

Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children

VIRAT SIRISANTHANA, MD, THANYAWEE PUTHANAKIT, MD AND THIRA SIRISANTHANA, MD

Background. Scrub typhus, a potentially fatal rickettsial infection, is common in Asia. Although serologic surveys suggested that as many as one-fourth of cases of scrub typhus might be in children, very few reports of childhood scrub typhus are available in the medical literature.

Objectives. To document the clinical, laboratory and epidemiologic characteristics of pediatric patients with scrub typhus.

Methods. From January 1, 2000 to December 31, 2001, all pediatric patients at Chiang Mai University Hospital who had obscure fever for >5 days were tested for indirect immunofluorescent antibody (IFA) against *Orientia tsutsugamushi*, the causative organism of scrub typhus. Scrub typhus was diagnosed on the basis of either a single IFA titer against *O. tsutsugamushi* $\geq 1/400$ or a 4-fold or greater rise in IFA titer to at least 1/200.

Results. Thirty children with scrub typhus were enrolled. Most were diagnosed during the rainy months of June to November. Common physical signs included lymphadenopathy (93%), hepatomegaly (73%), eschar (68%), conjunctival hyperemia (33%), maculopapular rash (30%) and splenomegaly (23%). Eleven patients had interstitial pneumonitis and 1 patient had meningitis. All patients responded well to doxycycline or chloramphenicol. The average interval to deferescence after treatment was 29 h (range, 6 to 72).

Conclusions. Clinical and epidemiologic features of 30 pediatric patients with scrub typhus are reported in a prospective study. The presence of eschar was helpful in making the diagnosis. Complications included pneumonitis and meningitis. All cases responded well to treatment with antibiotic.

INTRODUCTION

Scrub typhus is a febrile illness caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium in the Rickettsiaceae family. The organism is transmitted during the bite of trombiculid mites. Field rodents are the reservoir hosts. Scrub typhus is confined to a definite geographic region. It extends from northern Japan and far eastern Russia in the north, to northern Australia in the south and to Pakistan and Afghanistan in the west.¹ In 2000 there were 3914 cases (6.34 cases per 100 000 population) of scrub typhus reported to the Thai Ministry of Public Health (MOPH).² The true incidence is probably much higher because tests for anti-*O. tsutsugamushi* antibody are available in only a few medical centers in Thailand. One often overlooked aspect of scrub typhus is its occurrence among children.³ As many as one-fourth to one-half of cases of scrub typhus can occur in children.^{4, 5} A study in Japan showed that mite attacks on children are not uncommon.⁴ A survey in a rural Thai village showed a 52% prevalence of antibody against *O. tsutsugamushi* among children younger than 10 years of age.⁶ However, only one case series of scrub typhus in children is found in the MEDLINE database.⁷ In the present report we performed a prospective study of the epidemiologic, clinical and laboratory features of scrub typhus in 30 Thai children seen at a tertiary care hospital in northern Thailand.

PATIENTS AND METHODS

The study was performed at Chiang Mai University Hospital from January 1, 2000 to December 31, 2001. All pediatric patients (age ≤ 15 years) who had obscure fever for >5 days were tested for antibody against *O. tsutsugamushi*, *Rickettsia typhi* (the causative organism of murine typhus), *Leptospira* spp., *Mycoplasma* spp. and *Salmonella* spp. (Widal test). Scrub typhus was diagnosed on the basis of either a single indirect immunofluorescent antibody (IFA) titer against *O. tsutsugamushi* of $\geq 1/400$ or a 4-fold or greater rise in IFA titer to at least 1/200.⁸ Children with the diagnosis of scrub typhus were enrolled and followed prospectively. They would have had necessary laboratory tests performed as part of the initial workup for the diagnosis of obscure fever. These included complete blood count, urinalysis and peripheral blood smear for ma-

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From the Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

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larial parasites. After enrollment additional tests, e.g. example chest roentgenogram, hemoculture, lumbar puncture and liver biochemical tests, were performed when clinically indicated. The patients were treated with 2.2 mg/kg/day doxycycline orally for 4 to 7 days.

The IFA test for antibodies against *O. tsutsugamushi* was performed at the Chiang Mai Center for Medical Sciences of the MOPH using standard method.^{9, 10} The antigens used were pooled Karp, Kato and Gilliam strains of mouse fibroblast cell (L 929)-propagated *O. tsutsugamushi* prepared at the Department of Medical Sciences of the MOPH. The fluorescein conjugates used were rabbit anti-human Igs G and M (Dakopatts, Glostrup, Denmark; Codes F 202 and F 203). Serum samples were tested at dilutions of 1/50, 1/100, 1/200, 1/400, 1/800 and 1/1600, respectively.¹¹

RESULTS

Epidemiologic findings. Thirty children with scrub typhus were enrolled in the study. Twenty-eight were admitted to the hospital and 2 were followed as outpatients. Their mean age was 6.8 years (range, 1.25 to 13). Twenty-three were male, and 7 were female. All lived in Chiang Mai or neighboring provinces. Only 1 patient reported a definite history of mite bite. Figure 1 shows the number of cases by the month of diagnosis. Most cases were seen in the rainy months of June to November. Only 5 cases were diagnosed in the dry months of December to May.

Clinical and laboratory features. Table 1 shows the clinical features of the 30 patients with scrub typhus from this study as well as 15 children reported from southern Thailand.⁷ The average time between the onset of fever and hospitalization or outpatient clinic visit was 9 days (median, 8.5; range, 5 to 21). Although 8 patients reported past diarrhea or had diarrhea at the time of presentation, it was not severe and was not the major cause of admission or outpatient visit. Three patients with diarrhea also had nausea and vomiting. Two patients had underlying hemoglobinopathy.

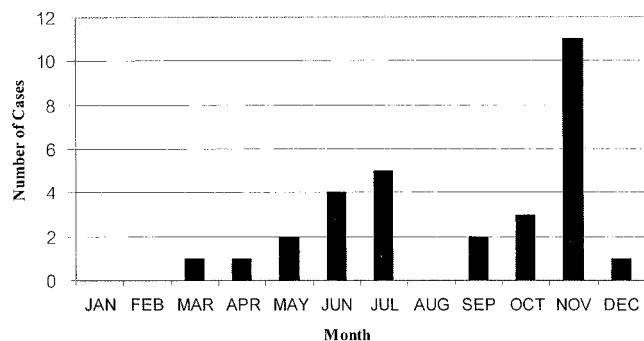


FIG. 1. Distribution of scrub typhus cases by month of diagnosis.

TABLE 1. Symptoms and signs of scrub typhus

Variable	This Series (N = 30)		Report by Silpapojakul et al. ⁷ (N = 15)	
	No.	%	No.	%
Symptoms and signs				
Fever				
Mean duration (days)	9		11	
Range (days)	5-21		7-30	
Lymphadenopathy	28	93		
Hepatomegaly	22	73	10	67
Eschar	21	68	0	0
Tachypnea	13	43	13	87
Conjunctival hyperemia	10	33		
Rash	9	30	1	7
Gastrointestinal				
Diarrhea	8	27	7	47
Vomiting	3	10	7	47
Constipation	1	3	0	0
Abdominal pain	0	0	5	33
Splenomegaly	7	23	7	47
Cough	0	0	4	27
Serious manifestations of scrub typhus				
Pneumonitis	11	37	4	27
Meningitis	1	3	2	13

The average peak temperature during the first 24 h of admission or at the time of outpatient visit was 39.7°C. The average liver enlargement was 3.5 cm below the right costal margin, excluding the 2 patients with hemoglobinopathy. In all patients the liver was nontender. Twenty patients had one eschar each, and 1 patient had 2 adjacent eschars. They were found at the following sites: genitalia and perineum (10); neck (6); inguinal area (3); umbilicus (2); and axilla (1). Eschars were nonpainful ulcers, surrounded by red areolae and usually covered by dark scabs. Their diameters ranged from 0.7 to 1.25 cm. The rash was maculopapular. It was not easily recognized without careful observation and was present for a few days in each patient.

Tachypnea (defined as respiratory rate >35 breaths/min in a patient >3 years old or >55 breaths/min in a patient <3 years old) was present in 13 patients (43%). Chest auscultation was normal in all 13 patients. Chest roentgenograms were obtained in 11 of 13 patients. They showed various degrees of perihilar peribronchial interstitial infiltrations. In the other 2 patients who did not have chest roentgenography, tachypnea improved after only a few hours. Their subsequent clinical courses were uneventful. The mean leukocyte count on admission was 9240 cells/mm³ (range, 4600 to 15 800). Leukocytosis >10 000/mm³ was present in 12 (40%) patients. The mean percentage of polymorphonuclear neutrophils was 56 (range, 40 to 83). Only 2 patients had polymorphonuclear leukocytosis. There was no significant increase in the number of atypical lymphocytes. Excluding the 2 patients with hemoglobinopathy, the mean hemoglobin was 11.3 mg/100 ml. Anemia, defined as hemoglobin <9 mg/100 ml, was present in 2 patients. Eight patients had a platelet

count of $<100\,000$ cells/mm³. Hemoculture, obtained in 24 patients, did not show any growth. Antibody against *R. typhi* was not presented in 23 patients who were tested, nor was there antibody against *Salmonella* spp. (Widal test, 21 patients), *Leptospira* spp. (5 patients) and *Mycoplasma* spp. (5 patients), respectively.

One 11-year-old boy was seen after fever for 6 days. One day before admission he complained of headache, vomiting and neck pain. Physical examination revealed a body temperature of 40°C, tachypnea, conjunctival hyperemia, nuchal rigidity, generalized lymphadenopathy and hepatomegaly. Ophthalmoscopic examination showed vasculitis of the blood vessels of the retina. Cerebrospinal fluid (CSF) examination revealed 8 white blood cells/mm³ (5 polymorphonuclear neutrophils and 3 lymphocytes), CSF protein of 51 mg/100 ml and CSF glucose of 69 mg/100 ml. Other laboratory abnormalities were platelet count of 62 000/mm³, total bilirubin of 2.38 mg/100 ml and direct bilirubin of 1.64 mg/100 ml. Serum aspartate aminotransferase and alanine aminotransferase values were 5 and 4 times upper normal limits, respectively. A chest roentgenogram showed bilateral perihilar interstitial infiltration. The IFA titer against *O. tsutsugamushi* was $<1/50$ on the 6th day of fever, rising to 1/800 on the 14th day.

Twenty-nine patients received 2.2 mg/kg/day doxycycline orally for 4 to 7 days as set out in the protocol. One patient received 70 mg/kg/day chloramphenicol orally for 5 days. All patients responded well to antibiotic therapy. The average interval to defervescence after treatment was 29 h (range, 6 to 72).

DISCUSSION

Scrub typhus is a common infection in many countries in Asia. A study of 1629 patients who were hospitalized for febrile illnesses in rural Malaysia showed scrub typhus as the cause of fever in 19.3%.¹² Pyrexia of unknown origin for which the doctor fails to make a diagnosis in the first week is an important public health problem in Thailand with 341.5 cases per 100 000 population reported to the MOPH in 2000.¹³ Scrub typhus was the cause of fever in 7.5%.¹⁴ Scrub typhus was an important cause of acute fever in soldiers deployed in the endemic areas in World War II,¹⁵⁻¹⁶ the Korean War¹⁷ and the Vietnam conflict.¹⁸ In these days of international travel, cases of scrub typhus have been reported with increased frequency from countries in Europe and North America.¹⁹⁻²⁴ If not diagnosed and treated in a timely manner, scrub typhus is a potentially fatal disease.²⁴⁻²⁵

O. tsutsugamushi does not grow on artificial media. Its isolation requires mice or chick embryo or tissue culture inoculation, which is potentially hazardous. Thus the diagnosis of scrub typhus relies mainly on serologic methods. The standard reference methods are

the IFA test⁸ and the indirect immunoperoxidase test using yolk sac-propagated or cell culture-derived *O. tsutsugamushi* antigens.²⁶ The specificity and sensitivity of the IFA test are 0.96 and 0.54, respectively, at the cutoff titers used in our study.⁸

Because of a limited supply of *O. tsutsugamushi* antigens, the study from southern Thailand used the Weil-Felix test as well as the duration of fever as screening criteria.⁷ Patients must have had fever for 1 week or more and a Weil-Felix OXK titer $\geq 1/320$ to be eligible for the indirect immunoperoxidase test for specific antibody against *O. tsutsugamushi*. Because the Weil-Felix test at the titer used was only 0.44 sensitive for detection of scrub typhus,⁸ the authors stated that they might have missed one-half of the actual cases. The present prospective study did not use the Weil-Felix test titer as a screening criterion. However, similar to the study from southern Thailand, fever for 5 days or more was used as an inclusion criterion in our study to exclude most of the self-limiting viral infections. This, together with the sensitivity of our IFA test at 0.54, may have also excluded some milder cases of scrub typhus.

More cases of scrub typhus were diagnosed during the rainy months of June to November. This correlated with the months with a higher number of field rats infected with *O. tsutsugamushi* reported by Trishnananda et al.²⁷ and the months with more mites attached to rodents.²⁸ The average time between the onset of symptoms and hospitalization was 9 days. This reflected the nonspecific nature of the symptoms and the fact that our study was conducted at a tertiary care center. A history of mite bite was obtained only in one patient. This is not surprising because the mite is small (<5 mm) and the bite is neither painful nor itchy.^{15, 29}

Like the presenting symptoms, the clinical signs, namely fever, lymphadenopathy, hepatomegaly, splenomegaly, hyperemia of the conjunctivae and rash, are similarly nonspecific. Eschar, present in 68% of our patients, is a very useful sign in making the diagnosis. Although eschar was described as an ulcer, surrounded by a red areolar and often covered by a dark scab, one-third of the eschars in our children did not have the dark scab. They were found in moist intertriginous areas, such as the genitalia and the perineum. Eleven of our patients had interstitial pneumonitis. This complication of scrub typhus was common among untreated soldiers during World War II¹⁵ and was the most common histologic finding in those who died.³⁰⁻³² However, the course of pneumonitis in our patients was mild and did not progress to the life-threatening adult respiratory distress syndrome as was described by others.³³

Central nervous system (CNS) involvement is another complication of scrub typhus.^{18, 34} It ranges from aseptic meningitis to frank meningoencephalitis. It

was found in only 1 case in the present study. In another study involving pediatric patients, aseptic meningitis was found in 2 of 15 cases.⁷ The finding of slight pleocytosis, mild protein elevation with normal sugar values in the cerebrospinal fluid in our case is similar to that in other studies.^{7,35} Vasculitis of the blood vessels of the retina seen in our case with CNS complication had also been described.³⁶

Silpapojakul et al.⁷ reported the presence of rash in only 1 of their 15 pediatric patients. This may be because the rash in scrub typhus is evanescent. The presence of lymphadenopathy and conjunctival hyperemia was not mentioned, and eschar was not found in any of their patients. This may reflect the fact that the study from southern Thailand was in a retrospective case series. Alternatively the difference in the occurrence of eschar, as well as in the incidence of CNS complication, may be explained by the fact that patients were infected with different strains of *O. tsutsugamushi*. The general course of scrub typhus as well as the prognosis varies considerably depending on the character of the endemic strain.¹

All our cases, including cases with pneumonitis and meningitis, responded well to doxycycline or chloramphenicol. This is similar to other reports,^{7,37} although cases of scrub typhus poorly responsive to doxycycline and chloramphenicol had been recently reported from northern Thailand.³⁸ One recent randomized clinical trial had shown that rifampin might be useful in treating these poorly responsive cases.³⁹

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Therapeutic vaccination in the immunotolerant phase of children with chronic hepatitis B infection

BUNYAMIN DIKICI, MD, AYHAN GAZI KALAYCI, MD, FUNDA OZGENC, MD, MEHMET BOSNAK, MD, MEHMET DAVUTOGLU, MD, AYDIN ECE, MD, TANJU OZKAN, MD, TURGUT OZEKE, MD, RASIT VURAL YAGCI, MD AND KENAN HASPOLAT, MD

Aim. Hepatitis B virus (HBV) infection is a major global health concern and is the most common cause of chronic liver disease worldwide. Our aim was to investigate the efficacy of specific HBV vaccination as active immunotherapy in treating chronic hepatitis B (CHB) infection during the immunotolerant phase of children with normal aminotransferase values and high viral load.

Materials and methods. Seventy-four patients never vaccinated before were randomly and prospectively recruited into two groups. Group 1 included 43 patients vaccinated with three standard injections of the GenHevac B vaccine at 30-day intervals. Group 2 contained 31 patients who did not receive any medication or vaccination (control group). Postvaccination serologic and virologic evaluation was performed 6 months after the first injection and at the end of the 12th month. Response to therapy was defined as loss of HBV DNA in serum and hepatitis B e

antigen (HBeAg) seroconversion (loss of HBeAg), development of hepatitis B e antibody (anti-HBe).

Results. The mean baseline alanine aminotransferase (ALT) value in Group 1 was 33.0 ± 9.6 IU/l, 34.6 ± 13.9 IU/l at 6 months after first injection and 34.3 ± 17.1 IU/l at end of 12 months ($P > 0.05$). In Group 1 the HBV DNA load at the start of immunization was 3571 ± 1292 pg/ml; this value was 3220 ± 1217 pg/ml at the 6th month and 2931 ± 1292 pg/ml at the 12th month ($P > 0.05$). In Group 2 the mean ALT values at the beginning of therapy and at the 6th and 12th months were 32.6 ± 7.8 , 32.3 ± 8.0 and 30.3 ± 7.3 IU/l, respectively ($P > 0.05$), and the mean viral load HBV DNA values were 3909 ± 1378 , 3546 ± 869 and 3106 ± 718 pg/ml, respectively ($P > 0.05$). There was no statistically significant difference between Group 1 and Group 2 at the end of the 6th and 12th months in the mean ALT values and mean viral load of HBV DNA ($P > 0.05$). Except for one patient in each group, hepatitis B surface antigen and HBeAg clearance or hepatitis B surface antibody and anti-HBe seroconversion were not observed during follow-up ($P > 0.05$).

Conclusion. In this multicentered study comparison of vaccinated and unvaccinated groups of immunotolerant children with CHB infection showed no difference in the clearance of HBV DNA or seroconversion from HBeAg to anti-HBe. Different immunization protocols should be con-

From the Department of Pediatrics, Dicle University Medical School, Diyarbakir (BD, MB, MD, AE, KH); the Department of Pediatric Gastroenterology, 19 Mayıs University Medical School, Samsun (AGK); the Department of Pediatric Gastroenterology, Ege University Medical School, Izmir (FO, RVY); and the Department of Pediatric Gastroenterology, Uludag University Medical School, Bursa (TuO, TaO), Turkey.

Key words: Chronic infection, hepatitis B virus, children, immunotolerance, therapy, vaccine.

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