ETIOLOGY OF OBSCURE FEVER IN CHILDREN AT A UNIVERSITY HOSPITAL IN NORTHEAST THAILAND

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Abstract. Obscure fever is not an uncommon problem in Thailand. We studied 25 children with obscure fever admitted to Srinagarind (university) Hospital in Northeast Thailand. The etiology was identified in 52% of the cases: dengue (40%), leptospirosis (8%), and micrococcus septicemia (4%). Two cases with primary dengue infection developed dengue shock syndrome. The case with leptospirosis developed infection-associated, hemophagocytic syndrome. We found no cases of Japanese encephalitis, scrub typhus or murine typhus.

INTRODUCTION

Obscure fever is not an uncommon problem in Thailand. Among adult patients 38% have identified causes, mainly due to some sort of infection, like scrub typhus (prevalence, 7.5%) (Leelarasamee, 2000). Thailand is also an endemic area for leptospirosis and 90% of infections are reported in the impoverished northeast region. Leptospirosis is the cause of 1.1% of obscure fevers in adults. In southern Thailand, scrub typhus is the causative organism of 5.6% of obscure fevers in children (Silpapojakul ***et al,*** 1991). Since the etiology of obscure fever in northeast Thailand is not well described, the authors conducted a prospective, descriptive study to document the etiology of obscure fevers among children.

MATERIALS AND METHODS

Study population

Our study was conducted between August 2002 and 2003 at Srinagarind Hospital, Khon Kaen University, one of the main tertiary referral hospitals in northeast Thailand.

Serum samples were collected from patients between 1 and 14 years of age, having a fever higher than 37.8ºC for between 6 and 21 days, without localizing signs. Informed consent was obtained from the parents and informed assent from the children.

The inclusion criteria of a fever lasting more than 6 days was to try to exclude cases of dengue, which usually has a fever duration of 4.6 ± 1.8 days (Pancharoen ***et al***, 2001). Immunocompromized patients or those with obvious signs and symptoms of a specific infection, such as profuse rhinorrhea, exudative tonsils, mucousy and/or bloody stools or urinary tract symptoms, were excluded.

Clinical data and acute serum samples were collected when the patient satisfied the inclusion criteria. Convalescent serum samples were collected whenever possible, ideally 7-14 days following collection the of the acute serum sample, though the range was actually between 4 and 33 days. All of the serum samples were frozen at -70ºC prior to assay. All of the serum samples were sent to the Regional Medical Science Center Khon Kaen, Ministry of Public Health, Thailand, where they were analyzed for evidence of dengue, Japanese encephalitis (JEV), Leptospira, *O. tsutsugamushi* and *R. typhi* infection.

Diagnostic criteria

Dengue infection, JEV infection, leptospirosis, scrub typhus and murine typhus were defined by clinical and serological diagnoses. The clinical diagnosis of dengue infection was categorized by severity as recommended by the World Health Organization (WHO) into: dengue

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shock syndrome (DSS), dengue hemorrhagic fever (DHF) grade II, DHF grade I and dengue fever.

Serological diagnosis and categorization into primary and secondary infection were based on antibody capture, enzyme-linked immunosorbent assay (ELISA) for dengue IgM and IgG. Evidence of a dengue infection included: 1) ≥40 U of IgM to dengue in single specimens; 2) ≥30 U of IgM to dengue in paired serum samples; 3) <15 U of IgM to dengue in an acute specimen; and, a dengue IgM greater than JEV IgM. A dengue IgM to IgG ratio ≥1.8:1 indicated a primary dengue infection, whereas a ratio of <1.8:1 indicated a secondary dengue infection (Innis *et al*, 1989).

Serologic diagnosis of Japanese encephalitis was based on antibody capture, enzyme-linked immunosorbent assay (ELISA) to JEV, which required a JEV IgM level greater than a dengue IgM level (Innis *et al*, 1989).

Clinical diagnosis of leptospirosis was categorized as per WHO recommendations. Serological diagnosis was based on the indirect immunoflourescent antibody test (IFA) or microscopic agglutination test (MAT). A four-fold rise in the IgM or IgG titer in the paired serum samples or ≥1:400 on a single serum sample was evidence for leptospirosis (Suputtamongkol *et al*, 1998).

Serological diagnosis of scrub typhus was based on the indirect immunoflourescent antibody test (IFA). A four-fold rise in the titer of *O. tsutsugamushi* IgM or IgG on paired sera to ≥1:200 or ≥ 1:400 in the single serum sample was evidence of scrub typhus (Brown *et al*, 1983).

Serological diagnosis of murine typhus was based on indirect immunoflourescent antibody test (IFA). A four-fold rise in the titer of *R. typhi* IgM or IgG on paired serum samples to ≥1:200 or ≥1:400 on a single serum sample was evidence of murine typhus (Chenchittikul and Saisongkorh, 1999).

RESULTS

Between August 2002 and 2003, 43 serum samples (18 pairs and 7 singles) were collected from 25 pediatric patients and analyzed. The etiologies of obscure fever are summarized in Table 1. The etiology was identified in 13 cases (52%): 10 (40%) had dengue infection.

Table 1
Etiologies of obscure fever in children in Srinagarind Hospital.

Etiology	Patients (%)
Dengue infection	10 (40)
Leptospirosis	2 (8)
Septicemia	1 (4)
Unknown	12 (48)
Total	25 (100)

Table 2
Signs and symptoms of dengue *vs* non-dengue infection.

Signs and symptoms (%)	Dengue infection (%) (n=10)	Non-dengue infection (n=15)
Fever	100	100
Myalgia	90	60
Nausea, vomiting and abdominal pain	80	67
Hepatomegaly	60	60
Headache	60	33
Conjunctival injection	70	6.7
Skin lesions	30	27
Diarrhea	20	33
Anemia	10	27
Lymphadenopathy	20	20
Splenomegaly	0	20
Jaundice	0	13.3
Edema	10	0
Epistaxis	10	0

Ten patients were clinically diagnosed with dengue infection, though only seven actually had dengue according to the serology. In three of the patients, the causative organism was unidentified.

Fifteen patients were clinically diagnosed as having a systemic infection, while the final serological diagnosis indicated 3/15 had dengue, 2 leptospirosis, 1 micrococcus spp septicemia, and 12 were unidentified. The signs and symptoms present are summarized in Table 2.

Among the cases that had dengue, the male

to female ratio was 4:1, averaging 9.2 ± 3.2 (range, 4.3-13.4) years of age. The duration of fever was 8.3 ± 2.3 (range, 6-13) days. Five cases (20%) had primary dengue, with a mean age of 8.1 ± 2.6 (range, 5.3-11.7) years, 2 had DSS and 3 DF. Of the 2 cases with DSS, the male to female ratio was 1:1, at 5.3 and 11.7 years of age, respectively. Five (20%) cases had a secondary dengue infection, averaging 10.4 ± 3.7 (range, 4.3-13.8) years, 2 DHF-grade II, 2 DHF-grade I, and 1 DF.

Two (8%) patients had leptospirosis (both males) 8.6 and 13.1 years of age, but the serology was positive by IFA only. The duration of fever was 21 and 23 days, respectively. One case developed infection associated with hemophagocytic syndrome (IAHS) with ascites, pericardial effusion, cardiogenic shock, leukopenia and thrombocytopenia with improvement after treatment.

One patient (4%) had micrococcus spp septicemia: he was 5 years old with underlying ß-thalassemia hemoglobin E disease. He recovered after treatment with intravenous ceftriaxone for 10 days.

We found no cases of JEV infection, scrub typhus or murine typhus.

DISCUSSION

Half (52%) of our pediatric patients with obscure fever had identified infectious causes, which is greater than a previous study on adults (Leelarasamee *et al*, 2000).

Dengue infection was the leading cause (40%), similar to most studies of causative agents of acute pyrexia of unknown origin, even though we tried to avoid enrolling cases of dengue infection (Pancharoen *et al*, 2001). This correlates with the high prevalence of dengue infection in Thailand between 2002 and 2003 (Division of Epidemiology, 2002, 2003).

Non-specific symptoms, such as fever, myalgia, nausea, vomiting and hepatomegaly were seen in both dengue and non-dengue infected groups. Cases with dengue infection had more conjunctival injection, edema and epistaxis. Anemia, splenomegaly and jaundice were more common in the non-dengue infection group.

Clinical over serological diagnosis of dengue *vs* non-dengue infection had a sensitivity and specificity of 70 and 80% *vs* 80 and 70%, respectively. Though clinical diagnosis plays a major role, serological diagnosis is still necessary for a definite diagnosis of these diseases.

Two of the 5 cases with a primary dengue infection experienced dengue shock syndrome at a higher prevalence (40%), and older age (8.1 years) compared with previous studies (prevalence of DSS in primary dengue infection, 17.3%; mean, 4.3 years of age) (Pancharoen *et al*, 2001). This suggests that primary dengue infection could have severe manifestations even in older children, not possessing passive maternal antibodies.

Across Thailand's four regions, the northeast has the highest prevalence of leptospirosis. From our study, the prevalence of leptospirosis was 8%, which correlates with the overall lower prevalence of the disease between 2002 and 2003 than in previous years (Division of Epidemiology, 2002, 2003).

One of our cases developed IAHS, which is a rare complication reported in only one adult patient (Yang *et al*, 1997). One case had *Micrococcus* spp septicemia. This organism constitutes normal flora, but its significance is emerging in immunocompromized hosts causing localized infections and septicemia (Geme, 2003). Our patient had ß-thalassemia hemoglobin E disease.

There were no cases of JEV infection, which is probably due to Thailand's expanded immunization program, which has included the JE vaccination for children since 1992. Scrub typhus or murine typhus, were also not detected. The prevalence of these two diseases may be lower than in other regions of Thailand.

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