

## GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY AND NEONATAL JAUNDICE IN AL-HOFUF AREA

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common red cell enzyme abnormality associated with hemolysis.<sup>1</sup> It is also known to be associated with neonatal jaundice, kernicterus and even death.<sup>2</sup> G6PD deficiency is common in the Saudi population, particularly in areas where there is a past or present history of malaria endemicity.<sup>3</sup> The development of malaria parasites highly susceptible to oxidative damage is probably impeded by an excess of oxidant radicals in G6PD deficient cells.<sup>4</sup>

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.<sup>5</sup> 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.<sup>6</sup>

Although the frequency of G6PD deficiency in the Al-Hofuf area is known,<sup>7</sup> the prevalence, course and severity of neonatal hyperbilirubinemia due to G6PD deficiency is not clear. The objectives of this study were to ascertain the causes of neonatal jaundice in the Al-Hofuf area, to study the pattern of jaundice in G6PD-deficient neonates, and to identify the possible ways of reducing the morbidity associated with neonatal jaundice due to G6PD deficiency.

### Materials and Methods

This study was conducted at King Fahad Hospital in Al-Hofuf in the Eastern Province of Saudi Arabia. The hospital is considered the only referral center for the area. Approximately 10,000 infants are delivered each year. The practice at this institution is to discharge newborn infants with their mothers at about 24 hours of age. Those readmitted for jaundice are admitted to the nursery if less than 48 hours of age and to the pediatric ward if older.

The usual work-up for neonatal jaundice in our hospital includes a complete blood count, blood smear for red cell

morphology, blood groups of mother and infant, Coombs' test, total serum bilirubin and G6PD screening test. G6PD activity is measured by the fluorescent spot method<sup>8</sup> (Boehringer Mannheim GmGH, West Germany), using 1 mL of whole blood collected in an EDTA tube.

The practice in this institution is to initiate phototherapy for term infants at a serum bilirubin level of about 255  $\mu\text{mol/L}$ . Depending on the age and clinical status, exchange blood transfusion is undertaken at 340 to 425  $\mu\text{mol/L}$ . Lower values are used for preterms.

The medical records of all neonates admitted with jaundice to the pediatric ward over the 12 months from May 1996 to May 1997 were reviewed. The causes of jaundice were identified according to the final diagnosis written by the treating pediatrician. Infants with proven G6PD deficiency were selected and studied further. Data obtained for each infant included the gestational age, sex, nationality, weight, age at admission and the age at onset of jaundice. The hemoglobin, reticulocyte count, blood groups, Coombs' test, serum bilirubin on admission and subsequently, were reviewed. The type of treatment and the length of hospital stay were recorded.

### Results

Over the study period, a total of 4388 children were admitted to the pediatric ward. Of these, 365 were neonates and 218 admissions were for neonatal jaundice. Four patients were excluded from the study as their data were inadequate for analysis, because they were discharged against medical advice shortly after admission. Three neonates were admitted twice for jaundice. The total number of neonates admitted for hyperbilirubinemia was 211, representing 5% of the total admissions to the pediatric ward. Approximately 92% of the total admissions were Saudis, 97% were full-term deliveries, and 64% were males and 36% were females.

Table 1 shows the causes of hyperbilirubinemia. Sixty-four patients (30.3%) were G6PD-deficient and 134 (63.5%) were normal. The results of 13 infants (6.2%) could not be traced. Two G6PD-deficient infants were admitted twice. Fifty-two of the G6PD-deficient infants were males and 12 (19%) were females. Sixty-three were Saudis. Sixty were term deliveries, and four were preterm.

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Six weighed below 2500 grams, two weighed more than 4000 grams and 56 (87.5%) weighed between 2500 and 4000 grams. Forty-six (72%) were admitted in the first week of life, 14 (22%) in the second, three in the third, and one in the fourth (Figure 1).

In 42 of the G6PD-deficient infants (66%), the onset of jaundice was on the second day of life (Table 2). Fifty-one had admission bilirubin levels of greater than 255  $\mu\text{mol/L}$ , with 33 having levels of more than 340  $\mu\text{mol/L}$ . Fifteen had bilirubin levels exceeding 425  $\mu\text{mol/L}$  (Table 3). The admission hemoglobin results were available in 59 patients. Fifty-two had hemoglobin levels of more than 12 g/dL, 33 (56%) had levels of more than 14 g/dL, and seven had levels of less than 12 g/dL. The reticulocyte counts were available for 41 infants. Sixteen had counts less than 5%, 24 between 5% and 10%, with one over 10%.

All the infants required phototherapy. Sixty received phototherapy for a week or less, and four for more than a week. Ten (16%) required double-volume exchange blood transfusion (7 were exchanged once and 3 were exchanged twice). Twenty-three (36%) were hospitalized for three days or less, 30 (47%) for 4 to 7 days, and 11 (17%) remained hospitalized for more than a week.

### Discussion

The association between G6PD deficiency with severe neonatal jaundice and kernicterus was first described in 1960.<sup>9</sup> The overall frequency of G6PD deficiency in the Al-Hofuf area is estimated at 0.2325 and 0.1250 in males and females, respectively.<sup>7</sup> G6PD-Mediterranean, associated with severe clinical manifestations, is the most common G6PD-deficient variant in the Eastern Province.<sup>10</sup> G6PD-Aures, associated with significant neonatal hyperbilirubinemia, has been reported recently in Saudi infants.<sup>11</sup>

In this study, the cause of jaundice could not be determined in 51% of the cases. Some of these cases were probably due to physiological jaundice. Others can be considered as nonspecific neonatal jaundice.<sup>2</sup> It is also possible that some could have been G6PD deficient with normal levels during hemolysis. Repeating the G6PD screen could have identified these individuals. Thirty percent of neonates admitted with jaundice were G6PD deficient. More than half of these had admission bilirubin levels of more than 340  $\mu\text{mol/L}$ . As neonates of less than 48 hours of age were not included in this study, the prevalence and severity of hyperbilirubinemia may be underestimated.

Nineteen percent of the G6PD-deficient infants were females. This is more than was observed by Kaplan and Abramov, who reported it to be 14%.<sup>12</sup> This high incidence of G6PD deficiency in females may be in part due to the high rate of consanguinity among the Saudi population,<sup>13</sup> leading to increased numbers of female homozygotes. In addition, the high frequency of inactivation of the normal

TABLE 1. *The causes of jaundice.*

Cause	Number (%)
G6PD deficiency	64 (30.3)
ABO incompatibility	21 (10)
Breast milk	11 (5.2)
Sepsis	4 (1.9)
Rh incompatibility	2 (0.9)
Other (elliptocytosis)	1 (0.5)
Undetermined	108 (51.2)
Total	211 (100)

TABLE 2. *The age at onset of jaundice in G6PD-deficient infants.*

Age in days	Number (%)
1	4 (6.3)
2	42 (65.5)
3	13 (20.3)
4	3 (4.7)
5	1 (1.6)
6	1 (1.6)
7	0

TABLE 3. *The serum bilirubin in G6PD-deficient infants upon admission.*

$\mu\text{mol/L}$	Number (%)
<170	3 (4.7)
170-255	10 (15.6)
256-340	18 (28.1)
341-425	18 (28.1)
426-510	10 (15.6)
>510	5 (7.8)

X-chromosome in female heterozygotes can also lead to disturbance of the Hardy-Weinberg equilibrium.<sup>7,14</sup>

In the majority of G6PD-deficient infants, the onset of jaundice, as in physiological jaundice, was from the second day onwards. The age at admission had two peaks, the first on the fourth day of life and the second on the seventh. G6PD-deficient infants are known to have bimodal peaks of maximum serum bilirubin concentrations.<sup>2</sup> It is also known that the earlier a hemolytic episode, the more pronounced the elevation of serum bilirubin.<sup>2</sup> The course of hyperbilirubinemia may therefore be anticipated.

More than half of the G6PD-deficient infants had a hemoglobin level of more than 14.0 g/dL, with 88% having levels more than 12.0 g/dL. Reticulocyte counts were less than 10% except in one infant. These findings do not suggest significant hemolysis as a cause of jaundice in these infants, which is a common observation in G6PD-deficient neonates.<sup>15</sup> There is evidence that in the newborn period, following exposure to hemolytic agents, jaundice rather than anemia predominates in the clinical presentation.<sup>2</sup> Exposure of the newborn infant to a hemolytic agent may be direct or indirect, transplacentally, via breast milk, inhalation, or absorption through the skin. Moreover, severe neonatal jaundice develops apparently spontaneously in a fraction of G6PD-deficient infants.<sup>2,16</sup>

In our study, 51% of the G6PD-deficient infants had serum bilirubin levels exceeding 340  $\mu\text{mol/L}$  at the time of

admission and 16% underwent exchange blood transfusion. Early neonatal discharge along with similarity to physiologic jaundice and lack of parental knowledge, lead to late presentation and delayed treatment of these G6PD-deficient neonates.<sup>17</sup> We recommend that cord blood G6PD screening be considered in high-risk populations such as ours.<sup>18</sup> This would help in identifying G6PD-deficient newborn infants who might require a longer hospital stay after birth, with closer monitoring of their serum bilirubin before and after discharge. On the other hand, those infants with normal G6PD activity might be discharged earlier and have regular routine follow-up.<sup>19,20</sup> In addition, health education is needed to increase the awareness of health professionals and the public about this problem.<sup>21</sup>

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