Evaluation of Infant with Prolonged Jaundice in Terms of Urinary Tract Infections

İnfantlarda Uzamış Sarılık ve İdrar Yolu Enfeksiyonu İlişkisinin Değerlendirilmesi

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ABSTRACT

Urinary tract infection (UTI) is a common disease in childhood. The incidence of bacterial infections in the neonatal period is 5-6%.Prolonged jaundice is one of the common problems of the neonatal period, and urinary tract infection is also included in the etiology. The aim of this study is to determine the incidence of urinary tract infection, which is one of the important causes in newborns with prolonged jaundice, and to determine accompanying etiological factors. In addition, to review clinical, laboratory and radiological findings and to compare cases with positive radiological findings, to prevent complications secondary to urinary tract infection with early diagnosis.

Key Words: Prolonged jaundice; urinary tract infection;newborns

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ÖZET

İdrar yolu enfeksiyonu (İYE) çocukluk çağında sık görülen bir hastalıktır. Yenidoğan döneminde geçirilen bakteriyel enfeksiyonlar içinde insidansı % 5-6'dır. Uzamış sarılık, ise yenidoğan döneminin yaygın sorunlarından biri olmakla birlikte etyolojide idrar yolu enfeksiyonu da yer almaktadır. Bu çalışmanın amacı, uzamış sarılıklı yenidoğanlarda önemli nedenlerden biri olan idrar yolu enfeksiyonu insidansını belirlemek, eşlik eden etyolojik faktörleri belirlemektir. Bununla birlikte klinik, laboratuvar ve radyolojik bulguları gözden geçirmek ve müspet radyolojik bulgusu olan olguları karşılaştırmak,erken tanı ile idrar yolu enfeksiyonuna ikincil gelişebilecek komplikasyonları önlemektir.

Anahtar Sözcükler: Uzamış sarılık; idrar yolu enfeksiyonu ; yenidoğan

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INTRODUCTION

Prolonged jaundice is defined as persisting hyperbilirubinemia after the 14th day following birth for term and after the 21st day for preterms. Urinary tract infections are a common infectious disease for children of all age groups, constitutes 5-6% of all infections and a large proportion of bacterial infections in the neonatal period (1).The urinary tract can be infected with organisms such as bacteria, viruses and fungi. Urinary tract infection (UTI) presents with different clinical findings in the neonatal period. Urinary tract infection and symptoms in the neonatal period; weight gain, vomiting, prolonged jaundice and high fever may manifest itself with many non-specific findings(2). Early recognition of urinary tract infection, due to pyelonephritis. It is very important in terms of preventing sequelae that may develop. According to the studies performed in the etiology of the prolonged jaundice, it was seen mostly in babies feed with breast milk .The most common cause of prolonged jaundice after breast milk is urinary tract infection (2).

In this study, it was aimed to determine the incidence of urinary tract infections, which is one of the most important causes of prolonged jaundice in neonates, by reviewing the clinical, laboratory and radiological findings and comparing with prenatal histories of radiological findings of the patients with radiologic findings, to prevent complications that may be secondary to early diagnosis and urinary tract infection.

MATERIALS and METHODS

Between January 2005 and October 2016, the patients who were examined and treated in the neonatal intensive care unit at Gazi University Health Research and Implementation Center, Department of Pediatrics and Diseases, were taken into the study. In the study, 226 infants with prolonged jaundice diagnosis recorded in the hospital registry system were reviewed and these datas were evaluated retrospectively. Of the 226 infants with prolonged jaundice diagnosis, 47 (20.7%) had urinary tract infections (UTI) (Group 1), 121 (53.5%) had no urinary tract infections (Group 2) and 58 (25.8%) 58 (25.8%) (Group 3) were patients without urine culture. Group 3 was excluded from the study. Completed weeks of gestation were recorded for gestational age in our study. Preterm births were categorized as very preterm (before 34 weeks of gestation) or late preterm (between 34 weeks and 36 weeks and 6 days). Full-term births are births at or after 37 weeks of gestation. Birth weights were categorized as very low (<1500 g), low (1500249 g), normal (2500-3999 g) or high (> 3999 g). Feeding modes were categorized as exclusive breastfeeding, mixed feeding or special formula feeding.

Using the recorded patient registration numbers, gestational age, birth weight, glucose6-phosphate dehydrogenase (G6PD) deficiency status, reticulocyte counts, thyroid hormone tests, radiological images and characteristics, nutrition pattern were taken from the clinical management system and electronic patient data. The electronic patient record was reviewed to ensure data accuracy, and all suspicious data were verified. A microscopic examination of the urine revealed 5 or more leukocyte infiltrations: pyuria, in each area, 100 000 colony / ml uniform microorganism or 10.000 colony / ml uniform microorganism reproduction in urine culture in catheterization with post urine in suspected positives.

Statistical method

Statistical Package for Social Sciences (SPSS) version 15 was used to evaluate the data obtained from the study and to create the tables. Quantitative data are presented with mean, standard deviation, median, minimum and maximum values, while categorical data (qualitative data) with frequency and percentage values. Chi-square test and Fisher exact test were used for statistical evaluation of categorical data. In the statistical evaluation of the quantitative variables, suitability of the data to the normal distribution data was investigated by the Shapiro wilk test. For the variables with normal distribution, whether there was a statistically significant difference between the two groups was investigated with "Student's t test in independent groups" and with the "Mann-Whitney U test" in non-normal distributions. Significance level was accepted as $p<0.05$ for all statistical analyzes.

RESULTS

226 infants with jaundice diagnosis recorded in the hospital registry system were included in the study. Of the 226 infants with prolonged jaundice diagnosis, 47 (20.7%) were UTI diagnosed (Group 1), 121 (53.5%) were no UTI detected (Group 2) and 58 (25.8%) (Group 3) were patients without urine culture, group 3 was excluded from the study.

Urinary tract infections were more common in term babies with long-term jaundice than preterms. 76.6% of the babies with urinary tract infection were term and 23.4% were preterm.Of the prolonged jaundice infants, mean gestational age was 38.3 ± 1.1 weeks in term infants, 34 ± 1.9 weeks in preterm infants, birth weight was 2530.5 ± 711.7 gr in term infants and 3286.7 ± 390.9 gr in term infants.In the group with urinary tract infection, although no statistically significant difference was available, males were seen to be more than females (p=0,054). In Group 1 and Group 2, in comparison of breast milk, baby food, mixed nutrition types in term and preterm infants, although no statistically significant difference (p= 0,379 and p = 0,789), breast milk was seen to be used more.(Table 1)

Table 1: Demographic characteristics of infants with prolonged jaundice (p> 0.05 - not statistically significant)

Variables		With UTI				P	Without UTI				P	P_1	P_2
		Term		Preterm			Term		Preterm				
		n	(%)	N	(%)		N	(%)	N	(%)			
Gender	Male	27	(75,0)	7	(63,6)	0,461	55	(56,7)	15	(62,5)	0,606	0,054	0,948
	Female	9	(25,0)	4	(36,4)		42	(43,3)	9	(37,5)			
Nutrition type	Breast Milk	29	(80,6)	10	(90,9)	-	68	(70,1)	21	(87,5)	0,371	0,379	0,789
	Formula Feeding	2	(5,6)	0	(,0)		13	(13,4)	1	(4,2)			
	Mixed Feeding	5	(13,9)	1	(9,1)		16	(16,5)	2	(8,3)			

P: Comparison of gender, mode of delivery and nutritional type of those who are with UTI and without UTI
P1: Comparison of gender, mode of delivery and nutritional type of term infants with Urinary tract infection and without
P2:Comparison of gender, mod of delivery and nutritional type of preterm infants with Urinary tract infection and without

In this study, at least one uridine diphosphate glucuronosyltransferase (UGT1A1) gene mutation. mutation was detected on the 16 of the 17 infants taking breast milk. CRP level was detected higher in term and preterm babies in Group 1 compared to Group 2. Serum total bilirubin level was found to be higher in preterms with UTI compared terms (p = 0.05). No significant difference was detected between white blood cell count in term and preterm infants in Group 1 and Group 2. Serum G6PDG level was found low in a term infant with UTI, and found normal in other infants.

In group 1 and 2, reticulocyte levels were found higher in term infants.(p = 0,578 and 0,999) In Group 2, TSH levels were detected in 2 in term infants. All five infants were diagnosed with congenital hypothyroidism and received euthyrox therapy (Table 2).

In Group 1, the preterm infants were more likely to have longer jaundice than term infants (p = 0.044). Preterm infants with UTI were seen to get more phototherapy compared to term infants with UTI.(P = 0.009) No exchange transfusion was performed in infants with prolonged jaundice. ABO incompatibility was found to be higher in preterm infants without UTI than in term infants without UTI (p = 0.042).

Table 2. Characteristics of reticulocyte,CRP, G6PDG and TSH values

Variables		With UTI				P	Without UTI				P	P_1	P_2
		Term		Preterm			Term		Preterm				
		n	(%)	n	(%)		n	(%)	n	(%)			
Reticulocyte	Normal	22	(78,6)	5	(62,5)	0,384	49	(73,1)	13	(68,4)	0,686	0,578	0,999
	High	6	(21,4)	3	(37,5)		18	(26,9)	6	(31,6)			
G6PDG	Low	1	(5,3)			0,999					-	0,264	-
	Normal	18	(94,7)	6	(100,0)		53	(100,0)	11	(100,0)			
TSH	Normal	36	(100,0)	11	(100,0)	-	96	(99,0)	23	(95,8)	0,359	0,999	0,999
	High						1	(1,0)	1	(4,2)			
CRP	Normal	17	(85,0)	8	(72,7)	0,638	31	(96,9)	15	(100,0)	0,999	0,285	0,063
	High	3	(15,0)	3	(27,3)		1	(3,1)					

P: comparison of reticulocyte, CRP, G6PDG, TSH values in those with and without UTI
P1: comparison of reticulocyte, CRP, G6PDG, TSH values in term babies with and without UTI
P2: comparison of reticulocyte, CRP, G6PDG, TSH values in preterm babies with and without UTI

Excessive reproduction of Klebsiella and E. coli was observed in microorganisms reproducing in term and preterm infants (p = 0,287). Reproducing microorganisms were evaluated in three groups according to the number of colonies. Pathological ultrasound findings were detected in 13.6% of term infants with urinary tract infection and in 12% of the group who did not have urinary tract infection.

Normal ultrasound findings were detected in preterm patients with urinary tract infection, and abnormal ultrasound findings were detected in 14.3% of the non-urinary tract group.İn infants with urinary tract infection have raciological findings such as posterior urethral valve, grade 1 hydronefrosis in the left kidney and grade 2 dilatation in the left collecting system were detected. n infants with no urinary tract, bilateral renal minimal caliectasis, extrarenal localization and focal caliectasis in the lower pole of the left renal pelvis, 1st degree echogenicity increase in bilateral kidneys, grade 1 dilatation was detected in the left kidney collecting system.In our study, antenatal ultrasonography of 41 patients was recorded and ıt was found to be normal in term infants with urinary tract infection.

Table 3. Characteristics of radiological findings of prolonged jaundice infants (p> 0.05 - not statistically significant)

Variables		With UTI				P	Without UTI				P	P_1	P_2
		Term		Preterm			Term		Preterm				
		N	(%)	N	(%)		n	(%)	n	(%)			
Urinary USG	Normal	19	(86,4)	9	(100,0)	0,537	22	(88,0)	12	(85,7)	0,999	0,999	0,502
	Finding available	3	(13,6)				3	(12,0)	2	(14,3)			
Antenatal USG	Normal	28	(100,0)	9	(100,0)	-	2	(40,0)	2	(100,0)	0,429	**0,002**	-
	Finding available						3	(60,0)					

P: Comparison of radiological findings of patients with and without urinary tract infection
P1: Comparison of radiological findings of patients with and without urinary tract infection in term infants
P2: Comparison of radiological findings of patients with and without urinary tract infection in preterm infants

DISCUSSION

Urinary tract infection is one of the most common infections in children. It constitutes 5-6% of all infections (1). Age, anatomic factors affect the risk of developing urinary tract infection (1). UTI in neonatal infants differ from UTI in infants and children. The frequency of UTI is more common in neonates in males and is usually accompany with bacteremia or underlying urinary tract anomalies (1). This is why it is important to examine the functional anomalies of the kidneys and urinary tracts as urinary tract infections in the neonates may cause parenchymal scarring and chronic renal failure in the kidney(1). As in many infections occurring during this period, jaundice in UTI is usually the first and most important finding in neonatal period. In a study conducted to investigate the frequency of urinary tract infections in the neonates, it was found that the most common clinical manifestation was jaundice (2).Hemolysis, deteriorated bilirubin congestion and excretion resulting due to hepatocellular injury is responsible for the pathophysiology of the jaundice of fever and malnutrition urinary tract infections (2). In our study, urinary tract infections were detected in 47 (20.8%) of 226 infants who were admitted to the neonatal intensive care unit, applied ambulatory to pediatrics and neonatal polyclinics and diagnosed with prolonged jaundice. Although UTI is prevalent in infants, it can easily be overlooked because it comes with nonspecific findings. In a study conducted by Hacer Yılmaz et. al., UTI have been detected in 66 (9,9%) of 667 prolonged jaundice infants (2). In a study conducted by Chamidine Omar et al. in Japan, UTI have been detected in 32 (21%) of 152 prolonged jaundice case (3).The prevalence of urinary tract infection varies according to onset day and gender. It was shown that it occurs in higher ratio in males compared to females in the first 3 month (4). Urinary tract infection was detected in 75% in term infants, 25% in term female infants, 63.6% in preterm male infants and 36.4% in preterm female infants in our study a significant difference was found between the urinary tract infection and the onset of jaundice (p = 0.044) and it was determined that the jaundice occurred later in preterm infants. N.Tuygun's study showed that jaundice occurred later in infants with urinary tract infections but no term and preterm discrimination were done (5). Preterm infants with urinary tract infections were found to have higher serum indirect bilirubin levels than term infants. There are no patients with direct hyperbilirubinemia in our study. In the study performed by N.Tuygun, of the 231 prolonged jaundice infants, UTI was detected in 17 of them (7.3%), and indirect hyperbilirubinemia (82.3%) in 14 of them and combined type hyperbilirubinemia (17.7%) in 3 of them(5). G. Öcal et. al, in their study reported that it caused combined type hyperbilirubinemia of urinary tract infections(6). In many studies, the incidence of urinary tract malformations in urinary tract infections has been reported to vary between 13 and 49% (7).In patients with a urinary tract infection, it is possible to identify both the localization of the infection and the medical and surgical approach to be applied to the patient with radiological examinations. In recent years, it has been suggested to perform radiologic imaging of infants and young children after first infection with both types (8). USG, a non-invasive imaging method, has gained importance for this purpose. In a prospective study, hydronephrosis, renal atrophy and vesicoureteral reflux (VUR) were detected in 22 (49%) out of a total of 45 infants under 8 weeks of age who were diagnosed with urinary tract infection but did not have antenatal USG (9). In some studies, no urinary system anomalies were encountered in neonatal groups with urinary tract infections (6,10,11). In contrast to these results, Bilgen H. et al.'s study revealed that newborn babies with UTI had a high rate of abnormalities in their urogenital systems (12).In our study, in radiological screening of prolonged jaundice infants, of the 47 (20,7%) infants with urinary tract infection, 1 (2,1%) had posterourethral valve (PUV), 1 (2,1%) had bilateral grade 1 echogenicity increase in the kidneys, 1 (2,1%) had minimal caliectasis in kidneys; in 121 (53,5%) infants whose urinary tract infection could not be detected, 1 (0,8%) had bilateral pelvicalyceal system slightly distinct, 1 (0,8%) had grade 1 dilatation in left collecting system, 1 (0,8%) had grade 1 hydronephrosis in left kidney, 1 (0,8%) had left kidney pelvis extrarenal localization with caliectasis in inferior pole, 1 (0,8%) had stage 2 expansion in left kidney collecting system. Three infants with pathologic USG findings in the urinary tract infection group had normal antenatal ultrasonography, while USG findings in the non-infected group of 5 infants, in antenatal ultrasonography of 3 infants, 1 had becoming apparent in the left kidney, 1 had stage 2 expansion in the left renal collecting system, 1 had stage 2 expansion in the left renal collecting system. Pathologic USG findings of prolonged jaundice infants were compared with findings of antenatal ultrasonography findings and there was a significant difference in the group without urinary tract infection (p = 0.002). This result shows that there may be urinary tract infection although antenatal ultrasonography is normal but prolonged jaundice may also be early finding of urinary tract infection. In our study, most (69%) of cases applying with prolonged jaundice constituted the cases in which there was no underlying cause and were considered to be prolonged jaundice due to breast milk. In the literature, it was reported that about three thirds of the infants fed with breast milk were clinically jaundiced during the third week of life and two thirds of these had high indirect hyperbilirubinemia (13). Although it has been suggested initially that pregnanediolum, which is found in the breast milk and is a hepatic glucuronyl transferase enzyme inhibitor may cause jaundice, it is now considered not to be the primary factor but contributes to the incidence. Today, the mechanism that attracts most attention and discussed is that an unidentified factor present in the breast milk increases the intestinal absorption of bilirubin. It has also been suggested that increased bilirubin absorption rather than high bilirubin production increases breast milk jaundice (14,15). In a study by Yoshihoro et al., they concluded that breast milk jaundice is associated with bilirubin uridine diphosphate glucuronosyltransferase (UGT1A1) gene mutation (16). In this study, at least one UGT1A1 mutation was detected on the 16 of the 17 infants taking breast milk. Although breast milk jaundice is prolongation of normal physiological jaundice, the causes of pathological jaundice must be ruled out in extremely high values(14). In our study, other pathological jaundice causes were also ruled out and breast milk jaundice was diagnosed. Hematologic causes constituted the third frequency with 8% in the etiologic ranking of our cases with prolonged jaundice. 94.5% of this group constituted ABO and RH incompatibility, 5.5% G6PDG deficiency. Tuygun et.al. report that in the study which they evaluated 231 patients with prolonged jaundice, the most frequent etiologic cause when the group which they couldn't identify the etiology were hematologic diseases with 14,7% and this was due to blood group incompatibilities (5). In our study, no significant difference was detected between white blood cell count in term and preterm infants in Group 1 and Group 2. Serum G6PDG level was found low in a term infant with UTI, and found normal in other infants. Congenital hypothyroidism constituted the fourth frequency with 2,2% in the etiologic ranking of our cases with prolonged jaundice. In the literature, this ratio has been reported as 1,2% to 25% in various studies(17,18). According to the etiology distribution in prolonged jaundice infants study of Çetinkaya et al., the most frequent was breast milk (53%), second was sepsis (29%), and third was urinary tract infection (14.9%)(18). In our study, the most common was detected as breast milk (69%). The second was the urinary tract infection (20,8%), which is detected at a higher rate in our study compared to the other study. Although the pathophysiological relationship between hyperbilirubinemia and UTI has not been fully demonstrated, one of the proposed mechanisms is hemolysis caused by E coli and other gram-negative bacteria. Even little hemolysis in newborns can cause significant hyperbilirubinemia due to immature conjugation mechanisms, and therefore serum bilirubin levels may increase as a warning sign even in mild clinical severity of UTIs. UTI-related conjugated hyperbilirubinemia may be associated with cholestasis. Although UTI is not well defined, how microcirculation problems in the liver and direct bacterial and endotoxin-mediated products are other recommended mechanisms (19). However, some authors claim that the relationship between UTI and neonatal jaundice is just a coincidence (20).

The frequency of prolonged jaundice and urinary tract infections in the neonatal period is known. However, it should be kept in mind that the diagnosis can be delayed and even overlooked, although it should be kept in mind that the most common cause after breastmilk jaundice in our country, where breastfeeding rate is high in prolonged jaundice, may be urinary tract infection. In addition, patients should be carefully evaluated in terms of congental anomalies of the urinary system while being monitored for diseases such as blood group incompatibilities, thyroid hormone disorders, and G-6PD. In this way, it should be kept in mind that the risk of renal damage due to infection will be reduced by detecting anomalies that predispose to the development of UTI, such as congenital anomalies of the urinary system.

In conclusion, the number of studies examining the relationship between UTI and prenatal imaging in neonates with prolonged jaundice is low. In this retrospective study, we showed that neonates with prolonged jaundice had a higher incidence of UTI compared to other etiologic factors, early diagnosis could be made with prenatal renal imaging and restricted examinations. Prospective multicentre metaanalysis studies are required in this context and these should be done with a rational algorithm.

Conflict of interest
No conflict of interest was declared by the authors.

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