The Egyptian Journal of Hospital Medicine (Apr. 2017) Vol.67 (2), Page 692-696

Incidence and Risk Factors for Neonatal Jaundice among Neonates with Urinary Tract Infection in Abha - Saudi Arabia

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ABSTRACT

Background: Hyperbilirubinemia is one of the presenting signs of bacterial infection in newborns, and the association of neonatal jaundice with urinary tract infection (UTI) has been particularly emphasized. The aim of this study was to determine the prevalence of UTI in asymptomatic jaundiced neonates younger than 4 weeks old. **Method:** A cross sectional survey has been conducted at Newborn Unit of Maternity & Pediatrics Hospital – Abha from January 2016 to August 2016. A total of 15 patients have been included in the study, who were diagnosed with hyperbilirubinemia due to urinary tract infection (UTI) after exclusion of unrelated criteria. **Conclusion:** It could be concluded that UTI should be routinely investigated in early (⩽10 days) idiopathic neonatal jaundice in which all other etiologic factors of neonatal hyperbilirubinemia are ruled out, and the presence of UTI should be considered in case of a poor phototherapy response in cases receiving phototherapy.

Keywords: neonate, jaundice, urinary tract infection, UTI.

INTRODUCTION

Neonatal jaundice is a benign condition that often does not require intervention [1]. Most cases of neonatal hyperbilirubinemia constitute physiological jaundice and do not have serious consequences. It is a common physiological occurrence in newborns [2-3]. About 60% of full term and 80% of premature neonates develop clinical jaundice in the first week of life [4-5] showing clinical signs including yellow discoloration of the skin and sclera resulting from high serum levels of bilirubin [6-7]. For the majority of these infants, hyperbilirubinemia is a natural transition that resolves within the first week of life with maturing of the liver; however, hyperbilirubinemia is also the main reason for hospital readmission during the neonatal period [8-10].

There are many factors implicated in the development of pathological jaundice, including perinatal factors (e.g., birth trauma or infections), maternal factors (e.g., Rh or ABO incompatibility), neonatal factors (e.g., prematurity or polycythemia), and genetic factors (e.g., Crigler-Najjar's or Gilbert's syndrome) [11]. In addition, the administration of drugs such as cephalosporin and glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency has been implicated in pathological jaundice [11]. The mechanism by which hyperbilirubinemia occurs is through either increased bilirubin production (resulting from hemolysis, sepsis, blood extravasation or polycythemia) or increased enterohepatic circulation (resulting from prematurity, pyloric stenosis, delayed bacterial gut colonization, gastrointestinal tract immobility or obstruction), or decreased bilirubin elimination which occurs in Crigler-Najjar's and Gilbert's syndromes [11]. Some studies have reported that unexplained hyperbilirubinemia may be associated with bacterial infections in the newborn, such as urinary tract infection (UTI) [12].

The clinical manifestations of UTI in neonates are extremely variable, ranging from severe illnesses to nonspecific signs and symptoms such as growth failure or jaundice [13]. UTI is thought to be the main reason for prolonged jaundice, thus urine culture is routinely performed in neonates with jaundice aged more than 3 weeks [14].

The aims of this study were to determine: (1) the prevalence of UTI in neonates with asymptomatic, unexplained unconjugated hyperbilirubinemia in the first 4 weeks of life; and (2) if urine culture should be considered a necessary procedure in these conditions.

Received: 22 / 03 /2017
Accepted: 30 / 03 /2017
DOI : 10.12816/0037823

SUBJECTS AND METHODS:

This study was conducted on 110 asymptomatic jaundiced infants at Newborn Unit of Maternity & Pediatrics Hospital – Abha from January 2016 to August 2016. All newborns who were diagnosed with significant hyperbilirubinemia and required phototherapy treatment were eligible for the study.

Patients jaundiced in the first 48 hours of life with signs of hemolysis, or cases with documented fever >38^{o} C and signs of sepsis (vomiting, poor feeding, lethargy, etc.) were excluded. Demographic data including prenatal events, such as gestational age, maternal infections, mode of delivery, and prolonged rupture of the membranes, birth weight, and weight loss as percent in comparison with birth Weight were recorded. Parents were questioned in detail regarding postnatal events including neonatal fever, lethargy, irritability, diarrhea, onset of jaundice, and whether the infant was breastfed or formula-fed, feeding intolerance (poor feeding, vomiting), and dirty skin color (poor tissue perfusion) were also collected.

With the aim to determine whether UTI was the cause of pathologic jaundice, urine samples for microscopic and bacteriologic examination were obtained via bladder catheterization in all cases. The urine culture obtained was considered positive if a single pathogen with more than 10 000 colony forming units per milliliter (CFU/ml) was isolated. In the case of a positive urine culture in the jaundiced neonates, a sepsis evaluation consisting of blood cell counts, C-reactive protein (CRP), and blood culture was performed. A lumbar puncture was also done in those cases with positive blood cultures.

The following tests were also performed: complete blood count, peripheral blood smear, glucose-6-phosphate dehydrogenase (G6PD), direct Coombs' test, immunization (ABO, Rh, or subgroup incompatibilities), total and direct bilirubin, and reticulocyte count to be excluded from the stud.Other exclusion criteria were the presence of any major congenital anomaly, respiratory distress, and clinical or culture-proven sepsis. Renal ultrasonography was performed on all newborns with UTI, and voiding cystoureterography (after obtaining a sterile urine culture, approximately 1 month after the diagnosis) and dimercaptosuccinic acid scintigraphy (3 months after the diagnosis) were performed on those with any abnormality on renal ultrasonography.

RESULT

The study population consisted of 110 asymptomatic jaundiced neonates. the mean age was 7 ± 4 days, 73 (66.36%) neonates had a birth weight more than 2500 g, and 93 (84.55%) neonates were born at term (37–42 weeks of gestation); 70 (63.64%) neonates were male and 40 (36.36%) were female.

Positive urine cultures were obtained for 15 (13.64%) of the 110 asymptomatic jaundiced infants enrolled ($p < 0.001$). Demographic characteristics of the jaundiced patients with positive and negative urine cultures are presented in Table 1. the prevalence of UTI was significantly higher in the male compared to the female neonates.

Table 1: Demographic characteristics of the neonates with positive and negative urine cultures

Characteristic		**Positive urine culture**	**Negative urine culture**
Age	**< 2 weeks**	12	85
	≥ 2 week	3	10
Sex	**male**	11	59
	Female	4	36
Birth weight	**< 2500 g**	5	32
	≥ 2500 g	10	63
Gestational age	**< 37 weeks**	4	13
	≥ 37 weeks	11	82
Vaginal delivery		13	97
Maternal infection		3	107
Feeding	**Breast feeding**	13	95
	Formula feeding	0	2

Bacterial pathogens, urine microscopy, and serum bilirubin levels in the jaundiced infants with positive urine cultures are shown in Table 2. Bacterial pathogens isolated from the urine cultures in the 15 cases were as follows: Klebsiella pneumoniae (7/15, 46.67%), Escherichia coli (5/15,33.33%), and Enterobacter (3/15, 20%). Four of the 15 neonates had pyuria, defined as ≥10 WBC/HPF. All the jaundiced patients with positive urine cultures had total serum bilirubin (mean 20±7).

Table 2: Bacterial pathogens, urine microscopy, and serum bilirubin level of the neonates with positive urine cultures

No.	Age	Sex	Bacteriology	WBCs count, 10^9/L.	Total bilirubin, mg/dl	Conjugated bilirubin, mg/dl
1	8	♂	Klebsiella	6	13	.5
2	9	♂	E. coli	7	25	1.3
3	7	♀	Enterobacter	5	27	.7
4	25	♂	E. coli	9	18	.6
5	8	♂	Klebsiella	12	22	1.6
6	7	♂	Klebsiella	4	17	.5
7	7	♀	Enterobacter	7	16	.8
8	6	♀	E. coli	5	14	1.2
9	4	♂	Klebsiella	13	16	.7
10	12	♀	Enterobacter	3	20	1
11	7	♂	E. coli	4	18	1.2
12	6	♂	Klebsiella	3	25	1.7
13	4	♂	Klebsiella	17	31	1
14	4	♂	E. coli	6	18	.6
15	7	♂	Klebsiella	21	20	1.4

After the initial study evaluation, these 15 patients with UTI were admitted to the hospital. Other blood cultures and all CSF cultures were negative. Renal ultrasounds were performed for these patients; three (20%) cases had hydronephrosis and the others were normal.

DISCUSSION

The incidence of non-physiological hyperbilirubinemia in neonates is significant [15], and sepsis has been documented as a cause of neonatal jaundice in seriously ill newborns [16]. However, jaundice may be one of the first signs of bacterial sepsis in the first few days of life [17]. Some studies have indicated that jaundice is the first sign of a newborn with a UTI [18]. Although the pathophysiologic relationship between hyperbilirubinemia and UTI has not exactly been revealed, one of the suggested mechanisms is hemolysis caused by E coli and other gram-negative bacteria. Even little hemolysis in the newborn may cause significant hyperbilirubinemia due to immature conjugation mechanisms, and thus, serum bilirubin levels may increase as an alerting sign even in UTIs with mild clinical severity.

Conjugated hyperbilirubinemia associated with UTI may be related to cholestasis. Although how UTI causes cholestasis is not well defined, microcirculatory problems in liver and direct bacterial and endotoxin-mediated products are the other suggested mechanisms [19]. However, some authors claim that the relationship between UTI and neonatal jaundice is just a coincidence [20]. In studies investigating the etiologic role of UTI in neonatal jaundice, the incidence of UTI has been reported between 5.8% and 21% [12, 21,22,23].

There are various ideas about the profile of microorganisms causing both jaundice and UTI. In a retrospective analysis of 120 asymptomatic jaundiced newborns, the most commonly detected (6 of 15) causative agent was Klebsiella pneumoniae[24]. In another retrospective study, the

most common (5 of 12) causative agent was E coli in 217 asymptomatic jaundiced infants [25]. In our study, the most commonly isolated agent was Klebsiella. However, geographical or environmental factors may contribute to bacteriologic and epidemiologic characteristics of UTI.

In infants with UTI, the prevalence of pyuria has reportedly been 58.3%, 52%, and 33% in 3 different studies, respectively [24,25,26] . In our study pyuria was present in 26.7% of 15 newborns with UTI.

Garcia and Nager [12], in their study analyzing the association of neonatal jaundice and UTI, have reported that UTI was present in all the cases who had conjugated hyperbilirubinemia. Singh-Grewal et al [27] have detected a stronger association with UTI due to E coli and conjugated hyperbilirubinemia compared with that of unconjugated hyperbilirubinemia. In our study, cases with both UTI and significant hyperbilirubinemia had significantly higher conjugated bilirubin levels and higher direct/total bilirubin ratio.

In most of the studies investigating the relationship between UTI and neonatal jaundice, male sex was a significant risk factor compared with female sex in the neonatal period [23,26,28,29]. In accordance with these studies reported, most of the cases (23 of 26) with both UTI and significant hyperbilirubinemia in our study were men. Ghaemi et al [23] have reported that 60% of their male cases with UTI were not circumcised, and Singh-Grewal et al [27] have reported that circumcision significantly reduces the risk of UTI. Garcia and Nager [12] have reported that infants whose jaundice presents after 8 days of life have UTI very likely. In our study, jaundice had occurred in 53.3% of cases in the first 7 days of life. Similarly, Bilgen et al [21] have reported that most of their cases developed jaundice after the seventh day of life.

Ghaemi et al [23] have reported that infants fed formula milk had a significantly higher risk of UTI compared with infants fed breast milk. Chen et al [25] have also reported similar results.

CONCLUSION

As a conclusion, UTI should be routinely investigated in early (⩽10 days) idiopathic neonatal jaundice in which all other etiologic factors of neonatal hyperbilirubinemia are ruled out, and the presence of UTI should be considered in case of a poor phototherapy response in cases receiving phototherapy.

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