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Investigation of Urinary Tract Infection in Neonates with Hyperbilirubinemia

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This study was performed on 100 jaundiced neonates as cases and on 100 neonates without hyperbilirubinemia as controls to investigate the incidence of UTI in neonates with hyperbilirubinemia. Medical history, physical examinations and laboratory tests were done on all cases and data was analyzed by SPSS software. The urinary analysis and culture (U/A, U/C) were performed on the urinary samples which were collected by bladder catheterization under sterile condition. Of the total of 100 jaundiced neonates, 11 cases had UTI, while there was no case of UTI in neonates without jaundice. This difference in the incidence of UTI between two groups was significance (p-value = 0.001). Vesicourethral reflux was the most common finding anomaly in the neonates with UTI. Our results indicate that UTI is one of the important factors in neonatal jaundice. Therefore it is necessary to do U/A and U/C in all the neonates with hyperbilirubinemia. In addition, radiological studies such as sonography and voiding cystourethrography (VCUG) in all the neonates with UTI are necessary.

Key words: Neonate, hyperbilirubinemia, urinary tract infection

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INTRODUCTION

Bilirubin is cleared by the liver and both certain genetic defects and liver diseases can cause hyperbilirubinemia (Kamisako *et al*., 2000). Jaundice, the accumulation of high levels of bilirubin in the circulation, is particularly common in human neonates (Dennery *et al*., 2001). The incidence of jaundice in the first week of birth is 60% among mature and 80% among premature neonates (Garcia and Nager, 2002; MacDonald *et al*., 2005). Although it is usually benign, the condition is of importance because, rarely, severe hyperbilirubinemia can lead to bilirubin encephalopathy or kernicterus (Kaplan *et al*., 2003).

Guidelines from the American Academy of Pediatrics have emphasized the need to identify neonates with hemolysis, a major risk factor for developing kernicterus (American Academy of Pediatrics, 2001). Based on the instruction of American Academy of pediatrics, the following tests are necessary in the neonates with hyperbilirubinemia; maternal blood group and Rh, direct coombs, umbilical cord blood group and Rh and serum total and direct bilirubin (MacDonald *et al*., 2005). Different studies were performed to investigate the etiology of neonatal hyperbilirubinemia. In a study of Taiwanese newborns by Huang *et al*. (2004) they provided challenging new evidence emphasizing the clinical importance of genetics in the development of neonatal hyperbilirubinemia. Their study investigated the effects of several risk factors such as; breast feeding, premature birth, glucose-6-phosphate dehydrogenase deficiency and some genetic polymorphisms in the genes supposed to be involved in the hepatic uptake of unconjugated bilirubin (UDP-GT1A1 and OATP-2).

Knowledge of bilirubin conjugation genetics and identifying genetic mutations of bilirubin conjugation may be a useful parameter in identifying neonates at risk for developing severe hyperbilirubinemia. However, not every neonate with hyperbilirubinemia requires full genetic consultation and laboratory analysis. Many infants at risk for hyperbilirubinemia may be identified by other methods such as physical examination and a few simple laboratory tests. There are reports that idiopathic hyperbilirubinemia in infants could be in combination with bacterial infections (Linder *et al*., 1988).

It was reported that UTI incidence among febrile neonates under 8 weeks old is 5-11% (Garcia and Nager, 2002; Biyikli *et al*., 2004). In addition, the incidence of bacterimia and sepsis among infants with UTI is reported to be 6 to 36% (Wang *et al*., 1994; Garcia and Nager, 2002). Furthermore, the incidence of urinary tracts abnormalities among infants with UTI is 30-55% and vesicourethral reflux is the most common abnormality (Cleper *et al*., 2004). Most cases of UTI in infants are diagnosed as acute pyelonephritis (Behrman *et al*., 2004). The clinical symptoms of UTI in infants contain wide ranges including growth retardation, nausea, irritability, lethargy, oliguria, polyuria, bad smell of urine and jaundice (Garcia and Nager, 2002; Behrman *et al*., 2004).

Jaundice can be one of the early symptoms of UTI. Therefore investigating UTI in the infants with unexplained hyperbilirubinemia is part of the work up for jaundice. This will help finding the cause of jaundice, the source of UTI and its management. The importance of UTI, in addition to its high incidence in infancy promotes us to investigate this problem in neonates with hyperbilirubinemia.

MATERIALS AND METHODS

This analytical case-control study was done on 100 infants without any clinical jaundice, referring to the Shahid Sadoughi Hospital (main University Hospital in Yazd) when they were 7 days old as controls and on 100 infants with clinical jaundice as cases from April 2004 to April 2006. Jaundiced infants with a total bilirubin level above 15 mg dL^{-1} were eligible for the study. The infants with fever, diarrhea, vomiting, poor breast feeding and weakness were excluded from the study. The maximum age for the infants to be included in the study was 30 days. A sample of urine was taken from all the infants for urine analysis and culture (U/A and U/C). This urine sample was taken by sterile gloves and bladder catheterization in aseptical condition. UTI was detected when more than 10,000 colony-forming units per milliliter of a single pathogen obtained by bladder catheterization. A peripheral blood sample was taken from all the infants with clinical jaundice and then bilirubin was measured by spectrophotometry method. The data of clinical examination, history and laboratory analysis was collected from their files and was analyzed by SPSS software using Chi-square test. The p-value less than 0.05 was considered to be significant.

RESULTS

From the total of 200 studied infants, 106 were boys (53%) and 94 were girls (47%). There were 58 boys in the case group, while 48 boys were in the control group. The gender differences in two groups were not statistically significant. Overall, there was no significant difference in demographic data between case and control groups expect their ages (Table 1). The urine culture was positive in 11 out of 100 case infants, while there was no positive

Table 1: Demographic characteristics of infants in case and control groups

Variable	Case group (n = 100)	Control group (n = 100)	p-value
Age in days (range)	8.8 (1-29)	14.7 (8-21)	0.000
Weight in gr (range)	3055 (1850-4990)	3079 (2200-4000)	0.727
Gender (number)	Boys (58)	Boys (48)	0.57
	Girls (42)	Girls (52)	
Gestational age in weeks (range)	39 (36-42)	40 (36-42)	0.376

Table 2: Gender, maturity status, age of jaundice appearance (age J.), urine culture results (U/C), urine analysis results (U/A), total bilirubin (T. bil.) and Direct bilirubin (D. bil.) in the 11 cases with UTI

Gender	Maturity	Age J.	U/C*	U/A*	T. bil. (g dL^{-1})	D. bil. (g dL^{-1})
Boy	Preterm	Day 3	*Klebsiella*>100000	Normal	25.2	0.7
Boy	Term	Day 3	*E. coli* > 50000	Normal	14.5	0.2
Girl	Term	Day 2	*E. coli* > 100000	Normal	18.5	0.5
Boy	Term	Day 3	*E. coli* > 50000	WBC=10-11	14.5	2
Boy	Term	Day 8	*Klebsiella*>100000	Normal	14.5	0.5
Boy	Term	Day 8	Gram positive cocci	Normal	14.8	0.2
Boy	Term	Day 8	*E. coli* > 50000	Normal	19.8	0.3
Boy	Term	Day 10	*Proteus* > 100000	Normal	9.4	0.6
Girl	Preterm	Day 4	*Klebsiella*>100000	Normal	17	0.4
Girl	Preterm	Day 2	*E. coli* > 100000	WBC=10-20	9	0.5
Boy	Term	Day 8	*Citrobacter* >100000	WBC=10-20	14.7	0.2

* The urine sample was taken by catheter and under sterile conditions

urine culture in the control group. This difference was significant statistically by Chi-square test (p-value = 0.001). The most common detected organism in urine culture was Escherichia coli (*E. coli*) which was positive in 5 out of 11 urine culture (45.5%), followed by *Klebsiella*, *Proteus* and Citrobactrococci gram positive. From the total of 11 positive U/C, in only 3 cases WBC>5 was reported, while U/A was reported to be normal in 8 cases (Table 2). All of the infants with positive U/C were hospitalized and sepsis workup was done on them and they were treated by antibiotics therapy. At the end of the treatment, all of these infants were investigated by ultrasonography and voiding cystourethrography (VCUG) to detect any abnormalities in the urinary tract. Three abnormalities were reported by these tests including 2 infant boys with unilateral reflux grade I and one infant girl with bilateral reflux and hydronephrosis grade III.

DISCUSSION

Present study indicated a significant difference (p-value = 0.001) in the incidence of UTI between case and control group (11 out of 100 and 0 out of 100, respectively). In a study by Garcia and Nager (2002) in USA on 160 jaundiced infants, 12 case of UTI (7.5%) were detected. In another study by Bilgen *et al.* (2006) in Turkey from the total of 102 jaundiced neonates, 8 cases (8%) had UTI by *E. coli*. Comparing our study with these two studies indicated that the incidence of UTI is higher in our cases. Overall, these studies indicated the importance of investigating UTI in all of the jaundiced infants. The most common detected organism in our study was *E. coli* (5 out of 11 cases, or 45.5%) and the other organisms were *Klebsiella*, *Proteus* and Citrobacterococci gram positive. Similarly, other studies reported that *E. coli* is the most common organism responsible for UTI. Wang *et al.* (1994) reported that among 95 infants under 2 months old who diagnosed suffering from UTI, the most common organism in U/C was *E. coli*. In another study by Biyikli *et al.* (2004) in Turkey the high rate of 63% of *E. coli* was reported among 71 jaundiced infants whom were diagnosed and treated for UTI. The other reported organisms, with lower frequencies, are *Klebsiella*, *Enterobacter*, *Streptococcus viridans*, *Enterococcus*, *Streptococcus* group B and *Staphylococcus aureus* (Garcia and Nager, 2002). Therefore we can conclude from our study and the other studies that *E. coli* is a common and important organism in infants with UTI.

Wang *et al.* (1994) reported that 96.1% of the infants with UTI were boys. The percentage of boys was higher than girls in the other studies as well, such as the study by Cleper *et al.* (2004) which reported the rate of UTI in boys was 6 times more than this rate in girls. Similarly, this rate was 3 times more in boys in the study of Garcia and Nager (2002). Based on the pediatric texts, most of the UTI in boys occur in the first year of life and in this time the rate of UTI in boys is 2.8 times more than this rate in girls. While after this period, the rate of UTI in girls is 10 times more than this rate in boys. In this study 8 out of 11 infants with UTI were boys. In fact the rate of UTI in boys was nearly 3 times more than this rate in girls but because of the small number of cases, this difference was not statistically significant (p-value = 0.35).

In the present study, only 3 out of 11 (27.4%) infants with positive U/C showed abnormal U/A with pyuria while U/A reported to be normal in 8 other infants. Crain and Gershel (1990) reported that 50% of the U/A was

normal among 32 infants with UTI. Similarly only 5 infants (42%) among 12 infants with UTI had abnormal U/A in the study by Garcia and Nager (2002). These results indicated that by relaying only on U/A many of the UTI cases will be missed.

Regarding the abnormalities in urinary tract, in the present study, from the total of 11 neonates with UTI, 2 boys had unilateral reflux grade I and 1 girl had bilateral reflux grade III. Wang *et al.* (1994) reported a 25.5% rate of vesicourethral reflux among 95 neonates with UTI, while this rate was 15-20% in the other studied (Biyikli *et al.*, 2004; Cleper *et al.*, 2004). It seems that abnormalities of urinary tract is an important issue in the neonate's UTI. More studies on more cases are necessary to confirm these finding.

CONCLUSIONS

Our results in combination with results from similar studies indicated that UTI is a common problem in jaundiced infants Therefore it is necessary to do a U/C in all jaundiced infants. U/A is not a sensitive test for UTI and had many false negative results which lead to misdiagnosis of UTI. In addition, ultrasonography and VCUG are necessary in all of neonates with UTI to detect urinary tract's anomalies such as vesicourethral reflux.

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