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Hyperbilirubinemia With Urinary Tract Infection in Infants Younger Than Six Weeks Old-A Hospital Based Study

Medical Science

KEYWORDS : Indirect hyperbilirubinemia;Urinary tract infections; Neonatal jaundice; Infant

*** Dr Dillip Kumar Dash**	M.D, Associate Professor, Department of paediatrics, IMS & SUM Hospital,Bhubaneswar
Dr M.D Mohanty	M.D, Professor, Department of paediatrics, IMS & SUM Hospital, Bhubaneswar
Dr Naresh Chandra achary	Senior resident,, Department of paediatrics, IMS & SUM Hospital, Bhubaneswar.

ABSTRACT

Background: Neonatal Hyperbilirubinemia is one of the leading causes for hospital admission in newborn period. Previous studies have found that jaundice may be one of the initial symptoms related to urinary tract infection (UTI) in infants. There have been some reports regarding the relationship of idiopathic hyperbilirubinemia and bacterial infections,(3,5) such as urinary tract infection (UTI)(23).This study is intended particularly 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.

Aim: Is to assess the presence of urinary tract infection in new-born's with unexplained ,hyperbilirubinemia in the first six weeks of life.

Methods: We evaluate retrospectively the admitted infants younger than six weeks old with hyperbilirubinemia at our hospital for evaluation & treatment of jaundice between June 2015 and May 2016 for a span of one year. 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. 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 6 weeks old and having the initial presentation of hyperbilirubinemia and final diagnosis of UTI in a tertiary teaching hospital at eastern part odisha , India.

Results: A total of 100 neonatal jaundiced infants were enrolled. Among them, 24 cases (24%) were grouped into the UTI group, and the most common cultured bacterium from their urine was Escherichia coli (37.5%). There was no significant difference in the babies' birth weight, gestational age, modes of delivery, gender and total bilirubin levels between the two groups. There was also no significant difference between the two groups in their admission age by days in UTI and no UTI groups, respectively).The ratio of outpatients (34.78% vs. 65.21% in UTI and no UTI groups, respectively) . The cases of UTI group had significantly lower hemoglobin12.22±2.3g/dL vs. 15.1± 2.8 g/dL, respectively) and higher formula feeding rate than the no UTI group (50% vs. 19.44%, respectively ($p < 0.05$).Male gender baby are more commonly affected than female 31.03% VS 14.28% respectively. Presence of Maternal risk factor increases the occurrence of UTI i.e. sixteen out of twenty four cases are associated with maternal risk factor.

Conclusion: The incidence of UTI in the admitted infants with hyperbilirubinemia was as high as approximately 24%. 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 6weeks old to attain a faster recovery of the diseases and avoid morbidity and mortality.

Introduction

Jaundice is one of the most common encountered problems during the new born period. Although up to 60% of term, and 80% of preterm new-borns have clinical jaundice in the first week of life, few have a significant underlying disease. However, it can be associated with severe illnesses such as haemolytic disease, metabolic and endocrine disorders, enzymatic deficiencies of the liver and infections [6]. Urinary tract infection (UTI) is a common clinical problem in febrile infants younger than 8 weeks old, with prevalence between 5% and 11%[15,17].. Previous studies have noted that jaundice may be one of the first signs of a bacterial infection in infants [12,15].

Patients and Methods

This study was conducted on 100 numbers of neonates with neonatal jaundice, 64 males and 36 females. They were selected from the SNCU ofIMS& SUM Hospital under SOA University, Bhubaneswar. Exclusion criteria: neonates above 6 weeks of age, jaundiced neonates with bilirubin levels < 15 mg% for term &< 12 for pre-term, Patients with jaundice in the first 24 hours with signs of haemolysis and also cases with fever and signs of sepsis.

All case records were subjected to through case history& required investigation recording i.e. including mode of delivery & instrument use, Factors that might responsible for sepsis & urinary tract infections as premature rupture of membranes, maternal fever, Family history of jaundice in a previous sibling, duration of jaundice, maternal RH or ABO for detection of in-compatibility. Following investigations also noted i.e. serum bilirubin (total and direct) at admission and follow up, complete blood picture, reticulocyte count, coomb's test (direct), neonatal blood group & RH typing, serum C- reactive protein (CRP), urine analysis and urine culture & sensitivity were taken from records that has been done as rule of routine investigations of new born admitted to special care neonatal unit (SNCU).

Urine Culture & Sensitivity

Urine was collected by the following methods: urethral catheterization, suprapubic aspiration. The dye used for identification of organisms was gram stain. Organisms were either gram positive or gram negative. Media used were Blood Agar for gram positive bacteria, and Mac-cockney medium for gram negative bacteria. For further identification of gram negative bacteria, biochemical reaction was done. Nutrient Agar was used for sensitivity test. For colony count the calibrated loop was used. Only colony counts ≥ 105 were considered positive.

Results

Basic data of the enrolled UTI patients are depicted in table -3 including both mother & babys blood group .out of 100

patient 58 was male & 42 are female. The results of the present study showed that twenty four of one hundred neonates had positive urine culture. Most of the subjects with UTI by urine culture were males than female (18% VS 6%) respectively. Table -7 shows some comparision charecterstics between UTI & NO UTI groups. And also more than 33.33% of positive cases by culture were preterm with no a statistically significant correlation regarding gestational age. Present study showed that there was a statistically significant correlation between prolonged jaundice beyond 14 days and UTI and so also between maternal infection and neonates with positive urine culture (66.66%) (Table -1). The results of the present study showed that there is a strong correlation between UTI and unexplained jaundice which justifies the important of testing for a UTI as a part of the routine evaluation of asymptomatic jaundiced infants. Absence of urinary pus cells in present study showed no statistically significant difference (by urine analysis and culture).None of the neonates had significant microscopic haematuria. Mixed and non-breast feed babies were have more association with UTI (Table-5).laboratory data were presented in Table 4 which shows good correlations with direct hyperbilirubinemia and UTI. Disappearance of jaundice by phototherapy requires more time in UTI groups than NO UTI groups (Table-6).

Escherichia coli is the most common cause of UTI in neonates less than 6 weeks (37.5% of our cases) followed by Klebsiella species(Klebsiellapneumonia,Klebsiellaoxyto xa) infection (20.83%),Enterococcus species(16.6%),Coagula senegativestaphylococcusspecies(8.3%),

Proteus mirabilis(8%)Grampositive bacilli(4%) and acinetobacter(4%) respectively(Table-3).

Table 1
Demographic and historical characteristics of jaundiced infants with orwithout urinary tract infection

Charecsterestic	UTI	NO UTI	P value
Birth weight (g)	2.80±3.6	2.92±3.2	>0.05
Admission weight (g)	2.72±3.1	2.83±2.9	>0.05
Admission age (range) (d)			
<3	14	45	
4-7	6	25	>0.05
>8	4	6	
Gender			
Male	18	40	>0.05
Female	06	36	
Gestational age			
<37	8	5	
37-41	15	70	>0.05
>41	1	1	
Feeding practice			
Breast feeding	14	58	
Formula feeding	05	05	>0.05
Mixed feeding	05	13	
Patient			source
Inpatient	8	46	>0.05
Outpatient	16	30	
Mode of delivery			
Vaginal delivery	18	56	>0.05
Caesarean section	6	20	
Maternal condition (Fever,PROM,Infection)	16	84	<0.05

Table 2
Basic data of enrolled infants with hyperbilirubinemia and urinary tract infection

P	Sex	Age on admission (Day)	Birth weight(g)	Maternal blood type	Infant blood type	Mode of delivery	Feeding
1	M	4	3.425	O+	O+	VD	BF
2	M	3	3.567	AB+	B+	VD	BF
3	M	5	2.568	AB+	A+	CS	MF
4	F	3	2.450	B+	O+	VD	MF
5	M	4	2.876	AB+	B+	VD	BF
6	M	2	2.123	O+	A+	VD	FF
7	M	28	2.987	B+	O+	VD	MF
8	F	7	3.678	O+	B+	CS	BF
9	M	6	2.545	B+	B+	VD	BF
10	M	3	2.675	B+	O+	VD	FF
11	F	3	3.238	AB+	A+	VD	BF
12	M	3	2.386	AB+	B+	VD	BF
13	M	3	2.765	O+	B+	CS	BF
14	M	2	2.986	O+	O+	VD	FF
15	M	34	2.674	B+	B+	VD	BF
16	F	3	3.334	O+	O+	CS	BF
17	M	3	3.645	AB+	A+	VD	FF
18	M	12	2.347	O+	B+	VD	MF
19	M	3	2.876	B+	O+	CS	BF
20	F	7	2.967	AB+	B+	VD	MF
21	F	43	2.674	B+	O+	VD	BF
22	M	3	2.574	AB+	A+	VD	BF
23	M	4	2.668	O+	B+	VD	FF
24	M	5	2.954	B+	AB+	CS	BF

P-Patient F- Female M- Male BF- breast feeding MF-Mixed feeding FF- Formula feeding VD-Vaginal delivery
CS- Caesarean section +-Positive Rh blood type

Table 3

Organisms cultured from the urine of 12 jaundiced neonates diagnosed as Urinary tract infection

Bacteria	Number	Percentage(%)
Escherichia coli	9	37.5
Enterococcus species	4	16.6
Klebsiellaspecies	5	20.83
Coagulase-negative staphylococcus species	2	8.3
Proteus mirabilis	2	8.3
Gram-positive bacilli	1	4.1
Acinetobacter sepsis	1	4.1

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Table 4
Laboratory data of jaundiced infants with or without urinary tract infection

Characteristics	UTI (N-24)	NO UTI (N-76)	Pvalue
Total bilirubin level mg/dL	16.4±2.92	15.8±2.71	> 0.05
Direct bilirubin level (mg/dL	0.9±0.4	0.4±0.2	**< 0.05**
White cell count (/cumm)	13.834±424	12.567±928	
Hemoglobin (g/dL)	13.22±2.3	15.1± 2.8	
Platelet count (/cumm	258725±	32445±	
HCT %	40.66±5.2	35.9±8.9	
WBCs(/cumm)	10.86±1.8	11.91±3.9	
Netrophils %	32.2±9.61	35.29±13.26	> 0.05
Monocytes %	7.9±2.9	6±3.1	
Lymphocytes %	56.39±5.10	61.02±12.26	
Eosinophils %	2.72±0.32	1.9±1.90	
Basophils %	0.7±0.32	0 .62±0.49	

Table 5
Urinary tract infection, jaundice & type of milk consumed

Group's		positive	Negative	total
BM	%	19.44	80.55	
	Count	14	58	72
NBM	%	50	50	
	Count	05	05	10
Mixed	Count	05	13	18
	%	27.77	72.22	

Table 6:
jaundice data of 153 neonates with and without UTI

Jaundice data neonates (n=24)	with UTI neonates (n=76)	without UTI	p value
TSB (mg/ dl)	16.4±	15.8±	>0.05
Decrease of TSB after 24hrs Of photo therapy mean ±SD	1.9±1.8	3.2±1.3	<0.05
Direct hyperbilirubinemiaN (%)	7(29.16)	0	<0.05

Table 7: Comparison of characteristics of neonates with and without UTI

	Without UTI	With UTI	P value
Gestational age (weeks)	39.6±0.73	39.5 ±0.8	>0.05
Percent of male	52.6	37.5	**<0.05**
Per cent of caesarean section	83.33	25	>0.05
Onset of jaundice (day)	3.4 ±0.63	3.6±0.46	>0.05
Age of admission	5.4±2.4	4.9±2.3	>0.05

Discussion

The clinical manifestation of UTI presenting as jaundice has been mentioned since 84 years ago(17-18) and re-emphasized during the past 40 years.(7,17,19) The presentation of jaundice in cases of UTI has been reported in all age groups i.e. neonates, children, and adults.(19-22). Many possible mechanisms for UTI-causing jaundice have been demonstrated, including: hemolysis, direct invasion of the liver parenchyma by blood-borne or lymph borne microorganisms, hepatocellular injury by circulating endotoxins, and non-specific injury to the liver related to hyperpyrexia, malnutrition and toxemia. Jaundice can lead to UTI by altering bactericidal activity in the sera of jaundiced newborns making them more prone to infections as that reported in the study by Cisowska et al. [2]. Also, Linder et al. reported that there were around 3.2% of jaundiced and asymptomatic neonates being diagnosed as septicemia.(23) Therefore, the presence of jaundice may be an early sign of infection in neonates, should be evaluated especially for UTI. 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 co-

incidence of UTI is important in jaundiced infants. In the present study the incidence of UTI among neonates with jaundice was 24% and the most common pathogen isolated was E.coli. These findings are more than other studies conducted by Garcia and Nagar (5)and Bilgen(26) ,where incidence of UTI was (7.5% & 8%) respectively, but the incidence much higher than reported (2.9%) by Chavalitdhamrong(27) in small series of asymptomatic jaundiced infants .Similar to the data indicated in the literatures and other studies (28,29) UTIs were found to be more frequent in male .It is conceivable that the urethra of male is unable to prevent ascending infection during the first months of life and that perineal bacteria are present in large enough numbers at the meatus to allow attachment and ascension to the bladder.(30).

The incidence of UTI is low in the first few days of life (2 %) even in neonates who are bacteremia, as a result urine cultures are not obtained for term infants who are being evaluated for early-onset sepsis before the first six days of life.[4].Bacteremia and sepsis have been well described as a cause of neonatal jaundice in seriously ill newborns and jaundice may be one of the first signs of bacterial sepsis in neonates in the first few days of life [5,24].In one large cohort study based on data from neonatal intensive care units, there was a 13 % rate of a positive blood culture collected within three days of the urine culture with the same pathogenic organism [15].

We found that 24% of our cases had growth in their urine cultures, 37.5% of them had Escherichia coli infection, while 20% had Klebsiella pneumonia infection. A study by Wang et al. [11] who found that among 95 infants under 2 months of age diagnosed with UTI, the most common organism in urine culture was E-coli with no statistically significant correlation.Another study by Biyikli et al. [9] in Turkey, the high rate (63%) of E-coli was reported among 71 jaundiced infants who were diagnosed and treated for UTIwith statistically significant correlation. Other Garcia and Nager[5] and Omar et al. [10]also reported other organisms, with lower frequencies, which are Enterobacter, Streptococcus viridans, Enterococcus, Streptococcus group B and Staphylococcus aureus. In our present study 62% of neonates with UTI having pyuria, but without a statistically significant difference. On the other hand, the no UTI group showed 60% of neonates with negative urine culture had no pyuria without a statistically significant difference which closely correlate study by Wang et al. [11] who reported no statistically significant difference between urinary culture and urinary pus cells..

UTI (by urine analysis) was more common among boys in our current study but without significant correlation regarding gender, which agreed with Ghaemi et al. [8] who reported that UTI was more common in boys with no significant correlation. Based on the paediatric texts, most of the UTIs in boys occur in the first year of life, during which the percentage of UTI in boys is 2.8 times more than in girls. While after this period, the percentage in girls is 10 times more than in boys. In our current study the percentage of boys 18 males and only 6 females among the positive UTI group with no a statistically significant difference between positive and negative UTI groups (p-value > 0.05.).other studies which support our finding by Lee et al. [12] and Chang et al. [13] showed a male predominance. Ghaemi et al. [8] found that nearly 60% of male infants with UTI were uncircumcised and Singh-Grewal et al. [14] found that circumcision was associated with a significantly reduced risk of UTI. We found there is a significant correlation between the duration of jaundice (≥14 days) from one side and positive urine culture and maternal infection history (p-value <0.05) from the other side. These findings are in agreement with Chin et al. [1] who found that urinary tract infections (UTI) are attributed as one of the main reasons for prolonged jaundice.

Some cases of hemolysis (a diagnosis based on the presence of anemia and elevated reticulocyte counts) have been reported to contribute to jaundice in patients with infections caused by E-coli, Enterobacteraerogenes and Enterococcus. (16). some strains of E-coli produce a hemolysis demonstrated by a high titer of anti-α-hemolytic antibodies in a patient's serum and by hemolytic zones on a blood agar plate. Increased red cell fragility in E- coli sepsis is also supposed to be a common region of haemolysis. However, haemolysis is not thought to be the major cause of UTI-related jaundice, although even mild haemolysis can overload the immature liver conjugating mechanism, leading to an increase in serum bilirubin levels. Direct bacterial invasion of the liver parenchyma leading to toxic hepatitis and jaundice might explain some cases of UTI related prolonged jaundice.Pro inflammatory cytokines can either reduce transporter gene expression or directly inhibit transport protein function [16,25].

In a retrospective study performed by Singh-Grewal et al. [14] reported that infection with E-coli had a stronger association with conjugated than unconjugated hyperbilirubinemia. Such association was not found with Klebsiella pneumonia infection. Our results did not demonstrate such a correlation.

Conclusion

The study revealed that UTIs can occur in asymptomatic jaundiced neonates in the first few weeks of life. Testing for UTI should be a part of the diagnostic evaluation of neonates with prolonged unexplained jaundice. It is necessary to do a urine culture in those infants as urine analysis is not a sensitive test for UTI and has many false negative results which may leads to many misdiagnoses & overzealous treatment. In addition, neonates with direct hyperbilirubinemia, slow decrease in serum bilirubin levels and onset of jaundice after 8 days of life were more likely to have UTIs. Therefore, we suggest that UTIs must be considered in neonates with jaundice and it is advised to perform urine culture if they have one or more of the following conditions:

1- High direct bilirubin level.

2- Slow decrease in serum bilirubin level with phototherapy.

3- Onset of jaundice after 8 days of age especially in male, bottle –fed infants.

4-Presence of Maternal factors i.e. premature rupture of membranes, maternal fever etc.

In conclusion, in admitted infants younger than 6 weeks old, approximately 24% of jaundiced cases had UTI. The most common cultured bacterium was E coli. . Therefore, we suggest that UTIs must be considered in neonates with hyperbilirubinemia especially if associated with above described risk factors.

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