Urinary tract infections in neonates with jaundice in their first two weeks of life

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Original article

Background: **Hyperbilirubinemia is a frequently seen condition in neonates. This study was undertaken to determine the role of urinary tract infections (UTIs) in the etiology of indirect hyperbilirubinemia in neonates with jaundice in their first two weeks of life.**

Methods: **The study was conducted prospectively. The subjects were neonates aged 4-14 days with hyperbilirubinemia which could not be detected by routine tests and was sufficiently severe to necessitate phototherapy.**

Results: **The study was performed in 104 neonates, of whom 18% (*n*=19) had UTI. The most frequently identified micro-organism was *Escherichia coli* (43%). Phototherapy duration and rebound bilirubin level were higher in neonates with UTI (*P*<0.05).**

Conclusion: **UTI should be investigated in neonates with hyperbilirubinemia of unknown etiology in the first two weeks of life.**

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Key words: **hyperbilirubinemia;**
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Introduction

Hyperbilirubinemia is a frequently seen condition in the newborn period. While bilirubin levels remain within physiological limits in some newborns, they may rise to pathological levels necessitating treatment in others. While a specific cause, such as blood group incompatibility, may be determined with first-stage tests in some neonates with hyperbilirubinemia, in others the cause cannot be determined. Urinary tract infection (UTI) can lead to prolonged jaundice.[1,2] However, reports on the role of UTI in unexplained neonatal hyperbilirubinemia in the first two weeks of life are rare.[3,4] This study was undertaken to determine whether UTI should be investigated in newborns aged 4-14 days with indirect hyperbilirubinemia, of which the cause could not be determined with routine examinations, but it is severe enough to require treatment. Another objective of the study was to find the characteristics of cases determined with UTI.

Methods

Subjects

This descriptive study was performed in the Newborn Intensive Care Unit at the Erzurum Regional Training and Research Hospital in Turkey between October 1, 2010 and July 1, 2011. Subjects enrolled in the study were neonates at age of 4-14 days and had a gestational age greater than 35 weeks, with jaundice above the phototherapy limits set by the American Academy of Pediatrics.[5] They had no signs of systemic infection such as fever or hypothermia, tachypnea, tachycardia, an abnormal white cell count and increased immature cells, nor prolonged rupture of membranes, no history of maternal infection and no identified causes such as isoimmunization, sequestration or polycythemia that might account for the jaundice.

Gestational and postnatal age, birth weight, postnatal weight, type of delivery, sex, feeding type, bilirubin level at presentation, phototherapy duration and rebound bilirubin level were recorded for all the neonates enrolled. Baby's blood group, mother's blood group, direct Coombs test, hemogram, peripheral blood smear, reticulocyte count, total and direct bilirubin level and full urine analysis, including urine microscopy, were determined or performed for all cases. Thyroid function tests were also performed. Urine sample was obtained using the catheterization technique from

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neonates who could not be explained in terms of blood group (with no reticulocytosis and no hemolytic findings in peripheral smear or with negative direct Coombs test). Glucose-6 phosphate dehydrogenase and pyruvate enzyme levels and reductant matter in urine were not analyzed since testing facilities are not available in our hospital. Immediate renal ultrasonography (USG), voiding cystouretherogram (VCUG) when urine cultures were sterile and dimercaptosuccinic acid scintigraphy (DMSA) were planned for neonates with UTI.

Ethical committee approval was granted, and informed consent forms were obtained from patients' families.

Definition

A single pathogen growing at 10 000 colony forming units (CFUs) or above in urine culture was regarded as significant.[6] White cell counts of >5 in every field (high power field) following centrifugation of urine samples was regarded as pyuria.[7] Before beginning antibiotic treatment, confirmatory urine culture, blood culture and hemograms were taken from culture-positive cases, and an immature/total neutrophils ratio was calculated using peripheral smear. C-reactive protein (CRP) levels were measured. CFUs of 10 000 or above in confirmatory urine cultures with the same micro-organisms growing in culture and antibiograms were regarded as UTI. Cases with no growth in confirmatory urine culture, growth of less than 10 000 CFUs, and the growth of different micro-organisms and/or more than one micro-organism or different antibiograms were excluded.

Statistical analysis

SPSS 17 was used for statistical analysis. Variables determined by measurement are expressed as mean±standard deviation, and those determined arithmetically as percentages. Non-UTI cases were classified as group 1, and UTI cases as group 2. The data obtained were then compared. Student's *t* test was used to compare variables determined by measurement between the two groups, and the Chi-square test or Fisher's exact test was used to compare those determined arithmetically. $P<0.05$ was considered statistically significant.

Results

One hundred and thirty-five neonates with jaundice presented to our department in the study period. Of these, 104 (77%) meeting the inclusion criteria were enrolled. UTI was determined in 18% (n=19) (group 2). Demographic characteristics of the neonates included are presented in Table 1, and their clinical and laboratory characteristics in Table 2. Phototherapy was given to all neonates. UTI was more frequent in male neonates ($P<0.005$). There was no statistically significant difference between the two groups in terms of other demographic characteristics ($P>0.05$).

Table 1. Demographic characteristics of infants (mean±standard deviation)

Variables	Group 1 (n=85)	Group 2 (n=19)	P value
Gestational age, wk	37.9±2.1 (35-41)	37.7±1.0 (37-41)	>0.05
Types of delivery			
Vaginal, n (%)	57 (67)	13 (68)	>0.05
Cesarean, n (%)	28 (33)	6 (32)	>0.05
Male/female, n	45/40	17/2	<0.005
Birth weight, g	2989±406 (2210-4100)	3049±351 (2400-3800)	>0.05
Types of feeding			
Breastfeeding, n (%)	80 (94)	16 (84)	>0.05
Breastfeeding and/or formula, n (%)	5 (6)	3 (16)	>0.05
Postnatal weight, g	2788±380 (2000-3600)	2817±351 (2110-3620)	>0.05
Postnatal age, d	6.4±3.5 (4-13)	6.5±1.7 (4-10)	>0.05

Table 2. Clinical and laboratory characteristics of infants (mean±standard deviation)

Characteristics	Group 1 (n=85)	Group 2 (n=19)	P value
Bilirubinemia at presentation, mg/dL	18.8±2.5 (17.6-24.9)	18.8±1.9 (17.7-23.8)	>0.05
Reticulocyte percentage, %	1.2±0.2 (1-2)	1.3±0.3 (1-3)	>0.05
Rebound bilirubin, mg/dL	10.3±1.8 (8.6-13.3)	12.3±1.6 (9.2-13.6)	<0.005
Hemoglobin, g/dL	16.9±2.1 (13.9-20.8)	16.5±2.0 (13.4-21.2)	>0.05
White cell count, $\times 10^3/\mu L$	11.0±3.9 (6.5-28.6)	10.8±3.1 (7.3-21.1)	>0.05
Phototherapy duration, h	32.6±9.3 (24-48)	42.9±9.2 (36-60)	0.01

Mean phototherapy duration and rebound bilirubin levels were significantly higher in group 2 than in group 1 ($P<0.05$). Pyuria and bacteriuria were determined in 32% (6) of the neonates with UTI, bacteriuria alone in 21% (4) and pyuria alone in 11% (2). The most frequent micro-organisms seen in urine culture were *Escherichia coli* (42%), *Enterobacter cloacae* (37%), *Klepsiella pneumonia* (15%), and *Enterobacter aerogenes* (5%). There were no abnormalities in blood culture in any neonates, and CRP levels were negative.

Urinary USG was performed in all neonates with UTI; fullness in left pelvicalyceal structures was determined in four cases and bilateral hydronephrosis in one. Vesicoureteral reflux (VUR) was identified in two cases, grade 3-4 on the right in one, and bilateral grade 5 in the other. Posterior urethral valve was determined in a male neonate with bilateral VUR. A hypoactive field was observed in the upper and lower poles of the right kidney in one of the neonates who underwent DMSA.

Discussion

Early diagnosis and treatment of UTI are essential to prevent serious complications such as renal scarring, proteinuria, hypertension and end-stage renal failure.[8] Childhood UTI exhibits non-specific findings and symptoms.[8] Jaundice has been reported to be the first sign observed in UTI in newborn babies.[9]

It is uncertain whether there is any correlation between jaundice and UTI in the first two weeks of life. Jaundice is observed during the first two weeks of life in approximately 2/3 of neonates. UTI investigation is considered unnecessary in the analysis of newborn jaundice during the first two weeks of life, since urine culture for every case is expensive and culture by catheterization is invasive and causative to UTI.[5,10,11] However, studies[3,4,12,13] have recommended UTI investigation in neonates with no symptoms other than jaundice.

Garcia and Nager[3] found UTI in 7.5% of 160 infants with unexplained jaundice; 75% of the infants with UTI were less than 14 days old. Bilgen et al[4] found UTI in 8% of 102 term newborns with unexplained jaundice in the first two weeks of life. Xinias et al[12] reported a UTI rate of 6.5% in newborns with jaundice aged between 3 and 25 days. On the other hand, Chavalitdhamrong et al[13] reported a UTI rate of 3% in 69 newborns with unexplained jaundice aged less than two weeks. In our study, the UTI rate was 18% in newborns with unexplained jaundice who required phototherapy. This rate of UTI was higher than that reported previously. This rate may be due to the socioeconomic status of our region and families lacking sufficient knowledge of baby care.

UTIs in the neonatal period are frequently seen in males, as in our series.[3,4,12] Bilgen et al[4] reported VUR in 13% of UTI infants with jaundice but no renal scarring in any infant who received DMSA. Xinias et al[12] reported VUR in 13.3% of UTI infants with jaundice and cortical defect in 47% of infants who were subjected to DMSA. In our study the VUR prevalence was 10.5% in newborns with UTI, and cortical defect was noted in 5% of the infants who were administered DMSA.

Bilgen et al[4] reported a similar mean duration of phototherapy and a rebound bilirubin level in newborns with hyperbilirubinemia with or without a diagnosis of UTI. In our study, the mean duration of phototherapy and rebound bilirubin level were higher in neonates diagnosed with UTI than in those without a diagnosis of UTI.

The causes of coincidental hyperbilirubinemia and UTI are still not fully understood. Neonatal infections may lead to hyperbilirubinemia through hemolysis, conjugation failure and reduced expulsion to the intestine. Heme oxygenase (HO) can be induced by oxidant stresses during infection. The increasing HO accelerates the conversion of Heme to bilirubin.[14] Bilirubin has protective antioxidant properties. An increased bilirubin level may be associated with the use of bilirubin as an antioxidant at the beginning of infection.[14] The higher duration of phototherapy and a rebound bilirubin level in our infants with UTI support this point of view. One limitation of our study was that patients were not followed up for a long period.

In conclusion, UTI had a higher incidence rate of 18% in newborns with jaundice whose etiology could not be confirmed by routine tests. Thus it is useful to investigate UTI in newborns with unexplained indirect hyperbilirubinemia in their first two weeks of life.

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