists of RBCs with normal G6PD activity and the other consists of G6PD-deficient cells. X-inactivation may be non-random or one or the other clone may be selected preferentially. There may be varying phenotypes and the RBCs of heterozygotes may exhibit normal, intermediate, or grossly deficient G6PD activity (Pao *et al*., 2005). The most devastating clinical consequence of G6PD deficiency is neonatal hyperbilirubinemia which can be severe and result in kernicterus or even death (Kaplan *et al*., 1997; Pao *et al*., 2005). Brown and Johnson reported 23 cases of kernicterus occurring since 1989, 16 in term newborns and seven in near-term newborns (Brown and Johnson, 1996). In these newborns, peak unconjugated bilirubin concentrations measured 22-50 mg dL^{-1}. Following the introduction of neonatal population screening programmes and major health awareness campaigns by the government, there was a drastic decrease in the incidence of neonatal hyperbilirubinemia and acute hemolytic anemia in G6PD-deficient patients in Taiwan and Singapore (Pao *et al*., 2005).

According to the report of World Health Organisation (WHO), 2.9% of the world's population are G6PD deficient and Iran is in a moderately high incidence area (10%-15%) for G6PD deficiency (Abolghasemi *et al*., 2004). The WHO recommends neonatal screening on cord blood samples in populations where G6PD deficiency is common (Abolghasemi *et al*., 2004). Cord blood screening of newborns for G6PD deficiency in 2,000 neonates (50.3% were boys) in two hospitals in Tehran (capital of Iran) was done from April to December 1999 (Abolghasemi *et al*., 2004). Their results showed that 2.1% of the total population (3.6% of males and 0.6% of females) were G6PD-deficient. There are reports of G6PD deficiency prevalence in other parts of Iran that differ from the Tehran study (Brown and Johnson, 1996). These reports indicate that the northern and southeastern provinces of Iran have higher rates of G6PD deficiency (16.4% in the northern part [Guilan Provinces], 12% in the southern part [Shiraz] and 19.3% in the southeastern part of Iran). Our study showed that the prevalence of G6PD deficiency was 13.6% in the northern part of iran [Mazandaran Provinces]. High rates of G6PD deficiency in certain areas of Iran such as Mazandaran Provinces may represent the higher rate of G6PD deficiency throughout the country, compared to those from the Tehran report (Abolghasemi *et al*., 2004). These differences are mainly due to geographical and population variations, but there are also differences in study population. The population of Mazandaran and Guilan Provinces differ from the Shiraz and Tehran populations in ethnicity. The Tehran population was mostly from the central provinces of Iran and included some immigrants from other provinces and did not represent the population of all parts of Iran. Very high rate of G6PD deficiency in certain areas of Iran could explain the higher rate of G6PD deficiency in the whole country compared to our population.

While, studies from the northern Pakistan (predominantly of Path ethnicity) reported a 7-8% prevalence of G6PD deficiency, the results from Karachi (a multiethnic city in southern Pakistan) revealed only a 2% prevalence (Arif and Bhutta, 1999). This is comparable to reports from Singapore and Malaysia, although the prevalence is less than reports from the Middle East and India (Arif and Bhutta, 1999). The etiological relationship between G6PD deficiency and neonatal hyperbilirubinemia has been confirmed by several studies. G6PD-deficient babies are 3-fold more prone to neonatal jaundice than G6PD-deficient infants (Al-Naam *et al*., 1987; Bawoda *et al*., 1998; Meloni *et al*., 1983; Ainoon *et al*., 1999). Our study not support these findings as 79% of G6PD-deficient babies developed hyperbilirubinemia compared to 69% of nondeficient control group.

The major limitation of this study is that it has an analytical retrospective design. In our residency teaching hospitals, nearly all patients were examined thoroughly and deliberately by the attending clinicians and residents, as well as by medical students. Moreover, all medical records were written correctly and completely every day, and were reviewed carefully.

CONCLUSION

In conclusion, neonatal hyperbilirubinemia is one of the most common problems and requires hospital admission for investigation and treatment. Despite a high prevalence of G6PD deficiency in our study, we recommend that G6PD deficiency tests be performed in all Iranian and Mediterranean icteric newborns, unless other investigators ascertain and document that G6PD deficiency tests are not necessary to be done routinely.

Also, due to a lack of funding and inavailability of quantitative G6PD enzyme assay kit, the program was applying qualitative methods which can lead to misdiagnosis of some cases of enzyme deficiency. So screening with quantitative tests at birth for every newborn, both sexes is recommended. In addition, we recommend that measurement of the enzyme UGT be made available for the clinical use in the evaluation of neonatal hyperbilirubinemia.

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