Original Article

Urinary tract infection and prolonged neonatal jaundice in term infants during the first two months of life: a descriptive study

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Summary:

Background: Several causes stand behind prolonged neonatal Jaundice (Jaundice that persists more than 2 weeks).

Objectives: To find out the frequency of association between Urinary tract infections (UTI) and prolonged neonatal jaundice in term infants during the first two months of life.

Patients and methods: We conducted an observational prospective study in children welfare teaching hospital, Medical City Complex, Baghdad. Fifty term infants, less than two months of age, with clinically evident jaundice that has persisted for more than 14 days of life were enrolled; UTI was confirmed by urine culture and sensitivity. Demographic features, historical characteristics, laboratory investigations, abdominal ultrasound findings recorded and analyzed for each patient.

Results: UTI was confirmed by urinary culture in 6 infants (12%). E. coli was the most common isolated microorganism. UTI was more common in female patients during the first 2 months of life (66%). Irritability was the most common associated clinical feature (83%). Conjugated bilirubin was found to be the most raised fraction among jaundiced infants with UTI. Jaundice resolved gradually upon treating UTI with proper antibiotics.

Conclusions: UTI was found in 12% of infants of less than two months of age with prolonged neonatal jaundice; urine culture should be considered as a part of the diagnostic evaluation for any infant with prolonged neonatal jaundice beyond 14 days of life with unexplained etiology.

Key words: Neonatal jaundice, Urinary tract infection (UTI), infants.

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Introduction:

Urinary tract infection (UTI) is attributed as one of the treatable causes of prolonged neonatal jaundice, its treatment is necessary to resolve jaundice and to prevent future renal damage [1, 2]. It is well known that the clinical manifestations of UTI can cover a wide spectrum, ranging from severe illness to non specific signs and symptoms such as growth failure and jaundice. Physician need to be aware about this problem and to screen for UTI and treat it as soon as possible [2]. However, it is still not recommended to perform routine urinary tests in jaundiced infants, and a urinary culture is only recommended under some certain conditions [3]. We believe that it was worthwhile to evaluate the relationship of UTI and hyperbilirubinemia in young infants who were admitted to hospital with clinical evidence of prolonged neonatal jaundice, as long as it is one of its
treatable causes that could prevent subsequent renal damage in young infants, who are the most vulnerable group of patients to such damage [4]. This study was conducted to find out the frequency of association between UTI and prolonged neonatal jaundice in young infants less than 2 months of age.

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Patients and Methods:

An observational prospective study of 50 term infants less than 2 months of age with prolonged neonatal jaundice, who were admitted to Children Welfare Teaching Hospital / Medical City complex, Baghdad from May, 1st 2012 to November, 1st 2012. The ethical committee on human research of Children welfare teaching Hospital, Medical City Complex, Baghdad, approved the study protocol at 2.4.2012.Oral consent and agreement of parents were taken to enroll their neonates in the study. The urinary catheterization was performed as part of the hospital policy for the diagnosis of UTI in neonates. Complete history for all infants was taken from their parents and physical examination was done to all, demographic features were recorded, including age, gender, body weight, mode of delivery, onset of jaundice, type of feeding, family history of similar condition, received phototherapy or not and had a blood exchange transfusion procedure, complaints and symptoms other than jaundice. All male infants were uncircumcised. Exclusion criteria were preterm infants and

infants who were already being started on antibiotic therapy before collection of urine sample. Cholestasis was defined by the presence of jaundice associated with increased serum conjugated bilirubin levels (direct bilirubin fraction is greater than 15% of the total) and/or elevation in hepatic transaminases. [5]Pyuria which is leukocytes in the urine suggests infection, but infection can occur in the absence of pyuria; this finding is more confirmatory than diagnostic. Conversely, pyuria can be present without UTI.[6] The urine samples were collected from the studied infants by urethral catheterization after proper sterilization and before starting any antibiotic (at least before the last 7 days of admission). Urine specimens were sent for standard quantitative culture and sensitivity at the hospital laboratory and were considered to be positive if a single pathogen (equal or more than 10,000 colony-forming units) was isolated. In addition, laboratory investigations and ultrasound studies of the abdomen were done and results were recorded for all infants, these investigations included : Blood groups (for both mother and baby), complete blood count (including differential count and platelets, reticulocyte count and blood film), initial total and differential (direct/indirect) serum bilirubin levels, urinalysis, urinary culture, blood culture, C-reactive protein, renal function tests, liver function tests, serum levels of electrolytes (Na, K, Cl). Other investigations were done individually according to the clinical presentation of the case, including: serum level of G6PD, coomb's test, thyroid function tests (TSH, T4), serological screen for antibodies against TORCH infections for infants and their mothers (including Toxoplasma, rubella, cytomegalovirus, herpes virus types I and II), Viral Hepatitis screen, Tandem Mass Spectrometry for Metabolic disease Screening (MS/MS), serum level of alpha-one antitrypsin enzyme and its phenotype, and serum alpha fetoprotein level.Data of all infants were entered in a computerized data management software, SPSS version 16 (statistical package for the social sciences) and statistical analysis and calculations of means, frequencies and percentages was done.[7] Descriptive data were presented as mean ± standard deviation for the continuous variables (age, weight, onset of jaundice, TSB, LFT, RFT,...), and as frequencies and proportions for categorical variables (Sex, Blood groups, mode of delivery, feeding type, family history of similar condition, receiving phototherapy ,blood exchange,..).Chi square test was used to compare between UTI group and non UTI groups regarding the categorical variables, Fisher exact test was used alternatively when chi square was not applicable. Student's t test independent model was used to compare in between groups regarding continuous variables (two means), ANOVA test was used in comparison of more than two means. Level of significance (P. value) of less than 5% (0.05) was considered as statistically significant. Finally, results were presented in tables and figures.

Results:

Among 50 jaundiced infants, 24 (48%) were males and 26 (52%) were females, with female to male ratio was (1.1: 1). The mean age of infants was (28.6 days) with a range of (15 – 58 days) and the mean body weight was (3.65 kg) and the range was (2.5 – 6.0 kg). The onset of jaundice ranged from the first day of life to the 14th day, and the mean time of onset was the 7th day of life. Based on the positive urine culture, 6 infants (12%) were diagnosed to have UTI. The most common isolated bacterial pathogen was E. coli in 4 patients (66.6%), followed by Klebsiella pneumonia in 1 patient (16.7%) and Proteus mirabilis in 1 patient (16.7%).The final diagnosis for all infants includes 6 patients with UTI and 44 patients with other diagnoses rather than UTI. Sepsis was the most frequent in 11 patients (22%), followed by Breast milk jaundice in 7 (14%), TORCH in 4 (8%), ABO incompatibility, congenital hypothyroidism, Galactosemia and Tyrosinemia were present in 3 cases (6%). The infants characteristics including, sex, onset of jaundice (categorized according to the mean time of onset into before and after 7th day of life), delivery mode, feeding type, family history of similar condition, receiving phototherapy and blood exchange either done or not. No statistically significant difference was found between patients with UTI and those without UTI regarding these characteristics, in all comparison (P>0.05). (Table 1) The most frequent clinical feature of infants was lethargy in 32 patients (64% of the total jaundiced infants), followed by reluctance to feed in 30 patients (60% of the total), and vomiting in 29 patients (58% of the total), while the least frequent symptom is hematuria in one patient (16.7%). Irritability was the most frequent clinical feature among patients with UTI (83.3%) vs. (20.5%) in patients without UTI (P<0.05), on the other hand, lethargy was more frequent among patients without UTI (72.7%) vs. none in patients with UTI, (P<0.05), whereas no significant differences was found concerning all other clinical features, (P>0.05). (Table 2) The mean total serum bilirubin (TSB), and indirect serum bilirubin were significantly lower in patient with UTI compared to patients without UTI, (6.8 mg/dl vs. 9.3 mg/dl) and (1.8 mg/dl vs. 4.6 mg/dl) respectively, (p<0.05), while no significant difference in the mean direct serum bilirubin (P>0.05). (Table 3) Data regarding Blood culture and serum bilirubin (TSB, Direct and Indirect) of the 6 UTI cases were shown in table 4. It had been found that 5 cases with UTI had direct-reacting hyperbilirubinemia and only one with indirect hyperbilirubinemia, and this case had positive blood culture for Ecoli, (this result was negative at admission, but as his jaundice persisted due to having a concomitant UTI, his blood culture became positive and yielded a bacterial growth later on further follow up, pointing to that his sepsis and jaundice was secondary to his UTI). CRP testing and blood culture were not significantly different between both groups (P>0.05). (Table

5) It was found that all patients with UTI had normal findings on abdominal ultrasound, as compared to 24 patients (53.5%) among non UTI group who have abnormal positive ultrasound findings (P<0.05). (Table 5) During the follow up of infants with UTI, it had been found that their TSB levels decreased gradually in a significant way till discharge from hospital as a response to 10 days treatment with appropriate antibiotic therapy, P<0.05. (Figure 1)

Despite the mild elevation in hepatic transaminases in patients with UTI, it had been significantly found that they had lower levels of SGOT, SGPT and ALP as compared to patients without UTI, in all comparison, P<0.05. (Table 6).

Table 1: Distribution of historical characteristics of 50 infants with and without UTI

Characteristics		Patients with UTI (N=6)		Patients without UTI (N=44)		P. value
		N	%	N	%	
Sex	Male	2	33.3	22	50	0.67
	Female	4	66.7	22	50	
Onset of jaundice	before 7th day	3	50	25	56.8	0.54
	After 7th day	3	50	19	43.2	
Delivery Mode	CS	4	66.7	17	38.6	0.22
	NVD	2	33.3	27	61.4	
Feeding type	Breast	1	16.7	11	25	0.86
	Bottle	2	33.3	18	40.9	
	Mixed	3	50.0	15	34.1	
Family history of similar condition	Positive	1	16.7	18	40.9	0.39
	Negative	5	83.3	26	59.1	
Received Phototherapy	Received	4	66.7	31	70.5	0.59
	Not received	2	33.3	13	29.5	
Blood Exchange	Done	0.0	0.0	1	2.3	0.88
	Not done	6	100.0	43	97.7	

Table 2: Distribution of the clinical features of 50 infants with prolonged neonatal jaundice

Clinical feature	infants with UTI (N=6)		infants without UTI (N=44)		P. value
	N	%	N	%	
Irritability	5	83.3	9	20.5	0.005
Lethargy	0	0.0	32	72.7	0.001
Fever	3	50.0	11	25.0	0.21
Hypothermia	1	16.7	14	31.8	0.65
Reluctance	4	66.7	26	59.1	0.54
Vomiting	5	83.3	24	54.5	0.18
Constipation	1	16.7	22	50.0	0.2
Diarrhea	2	33.3	8	18.2	0.63
Hematuria	0	0.0	1	2.3	0.88
Oedema	0	0.0	5	11.4	0.51

Table 3: Comparison of mean values of Total, direct and indirect serum bilirubin

Variable	statistics	Patients with UTI (N=6)	Patients without UTI (N=44)	P. value
Total serum bilirubin (TSB) (mg/dl)	mean± SD	6.8 ± 1.43	9.3 ± 5.46	0.02
	range	5.2 – 8.7	3.8 – 28	
Direct serum bilirubin (mg/dl)	mean± SD	5 ± 2.5	4.73 ± 3.2	0.87
	range	0.7 – 7.4	0.3 – 13.8	
Indirect serum bilirubin (mg/dl)	mean± SD	1.83 ± 0.6	4.6 ± 4.5	0.016
	range	0.2 – 5.5	0 – 22.5	

Table 4: Distribution of Serum bilirubin levels (TSB, direct and indirect) and results of blood culture for the six infants with UTI

Case	TSB mg/dl	Direct mg/dl	Indirect mg/dl	Bacterial growth on blood culture
1	6.2	0.7	5.5	Positive for E. coli
2	6.7	5.5	1.2	Negative
3	8.7	7.4	1.3	Negative
4	8.3	7.1	1.2	Negative
5	5.6	4	1.6	Negative
6	5.2	5	0.2	Negative

Table 5: Distribution of results of CRP testing, Blood culture and U/S finding

Variable		Patients with UTI (N=6)		Patients without UTI (N=44)		P. value
		N	%	N	%	
Blood C&S	E coli	1	16.7	6	13.6	0.86
	Staphylococcus	0	0.0	3	6.8	
	Streptococcus	0	0.0	2	4.5	
	No growth	5	83.3	33	75.0	
CRP.	Positive(>10 mg/dl)	4	66.7	12	27.3	0.075
	Negative(<10 mg/dl)	2	33.3	32	72.7	
U/S of abdomen	Normal	6	100.0	20	46.5	0.021

* Positive findings includes: Hepatomegaly (in 34%), Splenomegaly (in 13%), ascites (in 9%), hydronephrosis with multiple renal cystic lesions (in 2%), thick pyloric canal (4.5%) and choledochal cyst (in 4.5%) of patients respectively.

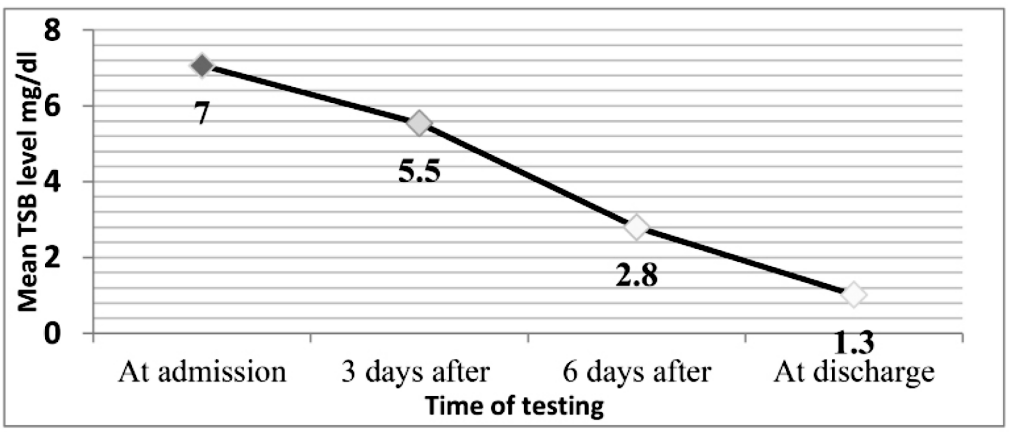

Figure 1: Reduction in mean TSB level in a response to antibiotic treatment in jaundiced infants with UTI.

Table 6: Distribution of renal function tests, serum electrolytes and liver function tests compared between infants with and without UTI.

Variable	statistics	Patients with UTI (N=6)	Patients without UTI (N=44)	P. value
Blood urea (mg/dl)	Mean ± SD	36.8 ± 2.4	47.5 ± 6.9	0.57
	Range	31- 44	19 - 260	
S. creatinine (mg/dl)	Mean ± SD	0.87 ± 0.2	0.99 ± 0.4	0.43
	Range	0.6 - 1.1	0.7 - 2.9	
S. sodium (mEq/dl)	Mean ± SD	143 ± 4.8	140 ± 5	0.029
	Range	140 – 150	130 - 145	
S. potassium (mEq/dl)	Mean ± SD	4.3 ± 0.5	6.5 ± 1.3	0.71
	Range	4 -5	2 - 8.3	
S. chloride (mEq/dl)	Mean ± SD	101 ± 3.2	100 ± 4.7	0.64
	Range	96 – 104	88 - 108	
SGOT (IU/L)	Mean ± SD	31 ± 14.8	51.2 ± 23.8	0.02
	Range	12 – 48	12 - 89	
SGPT (IU/L)	Mean ± SD	32.5 ± 12.5	57.6 ± 23	0.014
	Range	18 – 48	15 - 94	
S.ALP (K.A.U)	Mean ± SD	9.8 ± 6.8	23.2 ± 13.4	0.036
	Range	3 – 20	8 - 68	

Discussion

Prolonged neonatal jaundice is one of the presentations of UTI in young infants and sometimes being the only manifestation [8,9]. UTI was detected in 6 patients (12%), this was in accordance with Shahian M. et al study [10]. The isolated microorganisms in this study included E.coli (66.6%), Klebsiella (16.7%) and Proteus mirabilis (16.7%), that are among the common causes of UTI in early infancy [5]. Chen HT et al, Garcia F.J and Nager, Hussein T.K and colleagues, also reported that E. coli was the most common isolated microorganism from urine of their jaundiced infants [11,12,13]. In fact both E. coli and Klebsiella species are commonly seen in stool of infants and stool on the diaper may spread over the perineum, hygiene care is very important, and the authors noted that poor hygiene was a common factor in these jaundiced infants with UTI [14]. Sepsis was found to be a cause of prolonged neonatal jaundice in 22% of patients and this was in agreement with Narang A. et al (14) and Tiker F. et al [15] studies, where sepsis was identified as a cause of prolonged jaundice in 24% and 35.7% of their patients respectively.Prolonged neonatal jaundice due to breast feeding was found in 14% among our patients, which disagree with Milani SM et al (76%) [16] and this could be explained on the basis that the study sample by Milani SM included only the breast fed infants, while in this study infants on breast feeding, bottle and mixed feeding all were included.It is well known that the incidence of UTI in boys is higher than in girls during the first year of the life [6]. It was noted in our study that only two of 6 UTI patients (33.3%) were males, whereas the remaining (66.7%) were females, so UTI was more common among female patients, the result was similar to that reported by Chen H.T et al [11] who found that (58.3 %) were females, but it disagreed with Shahian M et al [10] and Garcia F.J and Nager [2] who found that (61%) and (87%) of their studied samples respectively were males.Weight, Mode of delivery, family history, and phototherapy and/or exchange transfusion, had no statistical significance regarding patients with or without UTI, this was also concluded by Shahian M et al [10]. There was no significant difference between onset of jaundice and UTI occurrence which was consistent with Bilgen H. et al [17], but inconsistent with Garcia F.J and Nager [2] who reported that patients with onset of jaundice after 8 days of life had a higher incidence of UTI.The most common clinical manifestations of UTI were irritability (83.3%) and vomiting (83.3%) and they were statistically significant, followed by reluctance to feed (66.7%) and fever (50%). While the most common clinical manifestations of UTI in Movahedian AH et al [18] included lethargy in (36.8%), fever (34.6%), reluctance to feed (13%) and vomiting (10.5%) of the studied patients respectively. The conflict behind these results is attributed to that signs and symptoms of UTI in young infants are nonspecific; they may appear acutely ill and may show lethargy or irritability. Studies have indicated that jaundice may be one of the first signs in UTI [2]. 83.4% of infants with UTI had direct hyperbilirubinemia and only one patient (16.6%) had indirect hyperbilirubinemia, this was similar to studies done by Lee HC. et al [19], Hussein T.K and colleagues [12], Garcia F.J and Nager [2] who found that conjugated (direct) hyperbilirubinemia is more commonly observed in jaundiced infants who have UTI when compared to jaundiced infants without UTI but some studies showed that newborn infants with UTI present mainly with unconjugated (indirect)hyperbilirubinemia [10,17]. Hyperbilirubinemia in UTI is still not fully understood, some authors suggested that hepatotoxins produced from the infecting gram-negative bacilli especially E.coli, and the production of hemolysin might increase RBC fragility and this could be the cause behind indirect hyperbilirubinemia, whereas the nonspecific injury to the liver induced by UTI related to hyperpyrexia, malnutrition, anoxemia changes in hepatic microcirculation, direct effects from bacterial products, and effects caused by endotoxin-induced mediators all are potential factors for direct hyperbilirubinemia in UTI infants.[20] Neonatal UTI could occur through ascending route or hematogenous spread [6]. It is often difficult to identify whether UTI was the cause or the effect of bacteremia (21). we had only one patient (16.6%) who had positive blood culture and urine culture of same microorganism (E.coli), it's worthy to note that the patient's blood C&S result was negative firstly at admission, but as his jaundice persisted due to having a concomitant UTI, his blood culture became positive and yielded a bacterial growth of E.coli later on further follow up, pointing that his sepsis and jaundice were secondary to his UTI and this suggests that hematogenous route is the least common route of UTI in infants [6], a result that is similar to Amelia N. et al [22].Concerning laboratory findings, it was found that both blood culture and CRP level testing were not significantly different between UTI and non UTI groups of patients ($P>0.05$), which points out that a negative sepsis screen is not sufficient to rule out UTI. Four out of 6 jaundiced infants with UTI (66 %) had positive CRP value (>10 mg/dl). Both Bilgen H. et al [17] and Nejad NH et al [23] had reported that few of their studied UTI patients had elevation of CRP serum levels, however, CRP is a nonspecific marker of bacterial infection, and its elevation does not prove that the patient has acute pyelonephritis [6].The six studied infants with UTI had normal findings on abdominal ultrasound, and it was statistically significant as compared to the twenty four patients without UTI who have abnormal positive findings, these findings were related to their diseases, including: (hepatomegaly, splenomegaly, ascites, hydronephrosis with multiple kidney cysts, choledochal cyst

and others). Vesicoureteral reflux (VUR) is a potentially serious underlying cause of UTI in infants. It has been proved that the presence of VUR is significantly related to a younger age at time of UTI presentation [24], especially in young infants who had UTI caused by Klebsiella species [25], in our present cases, there was only one case with Klebsiella-induced UTI who suffered from unilateral vesicoureteral reflux of grade II, and it was confirmed by the VCUG on follow up visits, despite having normal findings on abdominal U/S during admission for jaundice. This implies to the unreliability of ultrasound technique in predicting the possible presence of vesicoureteric reflux (VUR) as a major risk factor for UTI in infants, this was also by Pashapour N. [26], that revealed that one male infant of the studied sample with VUR of grade III to IV on VCUG whereas his ultrasound did not show any significant pathological findings. Mild elevation in liver transaminases (SGOT, SGPT and ALP) which is defined as 1-3 times the upper normal level i.e.(less than 60 U/L) [27,28] was significantly noticed in all jaundiced infants with UTI in this study, this also had been found by Tiker F. et al [15] and Lee HC et al [19]. UTI and fever both may induce nonspecific injury to the liver; damage to liver cells is responsible for the hepatic enzymes elevation [29]. After proper antimicrobial treatment of UTI according to results of urine culture and sensitivity, all of the 6 infants with increased serum bilirubin level had resolution of their jaundice gradually over 10 days to 2 weeks of initiation of antibiotic therapy, non of UTI patients required blood exchange, and none responded properly to phototherapy alone and this was not consistent with result of Omar C. et al [30], who reported that all of the jaundiced patients with UTI responded to phototherapy. Failure of phototherapy in total resolution of jaundice and the effectiveness of the right chosen antibiotic in the management of UTI-associated hyperbilirubinemia was concluded by both Garcia F.J and Nager [2] and Tiker F. et al [15] in their studies. The possible explanation behind the difference in patients' response to therapy modalities is related mainly to the preponderant fraction of the raised serum bilirubin level which was the direct fraction among UTI patients in this study. Direct hyperbilirubinemia usually does not resolve upon phototherapy(6), and the response to proper antibiotics in the management of jaundice supports the presumed hypothesis of pathogenesis concerning hyperbilirubinemia in UTI patients, which is said to be related to bacterial endotoxins with the resultant cholestasis [11].

Conclusions:

UTI was found in 12% of infants less than two months with prolonged neonatal jaundice; urine culture should be considered as a part of the diagnostic evaluation for any infant with prolonged neonatal jaundice beyond 14 days of life with unexplained etiology.

Author's contributions:

NNH participated in the study design, sequence alignment and drafting and finalization of the manuscript. NFA participated in the study design, sequence alignment and drafting and finalization of the manuscript. QFH participated in the design of the study, collection of data and performed the statistical analysis. All authors read and approved the final manuscript.

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