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Retrospective Evaluation of Term Neonatal Cases with Indirect Hyperbilirubinemia

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ABSTRACT

Although jaundice is very common in the neonatal period, it often recovers spontaneously without the need for treatment. In this study, it was aimed to retrospectively evaluate the patients hospitalized with the diagnosis of hyperbilirubinemia and to determine the risk factors, thus, to early diagnose and guide treatment of severe hyperbilirubinemia.
In this study, 250 infants who were followed up and treated for hyperbilirubinemia in Neonatal Intensive Care Unit.
When all cases were evaluated etiologically, the highest reason was found to be AB0 incompatibility. In 30% of the cases, the direct Coombs test was positive and the most common reason in the cases with positive direct Coombs test was the association of Rh and subgroup incompatibility with a rate of 29.3%. When the treatments applied to the cases were evaluated, phototherapy was given to all patients. It was found that of the patients, 84% received only phototherapy treatment, 6.4% underwent exchange transfusion with phototherapy, 5.2% received IVIG treatment, 4.4% received exchange transfusion and IVIG treatment.
If neonatal hyperbilirubinemia is not diagnosed and treated early, the morbidity and mortality of the brain damage that can occur is high. Today, while AB0 and Rh incompatibilities, which are an important etiologically important problem, are closely monitored, other etiological conditions such as infections, G6PD deficiency, subgroup incompatibility, hypothyroidism should also be kept in mind and early diagnosis and treatment should be performed.

Keywords: Indirect Hyperbilirubinemia, Phototherapy, Exchange transfusion, Direct coombs test

Introduction

Neonatal jaundice, due to indirect hyperbilirubinemia is one of the most common health problems in neonatals and is the main reason for hospitalization in the first year of life. (1) For the evaluation of neonatal hyperbilirubinemia, Bhutani et al. (2) have developed nomograms; nomograms are based on percentages of bilirubin values by hours after delivery and are still widely used to classify neonatals by risk groups. Although a certain level of jaundice is observed in approximately 50% -70% of healthy term neonatals and 80% of preterm infants, hyperbilirubinemia develops in almost 10% of neonatals at a level that requires treatment at certain hours after delivery and almost all of them are given phototherapy treatment, while a few of them require exchange transfusion. (2,3) Although the etiological factors of neonatal jaundice may vary from region to region depending on the genetic structure of the population, socioeconomic status and health opportunities, the most common etiological factors are Rh and AB0 blood incompatibilities, subgroup blood incompatibilities, malnutrition, urinary tract infections, G6PD, hemolytic blood diseases. (4) Infants with neonatal jaundice should be closely monitored due to acute bilirubin encephalopathy, kernicterus, and severe hyperbilirubinemia, which are potentially toxic effects of bilirubin. (3) If neonatal jaundice is not treated effectively, it may cause significant disabilities with life-long sequelae. (1) For this reason, determining the risk factors in the early period and taking precautions accordingly in neonatal jaundice significantly reduces the complications associated with jaundice. (5)

The aim of this study was to investigate the demographic features, etiological causes, risk factors and clinical approaches of infants with neonatal jaundice.

Materials and Methods

In this study, 250 infants who were followed up and treated with the diagnosis of hyperbilirubinemia in Neonatal Intensive Care

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Unit between January 2016 and October 2018 were retrospectively analyzed.

Neonatals clinically have neonatal jaundice between 37 and 42 weeks of gestation, with birth weight over 1500 g, and with indirect hyperbilirubinemia detected in laboratory tests were included in the study. Infants with multiple congenital anomalies, those who weighted 1500 g or less, those who were born before 37 weeks of gestation, those who were born after 42 weeks of gestation, those with cyanotic congenital heart disease, those with hyperbilirubinemia secondary to nosocomial infection, those with neural tube defects, those with bleeding diathesis, those with hypoxic ischemic encephalopathy, those with neurometabolic disease, trisomies, those with gastrointestinal anatomic obstruction, those with renal cystic disease or urinary system anatomical abnormality were excluded from the study.

Hemogram, biochemical examinations, Direct coombs test, mother and baby blood groups and subgroups of all cases were examined. It was defined as Rh incompatibility in case where the blood type of infants born from Rh negative mothers was Rh positive, and it was defined as AB0 incompatibility in case where the mother's blood type was 0, and the infant's blood type was A, B or AB. The case, where D^4+, C, E, c, eC^w, Kell antigen was negative in the mother, while D^4+, C, E, c, eC^w, Kell antigen was positive in the infant, was evaluated as subgroup incompatibility.

The program "Statistical Package for Social Sciences v17.0.0" is used for statistical analysis. While evaluating the obtained data, besides descriptive statistical methods(mean, standard deviation). Comparison of percentages between groups was made using the Chi-square test. The $p<0.05$ values were considered as statistically significant in all tests.

Results

Of 250 cases, 108(43.2%) were females, 66% of those born by normal spontaneous vaginal delivery according to the type of delivery, and 97.6% of the cases were singleton deliveries (Table 1). Gestational week of the cases was 38.42±1.30 and birth weight was 3051.2±457.1 grams. The postnatal age of the cases at the time of admission was 5.46±3.9 days.

The rate of the cases with a history of jaundice in the siblings was 17.6%, and the most common etiological cause detected in cases with a history of jaundice in their siblings was the association of Rh and subgroup incompatibility with a rate of 25%. The rate of cases with a history of phototherapy in the siblings was 13.6%, and in cases with a history of phototherapy the most common etiological cause was Rh and subgroup incompatibility with a rate of 23.5%.

When the cases were evaluated according to etiological reasons, AB0 incompatibility was detected in 42.4% of the cases, and the cases with AB0 incompatibility alone were 15.2%, those with AB0 incompatibility with subgroup incompatibility were 10%, those with nutritional deficiencies with AB0 incompatibility were 2.4%, and those with AB0 incompatibility with Rh incompatibility, and subgroup incompatibility were 2%. In 40(16%) of the cases, Glucose 6-phosphate dehydrogenase (G6PD) deficiency was found. Of the 40 patients with G6PD deficiency, 77.5% were males and 22.5% were females, and a significant relationship was found between gender and G6PD deficiency ($p=0.005$). Congenital Hypothyroidism was found in 11 (4.4%) of the cases hospitalized for neonatal jaundice. In 27.2% of these cases, no etiology other than congenital hypothyroidism was found. Urinary tract infection was detected in 71(28.4%) of the cases hospitalized for neonatal jaundice. In 25.3% of these cases, no etiology other than UTI was found. The rate of patients with other metabolic causes was 2%, and 2 patients had classic galactosemia and 1 patient had biotinidase deficiency. The rate of those with bilirubin metabolism disorder was 1.2%, the rate of those with suspected breast-milk jaundice was 0.4%, and the rate of those with unknown cause was 3.6% (Table 2).

When the treatments applied to the cases were examined, phototherapy was given to all patients. The average phototherapy time was 24.07±17.85 hours. The rate of cases who received only phototherapy treatment was 84%, the rate of cases who received exchange transfusion was 6.4%, and the rate of cases who received IVIG treatment was 5.2%, and the rate of cases who received exchange transfusion and IVIG treatment was 4.4%.

The most common etiology in cases who underwent phototherapy and exchange transfusion was the association of Rh and subgroup incompatibility with a rate of 50%. The number of cases who received IVIG treatment with phototherapy was 13. The most common etiology was the association of Rh and subgroup incompatibility with a rate of 46.1%.

Table 1. Comparison of the General Characteristic of The Cases

	n (%) / Mean ± SD	p	Total Bilirubin Mean ± SD
Gender			
Girl	108(43.2)	0.172	21.98±6.78
Male	142(56.8)		22.69±6.06
Form of delivery			
NSVD	165(66)	0.001	23.35±6.4
C/S	85(34)		20.52±5.8

NSVD: Normal spontaneous vaginal Delivery, C/S: Cesarean section

Table 2. Evaluation of the Cases According To Etiological Reasons

Etiology	n(%)
ABO incompatibility	38(15.2)
Rh incompatibility + Subgroup incompatibility	26(10.4)
ABO incompatibility + Subgroup incompatibility	25(10)
Urinary tract infection	18(7.2)
Subgroup incompatibility	13(5.2)
ABO incompatibility + Urinary tract infection	12(4.8)
G6PD deficiency *	10(4)
G6PD deficiency + Urinary tract infection	10(4)
Nutritional deficiency	8(3.2)
Nutritional deficiency + Urinary tract infection	8(3.2)
Subgroup incompatibility + Urinary tract infection	7(2.8)
ABO incompatibility + Nutritional deficiency	6(2.4)
ABO incompatibility + Rh incompatibility + Subgroup incompatibility	5(2.2)
ABO incompatibility + Hypothyroidism	4(1.6)
Hypothyroidism	3(1.2)
Rh incompatibility	2(0.8)
Others (Other metabolic causes, unknown causes, combinations of those with multiple etiological causes)	55(22)
Total	250(100)

*G6PD: Glucose 6-phosphate dehydrogenase

Phototherapy, exchange transfusion, and IVIG treatment were applied together in 11 cases, and the most common etiology was Rh and subgroup incompatibility with a rate of 72.7%.

Direct Coombs test (DCT) was found to be positive in 30% of all cases. DCT was found to be positive in 38.6% of 106 cases with AB0 incompatibility, in 62.2% of 45 cases with Rh incompatibility, and in 40.1% of 102 cases with subgroup incompatibility (Table 3). Exchange transfusion was performed in 4.7% of 106 cases with AB0 incompatibility, in 35.5% of 45 cases with Rh incompatibility and in 17.6% of 102 cases with subgroup incompatibility, and the exchange transfusion rate in all cases was found to be 10.8% (Table 3).

Discussion

Many risk factors have been identified in neonatal jaundice. (6) It has been shown in many studies that male gender is a risk factor for hyperbilirubinemia and is among the minor risk factors by the American Academy of Pediatrics. (6) In a multi-centered study conducted by Erdeve et al. (7), 53.3% of hyperbilirubinemia cases have been found to be male. In this study, 142(56.8%) of the cases were male and the male/female ratio was found to be 1.31. This study showed that although hyperbilirubinemia was more common in males, like other studies, there was no significant relationship between bilirubin elevation and gender (p=0.172).

Table 3. DCT, Exchange Application, IVIG Administration and Mean Total Bilirubin Values of Cases With Blood Group Incompatibility

Blood type incompatibility	(n)	DCT positivity * n (%)	Exchange n (%)	IVIG * n (%)	Total bilirubin (mg / dl) Mean ± SS
ABO incompatibility (Total)	106	41(38.6)	5(4.7)	4(3.7)	21.78±6.35
ABO incompatibility (Alone)	38	19(50)	2(5.3)	0(0)	21.30±6.50
ABO incompatibility + Subgroup incompatibility	25	8(32)	2(8)	2(8)	21.70±6.05
ABO incompatibility + Rh incompatibility + Subgroup incompatibility	5	1(20)	0(0)	0(0)	19.46±5.16
Rh incompatibility (Total)	45	28(62.2)	16(35.5)	18(40)	20.00±6.10
Rh incompatibility (Alone)	2	1(50)	2(0)	1(50)	20.70±0.20
Rh incompatibility + Subgroup incompatibility	26	22(84.6)	13(50)	14(53.8)	20.38±7.10
Subgroup incompatibility (Total)	102	41(40.1)	18(17.6)	22(21.5)	21.63±6.52
Subgroup incompatibility (Alone)	13	3(23.1)	1(7.7)	2(15.4)	22.69±6.82

* DCT: Direct Coombs test, IVIG: intravenously immunoglobulin

When the relationship between the mode of delivery and hyperbilirubinemia was examined, it was seen in some studies that the rate of jaundice was higher in those born with NSVD. In the study conducted by Phuapradit, no relationship has been found between the mode of delivery and total bilirubin levels. (8) In various studies, the mean total bilirubin level has been found to be higher in infants born by normal spontaneous vaginal delivery(NSVD) than those born by cesarean section(C/S), and this difference has been considered statistically significant.[9,10] In this study, the mean total bilirubin value of those born with NSVD was 23.35±6.4 mg/dL, and the mean total bilirubin value of those born with a C/S section was 20.52±5.8 mg/dL, and it was found to be statistically significantly higher in those born with NSVD. A significant relationship between mode of delivery and bilirubin level should be considered as a risk factor and closer monitoring of bilirubin levels in infants born with NSVD should be considered.

The history of siblings with jaundice is among the minor risk factors by the American Academy of Pediatrics[6]. In our study, a history of siblings with jaundice was detected in 44(22.9%) of the patients who had siblings. The association of Rh and Subgroup incompatibility was the most common in patients with a history of sibling with jaundice.

There are several risk factors for hyperbilirubinemia. Jaundice observed in the first 24 hours, DCT positivity, other known hemolytic diseases (eg G6PD deficiency), blood group incompatibility, 35th-36th week of gestation, previous sibling phototherapy history, East Asian breed are considered among the major risk factors[6]. However, 37th-38th week of gestation, jaundice before discharge, sibling with a history of previous jaundice, mother being at the age of 25 years and above, and Male gender are among minor risk factors. (6) Neonatal hemolytic disease due to blood incompatibility is a condition in which the antibodies formed in the mother against the antigens in the erythrocytes of the infant.[11] AB0, Rh and subgroup incompatibilities can lead to this. The estimated global prevalence of hemolytic disease (HDFN) of fetus and neonatal due to Rh isoimmunization is 276/100.000 live births per year. (11) With the widespread use of anti-D gamma globulin, the frequency of neonatal hemolytic disease and indirect hyperbilirubinemia due to Rh sensitization has decreased. Therefore, the rate of minor blood group incompatibilities other than Rh (D) antigen such as kell, c, C, E, e are gradually increasing in HDFN. (12) In the presence of hyperbilirubinemia and severe hemolysis without Rh and AB0 incompatibility,

the possibility of subgroup incompatibility should be considered in neonatals with DCT positive and/or deep anemia. (13) Neonatals with subgroup blood group incompatibility may be asymptomatic or the clinical picture may vary from mild anemia, reticulocytosis, neonatal hyperbilirubinemia to severe hydrops fetalis. (14) In this study, the rate of cases with AB0 incompatibility was found to be 42.4%, those with AB0 incompatibility alone were 15.2%, and those with AB0 incompatibility and subgroup incompatibility were 10%. The rate of patients with Rh incompatibility was found to be 18%, those with Rh incompatibility alone were 0.8%, and those with Rh incompatibility and subgroup incompatibility were found to be 10.4%. The rate of patients with subgroup incompatibility was 40.8%, and those with subgroup incompatibility alone were 5.2%. Those with AB0, Rh and subgroup incompatibility were found to be 2%. The fact that subgroup incompatibility was observed more than known, suggests that there may be subgroup incompatibilities among the cases whose cause is unknown. Therefore, subgroup incompatibility should also be investigated in hyperbilirubinemia cases. Antibodies detected with DCT have IgG structure. Since all anti-D antibodies and some of the anti-A antibodies are in the IgG structure, DCT is observed in Rh incompatibility at a high rate.[15] In a study conducted by Kappas et al.[16], the incidence of DCT positive AB0 incompatibility has been found to be 7.3% and 22% in two different groups. In our study, 75(30%) of the patients hospitalized due to hyperbilirubinemia were DCT positive, and 22(29.3%) of them had Rh and Subgroup incompatibility, and 19(29.3%) had AB0 incompatibility.

G6PD enzyme deficiency is the most common enzyme defect, affecting approximately 400 million people worldwide.[17] G6PD enzyme deficiency, which shows X-linked recessive inheritance, is highest in Africa, Asia, the Middle East, Latin America and the Mediterranean region.[18] In this study, the number of cases with G6PD deficiency was 40(16%), and those with G6PD deficiency alone were found to be 10(4%). G6PD enzyme deficiency should definitely be investigated in cases with hyperbilirubinemia in countries at risk for G6PD deficiency.

There are many studies that reveal the relationship between jaundice and urinary tract infection (19-21). Omar et al. (19) have detected growth in the urine culture in 21.1% of 152 patients hospitalized for indirect hyperbilirubinemia. Shahian et al. (20) have detected urinary tract infection in 12.5% of patients with asymptomatic indirect hyperbilirubinemia within the first 7 days. Bilgen et al. [21] have found urinary tract infection in 8% of patients who had no symptoms other than jaundice in their study with 102 patients. In this study, the rate of patients with urinary tract infection was found to be 71(28.4%), and 74.7% of patients with UTI were found to be associated with other etiologies of jaundice. The rate of patients with only UTI as the cause of jaundice was found to be 7.2%. AB0 incompatibility was most commonly accompanied by UTI (4.8%). With these results, it was thought that routine complete urinalysis and urine culture are important in patients with indirect hyperbilirubinemia.

Another etiology of neonatal jaundice is congenital hypothyroidism. Thyroid hormones are essential in most of the evolutionary processes of liver enzymes, and their deficiency probably retards the activity of enzymes involved in bilirubin metabolism and transport.[4] Therefore, it has been stated that prolonged hyperbilirubinemia may be the first symptom in neonatals with congenital hypothyroidism. (22) In a study, it has been found to be 4.2% as the etiology of neonatal jaundice. (23) In our study, congenital hypothyroidism was 11(4.4%), and congenital hypothyroidism alone was found as 3(1.2%), and hypothyroidism and AB0 incompatibility were found as 4(1.6%). We think that screening tests should be performed and closely monitored in congenital hypothyroidism, where early diagnosis and treatment are of great importance, and it should be investigated in infants with neonatal jaundice.

In some studies conducted on indirect hyperbilirubinemia seen in the neonatal period, the rate of cases for which no etiological cause was found varies. No cause was found in 64% of the cases in a study conducted in Canada, in 50.7% of the cases in a study conducted in Iran, and in 18.4% of the cases in a multi-centered study conducted in Turkey. (15,23,24) In this study, no cause was found in 9(3.6%) of the patients hospitalized for indirect hyperbilirubinemia. The reason for the lower rate compared to other studies was thought to be due to the fact that many examinations for hyperbilirubinemia could be performed in our unit. As seen in our study, the etiology of hyperbilirubinemia can be elucidated when extensive etiological investigations are conducted on neonatal hyperbilirubinemia. Thus, adverse effects due to bilirubin encephalopathy in both sick and future children will be reduced, and the frequency of kernicterus will decrease.

Phototherapy is a basic and safe therapeutic method used in the initial stage of the treatment of neonatal jaundice with indirect hyperbilirubinemia, lowering serum bilirubin levels and reducing the need for exchange transfusion (ET), a potentially more invasive treatment approach. (25) ET is a type of blood transfusion in which the patient's blood or its components are replaced with other blood or blood products, the purpose of which is to lower the serum bilirubin level to reduce the risk of kernicterus. (26) Narlı et al. (4) have found the exchange transfusion rate to be 10.8% in babies followed up for hyperbilirubinemia and the most common cause was AB0 blood group incompatibility. In our study, 27(10.8%) of the cases underwent exchange transfusions, and it was observed that the most common cause was Rh and Subgroup incompatibility. With the effective use of phototherapy and the use of Rhogam and intravenous immunoglobulin (IVIG) in hemolytic diseases, a significant decrease in the number of patients requiring exchange transfusion has been observed.

The prevention of hyperbilirubinemia is based on the identification of infants at risk and the effective use of treatment modalities to reduce Total Bilirubin as needed. When to start treatment and the decision of treatment choice is based on the evaluation of the probability of developing hyperbilirubinemia and the presence or absence of additional risk factors, including the week of gestation. If neonatal hyperbilirubinemia is not diagnosed and treated early, the morbidity and mortality of the brain damage that can occur is high. Early diagnosis and treatment in these patients will reduce morbidity and mortality. Today, while AB0 and Rh incompatibilities, which are an important etiologically important problem, are closely monitored, other etiological conditions such as infections, G6PD deficiency, subgroup incompatibility, hypothyroidism should also be kept in mind and early diagnosis and treatment should be performed.

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