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Original Article

Hyperbilirubinemia with urinary tract infection in infants younger than eight weeks old

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Abstract

Background: Hyperbilirubinemia is one of the most common causes for hospital admission in neonatal infants. Previous studies have found that jaundice may be one of the initial symptoms related to urinary tract infection (UTI) in infants. This study is to evaluate the incidence and related factors of neonatal infants with the initial presentation of hyperbilirubinemia and final diagnosis of UTI in a tertiary teaching hospital.
Methods: We retrospectively investigated the medical records of admitted infants younger than 8 weeks old with hyperbilirubinemia between January and December 2008. The jaundiced infants having tests of urinalysis were enrolled into our study and grouped into UTI or no UTI group according to the findings of urinary culture.
Results: A total of 217 neonatal jaundiced infants were enrolled. Among them, 12 cases (5.5%) were grouped into the UTI group, and the most common cultured bacterium from their urine was *Escherichia coli*. There was no significant difference in the babies' birth weight, maternal conditions, or total bilirubin levels between the two groups. There was also no significant difference between the two groups in their admission age (9.7 $\pm$ 13.5 days *vs*. 6.1 $\pm$ 6.7 days in UTI and no UTI groups, respectively) or the ratio of outpatients (50% *vs*. 25% in UTI and no UTI groups, respectively) ($p > 0.05$). The cases of UTI group had significantly lower hemoglobin (15.2 $\pm$ 2.7 g/dL *vs*. 17.2 $\pm$ 2.3 g/dL, respectively) and higher formula feeding rate (8.3% *vs*. 2.9%, respectively) than the no UTI group ($p < 0.05$).
Conclusion: The incidence of UTI in the admitted infants with hyperbilirubinemia was as high as approximately 5.5%. The most common cultured bacterium in urine was *E coli*. Therefore, performing urinary tests to exclude the possibility of coincidental UTI may be necessary for admitted jaundiced infants younger than 8 weeks old.

Keywords: Infant; Jaundice; Urinary tract infection

1. Introduction

Neonatal jaundice is one of the most common reasons for admission in neonates and young infants, observed in the first week of life in 60% of term infants and 80% of preterm babies.[1–3] Although it is mostly benign, some cases may have the possibility of having other diseases in combination.[4] There have been some reports regarding the relationship of idiopathic hyperbilirubinemia and bacterial infections,[5] such as urinary tract infection (UTI).[6] However, it is still not recommended to perform routine urinary tests in jaundiced infants for such infections.[7] Urinalysis and a urinary culture are only recommended under some certain conditions, such as infants who have an elevation of direct-reacting or conjugated bilirubin, and infant readmitted for phototherapy or exchange transfusion.[7] However, coincidental UTI in jaundiced infants were not uncommon in our clinical practice. We believe that it was worthwhile to evaluate the relationship of UTI and

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hyperbilirubinemia in young infants who were admitted with only the diagnosis of jaundice.

With retrospective review of the whole year's admission for hyperbilirubinemia in infants, the goal of the study was to evaluate the incidence and related factors in infants younger than 8 weeks old and having the initial presentation of hyperbilirubinemia and final diagnosis of UTI in a tertiary teaching hospital.

2. Methods

2.1. Subjects

We retrospectively reviewed the medical records of admitted infants younger than 8 weeks old in the intermediate nursery of a tertiary teaching hospital between January and December 2008. Infants admitted with the diagnosis of hyperbilirubinemia were enrolled into our study, but the cases having no data of urinalysis were excluded from our analysis.

The demographic features, including admission age, gender, body weight, birth body weight, gestational age, mode of delivery, postnatal events, feeding, admission sources, maternal and baby's blood types were recorded and analyzed. In addition, the results of all laboratory data and image study including complete blood count, initial total and direct bilirubin levels, urinalysis, urinary culture, renal ultrasonography, voiding cystourethrogram, and Tc 99m-dimercaptosuccinic acid renal scan were recorded. Pyuria was defined as the presence of more than 5 white blood cells per high power field of microscopy.

2.2. Grouping

The enrolled patients were divided into UTI or no UTI group according to the results of urinary culture. Cases with UTI were defined as the presence of more than any colony-forming units (CFU)/mL of pathogens obtained by suprapubic puncture, collection more than 10,000 CFU/mL obtained by bladder catheterization, or more than 100,000 CFU/mL of pathogens obtained by urinary bag collection. Otherwise, the patients would be grouped into the no UTI group.

2.3. Statistical analysis

All statistical analysis was carried out using Statistical Product and Service Solutions (IBM Corporation, USA). Continuous variables were presented as mean ± standard deviation and associations between categorical variables as percentages. Analyses comparing patients' characteristics, patients' medical histories, and variables were performed by using the independent t test and χ^2 test. Statistical significance was defined as a p value < 0.05.

3. Results

A total of 345 infants were admitted for phototherapy with the initial diagnosis of hyperbilirubinemia during the study period. Among them, 128 cases were excluded due to lack of the data of urinalysis. Therefore, there were 217 patients enrolled into our analysis, and 58.1% (126/217) of them were male. Their mean age was 6.3 days, and mean total bilirubin on admission was 16.0 mg/dL. After being divided into two study groups, there were 12 (5.5%) cases fitting the criteria of "UTI" group, while the other 205 (94.5%) cases were grouped into the "no UTI" group.

The basic characteristics of the 12 jaundiced cases with UTI are listed in Table 1. As shown, most of them were admitted within 2 weeks after birth except one case who was admitted with an age of 7 weeks. Most admission durations were less than one week except case number 1, who was also diagnosed as glutaric aciduria type I and received phototherapy for only 2 days. In all cases with UTI, seven (58.3%) of them were female, all (100%) of them were full-term, three (25%) of them had ABO blood type incompatibility with their mother, ten (83.3%) of them were born with vaginal delivery, and eight (66.7%) of them were fed with only breast milk. In addition, half (50%) of these UTI cases were outpatients, and every one of them had an age older than 1 week old (range, 7–53 days). The total bilirubin level of all UTI cases was 16.1 ± 3.3 mg/dL, and the direct bilirubin was 0.9 ± 0.6 mg/dL. Among them, only two cases had direct bilirubin levels higher than 1.5 mg/dL, but they were both less than 15% of the total bilirubin (12.0 and 12.3%, respectively). Therefore, all cases were diagnosed as indirect-type hyperbilirubinemia (Table 1).

Among the cases, number 4 was the one with the highest total bilirubin (22.5 mg/dL) when admitted (40 h of age), and blood type incompatibility (maternal type: O+, baby's type: B+) was also noted (Table 1). Fortunately, the bilirubin level dropped effectively to 15.6 mg/dL with intensive phototherapy in 6 h, and was 15.6, 12.2, and 8.1 mg/dL on the following days. Cases number 8 and 10 also had blood type incompatibility with their mothers, but their highest total bilirubin levels were less than 15 mg/dL. Between them, case number 10 was a case whose jaundice developed when he was younger than 24 h of age, and his condition also responded well to intensive phototherapy, with bilirubin levels of 11.0, 11.6 and 10.0 mg/dL the following days. In addition, case number 8 was the one admitted with the oldest age (53 d old) with prolonged jaundice (13.4 mg/dL).

The comparisons of the basic data between UTI and no UTI groups are summarized in Table 2. As shown, most of the data were not significantly different between two groups. There was a tendency of older admission age in the UTI group (9.7 ± 13.5 days) than the no UTI group (6.1 ± 6.7 days), but it was of no significance ($p = 0.094$). Additionally, the percentage of the cases fed with complete infant formula showed significantly higher in the UTI group (1/12, 8.3%) than the no UTI group (6/205, 2.9%) ($p = 0.009$). However, there may be no clinical significance because of the small case number in the UTI group.

Laboratory data of the two groups are summarized in Table 3. As shown, the hemoglobin level was significantly lower in the UTI group (15.2 ± 2.7 g/dL) than the no UTI group (17.2 ± 2.3 g/dL) ($p = 0.004$). All of the other laboratory data

Table 1
Basic data of enrolled infants with hyperbilirubinemia and urinary tract infection

Patient	Age on admission (d)	Admission duration (d)	Sex	Birth weight (g)	Admission weight (g)	Gestational age (wk)	Materal blood type	Infant blood type	Mode of delivery	Feeding	Patient source	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)
1	7	18	F	3,305	3,305	38.3			VD	FF	O	15.8	1.9
2	3	3	M	3,660	3,370	39.7	O+	O+	VD	BF	I	16.6	0.9
3	3	2	F	2,876	2,606	39.4	B+	AB+	VD	BF	I	16.6	2.1
4	2	4	F	3,690	3,600	39.6	O+	B+	VD	BF	I	22.5	1.4
5	3	2	F	3,160	2,936	39.1	AB+	B+	VD	BF	I	14.9	0.9
6	5	1	F	3,026	3,044	38.7	AB+	B+	CS	MF	I	11.6	0.9
7	8	6	M	3,190	3,190	38.9	AB+	A+	VD	BF	O	15.63	0.39
8	53	3	M	2,564	3,740	33.7	O+	A+	CS	FF	O	13.4	1
9	8	3	F	4,028	4,100	40.7			VD	BF	O	18.9	0.4
10	1	4	M	2,698	2,650	37.6	O+	B+	VD	FF	I	10.0	0.36
11	13	3	F	3,140	3,265	37.7	B+	O+	VD	BF	O	19.14	0.38
12	10	2	M	2,708	2,642	38.4	B+	B+	VD	BF	O	18.34	0.72
Mean ± SD	9.7 ± 13.5	4.3 ± 4.3		3,170 ± 426	3,204 ± 444	38.5 ± 1.7						16.1 ± 3.3	0.9 ± 0.6

BF = breast feeding; CS = Caesarean section; F = female; FF = formula feeding; I = inpatient; M = male; MF = mixed feeding; O = outpatient; SD = standard deviation;VD = Vaginal delivery; + = Positive Rh blood type.

Table 2
Demographic and historical characteristics of jaundiced infants with or without urinary tract infection[a]

Characteristics	UTI (n = 12)	No UTI (n = 205)	p
Birth weight (g)	3,170 ± 426	3,160 ± 452	0.941
Admission weight (g)	3,204 ± 444	3,048 ± 464	0.258
Admission age (range) (d)	9.7 ± 13.5 (1–53)	6.1 ± 6.7 (1–40)	0.094 0.287
≤3	5 (41.6)	118 (57.5)	
4–7	2 (16.7)	42 (20.5)	
≥8	5 (41.6)	45 (22.0)	
Gender			0.236
Male	5 (41.7)	121 (59.0)	
Female	7 (58.3)	84 (41.0)	
Gestational age (wk)			0.877
< 37	1 (8.3)	26 (12.7)	
37–41	11 (91.7)	178 (86.8)	
> 41	0 (0)	1 (0.5)	
Mode of delivery			0.247
Vaginal delivery	10 (83.3)	138 (67.3)	
Caesarean section	2 (16.7)	67 (32.7)	
Feeding practice			0.587
Breast feeding	10 (83.3)	180 (87.8)	
Formula feeding	1 (8.3)	6 (2.9)	
Mixed feeding	1 (8.3)	19 (9.3)	
Patient source			0.061
Inpatient	6 (50)	153 (74.6)	
Outpatient	6 (50)	52 (25.4)	

[a] Data are presented as mean ± standard deviation, mean ± standard deviation (range) or n(%).
UTI = urinary tract infection.

were not significant different between the two groups ($p > 0.05$). Although there were two cases of the UTI group who had an initial direct bilirubin higher than 1.5 mg/dL (16.7%), it was not significantly different from the no UTI group (12/205, 5.9%) ($p = 0.118$).

Further analyzing the urinalysis of cases with UTI, we found that presence of pyuria was observed in 7 cases (58.3%), and presence of bacteria was noted in 3 (25%). In urinary cultures, we found that a single organism was isolated in 10 cases (83.3%), and double organisms were isolated in 2 cases (16.7%), including *Psuedomonas aeruginosa* plus *Enterococcus* spp. and *Escherichia coli (E coli)* plus *Klebsiella*

Table 3
Laboratory data of jaundiced infants with or without urinary tract infection

Characteristics	UTI (n = 12)	No UTI (n = 205)	p
Total bilirubin level (mg/dL)	16.1 ± 3.3	16.0 ± 3.1	0.914
Range			0.895
≥15.0	4 (33.3)	82 (40.0)	
15.1–20	7 (58.4)	106 (51.7)	
≥20.1	1 (3.3)	17 (8.3)	
Direct bilirubin level (mg/dL)	0.9 ± 0.6	1.0 ± 1.4	0.806
Range			0.138
≥1.5	2 (6.7)	12 (5.9)	
<1.5	10 (93.3)	193 (94.1)	
White cell count (/cumm)	12,383 ± 426	11,777 ± 6,283	0.739
Hemoglobin (g/dL)	15.2 ± 2.7	17.2 ± 2.3	0.004
Platelet count (/cumm)	353,750 ± 119,024	346,138 ± 153,848	0.866

Data are presented as mean ± standard deviation, or n(%).

Table 4
Organisms cultured from the urine of 12 jaundiced neonates diagnosed as urinary tract infection

Bacteria	*n*
Escherichia coli	5
Enterococcus species	2
Enterobacter cloacae	1
Klebsiella pneumoniae	1
Klebsiella oxytoxa	1
Coagulase-negative staphylococcus species	1
Psuedomonas aeruginosa	1
Proteus mirabilis	1
Gram-positive bacilli	1

pneumoniae. Table 4 is the list of all 14 cultured organisms from the urine of 12 cases. As shown, *E. coli* was the most common cultured bacteria (5 cases, 41.7%), and *Enterococcus* species was the second most common (2 cases, 16.7%).

4. Discussion

Our study demonstrated that approximately 5.5% of admitted neonates with hyperbilirubinemia had a coincidental finding of UTI, with the most common cultured bacteria from their urine being *E coli.* The cases of the UTI group had significantly lower hemoglobin and higher formula feeding rate. In addition, the age on admission tended to be older in the UTI than the no UTI group, but there was no significant difference. Therefore, the presence of UTI in admitted infants with hyperbilirubinemia is an important issue, and needs an adequate diagnosis and appropriate managements.

The consideration of UTI presenting as jaundice has been mentioned since 80 years ago,[8,9] and re-emphasized during the past 40 years.[8,10] The presentation of jaundice in cases of UTI has been reported in neonates, children, and adults.[10–14] Also, Linder et al. reported that there were around 3.2% of jaundiced and asymptomatic neonates being diagnosed as septicemia.[6] Therefore, the presence of jaundice may be an early sign of infection in neonates, especially UTI, so we need to pay it much attention in clinical practice. Our investigations also demonstrated that asymptomatic jaundice in neonates may be the first presentation of UTI, so a further check-up on the urine to exclude the coincidence of UTI is important in jaundiced infants.

Prolonged jaundice (past 1 week of age) has been reported to have a high incidence of UTI in infants younger than 3 months old.[15–17] In our study, there were 6 cases (50%) admitted with UTI with age older than 7 days, and that age tended to be higher than those cases (45/205, 22%) without UTI ($p = 0.670$) (Table 2). If we count the ratio of UTI in all cases with prolonged jaundice, the results were 10% (5/50) in infants older than 1 week old and 2% (1/50) in infants older than 2 weeks, which is lower than the report of Pashapour et al.[17]

Conjugated hyperbilirubinemia has been considered a presentation of UTI.[3] Furthermore, the American Association of Pediatrics (AAP) clinical practice guideline for the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation also recommended clinicians perform urinalysis in the presence of an elevated direct bilirubin level or readmission for phototherapy or exchange transfusion.[18] Additional laboratory evaluation for sepsis should be performed if indicated by history and physical examination.[18] However, UTI in infants presented with unconjugated hyperbilirubinemia in the early days has been mentioned by Lee et al.[19] In our presented cases, none of the jaundiced infants with UTI presented as conjugated hyperbilirubinemia. Therefore, urinary tests for UTI should not be absolutely excluded or neglected in neonates without conjugated hyperbilirubinemia.

The routine testing of the urine in jaundiced neonates is controversial. There are more than two thirds of normal infants that are jaundiced during the first 2 weeks of age, especially in Asian neonates.[3,20,21] The reported incidence of UTI in jaundiced infants was variable, ranging from 1% to 11% in different countries.[2,22–24] In our study, 7 cases (7/12, 58.3%) of UTI had the presence of pyuria in the urinalysis. In other reports, only 27.4% in Iran,[22] 50% in Turkey, and 41.7% in United States[2] were found to have the presence of pyuria in jaundiced infants with UTI. Crain et al. also mentioned that around 50% of the urinalysis was normal in febrile infants with UTI.[25] The report of Fang et al. showed even high fever and pyuria were unreliable criteria for screening for UTI in young infants presenting with prolonged jaundice.[15] Therefore, performing noninvasive urinalysis for a urinary screening may be helpful to identify some cases with UTI in jaundiced infants. However, sometimes a simple urinalysis may not reflect the real existence of UTI, so urinary culture for high-risk infants, such as prolonged jaundice or fever, have been highly suggested.[15,17,24]

The reasons for coincidental hyperbilirubinemia and UTI are still not fully understood. The potential pathogenesis has been discussed, including the formation of some hepatotoxins from the infected gram-negative bacilli,[8] especially *E coli*, which might increase the fragility of red blood cells and the production of hemolysin.[14,26] In addition, fever may itself damage the liver and produce jaundice,[8] and nonspecific injury to the liver related to hyperpyrexia, malnutrition, anoxemia, hemolysis and cholestatsis are all potential problems.[12]

E coli is the most common organism cultured from the urine of jaundiced infants, ranging from 45% to 63%.[22,27] In our study, *E coli* was also the most common organism cultured in 5 cases (41.7%), and the second most common organism was *Enterococcus* species. Since both of these two organisms are commonly seen in stool and stool on the diaper may spread over the perineum, hygiene care is very important. In the report of Ng et al., the authors noted that poor hygiene was a common factor in these jaundiced infants with UTI.[13]

Vesicoureteral reflux is a potentially serious underlying disease in infants with UTI, especially in younger age at presentation of *Klebsiella*-induced UTI.[28,29] In our present cases, there were fortunately none who suffered from this anomaly.

The main limitation of the present study is the lack of the comparison with the group of neonatal infants without jaundice. Therefore, it was hard to tell that jaundice was the initial presentation of the UTI, or just a coincidence, especially in the

cases of age younger than 3 days. A further study to clarify this question may be necessary for clinical practice. Another limitation was that this is a retrospective study in which the urinary collecting methods could not be completely the same, and some jaundiced cases were not included into the study because of no data of initial urinalysis. In addition, this was a clinical observational study, so the pathogenesis regarding UTI and jaundice could not be investigated. Future studies with a prospective design, larger study population, or pathogenesis research will be helpful for more understanding of this issue.

In conclusion, in admitted infants younger than 8 weeks old, approximately 5.5% of jaundiced cases had UTI. The most common cultured bacterium was *E coli*. Performing urinalysis and/or urine culture to exclude the possibility of UTI may be necessary in admitted young infants with hyperbilirubinemia.

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