Urinary tract infection and hyperbilirubinemia

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The aim of this study was to evaluate the incidence of urinary tract infection (UTI) in newborns with asymptomatic, unexplained indirect hyperbilirubinemia in the first two weeks of life.

Jaundiced infants, otherwise clinically well, less than two weeks of ages, with a total bilirubin level above 15 mg/dl were eligible for the study. A bilirubin work-up including glucose-6-phosphate dehydrogenase (G-6 PD) level, as well as urinalysis and a urine culture were performed in all patients. Patients with UTI, defined as more than 10,000 colony-forming units per milliliter of a single pathogen obtained by bladder catheterization, were evaluated for sepsis. Renal function tests and renal ultrasound were performed in cases with UTI. During follow-up, voiding cystourethrogram (VCUG) and dimercaptosuccinic acid scintigraphy (DMSA) were performed as well.

A total of 102 patients were enrolled. The bilirubin work-up of patients did not demonstrate any significant underlying disorder. None of the infants had a high direct bilirubin level. UTI was diagnosed in eight (8%) cases [Enterobacter aerogenes (3/8:38%), Enterococcus faecalis (2/8:25%), Klebsiella pneumoniae (2/8:25%) and Escherichia coli (1/8:12%)]. Of those eight patients, only four (50%) had pyuria. Bacteriuria was present in seven (88%) patients. The sepsis screen was negative in all but one case with a high C-reactive protein (CRP) level. None of the patients had a positive blood culture. Renal function tests were within normal levels in all patients. Renal ultrasound showed urinary tract abnormalities in three (38%) patients (hydronephrosis, n=1 and pelviectasis, n=2). VCUG was performed in all patients during the study period and one had unilateral grade 3-4 reflux, while only one patient had a diverticulum of the bladder. DMSA was performed in seven patients and none had renal scars.

It is of importance that UTI can occur in asymptomatic, jaundiced infants even in the first week of life. Although it is well known that UTI is a common cause of prolonged jaundice, urine culture should be considered in the bilirubin work-up of infants older than three days of age with an unknown etiology.

Key words: hyperbilirubinemia, urinary tract infection, newborn.

Jaundice is a frequently encountered problem during the newborn period. Although up to 60% of term newborns have clinical jaundice in the first week of life, few have a significant underlying disease[1]. However, it can be associated with severe illnesses such as hemolytic disease, metabolic and endocrine disorders, enzymatic deficiencies of the liver and infections[2]. Although some studies have reported that unexplained hyperbilirubinemia may be associated with bacterial infections in newborns, the American Academy of Pediatrics (AAP) guidelines do not recommend an evaluation for such infections[1]. Urinary tract infections (UTI) are attributed as the main reason for prolonged jaundice[3]. It is well known that the clinical manifestations of UTI can cover a wide spectrum, ranging from severe illness to nonspecific signs and symptoms such as growth failure and jaundice[2]. The aim of this

study was to determine the incidence of UTI in infants with asymptomatic, unexplained indirect hyperbilirubinemia in the first two weeks of life.

Material and Methods

Jaundiced infants, otherwise clinically well, younger than two weeks, with a total bilirubin level above 15 mg/dl who presented to the newborn nursery for the evaluation of jaundice from May 2002 to December 2003 were eligible for the study. The demographic features, including gestational age, maternal infections, mode of delivery, maternal fever and postnatal events including fever and sepsis, were recorded. Significant weight loss was defined as a decrease in weight of more than 3% per day in the first four days of life or a weight measurement below birth weight at the 10th day of life[4]. Patients jaundiced in the first 24 hours with signs of hemolysis and cases with fever and signs of sepsis were excluded. A direct Coombs' test, blood types of the baby and mother, complete blood count (CBC), blood smear, glucose-6-phosphate dehydrogenase (G-6PD) level and reticulocyte count were performed. All study participants older than three days had a urine sample obtained by a catheter. The urine sample was tested using Multistix 10 (Bayer) for standard urinalysis. For microscopical analysis, urine specimens were centrifuged at 2000 revolutions per minute for five minutes, resuspended and stained, and examined microscopically under high power field (HPF) for pyuria. Pyuria was defined as >5 white blood cell (WBC) per HPF[5]. All urine specimens were sent for Gram stain and standard quantitative culture and considered positive if a single pathogen with more than 10,000 colony forming units was isolated[6]. All positive urine cultures were repeated before starting antibiotics. If the urine culture became positive, a sepsis work-up, including a CBC, C-reactive protein (CRP), blood smear (immature/total neutrophil ratio), micro sedimentation rate and blood culture, was performed. A lumbar puncture was to be performed in infants with a positive blood culture. Renal ultrasound and renal function tests were performed in cases with UTI. During follow-up, voiding cystourethrogram (VCUG) was performed in the first month after a sterile urine culture was obtained, while dimercaptosuccinic acid scintigraphy (DMSA) was performed at the third month of life. The demographic characteristics of the infants, initial day of jaundice, referral day, initial bilirubin levels, number and level of rebounds at 24 h and the duration of phototherapy were compared between patients with positive (group 1) and negative (group 2) urine culture results.

Statistical Analysis: For statistical analysis, SPSS for Windows 10.0 software package was used. The comparison of groups for dichotomous variables was performed with Fisher's exact test. Mann-Whitney U test was used in comparison of group means and a value of $p<0.05$ was considered significant.

Results

During the study period, 102 asymptomatic jaundiced term newborns were enrolled in the study. The mean age of the study population was $5.7\pm2.5^{3-13}$ days. The initiation of jaundice, reported by the family member, was $3.3\pm1.5^{1-7}$ days. Sixty-two percent of the infants were males. The mean birth weight and mean gestational age of the patients were 3356±403 (2490-4510) g and 38.8±0.9 (37-41) weeks, respectively. Forty-five percent of the infants were born vaginally. The infants were exclusively breastfed. All the male infants were uncircumcised. Significant weight loss was found in 23% of cases. Demographic characteristics of patients with positive (group 1) and negative (group 2) urine cultures are compared in Table I. No statistically significant difference was found between groups with regard to age, gender, birth weight, gestational age, mode of delivery and weight loss. None of the mothers had an infection or pregnancy complication.

The mean initial bilirubin levels of 102 infants were 18.4±2.2 (15-26) mg/dl. The bilirubin work-up of patients did not demonstrate any significant underlying disorder. None of the infants had a high direct bilirubin level. When we compared the groups regarding the referral day, initial day of jaundice, initial bilirubin levels, number of rebound cases at 24 hours and the duration of phototherapy, we again could not find any statistical significance (Table II). All of the cases were treated with phototherapy and none of the cases required an exchange transfusion.

Table I. Demographic Characteristics of Patients with Positive (Group 1) and Negative (Group 2) Urine Cultures

Characteristics	Group 1 (n=8)	Group 2 (n=94)	P value
Gender Male/Female (n)	6/2	57/37	0.42
Birth weight (g) Mean (standard deviation) Range (min-max)	3556±464 (2910-4510)	3338±391 (2490-4400)	0.18
Gestational age (weeks) Mean (standard deviation) Range (min-max)	38.8±0.46 (38-39)	38.7±0.91 (37-41)	0.81
Mode of delivery (n) Vaginal/C/S (n)	2/6	44/50	0.29
Weight loss (n)	1/7	18/76	0.42

Table II. Jaundice Data of Patients with Positive (Group 1) and Negative (Group 2) Urine Cultures

Characteristics	Group 1 (n=8) Mean (standard deviation)	Group 2 (n=94) Mean (standard deviation)	P Value
Age at referral (day) Mean (standard deviation) (range)	5.7±0.9 (4-7)	5.8±2.6 (2-13)	0.74
Jaundice first noticed (day) Mean (standard deviation) (range)	3.6±1.5 (1-6)	3.3±1.5 (1-7)	0.78
Initial bilirubin level (mg/dl) Mean (standard deviation) (range)	19.5±3.7 (15-26)	18.3±2.1 (15-24)	0.73
Rebound cases at the 24th hour (%)	0	9	0.39
Duration of phototherapy (hour) Mean (standard deviation) (range)	16.0±9.1 (2-30)	18.2±9.8 (4-72)	0.81

Among 102 patients enrolled in the study, eight (8%) had UTI. Most of the cases with UTI were males (75%). A single organism was isolated in all cases. Enterobacter aerogenes (3/8:38%), Enterococcus faecalis (2/8:25%), Klebsiella pneumoniae (2/8:25%) and Escherichia coli (1/8:12%) were the organisms isolated. Of those eight patients, only four (50%) had pyuria. None of the infants had significant microscopic hematuria. Bacteriuria was present in seven (88%) patients. The sepsis screen of the patients was negative except for one case with a high CRP level. None of the patients had a positive blood culture.

Renal function tests were within normal levels in all patients. The renal ultrasound showed urinary tract abnormalities in three (3/8) patients which included hydronephrosis (1 patient) and pelviectasis (2 patients). VCUG was performed in all patients during the study period and one of them had unilateral grade 3-4 reflux, while only one patient had a diverticulum of the bladder. DMSA was performed in seven patients and none had renal scarring.

Discussion

The incidence of nonphysiologic hyperbilirubinemia in full-term neonates was reported in different studies to be between 4.8 and 15.5% during the first week of life[7-9]. Sepsis is a well-known cause of neonatal jaundice in seriously ill newborns and it is reported in some studies that jaundice may be the first sign of sepsis in the first few days of life[10]. A study recently reported showed that hyperbilirubinemia was the main clinical finding among term newborns with UTI[11]. Although similar results were reported from different studies indicating jaundice as the initial finding of UTI, it is more frequently screened in patients with prolonged jaundice. Maisles[12] reported that no case of sepsis and

UTI was diagnosed in 306 newborns admitted to a pediatric ward within 21 days of birth with indirect hyperbilirubinemia. However, only 41% of these cases were investigated for UTI. In conclusion, they limited the investigation for sepsis and UTI only for infants who appeared sick, had late-onset jaundice and direct hyperbilirubinemia or abnormal physical examination or laboratory investigation. Another study showed that among 80 infants younger than one month of age with UTI, 11 (14%) had hyperbilirubinemia, while only four had bacteriemia[13].

The incidence of UTI in newborn infants is 0.1-1% and can be as high as 10% in low-birthweight and preterm infants[14]. Several studies showed that the incidence is higher in febrile or hyperbilirubinemic patients[15-17]. In a recent study, it has been reported that UTI was found in 7.5% of asymptomatic jaundiced infants younger than eight weeks[3]. The incidence of UTI (8%) in our study group was comparable to the incidence of UTI in febrile infants, which is reported to be between 5% and 11%[15-17], but higher than reported in the study group of Garcia et al[3]. They reported that infants with the onset of jaundice after eight days and with an elevated conjugated bilirubin fraction were more likely to have UTI, and they therefore recommended testing for UTI to be included as a part of the evaluation in asymptomatic jaundiced infants. When we compared our study with that of Garcia[3], we found that the onset of jaundice was even earlier in most of our cases (<7 days), which prompts us to evaluate infants with unexplained jaundice for UTI after the fourth day of life as well.

Similar to the data indicated in the literature, UTI was found to be more frequent in males in our study group. However, when we compared the characteristics of the groups with positive and negative urine cultures regarding age, gender, birth weight, gestational age and mode of delivery, we could not find any data of statistical significance. Although poor weight gain can be the presenting sign of UTI, it was not found to be statistically significant between the study groups. The explanation for no difference in our study groups could be the early diagnosis of these cases. As all male infants in the study group were uncircumcised, we could not compare its effect on UTI.

E. coli is responsible for the vast majority of UTI in infants younger than three months of age[14]. In our study group, Enterobacter aerogenes (3/8) was the predominating organism, followed by Enterococcus faecalis (2/8), Klebsiella pneumoniae (2/8) and Escherichia coli (1/8).

It is well known that UTI can occur without apparent signs, and jaundice is an important and sometimes the presenting feature of UTI[14]. The initial bilirubin levels, number of rebound cases at 24 hours and the duration of phototherapy of the patients with and without UTI did not show statistical difference. Although pyuria commonly accompanies significant bacteriuria, cells can be few or absent in the presence of bacteriuria in as many as one half of the patients, as was determined in our study and in other studies[16]. Pyuria was present in only four (50%) of 10 patients. Thus, neither presence nor absence of pyuria is completely reliable evidence for or against UTI. Bacteriuria, which can be demonstrated in 0.5% to 1% of full-term infants and in as many as 3% of premature infants in studies using the bladder aspiration technique, was found in 88% of our patients with UTI; none of the cases without UTI had bacteriuria[18].

It is very common to diagnose UTI in cases with prolonged jaundice[3,14]. Interestingly, all of our patients were younger than one week at the time of diagnosis, which makes it important that a urine culture and analysis be included in the bilirubin work-up in healthy appearing infants in the first week of life. Patients with recurrent UTIs may be at increased risk of hypertension or renal insufficiency, but the magnitude of this threat is poorly defined[5].

Although Garcia et al.[3] reported that patients with an elevated conjugated bilirubin fraction were more likely to have UTI, none of our patients had a high direct bilirubin level. It is also of importance that only one of our patients had a high CRP level, which points out that a negative sepsis screen is not sufficient to rule out UTI.

In conclusion, it is necessary to point out that UTI can occur in asymptomatic, jaundiced infants even in the first week of life. Although it is well known that UTI is a common cause of prolonged jaundice, urine culture should also be considered in the bilirubin work-up of infants older than three days with hyperbilirubinemia of an unknown etiology.

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