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Epidemiology of Haemophilus Influenzae Invasive Disease in Hospitalised Kelantanese Children, 1985 – 1994

N Y Nik Khairulddin, K E Choo, M R Johari

ABSTRACT

Aim: Data is lacking with regard to the epidemiology of invasive haemophilus influenzae (HI) disease in Malaysia. This study was carried out to document the epidemiology of invasive HI disease in hospitalised Kelantanese children.

Methods: We conducted a retrospective study of 65 children who had invasive HI disease from June 1985 to December 1994. Data regarding age, sex, duration of illness, weight, diagnosis, complications, duration of hospitalisation, outcome, full blood count and sensitivity pattern of HI to various antibiotics were reviewed.

Results: The age distribution varied from one day to 72 months with a mean of 13 months. Peak incidence occurred in the 7 – 12 months age group. Majority (89.1%) was below two years of age. The relative frequencies of the 75 clinical entities documented were as follows: meningitis 64%, pneumonia 29.3%, septicaemia 5.4%, and abscess 1.3%. In addition, 13.5% of cases had meningitis associated with pneumonia. Serotype b accounted for all strains in cases where serotyping was done. Anaemia (Hb < 10g%) was seen in 71.4% of cases. Long term complications were noted in 41.5% of cases of meningitis. Case fatality rate was 12.3%. The percentage of HI strains sensitive to penicillin, ampicillin, chloramphenicol and co-trimoxazole were 83.7%, 87.7%, 98.2% and 89.7%, respectively.

Conclusion: The data suggest that invasive HI disease causes considerable morbidity and mortality in Kelantanese children.

Keywords: children, epidemiology, haemophilus influenzae, hospitalised, invasive

Department of Paediatrics
Hospital Universiti Sains Malaysia
16150 Kubang Kerian
Kelantan, Malaysia

N Y Nik Khairulddin, MBBS (UNSW), MRCP (UK)
Paediatrician

K E Choo, MBBS, FAMM, FRCP (Lond, Edin, Glas)
Consultant

Department of Microbiology & Parasitology
Hospital Universiti Sains Malaysia

M R Johari, MBBS, MSc
Lecturer

Correspondence to:
Dr K E Choo

INTRODUCTION

Haemophilus influenzae (HI) disease is recognised as one of the major causes of morbidity and mortality in children worldwide. The spectrum of diseases caused by the organism includes meningitis, epiglottitis, pneumonia, arthritis, cellulitis and septicaemia. Since the introduction of haemophilus influenzae type b (HIB) vaccine in Europe and the United States, the incidence of the disease in these regions has dropped dramatically[1-3]. Despite obvious efficacy of the vaccine shown in the developed countries, the use of the vaccine in developing countries is still debatable. Apart from the high cost of the vaccine (one course of HIB vaccine is more expensive than the entire vaccines in WHO Extended Programme for Immunisation), a key problem in recommending routine use of the vaccine is the lack of data on the epidemiology of HI disease from this part of the world[4].

Incidence of HI disease in Asia, while lower than those in North America and Northern Europe is thought to be similar to that in Southern Europe before routine immunisation was adopted[5]. HI is known to be the major cause of bacterial meningitis in various surveys of cases of meningitis in Southeast Asia[6,7]. However, until now, there has been only one published report on the full spectrum of HI disease in Malaysia[8]. The aim of this study was to document the epidemiology of HI disease in hospitalised Kelantanese children less than 12 years old over a 10-year period.

METHODS

Hospital Universiti Sains Malaysia (HUSM) is one of two tertiary hospitals in the state of Kelantan, which is situated on the northeast of peninsular Malaysia. The source of identification of the patients was the records of isolates of HI kept in the Department of Microbiology at HUSM. All children aged 0 – 12 years who were hospitalised in HUSM from June 1985 to December 1994 with a positive culture for HI from a normally sterile body site and with the clinical signs compatible with HI disease, were enrolled in this study. Meningitis was defined by positive cerebrospinal fluid (CSF) culture. In cases with negative CSF, culture for HI diagnosis was made by positive blood culture and/or positive HI antigen in CSF of the patient with CSF pleocytosis. The criteria for pneumonia were clinical chest findings, positive chest roentgenogram and a positive blood culture. Septicaemia was defined as a positive blood culture without documentation of organ involvement. In cases where serotyping was done, isolates were serotyped by slide agglutination with specific antisera (Murex Diagnostics Limited, Dartford,

UK). Antibiotic susceptibility testing was carried out by disc diffusion test[9].

The following demographic and clinical information was obtained from the 65 patient records that met the criteria: age, sex, race, date of illness, duration of illness prior to admission, weight, diagnosis, complications, duration of hospitalisation, outcome, full blood count and sensitivity pattern of HI to various antibiotics. Data were analysed by computer using Epi Info v6.

RESULTS

Sixty-five cases of invasive HI disease were detected from 59,274 children (11.0 per 10,000) admitted to HUSM during the study period. The median age was nine months with a range of one day to 72 months. Of all cases, 29.2% were in children less than 6 months old, 75.4% in less than 1 year and 89.1% in less than 2 years old. There were 43 males and 22 females, giving a male to female ratio of 1.95:1. All the children were Malays except for one Indian girl. This approximately paralleled the demographic distribution by race of the healthy paediatric population in Kelantan.

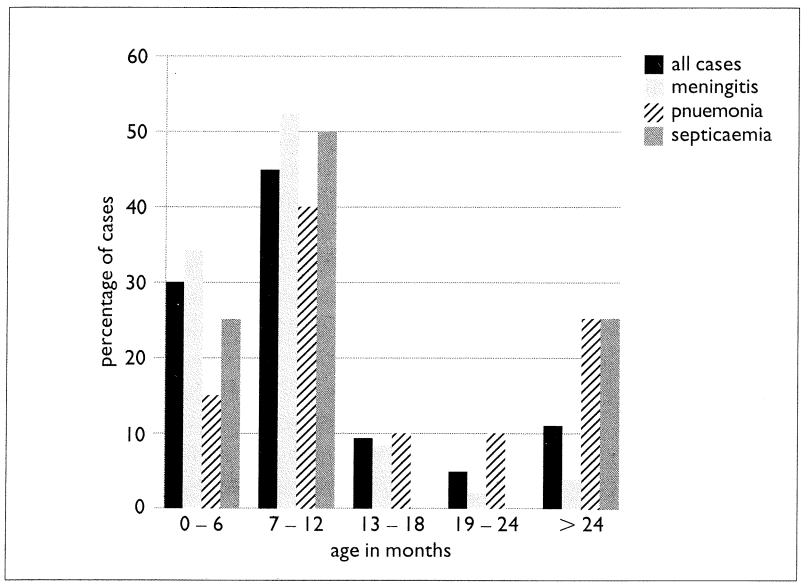

Fig 1 – Age distribution of children with invasive H. influenzae infections.

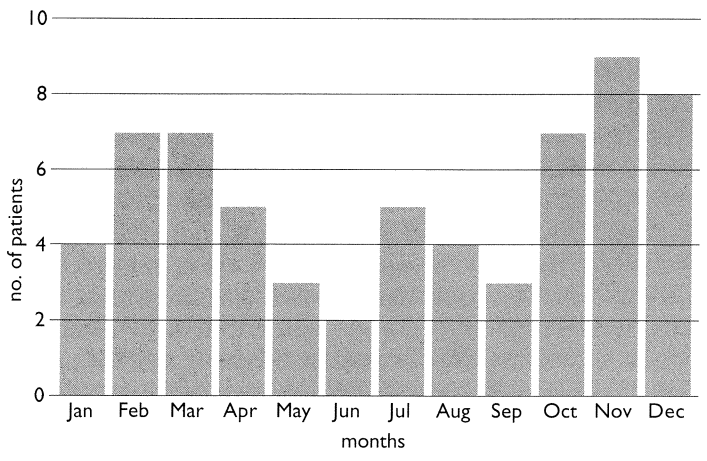

Fig 2 – Monthly distribution of 65 cases of H. influenzae infections

Seventy-five clinical entities were found in the 65 children. Of the 75 entities seen, 48 (64.0%) were cases of meningitis (all 48 cases had lumbar puncture done), 22 (29.3%) were cases of pneumonia, four (5.4%) were cases of septicaemia and one (1.3%) was a case of abscess. Ten children were noted to have two clinical entities each ie. nine with meningitis/pneumonia and one with septicaemia/abscess (the latter was a two and a half year old boy with underlying juvenile rheumatoid arthritis and who presented with multiple abscesses on the right forearm and ankle). There were no cases of epiglottitis, cellulitis or sinusitis detected. The age distribution of each clinical entity is given in Fig 1.

Underlying diseases were documented in seven children. Five children had congenital heart disease and one child each had thalassaemia major and juvenile rheumatoid arthritis.

Monthly distribution of the cases is presented in Fig 2. Overall, peak number of cases occurred during the rainy season ie. October to December.

The nutritional status (% of expected weight) of children according to diagnosis is shown in Table I. Children with meningitis appeared to be more malnourished than other disease entities. However, this did not reach statistical significance ($p = 0.69$). The mean duration of illness prior to admission was 6.5 days, with a range of one to 21 days. Duration of hospitalisation ranged from one to 49 days with a mean of 16.6 days. Forty-nine children (75%) were hospitalised for more than 10 days. Hospitalisation was more prolonged for children with meningitis (19.6 days) compared to those with pneumonia (13.5 days) and septicaemia (9.0 days) ($p < 0.01$).

Acute complications of the disease were documented in 36 children. Thirty-five had convulsions, 11 had subdural effusions, two had coma and one child each had cerebral oedema, cerebral abscess, pleural effusion and empyema thoracis.

Long-term complications were restricted to neurological abnormalities, which were documented in 17 of 41 children with meningitis who survived (41.5%). The abnormalities noted on discharge or subsequent follow-up were as follows: hemiplegia in 10 children, hydrocephalus in six, epilepsy in five, mental retardation in four, spasticity in three and cranial nerve palsies in two. Of all the children with pneumonia, only two developed complications (pleural effusions and empyema thoracis) requiring chest tube insertion. Both children were clinically assessed to have no residual pulmonary abnormalities on subsequent follow-up.

The case fatality rate for invasive HI disease was 12.3% (eight of 65). Of the eight children who died, seven had meningitis and one had septicaemia. Acute complications that contributed to mortality were recorded in three cases – acute hydrocephalus with coning, cerebral oedema with bilateral subdural effusions and cerebral (fronto-temporal) abscess. The mortality due to septicaemia occurred in a one-day-old preterm infant who required ventilatory support soon after delivery for respiratory distress syndrome. His clinical condition deteriorated rapidly and he died

Table I – Age distribution, duration of illness prior to admission, nutritional status (% of expected weight) and length of hospital stay according to diagnosis.

	Age (months)	Duration of illness (days)	% of expected weight	Hospital stay (days)
All patients	13.0 (6, 9, 12)	6.5 (3, 5, 10)	85.5 (76, 83, 95)	16.6 (10, 15, 22)
Meningitis	10.5 (5, 8, 11)	6.3 (3, 5, 10)	84.6 (75, 83, 97)	19.6 (14, 17, 27)
Pneumonia	18.4 (8, 12, 22)	6.8 (3, 6, 7)	88.0 (79, 84, 89)	13.5 (5, 13, 20)
Septicaemia	12.2 (4, 10, 21)	7.8 (2, 9, 14)	92.3 (83, 86, 108)	9.0 (3, 10, 16)
Abscess	30.0	14.0	108.0	15.0

Figures refer to mean (25th percentiles, median, 75th percentiles)

within 24 hours after delivery. Post-mortem intracardiac blood grew HI type b.

HI was isolated from 38 CSF cultures, 47 blood cultures and one pus culture. Sixty-four isolates were serotype b, while in the other 22 isolates, serotyping was not done.

The total white cell count varied from 4,000 – 63,800/mm^3. Twenty (32.8%) had a count of more than 20,000/mm^3, 27 (44.2%) had a count of 10,000 – 20,000/mm^3. Only 14 (23%) had a count of less than 10,000/mm^3. Anaemia (defined as haemoglobin of less than 10g%) was noted in 45 of 63 children where full blood counts were done (71.4%). However, the underlying cause of anaemia was not clearly elucidated.

Analysis of sensitivity pattern of HI to various antibiotics was obtained from 61 strains. The results are shown on Table II. Of the 7 strains resistant to ampicillin, three were cases of meningitis and the other four were cases of pneumonia. Only one strain was noted to be resistant to chloramphenicol. The strain was also resistant to cefotaxime and cefoperazone but was sensitive to ampicillin and cefuroxime. It was cultured from CSF of an 11-month-old infant child with meningitis complicated by ventriculitis and acute hydrocephalus. He was treated for six weeks with ampicillin/chloramphenicol and had a ventriculoperitoneal shunt insertion. He made a full recovery and on follow-up, had no documented neurological abnormality. All the resistant strains to ampicillin and chloramphenicol were isolated in children presented before 1992.

Table II – Sensitivity pattern of H. influenzae isolates

Drug	No. sensitive/	Sensivity (%)
Penicillin	41/49	83.7
Ampicillin	50/57	87.7
Erythromycin	37/39	94.9
Co-trimoxazole	26/29	89.7
Chloramphenicol	54/55	98.2
Cefuroxime	27/30	90.0
Cefotaxime	7/8	87.5
Ceftriaxone	1/1	100

DISCUSSIONS

Invasive HI disease occurred at a young age group in our population (median age of 9 months). This conforms to the earlier study by Puthucheary in Kuala Lumpur[8] where she found that all the children were below two years of age. The age distribution of our cases are also similar to that of other less industrialised populations such as Thailand[10], native population of Australia[11] and North America[12], Chile[13] and Israel[14]. This is notably different from Western countries. Whereas 89.1% of our cases were below two years of age, 53.5% of patients in Switzerland[15], 54% in Sweden[16], 59% in Finland[17], 64% in the Netherlands[18] and approximately 70% in the US[19], were in this age group.

Peak incidence was noted in October to December with a smaller peak in February and March, which corresponds to the rainy season. Similar association with rainy season was noted in the two series from Thailand[10,20]. Studies from Israel[14] and the US[19] suggested a bimodal distribution with a major peak in winter and a less marked peak in early summer. On the other hand, a study from South Africa only noted a single peak corresponding to winter months[21]. The seasonality of the disease may also vary among populations in the same area[22]. These observations have led to the suggestion that viral infection may predispose children to invasive HI infection although the exact mechanism is still under investigation[23].

In this study, we found meningitis to be the most common manifestation (64%), followed by pneumonia (29.3%) and septicaemia (5.3%). This spectrum is in accord with a study by Puthucheary[8] and previous published data from various Asian and African countries[10,21,24]. Our data reaffirmed the fact that meningitis is the major manifestation of invasive HI disease as previously reported in most studies throughout the world.

Pneumonia is the second most common presentation of HI disease. This is consistent with studies from developing countries like Thailand[10] and South Africa[21]. It is believed that HI may be responsible for some 2.2 million pneumonia cases and 515,000 paediatric deaths annually world-wide[5]. The number of cases of HI pneumonia in our study was probably an underestimation. Blood cultures were not

routinely done in all patients presenting with acute respiratory tract infections. In addition, blood cultures may be negative in cases of bacterial pneumonia. Studies have shown that the ratio of positive blood cultures to lung aspirates in children with acute bacterial pneumonia varies from 1:4 to 1:8[25].

We have also found that 13.5% of our cases had both meningitis and pneumonia. The association of pneumonia with meningitis was observed in several previous studies. Puthuchery[8] found 10.8% while Likutnikul[10] reported 28%. This association emphasises the need for serious consideration for CSF examination in infants with HI pneumonia and chest roentgenogram for children with HI meningitis.

Epiglottitis is usually reported as a major entity of invasive HI disease in Western Europe and the US but is rarely reported in indigenous populations and in non-industrialised countries[26]. We found no case of epiglottitis, as had series from Thailand[10] and Hong Kong[24], while reports from Israel[14], Aboriginal Australians[11], Alaskan Eskimos[25], American Indians[12], Chileans[13] and Saudi Arabians[28] showed very low incidences of the disease. Postulations regarding such difference include possibility of genetic predisposition or simply a reflection of age-specific susceptibility to the disease[29].

In this study, we found that seven children had underlying diseases (10.8%). The increased risk of HI disease in children with pre-existing medical illnesses had previously been described[30,31]. In a population-based study in Sydney, McIntyre found that 6% had significant underlying diseases compared to only 1% in a matched-controlled group[32]. Higher figures were noted in hospital-based studies from Hong Kong[24] and Thailand[10] where 25.3% and 30% of children, respectively, had underlying medical illnesses. Higher figures found in hospital-based studies may be due to diagnostic bias as children with underlying diseases were more likely to be admitted to hospitals and were also more likely to have blood cultures taken.

The acute impact of the disease was significant in that the total hospital stay amounted to 1061 days and 75% of children were hospitalised for more than 10 days. These findings were remarkably similar to the studies in Israel and South Africa where 64% and 72% of children were hospitalised for more than 10 days, respectively[14,21].

Our case fatality rate of 12.3% was consistent with those of other developing countries, where it ranged from 12% – 47%[13,33], but considerably higher when compared to the figure from the Western countries (1%-5%)[15-17]. Majority of our cases had meningitis. Morbidity was significant but was exclusively seen in patients with meningitis where over 40% of survivors had at least one neurological abnormality. The rate was probably an underestimation since deafness was not consistently recorded in the children's notes. Moreover, proper hearing assessment was not done routinely in all cases prior to discharge.

Peripheral white cell counts showed a wide range of cell numbers with more than half of the cases having leukocytosis, similar to that reported by Likutnikul[10] and Asmar[34]. Anaemia was also a common finding with 71.4% of cases having haemoglobin less than 10g%. The association of HI (especially type b) meningitis and anaemia on admission is well known. Accelerated red blood cell destruction and diminished erythropoeisis may play a role. The haemolysis has been shown to be partially due to a decrease in red blood cell deformability[35].

HI strains resistant to both ampicillin and chloramphenicol, rare in the late 1970s, have increasingly been reported in the 1980s. Majority of the resistant strains were from Spain, developing countries like Thailand, South Africa, Kuwait and Mexico, and developed countries like the US, Britain and Australia[36]. Fortunately, except for endemic multiple resistance in Spain, other reports remain sporadic. In our study, 12.3% of the strains tested were resistant to ampicillin whereas, all cases except one, were sensitive to chloramphenicol. More importantly, we found that the resistant strains were isolated between 1987 and 1991 and that all strains after that remained sensitive to these two antibiotics. The present combination of ampicillin with chloramphenicol as an empirical treatment for meningitis in our institution is thus still justified.

The small number of cases (65) encountered in our hospital is probably an underestimation of the true burden of invasive HI disease in our community. Apart from the facts that blood culture is not routinely done for all febrile children and the low yield of positive blood culture in pneumonia that we have alluded before, HI is a difficult organism to culture. Special attention needs to be given to the culture media. HI may be missed entirely if proper medium is not used[37]. In addition, many of the children had received oral antibiotics prior to admission which further reduced the positive yield from culture. Another important explanation was the low number of lumbar puncture done in suspected cases of meningitis due to parental refusal to give consent for the procedure[38].

The present study suggests that invasive HI disease is important and contributes considerably to mortality and morbidity in children. The availability of HIB vaccine and its proven efficacy in reducing incidence of HI disease warrants serious consideration. However, further data from community based, prospective studies to delineate the true incidence and severity of the disease in Malaysia is urgently required so that cost effective analysis can be performed before routine immunisation with HIB vaccine is recommended in Malaysia.

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