

Relation between Hyperbilirubinemia and Urinary Tract Infections in the Neonatal Period

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Abstract

Jaundice is a frequently encountered problem in the neonatal period. It may be associated with hemolytic, enzymatic, metabolic, endocrine disorders or infections. Recently it has been thought to be one of the clinical signs of urinary tract infections (UTIs) in the neonatal period. Although they are concurrently observed, the association between neonatal jaundice and UTI is still unidentified. Common belief is that the bilirubin levels rise as a result of UTIs and jaundice may be considered as an important clinical sign in that period. However, there is no strong recommendation for screening UTI in all neonates with jaundice. It is only recommended to screen for UTI in neonates with prolonged hyperbilirubinemia and direct bilirubinemia. On the other hand, there are conflicting data on the protective effects of bilirubin on renal tissue. In this review, all those questionable topics were discussed in the light of clinical and experimental studies.

Keywords: Urinary tract infections; Neonatal period; Hyperbilirubinemia

Introduction

Neonatal jaundice is rarely a pathological problem in the newborn period and it is encountered in 60% of the babies [1,2]. A very few of these babies have underlying hemolytic disease, metabolic or endocrine disorders, enzymatic deficiencies of liver, bacteremia or sepsis [1-3]. However, jaundice, which is the clinical manifestation of hyperbilirubinemia, may be the first sign of neonatal Urinary Tract Infections (UTIs). The decreased uroepithelial bactericidal activity, low levels of local immunoglobulin A, low urinary acidification capacity, and high periurethral colonization in the neonatal period lead to increased susceptibility to UTI [4]. However, diagnosing UTI is difficult in this period because of the non-specific symptoms including fever, irritability, vomiting, feeding refusal, diarrhea, failure to thrive, irritability, lethargy, oliguria or polyuria, malodorous urine and jaundice [5,6]. Thus, jaundice may be considered as one of the initial symptoms related to UTIs in newborns.

What is the Importance of Jaundice in Diagnosing UTI in the Neonatal Period?

The association between unexplained neonatal jaundice and UTI is well known [3,7,8]. The incidence of UTI in asymptomatic, a febrile and jaundiced infants was 5.5% in 217 patients [9], 5.8% in 400 patients with a mean age of 10 days [10], 6% in 100 neonates between 2 to 4 weeks of age [8], 7.5% in 160 patients younger than eight weeks [7], 7.8% in 102 neonates younger than two weeks [3], 12.5% in 120 neonates younger than four weeks [11], 18% in 104 neonates between 4 and 14 days of age [12], and 21% in 152 neonates younger than four weeks [13] (Table 1). UTI was found in 6.5% of 462 jaundiced neonates, ages ranging from 3 to 25 days, 68% of whom were asymptomatic and a febrile [5]. The only study with a control group among these studies was that performed by Shahian et al. [11]. In that study, incidence of UTI was 12.5% in 120 asymptomatic jaundiced neonates vs. none in 122 healthy neonates younger than four weeks [11].

Although methods for obtaining urine specimen and the threshold values to accept the results compatible with UTI differ among the aforementioned series in asymptomatic and afebrile infants, the incidence of UTI is much higher than those of the febrile infants younger than eight weeks which was reported as 5-11% [14-16]. Thus,

jaundice may be considered as important as fever in diagnosing UTI in the neonatal period.

In those series, up to 55% of the jaundiced infants were found to have urinary tract abnormalities (Table 1). The susceptibility of UTI increases in patients with urinary tract abnormalities and hyperbilirubinemia is thought to occur as a result of UTI [7]. Cleper et al. [17], found that the risk of jaundice was three times more likely in patients with vesicoureteral reflux during a UTI.

Is UTI Associated with Early or Late Neonatal Hyperbilirubinemia?

UTI has been accused as one of the reasons for prolonged (which persists after the second week in term infants and third week in premature infants) neonatal jaundice and a routine screening for UTI has been recommended in these infants [3,7,8,10]. Garcia and Nager [7] observed that the incidence of UTI was especially higher in infants who had jaundice after the postnatal eighth day. In another study conducted by Ghaemi et al. [10], the rate of UTI in patients with prolonged jaundice was similar to that of the febrile cases of similar age [8], and therefore assessing routine urinalysis and urine culture were recommended in patients with prolonged jaundice. On the other hand, Omar et al. [13] found that in jaundiced and otherwise asymptomatic neonates with UTI, jaundice emerged before the eighth day and Bilgen et al. [3] found that it emerged before the seventh day in the majority of cases. Thus, they suggested the urinalysis be included in the diagnostic routine studies of otherwise asymptomatic jaundiced newborns without an unknown etiology in the early neonatal period. In addition, Garcia and Nager [7] also stated that all asymptomatic infants with

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Received February 10, 2014; **Accepted** March 27, 2014; **Published** March 31, 2014

Citation: Kasap B, Soylu A, Kavukçu S (2014) Relation between Hyperbilirubinemia and Urinary Tract Infections in the Neonatal Period. J Nephrol Therapeutic S11: 009. doi:10.4172/2161-0959.S11-009

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	Garcia et al. [7]	Bilgen et al. [3]	Pashapour et al. [8]	Ghaemi et al. [10]	Xinias et al.* [5]	Chen et al. [9]	Omar et al. [13]	Shahian et al. [11]	Mutlu et al. [12]
Age	<8 weeks	<2 weeks	2-4 weeks	~10 days	3-25 days	<8 weeks	<4 weeks	< 4 weeks	4-14 days
No of patients	160	102	100	400	462	217	152	120	104
Patients with UTI	12 (7.5%)	8 (7.8%)	6 (6%)	23 (5.8%)	30 (6.5%)	12 (5.5%)	32 (21%)	15 (12.5%)	19 (18%)
Urine collection method	Catheter	Catheter	Suprapubic aspiration	Suprapubic aspiration	Suprapubic aspiration	Suprapubic aspiration + catheter + urine bag	♀: Catheter ♂: Urine bag	Catheter	Catheter
Patients with urinary tract abnormalities in US	6 (55%)*	3 (37.5%)	1 (16.6%)	4 (17.4%)	5(16.6%)	?	7 (4.6%)	3 (20%)	5 (26%)
(+) finding in ultrasonography	HN: 3 PE: 2 Stone: 1	HN: 1 PE: 2	HN: 0 PE: 0	HN: ? PE: ?	HN: 1 PE: 2	?	PE: 7	HN: 3	HN: 1 PE: 4
VUR	0**	1 (12.5%) Grade III-IV (U)	1 (16.6%) Grade III-IV (U)	1 ?	5 (16.6%) Grade II (U): 2 Grade III (U): 2 Grade IV (B): 1	?	0****	0	2 (1%) Grade III-IV (U):1 Grade V(B) + PUV: 1
(+) finding on scintigraphy	-	0***	1 (16.6%)	-	14 (46.7%)	?	-	-	1 (5%)
Timing of scintigraphy	-	3 rd month	?	-	Acute phase (?)	?	-	-	Acute phase (?)

UTI: urinary tract infection, US: Ultrasonography, VUR: vesicoureteral reflux, HN: hydronephrosis, PE: pelvictasis, U: unilateral, B: bilateral
#: 32% of the patients were symptomatic.

*: Ultrasonography was performed in 11 of 12 patients.

**: Voiding cystourethrogram was performed in 4 of 6 patients.

***: Scintigraphy was performed in 7 of 8 patients.

****: Voiding cystourethrogram was performed in 12 of 32 patients.

Table 1: Clinical studies on asymptomatic and afebrile jaundiced infants.

jaundice should be evaluated for UTI. However, Maisels and Newman [18] implied that, in this case, about 2.4 million babies per year should be catheterized, and this is expensive, invasive, and would be risky for the development of UTI and thus screening for UTI is only convenient for babies older than one week old.

What do the Guidelines Recommend?

Nonetheless, American Academy of Pediatrics (APA) guidelines recommend routine urine analysis neither in the early nor in the late neonatal period for hyperbilirubinemic neonates [1,19]. For instance, in 1994 APA guideline, screening for UTI was not recommended for late-onset hyperbilirubinemia [1]. In 2004 guideline, urinalysis was only recommended for babies with direct hyperbilirubinemia who were older than 35th gestational week [19]. Garcia and Nager [7] reported that the presence of UTI was more likely in patients with direct bilirubinemia, however, in most of the other studies, direct bilirubinemia was not observed in patients with UTI [3,8,11,17,20,21]. Consequently, common belief is that screening for UTI is needed in prolonged (indirect) hyperbilirubinemia and direct hyperbilirubinemia, and there is no such recommendation for jaundiced neonates in the early period.

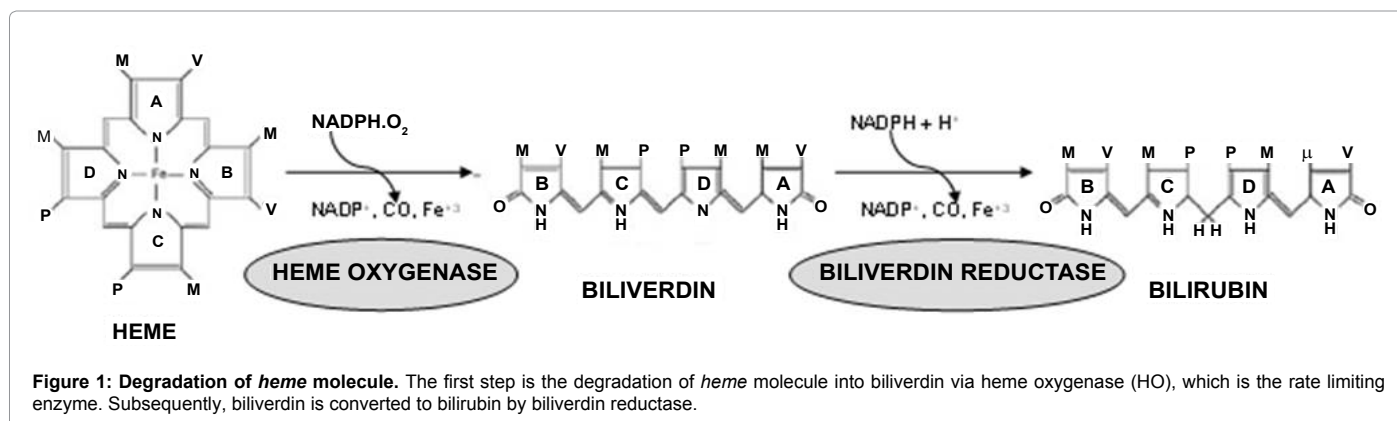
What is the Relationship between UTI and Hyperbilirubinemia?

Despite these data showing their frequent coexistence, the relationship between UTI and hyperbilirubinemia has not been fully revealed yet [7,8]. Indirect hyperbilirubinemia associated with UTI was considered to be due to hemolysis caused by *E. coli* and other *Gram (-) microorganisms* [7]. Even slight hemolysis may increase the levels of serum bilirubin due to immature conjugation mechanisms in infants [7]. Thus, bilirubin levels may rise as an alerting sign even in clinically less severe UTIs. Direct hyperbilirubinemia associated with UTI may

be due to cholestasis [7]. Although it is not exactly known how UTI may lead to cholestasis, microcirculatory disorders in the liver, direct bacterial products or endotoxin-induced mediators have been suggested as the cause [22,23]. Bilirubin is an endogenous molecule, which emerged as a result of reduction of *heme* molecule (Figure 1). Recently, attention has been focused on anti-oxidant and renoprotective effects of the substance [24,25]. Heme oxygenase-1 (HO-1), which catalyzes the first step of the reduction of the *heme* molecule may be induced by cytokines, enzymes, bacterial endotoxins, reactive oxygen species, ischemia/reperfusion injury (IRI) and hypoxia in mammals [26-28]. All these factors contribute to the pathogenesis of UTI, which causes renal injury [29]. Therefore, hyperbilirubinemia may be considered as a result of increased HO-1 enzyme activity during UTI.

May High Levels of Bilirubin protect the Kidney?

There are many studies evaluating the effects of bilirubin on renal tissue. Exogenous bilirubin was shown to be protective against IRI in the isolated perfused rat kidney [30]. Another study by the same team demonstrated that intravenous administration of bilirubin did not equally have the same protective effect and they thought that it was associated with a technical error about timing of removal of the kidney tissues [31]. In "Gunn rats", which are hyperbilirubinemic due to a genetic defect in uridine diphosphate glucuronyl transferase enzyme, thiobarbituric acid reactive substance levels were inversely correlated with serum bilirubin levels in the neonatal period, and this free radical resistance was considered to be provided by bilirubin [32]. Also, kidneys of Gunn rats were protected as compared to Wistar rats in a cisplatin nephrotoxicity model [33]. In cholestatic rats, in which cholestasis was induced by ligation of the common bile duct, glycerol-induced acute renal failure was prevented, and thus bilirubin was shown to be protective against renal IRI [34]. In another *in vitro* study on human proximal epithelial cells, it was reported that conjugated



bilirubin reduced the sensitivity of the cells to cisplatin and showed cytoprotective effects [35].

These data showing the renoprotective effects of bilirubin suggest that neonatal hyperbilirubinemia may play a protective role in preventing renal damage. The risk of renal injury varies inversely with age and patients of younger ages are known to be more susceptible to renal damage [4,36]. Diagnosing UTI in the neonatal period is difficult as patients are usually asymptomatic or show non-specific symptoms, and obtaining a proper sample of urine requires invasive procedures such as supra pubic aspiration or catheterization [5]. In addition, verifying renal parenchymal damage in the acute period with dimer captosuccinic acid (DMSA) is also difficult in this age group due to tubular immaturity. Thus, planning a clinical study comparing the effects of UTI in newborns with and without hyperbilirubinemia is difficult, and there has been no such study in the literature yet. To investigate this effect, we used exogenous bilirubin in rats with pyelonephritis and found that exogenous bilirubin in addition to antibiotics demonstrated positive effects on inflammation, fibrosis and apoptosis [37]. In a clinical study by Bilgen et al. [3], scintigraphic studies were made in seven of eight icteric neonates diagnosed with UTI at the third month and no pathological finding was found in any of them. However, in another study conducted by Xinias et al. [5], the bilirubin levels of neonates with positive cortical DMSA findings were significantly higher than those of with negative DMSA findings. These findings suggest that the patients with cortical damage have a higher amount of bacteremia and the severity of the infection lead to a more severe hemolysis. According to this study, it does not seem possible to conclude that bilirubin has protective effects of on renal damage.

May Hyperbilirubinemia Lead to UTI?

In our previous *in vitro* study investigating the effects of bilirubin on rabbit bladder and ureteral smooth muscle, hyperbilirubinemia was shown to cause dilatation, which may lead to urinary stasis and susceptibility to UTI [38]. However, in another study on hyperbilirubinemic newborns, no significant relation was found between bilirubin levels and pelvic diameters [39]. In addition, we could not demonstrate that the urine of hyperbilirubinemic newborns impede the growth of uropathogenic *E. Coli* in our recent study [40].

Does Hyperbilirubinemia Associated with UTI have a Different Clinical Course?

Omar et al. [13] found that the duration of phototherapy is shorter and exchange transfusion requirements were less likely in hyperbilirubinemic neonates with UTIs. This data suggested that

neonatal hyperbilirubinemia associated with UTI leads to fewer complications.

In conclusion, newborn jaundice associated with UTI is related to increased levels of bilirubin due to the infection itself. This seems to be associated with increased HO-1 enzyme activity induced by endotoxins, cytokines, etc. UTI induced hyperbilirubinemia usually emerge in the form of prolonged jaundice and seems to have a more benign course. Although there is supporting data that increased levels of bilirubin have renoprotective effects, it is still controversial. As a result, neonatal jaundice associated with UTI may facilitate early detection of UTI rather than being a threat in terms of complications.

Support or Financial Disclosure

None.

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This article was originally published in a special issue, **Pediatric Nephrology** handled by Editor(s), Moazzam Hossain, Bangabandhu Sheikh Mujib Medical University, Bangladesh