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Incidence and etiological agents of concomitant acute bacterial meningitis in neonates with febrile urinary tract infection.

Fatma S Alzhrani[1*], Fayza Al Siny[1], Sumaih Abdullah Alsadiq[1], Mai Mohammed Ghaith[2], Nouf Nawaf Simsim[2], Noha Hassan Kommosani[2], Wejdan Hussain AL-Qahtani[3],

[1]Department of Paediatrics, College of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[2]Department of Paediatrics, College of Medicine, Ibn sina University, Jeddah, Saudi Arabia

[3]Department of Paediatrics, College of Medicine, King Khalid University, Abha, Saudi Arabia

Abstract

Background: Concomitant Acute Bacterial Meningitis (ABM) in febrile neonates with Urinary Tract Infection (UTI) considered a severe condition that may lead to permanent disabilities if it is not treated correctly. In order to understand the real burden of this problem, we aimed to investigate the incidence rate of the concomitant ABM in neonates with febrile UTI.
Methods: This is a retrospective study reviewing the medical records of all neonates who were presented to the Emergency Department (ED) in a tertiary hospital, Jeddah, Saudi Arabia from 1 May to 31 July 2019 and diagnosed with UTI to look if they had a diagnosis of acute bacterial meningitis or not.
Result: from 159 pediatric patients presented with UTIs, there were 3 (1.9%) patients with bacterial meningitis, two of them were males. For the neonatal age, 49 neonates presented with UTI, only one patient (2%) was diagnosed with bacterial meningitis. The isolated organisms that caused meningitis were: yeast, *Klebsiella pneumoniae* **(***K. pneumoniae), Escherichia coli (E.coli).*
Conclusion: even though our findings suggest that the incidence of ABM among neonates who have UTI is relatively low, it still exists, and clinicians should consider them at the same time clinicians should balance between benefit and harm of doing lumbar puncture to every febrile neonate. A larger sample and multicenter studies must be conducted in the future to look for the issue explicitly and to make the result applicable to the whole population.

Keywords: Neonates, Infections.

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Introduction

Fever is a common feature of numerous diseases that can be presented at different ages. Unlike the adults, fever in neonates could be the only sign of some severe infections. As per protocol, multiple tests recommended being ordered in each febrile neonate, such as Lumbar Puncture (LP) and Urine Culture (UC) [1]. One of the severe infections that may affect febrile neonate is Urinary Tract Infections (UTI). UTI is an infection that affects the urinary pathway from the urethra to the kidneys, which can be a community-acquired or hospital-acquired. In United States, it is estimated that 10.5 million office visits and 2-3 million emergency department visits are due to an issue related to UTI [2]. Regarding the pathogens entering the tract, *E. coli* is the most common cause of UTI [2]. In specific, one of the sub-groups of E. coli that can hit more than one system is called extra-intestinal pathogenic *E. coli* (ExPEC), which is the most common gram-negative bacteria invading humans [3]. One extreme example of systems that can be contaminated with such type is the Central Nervous System (CNS), and that is a result of entering a sterile area such as Cerebrospinal Fluid (CSF), causing various manifestations, particularly in neonates [3]. Acute Bacterial Meningitis (ABM) is an example of a severe inflammation of the meninges, which occurs in response to bacterial products and carries a high rate of mortality demanding immediate medical intervention [4]. ABM frequently occurs in neonates and can lead to severe complications and even long-term disabilities [5]. Although it is rare, ABM can occur as a result of primary UTI because of the seeding of bacteria in the bloodstream, which is a standard route of infection of CNS due to immature blood-brain barriers in neonates [6].Therefore, testing of CSF is needed for young infants who have UTI [6].

In a previous study conducted in Royal Children's Hospital in Melbourne, Australia found that Australian infants ≤ 90 days of age rarely have UTI associated with meningitis [7]. In a recent study conducted in 2017 which looked mainly in patients within the age group of interest (neonates), from 236 neonates were inspected there were 3/4 males and around 10% had bacteremia as a consequence of UTI, but no one developed acute bacterial meningitis; nevertheless, only two were considered suspicious [6]. In a review of about 14 studies most of those studies involve infants less than 90 days old showed that the prevalence of concomitant acute bacterial meningitis with febrile UTI ranked between 0% to 2% [8]. A retrospective review was reported in 2010 found that out of 1609 febrile infants with UTI aged 29-60 days old there was only 0.3% of

them had ABM [9]. Besides, a study was conducted in Australia looking for the rate of co-existence of bacterial meningitis with UTI in children, which found that only two patients out of 736 get both infections. Interestingly, both patients who got the two infections simultaneously were between 0-28 days [10]. In one of the latest and largest reports that highlighted the prevalence of bacterial meningitis among patients aged ≤ 60 days and having UTI, there was a low percentage of patients get both infections together; however, patients ≤ 28 have an increased risk of acquiring both diseases when they compared to the older infants [11].

A multi-center prospective study was done between the period 2008 until 2013, which shed light on the risk of bacterial infections among infants ≤ 60 days old and found that 2592 were presented with fever. Also, there were 285 (11%) have UTI, 61 (2.4%) had bacteraemia, and 17 (0.7%) have bacterial meningitis [12]. Lastly, in a study was published in 2003 which include all infants ≤ six months who had UTI and hospitalized at Miller Children's Hospital, 31 (11.9%) had aseptic meningitis, and one infant had bacterial meningitis; however, no one having UTI and bacteremia developed aseptic meningitis [13].

Because of the low number of studies looking in this specific relationship and to understand the real burden of this problem, this study aimed to investigate the incidence rate and the etiological organisms of the concomitant ABM in neonates with febrile UTI among neonates diagnosed with UTI in Emergency Department at a tertiary Hospital in Jeddah, Saudi Arabia, throughout May to July 2019.

Methodology

This study aims to identify the incidence and etiological agents of acute bacterial meningitis among neonates diagnosed with UTI at a tertiary hospital in Jeddah, Saudi Arabia. The medical records of patients diagnosed with UTI in the Emergency Department (ED) in the period between 1 May 2019 to 31 July 2019 to investigate if they developed concomitant bacterial meningitis or not.

UTI was confirmed by urine analysis and urine culture

Inclusion criteria: All patients aged 3 or less who were presented to ED with UTI.

Exclusion criteria: Patients whose urine specimens collected by means other than suprapubic aspiration and urethral catheterization and patients who did not have the results of CSF, urinalysis, and urine culture.

Data collection sheet included: Demographic data, body temperature, and the total number of WBC, presence of renal abnormalities, the result of CSF, urinalysis urine culture, and lumbar puncture, which were considered as variables.

Data entry: The collected data was entered in an appropriate data collection sheet using Microsoft Excel 2019. After entering the required data, IBM SPSS v21 was used for the analysis of recorded data. Categorical variables were shown as frequency and percentages, while numerical variables were presented in mean and standard deviation.

Results

Demographics

A total of 159 pediatric patients who had a diagnosis of UTI were recruited in the study. Median age of patients was 120 (30-360) days. Out of 159 patients included in the study, there were 49 (30.8%) patients who were considered as neonates (Figure 1). Mean age of neonates were 16.2 days (SD 10.47). There were 93 (58.5%) males and 66 (41.5%) females (Table 1).

A total of 85 (53.5%) presented to ER with fever, 56 (35.2%) of patients had renal abnormalities. Regarding the types and characteristics of bacteria isolated from specimens, *E.coli* was the most common pathogen isolated in urine culture 57 (35.8%) followed by *K. pneumoniae* 35 (22%), *Enterococcus faecalis* 19 (11.9%), *Pseudomonas aeruginosa* 12 (7.5%) mixed growth 9 (5.7%) and lastly, yeast cell 3 (1.9%) (Table 2). For the drug resistance, *E.coli* showed multidrug-resistant strains in 11 (22.4%), and around 17 (34.7%) had positive results with extended-spectrum beta-lactamase ESBL-producing bacteria.

		No.	%
Sex	Male	93	58.50%
	Female	66	41.50%
Nationality	Saudi	95	59.70%
	Non-Saudi	64	40.30%

Table 1. Patients Demographics and characteristic.

Investigations Ordered for Patients		No.	%
Organism Isolated from Urine Culture	No Growth	18	11.30%
	E.coli	57	35.80%
	K.pneumoniae	35	22.00%
	Enterococcus faecalis	19	11.90%
	Yeast Cells	3	1.90%
	Mixed Growth	9	5.70%
	P. aeruginosa	12	7.50%
	Others	6	3.80%

Table 2. Organisms isolated from urine culture.

Characteristics of patients with concomitant Bacterial Meningitis

Out of 159 patients, there were 3 (1.9%) patients with bacterial meningitis, two of them were males. From the 49 neonates presented with UTI, only 1 patient (2%) was diagnosed with

bacterial meningitis. 2 out of the 3 patients diagnosed with ABM were male, and the third patient was a female, the ages of those patients were: 5 days, 16 months, and 24 months. The isolated organisms that caused meningitis were: yeast, *Klebsiella pneumoniae* (*K. pneumoniae), Escherichia Coli (E.coli)* (Table 3).

	Patient A	Patient B	Patient C
Age	24 month	16 month	5 days
Sex	Female	Male	Male
Nationality	Non-Saudi	Saudi	Non-Saudi
Presence of Fever	No	Yes	No
Renal Abnormality	No	Yes	No
WBC Counts	7.79x109	8.60x109	9.21x109
Urinalysis	+	+	+
Urine Culture	+	+	+
Organism Isolated	Yeast Cells	K.pneumoniae	E.coli
Extended Spectrum Beta Lactamase (ESBL) Bacteria	-	-	-
Multi Drug Resistance E.coli	-	-	-

Table 3. Characteristics of patients with UTI who developed Acute Bacterial Meningitis.

Discussion

Our aim by the end of this study is to reach the proportion of neonates who get ABM and, at the same time, having UTI. What is found is that the percentage of ABM is significantly low among UTI patients both in the whole pediatric age group (1.9%) and the neonate group (2%). These findings were similar to the global rate which range from 0-2% [8]. In particular, Wallace et al. Found no one met the criteria of ABM from 236 infants (≤ 30 days old) who were presented with fever (0%; 95% CI: 0-1.6%), and only two were probably had meningitis but still not confirmed. Likewise, Vuillermin and Starr did not find any growth of bacteria in 75 infants whose age ≤ 90 days and who had a sample of their CSF; nonetheless, only one patient had probable bacterial meningitis. In another study in patients (≤ 60 days), what is identified is that nine infants (0.5%; 95%: 0.2-1.0%) diagnosed with ABM and UTI together, and 7 out of them were less than 30 days [11].Moreover, Young et al. estimated that the prevalence of bacterial meningitis among UTI patients is around 0.9% in patients between 29-60 days, and Tebruegge et al. Found that the prevalence is about 1.2% in neonates [10,14]. In a review of 15 studies, 14 studies concluded that 0-2% of infants less than three months who presented with UTI had associated bacterial meningitis, which supports our findings. The low global percentage could be attributed to the fact that there is an increase in the quality of care that is offered, especially for the young patients and the immediate interference if there is any sign of meningitis by giving antibiotics empirically (Figure 1).

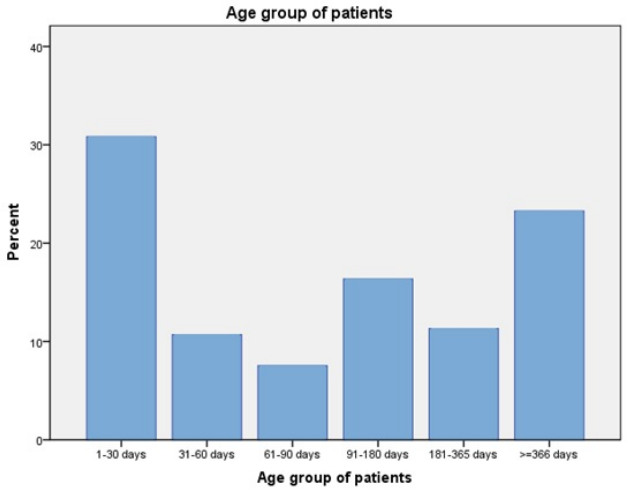

Figure 1. Depicts the age groups of patients included in the study.

The clinical presentation of the three patients who developed ABM was diverse, yet there are some standard features. For instance, all three patients had a positive urinalysis and urine culture which can be used as a method to classify patients presented with UTI who need (LP) to make sure about their status if they develop co-existent meningitis or not; though, it is not the safest way to do so. Furthermore, WBC counts of the patients with ABM were within normal range. Young et al state that the prevalence of patients with bacterial meningitis who had positive or negative urinalysis was the same and this finding oppose our hypothesis [14]. Tebruegge et al. found in the two patients presented with bacterial meningitis there is more predisposition that males become more at risk of concurrent infection, which is resembling our result, and this finding could be a result of increased risk to develop UTI at this age mainly if the males are uncircumcised [10]. On the contrary, both patients in their study were less than 28 days, and one of them had slightly higher WBC than the normal range, which oppose our findings [10].

Regarding the causative agents, *E. coli*, yeast and *Klebsiella pneumonia* were the three isolated organisms from the patients who developed ABM, Similarly, In Vuillermin and Starrs' study, isolated urinary pathogens were the same as what we found and all the cases with sterile CSF pleocytosis contain those bacteria i.e. *E.coli* and *Klebsiella* species in the urine specimens [7]. Additionally, urine cultures of cases of bacterial meningitis in Young et al. article were either to be or growing E.coli species [14]. On the other hand, Terbuegge et al. ended up with a similar order of bacteria. Still, *Enterococcus faecalis* was the second most common, which is the third in the other studies, including ours [10]. This trend of bacteria affecting urinary tract is well known to be the most common, especially in pediatrics [15,16].

This study contains some limitations, and the first on the list is that the period that the study covers is relatively short, which affects the number of the sample that can be involved in the

study. As well, the study is not multi-center in which a more significant number of patients from different areas and backgrounds can be included. In that case, our results may not be generalizable. On top of that, the results are still not specific for a certain age groups, and more variables need to be taken to increase the accuracy of the findings. Also, precisely defining what UTI, bacterial meningitis is, and methods of collecting the samples is an issue that has to be resolved in future studies. Looking for the other causes of meningitis is critical to be investigated and not to be overcome. This study, which looked for a region that was not covered yet, may add to the other epidemiological studies that estimated the prevalence of ABM in UTI patients worldwide.

Conclusion

Even though our findings suggest that the incidence of ABM among neonates who have UTI is relatively low, it still exists. Clinicians should consider them at the same time clinicians should balance between benefit and harm of doing lumbar puncture to every febrile neonate. A larger sample and multi-center studies must be conducted in the future to look for the issue explicitly and to make the result applicable to the whole population.

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*Correspondence to

Dr. Fatma S Alzhrani

Assisstant Professor

Department of Pediatrics

College of Medicine

King Abdulaziz University

Jeddah, Saudi Arabia

Tel: 0567855009

E-mail: Falzahrani@kau.edu.sa