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Childhood meningitis in Kuwait in the era of post pneumococcal conjugate vaccination: A multicenter study

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ABSTRACT

This is a retrospective study to evaluate epidemiology and etiologies of childhood meningitis in Kuwait after the routine introduction of the pneumococcal conjugate vaccine. The data was collected from 196 patients in the period of 2010–2014. Aseptic meningitis accounted for 51% of the cases, bacterial meningitis accounted for 29% cases and partially treated meningitis were 20%. Organisms causing bacterial meningitis were: *Streptococcus pneumoniae* 40.4%, *Neisseria meningitidis* 17.6%, *Haemophilus* spp. 12.2%, other gram positive or negative 19.3%, and Group B Streptococcus 8.8%. The hospitalization was complicated by admission to the ICU in 16.3% patients. Sequelae on discharge were seen in 4%, and 2.5% died of complications of meningitis. In children with pneumococcal meningitis, 48% were admitted to the ICU, 35% were discharged with sequelae and 13% died. In the era of post pneumococcal conjugate vaccination, *S. pneumoniae* remains the leading cause of bacterial meningitis with the greatest morbidity and mortality.

Introduction

Meningitis is a serious infection of the central nervous system resulting in significant mortality and morbidity in children. The three leading organisms in children older than one month of age are *Haemophilus influenzae*, *Streptococcus pneumoniae and Neisseria meningitidis*, accounting for 70% of acute bacterial meningitis in this age group [1].

The introduction of the conjugate vaccines into routine childhood vaccination schedules has reshaped the epidemiology of meningitis in the last decade. When Haemophilus B conjugate vaccine was introduced in 1990, the incidence of bacterial meningitis was decreased by 55% in the United States [2]. Similarly, the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7; serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) in 2000 has led to 64% reduction of pneumococcal meningitis in children aged less than 2 years [3]. The 13-valent pneumococcal conjugate vaccine (PCV-13) with the addition of serotypes of 1, 3, 5, 6A, 7F and 19A to PCV-7, was introduced in 2010 and has resulted in further reduction of invasive pneumococcal infections including meningitis [4].

In Kuwait, there are four studies that have evaluated the epidemiology of meningitis. Shaltout et al. and Zaki et al. have shown that *H. influenzae* type b was the dominant organism of meningitis during 1981–1990 [5,6]. After the introduction of Haemophilus B conjugate vaccine into routine childhood immunization schedule in 1996, there was a dramatic drop in the incidence of *H. influenzae* meningitis [7,8]. A limited one-year retrospective study by Shabani et al. has shown that *S. pneumoniae* was the most common organism causing meningitis among children in 2001 [7]. Husain et al. has shown that *N. meningitidis* was the leading cause of meningitis between 2001 and 2003 [8].

PCV-7 was introduced in Kuwait in August 2006 [9] as part of national immunization program provided by the Ministry of Health for free to all children born and residing in Kuwait. It is given as 3 doses at 2, 4 and 6 months of age then a booster dose is given at 18 months. In August 2010, PCV-7 was replaced by PCV-13 [9]. In addition, a quadrivalent polysaccharide ACYW-135 is administered

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routinely at the age of 2 years since 2008 [10]. According to Health Kuwait Statistics 2014, vaccination uptake is 98% and 97% in the first and second year's life respectively [11].

There are no studies to evaluate the effect of pneumococcal conjugate vaccine on childhood meningitis in Kuwait. This study describes the epidemiology of meningitis in Kuwait after the introduction of pneumococcal conjugate vaccine.

Subjects and methods

This is a retrospective chart review of patients admitted to all of the six pediatric wards in Kuwait governmental hospitals from January 1st 2010 to December 31st 2014. Subjects were children between 28 days and 12 years old admitted to any of these six hospitals with any of the following diagnoses: meningitis, bacterial meningitis, viral meningitis, aseptic meningitis, tuberculosis (TB) meningitis, or partially-treated meningitis. The cases were identified based on preventive medicine records in the six hospitals. Cases were included if had at least one of the following: cerebrospinal fluid (CSF) with pleocytosis (white blood cell count (WBC) count in CSF $\geq 5/mm^3$), CSF with an organism identified by either gram stain or culture or antigen detection, or a clinical presentation of meningitis and a positive blood culture. Cases were classified as aseptic meningitis if the patient had CSF pleocytosis and negative blood and CSF cultures and no antibiotic was taken prior to lumbar puncture (LP). Partially treated meningitis was considered if the patient had taken antibiotics in the presence of CSF pleocytosis and negative blood and CSF cultures. Bacterial meningitis is confirmed if CSF or blood was positive for bacterial organism. TB meningitis was considered in all patients with clinical diagnosis of meningitis and CSF positive for Acid-Fast Bacilli (AFB) stain, positive mycobacterium culture, or positive PCR for TB [12]. Cultures negative CSF was sent to the virology laboratory for enterovirus and Herpes simplex testing by PCR [13]. There is no PCR available in the country for testing for bacterial agents. Exclusion criteria were subjects with meningitis secondary to ventriculo-peritoneal shunt, fungal or parasitic meningitis, herpes simplex encephalitis and neonates with meningitis who have been hospitalized since birth and never left the hospital (i.e. neonates who have acquired meningitis while staying in NICU).

A standardized data collection sheet was completed for each patient including demographic data, clinical, and laboratory data, management in the hospital and the clinical outcome. The collected data were entered using the Statistical Package for Social Sciences (SPSS v23.0, IBM Inc., Chicago, Ill., USA). All data were expressed in numbers and proportions.

Results

During the study period (2010–2014), 239 charts were assessed for eligibility in the study. Only 196 patients were included in the final analysis as they fulfilled our inclusion criteria. Forty-three cases were excluded as they did not meet the inclusion criteria: 5 cases were diagnosed with herpes simplex virus (HSV) encephalitis, 5 cases had normal LP findings, 11 cases had missing data, and 22 cases were with no clinical criteria for meningitis and parents have refused lumbar puncture.

Patient's characteristics and clinical presentation

Of the 196 who met the inclusion criteria, 120 (61.2%) were males and the remaining 76 (38.8%) were females. The median age was 6.5 months (25th quartile is 2 months and 75th quartile is 60 months). There were 117 (59.7%) infants (age: ≥1–≤12 months), 10 (5.1%) toddlers (>1–≤3 years), and 69 (35.2%) children (>3–≤12 years). Only 21 cases (10.7%) were ex-preterm. Fifty-five (28.1%) were admitted during May–June. The majority of the patients (94.4%) were experiencing fever as the most common presentation prior to the admission. There were 9 (6%) patients who were not fully vaccinated. Decreased feed and vomiting were reported by 91 (46.4%) and 98 (50%) patients, respectively. Only 38.3% of the cases presented with drowsiness, while 33.7% of patients presented with headache. Thirty-six children (18.4%) presented to the hospital with seizure attack. Only 3 patients (1.5%) were considered immune-compromised because they were on prolonged duration of steroid therapy. One-hundred and thirty-seven patients (70%) were not on antibiotics one week prior admission.

Ninety-two patients (47%) were looking ill upon arrival to emergency room (ER). One patient (0.5%) arrived to ER in coma. Fifty-two children (26.5%) had nick stiffness, while bulging anterior fontanelle was noticed in 11.7% of cases. Focal neurological signs were observed in four patients (2%) and included right-sided weakness, acute squint, unsteady gait, and cerebral palsy with spastic quadriplegia.

Etiologic agents

Aseptic meningitis accounted for 100 (51%) of the cases, bacterial meningitis accounted for 57 (29%) cases, and partially treated meningitis for 39 (20%). No TB meningitis cases were found. For patients with bacterial meningitis: 17 (29.8%) were diagnosed based on positive blood culture only, 21 (36.8%) were diagnosed based on positive CSF culture only, 14 (24.6%) patients had both blood and CSF cultures positive and five (8.8%) were diagnosed based positive antigen test.

From patients with aseptic meningitis, 17 (17%) were enterovirus positive by PCR testing. The causative organisms of bacterial meningitis were: *S. pneumoniae* 23 (40.4%), *N. meningitidis* 10 (17.6%), *Haemophilus* spp. 7 (12.2%), other gram positive or negative organism (*Enterococcus faecium*, *Serratia* spp., Group A Streptococcus, Group C Streptococcus, *Salmonella* spp., and *Escherichia coli*) 11 (19.3%), and then Group B Streptococcus (GBS) 5 (8.8%). There was one case caused by *Listeria monocytogenes* (1.7%). Bacterial meningitis distribution according to age group is shown in Fig. 1. Out of patients with *S. pneumoniae* meningitis, 11 (48%) did not receive full pneumococcal conjugate vaccine (i.e. at 2, 4, and 6 months). Three children (43%) out 7 patients with *Haemophilus* spp. did not receive their three doses of vaccine. Of patients with meningococcal meningitis, 7 (70%) were not vaccinated against *N. meningitidis.*

Hospitalization and outcome

The mean duration of hospitalization was 13 ± 10 days. Neuroimaging studies were performed for 100 children (51%) on admission. Only 26 (13.3%) were abnormal. All patients have received third generation cephalosporin (cefotaxime or ceftriaxone) antibiotic as an empiric therapy but only 21% have received vancomycin. In addition to antibiotics 20 (10%) patients have received steroids, 33 (17%) have received anticonvulsants and 11 (5.6%) have received manitol. The hospitalization was complicated by admission to the intensive care unit in 33 (16.3%) patients, of which 21 needed artificial ventilation.

On discharge, 6 (3%) patients had seizure disorder, 1 (0.5%) had hydrocephalus, and 1 (0.5%) had motor palsy (bilateral lower limb weakness). There were 183 patients (93.5%) who recovered fully without significant sequel. Unfortunately, 5 children (2.5%) died of complications of meningitis. Table 1 shows the details of sequelae and mortality for each organism.

Discussion

This is the fifth and largest study evaluating childhood meningitis in Kuwait and the first to describe the outcome of the

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