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Complications of Neonatal Jaundice and the Predisposing Factors in Newborns

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ABSTRACT

BACKGROUND AND OBJECTIVE: Hyperbilirubinemia is one of the most common problems during the neonatal period. Despite the severe complications of jaundice, no reliable data is available regarding the prevalence of acute and chronic complications of jaundice and the predisposing factors in our community. Therefore, this study aimed to determine the complications of neonatal jaundice and the predisposing factors in neonates.

METHODS: This cross-sectional study was performed on icteric, term newborns with bilirubin level higher than 20 mg/dl, referring to Ghaem Hospital during 2003-2013. After history taking and physical examinations, developmental status of infants was followed within six and twelve months after birth, using Denver Developmental Screening Test-II. The newborns were divided into two groups, based on the occurrence or non-occurrence of complications (e.g., acute or chronic kernicterus, auditory disorders and developmental disorders). Afterwards, predisposing factors for these complications were evaluated.

FINDINGS Complications of jaundice were reported in 143 (13.37%) out of 1069 neonates. The two groups were not significantly different in terms of variables such as neonatal age and gender or maternal age. However, there was a significant difference between the children with and withod complication regarding treatment modality and mean total serum bilirubin level (27 mg/dl vs. 32 mg/dl) ($p<0.05$). The predisposing factors for neonatal complications were as follows: idiopathic jaundice (30%), ABO incompatibility (18%), Rh incompatibility (14.8%), G6PD deficiency (12.6%) and sepsis (3.3%).

CONCLUSION: Our findings showed that ABO incompatibility, Rh incompatibility and G6PD deficiency were the most common risk factors for jaundice, followed by idiopathic jaundice.

KEY WORDS: Kernicterus, Developmental Disorders, Hearing Loss, Jaundice, Hemolysis.

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Introduction

Hyperbilirubinemia is one of the most common and major problems during the neonatal period (1). In 8-11% of cases, the bilirubin level rises to > 95% percentile, indicating the need for further evaluations and treatment. Kernicterus is a serious complication, associated with jaundice, which may lead to lifetime disabilities in the absence of proper treatment (2-4). Diagnosis, treatment and follow-up of infants are the main challenges of neonatology. Prevention of hyperbilirubinemia and its complications, early diagnosis and proper treatment may decrease problems in icteric neonates. Today, phototherapy is the most effective and most common modality for the treatment of neonatal jaundice. However, in treatment-resistant infants, cases with bilirubin level exceeding the “high-risk” zone and those presenting with kernicterus, blood transfusion, combined with phototherapy, is regarded as the treatment of choice (4). Bilirubin encephalopathy or kernicterus is a bilirubin-induced brain dysfunction. It is a preventable neurological syndrome with

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adverse effects due to deposition of non-conjugated bilirubin in the basal ganglia and brainstem (4,5). Normally, the symptoms of kernicterus are manifested 2-5 days after birth in term infants and 7 days after birth in preterm newborns. Hyperbilirubinemia can lead to kernicterus at any time during infancy. Initial symptoms of kernicterus include lethargy, poor feeding and loss of Moro reflexes, followed by infant's extreme weakness, decreased deep tendon reflexes, respiratory distress, opisthotonos (occasional), bulging fontanelle, abnormal movements of the face and extremities and shrill cry. Most infants, who experience these severe neurological symptoms, die early, and those who survive suffer from extreme damages. Patients with kernicterus appear normal within 2-3 months of age, whereas opisthotonos, muscular rigidity, abnormal movements and recurrent seizures occur later in the first year of life. Opisthotonos and seizures normally stop in the second year of life, whereas irregular and involuntary muscular rigidity and hypotonia increase in some newborns. At 3 years of age, full neurological symptoms of kernicterus including bilateral athetosis with involuntary muscular spasms, extrapyramidal symptoms, seizure, mental retardation, dysarthria, high frequency hearing loss, strabismus and eye movement abnormalities appear. Mild and moderate neuromuscular imbalance, deafness and mild cerebral dysfunction (single or multiple) are observed in children with mild kernicterus, which may not be recognizable before school years (5). According to pathological criteria, kernicterus is seen in one-third of untreated infants (at all gestational ages) with hemolytic anemia and bilirubin level higher than 20-30 mg/dl. The incidence of kernicterus has been estimated at 2-16%, based on the autopsy results in premature infants with hyperbilirubinemia. Also, delays in motor skills are observed in term infants at six months of age with a history of hyperbilirubinemia (6). In countries without any formal programs for the prevention of kernicterus, bilirubin toxicity is considered as one of the major problems of neonatal health. According to many reports, presentation of the symptoms of neuropathy, without the usual signs of kernicterus, emphasizes the need for greater awareness and understanding of the causes and symptoms of this disorder (4). According to a study by Gordon, neonatal jaundice leads to the high prevalence of neurological and developmental disorders in infants, aged 18-32 months. Also, the mentioned study showed that approximately 4.3% of infants with jaundice cannot normally sit or stand (7). Despite the reduced incidence of complications associated with hyperbilirubinemia in developed countries, blood transfusion is performed in three newborns weekly in some health centers. In fact, diagnosis and appropriate treatment of newborns are not performed promptly, leading to widespread complications of jaundice in newborns. A wide range of complications are associated with jaundice. Despite the occurrence of these severe complications, no reliable data are available on the occurrence of jaundice complications and the predisposing factors in our community. Considering the high prevalence of jaundice and lack of appropriate preventive programs, we aimed to determine severe complications of hyperbilirubinemia (higher than 20 mg/dl) and the risk factors in neonates.

Methods

This cross-sectional study was performed on icteric term newborns with bilirubin level higher than 20 mg/dl. The study sample included infants admitted to the neonatal intensive care unit (NICU) of Ghaem Hospital of Mashhad, located in northeast of Iran in 2003-2013. In this study, 1069 neonates older than 2 days of age, referring to the pediatric ward, NICU or emergency ward of Ghaem Hospital, were selected via census sampling (7). The patients were assessed after obtaining consent forms from the parents. The exclusion criteria were as follows: 1) premature infants; 2) weighing less than 2.5 kg; 3) multiple anomalies, chromosomal diseases and asphyxia; 4) nn-evaluated newborns; 5) infants discharged before assessment; and 6) neonates who could not be followed-up. After the study was approved by the ethics committee of Mashhad University of Medical Sciences, data were gathered, using a questionnaire. This questionnaire consisted of three sections: maternal demographic characteristics, neonatal information and Denver Developmental Screening Test-II (DDST-II). First, all infants were examined and the test results were recorded. Also, maternal and neonatal histories were obtained. Characteristics such as age, sex, birth weight, gestational age and Apgar score were recorded. Also, in history taking, maternal age, birth defects, the required length of hospital stay or blood transfusion in the previous infant and mother's

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blood type were recorded. Bilirubin level, hematocrit, direct and indirect Coombs' tests, reticulocyte count, glucose-6-phosphate dehydrogenase (G6PD), maternal and fetal blood types and complete blood count were recorded for assessing the newborns. Rh incompatibility was highlighted in case maternal and neonatal blood groups were Rh negative and Rh positive, respectively, direct Coombs' test results were positive or a decrease in hematocrit level was reported. ABO incompatibility was confirmed if the mother's blood type was O^+ (Rh+) and the neonate's blood type was A or B. Also, at least two of the following factors needed to be met: 1) jaundice on the first day; 2) positive direct Coombs' test results; 3) presence of microspherocytes in the peripheral blood; and 4) positive indirect Coombs' test results. If direct Coombs' test results were positive and no Rh or ABO incompatibility was detected, minor blood incompatibility was identified (7).

G6PD enzyme was measured via point-detection fluorescence. Generally, enzyme activity less than 30% is reported to be insufficient (8). Symptoms of acute kernicterus including lethargy, poor nutrition, lack of Moro reflexes, decreased deep tendon reflexes, opisthotonos, bulging fontanelle, abnormal movements of the face and extremities, shrill cry, seizures, spasms and muscular rigidity were assessed in our study. Chronic symptoms of kernicterus have been defined as bilateral athetosis, along with involuntary muscular spasms, extrapyramidal symptoms, seizure, mental retardation, dysarthria, sensorineural hearing loss and eye movement abnormalities (9).

Also, hidden kernicterus or neurological dysfunction due to kernicterus was defined as neuromotor impairment, without the classic symptoms of kernicterus (10). The newborns with symptoms of acute kernicterus were allocated to the case group. Follow-up was performed, using DDST-II within 6 and 12 months after birth. This questionnaire was completed by asking the parents about the infants' status and examination by pediatricians. DDST-II is a test for screening cognitive and behavioral problems in pre-school children, assessing four general dimensions: personal-social, fine motor adaptive, language, and gross motor. Disorder in each of these dimensions is indicative of developmental delay. Mild and moderate developmental delays are defined as disorders in one and two dimensions, respectively. Also, severe developmental delay was introduced as disorders in three or more dimensions (5). In addition, in our study, all complications of jaundice such as eye symptoms, motor symptoms and hearing impairment were assessed. Newborns with acute and chronic kernicterus, auditory disorders, developmental disorders and abnormal neurological examinations were included in the case group. Newborns without any symptoms of acute and chronic kernicterus, with normal neurological and developmental status, were considered as the group without complications. Data were analyzed using SPSS version 16.5. Independent t-test was used for parametric data and Mann–Whitney test was applied for the evaluation of non-parametric data. Chi-square test was used to analyze the relationship between nominal variables. P-value less than 0.05 was considered statistically significant.

Results

Among 1069 newborns evaluated in this study, 143 icteric cases (13.37%) and 204 newborns without complications were compared. Acute kernicterus, chronic kernicterus, developmental disorders and sensorineural hearing loss were observed in 52, 21, 41 and 29 newborns, respectively. There was no significant difference between the two groups in terms of neonatal age and gender, maternal age, age at the onset of jaundice or weight loss per day. However, there was a significant difference between the two groups in direct Coombs' test results ($p=0.014$), treatment modality ($p=0.001$), mean bilirubin level based on treatment modality and final diagnosis ($p<0.05$) and total serum bilirubin level ($p<0.05$) (table 1). Serum bilirubin level was 32 mg/dl in newborns with complications and 27 mg/dl in newborn without complications (fig 1). Comparison of bilirubin level in sub-groups with complications showed that bilirubin level in newborns with acute and chronic kernicterus was 34.6 and 32.3 mg/dl, respectively. Also, the bilirubin level was estimated at 30.8 and 30.6 mg/dl in newborns with developmental disorders and sensorineural hearing loss, respectively (fig 2). Finally, the most common cause of hyperbilirubinemia in the case group was idiopathic jaundice (30%). ABO incompatibility (18%), Rh incompatibility (14.8%), G6PD deficiency (12.6%) and sepsis (3.3%) were the next most common causes, respectively (fig 3). The mean bilirubin levels in the sub-groups were as follows: idiopathic jaundice (30.8 mg/dl), ABO

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incompatibility (28.2 mg/dl), Rh incompatibility (36.32 mg/dl), G6PD deficiency (39 mg/dl), sepsis (29.16) and infants of diabetic mothers (27.14 mg/dl). The median age at the onset of jaundice in newborns with and without complications was 3 and 2 days, respectively (p=0.460). Also, the median of total serum bilirubin was 32 mg/dl in newborns with complications and 27 mg/dl in newborns without complications (p<0.05).

Table 1. Comparison of demographic characteristics between newborns with and without jaundice complications

Groups / Variables	Without complications Mean±SD	With complications Mean±SD	p-value
Age of the newborn(days)	7±4.2	7±3.8	0.6999
Age of the mother(years)	27±6.9	27.5±6.3	0.302
Direct bilirubin level(mg/dl)	0.7±0.47	1.8±2.5.	<0.05
Hematocrit	45.3±6.9	42.9±8.6	0.284
weight loss per day	1.27±4.5	1.94±7.9	0.555

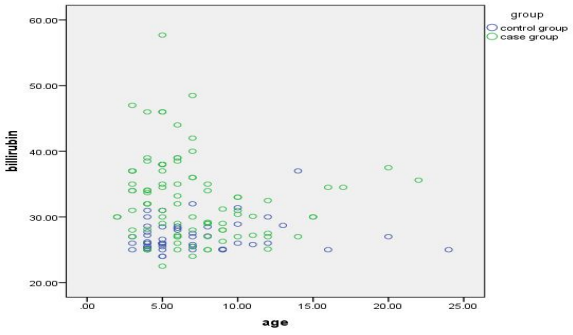


Figure 1. Comparison of serum bilirubin level between newborns with and without complications based on the age at hospital admission

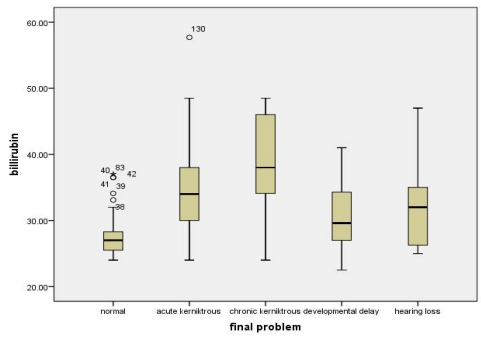


Figure 2. Evaluation of hyperbilirubinemia in the sub-groups of the case group

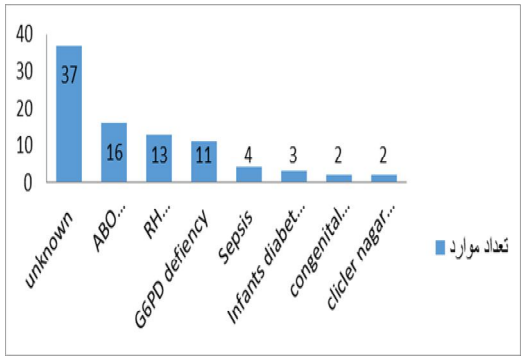


Figure 3. Causes of hyperbilirubinemia complications in the case group

Discussion

Based on the findings of this study, after idiopathic jaundice, ABO incompatibility, Rh incompatibility and G6PD deficiency were the most common causes of severe jaundice leading to serious complications, respectively. Complications of jaundice were observed in 143 (13.37%) out of 1069 term neonates, hospitalized due to bilirubin level higher than 20 mg/dl over the past 10 years; this rate was much higher than the rates reported in other parts of the world. The incidence rates of acute kernicterus, chronic kernicterus and developmental disorders were reported to be 8.4%, 9.1% and 3.8%, respectively. In total, the incidence rate of acute kernicterus ranged between 1.5 and 7% (7, 11). According to a previous study, acute kernicterus was reported in 25 out of 305 neonates, who were admitted to the NICU.

The mean total bilirubin level was 32 mg/dl in patients with kernicterus and 20 mg/dl in other icteric neonates (12). In another study, performed on 795 icteric neonates, the most common causes of kernicterus were blood type incompatibility, iatrogenesis, G6PD deficiency and Rh incompatibility, respectively (4). According to previous research, the incidence rates of acute and chronic kernicterus were estimated at 1 per 49,000 births and 1 per 43,000 births in Canada, respectively. The corresponding rates were reported to be 1 per 100,000 births and 1 per 150,000 births in England, respectively (10, 13, 14). The discrepancy in the incidence rates may be due to differences in the study populations and absence of preventive programs for jaundice. In our study, the incidence rate of kernicterus was higher than other similar research. This may be related to the early discharge of mothers and neonates, lack of attention to the risks of jaundice, use of traditional outpatient treatments and inappropriate phototherapy at home.

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Our findings showed that the mean age of newborns with jaundice, referring to the hospital, was 7 days. This is a clear indication of delayed referral of neonates after the peak risk period (i.e., 4-7 days after birth). According to a review study, severe hyperbilirubinemia and kernicterus could be partially prevented by blood transfusion, although kernicterus was not fully eradicated. Overall, kernicterus is a preventable cause of cerebral palsy and can be prevented using a proper treatment plan. Therefore, evaluation of the risk factors of kernicterus and appropriate interventions with respect to the risk factors are the main solutions for kernicterus prevention (13). As the present study indicated, the importance of jaundice has not been well explained to the community, healthcare teams, nurses, midwives and even physicians. This calls for reforms in public education, student training and healthcare systems. According to our study, delayed referral is one of the major causes contributing to the high incidence of kernicterus complications, since duration of jaundice is an important risk factor for the occurrence of these complications.

Moreover, delayed referral may deter the reduction of complications associated with kernicterus, despite exchange transfusion in newborns. Moreover, use of non-approved and outpatient treatments (such as using phenobarbitals, plant extracts, manna and sisymbrium irio), inappropriate phototherapy at home and termination of breastfeeding play an important role in delayed referral (2). Hemolytic factors (e.g., blood type incompatibility, Rh incompatibility and G6PD deficiency) account for approximately 78% of known causes of jaundice. Also, these factors lead to 46% of cases of jaundice with complications. According to a previous study, blood type and Rh incompatibilities were the major causes of kernicterus in 62% of cases (4).

The incidence of kernicterus caused by blood type and Rh incompatibility has decreased in developed countries and kernicterus is usually idiopathic. This emphasizes the importance of prevention and early treatment of kernicterus caused by ABO and Rh incompatibility. Among neonates with jaundice due to hemolysis, ABO incompatibility (18.2%), Rh incompatibility (15.6) and G6PD deficiency (12.5%) were the most common causes of jaundice leading to complications, respectively. According to a review study on 795 icteric neonates in our center in2008, the most common causes of acute kernicterus were ABO incompatibility, idiopathic jaundice, G6PD deficiency and Rh incompatibility, respectively (4). Decreased hemolytic causes in the mentioned study, compared to increased idiopathic jaundice in our study, highlights the need for better management of jaundice caused by hemolytic factors. In our study, ABO incompatibility between the mother and infant (mother's blood type was O and the neonate's was A or B) was reported in 18% of neonates, a third of whom were diagnosed with kernicterus. The incidence of kernicterus due to ABO incompatibility in our study was very low since our study was performed on neonates with bilirubin level higher than 20 mg/dl.

The incidence of ABO incompatibility between mothers and neonates has been estimated at 7% in the United States. According to a previous study, in 15% of all live births, women with blood type O gave birth to infants with blood type A or B and 0.3-2.2% had ABO incompatibility (4, 15). The incidence of hemolytic causes in newborns due to ABO incompatibility ranged between 0.7% and 4% (16). In the present study, the infant's blood type was not routinely tested if the mother's blood type was O. Also, an accurate follow-up was not performed; even outpatient follow-up was not recommended. This is another reason for the high prevalence of jaundice due to ABO incompatibility in our study. In total, lack of appropriate follow-ups in icteric neonates due to ABO incompatibility, physicians' insensitivity, lack of routine check-up of the blood type of newborns born to mothers with O (Rh+) blood type and parents' insensitivity to the importance of jaundice are the main causes of the high prevalence of jaundice complications in icteric neonates due to ABO incompatibility.

It seems that raising the awareness of physicians, nurses, midwives and families about the importance of follow-up in newborns and mothers with ABO incompatibility can lead to the decreased incidence of jaundice, its early treatment and prevention of complications. In our study, about 15.6% of newborns had Rh incompatibility. The prevalence of Rh incompatibility was reported to be 6.2% in the study by Rostami et al., which was lower than the present study (17); this may be due to differences in the sampling methods. The samples included in Rostami's study were selected among all icteric newborns via screening, while our samples were selected from all admitted newborns. In our study, blood test was routinely performed in mothers and the blood type of newborns was checked if the mother's blood was Rh negative.

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However, there were no outpatient follow-up programs to prolong the length of hospital stay and be ensured about the absence of jaundice; this could lead to severe cases of jaundice and kernicterus. Prevention of Rh-negative mothers' sensitivity before pregnancy, treating mothers, Rhogam treatment in ectopic pregnancies, abortions and intrauterine manipulations, minimizing the diagnostic procedures and maternal/fetal monitoring regarding the incidence of incompatibility and early treatment of hydrops can lead to the decreased rate of complications, since the third trimester is the most common time for blood transfer from the fetus to the mother. To the best of our knowledge, Rhogam treatment at 28 weeks' gestation within 72 hours after delivery is helpful in preventing mothers' sensitivity. Direct Coombs' test samples from the cord blood in Rh-positive newborns can be a very good predictor of severe jaundice, leading to early intervention, i.e., administration of intravenous immunoglobulin and early onset of phototherapy. In our study, kernicterus due to G6PD deficiency was reported in 12.6% of newborns. In this regard, in a previous study, G6PD deficiency was reported in 14% of subjects (3). In addition, the prevalence of kernicterus due to G6PD deficiency was reported to be 21% in the United States (18), which is probably due to the use of proper preventive programs and reduced incidence of Rh and ABO incompatibility; however, in our study, the prevalence of kernicterus due to ABO and Rh incompatibility was higher. Despite sufficient knowledge about hyperbilirubinemia due to G6PD deficiency, its physiopathology is not well known in newborns. Jaundice caused by G6PD deficiency is most likely caused by decreased hepatic conjugation and excretion of bilirubin rather than increased production of secondary bilirubin (19). G6PD deficiency may simultaneously occur with genetic factors such as Gilbert's syndrome, especially in Mediterranean regions (20). In a previous study, performed at the University of Pennsylvania, the preventive strategy of kernicterus was based on a system-based approach. According to this study, early diagnosis and prevention of severe jaundice were known as the main factors in controlling kernicterus. According to this study, jaundice resulting from lysis, G6PD deficiency, idiopathic factors and birth trauma were known as the main causes of kernicterus (21). According to our study, phototherapy at home was performed on 12 newborns with jaundice complications due to unknown causes. Phototherapy at home is a useful method for the prevention of jaundice. Also, it can lead to the treatment of icteric neonates (when the bilirubin level is low) and prevention of neonatal hospitalization. However, all newborns requiring treatment, as well as high-risk cases, should be hospitalized. The major role of jaundice meter is screening and diagnosing cases requiring further examinations. Even cases requiring outpatient treatment or home treatment need to be evaluated in terms of the causes and severity of jaundice. Some physicians aim for the treatment of jaundice by only using jaundice meter, without investigating the causes. The importance of treatment based on the causes may be neglected by parents and the newborns may be admitted to the hospital after the occurrence of complications. In our study, three patients who received phototherapy at home had jaundice due to G6PD deficiency and were admitted to the hospital after the occurrence of complications. Hemolytic causes are the most common causes of kernicterus and developmental defects. For this reason, diagnosis, prevention and treatment of hemolytic causes of jaundice can be useful for saving the patients. Considering the high prevalence of kernicterus in this study, we can claim that physicians and treatment systems are not aware of the importance of ABO and Rh incompatibility and G6PD deficiency in the formation of jaundice. Prevention of hospital discharge in high-risk neonates for full treatment of jaundice, developing appropriate follow-up programs, raising public awareness about the importance of jaundice and appropriate follow-up, using proper diagnostic and therapeutic procedures and blood transfusion in newborns can lead to decreased rates of jaundice complications. As the results indicated, icteric newborns should be evaluated in terms of sensorineural hearing loss, developmental status, eye disorders and growth status, especially in cases with mean total bilirubin level higher than 20 mg/dl. Prompt actions should be taken to control the associated complications and prevent the exacerbation or development of problems in case abnormalities in brainstem auditory responses, eye problems or developmental disorders are suspected.

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