Research Article / Araştırma Makalesi

An Evaluation of Infants Followed up With a Diagnosis of Indirect Hyperbilirubinemia

İndirekt Hiperbilirubinemi Tanısı ile Takip Edilen Bebeklerin Değerlendirilmesi

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Abstract

Background: It was aimed to investigate the clinical and demographic characteristics, risk factors and treatment methods of newborns hospitalised with a diagnosis of indirect hyperbilirubinemia.
Materials and Methods: Demographic characteristics, laboratory data, and risk factors for neonatal jaundice were retrospectively examined in 615 newborn infants with jaundice admitted to the Neonatal Intensive Care Unit.
Results: The infants comprised 340 (55.3%) females and 275 (44.7%) males; of which 532 (86.50%) were born at full-term, 80 (13%) premature, and 3 (0.50%) post-full-term. Birth weights; It was 3185±50 gr. The most common cause of jaundice was physiological jaundice/jaundice of unknown cause (25.7%) wheras the lowest rates were intracranial bleeding (0.3%) and congenital central nervous system anomalies (0.3%). In treatment, 406 (66.0%) of the babies received only phototherapy, and 35 (5.7%) of them also received exchange transfusion. To the remained 174 (28.3%) cases, antibiotics, sodium L-thyroxin, and/or intravenous fluid treatment were given according to the primary disease, together with phototherapy. Rebound jaundice developed in 13 (2.1%) infants, temporary hypocalcemia in 3 (0.5%), anemia in 1 (0.2%), and diarrhea in 1 (0.2%). Mortality associated with an underlying cause developed in 7 (1.1%) cases, kernicterus developed in 1 (0.2%), and 607 (98.7%) were discharged with medication.
Conclusions: Hyperbilirubinemia is frequently seen in the neonatal period. Timely treatment of hyperbilirubinemia is extremely important for the prevention of morbidity and mortality.

Key Words: Jaundice, Newborn, Kernicterus

Öz

Amaç: İndirekt hiperbilirubinemi tanısıyla yatırılan yenidoğanların klinik ve demografik özellikleri, risk faktörleri ve tedavi yöntemlerinin araştırılması amaçlandı.
Materyal ve Metod: Yenidoğan yoğun bakım ünitesine yatırılan 615 sarılıklı yenidoğan bebeğin demografik özellikleri, laboatuvar verileri ve yenidoğan sarılığı açısından risk faktörleri retrospektif olarak incelendi.
Bulgular: ebeklerin 340 (% 55,3)' ı kız, 275 (% 44, 7)' i erkek idi. 532 (% 86,50)' si matür, 80 (% 13)'i prematür ve 3 (% 0,50)'ü ise postmatür idi. Doğum ağırlıkları; 3185±50 gr idi. Olgularda en sık sarılık nedeni, Fizyolojik sarılık / Nedeni tespit edilemeyen sarılıklar iken (%25.7), en az oranda tespit edilen sarılık nedeni ise intrakranial kanama (%0.3) ve konjenital santral sinir sistemi anomalileri idi (%0.3). Tedavide, bebeklerin 406 (% 66,0)'sına sadece fototerapi, 35 (% 5,7)'ine ise ek olarak kan değişimi de yapıldı. Geriye kalan 174 olguya (% 28,3) fototerapi ile birlikte primer hastalığa bağlı olarak antibiyotik, sodium L-tiroksin ve/veya intravenöz sıvı tedavileri de verildi. Olguların 13 (% 2,1)'ünde rebound sarılık, 3 (% 0,5)'ünde geçici hipokalsemi, 1 (% 0,2)' inde anemi ve 1 (% 0,2)' inde ise ishal gelişti. 7 (% 1, 1) olgu altta yatan nedene bağlı olarak ex olurken, 1 (% 0,2) bebekte kernikterus gelişti; ve 607 (% 98,7) olgu şifa ile taburcu edildi.
Sonuç: Hiperbilirubinemi, yenidoğan döneminde sık görülmektedir. Mortalite ve morbidite engellenmesinde hiperbilirubinemi tedavisinin zamanlaması son derece önemlidir.

Anahtar kelimeler: Sarılık, Yenidoğan, Kernikterus

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Introduction

Indirect hyperbilirubinemia (IHB) is one of the most common reasons for hospitalization in the neonatal period (1). It is seen at a frequency of 60% in healthy term infants and the majorities are observed to be within physiological limits. Although rare, when hyperbilirubinemia develops at a severe level, it can lead to neurotoxicity. The level to which total serum bilirubin will rise in which newborns, and at what value it will create neurotoxicity in which infants is not fully known (2). Blood exchange in addition to intense phototherapy in early and rapid treatment of severe hyperbilirubinemia is lifesaving and can prevent the development of neurotoxicity (3). The aim of this study was to investigate the demographic characteristics of infants admitted to the Neonatal Intensive Care Unit with a diagnosis of IHB, the risk factors affecting IHB and total bilirubin levels, and treatment methods.

Materials and Methods

In this study, 615 newborn babies admitted to Adana Numune Training and Research Hospital Neonatal Intensive Care Unit between January 2008 and June 2010 were examined. In this study, research data before 2020 was used, and the article was produced from the thesis (master's/doctoral) study. For this reason, a new retrospective ethics committee permission was not obtained.

The cases included in the study were evaluated in respect of age, gender, birthweight, blood group incompatibility, risk factors causing hyperbilirubinemia, treatment methods, and complications that developed. For all the patients, the mother and infant blood groups were examined, the levels of total bilirubin and direct bilirubin, thyroxin (T4) and thyroid stimulating hormone (TSH) levels, peripheral smear and direct Coombs test, glucose-6-phosphate dehydrogenase (G6PD) enzyme level, and full urine analysis. Phototherapy was applied to all the infants in treatment. For the infants with indication for blood exchange, this was performed with full blood at double volume (160-170 cc/kg) for a maximum of 5 days.

Statistical Analysis

SPSS 15.0 package program was used in the statistical analysis of the data obtained in the study. Continuous variables were expressed as mean and standard deviation values, or median and minimum-maximum when necessary, and categorical data were expressed as numbers (n) and percentage (%).The conformity of the data to the normal distribution was examined with the Kolmogorov Smirnov test.

Results

Evaluation was made of 615 infants, comprising 340 (55.3%) females and 275 (44.7%) males, giving a male/female ratio of 0.81. Of the total cases, 80 (13%) were born premature (<37 weeks), 532 (86.50%) at full-term (37-41 weeks), and 3 (0.50%) at post-full-term (≥ 42 weeks). Birthweight was mean 3185±50 gr and median 3200 gr (range, 1300-5000 gr).

The etiological causes of the cases with neonatal jaundice are presented in order of frequency in Table 1.

Table 1. Causes of indirect hyperbilirubinemia of the cases

Causes of indirect hyperbilirubinemia	n (%)
Physiological jaundice/jaundice of unknown causes	158 (25.7)
Sepsis and other infections	120 (19.5)
ABO incompatibility	101 (16.4)
Respiratory problems (RDS, MAS**,** NTT)	68 (11. 1)
Other causes	34 (5.5)
Sepsis+ABO incompatibility	30 (4.9)
Rh incompatibility	23 (3.7)
Diabetic mother and infant	17 (2.8)
Birth trauma	13 (2. 1)
Congenital hypothyroidism	12 (2)
G-6PD enzyme deficiency	9 (1.5)
Rh+ABO incompatibility	8 (1.3)
Sepsis + Rh incompatibility	6 (1)
Subgroup incompatibility	5 (0.8)
Infections + congenital hypothyroidism	4 (0.7)
Hemolytic diseases	3 (0.5)
Intracranial bleeding	2 (0.3)
Congenital central nervous system anomalies	2 (0.3)
Total	**615 (100)**

G-6PD: Glucose-6 -phosphate-dehydrogenase enzyme deficiency, MAS: Meconium Aspiration Syndrome, NTT: Neonatal Temporary Tachypnea, Other Causes: Intrauterine and placental diseases, diseases occurring in pregnancy and at birth, In the mother; drug/substance use, infections, hypertension, diabetes mellitus, bleeding-clotting diseases, In the infant; insufficient suction, insufficient nutrition, dehydration, metabolic diseases, RDS: Respiratory Distress Syndrome.
Note: Apart from combined blood incompatibility, sepsis and other infections were also given with other causes of jaundice, resulting in combined etiologies.

Direct Coombs test was positive in 61 (9.9%) of our cases. Treatment of the infants was applied with phototherapy in 406 (66.0%) cases and blood exchange was performed together with phototherapy only in 35 (5.7%). To the other 174 (28.3%) cases, antibiotics, sodium L-thyroxin, and/or intravenous fluid treatment was given according to the primary disease, together with phototherapy. As complications, rebound jaundice developed in 13 (2.1%) infants, temporary hypocalcemia in 3 (0.5%), anemia in 1 (0.2%), and diarrhea in 1 (0.2%). Mortality associated with an underlying cause developed in 7 (1.1%) of the cases included in the study who received phototherapy for the development of jaundice because of sepsis and other pathological reasons. Kernicterus developed in 1 (0.2%) case, and 607 (98.7%) were discharged with medication (Table 2).

Table 2. Complications due to phototherapy and underlying etiological reasons.

Complication	n (%)
Rebound jaundice	13 (2.11 %)
Temporary hypocalcemia	3 (0.48 %)
Anemia	1 (0.16 %)
Diarrhea	1 (0.16 %)
Mortality*	7 (1.13 %)
Kernicterus	1 (0.16 %)
Total	26 (4.22 %)

**Mortality was not due to jaundice or the treatment applied, but to the underlying etiological reasons.*

Discussion

Jaundice, which is frequently seen in the neonatal period and requires an emergency approach as it leads to permanent neurological sequelae and even death, remains an important health problem (4). Male gender is a risk factor for hyperbilirubinemia and higher levels of bilirubin have been reported in male infants than in female infants (5). Bülbül et al. reported that despite hyperbilirubinemia being seen more often in males there was no direct relationship between male gender and the severity of hyperbilirubinemia (6).

Low birthweight and low gestational age increase the risk of hyperbilirubinemia. In cases with low birthweight and low gestational age, pathological conditions such as intracranial bleeding, hemolysis, and hypoxia are often encountered. It has been reported that because of delayed expression of uridyl diphosphate glucuronyl transferase (UDPGT), which has an important role in transport with bilirubin metabolism, the duration and severity of physiological jaundice in preterm births is increased compared to mature infants (7). As few preterm and low birthweight infants are admitted to our clinic, the data determined were different to previous results in literature. In a large proportion of cases of neonatal jaundice, a definitive cause can still not be determined and the rates of jaundice of indeterminate cause have been reported as 24% and 40.9% (8). In the current study, the reasons leading to neonatal jaundice were primarily physiological jaundice or jaundice of unknown cause in 158 (25.7%) cases, and this rate was consistent with findings in literature.

The frequency of sepsis and respiratory problems in the etiology of neonatal jaundice was reported as 4% by Guaran et al., and Polat et al (9,10). Urinary tract infection (UTI), which is among the etiological factors of prolonged neonatal jaundice, has been reported at rates between 4.9% and 7.4% in literature (11,12). In the current study, different infections were determined as the cause of neonatal jaundice in 26% of the cases. This rate in the current study was higher than data in literature as sepsis was evaluated together with other infections (lung infections, meningitis, omphalitis, gastroenteritis, skin infections, etc). The frequency of ITU was determined to be lower at 3.41%, which was a lower level than reported in literature. The incidence of congenital hypothyroidism, which has been reported to play a role in the etiology of neonatal jaundice, has been reported at rate of 6.3% (13). The frequency of hypothyroidism in the current study was determined to be 2.7%, which was consistent with the literature.

In cases of jaundice emerging in newborns in the first 24 hours, maternal diabetes has been shown to be a risk factor for the infant (14). Ince et al. determined the frequency of hyperbilirubinemia as 41.9% in the infants of diabetic mothers, and Akarsu et al (15,16). determined this rate to be higher at 50%. In contrast, this rate was determined as 2.8% (n: 17) in the current study, which was a much lower level than the data in literature. At the time of this study, there was no pediatric cardiologist in our clinic. Since babies of diabetic mothers may also have cardiological pathologies, these babies were not referred to us. Therefore, this rate was found to be lower than the literature.

The incidence of ABO incompatibility in neonatal jaundice was reported as 10% by Guaran et al., 13.6% by Polat et al. and 33.4% by Vitrinel et al. (9,10,17). In our study, ABO incompatibility was found to be the cause of jaundice alone or in combination with other diagnoses at a rate of 22.6%. This rate was consistent with the literature data. The incidence of Rh incompatibility was reported as 3% by Guaran et al., 8% by Polat et al. and 8.4% by Vitrinel et al. (9,10,17). This rate in the current study was consistent with literature

at 6.01%. In previous studies of neonatal hyperbilirubinemia, direct Coombs positivity has been reported at the rate of 5.7% by Kılıç et al., as 20 % by Sarıcı et al., and as 4% by Lucas et al. (18,19,20). Our rate of direct coombs positivity (9.9%) in our cases was consistent with the literature data. A study which evaluated neonatal jaundice reported severe hemolytic disease at the rate of 4.4% (19). Rates of indirect hyperbilirubinemia associated with hemolytic disease have been reported as between 0.3% and 2.2% depending on the blood incompatibility type (21).

In the current study, there were hemolysis findings in peripheral smears in 2.9% of the cases, consistent with the literature. The frequency of G6PD enzyme deficiency in jaundice etiology was reported as 1.2% by Tekinalp et al., 0.5% by Haberal et al., and 1.2% by Yiğit et al (11,12,22). In contrast to those studies, in a study conducted in the Mediterranean region, where G6PD enzyme deficiency is frequently seen, Narli et al. reported a higher rate of 19.2% (23). Another study of cases of neonatal jaundice that developed kernicterus found this rate to be 22% (24). In the current study the rate of G6PD enzyme deficiency was determined to 1.5%, higher than some studies in literature and lower than some others.

Although phototherapy is often used in the treatment of neonatal jaundice, blood exchange or intravenous immunoglobulin is used in some cases (3). Phototherapy was applied alone or together with other treatment methods to all the cases of neonatal jaundice in the current study. In 406 (66.0%) cases, phototherapy was applied alone and in 35 (5.7%), blood exchange was performed followed by phototherapy. In the other 174 (28.3%) cases, additional treatments of antibiotics, sodium L-thyroxin, and/or intravenous fluid treatment were given according to the primary disease, together with phototherapy. The frequency of blood exchange in the treatment of neonatal jaundice in Turkey (2.3-7.8%) is lower than that of developing countries (28-30%), but is at a higher rate than reported from European countries (25). The blood exchange rate of 5.7% in the current study was seen to be consistent with literature. Although benign complications such as insensible fluid loss, soft stools, and skin rashes have been reported related to phototherapy, severe bullous lesions of the skin, hemolysis, and even death have been reported in infants with congenital erythropoietic porphyria who have received phototherapy (26,27).

In the current study, rebound jaundice developed in 13 (2.1%) cases, temporary hypocalcemia in 3 (0.5%), anemia in 1 (0.2%), and diarrhea in 1 (0.2%). In the past, the countries with the highest incidence of kernicterus were the USA (27%), Singapore (19%) and Turkey (16%) (28). Although there are studies reporting the incidence of acute bilirubin encephalopathy as 9.8% in infants undergoing exchange transfusion, these high rates have decreased in recent years all over the world and in our country (29). In a multicenter study conducted in our country, bilirubin levels were found to be >25 mg/dL in 6.4% of infants, acute bilirubin encephalopathy findings in 0.23% and hearing loss in 0.2% (30). Kernicterus developed in only 1 (0.2%) case in this study, which was well below the rate in literature. We think that in our clinic serving in a training and research hospital, the measurement of early bilirubin values in jaundice patients, timely intensive phototherapy treatment and blood exchange procedures applied when necessary are effective at this rate.

Mortality associated with an underlying cause developed in 7 (1.1%) cases, and 607 (98.7%) infants were discharged with medication when the treatment was completed.

Conclusion

Early recognition of hyperbilirubinemia is based on detailed examination of infants and accurate evaluation of clinical and laboratory findings. In addition, the effective use of early diagnosis and treatment methods and the reduction of total bilirubin levels depend on the correct determination of risk factors. Because both brain damage due to encephalopathy and complications related to exchange transfusion have a high risk of morbidity and mortality.

Limitations

The most important limiting factors in this study are the fact that this study was conducted in a single center and the patients could not be evaluated clinically and neurologically after discharge.

Ethical Approval: In this study, research data before 2020 was used, and the article was produced from the thesis (master's/doctoral) study. For this reason, a new retrospective ethics committee permission was not obtained.

Author Contributions:
Concept: A.D., M.T.
Literature Review: A.D., H.G.
Design : A.D., M.T.
Data acquisition: A.D.
Analysis and interpretation: A.D., H.G., M.T.
Writing manuscript: A.D.
Critical revision of manuscript: H.G., M.T.

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References

1. Zipursky A, Bhutani VK. Impact of Rhesus disease on the global problem of bilirubin-induced neurologic dysfunction. Semin Fetal Neonatal Med. 2015;20(1):2-5.
2. Bhutani VK, Johnson-Hamerman L. The clinical syndrome of bilirubin-induced neurologic dysfunction. Semin Fetal Neonatal Med. 2015;20(1):6-13.
3. Çoban A, Türkmen MK, Gürsoy T. Turkish Neonatal Society guideline to the approach, follow-up, and treatment of neonatal jaundice. Turkish Archives of Pediatrics 2018;53(Suppl 1): 172-9.
4. Alpay F. Sarılık, Yurdakök M, Erdem G (Editörler). 1.Baskı, Ankara: Güneş Tıp Kitabevi (2004): 560-78.

5. AAP Subcommittee on Neonatal Hyperbilirubinemia. Neonatal jaundice and kernicterus. Pediatrics. 2001;108(3):763-65.
6. Bülbül A, Fusün O, Uslu S, İşçi E, Nuhoğlu A. Term bebeklerde hiperbilirübineminin klinik özellikleri ve risk etmenlerinin araştırılması, Türk Pediatri Arşivi 2005; 40(3): 204-10.
7. McMahon JR, Stevenson DK, Oski FA. Physiologic Jaundice. in: Taeusch HW, Ballard RA (Editors). Avery's Disease of the Newborn. 7. Baskı, Philadelphia: WB Saunders, 1998: 995-1002.
8. Dzinović A, Heljić S, Maksić H, Hrnjić Z. Neonatalna hiperbilirubinemija: evaluacija i tretman [Neonatal hyperbilirubinemia: evaluation and treatment]. Med Arh. 2002;56(3 Suppl 1):44-5.
9. Guaran RL, Drew JH, Watkins AM. Jaundice: clinical practice in 88,000 liveborn infants. Aust N Z J Obstet Gynaecol. 1992;32(3):186-92.
10. Polat A, Öktem F, Koç H. Yenidoğan hiperbilirubinemili 963 hastanın değerlendirilmesi. Türkiye Klinikleri Pediatri 1993; 2(2): 26-30.
11. Tekinalp G, Ergin H, Erdem G, Yurdakök M, Yiğit Ş. Yenidoğan döneminde uzamış sarılıklar. 82 vakanın değerlendirilmesi. Çocuk Sağlığı ve Hastalıkları Dergisi 1996; 39(3): 441-8.
12. Haberal Ş, Özkan H, Oğuz A, Gülen H, Sarıgül F. Neonatal indirekt hiperbilirübinemili olguların retrospektif incelenmesi. Dokuz Eylül Üniversitesi Tıp Dergisi 1996; 10 (2-3): 86-90.
13. Çöl Araz N. Uzamış sarılığı olan yenidoğanlarda konjenital hipotiroidi sıklığı. Gaziantep Tıp Dergisi 2009; 15 (1): 28-30.
14. Ambalavanan N, Carlo WA. Jaundice and Hyperbilirubinemia in the Newborn. In: Kliegman RM, Stanton BF, Schor NF, et al (Editors). Nelson Textbook of Pediatrics. 19. Baskı, Philadelphia: Elsevier Saunders, 2011: 603-4.
15. Anuk-ince D, Takcı Ş, Gümüşer R. DİYABETİK ANNE BEBEKLERİNİN YENİDOĞAN DÖNEMİ SORUNLARI. Çağdaş Tıp Dergisi 2014; 4(3): 115-20.
16. Akarsu S, Kurt ANÇ, Kurt A, Yılmaz E, Aygün AD. Diyabetik anne bebeğinde klinik ve laboratuar bulguları. Fırat Tıp Dergisi 2008; 13(3): 199-204.
17. Vitrinel A, Yavrucu S, Raif AO. 1987-1990 yılları arasında kliniğimizde izlenen yenidoğan sarılıkları. Haydarpaşa Numune Hastanesi Tıp Dergisi 1992; 32: 81-3.
18. Kılıç B, Ergin H, Çakaloz İ. Yenidoğan dönemi indirekt biperbilirubinemili olgularımızın değerlendirilmesi. Türkiye Klinikleri Journal of Pediatrics 2005: 14; 25.
19. Sarici SU, Yurdakök M, Serdar MA, Oran O, Erdem G, Tekinalp G et al. An early (sixth-hour) serum bilirubin measurement is useful in predicting the development of significant hyperbilirubinemia and severe ABO hemolytic disease in a selective high-risk population of newborns with ABO incompatibility. Pediatrics. 2002;109(4):e53.
20. Lucas GN. Neonatal jaundice due to ABO incompatibility in Sri Lankan. Indian J Pediatr. 1996;63(3):381-4
21. Clemons RM. Issues in newborn care. Prim Care. 2000;27(1):251-67.
22. Yiğit Ö, Sezgin B, Özgürhan G, Cambaz N. İndirekt hiperbilirübinemili olguların değerlendirilmesi. Bakırköy Tıp Dergisi 2006; 2(2): 41-6.
23. Narlı N, Satar M, Özlü F, Yapıcıoğlu H, Özcan K. Çukurova Üniversitesi yenidoğan yoğun bakım ünitesine yatırılan hiperbilirübinemili bebeklerin etiyolojik yönden değerlendirilmesi. Çukurova Üniversitesi Tıp Fakültesi Dergisi, 2004; 29(2): 51-5.
24. Johnson LH, Bhutani VK, Brown AK. System-based approach to management of neonatal jaundice and prevention of kernicterus. J Pediatr. 2002;140(4):396-403.
25. Slusher TM, Zamora TG, Appiah D, Stanke JU, Strand MA, Lee BW et al. Burden of severe neonatal jaundice: a systematic review and meta-analysis. BMJ Paediatr Open. 2017;1(1):e000105.
26. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation [published correction appears in Pediatrics. 2004 Oct;114(4):1138]. Pediatrics. 2004;114(1):297-316.
27. Maisels MJ. Neonatal jaundice. Pediatr Rev. 2006; 27(12): 443-54.
28. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics. 2004;114(1):e130-e153.
29. Okulu E, Erdeve Ö, Tuncer O, Ertuğrul S, Özdemir H, Aladağ Çiftdemir N, et al. Exchange transfusion for neonatal hyperbilirubinemia: A multicenter, prospective study of Turkish Neonatal Society [published correction appears in Turk Arch Pediatr. 2021 Nov;56(6):657]. Turkish Archives of Pediatrics 2021;56(2):121-126.
30. Erdeve O, Okulu E, Olukman O, Ulubas D, Buyukkale G, Narter F et al. The Turkish Neonatal Jaundice Online Registry: A national root cause analysis. PLoS One. 2018;13(2):e0193108.