Some of the Meningococcal Meningitis in Qatar: Epidemiology, clinical and laboratory features

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Abstract:

To define the demographic, clinical and laboratory features, methods of diagnosis and outcome, in patients with meningococcal meningitis in Qatar, records were reviewed retrospectively to 25 patients (21 male, 4 female; mean age 24 years) treated for meningococcal meningitis at the Hamad Medical Corporation (HMC) between 1992 and 2008). Most (88%) were expatriates. The most common presenting symptoms were fever, vomiting, headache and altered consciousness. Neck stiffness and impaired level of consciousness were the most common signs. Elevated WBC, elevated protein and low glucose in CSF were present in 95.6%, 84% and 80% of cases respectively. Positive CSF Grain-stain showing gram negative diplococci and culture growing N. meningitidis in CSF and blood were seen in 64%, 44% and 72.7% of cases respectively. The most common serotypes were Groups A and W 135 accounting for 50% and 25% respectively. 15.8% of isolates were intermediately resistant to penicillin, while all were sensitive to ceftriaxone. One patient (4%) died and 24 (96%) survived. Six of those who survived developed neurologic sequelae. Meningococcal meningitis remains uncommon in Qatar but the incidence has increased markedly recently especially among expatriates. Because the clinical features of the disease are non-specific, a high index of suspicion is essential for early diagnosis. Empirical treatment with ceftriaxone in a patient with suspected meningococcal meningitis seems prudent to avoid an unfavorable outcome.

Key words: Meningitis, Neisseria Meningitidis, Meningococcal Meningitis, Meningococcemia

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Introduction:

Neisseria meningitidis is an important cause of meningitis worldwide and following the introduction of the conjugate pneumococcal and Hemophilus influenza type b (HIB) vaccine, Neisseria meningitidis has become the leading cause of meningitis in the United States and many other countries including the Arabian Gulf states.[1,2] N. meningitidis is also important because of its potential to cause large epidemics in which all age groups are at risk.[3] Neisseria meningitidis, first identified in 1887,[4] is known to have 12 serotypes of which five major serotypes (A, B, C, Y and W 135) are associated with the disease.[5] Meningococcal meningitis is a serious disease with a mortality of 10-15%, rising to 60% in patients presenting with shock.[6] Reports from the Centers of Diseases Control and Prevention (CDC) in USA show that approximately 2,500 to 3,500 cases occur per year, with an attack rate reaching 1 in 100,000 population,[7] even higher in children under two years of age.[8] The disease occurs sporadically in clusters throughout the world, with seasonal variation.[9] It has been found that the most common serogroups in USA are Groups B, C and Y,[6,10] but the most common in Asia is Group A.[11] A few published reports, mostly from Saudi Arabia, none from Qatar, have described the epidemiology of meningococcal disease in the Arabian Gulf states.[12,13] In the present retrospective study, we describe our experience with meningococcal meningitis, discuss the epidemiologic and clinical features and factors influencing the outcome, and compare our results with those reported by others.

Methods:

The medical records of 25 patients diagnosed of meningococcal meningitis at HMC were reviewed retrospectively between March 1992 to March 2008.

The five hospitals of HMC with a capacity of 1,547 beds provide the only government-supported primary, secondary and tertiary care to the citizens and expatriates of Qatar and statistics derived from them are reasonably indicative of the health of the population as a whole. The patients were identified from records in the infectious disease logbook, the Microbiology Laboratory, the Preventive Health Department and General Medical Records.

Data collected: included age, sex, nationality, associated medical conditions, clinical features on admission, laboratory data, antimicrobial therapy, and clinical outcome.

A diagnosis of Meningococcal meningitis was established on the basis of one of the following criteria:

1. Culture of N. meningitidis from cerebro-spinal fluid (CSF).
2. Culture of CSF negative but clinical course consistent with meningococcal meningitis plus two of the following:
   a. CSF pleocytosis
   b. Gram stain of CSF showing Gram-negative diplococci
   c. Positive bacterial antigen testing for N. meningitidis in CSF
   d. Positive blood culture for N. meningitidis

Results:

Demographic and Clinical Features

Between March 1992 and March 2008, 28 patients were diagnosed with meningococcal meningitis but files were available only for 25 patients. Five more patients with N. meningitidis bacteremia and suspected meningitis were diagnosed clinically during that period but CSF examination was not done. These were not included in the study. Of the twenty five patients, (21 males and four females; aged 1 month-68 years, mean 24 years) 10 were Indian, 5 Nepali, 3 Qatari, 2 Jordanian, and 5 nationality were not recorded. Six were diagnosed in the first 12 years of the study (average 0.5 patient/year) and 19 in the last four years (4.75 patient/year) **(Table 1)**.

Associated illnesses were diabetes mellitus in three patients and hypertension in one. None were recorded as positive for HIV infection. Six patients had been outside Qatar recently; a mother and her son had been to Jordan, two had been to India, and one each to Sri Lanka and Egypt. None reported recent travel to Sub-Saharan Africa or had returned from pilgrimage to Mecca (Saudi Arabia). Most cases had occurred between October to March (76%), none being reported between June and August.

The average duration of symptoms before seeking medical advice was 2.9 days (range 1-10 days). The most common presenting symptoms were fever (80%), vomiting (56%), altered consciousness (48%) and headache (48%). Neck stiffness and impaired level of consciousness were the most common physical signs occurring in 52% and 40% respectively. Rash was seen in 28% of cases.

Laboratory Investigation

Elevated peripheral white blood cells (>11,000/mm^3) were seen in 19 patients (78%), and leucopenia (<4,000/mm^3) in two (8%). Thrombocytopenia (<100,000/mm^3) was seen in two patients (8%). Elevated WBC (>5 cells/mm^3), elevated protein and low glucose in CSF were present in 95.6%, 84% and 80% of cases respectively. The average White Cell Count in CSF was 8,468 cells/mm (range 5-30,625/mm). The CSF showed predominance of neutrophils in 83.3%, while lymphocytic predominance was present in 16.7%. Positive CSF Gram-stain showing gram-negative diplococci and cultures growing N. meningitidis were seen in 64% and 44% of cases respectively. Positive blood culture for N. meningitidis was seen in (72.7%). Antibiotic use prior to obtaining cultures was reported in four patients of whom three had positive blood cultures, the fourth was not cultured; CSF culture was positive in only one of these four.

Latex test for N. meningitidis in CSF was positive in 20 (80%) of 25 patients tested. Serogroup was determined in 16 of 25 patients, with Serogroup A being most common (50%), followed by W135 (25%). Serogroups B, C, and D accounted for 12.5%, 6.25%, and 6.25% respectively.

Sensitivity of N. meningitidis isolates to ceftriaxone and penicillin were 100% and 84.2% respectively. Some (15.8%) isolates were intermediately resistant to penicillin and none was fully resistant. Sensitivity to rifampin and ciprofloxacin was performed infrequently but resistance was found in one patient for each.

Table 1: Number of patients with meningococcal meningitis stratified by period of diagnosis and country of origin

Country of Origin	Number of patients during indicated year								
	1992-1994	1994-1996	1996-1998	1998-2000	2000-2002	2002-2004	2004-2006	2006-2008	Total
India	0	0	1	0	1	0	2	6	10
Nepal	0	0	0	0	0	0	2	3	5
Qatar	0	0	1	0	1	0	1	0	3
Jordan	0	0	0	0	0	0	2	0	2
Others	1	0	0	1	0	0	1	2	5
Total	1	0	2	1	2	0	8	11	25

Table 2: Demographic and clinical features of patients at the time of presentation

Age: Mean (range)	24 years (1 M- 68 Y)
Sex: Male	21
Female	4
Duration of symptoms before presentation	Mean (range) 2.9 days (1-10 days)
Symptoms N (%)	
Fever	20 (80%)
Vomiting	14 (56%)
Altered consciousness	12 (48%)
Headache	12 (48%)
Focal findings	4 (16%)
Seizure	3 (12%)
Signs No. (%)	
Neck stiffness	13 (52%)
Altered consciousness	10 (40%)
Rash	7 (28%)
Outcome No. (%)	
Survived without sequelae	18/25(72%)
Survived with sequelae	6(24%)
Died	1(4%)

Treatment

The time from presentation at the hospital to start of antibiotic therapy ranged from half an hour to three days (mean 9.69 hours). Ceftriaxone was used in 20 patients and penicillin in five. The duration of treatment ranged from one to three weeks. Steroids were used in 13 patients.

Outcome

One patient died (4%) - the mother of the infant who also had meningococcal meningitis. She had received both ceftriaxone and steroids but for a short duration only because death occurred within few hours of admission. In the 24 survivors, neurologic sequelae developed in six (25%); two of whom had limb weakness, two aphasia, and convulsions and cranial nerve palsy in one each. The average WBC in those with sequelae was 7,913/mm3 compared to 9,061/mm3 in those without (p=0.85). The average CSF glucose in those with sequelae was 2.2 mmol/L compared to 1.6 mmol/L in those without (p=0.012). The average CSF protein in those with sequelae was 4.7 gm/L compared to 3.75 gm/ L in those without (p=0.93). Steroids were used in three patients (50%) who had neurologic sequelae and in nine (50%) who had not. The average time to start antibiotic in the patients who survived without sequelae was 7.91 hours compared with 11 hours for those who developed neurologic sequelae (p=0.51).

Table 3: Laboratory Findings

Findings	Mean (range)
WBC/mL	18560 (2000-34800)
HB gm/dL	13.4 (7.3-16.7)
Platelet/mL	213,580 (47000-640,000)
Cerebrospinal Fluid	
WBC	8468 (5-30,625)
Protein	3.99 (0.23-8.02)
Glucose	1.7 (0.1-5.1)
Diplococci seen on gram-stain	16 (64%)
Positive latex antigen test	20 (80%)
Positive culture	11 (44%)
Blood culture positive	16/22 (72.7%)
N. Meningitidis Sensitivity	
Penicillin	
Sensitive	16/19 (84.2%)
Resistant	3/19 (15.8%)
Ceftriaxone	
Sensitive	19/19 (100%)
Resistant	0/19 (0%)
N. Meningococcus Serotypes	
Type A	8/16 (50%)
Type W125	4/16 (25%)
Type B	2/16 (12.5%)
Type C	1/16 (6.25%)
Type Y	1/16 (6.25)

WBC = white blood cells; HB = hemoglobin

Discussion:

We reviewed the records of 25 patients with meningococcal meningitis that were seen at our institution over a 16-year period. An average of 1.56 cases of meningococcal meningitis is diagnosed yearly in our institution but a marked increase in the number of cases was observed in the last three years of the study when the attack rate was 4.3/100,000 populations, higher than that reported in the United States (0.5-1.1/100,000) [14] although comparable to that reported in Europe (0.39-7.41/100,000[15] and lower than that reported in developing countries (10-25/100,000).[15] Qataris accounted for only 12% of cases and expatriates for 88%.

One possible explanation for the increase in those last three years, and the predominance of cases among expatriates (Non-Qataris) is the growth in the population of Qatar caused by an influx of a large work force of poor, malnourished immigrant laborers, mostly from the Indian subcontinent, living in crowded conditions with inadequate sanitation but constituting more than 80% of the population. Poverty and overcrowding such as that in dormitories and military barracks are known risk factors for meningococcal meningitis with N. meningitidis being

transmitted from person to another through coughing, sneezing or sharing eating or drinking utensils.[16]

The age distribution of the patients in this series showed adult predominance with adults accounting for 68% of cases in contrast to that seen in other countries where the disease affects mainly children and adolescents. The male to female ratio in our study was 5.25/1. Both the adult and male predominance may be explained by a significant proportion of the population in Qatar being the above unaccompanied adult male expatriates.

The clinical features in our patients included fever, headache, vomiting, neck stiffness, and an altered state of consciousness. Although these features point toward infection in the central nervous system, they are sufficiently specific to differentiate meningococcal meningitis from other causes of bacterial meningitis. The presence of a rash, seen in 28% of our cases, although not pathognomonic, should raise a strong suspicion of meningococcal meningitis and the need to start empiric therapy.

Absolute confirmation of the diagnosis of meningococcal meningitis requires the demonstration of N. meningitidis in the cerebrospinal fluid by Gram stain, culture, latex agglutination or polymerase chain reaction (PCR). Gram-negative diplococci were seen in 64% of our patients, and culture was positive in 44 %. The frequency of positive Gram stain in CSF has been reported as 75%.[17] Carpenter and Petersdorf indicated that 46% of their cases of meningococcal meningitis were positive by CSF culture, very similar to our result.[18] Latex agglutination test was positive in 80% of our patients compared to 50-93% reported by others.[19] The sensitivity and specificity of PCR for the diagnosis of meningococcal meningitis are greater than 90%[20] but this test is not available in our hospital.

Other CSF abnormalities seen in our patients included hypoglycorrhacia and an elevated protein level in 80% and 84% of cases respectively. CSF pleocytosis with a predominant neutrophilia was seen in most of our patients (83.3%). A presumptive diagnosis of meningococcal meningitis can also be made by growing N. meningitidis from the blood of a patient with a compatible clinical picture and CSF pleocytosis. Diagnosis based on these criteria was made in four of our patients (16%). Blood culture was positive in 72.7 % of our cases. All serogroups were represented among our N. meningitidis isolates although Group A and W135 were the most common, accounting for 75% of cases in contrast to those in the Americas and Europe where Serogroups B, C, and Y are the predominant serotypes.[6,10] Our finding conforms more to the situation in Africa and Asia where serogroup A and C account for most meningococcal disease.[11] Serogroup W-135 has been associated also with meningococcal epidemics in Saudi Arabia.[11] Our finding that serogroups A and W-135 are the predominant type can be explained by almost all our patients being Asians, plus our country borders Saudi Arabia.

The currently used meningococcal vaccine in Qatar is the quadrivalent meningococcal polysaccharide vaccine that contains Serogroups A, C, Y, and W-135. Since 12.5% of our isolates were Serogroup B, therefore with the use of the current vaccine, 12.5% of cases cannot be prevented and because the predominant serotypes in a country may change over time, continuous surveillance is very important to determine the degree of coverage by the available vaccine.

The sensitivity to ceftriaxone and penicillin among our isolates was 100% and 84.2% respectively with 15.8% of our isolates being intermediately resistant to penicillin. Relative penicillin resistance in N. meningitidis has been reported to be 30.2% in some studies.[21] Although no isolate among our patients with confirmed meningococcal meningitis demonstrated full resistance to penicillin. It might be significant that one isolate in a patient with suspected meningococcal meningitis was excluded because of non-fulfillment of the inclusion criteria. These findings may indicate that penicillin might not be the most appropriate empiric antibiotic therapy in a patient with suspected meningococcal meningitis or meningococcemia because of the risk of failure.

Twenty-four (96%) of our 25 patients survived. Six (25%) survivors had neurologic sequelae. Since only one patient died, we cannot come to any conclusion on risk factors for death. Fourteen (77.7%) of the 18 who survived without sequelae were treated with ceftriaxone and five (83.3%) who developed neurologic sequelae were also treated with ceftriaxone. An interesting but unexplained finding that was statistically significant is that CSF glucose was lower in those who survived without sequelae compared to those with sequelae. This finding is contrary to that reported by others.[22,23]

Several studies have investigated the relation of timing of antibiotics to outcome. In one of these studies it was found that a delay of more than three hours after hospital admission was a strong and independent risk factor for mortality (OR 14.1). In another study, the adjusted odds ratio (OR) for mortality was 8.4 for a door-to-antibiotic time greater than six hours when the patient presented as afebrile and 12.6 for patients with severely impaired mental status at presentation.[24] The average time from presentation to the start of antibiotics in our series was 9.69 hours; 7.91 hours in the group that survived without sequelae compared to 11 hours in those with sequelae, indicating that the time of door-to-antibiotic treatment, even in the group that survived without neurologic sequelae, is still high and should be made shorter to improve the outcome in future patients.

Our knowledge of the epidemiology of meningococcal disease in the Arabian Gulf States is limited. Apart from a few studies from Saudi Arabia describing the epidemiology of meningococcal diseases, studies from other countries are lacking.[12,13] Saudi Arabia has a special interest in N. meningitidis due to the Hajj and Umrah pilgrimages, which bring large numbers of people together, often in crowded conditions, setting the stage for epidemics. Two

major outbreaks of meningococcal meningitis occurred in Saudi Arabia in 1987 and in 2000,[13] both were Hajj related. The predominant serotype in the 1987 outbreak was Serogroup A, while in the 2000 outbreak it was serogroup W135, the shift in serotype being attributed to the use of the bivalent A/C vaccine for all persons coming for Hajj or Umra after the 1987 outbreak.[13] None of our patients reported recent travel for Hajj or Umra prior to their infection.

In a study of 64 cases of acute bacterial meningitis in Qatar published in 2006 by Elsaid F. et. al., only four were due to N. meningitidis, however this study was not aimed to study specifically meningococcal meningitis epidemiology.[25] To our knowledge, the present study is the first from Qatar to describe in detail the epidemiology of meningococcal meningitis.

Our findings have several implications to our country with regards to meningococcal meningitis. First, meningococcal meningitis in Qatar is a disease of the expatriates and interventions directed toward the local population such as vaccination with the polyvalent meningococcal vaccine will probably have little effect on the incidence. Major efforts should be directed toward the expatriates. One approach being to mandate all new applicants for residence in the country to be vaccinated in their own country before entering Qatar. The option of vaccinating them on entry might not be logistically possible because of their large number and it might not be cost effective. Second, improvement in the conditions where the laborers are housed such as reducing the overcrowding and improving sanitation may reduce the number of infections. Third, considering the results of susceptibility testing of our N. meningitidis isolates which showed that 15.8% were intermediately resistant to penicillin and that 54% of our Streptococcus pneumoniae isolates are either intermediately or fully resistant to penicillin,[26] the most appropriate initial empiric therapy for a patient with suspected bacterial meningitis will be ceftriaxone with vancomycin.

Conclusion:

Meningococcal meningitis in Qatar is primarily a disease of the expatriates, mostly those from the Indian subcontinent. The numbers of cases have increased markedly in recent years, probably reflecting the marked increase in the population of Qatar and the increase in people at risk. The disease affects mainly young adults with similar clinical presentation to those reported by others. Mortality and morbidity are significant and so keeping a high index of suspicion is essential for early diagnosis. Empiric therapy with ceftriaxone in patients with suspected meningococcal meningitis is recommended.

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