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Streptococcal meningitis in Qatar: A secondary analysis of a hospital-based study

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Abstract
Background and Objectives: Streptococcal meningitis is a recognized medical condition that confronts physicians in Qatar. The aim of this study was to describe the demographic, clinical characteristics, underlying conditions, and treatment outcome of streptococcal meningitis.
Patients and Methods: This was a secondary *post hoc* analysis of our previous study entitled "Acute Bacterial Meningitis in Qatar: A Hospital-Based Study from 2009 to 2013". It involved only patient with streptococcal meningitis.
Results: We identified 27 cases of streptococcal meningitis. The study sample comprised 16 (59.3%) male and 11 (40.7%) female patients. All episodes were community acquired and fever was the most frequent symptom 24 (88.9%), whereas bacteremia was found in 18(66.7%) cases. *S. pneumoniae* was the most frequent pathogen found in this study 19 (70.4%). The main affected age group was neonates under one year of age and the mortality was 3 (11.1%) cases
Conclusion: Streptococcal meningitis is a recognized clinical entity in Qatar that was caused by several species of streptococci, with S. pneumoniae being the most common. Despite vaccination, infants were the most affected group with high mortality from pneumococcal meningitis, suggesting that pneumococcal meningitis prevention strategies may need to be re-evaluated in this country.

Keywords: streptococcal meningitis, pneumococcal meningitis, pneumococcal vaccine

Introduction
Streptococcal meningitis can be caused by certain streptococci species, which are spherical Gram-positive bacteria with *Streptococcus* (*S.*) *pneumoniae* being the most important causative pathogen in adults and children [1]. Other streptococcal species that have been reported to cause meningitis include *S. agalactiae* [2], *S. bovis* [3], *S. milleri* [4], *S. mitis* [5], and *S. salivarius* [6], however, these species are an infrequent cause of bacterial meningitis in adults and children.
Meningitis caused by *S. pneumoniae* is described widely, however, there is lack of information on meningitis caused by streptococcal species other than *S. pneumoniae*. Few studies have been described meningitis caused by well-identified *Streptococcus* species [1, 8]. This *post hoc* analysis was performed to describe the demographic, clinical characteristics, underlying conditions, and treatment outcome of streptococcal meningitis.

Patients and methods
We performed a secondary *post hoc* analysis of collected data from our previous study entitled "Acute Bacterial Meningitis in Qatar: A Hospital-Based Study from 2009 to 2013" [7]. We retrieved patients with streptococcal meningitis from the primary study, which was a retrospective descriptive study that involved all in-patients with acute bacterial meningitis at Hamad General Hospital between January 1, 2009, and December 31, 2013.

Diagnostic criteria
Streptococcal meningitis was considered if at least one of the following compatible clinical pictures were met with no other apparent cause: fever (38°C), headache, meningeal signs, cranial nerve signs, and impaired mental status, plus one of the following [9, 10]: 1. Positive cerebrospinal fluid (CSF) culture; 2. Positive CSF bacterial antigen test (with latex agglutination counterimmunoelectrophoresis) associated with pleocytosis mainly neutrophilic, defined as absolute WBC ≥ 100 cells/mm [3], with a decreased glucose level ≤ 2.2 mmol/L and an increased protein concentration ≥ 60 mg/dL.

Definitions
Streptococcal meningitis was considered nosocomial if the diagnosis was made after more than 48 hours of hospitalization or within a short period of time (i.e., usually within one month after discharge from the hospital where the patient had received an invasive procedure, especially a neurosurgical procedure). On the other hand, ABM was considered as community-acquired if the diagnosis was made within the first 48 hours of hospitalization and the patient was not hospitalized in the preceding month [7].

Identifications of cases
We selected cases of streptococcal meningitis from the primary study. We described the demographic and clinical characteristics, of these patients as well as the underlying conditions, name of species, appropriateness and outcome of therapy.

Ethical consideration
The original study was approved by Medical Research Ethical Committee at HMC, Qatar. Since this was a secondary *post-hoc* analysis of collected data from our previous study, no ethics

committee approval or informed consent was required.

Data analysis

Data analysis was performed with SPSS software (v 23.0; IBM Corp, Armonk, NY, USA). The results of analyses of continuous variables are expressed as means and standard deviations (SD) unless otherwise specified.

Results

Demographic and clinical data

During the study period, we identified 27 cases of streptococcal meningitis. The study sample comprised 16 (59.3%) male and 11 (40.7%) female patients. Their mean age was 20± 23.1 (range: 0.01–74 years), and 12 (44.4%) patients were Qatari. The peak frequency of streptococcal meningitis episodes was noted among infants <1 year old, 6 (22.2%). Clinically, fever was the most frequent symptom 24 (88.9%), followed by headache 14 (51.9%), mental alteration 12 (44.4%), and vomiting 10 (37.0%). Meningismus was detected in 13 (48.1%) patients. *S. pneumoniae* and *S. agalctiae* were the two most frequent pathogens found in this study (see Table 2). The frequency of pneumococcal meningitis per year is described in figure 1.

Associated Medical conditions

Bacteremia was found in 18 (66.7%) cases, while otitis media and pneumonia were found in 3 (11.1%) cases each (see table 1).

Diagnostic work up

Cerebrospinal fluid (CSF) was obtained from all patients. Gram stain was positive in 88.8% of the cases. Table 3, summarizes the results of CSF analysis.

Trends of Antimicrobial Susceptibility

Among the *Streptococcus pneumoniae*, 3 (15.8%) episodes were resistant to ceftriaxone, while all are sensitive to vancomycin. Details of antimicrobial susceptibility are shown in table 2.

Treatment & outcome

Antimicrobial treatment was initiated for all patients. Ceftriaxone plus vancomycin combination were used most frequently followed by meropenem. The mean duration of therapy was 18.4±13.9 (1-27 days). Central nervous system complications include brain abscess 3 (11.1%), hydrocephalus 3 (11.1%) and stroke 3 (11.1%). The in-hospital mortality was 3 (11.1%) and all cases were infants with pneumococcal meningitis.

Table 1: Demographic and clinical data of the involved patients

Variable	
Age, mean±SD (range) years	20± 23.1 (0.01-74)
Age group	
<1	6(22.2%)
1-5	4(14.8%)
6-14	3(11.1%)
15-24	3(11.1%)
25-34	3(11.1%)
35-44	3(11.1%)
45-54	3(11.1%)
≥55	2(7.5%)
Sex	
M	16(59.3%)
F	11(40.7%)
Nationality	
Qatari	12(44.4%)
Non-Qatari	15(55.6%)
Associated medical conditions	
DM	2(7.5%)
HTN	1(3.7%)
Alcohol	1(3.7%)
Prematurity	1(3.7%)
Bacteremia	18(66.7%)
Otitis media	3(11.1%)
Immunosuppression	1(3.7%)
Chronic kidney disease	1(3.7%)
Pneumonia	3(11.1%)
Sinusitis	2(7.5%)
Clinical presentations	
Fever	24(88.9%)
Seizure	9(33.3%)
Headache	14(51.9%)
Anorexia	4(14.8%)
Vomiting	10(37.0%)
Photophobia	3(11.1%)
Focal signs	1(3.7%)
Meningism	13(48.1%)

Mental alteration	12(44.4%)
Acquisition of infection	
Community acquired	27(100%)
Mortality (%)	3(11.5%)

Table 2: Species distribution with their drug resistance to common antimicrobials

Streptococci species	n (%)	Pen	Cefr	cotr	Van	Mer
streptococcus agalactiae	3 (11.1%)	0	0	0	0	0
streptococcus bovis II	1 (3.7%)	1(100%)	1(100%)	1(100%)	0	0
streptococcus milleri	2 (7.4%)	2(100%)	2(100%)	2(100%)	0	0
streptococcus mitis	1 (3.7%)	1(100%)	1(100%)	1(100%)	0	0
streptococcus pneumoniae	19 (70.4%)	6(31.6%)	3(15.8%)	3(15.8%)	0	0
streptococcus salivarius	1 (3.7%)	0	0	0	0	0

TNP: total number of patients; pen: penicillin; cotr: cotrimoxazole; cefr: ceftriaxone; van: vancomycin; Mer: meropenem; NT: not tested

Table 3: Results of spinocerebral fluid study

Cerebrospinal fluid	Value
WBCs/µL, mean±SD (range)	5424.3±8966.4 (48-38575)
Neutrophils (%)	83.8±17.3 (12-98%)
Lymphocytes (%)	14.5±17.2 (2-88%)
Protein (g/dl)	300±249.9 (60-840 g/dl)
Glucose (mmol/l)	1.7±1.7 (1-6.3 mmol/l)
Positive gram stain	24(88.8%)
Positive culture	27(100%)
Positive latex agglutination	12(44.4%)

Table 4: Distribution of streptococcal species in relation to different age groups, complications and mortality

Variables	*S. agalactiae*	*S. bovis II*	*S. milleri*	*S. mitis*	*S. pneumoniae*	*S. salivarius*
<1	2	1	0	0	3	0
1-5	0	0	0	1	2	1
6-14	0	0	0	0	3	0
15-24	0	0	1	0	2	0
25-34	0	0	0	0	3	0
35-44	0	0	1	0	2	0
45-54	0	0	0	0	3	0
≥55	1	0	0	0	1	0
Complications						
Hydrocephalus	0	0	0	0	3	0
Brain abscess	0	0	2	0	1	0
Cerebral infarction	1	0	0	0	2	0
Mortality	0	0	0	0	3	0

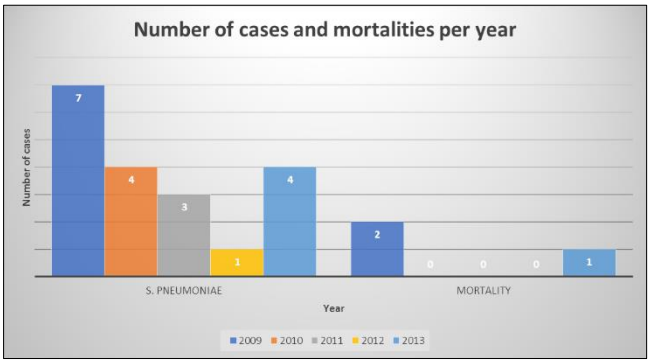

Fig 1: Number of pneumococcal cases meningitis and mortalities per year

Discussion

To our knowledge, this is the first report from Qatar and the Arab countries that describes clinical and epidemiologic features of streptococcal meningitis in different age groups, which will help to approach such cases properly and initiate appropriate empirical treatment as early as possible. Since the introduction of the seven-valent then 13-valent pneumococcal conjugated vaccines (PCVs), there was a decline in the number of reported cases of pneumococcal disease, including pneumococcal meningitis in both adults and children [11, 12]. PCV-7 was licensed in Qatar in August 2005, and PCV-13, in November 2010, nevertheless, the effectiveness of such preventive measures in Qatar and the actual disease burden have not been investigated. Similar to other reports, our study showed a reduction in the overall number of the cases of streptococcal meningitis that were reported before and after vaccine initiation (see figure 1). In addition to the implementation of vaccine programs, this decline can be attributed to several factors, including improved living conditions, easy access to healthcare facilities, the development of diagnostic facilities and improved prevention and control strategies by the Qatar health authorities against all types of meningitis including streptococcal meningitis.

The current study showed a predominance of male sex, similar to the previous two studies [1, 8], and the main affected age group was neonates under one year of age. It is interesting to note that despite the availability of the *S. pneumoniae* vaccine in Qatar, meningitis among 50% of this age group was due to *S. pneumoniae*, which is similar to reports from Northern America that show *S. pneumoniae* as an important cause of bacterial meningitis among neonates despite high vaccine coverage [13-15]. It is worth noting that despite the overall decrease in the number of pneumococcal cases in our study, the number of cases increased slightly in 2013 (see figure1). This may be due in part to the fact that a shift in disease causing strains towards non-vaccine serotypes may occur naturally with time in response to vaccine pressure that may eventually limit the effect of vaccination with currently available vaccines [12, 16]. Moreover, the heterogeneity of the society in Qatar due to the multinationals may affect the impact of the vaccine on the prevalence of pneumococcal meningitis.

In our study, we also found that *S. agalactiae* was the second most common causative pathogen of infant meningitis, which contradicts reports from European countries where S. agalactiae is the most common pathogen for neonatal meningitis [12, 17]. All of our cases of neonatal meningitis due to *S. agalactiae* were

community acquired as they occurred one month after delivery, therefore, transmission from colonized mothers is unlikely. In many centers, the prevention of *S. agalactiae* meningitis is practiced by the implementation of intrapartum antibiotic prophylaxis in pregnant women with high risk for neonatal *S. agalactiae* disease, because there is currently no vaccine against *S. agalactiae* [12, 13, 17, 18].

As noted in this and other reports [1, 8], the most consistent clinical features of streptococcal meningitis were fever, headache and mental alteration, which are non-specific and can be found in other infections such as septicemia. Moreover, meningism was found in 48% of our cases, which makes diagnosis a challenge requiring high index of suspicion especially among neonates.

The susceptibility profile of streptococcal species isolates to various antimicrobials in our series showed a 100% resistance to penicillin and ceftriaxone among *S. bovis II, S. milleri, S. mitis* species, while the resistance to these antibiotics among *S. pneumoniae* was 31.6% and 15.8% respectively. This finding is in line with many reports [19-21], that showed resistance of pneumococci to penicillin and cephalosporins, and support the guidelines that recommend initiating ceftriaxone and vancomycin as an empirical therapy of choice for suspected community acquired bacterial meningitis until the results of the sensitivity are available.

The mortality among our patients was 11.1%, and all were infants less than one-year-old infected with *S. pneumoniae*. Our finding is similar to findings from other countries which showed acute bacterial meningitis in childhood has considerable mortality and complications.

There are several limitations to our study. Firstly, it was a retrospective study, therefore we were unable to study many variables, such as the immunization status of the patients and the complications. Secondly, Streptococcus pneumoniae serotypes were not identified thus we lost the opportunity to be sure of the phenomenon of serotype replacement. Thirdly, it was hospital-based, thus we cannot generalized our results.

In conclusion, streptococcal meningitis is a recognized clinical entity in Qatar caused by various species of streptococci, with S. pneumoniae being the most common. Despite vaccination, infants were the most affected group with high mortality from pneumococcal meningitis, suggesting that pneumococcal meningitis prevention strategies may need to be re-evaluated in this country.

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