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Unexplained neonatal jaundice as an early diagnostic sign of urinary tract infection

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SUMMARY

Background: Hyperbilirubinemia is one of the presenting signs of bacterial infection in newborns, and the association of neonatal jaundice with urinary tract infection (UTI) has been particularly emphasized. The aim of this study was to determine the prevalence of UTI in asymptomatic jaundiced neonates younger than 4 weeks old.

Methods: We prospectively evaluated 120 asymptomatic jaundiced and 122 healthy neonates without jaundice younger than 4 weeks old for UTI. Patients with UTI, defined as >10 000 colony-forming units of a single pathogen per milliliter urine obtained by bladder catheterization, were evaluated for sepsis.

Results: Of 120 asymptomatic jaundiced neonates with a mean age of 7 ± 4 days, 15 (12.5%) had a UTI. Of 122 healthy neonates, positive urine cultures from a urine bag were found in eight cases; however on reevaluation, urine cultures from bladder catheterization were negative. The most common pathogen isolated from the UTI cases was Klebsiella pneumoniae. Also, unconjugated hyperbilirubinemia was detected in all jaundiced patients with UTI.

Conclusion: UTI was found in 12.5% of the asymptomatic jaundiced neonates with the onset of unconjugated hyperbilirubinemia in the first week of life. Therefore, we suggest that urine culture should be considered as a part of the diagnostic evaluation of jaundiced neonates older than 3 days with an unexplained etiology.

1. Introduction

Hyperbilirubinemia is a common disorder during the neonatal period. About 60% of full term and 80% of premature neonates develop clinical jaundice in the first week of life.[1,2] Some studies have reported that unexplained hyperbilirubinemia may be associated with bacterial infections in the newborn, such as urinary tract infection (UTI).[3]

The clinical manifestations of UTI in neonates are extremely variable, ranging from severe illnesses to nonspecific signs and symptoms such as growth failure or jaundice.[4] UTI is thought to be the main reason for prolonged jaundice, thus urine culture is routinely performed in neonates with jaundice aged more than 3 weeks.[5]

The aims of this study were to determine: (1) the prevalence of UTI in neonates with asymptomatic, unexplained unconjugated hyperbilirubinemia in the first 4 weeks of life; and (2) if urine culture should be considered a necessary evaluation in asymptomatic jaundiced neonates younger than 4 weeks of age.

2. Materials and methods

One hundred and twenty asymptomatic jaundiced neonates younger than 4 weeks of age, admitted to the newborn unit of Nemazee Hospital, affiliated with Shiraz University of Medical Sciences (intervention group), and 122 healthy neonates without jaundice who presented to the outpatient clinic (control group) from June 2007 through August 2008 were eligible for the study.

Patients jaundiced in the first 48 h of life with signs of hemolysis, or cases with documented fever >38 °C and signs of sepsis (vomiting, poor feeding, lethargy, etc.) were excluded. Demographic data including prenatal events, such as gestational age, maternal infections, mode of delivery, and prolonged rupture of the membranes, were recorded. Postnatal events including neonatal fever, onset of jaundice, and whether the infant was breastfed or formula-fed, were also collected. The following tests were performed in the intervention group: complete blood count, peripheral blood smear, glucose-6-phosphate dehydrogenase (G6PD), direct Coombs' test, blood typing of the neonate and mother, total and direct bilirubin, and reticulocyte count. A urine sample was collected from each neonate by bladder catheterization.

For the control group, urine samples were obtained using urine bags. Part of the urine sample was tested using Multistix 10 (Bayer,

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Germany) for standard urinalysis. For microscopic analysis, urine specimens were centrifuged at 2000 revolutions per min for 5 min, resuspended, stained, and examined microscopically under high-power field (HPF) for pyuria, which was defined as ≥10 white blood cells (WBC)/HPF.[6] All the urine specimens were sent for standard quantitative culture to the Prof. Alborzi Clinical Microbiology Research Center, Shiraz, Iran.

The urine culture obtained by bladder catheterization was considered positive if a single pathogen with more than 10 000 colony forming units per milliliter (CFU/ml) was isolated. A urine culture by urine bag was taken as positive if a single pathogen with more than 100 000 CFU/ml was detected. An antibiogram by disk diffusion was done on all the positive urine cultures. In the case of a positive urine culture in the jaundiced neonates, a sepsis evaluation consisting of blood cell counts, C-reactive protein (CRP), and blood culture was performed. A lumbar puncture was also done in those cases with positive blood cultures.

In the follow-up of the healthy neonates (control group), all the positive urine cultures were repeated by bladder catheterization, and in positive cases ($\geq 10^4$ CFU/ml) the patients were contacted and instructed to return to the hospital for admission and sepsis evaluation.

A renal function test, renal ultrasound, and voiding cystourethrogram were performed in all the neonates with UTI.

SPSS version 15 was used for the statistical analysis. Descriptive data were reported as mean ± standard deviation, and the associations between categorical variables were analyzed using Fisher's exact test. Statistical significance was defined as a p-value of <0.05.

3. Results

The study population consisted of 120 asymptomatic jaundiced neonates as the intervention group and 122 healthy neonates as the control group. In the intervention group, the mean age was 7 ± 4 days, 95 neonates (79%) had a birth weight more than 2500 g, and 92 neonates (77%) were born at term (37–42 weeks of gestation); 73 (61%) neonates were male and 47 (39%) were female. In the control group, the mean age was 5 ± 6 days, 97 neonates (80%) had a birth weight more than 2500 g, and 112 (92%) were term neonates; 95 (78%) neonates were male and 27 (22%) were female.

Positive urine cultures were obtained for 15 (12.5%) of the 120 asymptomatic jaundiced infants enrolled ($p < 0.001$). Positive urine cultures were obtained from the urine bags of eight of the 122 healthy neonates; however on reevaluation, the results of urine culture from bladder catheterization were negative. Demographic characteristics of the jaundiced patients with positive and negative urine cultures are presented in Table 1. No statistically significant differences were found between the two groups with regard to age, birth weight, gestational age, mode of delivery, or maternal infections. However, the prevalence of UTI was significantly higher in the male compared to the female neonates. In the present study none of the male cases were circumcised.

Bacterial pathogens, urine microscopy, and serum bilirubin levels in the jaundiced infants with positive urine cultures are shown in Table 2. Bacterial pathogens isolated from the urine cultures in the 15 cases were as follows: Klebsiella pneumoniae (6/15, 40%), Escherichia coli (4/15, 27%), Enterobacter (4/15, 27%), and Serratia (1/15, 7%).

Five of the 15 neonates had pyuria, defined as ≥10 WBC/HPF. There were no statistically significant differences in pyuria between the two groups of jaundiced infants, i.e., those with positive urine cultures and those with negative cultures.

All the jaundiced patients with positive urine cultures had unconjugated hyperbilirubinemia, and there were no differences in mean total serum bilirubin in these neonates (19.88 ± 5.5), as compared with jaundiced patients with negative urine cultures (19.88 ± 6.57).

After the initial study evaluation, these 15 patients with UTI were admitted to the hospital. One patient, a 6-day-old female, had UTI and bacteremia, both secondary to Enterobacter. Other blood cultures and all CSF cultures were negative. Renal ultrasounds were performed for these patients; three (20%) cases had hydronephrosis and the others were normal. No abnormalities were detected by voiding cystourethrogram in the three patients.

4. Discussion

The incidence of non-physiological hyperbilirubinemia in neonates is significant,[7] and sepsis has been documented as a cause of neonatal jaundice in seriously ill newborns.[8] However, jaundice may be one of the first signs of bacterial sepsis in the first few days of life.[9] Some studies have indicated that jaundice is the first sign of a newborn with a UTI.[10] Garcia and Nager found evidence of UTI in 12 of 160 (7.5%) asymptomatic jaundiced neonates presenting to an emergency department. A positive urine culture was more likely when the jaundice was first noted after 8 days of age.[3] Bilgen et al. reported the results of a series of 102 neonates with

Table 1
Demographic characteristics of the neonates with positive and negative urine cultures

Characteristics	Positive urine culture (n = 15)	Negative urine culture (n = 105)	p-Value
Age, n (%)			>0.05
<2 weeks	14 (93%)	99 (94%)	
≥2 weeks	1 (7%)	6 (6%)	
Sex, n (%)			0.03
Male	13 (87%)	60 (57%)	
Female	2 (13%)	45 (43%)	
Birth weight, n (%)			0.2
<2500 g	5 (33%)	20 (19%)	
≥2500 g	10 (67%)	85 (81%)	
Gestational age, n (%)			0.43
<37 weeks	4 (27%)	20 (19%)	
≥37 weeks	11 (73%)	85 (81%)	
Vaginal delivery, n (%)	9 (60%)	77 (73%)	0.66
Perinatal infections, n (%)			0.4
Prolonged rupture of the membranes ≥18 h	0	3 (3%)	
Maternal infections	1 (7%)	16 (15%)	
Feeding, n (%)			0.7
Breast feeding	13 (87%)	96 (91%)	
Formula feeding	0	1 (1%)	
Breast and formula feeding	2 (13%)	8 (8%)	

Table 2
Bacterial pathogens, urine microscopy, and serum bilirubin level of the neonates with positive urine cultures

Patient	Age, days	Sex	Urine culture, CFU/ml	Urine microscopy, WBC/HPF	Total bilirubin, mg/dl	Conjugated bilirubin, mg/dl
1	9	Male	$>10^4$ E. coli	>5	14	0.5
2	8	Male	$>10^5$ Klebsiella	>20	25	1.2
3	25	Male	$>10^5$ E. coli	6–8	19	0.8
4	7	Female	$>10^4$ Enterobacter	<5; WBC clamp: 1	20	0.8
5	7	Male	$>10^5$ Klebsiella	15–20	22	1.5
6	8	Male	$>10^4$ Klebsiella	10–12	15	0.6
7	6	Female	$>10^4$ Enterobacter	10–12	14	0.7
8	7	Male	$>10^5$ Klebsiella	<5	18	1
9	7	Male	$>10^5$ E. coli	<5	17	0.8
10	4	Male	$>10^4$ E. coli	5	20	1.1
11	4	Male	$>10^5$ Klebsiella	8–10	25	1.9
12	6	Male	$>10^4$ Enterobacter	<5	34	0.7
13	6	Male	$>10^4$ Enterobacter	<5	18	0.9
14	12	Male	$>10^4$ Serratia	<5	20	0.9
15	7	Male	$>10^5$ Klebsiella	10–12	17	1

CFU, colony-forming units; WBC, white blood cells; HPF, high-power field.

asymptomatic, unexplained unconjugated hyperbilirubinemia in the first 2 weeks of life. A UTI was present in eight (8%) cases.[11]

Furthermore, the finding of a positive blood or urine culture in a newborn with indirect-reacting hyperbilirubinemia does not prove that the infection is the cause of jaundice. However, neonates who appear sick or have late-onset jaundice, direct-reacting hyperbilirubinemia, and an abnormal physical examination or laboratory investigations, should be evaluated carefully for possible sepsis or UTI.[5]

As stated, the aim of this study was to determine the prevalence of UTI in asymptomatic jaundiced neonates younger than 4 weeks. The advantage of this study over those reported previously is the presence of a control group, i.e., the healthy neonates with no jaundice, for comparison with the intervention group. To the best of our knowledge, there has been no other comparative study as such.

In the present study, UTI was found in 12.5% of the asymptomatic jaundiced infants younger than 4 weeks. However, all the urine cultures in the age-matched and healthy neonates without hyperbilirubinemia were negative. Interestingly, the prevalence of UTI (12.5%) in our study was slightly higher compared to that of studies in febrile infants younger than 8 weeks, in which the prevalence was reported to be between 5% and 11%.[12,13] UTI was found more frequently among males in the present study. However, when we compared other characteristics of the jaundiced neonates with negative and positive urine cultures, we could find no data of statistical significance.

As none of the male neonates in the current study had been circumcised, we could not compare its effects on UTI. However, some studies have shown statistically higher local uropathogenic bacteria colony counts and a 10-times higher prevalence of UTI in uncircumcised male infants.[14,15]

Pyuria (≥10 WBC/HPF) was present in five (33%) patients with UTI and there were no statistically significant differences between positive and negative urine cultures in jaundiced neonates ($p = 0.9$). Although pyuria commonly accompanies significant bacteriuria, neither its presence nor absence can serve as completely reliable evidence for or against UTI.[16,17] It is important to point out that there were statistically significant differences in pyuria in negative urine cultures of the jaundiced infants compared to the control group ($p < 0.001$). Although we cannot provide with finality an explanation for the results obtained above, we may conclude that slight dehydration in the jaundiced neonates was probably responsible for the presence of WBC in their urine. Nonetheless, the findings lend support to the fact that pyuria cannot serve as a sensitive marker in the diagnosis of UTI, particularly in jaundiced neonates.

The question to be posed here is if the jaundiced patient could have bacteriuria rather than a UTI. Asymptomatic bacteriuria is defined as a condition in which the urogenital tract is thought to be colonized rather than infected. In the present study we can conclude that a positive urine culture is not indicative of incidental asymptomatic bacteriuria, because unlike in other reported studies, there was a control group with negative urine cultures, matched with the patient group in terms of age. Some studies have found the incidence of bacteriuria in asymptomatic neonates to be between 0.5% and 1%.[18–20]

None of our jaundiced patients with UTI had a high conjugated bilirubin level, in concordance with the study of Bilgen et al.[11] However, Garcia and Nager reported that all patients with an increase in the conjugated bilirubin fraction were diagnosed with a UTI.[3] Lee et al. reported the results of a retrospective study that indicated that infants with UTI may present with unconjugated hyperbilirubinemia in the early stages, and that after the age of 6 weeks it is always conjugated hyperbilirubinemia.[21]

In the current study, the most common pathogen isolated was K. pneumoniae, followed by Enterobacter, E. coli, and Serratia. All these organisms had 10% sensitivity to gentamicin, imipenem, and ciprofloxacin, and 100% resistance to ampicillin. We found urinary tract abnormalities in three (20%) of the 15 patients evaluated by renal ultrasound, which included hydronephrosis. All of them had a normal voiding cystourethrogram.

The present study had some limitations, namely that none of the neonates were circumcised, and thus we cannot draw any conclusions about the association between circumcision and the incidence of UTI. In addition, not all the infants with UTI and hydronephrosis had a dimercaptosuccinic acid renal scintigraphy radionuclide scan.

In conclusion, UTI can occur in asymptomatic, afebrile neonates presenting with unconjugated hyperbilirubinemia in the first weeks of life. In this study, the prevalence of UTI in asymptomatic jaundiced neonates was 12.5%, and jaundice may be the first sign of UTI before other signs become evident. We suggest that urine culture should be considered as a part of the diagnostic evaluation of neonates older than 3 days with hyperbilirubinemia of unknown etiology.

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Conflict of interest: No conflict of interest to declare.

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