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Original Article

Prevalence of Meningitis among Hospitalized Neonates with Urinary Tract Infection

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ABSTRACT

Background: Bacteremia is relatively common in children with urinary tract infection (UTI). The aim of the present study was to determine the frequency of bacterial meningitis among neonates with laboratory-confirmed UTI.

Methods: This retrospective cross-sectional study was performed on 163 hospitalized neonates in Ali Asghar and Shahid Akbarabadi hospitals affiliated to Iran University of Medical Sciences in Tehran, Iran. The demographic and clinical data of hospitalized neonates due to UTI during the recent 6 years (2010-2016) who were aged < 28 days and had cerebrospinal fluid (CSF) culture via lumbar puncture were extracted from medical records and recorded in some checklists.

Results: A total of 163 neonates with laboratory-confirmed UTI with the mean age of 18.25±5.41 days were included. In this study, 54% of the neonates were male. Out of all neonates, 23 (14.1%) cases had positive blood culture. The positive CSF culture was observed in only two (1.2%) neonates. Positive voiding cystourethrogram (VCUG) test was reported in 50% of the neonates with positive CSF culture (P=0.047). Although abnormal ultrasound findings related to the urinary tract in positive CSF neonates were higher by approximately twofold, compared to those reported for negative CSF neonates, this difference was not statistically significant (50% and 24.2%, respectively; P=0.432).

Conclusion: The frequency of the concurrent occurrence of UTI and meningitis in our neonates was 1.2%. Out of all indicators associated with meningitis occurrence, positive VCUG may be a risk factor. Further prospective studies are needed to approve these results.

Keywords: Meningitis, Neonates, Urinary tract infection

Introduction

Urinary tract infection (UTI) is a common complication reported as 1-15% among febrile children who referred to hospitals. Bacteremia is also observed in 3-6% of infants with UTI due to the immaturity of the immune system. Bacteremia can affect other organs, including the brain, spinal cord, and cerebrospinal fluid (CSF), resulting in acute and complicated situations. To investigate the causes of bacteremia, urine, blood, and CSF cultures are the integral parts of the diagnostic process (1-3). The diagnosis of concomitant bacterial meningitis with a UTI is important because of higher morbidity, mortality rate, and different treatment modality, compared to that of a UTI alone (4, 5).

Some conflicting limited data are available about the prevalence of concurrent UTIs and meningitis. The majorities of the reports are retrospective studies and carried out on children less than 3 years (6). The prevalence of bacterial meningitis after UTI has been estimated at about 2% in infants (7). However, due to the underestimation, the prevalence of this infection is estimated to be even more (8). Moreover, in some cases, the assessment of the true relationship between meningitis and UTI is difficult, and

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meningitis is mistakenly linked to UTI.

The oral or parenteral administration of antibiotics before obtaining fluid samples, such as urine and CSF, would lead to a false negative. In children under 3 months of age, the association of bacterial meningitis and cystitis has been reported less than 1%. It should be noted that aseptic meningitis, as well as an important diagnostic criterion, occur in about 5 to 18% of patients with the previous infection of the urinary tract (9-11). However, performing lumbar puncture for bacterial meningitis assessment is a safe diagnostic procedure, and its pain and potential complications should be considered among neonates and infants (12).

Former studies have shown that about 3% of children with UTI had positive CSF culture (13). To the best of our knowledge, there have been few investigations that assessed the frequency of coexisting meningitis in neonates with UTI. The aim of the present study was to determine the frequency of meningitis with positive CSF culture in neonates hospitalized due to UTI. Moreover, some related risk factors were also evaluated that would be of value in implementing some strategies for early diagnosis and treatment.

Methods

This retrospective cross-sectional study was carried out in 2017. The collected data were the medical records related to hospitalized neonates due to UTI in the neonatal intensive care units (NICUs) of Ali Asghar and Shahid Akbarabadi hospitals affiliated to Iran University of Medical Sciences in Tehran, Iran, within June 2010 to June 2016. All the aspects of this study were approved by the Ethics Committee of Iran University of Medical Sciences (IR. 1394, 9311216168).

The inclusion criteria were the age < 28 days, NICU hospitalization due to laboratory-confirmed UTI, and CSF obtained via lumbar puncture. The urine samples were collected by suprapubic aspiration, catheterization, or midstream specimen of urine (MSU) methods. The UTI was diagnosed based on the following definition in urine culture collected by:

- Suprapubic aspiration: the existence of single gram-negative bacteria or > 1,000 colony forming units (CFUs) of a pathogen on urine culture
- Catheterization: ≥ 50,000 CFUs of a pathogen on urine culture or > 10,000 CFU/mL
- MSU: ≥ 100,000 CFUs of a pathogen on urine culture (14)

The neonates whose urine samples were collected by other methods other than suprapubic aspiration or catheterization were excluded. Major congenital and neonatal complications, such as central nervous system anomalies, were considered additional exclusion criteria.

Neonatal Characteristics

All demographic and clinical data of neonates during the recent 6 years were extracted from medical records. Age, gestational age, gender, mode of delivery, anthropometric measures, including weight, height, and head circumference at birth, results of laboratory test (i.e., complete blood count, C-reactive protein, urine analysis and culture, blood and CSF cultures), number of lumbar puncture, timing of lumbar puncture, medications and antibiotics consumption, voiding cystourethrogram (VCUG) reports, urinary tract ultrasound findings, and length of hospital stay, were recorded in related checklists. Bacteremia and meningitis were defined as the growth of pathogenic bacteria in blood and CSF culture, respectively.

Outcome

The main outcome in this study was the frequency of concomitant bacterial meningitis in neonates with UTI. In addition, correlations between some related factors and meningitis were evaluated.

Statistical Analysis

With the proposed sample size of 163, the study had a power of 75% and an alpha error of 0.05. The data was computerized and analyzed using SPSS software (version 19) (SPSS Inc., Chicago, IL., USA). Descriptive statistics (i.e., mean±standard deviation, frequency, and percentage) were used to present the data. The Student's t-test and Fisher's exact test were performed for analyzing quantitative and qualitative variables, respectively. P-value less than 0.05 was considered statistically significant.

Results

In total, 218 neonates were identified who met the inclusion criteria. Out of 218 newborns, 55 neonates were excluded because of missing data. Ultimately, 163 neonates with laboratory-confirmed UTI were entered into the study. The mean values of age, birth weight, as well as the height and head circumference of the newborns, were 13.66±8.03 days, 2969.86±712.83 g, as well as 48.61±4.63 and 34.23± 2.95 cm, respectively. The demographic clinical characteristics of all

neonates are shown in Table 1.

According to the recorded data, the most prevalent organisms in the urine and blood samples were *Escherichia coli* (*E. coli*) and *Staphylococcus saprophyticus*, respectively. Bacteremia was detected in 23 (14.1%) neonates, in 13 (7.97%) cases of whom the same bacteria were isolated from the urine and blood culture. The list of organisms isolated from urine and blood cultures are presented in Table 2. For all neonates, lumbar puncture attempts were performed. The median number of lumbar puncture attempts was 2 (range: 0-5 attempts). In this study, five (3.06%) infants received > 3 lumbar puncture attempts.

Positive CSF fluid and urine culture were observed in only two (1.2%) cases by *Enterococcus* and *E. coli*, respectively. It is noteworthy that the blood culture of them was negative. There was no statistically significant relationship between positive CSF fluid and negative blood culture.

Also, there was a significant correlation between abnormal VCUG and positive CSF culture (P=0.047). Out of 2 neonates with positive CSF culture, 1 (50%) newborn had abnormal VCUG, while abnormal VCUG was reported in 14 cases (10.6%) with negative CSF culture. There was no

Table 1. Demographic and clinical characteristics of neonates

Variables		Total neonates (N=163)
Age(day)	Mean ± SD Min- Max	18.25±5.41 3-27
Gestational age (week) (N %)	≥37 <37	116(71.2) 47(28.8)
Sex	Male Female	88(54) 75(46)
Mode of delivery	C/S NVD	122(74.8) 41(25.2)
Birth weight (gram)	Mean ± SD Min- Max	2969.8±712.8 900-5200
Length(centimeter)	Mean ± SD Min- Max	48.6±4.6 42-52
Head circumference(centimeter)	Mean ± SD Min- Max	34.2±2.9 25-38
Positive CRP (N/%)		29(18)
Positives blood culture (N %)		23(14.1)
The number of lumbar puncture (N %)		163(100)
Positive CSF culture (N %)		2(1.2)
Abnormal VCUG (N %)		18(11)
Abnormal urinary tract ultrasound		40 (24.5)
The length of stay at hospital (day)	Mean ± SD Min- Max	6.93±1.4 2-26

Abbreviations: SD; Standard Deviation, C/S; Cesarean Section, NVD; Normal Vaginal Delivery, CRP; C-reactive protein, CSF; Cerebrospinal fluid

Table 2. Organisms in urine and blood samples (N=163)

Organisms	Number (%)	
	Urine	Blood
E. coli Bacteria	71(43.55)	13(7.97)
Gram-positive cocci	26(15.95)	0
Gram negative bacilli	28(17.17)	0
Klebsiella	22(13.49)	0
Enterococcus	4(2.45)	2(1.22)
Pneumococcus	2(1.22)	0
Staphylococcus saprophyticus	3(1.84)	3(1.84)
Enterobacter	4(2.45)	0
Acinetobacter	2(1.22)	1(0.61)
Staphylococcus epidermidis	1(0.61)	2(1.22)
Streptococcus viridians	0	2(1.22)
S. hemolyticus	0	0

Table 3. Comparison of variables between two groups with positive and negative CSF culture

Variables	CSF culture		P-Value
	Positive(N=2)	Negative(N=161)	
Age (d), mean±SD	23±2.83	13.54±8	0.105*
Preterm birth (N %)	2(100)	46(28.6)	0.495**
Mode of delivery; NVD (N %)	2(100)	39(24.2)	0.62**
Mean birth weight (gr)	2125±671.75	2981.44±708.55	0.319*
Length (cm), mean±SD	48±5.65	48.62±4.64	0.851*
Head circumference(cm), mean±SD	25±1.98	34.3±285	0.001*
Positive CRP (N %)	0	29(18%)	-
Abnormal VCUG (N %)	1(50%)	17(10.6%)	0.047*
Abnormal ultrasound finding (N %)	1(50%)	39(24.2%)	0.432*

Abbreviations: d; day, SD; Standard Deviation, N; Number, gr; gram, cm; Centimeter, CRP; C-reactive protein.
* Student's *t*-test
** Fisher's exact test

statistically significant relationship between abnormal ultrasound findings and positive CSF culture (P=0.432). There were also no significant differences between positive and negative CSF culture groups regarding age, prematurity, mode of delivery, birth weight, length, and positive CRP (P>0.05). The details of the comparison of the variables between the two groups with positive and negative CSF culture are presented in Table 3.

Discussion

This study was conducted to determine the frequency of bacterial meningitis among neonates with laboratory-confirmed UTI. According to the results of this study, positive CSF culture was observed in 1.2% of 163 neonates with laboratory-confirmed UTI. Overall, the results of this study are similar to the findings of prior studies that have measured the frequency of meningitis in young infants with UTI (15-18). In accordance with the results of the present study, Tebruegge et al. showed that only 2 cases of 163 (1.2%) neonates had concurrent UTI and meningitis (16).

Wallace et al. indicated that out of 236 neonates with UTI, no one had definite acute bacterial meningitis (7). Vuillermin et al. also demonstrated that out of 161 infants aged less than 90 days with UTI diagnosis, only 1 case had bacterial meningitis (18). Bonadio et al. determined the frequency of meningitis in 100 neonates with culture-confirmed UTI who were not pretreated with antibiotics; accordingly, none of them had meningitis (19). Syrogiannopoulos also found no cases of meningitis in 67 neonates (15). Consistent with the results of other studies, it is possible to conclude that UTI rarely correlated with meningitis in young infants (15-19).

The results of the present study are inconsistent with the findings of other studies showing that the risk of coexisting meningitis in infants with UTI is not significant and UTI is rarely related to bacterial meningitis (18). Goldman et al. have shown that out of 79 neonates with fever and pyuria, 81% of them had positive urine cultures. The rate of bacterial meningitis samples was 0%; however, three cases had positive CSF culture with Coagulase-negative Staphylococcus (two cases because of contamination and one case because of a ventriculoperitoneal shunt infection) (20).

Based on our data, in line with the results of other studies, the frequency of meningitis among neonates with UTI was low so the necessity of performing lumbar puncture with its potentially serious complications, such as brainstem herniation, introduction of infectious organisms into CSF, and epidermoid tumors, should be strongly considered (16). It seems that a wide range of different factors, such as prenatal and maternal complications, neonatal sepsis and bacteremia, immaturity of the immune system, impaired phagocytic ability, and lack of maternal antibodies, contributes to the increased risk of simultaneous occurrence of the UTI and meningitis (21, 22).

According to the recorded data, the most common organisms in urine samples were *E. coli*, followed by gram-negative bacilli, gram-positive cocci, and *Klebsiella*. Other studies also pointed to these frequent pathogens in UTI (16, 23). In the present study, the most frequent organisms in the blood samples were *Staphylococcus saprophyticus* followed by *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Enterococcus*.

In the present study, regarding staph epidermidis, we could not rule out contamination because blood culture results were prepared after starting antibiotic therapy. On the other hand, Bachur et al. indicated that *E. coli* was the most common pathogen in blood culture followed by *Staphylococcus aureus* among infants with UTIs (10). The aforementioned study has demonstrated

that *Enterococcus* and *E. coli* were common pathogens in CSF samples.

In another study carried out by Tebruegge et al., *Staphylococcus aureus* and *E. coli* were identified as the commonest pathogens in the CSF samples in children with culture-confirmed UTI (7). There was a significant correlation between abnormal VCUG and positive CSF culture. It seems that the impaired function of the urinary tract system is a predisposing factor for ascending infections and bacteremia. In accordance with our results, Kim et al. have shown a significant correlation between the abnormal findings of ultrasound and high-grade vesicoureteral reflux in 413 febrile infants with UTI.

Moreover, as bacterial meningitis was not identified in any cases by a lumbar puncture, in the above-mentioned study, it was concluded that both lumbar puncture and VCUG as invasive procedures should be performed if there is a strong necessity, especially in infants less than 3 months (24). In addition, it should be mentioned that some studies pointed to the significant correlation between bacterial meningitis and urodynamic abnormalities. Gupta et al. indicated that urinary symptoms and bladder dysfunction were present in one-third of 51 patients with meningitis (25). It is supposed that meningitis can cause urine stasis, vesicoureteral reflux, and UTI.

In summary, our results confirmed the results of previous studies based on which the risk of coexisting meningitis in neonates with UTI is not significant. A significant correlation was observed between abnormal VCUG and increased risk of bacterial meningitis. Moreover, as UTI was rarely related to bacterial meningitis, the authors suggest performing lumbar puncture as an invasive procedure if there is a strong necessity for neonates. Further large studies on the neonatal population are needed to investigate if certain clinical characteristics or laboratory values can be used to predict the risk of concomitant meningitis.

Conclusion

In this study, the frequency of the concurrent occurrence of UTI and meningitis was 1.2%. Out of all indicators associated with meningitis occurrence, positive VCUG may be a risk factor.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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