A STUDY OF FEBRILE ILLNESSES ON THE THAI-MYANMAR BORDER: PREDICTIVE FACTORS OF RICKETTSIOSES

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Abstract. We have performed a case-control analysis to determine the significance of clinical, laboratory and epidemiological features as predictive factors of rickettsioses among patients in Sangkhla Buri, Thailand (Thai-Myanmar border). Fifteen serologically-confirmed rickettsiosis patients including Spotted Fever Group (SFG) rickettsioses, scrub typhus, and murine typhus were classified as 'cases'; one hundred and sixty-three acutely febrile patients presenting to the same hospital during the same time period, who had no serological evidence of acute rickettsiosis, were classified as 'controls'. Patients' report of rash/arthropod bite [Odds ratio (OR) 22.90, 95% CI (confidence interval) 6.23, 84.13] and history of jungle trips (OR 5.30, 95% CI 1.69-16.62) were significant risk factors. Elevated ALT (OR 3.04, 95% CI 1.04, 8.88) and depressed platelet count (OR 3.38, 95% CI 1.13, 10.10) were also useful differentiating markers of rickettsioses in this population. Definitive diagnosis of rickettsioses is difficult without specialized diagnostic capabilities that are rarely available in remote areas such as Sangkhla Buri, where other acute febrile illnesses with similar presentation are commonly found. The relative importance of predictive factors presented here may provide clinicians with some useful guidance in distinguishing rickettsioses from other acute febrile illnesses. Timely administration of empiric treatment in highly suspicious cases can deter potential morbidity from these arthropod-borne infections.

INTRODUCTION

Rickettsioses are caused by obligate, intracellular, gram-negative coccobacilli bacteria in the Order Rickettsiales. For recent taxonomic reclassification within the Order Rickettsiales please refer to Dumler *et al* (2001). Rickettsial infections may vary in their manifestations from mild and self-limiting to severe and fatal. Scrub typhus (due to *Orientia tsutsugamushi* and transmitted by chiggers) and murine typhus (due to *Rickettsia typhi* and transmitted by fleas) have long been known as the most common rickettsioses in the Southeast Asian region (Sangkasuwan *et al*, 1969; 1973; Silpapojakul *et al*, 1993; Chen *et al*, 2001; Ong *et al*, 2001). However, tick- and flea-borne Spotted Fever Group (SFG) rickettsioses are also present (Sirisanthana *et al*, 1994; Parola *et al*, 2003b). Infections caused by rickettsiae are often undiagnosed outside of specialized referral centers, but the diseases are treatable. Fatal outcomes may result from misdiagnosis or delayed treatment.

Thailand's Sangkhla Buri district (Kanchanaburi Province), is a malaria endemic area on the Thai-Myanmar border. Patients presenting with acute fever in this region are first screened by malaria smear. If found to be malaria negative, spe-

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cific diagnosis is almost always a challenge to practicing physicians in this remote setting with limited diagnostic capabilities. The known clinical triad of fever, headache, and rash used for the diagnosis of rickettsial infections is not useful in this population where common febrile illnesses such as dengue, other viral infections and leptospirosis clinically mimic rickettsioses.

In a study to determine the causes of acute febrile illnesses in the people living in Sangkhla Buri, our group has documented 15 cases of rickettsioses as emerging arthropod-borne infections (Parola *et al,* 2003b). These cases of SFG rickettsioses, scrub typhus, and murine typhus were serologically confirmed. In this paper, we evaluated the clinical, laboratory and epidemiological characteristics of these cases in comparison to other febrile patients by a case-control analysis.

MATERIALS AND METHODS

The study was conducted at the Armed Forces Research Institute of Medical Sciences (AFRIMS)-Kwai River Christian Hospital Clinical Center (AKCC) in Sangkhla Buri district, Kanchanaburi Province, 350 km northwest of Bangkok, Thailand. AKCC is located on the same compound as the Kwai River Christian Hospital (KRCH), a 40-bed missionary hospital which primarily serves Myanmarese ethnic groups, both permanent residents and new migrants, but is also used by local Thai nationals.

The population of Sangkhla Buri is mainly composed of ethnic Karen, Mon and Burmese from Myanmar. Although a large number of the villagers are permanent residents, migration into Sangkhla Buri occurs year-round and peaks at the beginning of the rainy season in conjunction with the rice cultivation period. The majority of the people are engaged in occupations that may put them at high risk for zoonotic and arthropod-borne diseases. These occupations include rice farming, re-forestation, animal husbandry and rubber tapping.

Patients aged 20 years or older presenting to KRCH with a history of acute fever within 72 hours, who were willing to return for a follow-up appointment 3-6 weeks later, and who had lived in Sangkhla Buri for at least one year, were asked to participate in this study. Detailed medical history, animal and arthropod exposures, current symptoms and physical examination findings were recorded. This report is based on data accumulated from June 1999 to February 2002, during which period 593 patients were enrolled.

Routine laboratory evaluation including malaria smears, complete blood count (CBC), blood chemistries, liver function tests and BUN/creatinine levels were conducted upon the initial presentation. Additional diagnostic testing was available at the discretion of the physician in charge. Ten ml blood was drawn at this time and 5 ml at the follow-up visit. Sera were stored at -80°C at AFRIMS in Bangkok. Laboratory screening for rickettsial antibodies were done on all sera (acute and convalescent) using multi-test Dip-S-Ticks (INDX, Baltimore, MD, USA) for the detection of *R. rickettsii, O. tsutsugamushi* and *R. typhi* total Ig (Watt *et al,* 1998). Sera that were dipstick positive for one or more of these antibodies as well as those from clinically-suspicious patients were tested by indirect immunofluorescent assay (IFA) using a panel of antigens from 13 rickettsiae and related agents, namely *R. conorii* (strain Indian), *R. japonica, R. honei, R. helvetica, R. slovaca,* AT1 *Rickettsia, R. felis, R. heilongjiangii, R. typhi, O. tsutsugamushi (*strains Gilliam, Kato, Karp and Kawazaki*), Anaplasma phagocytophilum, Ehrlichia chaffeensis* and *Coxiella burnetii* (Parola *et al,* 2003b).

A case-control analysis was performed. The 15 serologically-confirmed rickettsiosis patients were classified as 'cases'. 'Controls' were selected from the same population of febrile patients who were 1) Giemsa smear-negative for malaria, 2) presenting to KRCH during the same time period as cases, and 3) serologically categorized in one of these two groups: 3.1) IgG and IgM negative by the panel IFA tests (N=29); 3.2) Non-reactive by dipsticks to *O. tsutsugamushi* and *R. typhi* total Ig and also IFA negative for *R. rickettsii* IgG (using CDC strain as antigen, positive cut-off: ≥1:64), or dipstick negative to all these three antigens (N= 134).

This study was approved by the Ethical Review Committee for Research in Human Subjects of the Thai Ministry of Public Health and the Human Use Review Committee of the Walter

Reed Army Institute of Research, Silver Spring, MD, USA.

RESULTS

The 15 cases of rickettsioses included 8 SFG rickettsioses (5 *R. helvetica*, 2 *R. conorii*, and 1 *R. felis*), 3 scrub typhus (*O. tsutsugamushi*), and 4 murine typhus (*R. typhi*). The final clinical diagnosis of the 163 controls were unspecified febrile illnesses (N=88, 54%), respiratory tract infection (N=43) including 1 case of pulmonary tuberculosis, leptospirosis (N=16), urinary tract infection (N=4), gastrointestinal tract infection (N=2), and others (N=10).

Except for 5 cases (33.3%) and 21 controls (12.9%), all subjects were treated on an out-patient basis (Table 1). The length of hospital stay for cases ranged from 2 days to 45 days (mean: 6 days, median: 4 days), and for the controls ranged from 2 days to 17 days (mean: 5 days, median: 4 days). Most cases were aged 20 to 55 years, but one was aged 70 years. Controls also ranged in age from 20 to 78 years. The cases were approximately evenly distributed between sexes, with 8 females (53.3%) and 7 males (46.7%). For the controls, 54.6% were female. Five of the cases (33.3%) worked outdoors in farming, forestry or other outdoor occupations. Four were employed by indoor activities (domestic, professional, etc) and the rest were unemployed or held other jobs. The distribution of occupations among controls was similar, as shown in Table 1.

All patients were asked about symptoms occurring in the time prior to presentation at the

Table 1
Demographic characteristics among riskettsiosis patients (cases) and their febrile controls, Kwai River Christian Hospital (KRCH), Sangkhla Buri, Thailand, 1999-2002.

	Cases (N=15)	Controls (N=163)	p-value[a]
Age in years			
Mean (sd)[b]	40.1 (13.0)	37.5 (14.0)	0.3523[3]
Age categories			
20-30	4 (26.7)	64 (39.3)	0.6604
31-40	5 (33.3)	46 (28.2)	
41 and older	6 (40.0)	53 (32.5)	
Patient status			
In-patient (%)	5 (33.3)	21 (12.9)	0.0480
Out-patient (%)	10 (66.7)	142 (87.1)	
Sex			
Female (%)	8 (53.3)	89 (54.6)	1.000
Male (%)	7 (43.7)	74 (45.7)	
Ethnicity			
Karen (%)	5 (33.3)	75 (46.3)	0.6863
Mon (%)	5 (33.3)	37 (22.8)	
Thai (%)	4 (26.7)	37 (22.8)	
Other (%)	1 (6.7)	13 (8.0)	
Employment			
Farm/Outdoor (%)	5 (33.3)	59 (36.4)	0.3171
Indoor (%)	4 (26.7)	67 (41.4)	
Other (%)	3 (20.0)	22 (13.6)	
Unemployed (%)	3 (20.0)	14 (8.6)	
No. of years residing in Sangkhla Buri	13 (missing data: 2)	159 (missing data: 4)	
Mean (sd)[b]	29.3 (15.6)	17.6 (14.2)	0.0071[c]

[a]P-values are from Fisher exact chi-square tests unless otherwise specified.
[b]sd- standard deviation.
[c]non-parametric Wilcoxon rank-sum test.

Table 2
Commonly reported symptoms among the 15 cases and 163 controls.

Symptoms/ History	Cases		Controls		Crude OR[b] (95% CI[c])
	N (%)	No. of days[a]	N (%)	No. of days[a]	
Rash/history of arthropod bite	7 (46.7)	3-60	6 (3.7)	2-14	22.90 (6.23, 84.13)
Shaking chills	6 (40.0)	1-14	91 (55.8)	1-30	0.53 (0.18, 1.55)
Headache	12 (80.0)	1-14	145 (89.0)	1-30	0.50 (0.13, 1.93)
Muscle pain	10 (66.7)	1-14	142 (87.1)	1-30	0.30 (0.09, 0.95)
Cough	5 (33.3)	1-12	83 (50.9)	1-240	0.48 (0.16-1.47)
Nausea	7 (46.7)	1-7	86 (52.8)	1-16	0.78 (0.27, 2.26)
Vomiting	5 (33.3)	1-3	43 (26.4)	1-7	1.40 (0.45, 4.31)
Abdominal pain	6 (40.0)	1-10	48 (29.5)	1-120	1.60 (0.54, 4.73)
Diarrhea	2 (13.3)	2-10	17 (10.4)	1-30	1.32 (0.27, 6.36)

[a]Number of days symptom was experienced; [b]OR = Odds ratio; [c]CI = confidence interval

Table 3
Selected clinical signs of the 15 cases and 163 controls.

Signs	Cases		Controls		Crude OR (95% CI)
	N	(%)	N	(%)	
Eschar	6	(40.0)	5	(3.1)	21.07 (5.39, 82.38)
Rash	4	(26.7)	13	(8.0)	4.20 (1.17, 15.04)
Hepatomegaly	4	(26.7)	16	(9.9)	3.32 (0.95, 11.64)
Lymphadenopathy	2	(13.3)	29	(17.9)	0.71 (0.15, 3.30)
Abnormal breath sound/chest x-ray	2	(13.3)	12	(7.4)	1.94 (0.39, 9.59)
Pulmonary rales	2	(13.3)	7	(4.3)	3.43 (0.65, 18.22)

hospital (Table 2). Besides fever, the most commonly reported symptoms among cases and controls were shaking chills (40.0% for cases and 55.8% for controls), headache (80.0% for cases and 89.0% for controls), and muscle pain (66.7% for cases and 87.1% for controls). Cases reported significantly more arthropod bites (Odds ratio (OR) 19.98, 95% confidence interval (CI) 4.61, 85.74) and rash (OR 29.27, 95% CI 4.82, 177.79) than controls. The presence of either or both of these resulted in an OR of 22.90 (95% CI 6.23, 84.13).

Upon physical examination by a study physician, significantly more eschar (OR 21.07, 95% CI 5.39, 82.38) and rash (OR 4.20, 95% CI 1.17, 15.04) were detected in cases than in controls (Table 3). Pulmonary signs (abnormal breath sounds and/or x-ray changes) and hepatomegaly also tended to be associated with cases. There was no significant difference in the presence of adenopathy between cases and controls (13.3% *vs* 17.9%; OR 0.71, 0.15, 3.30).

Ranges of values from hematological and other laboratory assays are shown in Table 4. On average, cases and controls were comparable in their hemoglobin levels and WBC counts. Thrombocytopenia was significantly more common among the cases with 46.67% having platelet counts below 150,000/μl *vs* 20.59% among controls (OR 3.38, 95% CI 1.13, 10.10). There is some indication of elevated GGT (≥79 U/l) among cases, but this finding was not significantly different from that of the controls. Cases had more elevated ALT (≥62 U/l for men, ≥43 U/l for women) than controls (53.3% *vs* 27.3%, OR 3.04, 95% CI 1.04, 8.88).

Table 4
CBC and blood chemistry results (mean, median and range). For measures with a logical cut-off value for abnormal levels, odds ratios and 95% CIs are also shown.

	Cases	Controls	Cut-off value	Crude OR (95% CI)
WBC ($x10^3/\mu l$)				
Mean	7.4	8.6	-	-
Median (Range)	6.0 (3.6-19.8)	7.6 (1.2-25.0)		
Lymphocyte ($x10^3/\mu l$)				
Mean	2.1	2.0	-	-
Median (Range)	1.7 (0.7-6.1)	1.8 (0.3-8.0)		
Hemoglobin (g/dl)				
Mean	12.5	12.6	-	-
Median (Range)	13.2 (5.2-15.4)	12.6 (6.4-17.3)		
Platelet ($x10^3/\mu l$)				
Mean	192	220	<150	3.38 (1.13, 10.10)
Median (Range)	174 (44-476)	209 (31-682)		
ALT (U/l)				
Mean	72	51	≥ 62 for males, ≥43 for females	3.04 (1.04, 8.88)
Median (Range)	67 (21-260)	28 (3-766)		
GGT (U/l)				
Mean	168	58	≥79	2.91 (0.96, 8.80)
Median (Range)	63 (20-726)	33 (9-695)		
BUN (mg/dl)				
Mean	11	12	≥21 for males ≥18 for females	0.82 (0.10, 6.77)
Median (Range)	10 (5-34)	10 (4-82)		
Creatinine (mg/dl)				
Mean	1.0	1.1	≥1.6 for males ≥1.2 for females	Not estimable
Median (Range)	1.0 (0.7-1.3)	1.1 (0.5-4.4)		

Possible exposure to arthropods was evaluated from questionnaire data. Cases were more likely to report having gone within the past month into the jungle than controls (40.0% of cases and 11.2% of controls, OR 5.30, 95% CI 1.69, 16.62). Cases and controls did not differ in exposure to domestic animals (cats, dogs) or farm animals (cattle/buffalo, pigs, poultry).

DISCUSSION

Clinical, laboratory and epidemiological characteristics of rickettsioses have been described for diverse patient populations and specific rickettsial disease entities, for example, murine typhus in Southern USA (Dumler *et al*, 1991), murine and scrub typhus in Singapore (Chen *et al*, 2001), scrub typhus in Thai children (Sirisanthana *et al*, 2003), SFG rickettsioses in Northern Thailand (Sirisanthana *et al*, 1994), and murine typhus on the island of Crete (Gikas *et al*, 2002). However, such descriptions are of limited value for epidemiologic studies or case management when other acute febrile illnesses also share those characteristics.

This is the first analytic study of rickettsioses in a remote border area of Southeast Asia that not only describes predictive factors but also estimates their odds ratios in relation to other febrile illnesses. Ethnicity, gender, and type of employment were all unrelated to case-control status. A survey for rickettsial seroprevalence at

health centers in Malaysia also found no association between gender and rickettsial antibodies (Tay *et al,* 2000). Our observation that rickettsiosis patients had a higher likelihood of being hospitalized than controls suggested that on average they tended to be more clinically severe.

Our patients from this rural setting represent a diagnostic and therapeutic challenge, as the majority of clinically-similar febrile patients were simply due to viral syndromes or other bacterial infections. Nonetheless, the analyses revealed that self-reported rash and arthropod bite as well as history of jungle exposure were strongly associated with rickettsioses. Thus careful history taking may provide useful clues for diagnosis. For example, patients may deny having been 'bitten' by an arthropod, but recall having 'removed' it. Rodents were common in the households but specific data on rodent exposures were not available. The fact that our cases commonly reported recent jungle trips and the predominance of patients with SFG rickettsioses and scrub typhus (11 of 15) over murine typhus in our series supported the supposition that patients' exposure to causative agents were likely to have occurred more in the jungles than in households. Recent tick and flea surveys in Sangkhla Buri suggested that wild animals as opposed to domestic animals were more commonly infested with ticks and fleas, particularly those infected with *Rickettsia* spp and *Ehrlichia* spp, which are related to known zoonotic agents (Parola *et al,* 2003a,c).

As expected, rash and eschar were significant findings on physical examination. Cases were 21-fold more likely to have eschar and 4-fold more likely to have rash detected by physicians. In a report of SFG rickettsioses and scrub typhus from northern Thailand (Sirisanthana *et al,* 1994), lymphadenopathy was a notable presentation. However, it was not more frequently observed among our cases than controls. Pulmonary involvement is a feature of rickettsioses since pulmonary microcirculations are a target of vascular changes following invasion by intracellular rickettsiae and basilar rales are known as a common pulmonary sign. Our data also showed that pulmonary rales were detected three times more often among the cases than the controls, although this association did not reach a statistically significant level (see Table 3).

In a series of scrub and murine typhus cases from Singapore, prominently increased ALT and GGT levels were noted in a third of patients (Chen *et al,* 2001). Our data was also in support of these findings.

Although it was not feasible to screen all the control sera by the 13 rickettsial antigens as we did for those of the cases, classification bias is unlikely. By applying the triple-negative (for *R. rickettsii, O. tsutsugamushi* and *R. typhi*) criteria to both acute and convalescent sera in our control selection, we have reasonably ascertained the presence/absence of rickettsioses among our case and control groups, and thus their valid comparison. Using *R. rickettsii* as representative of SFG antigen in an IFA test, 124 of 126 sera tested negative by Dip-S-Tick® were confirmed negative by IFA, thus a negative predictive value of 98.4% was obtained (SR Telford III, unpublished data). In an earlier evaluation of a dipstick for scrub typhus incorporated with the same antigen as that on the Dip-S-Tick® utilized in this study, Watt *et al* (1998) found the negative predictive value to be approaching 100%. Similarly, an early evaluation of a multi-test Dip-S-Tick® for detecting murine typhus showed a negative predictive value of 97.5% (77/79) (Sekhar and Devi, 2000).

The relatively small number of cases in our series limited the power of our analytical assessment. All ORs presented were crude as there were too few cases to allow for stratified analyses, thus they should be interpreted with caution. Some of the positive results observed could be partly due to chance and overestimates of the true association in the patient population may be possible.

Nonetheless, this study had some advantages. By case-control analysis, we were able to identify and quantify the odds of rickettsioses associated with clinical, laboratory and epidemiological features. This information is helpful to clinicians in early recognition of rickettsioses, thus initiating prompt and appropriate therapy. Our data suggest that history of recent jungle trips, patient's report of rash or arthropod bite, and physician's detection of rash or eschar are important diagnostic clues. Elevated ALT and depressed platelet count add to the degree of suspicion. Although diagnosis of infections caused by

rickettsiae has recently been improved, accurate, reliable and affordable, rapid diagnostic tools for field use are not immediately available (Coleman *et al*, 2002).

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REFERENCES

Chen MI, Chua JK, Lee CC, Leo YS, Kumarasinghe G. Epidemiological, clinical and laboratory characteristics of 19 serologically confirmed rickettsial disease in Singapore. *Singapore Med J* 2001; 42: 553-8.

Coleman RE, Sangkasuwan V, Suwanabun N, *et al*. Comparative evaluation of selected diagnostic assays for the detection of IgG and IgM antibody to *Orientia tsutsugamushi* in Thailand. *Am J Trop Med Hyg* 2002;67:497-503.

Dumler JS, Barbet AF, Bekker CP, *et al*. Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia* and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and 'HGE agent' as subjective synonyms of *Ehrlichia phagocytophila*. *Int J Syst Evol Microbiol* 2001; 51: 2145-65.

Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. *JAMA* 1991; 266: 1365-70.

Gikas A, Doukakis S, Pediaditis J, Kastanakis S, Psaroulaki A, Tselentis Y. Murine typhus in Greece: epidemiological, clinical, and therapeutic data from 83 cases. *Trans R Soc Trop Med Hyg* 2002; 96: 250-3.

Ong AK, Tambyah PA, Ooi S, Kumarasinghe G, Chow C. Endemic typhus in Singapore – a re-emerging infectious disease? *Singapore Med J* 2001; 42: 549-52.

Parola P, Cornet JP, Sanogo YO, *et al*. Detection of *Ehrlichia* spp, *Anaplasma* spp, *Rickettsia* spp, and other eubacteria in ticks from the Thai-Myanmar border and Vietnam. *J Clin Microbiol* 2003a; 41: 1600-8.

Parola P, Miller RS, McDaniel P, *et al*. Emerging rickettsioses of the Thai-Myanmar border. *Emerg Infect Dis* 2003b; 9: 592-5.

Parola P, Sanogo OY, Lerdthusnee K, *et al*. Identification of *Rickettsia* spp and *Bartonella* spp in fleas from the Thai-Myanmar border. *Ann NY Acad Sci* 2003c; 990: 173-81.

Sangkasuwan V, Dechkunchorn P, Prakobpanichkij B, Chuenchitra C, Chirasiri L, Onkasuwan K. Murine typhus, a report of 15 cases. *J Med Assoc Thai* 1973; 56: 175-8.

Sankasuwan V, Pongpradit P, Bodhidatta P, Thonglongya K, Winter PE. Murine typhus in Thailand. *Trans R Soc Trop Med Hyg* 1969; 63: 639-43.

Sekhar WY, Devi S. The increasing prevalence of endemic typhus in Kuala Lumpur and an evaluation of a diagnostic ELISA dot test for the detection of antibodies to *Rickettsia typhi*. *Singapore Med J* 2000; 41: 226-31.

Silpapojakul K, Chayakul P, Krisanapan S. Murine typhus in Thailand: clinical features, diagnosis and treatment. *QJ Med* 1993; 86: 43-7.

Sirisanthana T, Pinyopornpanit V, Sirisanthana V, Strickman D, Kelly DJ, Dasch GA. First cases of spotted fever group rickettsiosis in Thailand. *Am J Trop Med Hyg* 1994; 50: 682-6.

Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic clinical and laboratory features of scrub typhus in thirty Thai children. *Pediatr Infect Dis J* 2003; 22: 341-5.

Tay ST, Ho TM, Rohani MY, Devi S. Antibodies to *Orientia tsutsugamushi*, *Rickettsia typhi* and spotted fever group rickettsiae among febrile patients in rural areas of Malaysia. *Trans R Soc Trop Med Hyg* 2000; 94: 280-4.

Watt G, Strickman D, Kantipong P, Jongsakul K, Paxton H. Performance of a dot blot immunoassay for the rapid diagnosis of scrub typhus in a longitudinal case series. *J Infect Dis* 1998; 177: 800-2.