Haemophilus influenzae type b diseases in children: a pre-vaccination study

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أمراض المستدمية النزلية من النمط "بي" لدى الأطفال: دراسة سابقة للتطعيم

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الخلاصة: أصبح من الممكن في الوقت الحاضر الوقاية من المستدمية النزلية من النمط "بي" بالتطعيم. ونحن نعرض الخصائص السريرية والمختبرية لأمراض المستدمية النزلية التي تتّسم بالهجمات الحادة بين الأطفال الذين أدخلوا جناح طب الأطفال الثالثي بمستشفى منطقة العين الطبية على مدى أربع سنوات، قبل أن يتاح التطعيم في الإمارات العربية المتحدة. وقد تبيَّن أن 38 من مجموع هؤلاء الأطفال كانوا مصابين بصورة مؤكدة بالفحص الجرثومي بأمراض ناجمة عن المستدمية النزلية المهاجمة، كما كانت جميع المستفرَدات تنتمي إلى النمط المصلي "بي". وتم تشخيص التهاب السحايا في 60.5% من الأطفال، كما كان 66% من الأطفال الذين شملتهم الدراسة دون سن الثانية عشرة. ولم تكن هناك وفيات إلا أن المرض كان شديداً في 12 طفلاً.

ABSTRACT *Haemophilus influenzae* type b (Hib) can now be prevented by vaccination. We present the clinical and laboratory characteristics of acute invasive *H. influenzae* diseases in children admitted over a 4-year period to a tertiary paediatric ward of the Al-Ain medical district hospital, before vaccination became available in the United Arab Emirates. In all, 38 children had bacteriologically proven *H. influenzae* invasive diseases and all the isolates were serotype b. Meningitis was diagnosed in 60.5% of the children and 66% of the studied children were under 12 months. There were no deaths but substantial morbidity occurred in 12 children.

Infections à *Haemophilus influenzae de* type b chez les enfants : étude avant la vaccination

RESUME *Haemophilus influenzae* b (Hib) peut maintenant être évité grâce à la vaccination. Nous présentons ici les caractéristiques cliniques et celles qui concernent les laboratoires pour les maladies invasives graves dues à *H. influenzae* chez des enfants admis dans un service pédiatrique tertiaire de l'hôpital du district médical d'Al-Ain sur une période de quatre ans, avant que la vaccination ne devienne disponible aux Emirats arabes unis. En tout, 38 enfants étaient atteints d'infections à *H. influenzae* invasives prouvées sur le plan bactériologique et tous les isolats étaient du sérotype b. Une méningite a été diagnostiquée chez 60,5 % des enfants et 66 % des enfants faisant l'objet de cette étude étaient âgés de moins de 12 mois. Il n'y a eu aucun décès mais une morbidité importante est survenue chez 12 enfants.

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Introduction

Haemophilus influenzae type b (Hib) is the primary bacterial pathogen associated with childhood bacterial meningitis worldwide, except in countries where the effective conjugate vaccines have been introduced [*1–4*]. The incidence of Hib disease has fallen dramatically in optimally immunized populations. Unfortunately Hib infections are still a major cause of severe morbidity and mortality in many developing countries, including the United Arab Emirates (UAE) [*1,5*]. A previously published study from our region identified Hib as the pre dominant pathogen that accounted for more than 60% of treated cases of childhood meningitis [*1,5*]. Vaccination against Hib was introduced into the UAE in late 1999. The purpose of this review is to report on the disease frequency, clinical patterns and outcome of Hib infection as seen in our clinical setting just prior to the introduction of Hib vaccination.

Methods

We conducted a hospital-based descriptive survey of invasive Hib disease. This involved clinical and bacteriological surveillance for Hib invasive disease in children admitted to the paediatric wards of Al-Ain Hospital, which is the major referral hospital in the eastern region of the Abu Dhabi emirate. Children aged between 0 and 12 years with culture-proven Hib disease from January 1996 to December 1999 were enrolled in the study. Standardized protocols for clinical and laboratory procedures were followed throughout the study period. Parental consent was obtained for all diagnostic procedures, which conformed to the hospital's standards of medical research and ethics. The clinical diagnosis, the microbiological test results and the immediate disease outcome were reviewed systematically. For a case to be considered one of invasive Hib disease, the organism had to be isolated from an otherwise sterile body site. These culture sites included blood, cerebrospinal fluid (CSF) and other diagnostic materials aspirated from bone, pleural and joint cavities. Cases where the culture was negative but the specific bacterial antigen tests were positive were excluded from the analysis.

Microbiological culture was performed in the bacteriology section of the laboratory at Al-Ain Hospital. Standard isolation and serotyping procedures were adopted for identification of the pathogen. Blood cultures were inoculated onto commercially prepared BACTEC 9240 automated blood culture systems. Other specimens were inoculated directly onto thioglycollate plate medium and were subcultured onto chocolate agar medium. Organisms were identified biochemically (VITEK 32) and the identification was confirmed by conventional methods using a commercial latex agglutination test (LAT) for Hib. The records of the hospital clinical microbiology logbook were surveyed for *H. influenzae* cultures during the entire 4-year study period.

Antibiotic sensitivity was determined for all Hib isolates by the Kirby–Bauer disc diffusion method, and beta-lactamase production with cefinase discs (BBL Microbiology Systems, Cockeysville, Maryland, United States of America).

Individual cases were managed and the entire clinical course monitored by the authors up to the day of discharge.

Results

The clinical pattern of Hib cases that were diagnosed and managed in Al-Ain Hospital during the study period is shown in Table 1.

Table 1 ***Haemophilus influenzae*** **type b disease: clinical pattern, Al-Ain, 1996–98**

Illness	No.	%
Meningitis	23	60.5
Bacteraemia and septicaemia	5	13.1
Cellulitis, orbital/periorbital/buccal	3	7.9
Arthritis/osteomyelitis	2	5.3
Epiglottitis	2	5.3
Pericarditis	1	2.6
Pneumonia/empyema	2	5.3
Total	38	100.0

Table 2 **Distribution of cases of *Haemophilus influenzae* type b disease by month and year of onset**

Month	1996	1997	1998	1999	Total
January	1	3	–	–	4
February	5	1	–	1	7
March	–	1	2	1	4
April	1	1	–	–	2
May	1	1	1	–	3
June	–	–	2	–	2
July	–	–	–	–	0
August	–	–	2	–	2
September	–	–	–	–	0
October	–	1	1	–	2
November	2	1	–	1	4
December	–	4	3	1	8
Total	10	13	11	4	38

Meningitis was confirmed in 23 (60.5%) of the 38 children with Hib-related disease. The distribution of cases by month and year, the demographic features and the immediate outcome of the patients are summarized in Tables 2, 3 and 4.

A seasonal clustering of cases was observed during the cooler months. As regards nationality, 18 (47.4%) children were UAE nationals and 20 (52.6%) were other nationalities. The disease occurred only in children under 6 years of age, but most of the cases were under 12 months of age; 2 cases were neonates and their age at onset of illness was 15 and 23 days respectively. Meningitis was seen predominantly (70%) in younger infants under 6 months of age. Epiglottitis occurred in 2 children who were aged 18 and 24 months. Invasive infections were encountered only in 4 older children over 18 months of age.

A positive CSF culture alone was documented in 13 cases, while in 10 other children both CSF and blood cultures were positive. The cases with positive bacterial cultures are shown in Table 5.

Four of the 23 (17.4%) CSF isolates were found to be ampicillin-resistant, beta-lactamase producers. In three other children, strains resistant to chloramphenicol (two cases) and ceftriaxone (one case)

Table 3 **Distribution of cases of *Haemophilus influenzae* type b disease by age and sex**

Age	Males		Females		Total	
(months)	No.	%	No.	%	No.	%
< 6	12	52.2	3	20.0	15	39.5
6–11	5	21.7	5	33.3	10	26.3
12–17	1	4.3	1	6.7	2	5.3
> 18	5	21.7	6	40.0	11	28.9
Total	23	100.0	15	100.0	38	100.0

Table 4 **Distribution of cases of *Haemophilus influenzae* type b disease by immediate outcome**

Outcome	No.	%
Died	1	2.6
Recovered	25	65.8
Subdural effusion	5	13.1
Subdural empyema	1	2.6
Hydrocephalus	2	5.3
Bone synovial sepsis	2	5.3
Paralysis/blindness	2	5.3
Total	38	100.0

were encountered. One of these strains was resistant to both ampicillin and chloromphenicol.

There were no deaths directly related to Hib infection during the surveillance period. A 9-month-old infant who had a soft tissue infection over the orbital region associated with bacteraemia died some months after clinical recovery due to an underlying congenital mesoectodermal disorder, an inherited genetic condition associated with focal dermal hypoplasia (Goltz syndrome) and a tendency to recurrent bacterial infections. Ten (10) of the 23 meningitis cases (43.5%) developed neurological complications such as hydrocephalus, massive subdural effusion, subdural empyema, blindness and focal neurological deficits. Five of the 15 children with systemic diseases showed considerable morbidity and required prolonged hospitalization involving intensive medical and surgical support. Two children had residual skeletal deformity. Their long-term outcome remains to be seen.

Discussion

These data provide strong evidence that invasive diseases, including meningitis, caused by *H. influenzae* continue to represent a substantial cause of child morbidity in our region. The illnesses caused by Hib seen in our clinical settings included infection of the central nervous system (meningitis), the respiratory tract (epiglottitis, empyema and pneumonia), soft tissues

Table 5 ***Haemophilus influenzae* type b disease: culture-positive source (1996–98)**

Year	CSF	CSF/blood	Blood and other sites[a]	CNS	Systemic
1996	3	2	5	5	5
1997	5	2	6	7	6
1998	4	4	3	8	3
1999	1	2	1	3	1
Total	13	10	15	23	15

[a]*Including sterile sites, i.e. bone, joint, orbital and pleural cavities.*
CSF = cerebrospinal fluid.
CNS = central nervous system.

(buccal, orbital), bone and synovial (arthritis and osteomyelitis) sepsis, and purulent pericarditis. Meningitis occurred in approximately 61% of our culture-proven cases. Earlier hospital-based studies from our region have shown that Hib is the single most common pathogen, accounting for nearly two-thirds of all CSF culture-proven childhood bacterial meningitis [*6–8*]. These observations are in agreement with similar studies reported from other developing nations [*9–11*].

Before the introduction of conjugate vaccines, Hib was documented as a major paediatric pathogen in virtually all regions of the world where it has been studied. The reported overall annual incidence of Hib meningitis in our region ranges from 19 to 32 per 100 000 under 5 years of age [*6,8*]. The disease attack rate varies considerably from one country to another. Population-based studies in industrialized countries have demonstrated differences in the case attack rate for all invasive Hib diseases, and especially for meningitis and epiglottitis. In developing countries there have been relatively few reported studies and they have shown considerable differences from the industrialized world. The incidence rates among Alaskan Inuits, Navaho Indians, Australian Aboriginals and in some African populations were three- to fourfold higher than those in the United States of America, and up to ten times higher than in Europe [*11,12*].

In comparison with Western countries, meningitis in developing countries is characterized by younger age of onset as shown in this study. Nearly all infections occurred in children under 36 months of age and 90% of all cases of meningitis occurred in children under 18 months of age. Meningitis is predominantly a disease of infancy, most commonly occurring from birth up to 6 months of age. The highest attack rate of Hib meningitis has been reported to occur as the maternally derived protective antibody disappears during infancy [*13–15*]. Studies conducted in our region by Uduman et al. have also shown that many of our infants are at risk as a result of declining protective maternal antibodies [*6–8*]. Most of our infants are sero-susceptible and unprotected during this critical period of early childhood [*15*].

Despite intensive efforts at early diagnosis and initiation of prompt therapy, Hib infections caused significant morbidity in our series. In contrast to our earlier report [*6*], no deaths have occurred in recent years. This probably reflects improvements in our intensive care facilities.

The incidence of the different diseases caused by Hib differs geographically. Epiglottitis, a common presentation of Hib in Western countries such as the United States, Sweden, Australia and Finland, is rare in developing countries [*16*]. The relative incidences of Hib pneumonia, arthritis, osteomyelitis, and soft tissue inflammatory conditions are less clear and difficult to quantify. Studies, like ours, which rely solely on positive blood cultures will underestimate the incidence of disease since 20%–25% of infections do not lead to bacteraemia. Respiratory tract infections due to Hib are quite prevalent and it has been found to be a common pathogen in many of the reported cases of severe pneumonia in which lung aspirates were performed [*17,18*]. Thus, the proportion of acute lower respiratory tract infections due to Hib is likely to be much higher in our children than we report in this study.

The disease frequency, particularly of Hib pneumonia, is underestimated globally and most likely in the UAE as well. The technical difficulties of obtaining culture materials in cases other than meningitis and the use of antibiotics to treat vague symp-

toms at primary care levels will always hinder the accurate estimation of disease frequency. The true rates of Hib disease, and the associated morbidity and mortality, are expected to be higher than estimated by this report. This, and the high burden of disease occurrence in early infancy, suggests that prevention at an early age is the best solution.

The epidemiological data in our region, particularly for meningitis, are similar to those of neighbouring countries and parallel the pre-vaccination patterns of many industrialized countries [*6,10,14,19*]. Although we do not have precise data on the nationwide incidence of Hib infection, the disease pattern seen in hospitals is very strong evidence of the prevalence of the clinical problem in the community [*14,16,19*]. Conjugate vaccines are now available and widely used in many developing countries. The Hib vaccination programme was introduced to the UAE in October 1999. The continuation of the survey will permit ongoing monitoring of vaccine efficacy and reveal any changes required in the vaccination schedule. Such a comprehensive vaccine coverage against Hib could eventually prevent deaths and major neurodevelopmental handicap in a significant number of children. Moreover, the nationwide Hib vaccination programme, delivered along with other combination vaccines, is easy to administer and cost-effective.

In conclusion, the clinical observations described here document the existence and extent of childhood Hib disease and the associated morbidity prior to the introduction of conjugated vaccines to the UAE. These data form a base enabling us to document the success of the immunization programme in eliminating Hib disease in our country.

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