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UZAMIŞ SARILIKLI İNFANTLARIN KLİNİK ÖZELLİKLERİ

CLINICAL CHARACTERISTICS OF INFANTS WITH PROLONGED JAUNDICE

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ÖZ

AMAÇ: Uzamış unkonjuge hiperbilirubinemi, bir neonatal sarılık tipidir. Yenidoğanlarda, postnatal 14-21 günden daha uzun süren, yüksek bilirubin düzeyleri(<8 mgr/dl) ile karakterizedir. Bu çalışmada, uzamış sarılıklı bebeklerin klinik ve laboratuvar bulgularını değerlendirdik ve altta yatan sebepleri ele aldık.

GEREÇ VE YÖNTEM: Bu prospektif çalışmaya, Ocak 2018-Aralık 2018 tarihleri arasında pediatri polikliniklerimizde uzamış unkonjuge hiperbilirubinemi tanısı alan yenidoğan bebekler dahil edildi. Hastaların demografik, klinik ve laboratuvar bulguları kaydedildi ve değerlendirildi.

BULGULAR: Toplamda, uzamış sarılık tanısı alan 91 bebek ve kontrol grubu olarak 65 sağlıklı yenidoğan çalışmaya alındı. Uzamış sarılıklı bebeklerin, ortalama doğum kilosu 3152 ± 504 g (1800-4300 g), ortalama gestasyon yaşı 38.2 ± 1.6 hafta (35-41 hafta) ve tanı sırasındaki ortalama bilirubin düzeyleri 10.98 ± 2.3 mg/dL (8-18.7 mg/dL) olarak bulundu. Uzamış sarılıklı bebeklerde, erkek cinsiyet baskın bulundu (%61.5). Doğum kilosuna ulaşma zamanı, uzamış sarılıklı bebeklerde kontrol grubundan daha uzundu (p=0.02). Uzamış sarılığın altında yatan sebepler şunlardı: %45 anne sütü, %9.9 konjenital hipotiroidizm ve %4.4 idrar yolu enfeksiyonu.

SONUÇ: Yenidoğanlarda, uzamış sarılığın temel nedenlerini tespit etmek, oldukça önemlidir. Çoğu olguda, yenidoğan sarılığı anne sütü ile beslenme gibi fizyolojik faktörlerle birliktedir.

ANAHTAR KELİMELER: Uzamış unkonjuge hiperbilirubinemi, etiyoloji, anne sütü sarılığı, yenidoğan

ABSTRACT

OBJECTIVE: Prolonged unconjugated hyperbilirubinemia is a type of neonatal jaundice, which occurs in newborns with high bilirubin levels (> 8 mg/dl) persisting beyond 14-21 postnatal days. This study was carried out to evaluate and determine the clinical and laboratory characteristics of infants with prolonged jaundice and underling causes.

MATERIAL AND METHODS: This prospective study was conducted on newborn infants diagnosed with prolonged unconjugated hyperbilirubinemia during January 2018 and December 2018 at our pediatric outpatient clinic. The demographic, clinical and laboratory characteristics of these patients were recorded and then analyzed.

RESULTS: In total, 91 infants diagnosed with prolonged jaundice and 65 healthy newborn infants as control group were enrolled in this study. Of the infants with prolonged jaundice, mean birth-weight was 3152 ± 504 g (1800-4300 g), mean gestational age was 38.2 ± 1.6 weeks (35-41 weeks), and mean total bilirubin level at the time of diagnosis was 10.98 ± 2.3 mg/dL (8-18.7 mg/dL). There was male sex dominance in prolonged jaundice group (61.5%) Time to reach birth-weight was longer in infants with prolonged jaundice than control group (p = 0.02). The underlying etiologies of prolonged jaundice were as follows: breast milk (45%), congenital hypothyroidism (9.9%) and urinary tract infection (4.4%).

CONCLUSIONS: Determining the main causes of prolonged jaundice in neonates is of paramount importance. In the majority of cases, neonatal hyperbilirubinemia is associated with physiological factors like breastfeeding.

KEYWORDS: Prolonged unconjugated hyperbilirubinemia, etiology, breast milk jaundice, neonate

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INTRODUCTION

Hyperbilirubinemia is a common and usually benign condition which is seen in neonatal period. Prolonged jaundice is defined as visible jaundice beyond 14 days in full-term neonates and beyond 21 days in preterm infants (1). Prolonged unconjugated hyperbilirubinemia is the most common form of prolonged jaundice in neonates and it's the prevalence rate has been estimated at 2-15%. Although breast milk jaundice is the most common cause, it may also be a symptom of a serious underlying disease (2, 3). Other pathological causes associated with prolonged unconjugated hyperbilirubinemia are urinary tract infection (UTI), congenital hypothyroidism and hemolysis. Therefore, these factors should be taken into account in the evaluation of neonates for prolonged jaundice (4). In newborn infants with prolonged jaundice, the underlying causes should be determined in order to plan the follow-up and treatment. Therefore, various investigations which might be ordered would cause to parental anxiety as well as difficulty for the clinician, partly because of the need for extreme investigations.

The aim of this study was to investigate the etiologic factors of prolonged jaundice in newborns infants.

MATERIAL AND METHODS

This descriptive prospective study was conducted in Department of Pediatrics, Mugla Sitki Kocman University Hospital between January 2018 and December 2018. Before beginning to the study, it was approved by ethics committee of the institution. Clinical jaundice (serum total bilirubin ≥ 8 mg/dL) beyond 14 days of life was defined as prolonged jaundice. Newborn infants with conjugated hyperbilirubinemia (> 20% of total bilirubin), major congenital anomalies and underwent surgical interventions were excluded from the study. Demographic characteristics of the newborns including gestational age, gender, birth-weight, type of delivery, feeding status and family history for jaundice were recorded.

Laboratory examinations were included the mother-baby blood groups, direct coombs test, reticulocyte count, complete blood count, glucose-6-phosphate dehydrogenase enzyme level and thyroid function tests (TSH, fT4). Among the biochemical parameters, serum total and direct bilirubin, serum aspartate amino transferase (AST), alanine amino transferase (ALT), gamma glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels were evaluated. In cases where leukocytes were seen in five or more in each area on microscopic examination of urine, urine culture was taken with catheter. The growth of ≥ 10.000 CFU/mL microorganism in urine culture was accepted as UTI.

Infants with serum total bilirubin level below 8 mg/dL were included to control group. The birth-weight and actual weight of babies were recorded and then daily weight gain was calculated. Infants with prolonged jaundice and as control group were statistically compared in terms of the mentioned above parameters. Data analysis was performed by Statistical Package for the Social Sciences 20.0 (SPSS Inc. Chicago, Illinois, USA) using Chi-square and independent samples t-test. Obtained data were presented as mean ± standard deviation; $p < 0.05$ was considered as statistically significant.

ETHICS COMMITTEE

Muğla Sıtkı Koçman University Faculty of Medicine Clinical Research Ethics Committee was approved (22.03.2018, no:03/XII), then the data was collected.

RESULTS

During the study period, 91 infants diagnosed with prolonged jaundice and 65 healthy newborn infants as control group were enrolled in this study. Characteristics of the cases in prolonged jaundice and control groups were presented in **(Table 1)** .

Table 1: Characteristics of the cases in prolonged jaundice and control groups

	Prolonged jaundice (n=91)	Control group (n=65)	P
Gestational age (week)*	38.2 ± 1.6	37.9 ± 1.7	0.34
Birth-weight (gram)*	3152 ± 504	3038 ± 448	0.14
Gender			
Male, n (%)	56 (61.5)	36 (55.4)	0.51
Female, n (%)	35 (38.5)	29 (44.6)	
Type of delivery			
Vaginal, n (%)	21 (23)	19 (29.2)	0.45
Cesarean section, n (%)	70 (77)	46 (70.8)	
Age at admission (day)*	21.1 ± 8.2	26.5 ± 14.3	0.003
Weight at admission (g)*	3646 ± 602	3832 ± 691	0.07
Time to reach birth-weight (day)*	9.1 ± 4.3	7.5 ± 3.8	0.02
Weight at 1 month (g)*	3989 ± 568	3996 ± 605	0.94
Weight gain (g/d)			
≥ 30	37	36	0.07
< 30	54	29	
Previous phototherapy, n (%)	43 (47.2)	23 (52.8)	0.13
Peak total bilirubin level (mg/dL)*	15.6 ± 3.29	13.8 ± 4.8	0.006
Total bilirubin level at the time of diagnosis (mg/dL)*	10.98 ± 2.3	5.6 ± 1.67	< 0.001
Jaundice history in previous siblings, n (%)	14 (15.4)	18 (27.7)	0.47
Phototherapy in previous siblings, n (%)	8 (8.8)	4 (4.4)	0.21
Family history, n (%)	8 (8.8)	4 (4.4)	0.21

*Data are presented as mean ± standard deviation.

The mean gestational age and birth-weight of the newborns with prolonged jaundice were 38.2 ± 1.6 weeks and 3152 ± 504 g, respectively. There was no any difference between the groups in terms of gestational age, birth-weight and mode of delivery. Male sex was dominant in prolonged jaundice group (61.7% vs 55%) Time to reach birth-weight in prolonged jaundice group was longer than control group (p = 0.02). In addition, inadequate weight gain was also more frequent, but this difference was not statistically significant. The predisposing factors in both prolonged jaundice and control groups were shown in the **(Table 2)**.

Table 2: The underlying factors in both prolonged jaundice and control groups

Underlying factor	Prolonged jaundice (n=91)	Control group (n=65)	P
Breast milk jaundice, n (%)	41 (45)	36 (55.4)	0.25
Hypothyroidism, n (%)	9 (9.9)	3 (4.6)	0.22
Urinary tract infection, n (%)	4 (4.4)	4 (6.1)	0.62

The most common cause of prolonged jaundice is breast milk jaundice (58.2%). Hypothyroidism in 9.8% UTI in 4.3% of cases with prolonged jaundice. Although the incidence of hypothyroidism was higher in infants with prolonged jaundice, there was no statistical difference. The incidence of UTI was not different between the groups. ABO and Rh incompatibility was 11% in the study group. However, none of these patients had signs of hemolysis. Prolonged jaundice history was detected in siblings of the 14 (15%) newborn infants and in other family members of the 8 (8.7%) newborn infants.

DISCUSSION

Prolonged jaundice is one of the most common conditions during neonatal and early infancy period (5). Incidence of prolonged jaundice was reported 21.5 per 1000 live births (2).

Males had a higher incidence as compared to females in our study. Various studies have also shown similar result that there was a male preponderance. In the literature, the prevalence of male's predominance varies between 58% and 69% (6, 7).

A probable explanation may be due to social bias, males being more cared for and promptly brought to medical attention (4).

The most common causes of prolonged neonatal jaundice are breast milk jaundice, congenital hypothyroidism and UTI. According to several researches, since no specific etiologies could be confirmed in the majority of infants diagnosed with prolonged unconjugated hyperbilirubinemia, breast milk jaundice is the main cause of prolonged jaundice (2, 4, 8). In present study, we observed that breast milk jaundice is the most important factor of prolonged jaundice. In the literature, the prevalence of prolonged jaundice due to breast milk varies between 30% and 40% (2, 3, 9). Likely, in our study, the etiologic factor was breast milk jaundice in 58.2% of infants with prolonged jaundice. Breast milk jaundice typically develops after the first week after birth and lasts longer than breastfeeding jaundice. The mechanism of breast milk jaundice is not clearly understood (10). Firstly, it has been suggested that bilirubin uptake in the gut (enterohepatic circulation) is increased in breast fed babies, possibly as the result of increased levels of epidermal growth factor in breast milk (11). Secondly, the breast milk of some women contains a metabolite of progesterone called 3-alpha-20-beta pregnanediol which inhibits the action of the enzyme uridine diphosphate glucuronyl transferase (UGT) that is responsible for conjugation and subsequent excretion of bilirubin (12). Thirdly, an enzyme in breast milk called lipoprotein lipase produces increased concentration of nonesterified free fatty acids that inhibit hepatic glucuronyl transferase, which again leads to decreased conjugation and subsequent excretion of bilirubin (13).

More recent data showed a variation in the gene encoding bilirubin conjugating enzyme *UGT1A1* or hepatic uptake of unconjugated bilirubin solute carrier organic anion transporter 1B1 as a genetic basis of breast milk jaundice. Breastfeeding interruption is no longer recommended for breast milk jaundice which is the most common cause of prolonged jaundice because of its low specificity as a diagnostic procedure.

Congenital hypothyroidism largely contributes to the development of prolonged jaundice in newborn infants and its prevalence is reported as 1/2700 in Turkey (14). In our study, hypothyroidism was the second most frequent cause of prolonged jaundice in neonates. In this study, 9.8% of infants with prolonged jaundice have diagnosed as congenital hypothyroidism. Likely, Agrawal et al. (4) reported the congenital hypothyroidism in 7%, Sabzehei et al. (9) in 6% of newborns with prolonged jaundice. In Turkey, Çetinkaya et al. (15) reported the incidence of congenital hypothyroidism in newborns with prolonged jaundice as 8%. The mechanisms by which hypothyroidism raises bilirubin levels are not fully known. Animal studies have shown a decrease in hepatic ligandin level and bilirubin uptake in the liver. In addition, thyroid hormones may play a role in UGT protein expression (16).

In the present study, UTI was detected in 4.4% of the infants. In some studies, the prevalence of UTI in prolonged jaundice was as low as 5-8%, and in some other studies, it was found to be higher as 15-36% (15, 17, 18). Different incidence of UTI may be related to urine culture techniques. UTI increases the bilirubin load by causing hemolysis in erythrocytes, and it causes hyperbilirubinemia by reducing liver conjugation and bilirubin excretion (19).

In our study, there was no case with prolonged jaundice caused by hemolytic disease of newborn due to blood group incompatibilities. In the literature, the incidence of blood group incompatibility in prolonged jaundice is 0-14% (2, 20, 21).

In conclusion, prolonged jaundice is a common disease in newborns. Although breast milk jaundice is considered as a major cause of prolonged jaundice in neonates, identification of other etiological factors, such as congenital hypothyroidism, UTI is also of paramount importance. Early diagnosis and treatment of these disorders could effectively prevent further complication in neonates. It should be told to the family that although breastfeeding is the most common cause of prolonged jaundice, breastfeeding should not be interrupted.

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