Severe neonatal hyperbilirubinemia in the southeast region of Turkey

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Background/aim: Severe neonatal hyperbilirubinemia is an important cause of morbidity and mortality in developing countries. The aim was to assess etiologic reasons for development of severe hyperbilirubinemia and define risk factors for exchange transfusion and acute bilirubin encephalopathy (ABE) in Şanlıurfa located in the southeast region of Turkey.

Materials and methods: An observational cohort study included 115 infants with ≥35 weeks of gestation admitted with diagnosis of severe hyperbilirubinemia in a period of 18 months. Potential risk factors associated with exchange transfusion and development of ABE were analyzed.

Results: Among 115 infants, 67 (58.3%) received exchange transfusion and 45 (39.1%) developed ABE. Rh isoimmunization (OR: 24.6, 95% CI = 2.2–271, P = 0.009), glucose-6-phosphate dehydrogenase deficiency (G6PD) (OR: 21.1, 95% CI = 1.8–238.4, P = 0.01), early discharge (OR: 14.4, 95% CI = 4.2–48.9, P = 0.001), and male sex (OR: 4.3, 95% CI = 1.3–14.1, P = 0.02) were independently associated with an increased risk for exchange transfusion. Being a refugee (OR: 6.8, 95% CI = 1.8–25.8, P = 0.005) and G6PD deficiency (OR: 9.9, 95% CI = 1.3–71.9, P = 0.02) were associated with development of ABE.

Conclusion: Early discharge, Rh isoimmunization, and G6PD deficiency are significant risk factors for severe hyperbilirubinemia and exchange transfusion. Prevention of early hospital discharges, family education to increase awareness for hazardous effects of hyperbilirubinemia, and early follow-up visits after discharge would reduce the disease burden.

Key words: Neonatal hyperbilirubinemia, exchange transfusion, bilirubin encephalopathy, neurotoxicity, glucose-6-phosphate dehydrogenase deficiency

1. Introduction
Neonatal jaundice is usually a physiologic condition and is one of the most common causes of hospital admissions in otherwise healthy newborns [1,2]. However, in some infants the condition can be severe enough to cause serious hyperbilirubinemia progressing to acute bilirubin encephalopathy (ABE) and kernicterus [3–6].

With implementation of standardized and harmonized guidelines for management of hyperbilirubinemia, the incidence of severe hyperbilirubinemia has decreased markedly in high income countries (HICs) [1,7–11]. However, it is still an important problem resulting in significant disability and mortality in low and middle income countries (LMICs) [12–15]. The incidence of severe neonatal hyperbilirubinemia and ABE in Turkey is reported to be higher than in HICs and lower than in LMICs [16]. Şanlıurfa, located in the southeast region of Turkey, has the highest birth rate in Turkey with 4.29 children per year.1 Also, it is one of the cities harboring the highest Syrian refugee population, composing 23.6% of its population.2

The aim of this study was to assess etiologic reasons for the development of severe hyperbilirubinemia and define risk factors for exchange transfusion and ABE in Şanlıurfa.

2. Material and methods
This single-center observational cohort study was conducted at Şanlıurfa Training and Research Hospital between June 2017 and December 2018. Sixty thousand live births occur per year in Şanlıurfa. About 50% of all

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births take place in the Şanlıurfa Training and Research Hospital. The neonatal intensive care unit (NICU) of the hospital is the most important third level referral center with 107 bed capacity in the city. Another third level referral center for severe hyperbilirubinemia cases is the NICU of Harran University. According to the data obtained from the NICU of Harran University, about 30% of severe hyperbilirubinemia cases were admitted to their unit. Infants with severe hyperbilirubinemia are mostly referred to the NICU of Şanlıurfa Training and Research Hospital from the city center and districts and the unit serves about 2/3 of all severe hyperbilirubinemia cases in the whole city. Infants with ≥35 weeks of gestation, postnatal age of ≤14 days, and diagnosis of severe hyperbilirubinemia at admission, defined as serum bilirubin level at or above the exchange transfusion threshold according to the guidelines of the American Academy of Pediatrics (AAP) for exchange transfusion, were included in the study [7]. Infants born at <35 weeks of gestation and with congenital/ chromosomal anomalies were excluded.

The study was approved by the Harran University Institutional Ethics Committee (No: 74059997-050-04.04/05.07.18). Informed parental consent was obtained for each infant before the enrollment.

Patients were managed according to unit protocols based on the recommendations of the AAP for management of hyperbilirubinemia in infants with 35 or more weeks of gestation [7]. Accordingly, infants having findings of acute bilirubin encephalopathy or serum bilirubin levels that were 5 mg/dL above the exchange transfusion threshold underwent immediate exchange transfusion. For infants whose total serum bilirubin level was at or slightly above the exchange transfusion threshold, exchange transfusion was performed if serum bilirubin concentrations remained above the threshold levels after 3–4 h of intensive phototherapy. Hemolytic jaundice was defined as presence of anemia, hyperbilirubinemia, and hemolysis findings in peripheral smear. Direct Coombs test positivity was accepted as a supportive finding for hemolytic jaundice. Intravenous immunoglobulin (IVIG) was used in infants having hemolytic findings with direct Coombs positivity and bilirubin levels at exchange transfusion threshold. A neurologic evaluation was performed at admission and in the first 6 h of admission. Bilirubin induced neurological dysfunction score (BIND) was used to evaluate ABE [17]. According to the BIND score, ABE was graded as mild, moderate, or severe.

Birth weight, gestational age, sex, delivery type, maternal age, parity, early discharge, being a refugee, postnatal age of admission, postnatal age of exchange transfusion, weight loss on admission, total bilirubin level (mg/dL), bilirubin/albumin ratio, defined cause of hyperbilirubinemia, ABO incompatibility, Rh isoimmunization, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and sepsis were recorded.

G6PD activity was measured quantitatively by spectrophotometry with the cobas c501 analyzer (F. Hoffmann-La Roche Ltd., USA).

Early discharge was defined as discharge at 12 h after spontaneous vaginal delivery and discharge at 24 h after cesarean section (CS).

Sepsis was defined as presence of clinical signs of sepsis associated with (1) a positive blood culture and/or (2) an elevated c-reactive protein level, total leukocyte count of >25,000/mm³ or <5000/mm³, an immature to total neutrophil ratio of >0.2, or a band count of >10%.

3. Results

Between June 2017 and December 2018, there were about 90,000 live births in Şanlıurfa. In the study period, 3200 infants were hospitalized in the NICU of Şanlıurfa Training and Research Hospital. Out of these, 115 (3.6%) suffered from severe hyperbilirubinemia. The characteristics of the studied infants are presented in Table 1. The infants’ mean birth weight was 2935 ± 442 g and median gestational age was 38 (35–39) weeks. In total 57 (49.6%) infants were males and 42 (36.5%) infants were delivered by CS. The median postnatal age at admission was 5 (1–14) days. The mean total serum bilirubin concentration at admission was 28.2 ± 7.9 mg/dL. Fifty infants (43.5%) had a bilirubin concentration above 30 mg/dL at admission. The mean bilirubin/albumin ratio was 7.9 ± 2.2 and in 78 (67.8%) infants it was >6.8, while in 45 (39.1%) infants it was >8.6. The mean maternal age was 27.3 ± 6.5 and 20 (17.4%) women gave birth to their first child. Sixty-three (54.8%)
infants were discharged early and 32 (27.8%) infants were Syrian refugees. The most common etiology for severe hyperbilirubinemia was hemolytic reasons (n = 51) (44.3%) with ABO blood incompatibility being the leading cause (n = 35) (30.4%). Out of the 115 severe hyperbilirubinemia cases, 24 were due to improper feeding and dehydration (20.9%) and 15 were due to G6PD deficiency (13%) as the second and third most common reasons, respectively (Table 1). In 17.4% of infants (n = 20) the underlying etiology was not defined. Sepsis and galactosemia were other rare etiologies.

Exchange transfusion was performed for 67 patients (58.3%). The median postnatal age for exchange transfusion was 100 (24–244) h. The descriptive data of infants with and without exchange transfusion are presented in Table 2. Hemolytic causes such as ABO blood group incompatibility, Rh isoimmunization, and subgroup incompatibility constituted the most common etiologic reasons for exchange transfusion (n = 28) (41.8%). The second most common etiology was G6PD deficiency in the exchange transfusion group. The frequencies of G6PD deficiency (14 (20.9%) vs. 1 (2.1%), P = 0.02) and Rh isoimmunization (12 (17.9%) vs. 1 (2.1%), P = 0.008) were significantly higher in the exchange transfusion group when compared to infants who were not transfused (Table 2). In multiple logistic regression analysis, male sex (OR: 4.3, 95% CI = 1.3–14.1, P = 0.02), early discharge (OR: 14.4, 95% CI = 4.2–48.9, P ≤ 0.001), G6PD deficiency (OR: 21.1, 95% CI = 1.8–238.4, P = 0.01), and Rh isoimmunization (OR: 24.6, 95% CI = 2.2–271, P = 0.009) were found to be independently associated with an increased risk for exchange transfusion (Table 3).

Acute bilirubin encephalopathy developed in 45 (39.1%) infants. Eight infants had stage I, 28 infants had stage II, and 9 infants had stage III ABE. All infants with ABE underwent exchange transfusion except 2 infants. Characteristics of infants with and without ABE are summarized in Table 4. The most common etiologic reason for severe hyperbilirubinemia was G6PD deficiency (13 (28.9%) vs. 2 (2.9%), P ≤ 0.001) in infants with ABE. The second most common reason was Rh isoimmunization (8 (17.8%) vs. 5 (7.1%), P = 0.08) (Table 4). Multiple logistic regression analysis revealed that being a refugee (OR: 6.8, 95% CI = 1.8–25.8, P = 0.005) and G6PD deficiency (OR: 9.9, 95% CI = 1.3–71.9, P = 0.02) were independently associated with development of ABE in infants with severe hyperbilirubinemia (Table 5).

The mortality rate was 7% in the whole group; 87.5% of them were male and 50% were refugees. The mean postnatal day of admission was 3.5 days. The etiologic reasons were Rh isoimmunization in 3 (37.5%), G6PD deficiency in 3 (37.5%), ABO incompatibility in 1 (12.5%), and subgroup incompatibility in 1 (12.5%) of them. Exchange transfusion was performed for all 8 infants. All of them died within 48 h of admission. In all 8 infants c-reactive protein and total leukocyte values were within normal ranges and blood cultures were negative; correspondingly, the diagnosis of sepsis was excluded. Evaluations for metabolic diseases with tandem mass spectrometry and blood and urine amino acid analysis also revealed no significant pathology. All infants had severe ABE and 6 out of 8 infants were endotracheally intubated due to irregular and apneic breathing pattern at time of admission.

4. Discussion
In our study, more than half of the infants having severe hyperbilirubinemia underwent exchange transfusion and more than one-third developed ABE at admission. The most common underlying etiology for severe hyperbilirubinemia and exchange transfusion was found to be hemolytic reasons, consistent with the literature. A significant association between birth weight, male sex, early discharge, Rh isoimmunization, G6PD deficiency,
and increased risk of exchange transfusion was observed. While G6PD deficiency was the third most common etiologic reason in the whole population, it was the second most common underlying etiology for exchange transfusion cases. Strikingly, G6PD deficiency was the leading cause for development of ABE.

In the study period 90 thousand live births took place in Şanlıurfa. On the basis of the knowledge that 2/3 of all cases of severe hyperbilirubinemia were hospitalized in the NICU of Şanlıurfa Training and Research Hospital, the prevalence of severe hyperbilirubinemia was estimated to be 191/100,000 live births. The prevalence of ABE could be estimated as 71/100,000 live births. The incidence of severe hyperbilirubinemia is reported to be 7.1–45/100,000 live births in westernized HICs [10,11,18,19]. The situation is much worse in LMICs with reported frequencies of ABE of up to 1749/100,000 live births [13,20].

Similar to the results of the Turkish Neonatal Jaundice Registry, the most common risk factors for development of severe neonatal jaundice were hemolytic reasons, improper feeding, and dehydration. The most common hemolytic etiology was ABO blood group incompatibility in accordance with the literature [11,13,16]. However, Rh isoimmunization and G6PD deficiency caused more severe hyperbilirubinemia, as seen in our results. In previous research, hemolytic disease or direct Coombs test positivity was associated with higher risk of ABE and permanent neurological abnormalities [20–23]. The Child Health Epidemiology Reference Group's modeling study estimated that 78% of cases of extreme hyperbilirubinemia are attributable to Rh isoimmunization, 6% to G6PD deficiency, and 17% to other etiologies, and 80% of
affected infants are in countries with a mortality rate of >15/1000 live births. The model expected no severe hyperbilirubinemia due to Rh disease in HIC [24]. The Turkish Neonatal Registry reported the frequency of Rh disease as 5.4 % of all admissions due to hyperbilirubinemia [16]. Rh isoimmunization constituted 11.3% of all severe hyperbilirubinemia cases in our study population but its frequency increased to about 18% among infants receiving exchange transfusion and developing ABE.

G6PD deficiency leads to hyperbilirubinemia by acute hemolysis and mainly by decreased bilirubin conjugation. Most of the time G6PD deficiency causes rapidly rising severe hyperbilirubinemia [25,26]. Kilicdag et al. [27] reported a significant correlation between the severity of hyperbilirubinemia and G6PD activity. Since it is an X-linked disease, males are more frequently affected. G6PD deficiency was observed as 0.5% in the Turkish Neonatal Registry data [16], but in severe hyperbilirubinemia and ABE cases its frequency increases. The disease is mostly prevalent in Mediterranean and Middle East regions of the world. Şanlıurfa, by both its location and for harboring Syrian refugees from the Middle East, is expected to have a high prevalence of G6PD deficiency.

The rate of CS delivery was not high in our population (36.5%), contrary to the report of Turkish Neonatal Jaundice Registry [16]. However, the rate of early discharge was strikingly high. This can be attributed to low education level, long established attitudes, the desire of the population for early discharge, and the inevitable tendency of health professionals to allow early discharge because of overcrowding in the hospitals in this region of Turkey. Farhat et al. [28] reported that early discharge before 48 h increased the risk of readmission due to hyperbilirubinemia. Similarly, Bayoumi et al. [29] reported higher neonatal readmissions mainly due to hyperbilirubinemia in newborns discharged 24 h after CS

Table 4. Demographic and clinical characteristics of infants with and without ABE.

<table>
<thead>
<tr>
<th></th>
<th>With ABE n = 45</th>
<th>Without ABE n = 70</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>2899 ± 509</td>
<td>2958 ± 399</td>
<td>0.51</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38 (35–39)</td>
<td>38 (35–39)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>25 (55.6)</td>
<td>32 (45.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>15 (33.3)</td>
<td>27 (38.6)</td>
<td>0.56</td>
</tr>
<tr>
<td>Maternal age, years</td>
<td>26.9 ± 6.4</td>
<td>27.7 ± 6.5</td>
<td>0.55</td>
</tr>
<tr>
<td>Parity, n</td>
<td>3 (1–12)</td>
<td>3 (1–11)</td>
<td>0.23</td>
</tr>
<tr>
<td>Postnatal age of admission, days</td>
<td>4 (1–11)</td>
<td>5 (1–14)</td>
<td>0.48</td>
</tr>
<tr>
<td>Early discharge, n (%)</td>
<td>34 (75.6)</td>
<td>29 (41.4)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Being refugee, n (%)</td>
<td>17 (37.8)</td>
<td>15 (21.4)</td>
<td>0.056</td>
</tr>
<tr>
<td>Total serum bilirubin, mg/dL</td>
<td>33.9 ± 6.6</td>
<td>24.6 ± 6.5</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bilirubin/albumin, (ratio)</td>
<td>9.6 ± 1.9</td>
<td>6.9 ± 1.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Bilirubin/albumin &gt;8.6</td>
<td>34 (75.6)</td>
<td>11 (15.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>G6PD deficiency, n (%)</td>
<td>13 (28.9)</td>
<td>2 (2.9)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Rh isoimmunization, n (%)</td>
<td>8 (17.8)</td>
<td>5 (7.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>ABO incompatibility, n (%)</td>
<td>6 (13.3)</td>
<td>29 (41.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>8 (17.8)</td>
<td>0 (0)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

ABE: Acute bilirubin encephalopathy, G6PD: Glucose 6-phosphate dehydrogenase deficiency.

Table 5. Multivariate analysis of risk factors associated with development of ABE.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>G6PD deficiency</td>
<td>9.9</td>
<td>1.3–71.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Early discharge</td>
<td>2.5</td>
<td>0.8–7.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Being refugee</td>
<td>6.8</td>
<td>1.8–25.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Rh isoimmunization</td>
<td>1.7</td>
<td>0.6–4.9</td>
<td>0.09</td>
</tr>
</tbody>
</table>

ABE: Acute bilirubin encephalopathy, G6PD: Glucose 6-phosphate dehydrogenase deficiency.
delivery. In westernized countries, early hospital discharge was also associated with increased rate of readmissions due to severe hyperbilirubinemia [30,31]. In our study population, a significant percentage of newborns were discharged even without one night stay in hospital. The median day of admission was about 5 days, in parallel with previous publications [11,14]. Mean day of admission for the infants who died due to severe hyperbilirubinemia was 3.5 days. According to the report of Turkish Neonatal Registry, median age at admission was 3 days and their mean peak bilirubin concentration was around 17 mg/dL, which was lower than in our population [16]. Thus, with follow-up visits on the third day or just before the third day, we would be able to diagnose hyperbilirubinemia early and treat hyperbilirubinemia cases before they increase to severe levels. Once the bilirubin level is elevated above 30 mg/dL or bilirubin/albumin ratio is >8.6, advanced ABE that benefits little from therapy is often present and mortality is increased. The American Academy of Pediatrics and Canadian Pediatric Society recommends follow-up for newborns 48–72 h after hospital discharge [7,32]. Prevention of early discharges and, if it is inevitable, predischarge bilirubin measurement as suggested by Bhutani et al. [33], and follow-up 48 h after discharge or on the postnatal third day of life would be strategies to decrease severe hyperbilirubinemia cases.

The number of Syrian refugee births is increasing every year in Turkey [34,35]. Şanlıurfa, located on the southeastern border of Turkey, hosts a large refugee population composing about one-fourth of its population. Health care for these refugees is a major problem in this region of country. In our study, being a refugee was observed as an independent risk factor for development of ABE. Underlying reasons for severe hyperbilirubinemia were similar among Syrian refugees and Turkish citizens. Refugees utilize health care facilities offered by the Turkish government free of charge. However, most of them do not speak Turkish and have communication problems. Early hospital discharges combined with communication problems lead to inadequate feeding education and information about neonatal jaundice and the importance of early neonatal follow-up. Most of the refugee mothers also do not prefer to breastfeed because of sociocultural features. Another finding is that, although statistically not significant, the mean maternal age of Syrian refugees was younger than that of Turkish women. We think that all these conditions contribute to the development of severe hyperbilirubinemia and ABE in refugee infants.

One of the limitations of the study was that not all patients with severe hyperbilirubinemia were admitted to hospitals and health care facilities. Some superstitions and orientation towards nonmedical treatment options prevent families from seeking medical care. Therefore, the true incidence of severe hyperbilirubinemia and deaths due to this were probably underestimated in Şanlıurfa.

Another limitation was that the incidence of kernicterus and permanent neurologic sequelae due to bilirubin induced neurotoxicity were not known.

In conclusion, severe hyperbilirubinemia and ABE are still important but largely preventable conditions causing significant disability and mortality. Early discharge, Rh isoimmunization, and G6PD deficiency are significantly associated with exchange transfusion and development of ABE. During routine postnatal care, predischarge bilirubin measurements, blood group and Rh typing, and G6PD screening programs would be helpful to identify at-risk infants. Strategies to prevent early hospital discharges, defining at-risk infants before discharge, maternal education for breastfeeding, family education to gain insight into the hazardous effects of severe hyperbilirubinemia, early follow-up visits after discharge, and prompt and effective treatment of recognized cases with phototherapy would reduce undesirable and permanent morbidity and mortality due to hyperbilirubinemia. In addition, being a refugee is a special risk factor for development of ABE and special considerations should be made for these infants.

Conflicts of interest
The authors declare no conflict of interest. No funding was received for this manuscript.

References


