Bilirubin levels predict renal cortical changes in jaundiced neonates with urinary tract infection

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Background: **This study was undertaken to determine the incidence of urinary tract infection (UTI) and the frequency of anatomical abnormalities in newborns with unexplained jaundice and to find out if there is any correlation between bilirubin level and renal damage.**

Methods: **We studied 462 full-term neonates for UTI. They were aged 3-25 days, with either high (>10 mg/dL) or prolonged (>10 days) hyperbilirubinemia, with or without manifestations such as fever, vomiting, diarrhea, poor feeding, lethargy, and irritability. Neonates positive for UTI were further investigated with ultrasound, cystourethrography, and acute phase renal scintigraphy with technetium-99m dimercaptosuccinate acid (DMSA).**

Results: **Thirty neonates (6.5%) were found to have UTI. Twenty-eight of them had indirect hyperbilirubinemia and two had direct hyperbilirubinemia, with total bilirubin levels of 11.8-20.1 mg/dL. None of the neonates was found to have jaundice because of other reasons such as infection. Vesicoureteral reflux was found in 5 neonates and one of them was combined with hydronephrosis. Renal scintigraphy with technetium-99m DMSA showed renal cortex changes in 14 (46.7%) of the 30 neonates with UTI. These 14 neonates also had increased levels of bilirubin in comparison to those with normal findings of DMSA.**

Conclusions: **The incidence of UTI in uncomplicated neonatal jaundice is relatively high. Anatomical abnormalities of the urinary tract are not rare in infected children. Increased bilirubin levels are related to pathological findings in renal scintigraphy.**

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doi:10.1007/s12519-009-0007-4

World J Pediatr 2009;5(1):42-45

Key words: **hyperbilirubinemia; neonates; urinary tract infection**

Introduction

Jaundice is a common sign in the neonatal period. Each year 60% of newborns become clinically jaundiced.[1,2] Urinary tract infection (UTI) has previously been implicated for neonatal jaundice.[3-6] It is relatively frequent (5%-11%) among febrile infants and symptom free icteric neonates.[7-13] The incidence of UTI in symptom-free infants is 0.7% to 1.4%[14,15] and urinary tract abnormalities are present in up to 55% of affected jaundiced infants.[4,11-13] Symptoms and signs of UTI in neonates can be non-specific or absent.[11,13] Neonates with UTI may present discomfort, feeding refusal, vomiting, failure to thrive, and fever.[16-20] Whether higher bilirubin levels in affected jaundiced neonates are related to pathologic renal technetium-99m dimercaptosuccinate acid (Tc-99m DMSA) findings (renal damage) remains unknown. We aim to determine the incidence of UTI in newborns with unexplained jaundice, the frequency of anatomical abnormalities in neonates with jaundice and UTI, and the possible relationship between bilirubin level and renal damage.

Methods

We studied 462 neonates with jaundice, aged 3-25 days (mean age ± SD, 13.1±6.4 days) and birth weight >2500 g, who were referred to our clinic for further investigation. Jaundice in the neonates as referred by the attending physicians appeared between the 1st and 4th day of life. All neonates had either high (>10 mg/dL total bilirubin) or prolonged (>10 days) hyperbilirubinemia. Twenty-eight percent of them were fully bottle-fed for various reasons and 72% breast-fed.

Accompanying clinical symptoms presented in

148 (32%) of the 462 neonates included fever >38°C, vomiting, diarrhea, poor feeding, tachypnea, lethargy, and irritability. In 314 neonates (68%), no accompanying symptoms were recorded. Diagnostic approach was based on the protocol of our clinic for pathologic neonatal jaundice. Total and conjugated serum bilirubin concentrations, and glucose-6 phosphate dehydrogenase (G6PD) levels were determined along with full blood cell count and red cell volume. Blood group, liver function, Coombs reaction and thyroid function tests were also performed. Moreover, all the newborns were investigated for UTI. In jaundiced neonates presenting with accompanying symptoms (fever, vomiting, etc), urine specimens were obtained by suprapubic paracentesis of the bladder for urinalysis and urine culture. If no accompanying symptoms were present, two urine bag samples were obtained for urinalysis and culture.

All neonates were tested in the clinical laboratory by urinalysis, microscopy, Gram staining, and culture. A standard urinalysis was performed using Multistix 10 (Bayer) and urine specimens were centrifuged at 2000 revolutions per minute for 5 minutes, resuspended and stained. The specimens were then examined microscopically under high-power field (HPF) for pyuria (reported as leukocytes per HPF) and bacteriuria (reported as none, few, moderate, and many). The urine specimens obtained by suprapubic paracentesis were sent for standard quantitative culture and considered positive if any colony forming unit of a single pathogen was isolated. Samples collected with urine bag were also sent for standard quantitative culture and considered positive if >100 000 colony-forming units from a single pathogen were isolated.[14] In neonates with positive cultures from the bag-specimens, another urine sample was obtained by suprapubic paracentesis of the bladder (Diagnosis of UTI required any colony forming unit of a single pathogen).

After a diagnosis of UTI, the infant's primary care physician or the general pediatric service resident and attending physician, while in hospital, managed the patient. Further urinary tract investigation was conducted with ultrasound and acute phase cortical scintigraphy with Tc-99m DMSA. Cystourethrography (cyclic voiding cystourethrography, VCUG) was also performed a few days after completing antibiotic treatment.[21-23] Sonographic examination was performed before VCUG by the same two radiologists and the result was known at the time of VCUG examination. Tc-99m DMSA scans (Apex95 γ-camera; Elscint, Haifa, Israel) performed at the acute phase of the infection, examined whether the kidneys showed Tc-99m DMSA uptake defects (pyelonephritic changes), whether were small in size or had abnormal contours. The percentage of uptake of Tc-99m DMSA by the kidney was calculated as the percentage of total uptake by the two kidneys, and was considered abnormal when the uptake percentage was less than 45%.[24,25] Follow-up information was obtained from medical record review.

Statistical analysis

GraphPad InStat was the statistical program that was used according to the requirements of the study. Data were presented using descriptive statistics. Fisher's exact test was used for comparisons of incidence between groups. The non-parametric Mann-Whitney test was performed for unpaired comparison of continuous variables. A P value <0.05 was considered statistically significant.

Results

Thirty (6.5%) of the 462 jaundiced neonates were found to have UTI. Among them, no other potential causes for their hyperbilirubinemia were detected. Twenty-two of the 30 neonates with UTI were boys and 8 girls (P=0.0072). All the 30 patients had hyperbilirubinemia with highest total bilirubin level ranging from 11.8 to 20.1 mg/dL. The highest bilirubin values were recorded at different ages in proportion to age of each neonate. Direct bilirubinemia was found in 2 neonates, and anemia in 10. Twenty-two neonates (73.3%) suffered from bacteriuria and 8 (26.7%) from bacteriuria and pyuria. Cerebrospinal fluid cultures were negative in all neonates with positive urine cultures. The most frequent cause for UTI was *E. coli* (Table).

Further investigation of the urinary tract (ultrasound, cystourethrography, and 99Tc-DMSA scans) showed vesicoureteral reflux (VUR) in 4 neonates (13.3%), VUR and hydronephrosis in 1, and

Table. Incidence of urinary tract infection in 462 jaundiced neonates and the causes for infection

	Negative urine culture	Positive urine culture	Bacteriuria	Bacteriuria and pyuria	*E. coli*	*Proteus M*	*Enterococcus species*	*Klebsiela*
Boys	201	22 (10.9%)	18	4	17	3	1	1
Girls	231	8 (3.4%)	4	4	8	0	0	0
Total	432	30 (6.5%)	22 (73.3%)	8 (26.7%)	25 (83.3%)	3 (10.0%)	1 (3.3%)	1 (3.3%)

pelvicaliceal dilation in 2 (6.7%). Unilateral VUR of grade 2 was detected in 2 neonates and unilateral VUR of grade 3 in the other 2. Bilateral VUR of grade 4 and hydronephrosis were detected in 1 neonate. 99Tc-DMSA scans demonstrated cortical changes (focal defect of isotope uptake) in 14 (46.7%) of the 30 infected neonates. All the 14 neonates were symptomatic for sepsis. None of them had a low percentage of uptake or small kidneys. The mean total bilirubin levels in DMSA positive and DMSA negative neonates were 15.55±2.00 and 13.84±2.46 mg/dL, respectively (P=0.0323). Appropriate intravenous treatment was given to all infected neonates according to the result of the antibiotic sensitivity test. The total bilirubin level decreased 1-3 days after treatment.

Discussion

Bacteriuria in asymptomatic full-term neonates is reported between 0.7%-1.4% [14,15,26-34] and raises to 2.9% in preterm neonates.[14] In febrile infants younger than 8 weeks old and neonates with asymptomatic jaundice the prevalence of UTI is between 5% and 11%.[7-13] It was 6.5% in jaundiced neonates in our study. This finding shows that UTI is more frequent in jaundiced neonates than in asymptomatic neonates. The most common pathogen isolated in our study was *E. coli* (83.3%), followed by *Proteus M* (10.0%), *Enterococcus species* (3.3%), and *Klebsiela* (3.3%). Other studies reported similar findings.[4,11,31]

The incidence of UTI between boys and girls in our study was 10.9% and 3.4% respectively (P<0.05), as reported previously.[4] Other investigators reported vesicoureteral reflux in 16.6% of jaundiced neonates.[13] In another study, urogenital abnormality was detected in 17.39% of icteric neonates with UTI.[12] Ultrasonography revealed urinary tract abnormalities in 3 of 8 jaundiced neonates with UTI (hydronephrosis in 1 neonate and pelviectasis in 2) by Bilgen et al,[11] and VCUG detected unilateral vesicoureteral reflux in 1 (12.5%) of the 8 patients. In our study, vesicoureteral reflux and hydronephrosis were found in 16.7% and pelviectasis in 6.7% of neonates respectively.

Bilgen et al[11] performed DMSA scintigraphy in 7 of 8 icteric neonates with UTI, and found no renal scars in any of these neonates. Pashapour et al[13] found cortical defect in the kidney by renal scan in 33.3% of infected neonates with jaundice. In our study, renal DMSA was performed in 30 infected neonates with jaundice, and renal cortical changes were observed in 14 (46.7%) of 30 icteric neonates. This finding seems to be similar to other studies mentioned above.

Serum bilirubin levels were found to be correlated with DMSA findings in 30 icteric neonates. The levels of serum total bilirubin differed significantly between patients with positive DMSA findings (cortical changes) and those with normal DMSA findings (higher in patients with cortical changes). This finding may be attributed to the fact that neonates with cortical changes had probably higher levels of bacteremia, which could produce a higher rate of hemolysis and, consequently, increased bilirubin levels. On the other hand, cholestasis due to infection (bacteremia) and possible low activity of the enzyme glucuronic transferase may contribute to the high levels of total serum bilirubin in these neonates.

In conclusion, UTI is relatively frequent in neonates with unexplained jaundice. Anatomical abnormalities of the urinary tract (vesicoureteral reflux, hydronephrosis, and pelviectasis) are not rare in infected children. It seems that increased bilirubin levels are related to renal damage. Further studies are necessary in the future to confirm this finding.

Funding: None.
Ethical approval: Not needed.
Competing interest: None.
Contributors: Xinias I wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version.

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Received February 21, 2008
Accepted after revision November 28, 2008