SYSTEMIC *HAEMOPHILUS INFLUENZAE* DISEASE IN THAI CHILDREN

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Abstract. Fifty patients with systemic *Haemophilus influenzae* disease were indentified by hospital chart review between 1980-1992. The age distribution varied from 8 days to 14 years; the mean age of the patients was 12.7 months. The peak incidence was between 4 and 6 months of age. There were 27 male patients and 23 female patients for a male : female ratio of 1.17 : 1. The relative frequencies of 79 clinical entities encountered in 50 patients are as follows : meningitis 55.7%, bacteremia 13.9%, pneumonia 25.3%, cellulitis 2.5% arthritis 1.3%, septic shock 1.3%. There were 23 patients (46%) who had more than one disease entity. Most of the patients were anemic (Hb< 10 gm%) when hospitalization. Sixty-four percent of the patients had early complications. The mortality rate was 8%. Although serotyping was not done from the isolates, at least 33 cerebrospinal fluid samples were postitive for *H. influenzae* type b capsular antigen by counterimmunoelec-trophoresis. The percentage of susceptible *H. influenzae* to penicillin, ampicillin, chloramphenicol, co-trimoxazole were 57.1%, 76.4%, 87.5% and 54.2%, respectively. There was no strain resistant to third generation cephalosporin. Our data indicate that *H. influenzae* is a serious and life threatening infection. Early diagnosis and proper treatment will reduce the morbidity and mortality rates. For prevention of infection, an appropriate strategy for vaccination is required.

INTRODUCTION

Haemophilus Influenzae is one of the important bacteria causing serious infections in children. The organism is responsible for a varied spectrum of disease ranging from asymptomatic colonization in the upper respiratory tract to severe systemic diseases such as meningitis, pneumonia, acute epiglottitis, cellulitis, arthritis, osteomyelitis, pericarditis, otitis media, bacteremia, etc. Most of these serious infections have been attributed to encapsulated, typable strains, type b. Those most susceptible to disease are children younger than 2 years of age (Dajani *et al*, 1979). There have been few studies of *H. influenzae* disease from the Western Pacific and South East Asian regions (Sirinavin, 1993). Therefore, we performed a retro-specive study to present our experience with 50 children who had systemic *H. influenzae* infection.

MATERIALS AND METHODS

We reviewed the medical records of infants and children discharged from the Department of Pediatrics, Chulalongkorn Hospital aged 0-14 years, from whom *H. influenzae* was cultured or a positive antigen detection test for *H. influenzae* type b (Hib)

was obtained from normally sterile clinical specimens [blood, cerebrospinal fluid (CSF), pleural fluid, pus, synovial fluid, bone aspiration], during the period from January 1980 to December 1992. The following information was obtained from the record of each patient : age, sex, date of admission, clinical diagnosis, total white blood cell counts, bacteriologic results, sensitivity pattern, underlying disease, complication and survival or death of the patient from this infection.

RESULTS

The age of the 50 patients were from 8 days to 14 years with a median age of 6 months and a mean age of 12.7 months. The age distribution for all patients is shown in Fig 1. Eighty-six percent of all cases were younger than 2 years old with peak incidence between 4-6 months of age. There were 27 male patients and 23 female patients for a male-female ratio of 1.17:1. The monthly distribution showed a peak incidence in January, February and March which accounted for 54% (Fig 2). Five of the fifty cases were from orphanages.

The relative frequencies of 79 clinical entities found in 50 patients are shown in Table 1. Bactere-mia, meningitis, pneumonia and cellulitis were de-
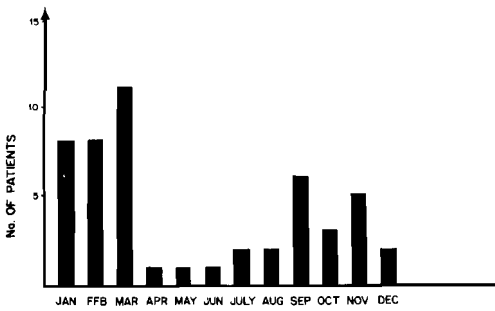
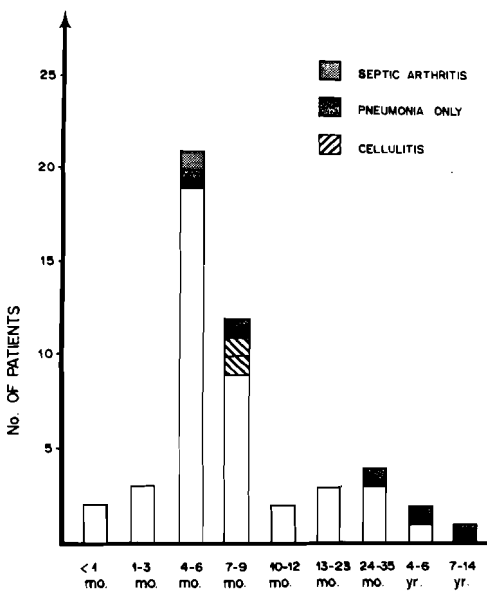Fig 1–Monthly distribution of 50 cases of *H. influeenzae* infections.

Fig 2–Age distribution and type of infection.

Table 1

Relative frequencies of different clinical entities due to *H. influenzae* infection.

Clinical entity	No. of cases	(%)
Meningitis	44	55.7
Bacteremia	11	13.9
Pneumonia	20	25.3
Cellulitis	2	2.5
Arthritis	1	1.3
Septic shock	1	1.3

tected in one patient. In each of 4 patients three disease entities were noted. Bacteremia, meningitis and pneumonia occured in two patients; bacteremia, meningitis and cellulitis in one; bacteremia, meningitis and septic shock in one. Two disease entities were detected in 18 patients : bacteremia and meningitis occured in three patients, bacteremia and pnueumonia in three; meningitis and pneumonia in twelve. In the remaining 27 patients, only one disease entity was noted. There was no occult *H. influenzae* bacteremia in this study.

Underlying diseases were noted in 15 patients, hemoglobinopathy was documented in 4 patients, glucose 6-phosphate dehydrogenase deficiency in one, malnutrition in seven, and one each of bronchopulmonary dysplasia, reactive airway disease, and congenital rubella.

H. influenzae was isolated from cerebrospinal fluid cultures of 31 patients, 11 blood cultures, 1 pleural fluid culture, 1 joint fluid culture and 1 pus culture. Serotyping was not done from the isolates. Thirty-three cerebrospinal fluid samples were positive for *H. influenzae* type b capsular antigen by counterimmunoelectrophoresis.

The total white blood cell (WBC) count varied from 3,700-43,450/mm^3 18 of 50 (36%), had total WBC count of $\geq$ 20,000/mm^3, only 13 of 50 (26%) had total WBC $\leq$ 10,000/mm^3. Anemia defined by hemoglobin less than 10 gm/dl was noted in 34 patients. Of the 34 patients, 5 patients had underlying hematologic diseases, 8 patients had iron deficiency anemia. The remaining patients' anemia had not been clearly elucidated.

Analysis of sensitivity pattern of *H. influenzae* to various drugs was obtained from 35 strains. The susceptibility testing of each drug was not done to all strains of *H. influenzae*. The results are shown in Tables 2,3. There was one strain of *H. influenzae* that was resistant to ampicillin and chloramphenicol, five strains resistant to ampicillin and cotrimoxazole and two strains resistant to chloramphenicol and co-trimoxazole.

Four deaths occurred among 50 patients; the sex and mortality from *H. influenzae* disease are shown in Table 4. Three occurred in patients who had meningitis with complications (subdural empyema and ventriculitis 1, subdural empyema and pneumonia 1, bacteremia with septic shock 1) and one occurred in a patient with pneumonia who subsequently developed a lung abscess.

Table 2

Sensitivity pattern of *H. influenzae* isolates during 1980-1992.

Drug	No.sensitive/tested	Sensitivity(%)
Penicillin	12/21	57.1
Ampicillin	26/34	76.4
Erythromycin	25/29	86.2
Co-trimoxazole	13/25	52
Chloramphenicol	28/32	87.5
Cefamandole	17/17	100
Cefuroxime	6/6	100
Ceftriaxone	13/13	100
Cefotaxime	19/19	100

Table 3

Sensitivity pattern of *H.influenzae* isolates.

Drug	Sensitivity (%) 1980-1986	Sensitivity(%) 1987-1992
Penicillin	6/12 (50)	6/9 (66)
Ampicillin	12/14 (85.7)	15/20 (75)
Erythromycin	8/11 (72.7)	17/18 (94.4)
Co-trimoxazole	6/11 (54.5)	7/14 (50)
Chloramphenicol	11/14 (78.5)	17/18 (94.4)
Cefamandole	8/8 (100)	9/9 (100)
Cefuroxime	2/2 (100)	4/4 (100)
Ceftriaxone		13/13 (100)
Cefotaxime	5/5 (100)	14/14 (100)

Table 4

Sex and mortality of patients with *H. influenzae* diseases.

Sex	No.	Deaths
Male	27	3 (11%)
Female	23	1 (4.3%)
Total	50	4 (8%)

Complications developed in 32 patients (64%); subdural empyema was the most frequent (Table 5). Eight patients had more than one type of complication.

Table 5

H. influenzae diseases : complications.

Type of complications	No. of cases
Subdural empyema	12
Subdural collection	11
Convulsive disorder	8
Hydrocephalus	5
Phlebitis	2
Cerebritis	1
Brain infarct	1
Epidural abscess	1
Ventriculitis	1
Pleural effusion	1
Pleural empyema	1
Lung abscess	1

DISCUSSION

Our data demonstrated that meningitis was the predominant manifestation of system *H. influenzae* disease which is similar to reports from various parts of the world (Dijani *et al*, 1979, Takala *et al*, 1989; Tudor-Williams *et al*, 1989; Kristensen *et al*, 1990). The second most common entity was pneumonia, accounting for 20 of 50 cases (40%) which appears to be comparable to a report from Israel (Halfon-Yaniv and Dagan, 1990), whereas lower percentages of pneumonia cases were reported from Europe and United States (Dajani *et al*, 1979; Takala *et al*, 1989; Tudor-Williams *et al*, 1989). It was suggested that *H. influenzae* plays an important role in lower respiratory infection in developing countries (Munson *et al*, 1989).

H. influenzae pneumonia cannot be distinguished clinically or radiologically from other pneumonia. *H. influenzae* bacteremia is commonly associated with other systemic infections. We found no occult bacteremia in our report. Out of 292 patients with systemic *H. influenzae* disease. Dajani *et al* (1979) found six patients not associated with a systemic infection. In such instances upper respiratory tract infection, otitis media or an underlying disease is commonly present.

H. influenzae is not a common pathogen causing cellulitis. Bada and Wright (1974) reported 73 patients with cellulitis admitted over an 8 year period;

only four cases (5.5%) of Hib infection were noted. Dajani *et al* (1979) reviewed 74 patients with Hib cellulitis and found that the most common sites were the face, head and neck (74%), the remaining 26% of cases were at the extremities. Whereas buccal cellulitis was the most commonly reported entity (34%), it was not found in this report. In the two cases reported here, cellulitis was noted at the extremities, one in the left hand, the other one was in the right leg. In both cases CSF and blood culture grew *H. influenzae* and had positive antigen detection test for *H. influenzae* type b in the CSF. Bacteremia is very common in patients with Hib cellulitis (Dajani *et al*, 1979).

Epiglottitis is a mojor entity of invasive Hib disease reported in Western Europe (Takala *et al*, 1989; Tudor-Williams *et al*, 1989; Claesson *et al*, 1984), but is a rare entity in indigenous populations and in non-industrialized countries (McIntyre, 1993). This entity was not seen either in this report or in Sirinavin's (1993) series. Other invasive infections due to *H. influenzae* besides meningitis and pneumonia are uncommon.

The peripheral white cell count showed a wide range of cell numbers with nearly half of the cases having leukocytosis, almost identical to that reported from Detroit (Asmar *et al*, 1978). The association of anemia with nearly half of the cases was striking. Anemia associated with *H. influenzae* meningitis had been described over 40 years ago (Schiavone and Rubbo, 1953). Kaplan and Oski (1980) suggested that the anemia was the result of accelerated red cell destruction. Sills *et al* (1987) found that the hemolysis in patients with *H. influenzae* meningitis results from a decrease in red cell deformability.

Systemic *H. influenzae* disease occurs in Thai populations in a very young age group (Sirinavin, 1993). Eighty-six percent of all the cases occur in children under 2 years of age. There were 2 patients aged 8 and 26 days old, both of whom had meningitis with positive *H. influenzae* type b capsular antigen in CSF. Neonatal *H. influenzae* infection has been described, only half were *H. influenzae* type b (Khuri-Bulos and McIntosh, 1975). *H. influenzae* disease in neonates is indistinguishable clinically from infections caused by other organisms. It has been suggested that neonatal *H. influenzae* infections are increasing (Khuri-Bulos and McIntosh, 1975; Pickering and Simon, 1977). The peak incidence between 4-6 months of age corresponds to the period where the lowest level of protective antibody to the cap-

sular polysaccharide of *H. influenzae* type b was found in Thai children (Lolekha, 1993). In contrast to Western European countries such as Finland (Takala *et al*, 1989) the median age was 2.3 years and only 3% were younger than 6 months old, while in England (Tudor-Williams *et al*, 1989) 10% were younger than six months of age. The age distribution of systemic *H. influenzae* disease in Thai children is similar to that reported in the Gambia (Bijlmer *et al*, 1990), Papua New Guinea, Chile, Nigeria, Senegal (Munson *et al*, 1989) and Alaskan Eskimos, Navajo Indians and Australian Aborigines (Ward *et al*, 1986 Rosenthal *et al* 1988).

Twenty-seven cases (54%) occurred in January, Febuary and March, which is almost identical to a report from another center in Bangkok (Sirinavin, 1993), this peak corresponded with acute lower respiratory infections in children under five years of age. It has been suggested that some viral infections predispose to Hib invasive disease (Krasinski *et al*, 1987; Kaplan *et al*, 1981; Takala *et al*, 1993). Differences in seasonality of disease were noted. A biphasic seasonal pattern of the occurrence of disease has been observed for *H. influenzae* meningitis in the United States. One peak of illness occured in October and November and a second between March and May (Wilfert, 1990). The seasonality of the disease may also vary among populations in the same area. In Southern Israel, an area that contains two ethnic populations, Jews and Bedouins, the peak seasonal incidence for Jews was during fall and coincided with respiratory disease, whereas the peak seasonal incidence for Bedouins was during summer, parallel with diarrhea (Halfon-Yaniv and Dagan, 1990).

The multiple resistant strains of *H. influenzae* gainst ampicillin and chloramphenicol are becoming more common (Simasathien *et al*, 1980; Nelson, 1980; Philpott-Haward and Williams, 1982; Kenny *et al*, 1980). The increase susceptibility of *H. influenzae* to chloramphenicol during 1987-1992 compared to 1980-1986 may have been due to decreased use of chloramphenicol. The license of choramphenicol powder supply in sachet that can be bought over the counter has been revoked since March 1987 by the Food and Drug Administration of Thailand.

The mortality in this study was slightly higher than that (5.8%) reported by Dajani *et al* (1979), with the same finding that there were more males than females. The recent development of safe and efficacious Hib conjugate vaccines has been well

described; in areas where Hib conjugate vaccines have been used, marked reductions in disease incidence have been documented (Ward, 1993). More information concerning the true incidence and severity of the disease in developing countries is required so that priority setting and cost-effective analyses can be performed before routine immunization with Hib vaccines is recommended in this region (Wattanasri, 1993).

References

Asmar BI, Slovis TL, Reed JO, Dajani AS. *Haemophilus influenzae* type b pneumonia in 43 children. *J Pediatr* 1978; 9 : 389-93.

Bada H, Wright SP. *Haemophilus influenzae* cellulitis : an overview of clinical manifestations and treatment. *Clin Pediatr* 1974; 13 : 658.

Bijlmer HA, Van Alphen L, Greenwood BM, *et al.* The epidemiology of *Haemophillus influenzae* meningitis in children under five years of age in the Gambia, West Afria. *J Infect Dis* 1990; 161 : 1210-5.

Claesson BA, Trollfors B, Ekstrom-Jodal B, *et al.* Incidence and prognosis of acute epiglottitis in children in Swedish region. *Pediatr Infect Dis* 1984; 3 : 534-8.

Dajani AS, Asmar BI, Thirumoorthi MC. Systemic *Haemophilus influenzae* disease : an overview. *J Pediatr* 1979; 94 : 355-64.

Halfon-yaniv I, Dagan R. Epidemiology of invasive *Haemophilus influenzae* type b infections in Bedouins and Jews in Southern Israel. *Pediatr Infect Dis J* 1990; 9 : 321-6 ·

Kaplan KM, Oski FA. Anemia with *Haemophilus influenzae* meningitis. *Pediatrics* 1980; 65 : 1101.

Kaplan SL, Tabler LH, Frank AL, *et al.* Nasopharyngeal viral isolates in childern with *Haemophilus influenzae* type b meningitis. *J Pediatr* 1981; 99 : 591-3.

Kenny JF, Isburg CD, Michaels RH. Meningitis due to *Haemophilus influenzae* type b resistant to both ampicillin and chloramphenicol. *Pediatrics* 1980; 66 : 14-6.

Krasinski K, Nelson JD, Butler S, *et al.* Possible association of *Mycoplasma* and viral respiratory infections with bacterial meningitis. *Am J Epidemiol* 1987; 125 : 494-508.

Kristensen K, Kaaber K, Ronne T, Olesen Larsen S, Henrichsen J. Epidemiology of *Haemophilus influenzae* type b infections among children in Denmark in 1985 and 1986. *Acta Paediatr Scand* 1990; 79 : 587-92.

Khuri-Bulos N, McIntosh K. Neonatal *Haemophilus influenzae* infection. Report of eight cases and review of the literature. *Am J Dis Child* 1975; 129 : 57-62.

Lolekha S. Prevalence of immunity against *Hemophilus influenzae* type b in Thai infants and children. Abstract presented at 36th in Thai Congress of Pediatrics 22-23 April, 1993, Bangkok.

McIntyre P. Worldwide epidemiology of invasive *Haemophilus influenzae* type b disease. *JAMA SEA* 1993; 9 (Suppl) : 5-10.

Munson RS, Kabeer MH, Lenoir AA, Granoff DM. Epidemiology and prospects for prevention of disease due to *Haemophilus influenzae* in developing countries. *Rev Infect Dis* 1989;11 (suppl 3) : S 558-97.

Nelson JD. The increasing frequency of beta-lactamase producing *Haemophilus influenzae* b. *JAMA* 1980; 244 : 239.

Pickering LK, Simon FA. Reevaluation of neonatal *Hemophilus influenzae* infections. *South Med J* 1977; 70 ; 205.

Philpott-Howard J, Williams JD. Increase in antibiotic resistance in *Haemophilus influenzae* in the United Kingdom since 1977: report of study group. *Br Med J* 1982; 284 : 1597-9.

Rosenthal J, Dagan R, Press J, *et al.* Differences in the epidemiology of childhood community-acquired bacterial meningitis between two ethnic populations cohabiting in one geographic area. *Pediatr Infect Dis J* 1988; 7 : 630-3.

Schiavone DJ, Rubbo SD. Anemia associated with *Haemophilus influenzae* meningitis. *Lancet* 1953; 2 : 696.

Sills RH, Caserta MT, Landaw SA. Decreased erythrocyte deformability in the anemia of bacterial meningitis. *J Pediatr* 1982; 101 : 395-8.

Simasathien S, Duangmani C, Echeverria P. *Haemophilus influenzae* type b resistant to ampicillin and chloramphenicol in an orphanage in Thailand. *Lancet* 1980; 2 : 1214-7.

Sirinavin S. Regional epidemiology of invasive *Haemophilus influenzae* type b disease. *JAMA SEA* 1993;9 (suppl) : 11-5.

Takala AK, Eskola J, Peltola H, Makela PH. Epidemiology of invasive *Haemophilus influenzae* type b disease among children in Finland before vaccination with *Haemophilus influenzae* type b conjugate vaccine. *Pediatr Infect Dis J* 1989; 8 : 297-302.

Takala AK, Meurman O, Kleemola M, *et al.* Preceding respiratory infection predisposing for primary and secondary invasive *Haemophilus influenzae* type b

disease. *Pediatr Infect Dis J.* 1993; 12 : 189-95.

Tudor-Williams G, Frankland J, Issacs D, *et al.* *Haemophilus influenzae* type b in the Oxford region. *Arch Dis Child* 1989; 64 : 517-9.

Word J. *Haemophilus influenzae* type b conjugate vaccines. *JAMA SEA* 1993; 9 (suppl) : 16-9.

Ward JI, Lum MK, Hall DB, *et al.* Invasive *Haemophilus influenzae* type b disease in Alaska : Background epidemiology for a vaccine efficacy trial. *J Infect Dis* 1986; 153 : 17-26.

Wattanasri S. Practical considerations for *Haemophilus influenzae* type b immunization programs. *JAMA SEA* 1993; 9 (suppl) : 24-7.

Wilfert CM. Epidemiology of *Haemophilus influenzae* type b infections. *Pediatrics* 1990; 85 : 631-5.