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Evaluation of hospitalized newborns due to indirect hyperbilirubinemia: A cross-sectional study

Yenidoğan ünitesine indirekt hiperbilirubinemi nedeniyle yatan hastaların değerlendirilmesi

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Abstract

Aim: Indirect hyperbilirubinemia, a widespread problem in the newborn period, may need emergency treatment for prevention of neurological sequelae and mortality in some cases. We aimed to report the incidence, etiological factors, clinical findings, and the treatment of neonates with indirect hyperbilirubinemia.

Methods: Ninety-six cases of non-physiological indirect hyperbilirubinemia and prolonged jaundice which were followed-up in the Neonatology Unit of Kafkas University Hospital between January 2018-October 2019 were evaluated. The therapeutic approach was determined according to the recommendations of American Academy of Pediatrics in 2004.

Results: The incidence of IHB was 24.8% (n=96) among 387 hospitalized neonates. The mean gestational age, birth weight (BW), and bilirubin level on admission were 36.2 (2.5) weeks, 2628.9 (820) g, and 12.1 (5.29) mg/dL, respectively. Among all, vaginal delivery ratio was 38.5%, and cesarean delivery rate was 61.5%. About 34.4% were first-time mothers. The rates of breastfeeding and formula feeding were 39.6% and 1%, respectively. Around 59.4% were both breast- and formula-fed. The etiological factors of IHB were as follows: Prematurity and/or low birth weight (LBW) (20.9%), breast feeding jaundice (8.3%), ABO incompatibility (17.7%), Rh incompatibility (7.3%), ABO+Rh incompatibility (3.1%), cephal hematoma (2.1%), urinary infection (4.2%), sepsis (4.2%), pneumonia (2.1%), omphalitis (1%), subgroup incompatibility (1%), Glucose 6 phosphate dehydrogenase deficiency (1%) and unknown etiology (7.3%). Exchange transfusion rate was 1% (n=1), and 5 neonates (5.2%) were administered immunoglobulin therapy among 27 (28.1%) with hemolytic hyperbilirubinemia.

Conclusion: Indirect hyperbilirubinemia is an important risk factor for mortality and morbidity in newborn period. Defining the risk factors for non-physiologic indirect hyperbilirubinemia, adequate follow up and prompt treatment would reduce neurological sequelae and mortality rates.

Keywords: Newborn, Indirect hyperbilirubinemia, Etiology, Risk factors

Öz

Amaç: İndirekt hiperbilirubinemi yenidoğan döneminde sıklıkla görülen sorunlardan birisidir. Ciddi olgularda kalıcı nörolojik sekeller ve ölüme neden olduğu için acil müdahale gerektirir. Bu çalışmada; yenidoğanlarda indirekt hiperbilirubinemi (IHB) sıklığı, klinik özellikleri, altta yatan nedenleri ve tedavinin belirlenmesi amaçlandı.

Yöntemler: Ocak 2018- Ekim 2019 tarihleri arasında Kafkas Üniversitesi Tıp Fakültesi Çocuk Sağlığı ve Hastalıkları AD Yenidoğan Bölümünde patolojik indirekt hiperbilirubinemi ve uzamış sarılık nedeni ile takip edilen 96 olgu değerlendirilmeye alınmıştır. Olguların tedavi şekilleri Amerikan Pediatri Akademisi'nin 2004 yılında yayınlanan önerileri kapsamında total serum bilirübin düzeyleri, doğum tartıları ve doğum yaşlarına göre belirlendi.

Bulgular: Servisimizde izlenen 387 hastadan 96'sına (%24,8) İHB tanısı kondu. Olguların ortalama doğum ağırlıkları 2628,9 (820) gr, gestasyon haftaları 36,2 (2,5)hafta, doğum sonrası yaşları 3,1 (2,75), anne yaşları 30,1 (5,41), başvuru bilirubin düzeyi 12,1 (5,29), vaginal doğum oranı %38,5, sezaryen doğum oranı %61,5 di. Annenin ilk bebek olma oranı %34,4 olarak saptandı. Anne sütüyle beslenme oranı %39,6, formula ile beslenme oranı %1, anne sütü+ formula ile beslenme oranı %59,4. İHB nedenleri olarak Prematürite ve/veya düşük doğum ağırlığı %20,9, anne sütü sarılığı %8,3, ABO uyuşmazlığı %17,7, Rh uyuşmazlığı %7,3, ABO+Rh uyuşmazlığı %3,1, sefal hematom %2,1, idrar yolu enfeksiyonu %4,2, sepsis %4,2, pnömoni %2,1, omfolit %1, subgrup uyuşmazlığı %1, Glukoz 6 fosfat dehidrogenaz eksikliği %1 ve bilinmeyen nedenler %7,3 olarak saptandı. Kan değişimi 1 (%1) yenidoğana, hemolitik hiperbilirubinemisi olan 27 (%28,1) yenidoğandan 5'ine (%5,2) immünglobulin tedavisi uygulandı.

Sonuçlar: İndirekt hiperbilirubinemi yenidoğan döneminde görülen önemli bir mortalite ve morbidite sebebidir. Fizyolojik olmayan indirekt hiperbilirubinemide risk faktörlerinin saptanması klinik izlem ve erken tedavi yaklaşımı nörolojik sekel ve ölüm oranını azaltacaktır.

Anahtar kelimeler: Yenidoğan, İndirekt hiperbilirubinemi, Etiyoloji, Risk faktörleri

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Introduction

Indirect hyperbilirubinemia (IHB) is one of the most common problems encountered in newborns and jaundice is one of the most common reasons for referral to a doctor [1]. Between 60-70% of term newborns and almost all (90%) premature infants suffer from hyperbilirubinemia in the first days of life [2,3]. Although IHB occurs physiologically in most newborns, the rate of pathological hyperbilirubinemia requiring hospitalization is reportedly between 4.8% and 15.5% [4,5]. The cause of physiological jaundice is increased bilirubin load which occurs due to high erythrocyte mass in newborns, shorter erythrocyte life span, and relatively low enzyme activity in bilirubin metabolism [6]. Increased bilirubin production, inadequate hepatic uptake, and conjugation, and increased enterohepatic circulation are among the causes of pathological jaundice [7,8]. It has been shown that the severity and duration of IHB in newborns varies according to gestational age, birth weight, race, heredity, nutritional status and concomitant disease [6-8]. IHB may cause severe neurotoxicity, especially in the basal ganglia, therefore, it should be distinguished from mild and non-pathological IHB. Although pathological IHB can be treated with phototherapy in most cases, advanced treatment methods such as blood exchange may be needed.

The aim of this study was to determine the frequency, clinical characteristics, underlying causes and treatment modalities of newborns hospitalized for IHB.

Materials and methods

In this cross-sectional study, 96 neonatal patients who were hospitalized and treated at Kafkas University Health Application and Research Hospital, Neonatal Intensive Care Unit between January 2018 and October 2019 were evaluated. Newborns who were followed up for other reasons, such as dehydration, transient tachypnea of newborn, respiratory distress syndrome, or congenital anomalies were not included in the study. The underlying causes, clinical course, and treatments of newborns with IHB who were hospitalized in our ward were evaluated. In addition, by examining demographic characteristics, age and weight at admission, weight loss ratio, gestational ages, birth weights, maternal ages, birth types were determined. Indirect bilirubin levels above 12.9 mg/dl in term babies were considered as pathological jaundice and term babies with 8.8 mg/dl indirect bilirubin at the end of the second week were considered to have prolonged jaundice [9,10]. Pathologic jaundice in preterm infants was accepted as bilirubin values above the threshold for starting phototherapy [8]. The decision to start phototherapy and other forms of treatment were determined according to the recommendations of the American Academy of Pediatrics published in 2004 [9].

Hemogram, total serum bilirubin levels, peripheral blood smears, direct coombs tests, mother and infant blood groups and serum electrolytes and urea/creatinine values of infants with weight loss above 10% were evaluated.

Newborns with maternal blood type ‘O’, infant's blood type ‘A’, ’B’ or ‘AB’ and positive direct coombs test were accepted as ABO blood type incompatibility. Newborns with Rh positive blood groups whose mothers’ blood groups were Rh negative, those with positive direct coombs tests and decreased hematocrit in follow-up, and whose peripheral blood smear findings are compatible with hemolysis were considered Rh-incompatible. Maternal-infant subgroups, glucose-6 phosphate dehydrogenase enzyme levels, serum acute phase reactants and blood culture were studied in patients with unexplained indirect hyperbilirubinemia. Physical and laboratory findings were normal except for IHB and infants with jaundice lasting more than 14 days fed exclusively with breast milk were evaluated as late breast milk jaundice. Liver function tests, direct bilirubin levels, thyroid function tests, urine tests, sepsis parameters, reductant substances in urine, and osmotic fragility tests were evaluated in infants with prolonged jaundice (IHB lasting more than 14 days). Phototherapy was provided with blue halogen lamp phototherapy devices. If the serum total bilirubin level was close to the blood exchange limit or the bilirubin level continued to increase during the follow-up under phototherapy, slow infusion of intravenous immunoglobulin at 1g/kg dose was given in 4-6 hours in cases with direct coombs positivity due to immune-hemolytic anemia. The amount of donor blood required for blood exchange was adjusted to a double volume of 80cc/kg. Umbilical venous catheter was used for the procedure and the amount of blood to be taken and delivered at each cycle was 5cc/kg.

Statistical analysis

All obtained data were analyzed by using the statistical package for the social sciences (SPSS) version 22.0 software (SPSS,Inc Chıcago,IL,USA). The number (N), percentage (%), mean, standard deviation (SD), median, minimum and maximum values were presented for descriptive data. *P*-value <0.05 was considered statistically significant.

Results

The female-male ratio of our patients was 0.8. Socio-demographic characteristics, birth histories and nutritional status of our patients and their mothers are shown in Tables 1-2.

Table 1: Socio-demographic characteristics of patients and their mothers

Characteristics	Mean (SD)	(Min-Max)
Mother Age	30.1 (5.41)	(18-40)
Gestational week	36.2 (2.5)	(32-41)
Postnatal age	3.09 (2.75)	(1-21)
Birth weight	2628.9 (820)	(1505-4260)
Bilirubin level at admission (mg/dl)	12.1 (5.29)	(9-26)

SD: Standard deviation, Min: Minimum, Max: Maximum

Table 2: Birth and nutritional history of patients

Delivery Route	n	%
Vaginal	12 (Birth in house)	12.5
	25 (Birth in hospital)	26
Cesarean section	59	61.5
Number of living siblings		
1 Child	33	34.4
2 Child	27	28.1
> 2 Child	36	37.5
Feeding characteristic		
Breast milk (BM)	26	27.1
Formula (F)	1	1
Mixed(BM+F)	69	71.9

The main reasons of IHB are the insufficient feeding of the newborn with breast milk, prematurity (PM) and/or low birth weight (LBW). The causes of IHB in our newborn cases are shown in Table 3. Phototherapy was started in all cases admitted to our neonatology clinic. After 2-4 hours, control bilirubin levels were measured and bilirubin decline rates were evaluated.

Among 11 cases diagnosed with pathological jaundice on the first day of life, ABO, ABO and Rh, and Rh

incompatibility were detected in 5 (45.4%), 1 (9.1%) and 4 (36.4%) patients, respectively. Early neonatal sepsis was a risk factor in 1 (9.1%) patient.

Table 3: Causes of indirect hyperbilirubinemia (IHB) in newborns

Causes	n	%
Prematurity/Low birth weight	20	20.9
ABO incompatibility	17	17.7
Nutritional deficiency	19	19.8
Rh incompatibility	7	7.3
Late breast milk jaundice	8	8.3
Cephalo-hematoma	2	2.1
ABO+Rh incompatibility	3	3.1
Urinary tract infection	4	4.2
Subgroup mismatch	1	1
Sepsis	4	4.2
Pneumonia	2	2.1
Omphalitis	1	1
G6PD deficiency	1	1
Congenital hypothyroidism	-	0
Unknown causes	7	7.3
Total	96	100

The time of onset of hyperbilirubinemia was not different in patients with and without hemolytic jaundice. Blood exchange was performed in 1 (1%) of our patients with IHB and intravenous immunoglobulin treatment was administered in 5 (5.2%) neonates.

It was found that 11 newborns who could not be fed with adequate breast milk in the early period had lost 9.4% (3.1%) (4.2-23%) of their birth weight by the time they were admitted to our newborn clinic, while the same parameter was 4.9% (2.67%) (1.2-13%) for others. The weight loss of the patients who could not be breastfed in the early period according to birth weight was found to be significantly lower than the cases who were hospitalized due to other IHB reasons (P<0.001). The number of living children, prematurity, low birth weight and early gestational age were factors affecting postnatal weight loss.

Jaundice lasted more than two weeks in 14 of our cases who were followed-up and treated for IHB. Etiological causes of prolonged jaundice in these cases include late breast milk jaundice (n=5), urinary tract infection (n=1), prematurity/low birth weight (n=5), and glucose 6 phosphate dehydrogenase enzyme deficiency (n=1). No etiological cause was determined for 2 cases.

Among insufficiently breast-fed infants, cesarean section deliveries were numerically and insignificantly higher than normal spontaneous vaginal deliveries (P=0.256). We found the incidence of IHB is 24.8% in our study.

Discussion

IHB, which is frequently seen in the neonatal period, can cause serious health problems if it is not diagnosed and treated in time. Therefore, it is particularly important to distinguish between pathological and non-pathological causes of IHB [11,12]. Nowadays, the importance of breastmilk is understood. Increase in rates of breastfeeding, survival among premature and low birth weight infants, neonatology clinics and early discharge are among the reasons for the increase in admission and diagnosis rates of newborn infants with jaundice. The prevalence of the IHB is so high that it raises the importance of IHB in terms of its possible complications.

It is known that male gender is a risk factor for IHB and in our study, similar results were obtained with those conducted in our country. Ünal et al. [13] found male gender as 59%, Narlı et al. [14] as 56%, and Kılıç et al. [15] as 55%. Similarly, male gender (58%) was found to be higher in our study (M / F: 56/40).

In this study, the most common etiological cause of IHB was PM/LBW (20.9%), nutritional deficiency (19.8%) and ABO incompatibility (17.7%). Low bilirubin metabolism and transport in PM / LBW infants as well as delayed UDP-GT expression in the liver is the main cause of increased duration and severity of physiological jaundice [16].

In the early period of the newborn, insufficient breastfeeding is related to inappropriate breastfeeding techniques rather than the characteristics of breast milk. Early breast milk jaundice is seen due to inexperience of mother, low amount of milk and being the first-born baby. In our study, the rate of early breast milk jaundice was higher in the first infant (19.8%). It is particularly important to start early breastfeeding, teach the techniques, and emphasize the importance of the continuity of breastfeeding.

Late breast milk jaundice is characterized by hyperbilirubinemia, which has a slow rate of increase after the first week of life and is associated with certain substances in breast milk content. Bilirubin elevation in breast milk jaundice can last for 3 weeks-3 months and may take several months to return normal values. Diagnosis is made by ruling out other causes that may cause IHB [1,3,6,13]. In our study, late breast milk jaundice was 8.3% (Table 3).

Although there are many factors in the etiology of IHB, the most important one is hemolytic hyperbilirubinemia due to blood type incompatibility, the rate of which was reported as 7.9% for Rh, 2.9% for ABO + Rh incompatibility by Kılıç et al. [15], 13.2% for Rh, 10.4% for ABO + Rh incompatibility by Narlı et al. [14], 9.6% for Rh, 4.8% for ABO + Rh for incompatibility by Özkaya et al. [16], and 2.3% for Rh, 1.9% for ABO + Rh, 14.3% for ABO incompatibility and 0.9% for subgroup mismatch by Ünal et al. [13]. In our study, we found 7.3% Rh incompatibility, 3.1% ABO + Rh incompatibility, 17.7% ABO incompatibility and 1% subgroup mismatch. In light of the available data, it is necessary to determine the blood groups of newborns of O or Rh (-) mothers and be mindful of possible hemolytic IHB. It should also be remembered that subgroup mismatch is an etiology of hemolytic IHB of unknown origin.

Glucose 6 Phosphate Dehydrogenase (G6PD) enzyme deficiency should be evaluated in newborns with a family history, those of a specific ethnic-geographical origin (Mediterranean, Africa, Middle East, Southeast Asia, Arabic Peninsula) or those inadequately responsive to phototherapy. In our country, Büyükokuyan et al. [17] found that the rate of G6PD deficiency in newborns diagnosed with IHB was 3.8% in the Marmara region and 8.3% in the Çukurova region. In addition, G6PD deficiency was 3.85% in the IHB newborns studied by Atay et al. [18]. In our study, the G6PD deficiency rate was 1%. This low rate of G6PD deficiency can be explained by the determination of enzyme level in unexplained IHB cases, which was also low. In the study of Ünal et al. [13], G6PD enzyme deficiency rate was found as 0.5% in unexplained IHB cases, like our study. In the studies conducted in our country, the rate of urinary tract infection as the cause of prolonged IHB cases was reported as 7.8% by Bilgen et al. [19] (bag culture, 100,000 colonies / ml and above, only single species were considered significant), and 1% by Ünal et al. [13] (suprapubic

aspiration, single bacterium is considered significant). In our study, the rate of urinary tract infection as a cause of prolonged IHB was 4.2%. We think that the difference between our rates and the literature was due to the fact that we obtained urine cultures both with a bag and suprapubic aspiration.

In neonatal hyperbilirubinemia, the primary approach is to protect the central nervous system from the toxic effects of bilirubin and to protect the newborn from possible permanent damage to the neuromotor system. All patients admitted to our neonatology clinic with the diagnosis of IHB were treated with phototherapy. Blood exchange was performed in 1 (1%) newborn patient with severe hemolytic hyperbilirubinemia. Five (5.2%) patients received intravenous immunoglobulin therapy and 4 of these patients did not need blood exchange.

We found that infection was the cause of IHB in 7.3% of our cases (4.2% sepsis, 1% omphalitis, 2.1% pneumonia), while in their series, the rate of infection was reported as 7.2% (3.6% sepsis, 2.4% omphalitis, 1.2% pneumonia) by Tekinalp et al. [20] and 13.1% (sepsis 1.8%, omphalitis 11.3%) by Kılıç et al. [15]. The low rate of omphalitis in our series may be related to high-standard umbilical care due to elevated birth rate in the hospital.

As a result of this study, IHB was seen to accompany ABO/Rh incompatibility, neonatal infections, and enzymatic deficiencies. Early diagnosis of possible pathological conditions in the perinatal period will significantly reduce the mortality and morbidity rates of the newborn and prevent permanent damage to the newborn's central nervous system [21]. Close monitoring of newborns who are at risk of possible IHD is vitally important in this respect and adequate treatment of newborns with hyperbilirubinemia will contribute to the growth of healthy generations.

The most important limitation of our study is the low number of cases. We think that a larger sample size can eliminate the current limitation.

Conclusion

Indirect hyperbilirubinemia is an important risk factor for mortality and morbidity in the newborn period. Defining the risk factors for non-physiologic indirect hyperbilirubinemia, adequate follow up and prompt treatment would reduce neurological sequela and mortality rates.

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