Glucose-6-Phosphate Dehydrogenase Screening in Israel-Arab and Palestinian-Arab Neonates

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Objective To evaluate the frequency of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, the incidence of clinically significant jaundice (any serum total bilirubin value >75th percentile on the hour-specific bilirubin nomogram), and the need for phototherapy in the pooled male Israeli-Arab and Palestinian-Arab population born at the Shaare Zedek Medical Center in Jerusalem, Israel.

Study design Quantitative G-6-PD enzyme testing of umbilical cord blood was performed during birth hospitalization. G-6-PD deficiency was defined as any G-6-PD value <7.0 U/gHb. Transcutaneous bilirubin was performed daily during birth hospitalization, with serum total bilirubin testing in those with a transcutaneous bilirubin value >75th percentile.

Results Ten of 286 (3.5%) consecutively delivered male Arab newborns had G-6-PD deficiency. Clinically significant jaundice was higher in the population with G-6-PD deficiency compared with normal controls (relative risk, 3.45; 95% CI, 1.24-9.58). Thirty percent of the newborns with G-6-PD deficiency met American Academy of Pediatrics indications for phototherapy according to the high-risk (middle) curve on the phototherapy graph.

Conclusion The frequency of G-6-PD deficiency in the Arab neonatal population delivering at this medical center meets World Health Organization criteria for neonatal G-6-PD screening (3%-5%). As in other ethnic groups, clinically significant jaundice is more frequent in newborns of this ethnic group with G-6-PD deficiency compared with G-6-PD–normal controls. Neonatal G-6-PD screening for both males and females of this population subgroup, in conjunction with parental education regarding the dangers of the condition and its prophylaxis, has now been incorporated into our institution's routine G-6-PD screening program. *(J Pediatr 2015;167:169-72)*.

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency is associated with a high incidence of neonatal hyperbilirubinemia, which occasionally can become extreme and result in bilirubin encephalopathy and subsequent chronic athetoid cerebral palsy, known as kernicterus.[1,2] Neonatal screening programs for the detection of G-6-PD deficiency before the onset of severe hyperbilirubinemia have been set up in some countries and geographic areas.[3] The aim of such screening programs is to increase awareness of the condition among parents and medical caretakers, to provide education regarding potential triggers of hemolysis to avoid, and to encourage the use of medical facilities for treatment as soon as developing jaundice is recognized. In 1989, the World Health Organization (WHO) Working Group issued a comprehensive statement regarding G-6-PD deficiency, including a recommendation that neonatal screening should be instituted in population groups with a 3%-5% male frequency of the condition.[4]

At the Shaare Zedek Medical Center in Jerusalem, Israel, a neonatal dual program for G-6-PD deficiency in conjunction with predischarge bilirubin screening has been operational for many decades. The program is targeted at ethnic groups in Israeli society at high risk for the condition.[5] The newborns include primarily Sephardic Jewish descendents whose families immigrated from the Middle East and Asia Minor. Until recently, neonates of Arab descent were not included in the screening program, because of the low frequency of the condition in this group.[5] A recent report from northern Israel in which a 6% frequency among Israeli-Arab male newborns was documented[6] prompted us to evaluate whether this population subgroup living in and around Jerusalem meets the criteria for G-6-PD screening. Because this subgroup tends to live and intermarry in relatively closed groups, we thought it possible that the incidence of G-6-PD deficiency in the Arab population in the Jerusalem region may differ from counterparts in other parts of the country.

The objectives of the present study were to determine the frequency of G-6-PD deficiency among a cohort of male Arab newborns delivered at the Shaare Zedek Medical Center, and to establish whether the incidence of clinically significant jaundice and the need for phototherapy identify this subset of the population as a high-risk group.

G-6-PD	Glucose-6-phosphate dehydrogenase
Hb	Hemoglobin
STB	Serum total bilirubin
WHO	World Health Organization

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Methods

Permission to perform the study was obtained from the Institutional Review Board of the Shaare Zedek Medical Center. Because the project was an expansion of the routine screening program, the Board waived the need for informed, signed parental consent. The Arab population included those living in and in the environs of Jerusalem who chose to deliver their infants at the Shaare Zedek Medical Center. Although this population subset currently comprises 2 subgroups, Israeli-Arabs and Palestinian-Arabs, they share, until recently, common ethnic ancestry and thus were pooled.

A sample of umbilical cord blood was routinely collected into an ethylenediaminetetraacetic acid–containing tube after delivery of the newborn and clamping of the umbilical cord.[7] This sample was labeled and stored in a refrigerator until processing on the next day.

Nursery care was routine. Breastfeeding was encouraged. Transcutaneous bilirubin testing was performed daily using a JM-103 bilirubinometer (Konica Minolta Sensing, Inc, Osaka, Japan), and the results were plotted on an hour-specific bilirubin nomogram.[8] Serum total bilirubin (STB) was determined in those subjects with a transcutaneous bilirubin value ≥75th percentile on the nomogram. Phototherapy and exchange transfusion were performed according to the guidelines of the Israel Neonatal Society,[9] which in turn are based on the guidelines of the American Academy of Pediatrics.[10] For those with G-6-PD deficiency, the line of the graph for newborns with risk factors was used. For newborns with normal G-6-PD activity in the absence of additional risk factors, the upper line was used, in accordance with American Academy of Pediatrics recommendations. Newborns with gestational age <36 weeks, a major congenital anomaly, hypoglycemia, respiratory distress, sepsis, or any other condition requiring treatment in the neonatal intensive care unit were excluded from the analysis.

G-6-PD test results were available on the day after delivery. Before discharge, parents were informed, orally and by written explanation in the Arabic language, of their baby's condition and of the potential associated dangers. They were instructed to avoid hemolytic triggers, including fava beans and potentially harmful medications, and to avoid clothing that had been stored in naphthalene-containing mothballs. They were instructed how to observe their baby for jaundice and to seek medical care should jaundice develop or worsen. Discharge from the birth hospitalization was planned for 48 hours after delivery. Any newborn with a STB value ≥75th percentile but not meeting the criteria for phototherapy was scheduled for a bilirubin test on the next day. Clinically significant jaundice was defined as any STB value >75th percentile on the bilirubin nomogram.

A commercial kit (Sentinal Diagnostics, Milan, Italy) was used to measure spectroscopic absorbance at 340 nm owing to reduction of oxidized nicotinamide-adenine dinucleotide phosphate to reduced nicotinamide-adenine dinucleotide phosphate at 37°C, reflecting G-6-PD enzyme activity.[7] Hemoglobin (Hb) was measured in the same sample spectrophotometrically at 540 nm with a commercial kit using the cyanmethemoglobin method (Pointe Scientific, Canton, Michigan). G-6-PD activity was recorded as U/gHb, with G-6-PD deficiency defined as any newborn with a G-6-PD activity value <7 U/gHb.[7] STB was determined routinely on heparinized, centrifuged capillary tube samples by absorbance of bilirubin at 455 nm (Bilimeter 3; Pfaff Medical, Germany).

Results

Between January and June 2013, a total of 286 consecutively delivered male Arab newborns were screened. Demographic data included a mean birth weight of 3250 ± 429 g and a mean gestational age of 38 ± 1 week. Forty-seven infants (16.4%) were delivered by cesarean. Two hundred and sixty-six (93%) were breastfed exclusively, and the remainder were mixed breastfed and formula-fed. ABO heterospecificity (mother blood group O, newborn group A or B) with a positive direct antiglobulin test was noted in 14 infants (4.9%).

The frequency of G-6-PD enzyme activity <7 U/gHb in the male infants was 3.5% (95% CI for rate, 1.68-6.43) (Table). Enzyme activity of the group with G-6-PD deficiency was strikingly low, and <1 U/gHb in 8 of the 10 neonates (0.26 ± 0.11 U/gHb).

The incidence of clinically significant jaundice was significantly higher in the newborns with G-6-PD deficiency (mean STB of those >75th percentile, 11.7 ± 3.0 mg/dL at 45 ± 20 postnatal hours) compared with those who were G-6-PD–normal (mean STB, 10.9 ± 2.7 mg/dL at 40 ± 20 postnatal hours) (Table). Indications for phototherapy were present in the 3 neonates with clinically jaundiced G-6-PD deficiency, all of whom responded to phototherapy. It is of note, however, that in the control group, 1 newborn (breastfeeding, birth weight 4.3 kg, O-B heterospecific, direct antiglobulin test–negative) was readmitted at age 144 hours with an STB of 24.3 mg/dL and was treated with exchange transfusion. The cause of the hyperbilirubinemia was not definitively determined. The remainder of the control group responded to phototherapy. There were no cases of acute bilirubin encephalopathy.

Table. Factors relating to G-6-PD deficiency in the screened Arab neonates (n = 286)

Variables	G-6-PD deficiency	G-6-PD normal
Number of newborns, n (%)	10 (3.5%)	276
G-6-PD enzyme activity, U/gHb, mean ± SD	0.58 ± 0.69	18.6 ± 2.7
G-6-PD enzyme activity, U/gHb, range	0.09-2.31	11.4-27.4
Clinically significant jaundice (STB >75th percentile), n (%)	3 (30)*	24 (8.7)

*Relative risk, 3.45 (95% CI, 1.24-9.58); $P = .02$.