CHILDHOOD MELIOIDOSIS IN NORTHEASTERN THAILAND

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INTRODUCTION

Melioidosis is a tropical disease caused by the gram-negative bacillus *Pseudomonas pseudomallei*. Most cases occur in countries within a belt between 20°N and 20°S of the equator, principally in Southeast Asia and Northern Australia (Howe *et al.*, 1971). The clinical spectrum of melioidosis in man varies so greatly that the classification differs from place to place. In 1985, the Infectious Disease Association of Thailand devised a classification based on 595 cases reported at the National Workshop on Melioidosis (Infectious Disease Association of Thailand, 1985). This includes six categories as follows: 1) disseminated septicaemic (the most severe form with a high rate of septic shock and death), 2) non-disseminated septicaemic, 3) localized, 4) transient bacteremic, 5) probable (seropositive with appropriate clinical findings), 6) subclinical (only seropositive). Although the majority of cases so far reported have been adults, increasing numbers of cases in children have been described (Patamasucon *et al.*, 1975; Wiangnon *et al.*, 1985; Thisyakorn, 1986). This report is to present 18 cases of childhood melioidosis seen at a 1000-bed hospital in Northeastern Thailand.

MATERIALS AND METHODS

The case notes of 18 children with melioidosis who were admitted to Maharaj Nakhon Ratchasima Hospital (250 km from Bangkok) were reviewed retrospectively. Sixteen cases were admitted to the Department of Pediatrics and the other two to the Department of Otolaryngology.

For each case, the diagnosis of melioidosis was based on either positive culture for *P. pseudomallei* or positive indirect hemagglutination (IHA) titer of 1:80 or higher (Leelarasamee, 1985). *P. pseudomallei* isolated from clinical specimens were identified by their colony morphology, staining reaction, motility, and biochemical and growth characteristics (Hugh *et al.*, 1980). The antimicrobial susceptibility testing was performed by using the disk agar diffusion method (Barry *et al.*, 1980). The clinical classification of the cases was according to the criteria of the Infectious Disease Association of Thailand.

RESULTS

The mean age of the 18 patients was 6.8 years with a range from eight months to 15

years. The majority of the children were between the ages of one and ten years. Eleven patients were male (M:F ratio of 1.6:1). Twelve cases occurred between August and October, the late months of the rainy season. The diagnosis of melioidosis was made in all while the patients were alive except the three dead cases.

The clinical features, antimicrobial therapy, and outcome are summarized in Table 1. Cases are numbered in order of date of presentation. Localized melioidosis was the most common clinical form (12 cases, 66.7%). Six of the twelve localized cases had pneumonia, and 3 had abscesses (parotid gland, submandibular node, and spleen and liver respectively). The other three had the newly recognized syndrome of pharyngocervical melioidosis (Silpapojakul *et al.*, 1985) though, in one case (case 10), only tonsillar exudate was found without enlargement of cervical nodes.

Ten cases had abnormal chest roentgenograms, including four septicaemic cases. A summary of the x-ray findings is shown in Table 2. Confluent bronchopneumonia was seen in both the septicaemic and the localized form but the more common pattern in the latter was mixed infiltration with cavity formation and pleural reaction such as pleural effusion or loculated empyema. Calcifications was not found in any of the cases.

Nine cases (50.0%) had associated diseases; five had dengue hemorrhagic fever (DHF), two had thalassemia, and one each had aplastic anemia and glucose-6-phosphate dehydrogenase deficiency.

In all five cases with DHF melioidosis was diagnosed during the convalescent or post-shock stage as a cause of pyrexia with or without pneumonia. The diagnosis of DHF was serologically confirmed in the last 3 cases as shown in Table 3. Case 1 and 2 were diagnosed clinically by using World Health Organization criteria (WHO, 1986). Both of them had fever, bleeding, hepatomegaly, hemoconcentration and thrombocytopenia with the addition of shock in case 2. Two out of five cases had recovered from dengue shock syndrome (DSS) complicated by hepatic encephalopathy (cases 15 and 16). Melioidosis in case 14 was classified as the probable form because only prolonged fever and a high IHA titer were found with negative investigations including chest roentgenographic and abdominal ultrasonic examinations.

In one thalassemic case (case 7), melioidosis was diagnosed after splenectomy was performed for hypersplenism. Multiple nodules of the spleen and liver were recorded as operative findings. Postoperatively the patient had prolonged fever despite vigorous antimicrobial therapy. Antituberculous drugs were prescribed later without improvement although the splenic tissue was reported to be fibrocaseous suggestive of tuberculosis. A melioidosis IHA was done and gave a titer of 1:320. Kanamycin was administered in combination with cotrimoxazole for two weeks after which it was replaced by tetracycline. The fever slowly subsided and had disappeared by four months of chemotherapy. Repeated ultrasonic examination of liver after one year of treatment still showed multiple, small, low echogenic lesions with ill-defined borders. However, the patient's general condition was good and his body weight had increased by 11 kg. He still appeared well after antimicrobials were stopped although IHA titer rose up to 1:640.

The organisms isolated from all 12 patients had similar antibiotic susceptibilities. All were sensitive to chloramphenicol, cotrimoxazole and kanamycin. One was resistant

Table 1

Summary of clinical findings in 18 cases of childhood melioidosis.

No.	Age (yr)	Sex	Clinical	Primary site of infection	Culture source	IHA titer	Associated disease	ATB	Duration (wks)
1*	2	F	DS	Unknown	Pus+	ND	DHF	Cl + A	1
2	11	M	L	Lungs	Pleural	ND	DHF/DSS	Ch	10
3	12	F	L	Pharyngo-cervical	Pus+	1:2560	–	D + C	4
4*	15	M	DS	Facial cellulitis	Blood	ND	Aplastic anemia	Cl + A	1d
5	7	M	L	Pharyngo-cervical	Pus+	>1:1280	–	D + C	8
6	10	M	L	Lungs	Pleural	1:320	–	D + C	4
7	15	M	L	Liver & spleen	–	1:640	Thalassemia	C + K/T	52
8	10	M	L	Parotid gl.	Pus	ND	–	C	2
9	2	F	L	Submandi-bular node	Pus	ND	–	C + A	2
10	6	M	L	Pharyngo-cervical	–	1:160	–	D + C	4
11	8m	F	L	Lungs	Pleural	1:320	Thalassemia	C + K/Ch	10
12	6	M	Non-Ds	Lungs	Blood	1:2560	G-6-PD	P + K, D + C	8
13	6	F	Non-Ds	Lungs	Blood	>1:5120	–	P + K, D + C	6
14	6	M	Probable	–	–	1:2560	DHF	D + C	8
15	3	F	L	Lungs	–	>1:1280	DHF/DSS‡	C + K	3
16	4	M	L	Lungs	–	1:320	DHF/DSS‡	C + K	2
17	2	F	L	Lungs	–	1:320	–	C (+ K in 1st 2 wks)	6
18*	4	M	DS	Lungs	Blood	ND	–	Ce + G	1d

* = death

\+ case 1 = pus from brain, visceral organs, knee joints.
case 3 and 5 = pus from cervical node and tonsillar exudate.

‡ complicated with hepatic encephalopathy.

DS = disseminated septicaemia; L = localized; Pleural = pleural fluid; ND = not done. ATB = antibiotics; Cl = cloxacillin; A = amikacin; Ch = chloramphenicol; D = doxycycline; C = cotrimoxazole; K = kanamycin; T = tetracycline; P = piperacillin; Ce = cefazolin; G = gentamicin.

Table 2
Chest roentgenographic findings in various clinical forms of childhood melioidosis*.

X-ray pictures	Disseminated septicemic	Non-disseminated septicemic	Localized
Nodular infiltrates	1	–	–
Confluent broncho-pneumonia	1	2	2
Mixed infiltration+	–	–	1
with cavity	–	–	3
Pleural reaction	1	–	3

* some had more than one finding.
\+ mixed pattern of mottled, patchy and streaky infiltration.

Table 3
Serology for dengue infection in 3 cases of melioidosis.

Case No.	IgM (units) 1st/2nd	IgG (units) 1st/2nd
14	71/191	508/516
15	114/191	562/485
16	121/243	499/477

IgM >= 50 units is positive for dengue.

to tetracycline. Among the aminoglycosides tested, excluding kanamycin, amikacin was the most effective. With the third-generation cephalosporins, all of six strains tested were sensitive to ceftazidime, cefotaxime and ceftriaxone. The broad-spectrum penicillin, piperacillin, was not studied *in vitro* but produced a good clinical response in the two non-disseminated septicaemic cases (cases 12 and 13).

Three cases died and all were diagnosed as having the disseminated septicaemic form of melioidosis at postmortem. They were treated empirically as septicaemia of unknown etiology using antimicrobials effective against *Staphylococcus aureus* and gram-negative enteric bacilli but which would have been inactive against *P. pseudomallei*. Excluding these three fatal cases, the median duration of antimicrobial therapy in fifteen survivors was 5.25 week. The overall mortality rate was 16.7%.

DISCUSSION

Melioidosis is considered to be rare in children (Leelarasamee, 1986).. In Thailand, a review of one hundred cases (Punyagupta, 1983) revealed only thirteen to be in children, the youngest age being 7 months. However, neonatal melioidosis has also been reported (Osteraas *et al.*, 1971; Lumbiganon *et al.*, 1985).

The range of clinical manifestations of the disease in adults and children is similar. Almost every organ can be involved, the lung is most frequently affected (Everett *et al.*, 1975; Girard *et al.*, 1976; *Rode et al.*, 1981). The study of Dhiensiri *et al.*, (1986) showed that nodular infiltration was the most common x-ray picture in acute septicaemic cases. However, this form of the disease is difficult to distinguish from septicaemia caused by *Staphylococcus aureus* or gram-negative organisms other than *P. pseudomallei*. Delay in diagnosis and treatment occurs unavoidably, hence the high mortality in this group of patients (Leelarasamee, 1986). In the chronic form, melioidosis can mimic pulmonary tuberculosis either clinically, radiographically or histopathologically (Spotnitz *et al.*, 1967; Piggott *et al.*, 1970; Everett *et al.*, 1975). Certain radiographic findings may help to differentiate these two diseases such as the sparing of the apical

region and the rarity of calcification in melioidosis (Dhiensiri *et al.*, 1988).

The definitive means of making a diagnosis of melioidosis is by culture of the causative organism, while serology is employed as a confirmatory method. However, definitive diagnosis is sometimes impossible in localized cases particularly cases of lung involvement without pleural reaction, since the patient may not be able to produce sputum for culture. If the disease is suspected, the diagnosis can be made on the basis of positive serology and a clinical response to appropriate chemotherapy (Guard *et al.*, 1984).

The localized form the so-called pharyngocervical melioidosis was recently reported from Southern Thailand (Silpapojakul *et al.*, 1985). The principal features are fever, sore throat and cervical lymphadenopathy with abscess formation. The diagnosis is confirmed by the isolation of *P. pseudomallei* from either cervical abscess pus or throat swab. Although this clinical presentation can resemble a variety of bacterial infections, more cases would be recognised if melioidosis was considered in the differential diagnosis especially in endemic areas.

The importance of associated diseases which may predispose to melioidosis has been stressed (Chayasirisobhon *et al.*, 1976; Lin *et al.*, 1980). The exact role of the immune system in the pathogenesis of melioidosis is not fully understood. Melioidosis may remain latent for a long time and be reactivated by an intercurrent infective illness (Mackowiak *et al.*, 1978). Dengue hemorrhagic fever was recently reported to be associated with melioidosis (Prapphal *et al.*, 1986). The positive dengue virus serology in three out of five cases with a clinical diagnosis of DHF in this report suggests that their initial illnesses were due to dengue virus, and that melioidosis did not account for the whole clinical picture. This and the previous report emphasize the potential role of DHF as another condition which may predispose to or reactivate melioidosis. In other words, melioidosis should be considered in the differential diagnosis in any DHF cases with prolongation or reappearance of fever with or without pneumonia. This will facilitate early diagnosis and commencement of appropriate antibiotics.

P. pseudomallei is susceptible to various antimicrobial agents including some newer drugs (Eickhoff *et al.*, 1970; Everett *et al.*, 1973; Chau *et al.*, 1986). The standard therapeutic regimen comprises of bacteriostatic drugs such as tetracycline or doxycycline, chloramphenicol and cotrimoxazole administered either singly or in combination (So, 1985). Among the newer bactericidal drugs, ceftazidime, piperacillin, carumonam and imipenem are the most active parenteral antibiotics (Chau *et al.*, 1986; Lolekha *et al.*, 1986; Aswapokee *et al.*, 1988) and are potentially useful for the treatment of septicaemic cases, either disseminated or non-disseminated. However, the mortality rate in disseminated group so far is still high although the appropriately combined antimicrobial drugs including some of these new agents were used (Aswapokee, 1986). To obtain a substantial decrease in the mortality rate of disseminated septicaemia, more awareness of the disease, and early treatment with the antimicrobials shown to be effective *in vivo* by controlled clinical studies in a sufficient number of patients are required.

SUMMARY

Eighteen cases of childhood melioidosis in Northeastern Thailand were reviewed. The mean age was 6.8 years with a range from

eight months to 15 years. Twelve cases (66.7%) had localized melioidosis, six of which had pneumonia. Three patients were diagnosed as pharyngocervical melioidosis, the newly recognized syndrome. Nine cases (50.0%) had associated diseases including dengue hemorrhagic fever (DHF) in five cases. In all five cases, melioidosis was diagnosed during the convalescent stage as a cause of pyrexia with or without pneumonia. *Pseudomonas pseudomallei* strains isolated from 12 patients were all sensitive to chloramphenicol, cotrimoxazole and kanamycin. Ceftazidime, cefotaxime and ceftriaxone were also active against all six isolates tested. Three cases died, all were diagnosed as disseminated septicaemic melioidosis at postmortem. The overall mortality rate was 16.7%. The septicaemic form of melioidosis can resemble many diseases such as septicaemia due to *Staphylococcus aureus* or gram-negative organisms other than *P. pseudomallei* while the localized form may mimic pulmonary tuberculosis. A high index of clinical suspicion is required in making a diagnosis of melioidosis, particularly in areas where the disease is endemic.

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