Incidence of Rickettsial Infection in Patients with Acute Fever in Provincial Thai Army Hospitals

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Scrub typhus is common among patients with acute fever in rural areas of Thailand. The authors prospectively recruited patients with acute fever from provincial Thai army hospitals. Dot-ELISA test for scrub typhus was done in hospitals and then compared with standard immunofluorescent assay for diagnosis of scrub typhus. Among 178 patients, scrub typhus was diagnosed by immunofluorescent assay in 10 patients (5.61%). The incidence was high in the northeastern and northern regions. Dot-ELISA gave positive results in 4 of 115 patients, while immunofluorescent assay gave positive results in 6 patients (sensitivity = 66.7 %). No false positive results of Dot-ELISA were found among 109 patients (specificity = 100 %). All patients gave negative results for murine typhus and Thai tick typhus using immunofluorescent assay. Regarding this present study, Dot-ELISA for scrub typhus has a good sensitivity and specificity and can be used in rural hospitals. This test could be useful for diagnosis of scrub typhus in hospitals where immunofluorescent assay is not available.

Keywords: *Scrub typhus, Dot-ELISA, Immunofluorescent assay, Incidence of rickettsial infection, Rural Thai Army Hospitals*

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Rickettsial infection, influenza and dengue fever are the most common identifiable diseases among patients with acute undifferentiated febrile illness in Thailand. Among 1,137 patients from ten community-based hospitals in a recent study[1], serological studies revealed positive results for scrub typhus in 91 patients (7.5%), influenza in 73 patients (6 %), dengue fever in 70 patients (5.7%) and murine typhus in 65 patients (5.3 %). Although some typical clinical signs such as an eschar in scrub typhus or pain when moving the eyes in dengue can help to make a diagnosis, these may be absent or unnoticed, making clinical diagnosis difficult.

In Thailand, rickettsial infection includes mainly scrub typhus and murine typhus[2-6]. Reports of serologically documented cases of spotted fever rickettsioses have been published[7,8]. Scrub typhus is a rickettsiosis caused by *Orientia tsutsugamushi* and transmitted by chigger bite. It is a rural disease prevalent in the Far East including Thailand. Outbreaks of scrub typhus are associated with military duty[9,10]. Most published studies on scrub typhus were case reports and clinical findings[3,4]. Hence, epidemiologic study on scrub typhus in Thailand is still needed. Definite diagnosis of scrub typhus relies mainly on serology testing. The indirect immunofluorescent

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assay (IFA) is the recommended method. However, this method can be conducted only in referral centers and need well-trained personnel. So the authors have developed a Dot-ELISA test for the detection of IgM and IgG antibodies to *O. tsutsugamushi*, and the results of a preliminary retrospective study of the test were encouraging. This test is simple to perform and suitable for rural hospitals. The authors prospectively studied the incidence of rickettsial infection in patients with acute fever in rural Thai army hospitals and evaluated the clinical use of the Dot-ELISA test compared with the immunofluorescent assay in the diagnosis of scrub typhus.

Material and Method

A prospective epidemiologic study was employed. A total of 21 provincial army hospitals agreed to participate in the present study: seven hospitals in the central region, four hospitals in the north-eastern region, five hospitals in the northern region and five hospitals in the southern region (Fig. 1). Each hospital enrolled patients from June 2005 to October 2006. Inclusion criteria included patients over 15 years from the Outpatient Department of hospitals who presented with acute fever; history of fever not more than two weeks, oral temperature equal to or more than 38°C. Exclusion criteria included patients who had clinical signs and symptoms of localized infection such as skin and soft tissue infection, urinary tract infection; those who had received clinical diagnosis of specific diseases such as acute appendicitis, acute pneumonia, acute pelvic inflammatory disease; and those who were in immunosuppressive states. The present study was approved by the Institutional Review Board (IRB) of the Royal Thai Army Medical Department. Informed consent was obtained from patients as well as patients' parents when the patient's age was less than 18 years.

After enrollment, the first serum sample were collected and divided into two samples for scrub typhus testing. One sample was tested by the Dot-ELISA for IgG and IgM antibodies to *O. tsutsugamushi*[10]. The test was performed by a trained technician at rural army hospitals and the results of the test were reported to the attending physician. A second serum sample was sent to the laboratory at the Armed Forces Research Institute of Medical Science (AFRIMS), The Royal Thai Army Medical Department. The samples were tested for IgG and IgM antibodies to *O. tsutsugamushi* by immunofluorescent assay[10]. The samples were also tested for IgG and IgM antibodies to *Rickettsia typhi* (the causative organism of murine typhus) and *Rickettsia honei* TT-118[11]. Further investigation and treatment were performed according to the attending physicians. Clinical and laboratory data were recorded in case record forms. At least one to two weeks after the first serum sample was drawn, the second serum sample was collected and tested similar to the first sample.

The IFA tests for antibodies against *O. tsutsugamushi*, *R. typhi*, and *R. honei* TT-118 were performed at AFRIMS. The *O. tsutsugamushi* antigens used were pooled Karp, Kato and Gilliam strains from mouse fibroblast cell culture. The *R. typhi* antigens were also from mouse fibroblast cell culture. *R. honei* TT-118 antigens were from vero cell culture (African green monkey, normal kidney cells)[11,12]. Serum samples were tested at a first dilution of 1:50. If the results were positive, they were further tested at dilutions of 1:100, 1:200, 1:400, 1:800, 1:1600, 1:3200, 1:6400, and 1:12800,

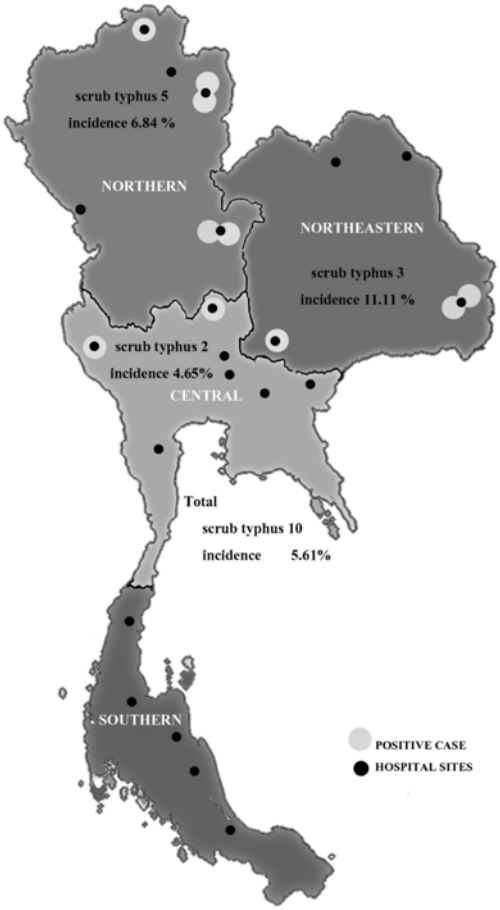

Fig. 1 Distribution of scrub typhus cases by region

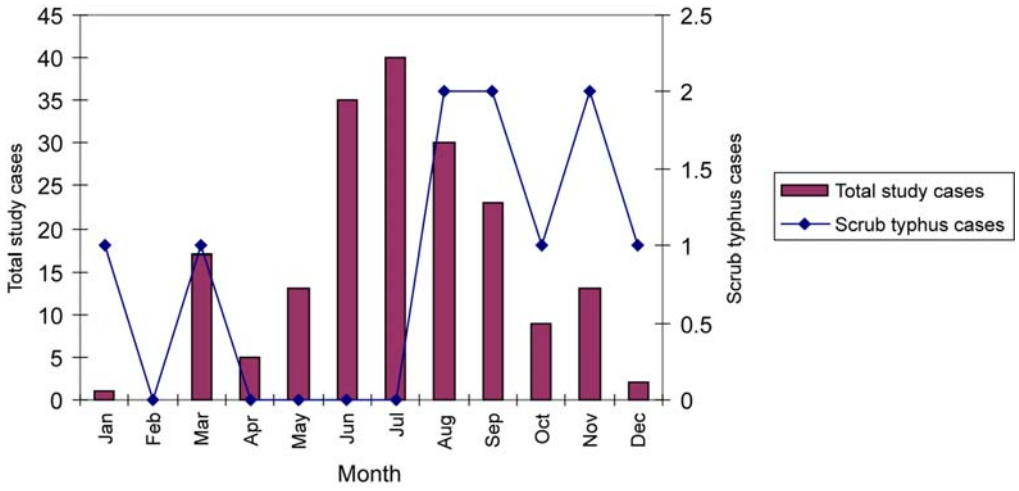

Fig. 2 Distribution of total study cases and scrub typhus cases by month

respectively. All IFA tests were interpreted as positive if the titer of IgM or IgG antibodies was equal to or more than 1:400[13,14]. All tests were performed with positive and negative controls.

For the Dot-ELISA test, the technicians participating in the present study were trained at AFRIMS to perform and interpret the test. Results of the Dot-ELISA tests were reported as positive or negative. The Dot-ELISA test used a nitrocellulose disc in a microtiter plate. An appropriate amount of *O. tsutsugamushi* antigens were absorbed into the nitrocellulose disc. After 30 minutes incubation with the patient serum and enzyme-conjugated anti-human immunoglobulin, then a precipitable, chromogenic substrate was added. The visible formation of a purple colored dot on the disc was used for positive results while no colored dot was found for negative results. The Dot-ELISA test for scrub typhus was produced by AFRIMS, The Royal Thai Army Medical Department, Bangkok, Thailand. The scrub typhus antigens were pooled cultures of Karp, Gilliam, and Kato strains of *O. tsutsugamushi* in irradiated mouse L929 cells. The antigens were applied onto nitrocellulose discs in 96 well microtiter plates. The antigen nitrocellulose discs were incubated with skimmed milk, tested sera, anti-human IgM and IgG peroxidase conjugates and 4-cholo-1-naphthol, respectively. Positive reactions, the presence of antibodies of scrub typhus, resulted IN purple-blue dots on nitrocellulose discs, which were easily read by the naked eye (Fig. 3). All the supplies for use in the tests were prepared by the AFRIMS.

Demographic data of the patients were presented as mean, standard deviation and percentage when appropriate. Incidence of scrub typhus was calculated using the number of scrub typhus cases as diagnosed by IFA tests and divided by the total number of cases in the present study and presented in percentage. The incidence of scrub typhus by region

Fig. 3 Dot-ELISA test. The positive and negative test results for IgG and IgM of *O. tsutsugamushi* antigens are shown in Row A and Row B
MC = IgM control, MT = IgM for the test serum
GC = IgG control, GT = IgG for the test serum
Row A: demonstrates the positive test (purple dot) (IgG and IgM)
Row B: demonstrates the negative test (IgG and IgM)

was also calculated. The sensitivity and specificity of the Dot-ELISA test as compared with the IFA test were calculated using a two-by-two table. Accuracy rates and both positive and negative predictive values (PPV and NPV) were also calculated. Clinical data of scrub typhus and non-scrub typhus cases were compared using *t*-tests and Fisher's exact tests. All p-values were two-sided and considered significant when less than 0.05.

Results

A total of 178 patients were enrolled in the present study. They were 138 males and 40 females, their ages ranging from 15 to 86 years with the mean age of 32 years. Only 155 patients could obtain the second serum samples. Characteristics of the patients are shown in Table 1. Seventy-three patients (41%) were from the northern part of Thailand; 43 patients (24.2%) from the central region, 35 patients (19.6 %) from the southern and 27 patients (15.2%) from the north-eastern. Most patients worked in the army (40.5%), 16.8% were farmers and 13.5 % were government officials and other occupations were 29.2%. The duration of fever before enrollment ranged from one to ten days was 3.8 ± 2.3 days. Among 178 patients, scrub typhus was diagnosed by immunofluorescent assay in ten patients (incidence, 5.61%). The high incidence rates of scrub typhus were 11.1%, 6.8% and 4.7% in the northeastern, north and central regions, respectively. Interestingly, no case of scrub typhus was found in the southern region. The distributions of scrub typhus cases by region and month are shown in Fig. 1 and Fig. 2, respectively. Most patients with acute fever came to the hospitals during the rainy season (from June to September). Scrub typhus cases occurred more commonly in the latter part of the year during the rainy and cool seasons (August to March) (incidence, 6.83 %) than in the former half (incidence, 2.90%).

Table 1. Characteristics of the study population (n = 178)

Characteristics	Number (%)
Sex	
Male	138 (77.5)
Female	40 (22.5)
Region	
Northern	73 (41.0)
North-eastern	27 (15.2)
Central	43 (24.2)
Southern	35 (19.6)
Occupation	
Army personnel	72 (40.5)
Farmers	30 (16.8)
Government officials	24 (13.5)
Others	52 (29.2)

Results of the Dot-ELISA test compared with IFA tests in 9 scrub typhus cases are shown in Table 2. Sensitivity and specificity of the Dot-ELISA test compared with IFA tests in 155 samples were 66.7 and 100%, respectively (Table 3). The Dot-ELISA tests gave positive results in four of six confirmed scrub typhus cases. No false positive results of Dot-ELISA tests were found among 109 non-scrub typhus cases.

Table 2. Results of Dot-ELISA as compared with immunofluorescent assay (IFA) in 9 scrub typhus cases

No.	1st serum				2nd serum			
	Dot-ELISA		IFA		Dot-ELISA		IFA	
	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG
1	ND	ND	1:200	1:400	ND	ND	1:400	1:800
2	Positive	Negative	1:800	1:800	Positive	Negative	1:800	1:800
3	ND	ND	1:800	1:800	ND	ND	ND	ND
4	Positive	Positive	1:800	1:800	ND	ND	ND	ND
5	ND	ND	1:200	1:200	ND	ND	1:200	1:800
6	Positive	Positive	1:800	1:800	Positive	Positive	1:800	1:800
7	Negative	Negative	1:800	1:800	Negative	Negative	1:800	1:800
8	Negative	Negative	1:3200	1:800	Negative	Negative	1:12800	1:12800
9	Negative	Negative	1:200	1:800	Positive	Positive	1:800	1:800
10	ND	ND	1:400	1:200	ND	ND	ND	ND

ND = not done

Table 3. Comparison of Dot-ELISA and IFA to diagnose scrub typhus in 115 samples

Dot-ELISA	IFA	
	Positive	Negative
Positive	4	0
Negative	2	109

Sensitivity = 66.7%, specificity = 100%
Positive predictive value = 100%, negative predictive value = 98.2%
Accuracy = 98.3%

The positive and negative predictive values were high, 100 and 98.2%, respectively.

Demographic and clinical data of ten scrub typhus cases are shown in Table 4. Most cases were male (seven cases), and lived in the northern and northeastern regions (seven cases). Three cases were military personnel, 3 cases were farmers, 2 cases were government officials and 1 case was an employee (where is the other 1 case). Seven of ten cases had a history of activity that might be at risk to chigger bite such as traveling in the forest, or participating in military field training exercises. Cervical lymphadenopathy was found in three cases, conjunctivitis in two cases, eschar in one case and rash in one case. Most cases had leukocytosis and abnormal liver function tests. Cervical lymphadenopaphy was significantly more common in scrub typhus cases ($p < 0.001$) and the alkaline phosphatase level was significantly higher ($p < 0.001$) as compared with non-scrub typhus cases (Table 5).

Discussion

Scrub typhus is expected to be endemic in the rural areas of Thailand. This observational study was the first prospective study to find the incidence of scrub typhus among provincial army hospitals in Thailand. Twenty-one hospitals that participated in the present study covered the north, north-eastern, central and southern regions. The present study took 17 months and covered all seasons: hot, rainy and cool. The physicians and technicians from participating hospitals were trained in study design, data collection and performing the Dot-ELISA test at the AFRIMS before processing. Children aged less than 15 years were excluded since most fevers are self-limiting and caused by viral infections. All 178 cases with acute fever were distributed mainly from June to September, which was similar to those with pyrexia of unknown origin reported by the Ministry of Public Health[15]. In addition, the distribution of scrub typhus cases was commonly found during the rainy season, similar to other studies[16,17]. This period correlated with the months reporting a higher number of field rats infected with *O. tsutsugamushi* and the months with more mites attached to rodents[18,19]. The overall incidence of scrub typhus in the present study was 5.61 %, which was slightly lower than 7.5 % from a recent study[1]. However, the incidence was high in the northern and northeastern regions, similar to cases reported from the Ministry of Public Health[16]. Moreover, cases of

Table 4. Demographic and clinical data of 10 scrub typhus cases

No.	Sex	Age (yr)	Region	Clinical	WBC (cells/mm^3)	Total bili. (mg/dl)	AST (U/L)	ALT (U/L)	Alk. phos. (U/L)
1	M	50	Northeastern	-	12,490	0.6	59	77	233
2	F	38	Northeastern	Conjunctivitis, LN	9,440	0.77	379	345	413
3	M	26	Central	-	-	-	-	-	-
4	F	59	Central	-	19,800	3.1	213	168	332
5	M	34	Northern	conjunctivitis	9,700	-	-	-	-
6	M	32	Northern	-	-	-	-	-	-
7	M	54	Northern	-	13,100	1.4	134	97	179
8	M	21	Northern	rash, LN	11,300	1.1	302	324	233
9	M	23	Northern	Eschar, LN	7,500	-	-	-	-
10	F	-	Northeastern	-	-	-	-	-	-

M = male, F = female, LN = cervical lymphadenopathy, WBC = white blood cell count (cells/cu.mm), bili. = bilirubin, AST = aspartate aminotransferase (0-31 U/L), ALT = alanine aminotransferase (0-31 U/L), Alk. phos. = alkaline phosphatase (U/L), - = No data

Table 5. Clinical data of scrub typhus cases as compared with non-scrub typhus cases

Clinical data	Scrub typhus n = 10	Non-scrub typhus n = 168	p-value
Eschar	1	3	0.203
Conjuctivitis	2	18	0.294
Cervical lymphadenopathy	3	1	<0.001
Alkaline phosphatase (U/L)	278 ± 93 (n = 5)	112 ± 71 (n = 33)	<0.001

p-value as determined by Fisher exact test or t-test when appropriate

murine typhus were not found in the present study differing from previous studies[1,20]. In addition, cases of Thai tick typhus were not found in the present study using IFA tests for antibodies to *R. honei* TT-118 antigens though cases have been reported and positive serosurvey in some population groups were published[7,21]. This may be due to the number of study patients being too small to detect Thai tick typhus cases.

Our ten scrub typhus cases were more common in males and ages ranged from 21 to 59 years. Seven of them had a history of activity that might be at risk to chigger bite such as traveling in the forest and participating in military field training exercise. However, only one case had an eschar lesion and no cases reported a history of chigger bite. Cervical lymphadenopathy was found in three cases and was significantly more common compared with non-scrub typhus cases. Interestingly, most cases had abnormal liver function test results. This clinical finding may help in suggesting the diagnosis of scrub typhus. All scrub typhus cases improved after receiving doxycycline and no fatal cases occurred among enrolled patients during the present study.

A preliminary study was performed to detect the IgM and IgG antibodies to scrub typhus by Dot-ELISA test and indirect immunoperoxidase test (IIP test) in 1283 serum samples. Only 21 serum samples gave different reactions between the two methods. 18 sera were considered positive by Dot-ELISA but negative by IIP test and 3 serum samples were negative by Dot-ELISA but positive by IIP test. The Dot-ELISA test was found to have a sensitivity of 98.63%, specificity of 98.31%, PPV of 92.31 % and NPV of 99.71%, compared with the IIP test. The Dot-ELISA test could be a reliable and useful method to diagnose scrub typhus. The test is easy to perform and does not require sophisticated electrical equipment, needs minimal training, and the results were available within 30 minutes. Although a preliminary retrospective study of the test was encouraging, it has yet to be tested in rural hospitals. The present study was the first to evaluate the usefulness of the Dot-ELISA test compared with IFA tests. The present results showed that the sensitivity was 66% and no false positive tests were found. Therefore, it gave a positive predictive value of 100 percent. In addition, the incidence of scrub typhus in the present study was low (5.6%) so the test gave a negative predictive value of 98.2%. The test was also proven to be practical in a rural environment. The advantage of the Dot-ELISA test compared with the IFA test is that it is quick, easy and relatively inexpensive. In contrast, the IFA test requires sophisticated and expensive equipment which is available only in referral centers. The present results suggest that the Dot-ELISA test is useful in the diagnosis of scrub typhus and suitable for rural hospitals.

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อุบัติการณ์โรคติดเชื้อริคเค็ทเซียในผู้ป่วยไข้เฉียบพลันในโรงพยาบาลทหารบกส่วนภูมิภาค

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โรคติดเชื้อริคเค็ทเซียเป็นสาเหตุของไข้เฉียบพลันที่พบบ่อยในประเทศไทย โรคติดเชื้อริคเค็ทเซีย ที่พบบ่อยได้แก่ โรคสครับไทฟัส (Scrub typhus) พบได้มากในบริเวณทุ่งหญ้า ชายป่าในต่างจังหวัด และยากที่จะวินิจฉัยจากอาการ วิธี Dot-ELISA จึงเป็นวิธีที่พัฒนาขึ้นมาเพื่อช่วยในการวินิจฉัยโรค ทำการคัดเลือกผู้ป่วยที่มีอาการไข้เฉียบพลันจากโรงพยาบาลทหารบกส่วนภูมิภาค ในประเทศไทย การทดสอบ Dot–ELISA สำหรับวินิจฉัยโรคสครับไทฟัส ทำในโรงพยาบาลแล้วเปรียบเทียบกับวิธีมาตรฐานคือ Indirect Immunofluorescent Assay (IFA) ในผู้ป่วยที่มีอาการไข้เฉียบพลัน 178 คน ได้รับการวินิจฉัยว่าเป็นโรคสครับไทฟัส โดยวิธี Immunofluorescent Assay จำนวน 10 คน (อุบัติการณ์ 5.61 %) วิธี Dot-ELISA ให้ผลบวก 4 ราย จาก 115 ราย ในขณะที่ Immunofluorescent Assay ให้ผลบวก 6 ราย (ความไว 66.7 %) ไม่มีผลบวกลวง และมีความจำเพาะ 100% ผู้ป่วยทุกรายให้ผลลบสำหรับ เชื้อมิวรีนและทิคไทฟัส โดยใช้ Immunofluorescent Assay สรุปว่า โรคติดเชื้อริคเค็ทเซียเป็นสาเหตุของไข้เฉียบพลันที่พบบ่อยในส่วนภูมิภาคของประเทศไทย และ วิธี Dot-ELISA ในการวินิจฉัยโรคสครับไทฟัสเป็นวิธีที่มีความไว และความจำเพาะสูง สามารถใช้วินิจฉัยโรคสครับไทฟัส และสามารถ ทำได้ในโรงพยาบาลส่วนภูมิภาคของประเทศไทยที่ไม่สามารถทำการวินิจฉัยโดยใช้วิธี Immunofluorescent Assay