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Hyperbilirubinemia and Neonatal Infection

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Abstract

Introduction:
Hyperbilirubinemia is a relatively common disorder among infants in Iran. Bacterial infection and jaundice may be associated with higher morbidity. Previous studies have reported that jaundice may be one of the signs of infection. The aim of this study was to determine the incidence rate, presentation time, severity of jaundice, signs and complications of infection within neonatal hyperbilirubinemia.

Materials and Methods:
This cross sectional study was conducted between 2003 and 2011, at Ghaem Hospital, Mashhad- Iran. We prospectively evaluated 1763 jaundiced newborns. We finally found 434 neonates who were categorized into two groups.131 neonates as case group (Blood or/and Urine culture positive or sign of pneumonia) and 303 neonates with idiopathic jaundice as control group. Demographic data including prenatal, intrapartum, postnatal events and risk factors were collected by questionnaire. Biochemical markers including bilirubin level, urine and blood cultures were determined at the request of the clinicians.

Results:
Jaundice presentation time, age on admission, serum bilirubin value and hospitalization period were reported significantly higher among case group in comparison with control group ($p<0.0001$). Urinary tract infection (UTI), sepsis and pneumonia were detected in 102 (8%), 22 (1.7%) and 7 (0.03%) cases, respectively.

Conclusion:
We concluded that bacterial infection was a significant cause of unexplained Hyperbilirubinemia among jaundice newborns (10%). Therefore, we advise performing screening test for UTI as part of the evaluation in asymptomatic jaundice infants presenting after five days of life and sepsis workup should be request in symptomatic infant especially in the first week of life.

Keywords:
Neonate, Urinary tract infection, Sepsis, Hyperbilirubinemia, Pneumonia

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Introduction

Hyperbilirubinemia is a common and in most cases benign problem in first mouth of life which is often physiologic and intervention is not usually necessary. Jaundice appears during the first week of life in approximately 60% of term and 80% of preterm infants. Jaundice may develop serious complications like kernicterus and lifelong disability (1,2).

Providing practitioners with new insights for predisposing factors, exacerbating or etiologic factors for jaundice could help them to the better management (3). One of these factors is infection which is a serious clinical problem among newborns (5,6). The incidence rate of hyperbilirubinemia due to infection is unknown (7,8). It is well known that clinical manifestations of neonatal infection pretends as a wide spectrum, ranging from nonspecific signs and symptoms to severe illness as well as poor feeding, fever, vomiting, renal failure and respiratory distress (9,10). Hyperbilirubinemia may be the only manifestation of infection, especially UTI within neonatal period (10-12).

Bacterial infection has been well-documented as a cause of neonatal jaundice in previous studies (6) but the prevalence rate, jaundice presentation time and the differences between the jaundice associated with infection and other types of jaundice was unknown yet.

The aim of this study was to determine the incidence rate, symptoms, and age at presentation, predisposing factors, characteristics, the severity of jaundice associated with infection and complications and the etiology of infection among neonates with hyperbilirubinemia in the first month- of life.

Materials and Methods

This study has been accomplished on 1763 neonates with jaundice aged 1-29 days who were admitted to Ghaem Hospital, Mashhad-Iran, between February 2003 and October 2011.The ethic committee of Mashhad University of Medical Science approved this study and all parents signed the informed consent.1763 neonates with the chief complaint of jaundice were admitted to our neonatal ward during this study period, but only 1269 infants were evaluated for infection. 827 cases were excluded from the study because of jaundice due to definite or probable reason. Neonates with hemolysis (ABO and Rh isoimmunization), hypothyroidism, G6PD Deficiency, congenital heart disease and etc were excluded from the study.

We finally found 434 neonates who were categorized into two groups.131 neonates as case group which had the criteria for infection (Blood or/and Urine culture positive or sign of pneumonia in Chest-X-Ray) and 303 neonates with idiopathic jaundice as control group (Figure. 1). Clinical jaundice was determined as yellowish color of the skin, mucous membranes or sclera. Information were collected and recorded by neonatal fellowship and neonatologist.

Maternal data like history of pregnancy and delivery, age, blood group, disease, type of delivery and duration of hospitalization after delivery were all recorded. Neonate's data like time of jaundice onset and discharge from hospital, signs and symptoms on admission, duration of hospitalization and treatment plan were recorded and complete physical examination was done.

Complete blood count (CBC) with differential, serum fractionated bilirubin level (direct and indirect), Coombs test, reticulocyte count, blood group of the baby and mother, thyroid function tests, glucose-6 phosphate dehydrogenase (G6PD) level, urinalysis and urine culture were performed for evaluation of etiology and severity of jaundice. Blood culture, urine culture, blood sugar, urea, creatinin, Na, K and calcium were determined at the request of the clinicians.

Urine sample obtained by suprapubic aspiration and its result was considered positive if any colony forming unit of a single pathogen was isolated. Urine samples were examined for leukocyturia and bactriuria in

the clinical laboratory by microscopy. Leukocyturia was defined as >5 leukocytes per HPF.

Treatment period, the result of blood and urine cultures were recorded and proper follow-up was performed after discharging from the newborn nursery. During follow-up, renal ultrasonography and voiding cystourethrogram (VCUG) were requested in cases of positive results for UTI.

Statistical analysis was carried out using SPSS 13.5 statistical package, for comparing groups. Descriptive data were reported as mean ± standard deviation, and were analyzed by Fisher exact test, the X^2 test and Student t test.

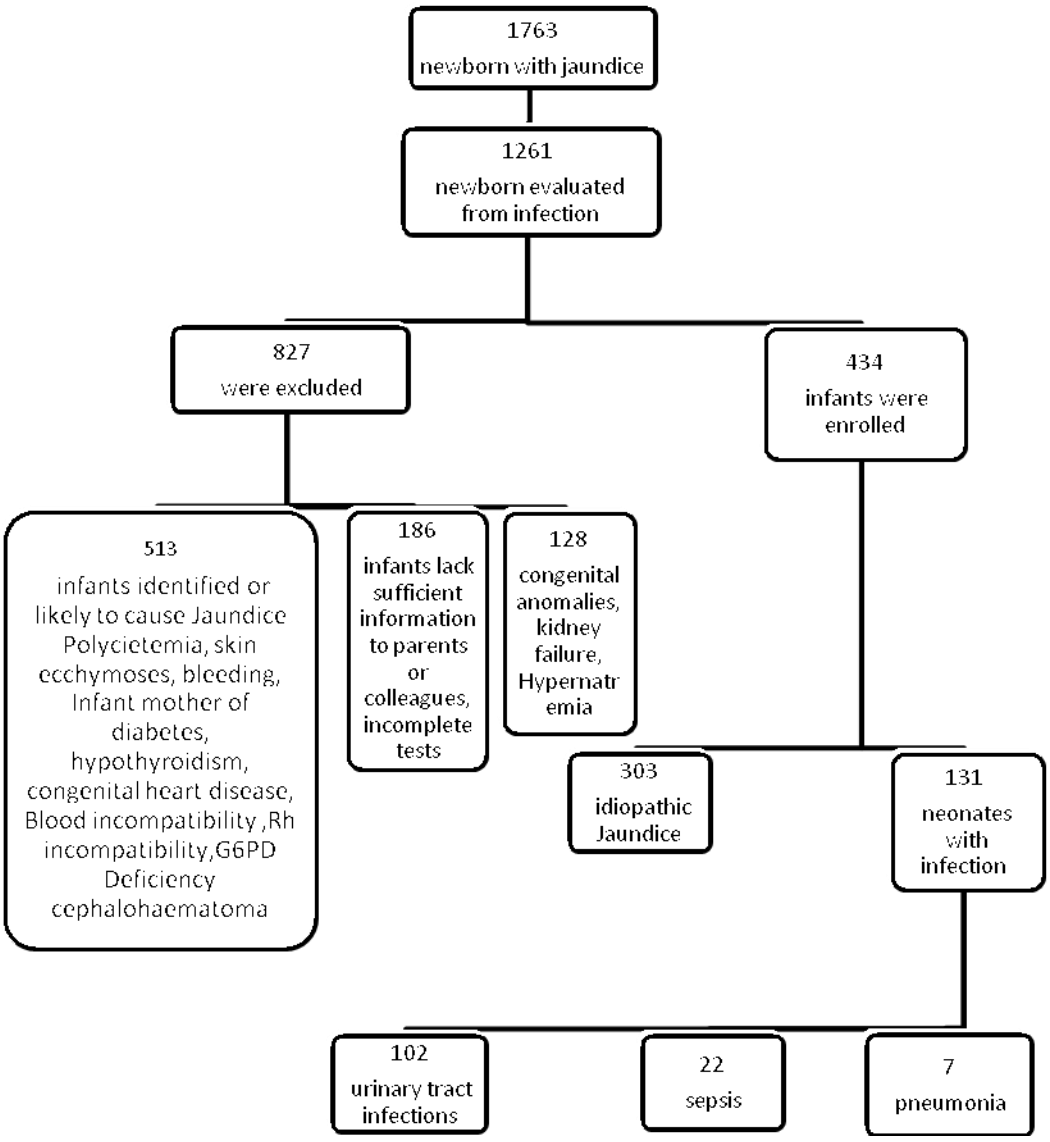

Fig 1: Selection, enrollment, and diagnosis of the study subjects.

Results

A total of 1763 jaundiced neonates were referred to the newborn nursery and emergency department of Ghaem Hospital, Mashhad from February 2003 to October 2011 for evaluation of jaundice and were enrolled for recruitment. Among them, finally 131 neonates that had the criteria for

infection and 303 jaundiced neonates with an unknown etiology were placed as case and control groups, respectively (Figure 1).

The mean age was reported 12.6±7.5 days in the case group and 8.7±6.0 days in the control group. Eighty-seven percent of neonates were born at term (37–42 weeks′ gestational ages) and forty-five percent of the case group was born via Caesarean section delivery (Table 1).

Table 1: Demographic characteristics of thecase and control groups.

Characteristics	Control group N=358	Case group N=132	P value
Age on admission (day)	8.7±6.0	12.6±7.5	0.000
Birth weight (g)	3000±610	3200±480	0.033
Weight on admission (g)	2940±680	3160±650	0.003
Gestational age (term/ preterm)	238/44	118/13	0.061
maternal age (year)	26.1±5.2	26.0±5.0	0.183
Mode of delivery (CS/NVD)	215/126	38/36	0.052
Jaundice presentation time (day)	2.5± 1.7	3.7± 1.9	0.000

No statistically significant differences were found for sex, gestational age, delivery type, birth weight and maternal age between two groups (P>0.05). Age and weight on admission, jaundice presentation time, hospitalization period, serum indirect and direct bilirubin values had significant differences between two groups (P<0.05), (Table 1,2).

Table 2: Comparison of clinical and laboratory findings in the subgroups study.

Characteristics	UTI group (N=102)	Sepsis group (N=22)	Pneumonia group(N=7)	P value
Age on admission (day)	13.9±7.3	6.6±3.6	9.0±5.2	0.000
Jaundice presentation time (day)	4.0± 1.9	3.0± 1.5	7.1± 2.1	0.000
Serum indirect bilirubin value (gr/dl)	16.8±4.9	23.8±6.0	16.4±6.3	0.000
Serum direct bilirubin value (gr/dl)	0.9±0.53	2.2±1.0	1.2±1.1	0.01
Hematocrit (%)	45±5.7	43.6±7.8	44.4±1.3	0.041
Hospitalization period (day)	5.6±1.9	12±2.6	10.1±2	0.000

Neonatal infection was found in approximately 10% of jaundiced newborns. The most common infection associated with neonatal jaundice was UTI (77.9%), Sepsis (16.8%) and pneumonia (5.3%), in order. The most common pathogen isolated from UTI was Klebsiella pneumonia (48 infant), followed by Escherichia coli 2 (38), proteus (6), Staphylococcus epidermidis (5), Staphylococcus aurous (3) and Acinetobacter (2). The most common pathogen isolated from sepsis was Staphylococcus aurous, followed by Staphylococcus epidermidis, proteus, entrobacter, Klebsiella pneumoniae and Escherichia coli (Figure 2).

81 cases with bacteriuria and 71 cases with leukocyturia were detected in the case group. Moreover 50 neonates had both bacteriuria and leukocyturia. Although, not statistically significant, infection was more common in male neonates comparison with females (P>0.9). In the current study we did not find UTI among jaundiced neonates aged 5 days and younger. UTI was detected among 24 neonates who presented with jaundice between 5–7 days of age. Patients who were jaundice after 7 days of age had a higher incidence of UTIs (78 cases) which means that it is necessary to screen jaundice neonates for UTI after the first week.

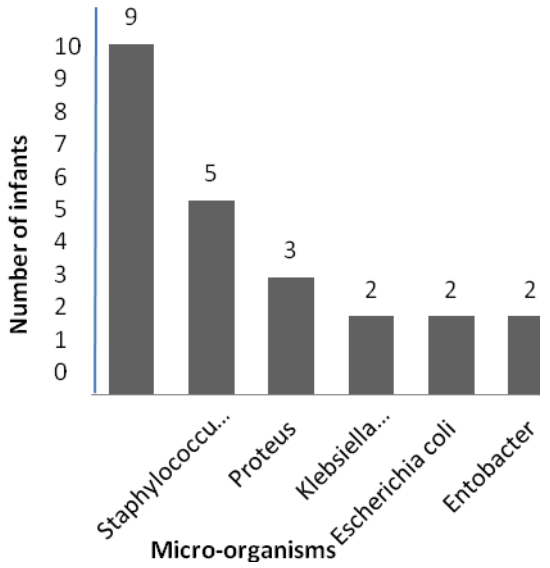

Fig 2: Bacterial Pathogens in the patients with Sepsis

Mean indirect bilirubin values were significantly lower in the case group in comparison with control group (17.9 vs 21.2 mg/dl, P<0.001). The jaundice associated with infection was moderate (17.9± 5.7 mg/dl).

Hospitalization period was longer in the case group (8 Vs 3.3 day, P<0.001). Age at jaundice presentation and age at jaundice resolving were later in the case group (P<0.05). Statistically significant differences were reported for direct bilirubin values between two groups (P<0.001).

There was not statistically significant differences between groups with regard to the mean values of hematocrit, platelet, reticulocyte count, sodium, potassium, urea and creatinine (P>0.05).Three cases had sepsis and Staphylococcus aureus were reported in their blood and urine cultures .

Renal ultrasonography was performed in 81 cases. Urinary tract abnormalities were found in 27 cases, which included hydronephrosis (12 patients), ureteropelvic junction obstruction (UPJO) (3 patients), urinary stones (8 patients), and pelviectasis (4 patients). VCUG was performed in 36 neonates during the study period and 16 cases had unilateral grade 1-3 reflux. Kernicterus was observed in one patient of sepsis group.

Discussion

By this large sample size we found that infection should be considered as a cause of jaundice especially in neonates with other symptoms. Jaundice associated with infection was appeared moderately although complications took place more than idiopathic hyperbilirubinemia. Our results show that jaundice may be manifested as a first sign of infection (especially UTI) in neonates.

In the present study, the incidence rate of jaundice due to infection was reported 10 % (UTI 8%, sepsis 1.7% and pneumonia 0.3%). Chavalitdhamrong et al (11), in a prospective study of 69 asymptomatic neonates with unexplained jaundice, found evidence of Gram-negative UTIs in only 2 (2.9%) infants.

To the best of our knowledge, no previous study with this sample size has been performed yet. Garcia et al [4], reported that UTI was occurred in 12 (7.5%) of 160 infants with asymptomatic, afebrile, jaundice infants younger than 8 weeks old. Xinias et al (7) reported results on a series of 462 full-term neonates in which thirty neonates (6.5%) were found to have a UTI. Another study reported the incidence rate of 3.5% for UTI (11).

High prevalence of urinary tract infections in our study compared with other studies may be related with age and later diagnosis of neonatal jaundice in our study and neonates were older than the ones in other studies. Our sample size was larger than others, which shows higher poverty of this study compared with previous studies. Late diagnosis of neonatal jaundice both increases the severity and complication. The most common pathogens isolated in current study were Klebsiella pneumonia and Escherichia coli which is consistent with the results of Garcia study (4).76.5% of the jaundice neonates with UTI in case group

referred after the first week. These findings indicate that jaundice associated with UTI is clinically appeared later. We should consider UTI as a probable cause of jaundice and neonates certainly should be evaluated for UTI, if there was a history of worsening jaundice while physiologic jaundice is expected to be improved or resolved. Usually the presence of a UTI within first days of life is rare unless it accompanies with sepsis and it will take some days to be clinically manifested.

We found evidence for sepsis in 1.7% neonates with hyperbilirubinemia and 95% of the jaundice neonates with sepsis in case group was symptomatic (poor feeding, fever, respiratory distress…). We should consider sepsis as a probable cause of jaundice among neonates especially in symptomatic cases.

To our knowledge, there is a little data in this regard and our study is performed with the largest sample size. Also, there is few data about the prevalence rate and progress of jaundice associated with sepsis. 73% of the jaundice neonates with sepsis (case group) were admitted in the first week. These findings indicate that jaundice associated with sepsis is clinically appeared earlier. The current prospective investigation was designed to determine the frequency of unexplained hyperbilirubinemia associated with neonatal bacterial infection especially within first week of life.

Mean bilirubin value was significantly lower in subjects with UTI and pneumonia subgroups in comparison with noninfectious cases (17.9 mg/dl vs 21.2 mg/dl). Jaundice associated with UTI is moderate and pretends as exaggerated physiologic hyperbilirubinemia and even may not require admission to the hospital for treatment. Hyperbilirubinemia associated with UTIs can be unconjugated and related to hemolysis caused by Eshershia coli and other Gram-negative organisms (12). However, hemolysis associated with UTI is mild and anemia is not a common finding (12).

The mechanism of jaundice in neonatal pneumonia is not well known. This partially may be related to the congstion of liver affected by pneumonia. Mean bilirubin value was significantly higher in sepsis subgroup as compared with noninfectious subjects (23.8 mg/dl versus 21.2 mg/dl). The mechanism of jaundice in neonatal sepsis maybe related to liver involvement by infection or hemolysis, although this mechanism is not well known. Conjugated hyperbilirubinemia was reported in 22 cases (17%) which were raised over 20% of total bilirubin (14% of UTI and 27% of sepsis infants). After treatment of infection, all neonates with an increase in the conjugated bilirubin fraction showed jaundice resolution requiring no additional work-up. Conjugated hyperbilirubinemia can be associated with cholestasis secondary to bacterial infection. The mechanism in which infection causes cholestasis is not clear, but possible mechanisms include microcirculatory changes in the liver, direct effects from bacterial products, and/or from endotoxin-induced mediators (13,14).

In our study, bactriuria and leukocyturia were defined in 64.8% and 63% of cases, respectively as well as 37% of neonates in case group showed both bactriuria and leukocyturia.The incidences rate of either bacteriuria or leukocyturia in neonatal UTI have been reported differently (28%-48%) (15). Garcia et al, detected that 50% of asymptomatic, jaundice babies with UTI, had an abnormal urinalysis or microscopy results. Bilgen et al (5), in a study of 102 neonates, determined UTI among eight (8%) of cases. The most common pathogens isolated from UTIs were Enterobacter aerogenes 38%, Enterococcus faecalis 25%, Klebsiella pneumoniae 25% and Escherichia coli 12%. Pyuria and Bacteriuria was present in 50% and 88% of these cases, respectively. Sepsis screen was negative in all except one case with a high C-reactive protein (CRP)

level. None of the patients had a positive blood culture.

We found urinary tract abnormalities in 27 cases (26.5%) including hydro-nephrosis, UPJO, urinary stones and pelviectasis. In the study by Bilgen et al (5), renal ultrasonography revealed urinary tract abnormalities in three (38%) patients with hydronephrosis and pelviectasis. VCUG was performed in all patients during the study period and one had unilateral reflux. They concluded that urine culture should be considered in hyperbilirubinemia work-up for jaundice infants older than three days of age with an unknown etiology. Ghaemi et al (16) conducted a prospective analytic study among 400 cases. UTI was found in 23 (5.8%) infants with late onset jaundice. from 23 neonates with UTI, 17.39% were found to have urogenital abnormality.In another study by Pashapour and colleagues (17), UTI was detected in 6% of neonates with prolonged jaundice who were evaluated for frequency of UTI. Reflux was detected on VCUG in 1 case. In our study 44% of evaluated neonates had unilateral grade 1-3 reflux including 16% of neonates with UTI. Other studies have reported the incidence of reflux as much as 18% (17). The explanation for this difference may be due to lack of neonates investigated with VCUG among our patients. Also, one case of kernicterus was observed among sepsis group which may be related to sever complication of co-insistency of these two events.

Conclusion

The incidence rate of bacterial infection associated with hyperbilirubinemia was determined prospectively in 1763 infants aged below one month. Sepsis was documented in 22 infants, who had symptoms of infection. We concluded that bacterial infection was a significant cause of unexplained Hyperbilirubinemia among jaundice neonates. Our results indicate that urinary tract infections after and sepsis before the first week of life may be associated with jaundice.

This indicates the importance of screening for UTI in asymptomatic, jaundice infants especially those with appearance of jaundice after the first week of life. Jaundice associated with UTI appeared later and was not severe, but sepsis usually presented in the first week of life, usually is severe and may be complicated.

Paying attention to UTI in infants with hyperbilirubinemia can decrease its complications before any signs or symptoms become evident.

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