SCRUB TYPHUS IN CHILDREN IN A TEACHING HOSPITAL IN EASTERN TAIWAN, 2000-2005

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Abstract. Scrub typhus is an endemic disease in eastern Taiwan. We conducted a study of scrub typhus cases among hospitalized pediatric patients. Twenty-eight pediatric cases were confirmed to be scrub typhus (either by immunofluorescence assay or polymerase chain reaction) from 2000 to 2005. The medical records of these patients were reviewed for demographics and clinical manifestations. The majority of the children (60.7%) diagnosed with scrub typhus were male. Approximately half the patients were <5 years old and the mean age (SD) was 6.1 (3.66) years. Patients were more likely to live in rural rather than urban areas. The greatest number of cases was seen in the spring and summer. The primary clinical symptoms included fever (100%), cough (50%), eschar (50%), rash (35.7%), poor appetite (42.9%), lymphadenopathy (42.9%), headache (39.3%), and hepatomegaly (35.7%). A C-reactive protein (CRP) was elevated in 100%, an aspartate aminotransferase (AST) was elevated in 100%, an alanine aminotransferase (ALT) level was elevated in 91.3%, hypoalbuminemia was found in 88.9% and proteinuria in 50%. The mean (SD) duration of antibiotics was 11.0 (2.68) days and the mean (SD) duration for fever resolution after treatment was 2.8 (2.51) days. Meningoencephalitis was noted in 6 patients. Our case series had no mortalities. These results suggest that a diagnosis of scrub typhus should be suspected in children with fever and laboratory evidence of liver dysfunction who live in rural eastern Taiwan.

INTRODUCTION

Scrub typhus is an acute febrile illness transmitted from rodents to humans by the bite of an infected larval-stage trombiculid mites (Elisberg *et al*, 1968). The causative agent is *Orientia tsutsugamushi*, a weakly staining gram-negative, obligate intracellular coccobacillus, which can be cultured in fertilized eggs or in cell monolayers, where it forms plaques. Different strains are classified based on serologic reactivity, and are not uniquely associated with specific vectors, geographic areas, or host species. The incubation period is approximately 1 to 3 weeks after the bite of an infected mite. Vesicular lesions develop at the site of the bite in about 75% of cases (Cohen *et al*, 2004), and these lesions frequently develop into necrotic eschars. Systemic scrub typhus occurs with a sudden onset of a high fever (>39ºC) and associated headaches, myalgia, and regional lymphadenopathy (Cohen *et al*, 2004).

Scrub typhus occurs most frequently in Southeast Asia, but has been reported from India, Australia, and from Astrakhan

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in central Asia (Cohen *et al*, 2004). Scrub typhus was first documented and characterized in Taiwan by Hatori *et al* in 1915. Lee *et al* (2006) recently discussed the epidemiology of scrub typhus in adults in eastern Taiwan during 2000 to 2004. Pediatric scrub typhus has been extensively studied in Thailand, India, and Korea (Lee *et al*, 2003; Sirisanthana *et al*, 2003; Silpapojakul and Varachit, 2004; Chauta and Chauta, 2005; Somashekar *et al*, 2006). However, few studies have characterized pediatric scrub typhus in Taiwan. We describe pediatric scrub typhus cases at a teaching hospital in eastern Taiwan from 2000 to 2005.

MATERIALS AND METHODS

The retrospective study was conducted at the Taitung Branch of the Mackay Memorial Hospital, a secondary-care teaching hospital and one of the major hospitals in Taitung County. Surveillance data suggests the majority of confirmed cases are in eastern Taiwan (including Hualien County and Taitung County). We reviewed 28 pediatric cases with confirmed scrub typhus admitted to our hospital from 2000 to 2005. The cases were confirmed by positive serology with an immunofluorescence antibody test (an IgM titer for scrub typhus ≥1:400) or a positive result with polymerase chain reaction (PCR). The tests were run at the Centers for Disease Control (CDC) in Taiwan. Epidemiological variables included in the analysis were gender, age, and city of residence. Clinical manifestations were fever, cough, rash, poor appetite, headache, vomiting, drowsiness, neck stiffness, lymphadenopathy, jaundice, eschar, abdominal pain, ascites, hepatomegaly, splenomegaly, and cholecystitis. Laboratory data were CRP, AST, ALT, and albumin levels, and white blood cell count in the blood and cerebrospinal fluid. The presence or absence of proteinuria was also documented.

RESULTS

Twenty-eight pediatric scrub typhus cases were diagnosed from 2000 to 2005 (Fig 1), with the greatest number of infections (*n*=7) seen in 2001. All cases were serologically confirmed. The demographic results are seen in Table 1. Both males (*n*=17) and females (*n*=11) were among identified cases. The mean age was 6.1 years old (range,

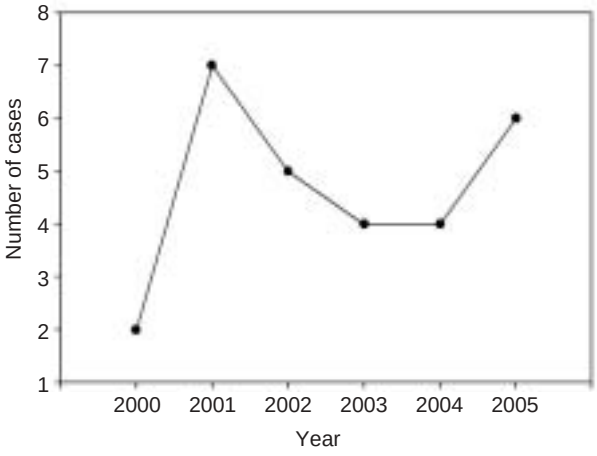

Fig 1–Number of scrub typhus pediatric cases by year from 2000 to 2005.

Table 1
Demographic data of pediatric scrub typhus cases.

	Number of cases	Percentage
Gender		
Male	17	60.7
Female	11	39.3
Age in years		
≤5	14	50.0
6 to 10	10	35.7
11 to 13	4	14.3
Residence		
City	4	14.3
Town	1	3.6
Township	23	82.1

Table 2
Clinical symptoms and signs in pediatric scrub typhus cases.

Symptoms and signs	Number of cases	Percentage
Fever duration	28	100.0
1 to 3 days	5	17.9
4 to 7 days	18	64.3
≥8 days	5	17.9
Eschar	14	50.0
Cough	14	50.0
Poor appetite	12	42.9
Lymphadenopathy	12	42.9
Headache	11	39.3
Rash	10	35.7
Hepatomegaly	10	35.7
Vomiting	8	28.6
Drowsiness	5	17.9
Abdominal pain	5	17.9
Splenomegaly	5	17.9
Neck stiffness	3	10.7
Jaundice	1	3.6
Ascites	1	3.6

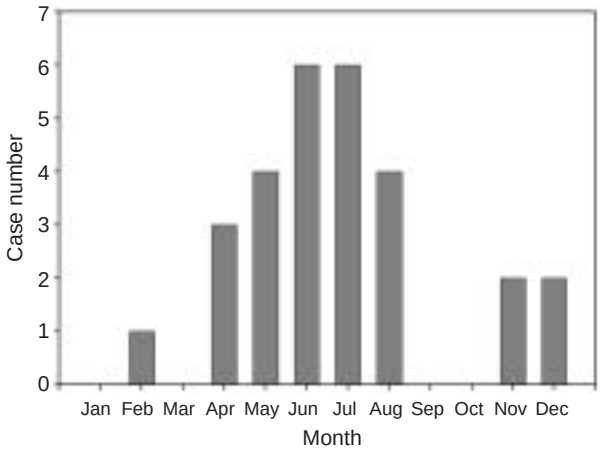

Fig 2–Number of pediatric scrub typhus cases by month from 2000 to 2005.

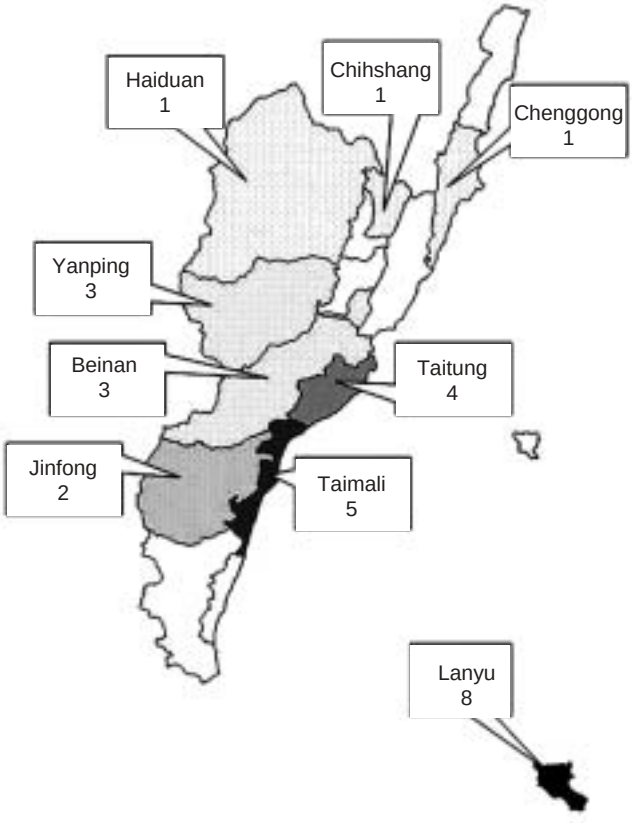

Fig 3–Distribution of pediatric scrub typhus cases in Taitung County from 2000 to 2005.

1-13 years). Children age 0 to 5 years old constituted for 50% of cases, children age 6 to 10 years old constituted 35.7% of cases, and children age 11 to 13 years old constituted 14.3% of cases. Cases stratified by month are shown in Fig 2, the majority of infections occurred between May and August. The geographic distribution of cases in Taitung is seen in Fig 3. Orchid Island (Lanyu) had the largest number of cases (n=8) in Taitung. Cases were also seen in Taimali (n=5), Taitung City (n=4), Beinan (n=3), Yenpin (n=3), Jinfong (n=2), Haiduan (n=1), and Chihshang (n=1).

The clinical symptoms are shown in Table 2. All patients presented with fever, ranging from 1 to 14 days prior to hospital admission (mean 6.3 days). Other symptoms included the presence of eschar (n=14), lymphadenopathy (n=12), poor appetite (n=12),

Table 3
Laboratory findings in pediatric scrub typhus patients.

Findings [a]	Number of cases	Percentage (Cases/Total)[b]
Leukocytosis(WBC > 10,000 cells/mm^3)	11/28	39.3
CRP elevation(CRP > 0.5 mg/dl)	23/23	100.0
AST elevation(AST > 40U/l)	26/26	100.0
ALT elevation(ALT > 40U/l)	21/23	91.3
Hypoalbuminemia(Albumin < 3.5 d/dl)	16/18	88.9
CSF leukocytosis(CSF WBC > 5 cells/mm^3)	6/8	75.0
Proteinuria(Urine protein ≥ 1+)	6/12	50.0

[a] CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CSF, cerebrospinal fluid
[b] Total case numbers did not include unknown cases.

headache (*n*=11), skin rash (*n*=10), and hepatomegaly (*n*=10). Table 3 shows the laboratory findings of the cases. Several laboratory values were consistently elevated among cases, including white blood cell count (>10,000 cells/mm^3, 39.3% of cases), CRP level (>0.5 mg/dl, 100.0%), ALT level (>40U/l, 91.3%), and AST level (>40U/l, 100.0%). Thrombocytopenia (<150,000/mm^3) was seen in 50% of cases and hypoalbuminemia (<3.5 g/l) was seen in 88.9% of cases. Urinalyses were conducted in 12 of the 28 patients, and proteinuria (≥1+) was identified in 50% of cases. Lumbar punctures were performed in 8 cases, 75% had cerebrospinal fluid leukocytosis (>5 cells/mm^3).

No mortalities occured in the subjects. Doxycycline was used as primary treatment in 6 patients (21.4% of cases), minocycline in 18 patients (64.3% of cases), and tetracycline in 4 patients (14.3% of cases). The mean (SD) duration of fever after antibiotic administration was 2.4 (1.79) days, and the mean (SD) duration of total antibiotic usage was 11 (2.68) days.

DISCUSSION

Scrub typhus is a common disease in Asia in both indigenous and visiting individuals (Elisberg *et al*, 1967; Berman and Kundin, 1973; Olson and Bourgeois, 1977; Brown *et al*, 1977, 1984; Tamura *et al*, 1984; Watt and Strickman, 1994; Eamsila *et al*, 1996; Richards *et al*, 1997; Kelly *et al*, 2002). It occurs throughout the year in tropical areas and seasonally in the spring and summer in temperate regions (Chanta and Chanta, 2005). We analyzed epidemiologic data and clinical features of Taiwanese children with scrub typhus from 2000 to 2005. Infected children in our study tended to be younger males who resided in rural areas or on offshore islands. We did not identify clear trends in our study associated with increases or decreases in scrub typhus numbers in children from 2000 to 2005. The greatest case numbers in our study were in the spring and summer months, with peaks in June and July. Such periods are likely influenced by the activities of infected hosts and mites. Wild rodents are the most important pathogen reservoir in the causative organism's life cycle, and the rodent species *Rattus losea* had the highest rate of positive sera among examined species (Cheng, 2000). The peak breeding season for *Rattus losea* in Taiwan is in July and August (Luo, 1988). These

months correlate with the highest numbers of infection in our study. Increased outdoor summertime activity may be a contributory factor to infection. The largest number of cases in our study was in the residents of Orchid Island, which is consistent with the results of a previous study (Tamura, 1984). The major clinical symptoms and signs of scrub typhus in our study were fever, eschar, poor appetite, headache, lymphadenopathy, and hepatomegaly (Chanta and Chanta, 2005). An eschar was found in only 50% of the patients in our study. The percentage of eschar occurrence in pediatric scrub typhus cases in other studies ranges from 7% to 75% (Sirisanthana *et al*, 2003; Silapapojakul and Varachit, 2004; Chanta and Chanta, 2005). Most patients in our study had elevated C-reactive protein, alanine aminotransferase and aspartate aminotransferase levels. Most also had hypoalbuminemia, all consistent with clinical hepatitis (Hu *et al*, 2005). Meningoencephalitis was present in 6 patients, a greater number than previously identified in other studies (3% to 13%) (Silpapojakul *et al*, 1991; Sirisanthana *et al*, 2003; Silpapojakul and Varachit, 2004). Pneumonitis was present in 2 patients, a small number than in previous studies (14% to 37%) (Sirisanthana *et al*, 2003; Silpapojakul and Varachit, 2004). It is possible the patients who suffered from serious complications, such as meningoencephalitis and pneumonitis, had an infection due to different strains of *O. tsutsugamushi*. The clinical course and prognosis with scrub typhus infection vary considerably depending on the characteristics of the strain (Seong *et al*, 2001).

All the patients in this study demonstrated positive clinical responses to doxycycline, minocin, or tetracycline antibiotics, similar to other studies (Silpapojakul *et al*, 1991; Yi *et al*, 1993; Sirisanthana *et al*, 2003). Possible explanations for the positive clinical outcomes in pediatric scrub typhus patients in this study included typical and straightforward case presentations and a high disease awareness among physicians in this endemic area. These characteristics may have led to early diagnosis and effective therapy.

This retrospective study had the potential bias of all retrospective research. A hospital-based study, such as this, tends to underestimate the incidence of disease or infection. An additional limitation of this study was not all the patients had the laboratory values for CRP, AST, ALT, albumin levels and white blood cell counts in the cerebrospinal fluid. This lack of data may bias the percentage of abnormal laboratory findings in these patients. In spite of these limitations we believe this study provides a better understanding of the clinical manifestations and outcomes of scrub typhus in children.

This study evaluated the epidemiological aspects and clinical features of scrub typhus in pediatric patients. Our findings suggest that a scrub typhus diagnosis should be considered in children with fever and signs of liver dysfunction in endemic areas. Effective empiric antibiotic therapy elicits rapid positive responses in patients with scrub typhus.

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