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Scrub Typhus Meningitis or Meningoencephalitis

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Abstract. *Orientia tsutsugamushi* induces vasculitis leading to symptoms of systemic organ invasion including meningitis and meningoencephalitis. We conducted a retrospective case-control study of scrub typhus patients to investigate the clinical and laboratory features of patients with scrub typhus meningitis or meningoencephalitis, and the therapeutic outcomes, and to determine the predictor factors. Cases were 22 patients with scrub typhus meningitis or meningoencephalitis, and controls were 303 patients without meningitis or meningoencephalitis. Multivariate analysis showed that the presence of pneumonitis was associated with the occurrence of scrub typhus meningitis and meningoencephalitis (odds ratio [OR] 8.9; $P < 0.001$; confidence interval [CI] 2.9–27.2). Although appropriate antimicrobials such as doxycycline agents were administered at an early stage, meningitis or meningoencephalitis still occurred in some cases. Physicians should be aware that meningitis or meningoencephalitis may develop during appropriate drug therapy such as doxycycline. Close observation and great care are essential for patients with risk factors, particularly pneumonitis.

INTRODUCTION

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi.* In humans, it spreads by the blood and lymphatics and induces generalized vasculitis, with clinical findings of multi-organ involvement such as fever, generalized lymphadenopathy, liver function impairment, pneumonitis, gastric ulcer, meningitis, meningoencephalitis, renal failure, and septic shock.[1–3] Meningitis and meningoencephalitis are life-threatening manifestations that can cause changes in mentation and death.[4] Thus, early diagnosis and treatment are mandatory. Although many sporadic cases have been reported since Palm first described scrub typhus in 1878, there have been few studies of the clinical features and factors associated with scrub typhus meningitis and meningoencephalitis employing a large series of patients.[5] Between 2004 and 2008, we treated 22 patients with scrub typhus meningitis or meningoencephalitis. In this study we surveyed the clinical and laboratory findings and therapeutic outcomes in these patients, and analyzed the factors associated with meningitis and meningoencephalitis by comparing cases and controls.

METHODS

Between September 1, 2004 and December 31, 2008, we enrolled patients who presented with acute febrile illness to the Department of Internal Medicine of Chosun University Hospital located in the southwestern part of Korea. Among these patients, we enrolled those ≥ 18 years of age who had eschars or maculopapular skin rashes, or were diagnosed clinically as having scrub typhus by a specialist in infectious diseases.

Clinical history and examination and the results of laboratory investigations were recorded on a previously validated proforma, from admission until discharge by previous prospective studies.[6–8]

We retrospectively analyzed the factors associated with meningitis or meningoencephalitis by comparing cases and controls.

The diagnosis of scrub typhus was confirmed when a positive nested polymerase chain reaction (PCR) using *O. tsutsugamushi*-specific primers targeting 56 kDa surface protein antigen encoding genes was obtained, or the indirect fluorescent antibody titer against *O. tsutsugamushi* increased 4-fold or more.[9]

Each patient's mental status was assessed daily and coded, as described previously.[10] Meningitis was defined as cerebrospinal fluid (CSF) cell counts ≥ 5 leukocytes/mm^3 and the presence of fever and/or neck stiffness and/or headache and/or nausea and/or vomiting. Patients were classified as suffering from meningoencephalitis when they had, in addition to findings of meningitis, abnormal findings on the electroencephalograph and/or focal neurologic symptoms and/or altered consciousness (confusion, obtundation, stupor, coma) without evident cause such as shock or hypoglycemia. The scrub typhus patients were divided into two groups: a case group with meningitis or meningoencephalitis and a control group without meningitis or meningoencephalitis.

At presentation, scrub typhus-like diseases, including murine typhus, leptospirosis, epidemic hemorrhagic fever, and systemic lupus erythematosus, were excluded based on clinical features and laboratory tests. This study was approved by the Institutional Review Board of our hospital (2012-05-003-01).

Continuous data are not normally distributed, therefore a nonparametric test (Mann-Whitney *U* test) was used to compare between the different groups. Nominal data are expressed as frequencies or fractions, and compared by the χ^2 test and Fisher's exact test. The associations between scrub typhus meningoencephalitis and its predictors were determined using the χ^2 test and univariate logistic regression analysis. Input variables for the multivariate analysis were selected from significant variables obtained from the univariate analysis. To determine the factors associated with scrub typhus meningitis or meningoencephalitis, we performed a multivariate logistic regression analysis using as independent variables shown by the univariate analysis to be associated with the occurrence of scrub typhus meningitis or meningoencephalitis. The multicollinearity among the independent variables was tested by calculating the variance inflation factor and tolerance (1/variance inflation factor).

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Odds ratios (ORs) and 95% confidence intervals (CIs) for examining statistical significance were derived with SPSS software, version 12.0 (SPSS Inc., Chicago, IL).

RESULTS

Three hundred and forty patients were diagnosed with scrub typhus based on positivity for PCR or a 4-fold or more increase in antibody titer. Thirty-seven of these patients were suspected of having meningitis or meningoencephalitis, but 15 were excluded because they did not undergo spinal tapping or had a CSF cell count of < 5 leukocytes/mm^3. Thus, when assessed by the previous criteria, meningitis or meningoencephalitis occurred in 22 of 340 patients with confirmed diagnoses of scrub typhus. The mean age of the case group was 70 years (median, 70 years), and that of the control group, 62 years (median, 64 years). The ages were significantly different (Table 1). In the case group, 18 (81.8%) of the 22 patients were farmers, whereas in the control group, 148 (53%) of the 303 patients were farmers. This result implies that farmers more frequently have meningitis or meningoencephalitis. However, the occurrence of meningitis or meningoencephalitis did not significantly correlate with the following factors: genotype of *O. tsutsugamushi*, sex, and presence or absence of chronic disease requiring ≥ 3 months of treatment. There were no significant differences in the time to resolution

TABLE 1

Demographic/clinical characteristics and laboratory findings in the scrub typhus patients evaluated in a comparative study of meningitis or meningoencephalitis

Characteristics	Meningitis or meningoencephalitis		*P* value
	Yes (*N* = 22)	No (*N* = 303)	
Demographic data			
Age, median years (range)	70.23 (43–88)	64.0 (18–91)	0.004
Gender, no. of males/no. of females (%)	8/14 (36.4)	103/200 (34.0)	1.00
Professional farmer (%)	18 (81.8)	148 (53.0)	0.017
Presence of disease being treated for ≥ 3 mo (%)	6 (28.6)	69 (23.2)	0.596
Duration of illness before admission, median days (range)	7.0 (2–22)	6.0 (0–80)	0.469
No. of the Boryoung genotype/total no. of the genotypes (%)	20/20 (100)	248/269 (92.2)	0.378
Therapeutic delay > 5 days (%)	11/11 (50.0)	161 (53.7)	0.911
Chest x-ray abnormality (%)	18 (81.8)	97 (32.1)	< 0.001
Modified APACHE II score, median (range)	9.32 (3–19)	6.0 (0–18)	0.001
Time to defervescence, median hr (range)	33.3 (0–105)	20.0 (0–144)	0.022
Time to resolve headache, median days (range)	8.8 (2–24)	4.0 (4–60)	0.001
Time to resolve myalgia, median days (range)	8.4 (1–29)	3.0 (0–48)	0.004
Time to resolve skin rashes, median days (range)	4.6 (1–13)	4.0 (0–60)	0.553
Associated complications			
Pneumonia on admission	15 (68.2)	46 (15.2)	< 0.001
Acute renal failure on admission	2 (9.1)	31 (10.2)	1.000
Gastrointestinal bleeding	2 (9.1)	12 (4.0)	0.243
Clinical symptoms and signs			
Headache, no. (%) of patients	17 (77.3)	255 (84.4)	0.370
Myalgia, no. (%) of patients	14 (63.6)	228 (75.5)	0.326
Cough, no. (%) of patients	13 (59.1)	84 (27.8)	0.004
Dyspnea, no. (%) of patients	9 (40.9)	51 (16.9)	0.010
Altered mental status, no. (%) of patients	11 (50.0)	8 (2.6)	< 0.001
Fever, no. (%) of patients	17 (77.3)	210 (69.5)	0.600
Tachycardia, no. (%) of patients	6 (37.5)	20 (8.4)	0.003
Skin rash, no. (%) of patients	19 (86.4)	263 (87.1)	1.000
Eschar, no.(%) of patients	19 (86.4)	285 (94.1)	0.161
Hematemesis or melena, no. (%) of patients	2 (16.7)	10 (5.6)	0.168
Shock, no. (%) of patients	3 (13.6)	12 (4.0)	0.072
Laboratory data (median [range])			
WBC count (no. of cells × 1,000/mm^3)	10,255 (6,550–18,170)	7,150 (1,100–20,000)	< 0.001
Hemoglobin (g/dL)	12.7 (9.6–16.6)	12.5 (5.9–17.6)	0.965
Platelet count (no. of cells × 1,000/mm^3)	136 (53.0–301.0)	137 (17.0–585.0)	0.565
AST (IU/L)	80.5 (19.0–335.0)	73.0 (17.0–1164.0)	0.476
ALT (IU/L)	64.5 (19–253)	58.0 (3–1221)	0.919
ALP (U/L)	158.0 (38–650)	84.0 (9–578)	0.668
Bilirubin (mg/dL)	0.8 (0.4–4.8)	0.7 (0–7.4)	0.118
Albumin (g/dL)	3.0 (2.5–4.1)	3.7 (1.9–5.0)	< 0.001
LDH (U/L)	739.0 (432–1326)	738.5 (2–3510)	0.526
CPK (U/L)	94.0 (12.0–1905.0)	100.0 (9.0–6114.0)	0.962
ADA (IU/L)	84.5 (54.0–144.0)	77.0 (12.0–144.0)	0.076
Serum creatinine (mg/dL)	1.01 (0.6–5.05)	1.0 (0.02–5.23)	0.845
Fibrinogen (mg/dL)	260.7 (118.0–698.0)	333.5 (40.8–671.4)	0.016
CRP (mg/dL)	9.8 (0.3–20.0)	6.9 (0.3–78.0)	0.011
ESR (mm/hr)	17.0 (2.0–42.0)	15.0 (2.0–86.0)	0.678
PT (sec)	12.0 (10.4–14.1)	12.1 (9.3–30.3)	0.937
aPTT (sec)	31.5 (23.1–48.3)	29.6 (18.2–57.0)	0.067

Values are median (range).

There were significant differences in baseline characteristics between the two groups ($P < 0.05$).

WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = Lactate dehydrogenase; CPK = Creatine kinase; ADA = adenosine deaminase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; PT = prothrombin time; aPTT = activated partial thromboplastin time.

of skin rashes. But the time to defervescence, resolution of the myalgia and the time to resolve headache were significantly prolonged in the case group.

As for clinical symptoms, cough, dyspnea, and tachycardia were more frequently observed in the case group, but the other symptoms were not. The average duration of symptoms before admission was 7.68 ± 4.4 days (median, 7.0 days) in the case group and 7.4 ± 6.2 days (median, 6.0 days) in the control group (Table 1). In laboratory findings, white blood cell (WBC) count was significantly higher, and albumin was significantly lower, in the case group (Table 1). Of the 22 case group patients, 10 had stiff necks. One patient was stuporous, six were obtunded, and seven confused. The CSF findings were as follows: WBC count, 53.4 ± 73.6/mm^3 (median, 24/mm^3); protein, 90.2 ± 49.9 mg/dL (median 78 mg/dL; range, 34–238 mg/dL). A protein concentration ≥ 45 mg/dL was observed in 19 of the 22 patients (86.4%). Glucose level was 69.0 ± 36.6 mg/dL (median, 56.6 mg/dL; range, 36.0–191.0 mg/dL). Fifteen (68%) of the 22 patients in the case group had interstitial pneumonitis on admission; this was significantly higher than the 46 (15.2%) in the 303 control group patients. Two of the case group patients had shock at presentation, two had renal failure, and two had gastrointestinal bleeding (Table 1).

We used the univariate logistic regression model to test for correlations between the occurrence of meningitis or meningoencephalitis and four factors, as follows: 1) age (OR 1.1; P = 0.009; CI 1.0–1.1), 2) occupation farmer (OR 4.0; P = 0.015; CI 1.3–12.1), 3) modified Apache II score (OR 1.2; P = 0.009; CI 1.1–1.4) on admission, and 4) pneumonitis (OR 12.0; P < 0.001; CI 4.6–31.0) on admission. Multivariate analysis showed that just one factor, presence or absence of pneumonitis on admission, was significantly associated with the occurrence of scrub typhus meningitis or meningoencephalitis (OR 7.7; P < 0,001; CI 2.7–21.7). There was no evidence of multicollinearity in the multivariate logistic regression (tolerance values were > 0.1).

Table 2 summarizes the clinical features and CSF profiles of the 22 patients with meningitis or meningoencephalitis, and the antimicrobial therapy used. Patient 1 was administered doxycycline 100 mg bid for 4 days in our hospital under a clinical diagnosis of scrub typhus. On the fourth day, the patient lapsed into delirium and became obtunded. For this reason, he underwent spinal tapping and received rifampin instead of doxycycline. Patients 2–7 were diagnosed with scrub typhus at a local clinic where they received doxycycline 100 mg bid for 2 to 6 days. Their fever improved but they were transferred to our hospital because of newly developed dysarthria or altered mentation. Two of them received rifampin after discontinuation of doxycycline, whereas four continued to receive doxycycline 100 mg bid, and one of the latter patients (patient no. 7) received a 5-day administration of rifampin after discontinuation of the 14-day doxycycline because of persistence of the altered mentation.

Patient 8 was administered doxycycline at a regional hospital, but her headache got worse and she was referred to our hospital. The headache improved after spinal tapping, and doxycycline was administered for 7 more days. Two patients (patients 9 and 10) received doxycycline 100 mg bid at a local clinic under a clinical diagnosis of meningoencephalitis; after transfer to our hospital one patient continued to receive doxycycline and the other received rifampin instead. Their symptoms improved in our hospital. The remaining patients were treated under a clinical diagnosis of meningitis or meningoencephalitis. Seven received doxycycline 100 mg bid, four rifampin 300 mg bid or 600 mg qd, one telithromycin 800 mg once daily; all recovered without neurological sequelae.

DISCUSSION

O. tsutsugamushi frequently invades the central nervous system (CNS); indeed the word "typhus" is derived from the term "typhos" meaning "stupor." The CNS is affected in 20–33% of patients infected by the *Rickettsia* that causes Rocky Mountain spotted fever,[1,11] and in a minority of cases of epidemic typhus or scrub typhus (2–5%).[10] Pai and others[12] identified *O. tsutsugamushi* DNA using nested PCR in the CSF in 6 of 25 patients with scrub typhus. It has been reported that mild pleocytosis with lymphocyte dominance and protein levels ≥ 45 mg/dL is present in the CSF in 48% of patients. In our study, WBC counts in the CSF were ≤ 250/mm^3, which points to mild pleocytosis; lymphocytes were dominant in six patients, and polymorphonuclear cells in another nine of 16 patients with CSF > 10. The findings of mild leukocytosis (≤ 250/mm^3 in most cases), slightly increased protein content, and normal glucose levels resemble those in viral meningoencephalitis, leptospirosis, and tuberculous meningitis, which must be differentiated from scrub typhus meningitis or meningoencephalitis. Most of the latter patients undergo changes of mentation and/or behavior, indicating generalized involvement of the CNS.

Doxycycline is the drug of choice for scrub typhus. Although appropriate antimicrobial agents were administered at an early stage in this study, meningitis or meningoencephalitis occurred in some of the patients during the doxycycline therapy. There are three possible explanations for therapeutic failure of doxycycline: 1) its bacteriostatic action, 2) difficulty in penetrating through the blood brain barrier and the resulting low concentrations in the CNS, and 3) resistance to the drug.[13]

The rate of penetration of doxycycline into the brain or CSF is only 15–30% of that into the bloodstream.[14–16] A study of doxycycline concentrations in the CSF,[4] reported that 5–8 days after the start of therapy in Lyme neuroborreliosis, doxycycline concentrations above the minimum inhibitory concentration for *Borrelia burgdorferi* (0.6 μg/mL) were present in nine of 10 patients treated orally with doxycycline 200 mg bid, but in only three of 12 patients treated orally with doxycycline 100 mg bid. In contrast, a study of patients with non-inflamed meninges showed that the mean rifampin concentration in brain tissue was 0.29 μg/mL, whereas in the CSF it was 0.73 μg/mL (range, 0.57–1.24 μg/mL). Because the minimum inhibitory concentration for *O. tsutsugamushi* is 0.0625–0.5 μg/mL,[17] rifampin is thought to be more effective. Randomized controlled trials of doxycycline and rifampin for meningitis and meningoencephalitis patients, and further systematic studies of the concentrations of doxycycline and rifampin achieved in brain tissue and CSF, are required to determine whether increasing the doxycycline dosage or using rifampin instead, is more effective.[18,19] And, scrub typhus causes profound disturbances in T cell homeostasis.[20] This opens the possibility that mechanisms other than antibiotic resistance/failure are causes of meningeal presentations.

Interestingly, headaches did not occur with increased frequency in the scrub typhus patients with meningitis or meningoencephalitis in this study. Similar results were reported in a study of mortality rates and predictors,[21] which found that

TABLE 2
Clinical, laboratory, and therapeutic findings in scrub typhus patients with meningitis or meningoencephalitis

Patient/ Age/ sex	IgM/IgG (at admission) IgM/IgG (follow up)	Associated complications	Headache	Neck stiffness	Mental status	Admission days after onset of symptoms	CSF study Tapping Days after admission	CSF study WBC	CSF study Protein	CSF study Glucose	Antibiotics	Mental status recovery time after admission
1/79/M	160/64	ARF, Pneumonitis GI bleeding	Yes	No	3	7	4 d	43 (67/33)	62.3	52.9	D for 5 d R for 9 d	8 d
2/76/F	320/4096 320/4096	Pneumonitis	No	Yes	3	7	0 d	38 (90/10)	144	36.8	D for 6 d (before admission) R for 10 d	5 d
3/72/M	80/256 80/1024	Pneumonitis ARF CN palsy	No	No	1	5	0 d	205 (90/10)	170	57	D for 4 d (before admission) R for 11 d	3 d
4/76/F	0/512 640/512	Meningitis, Gastric ulcer, Duodenal ulcer	Yes	No	2	22	0 d	70 (75/25)	100.9	46.1	D for 4 d (before admission) D for 5 d	2 d
5/82/F	0/1024 0/4096	Pneumonitis GI bleeding	No	No	2	4	0 d	6	104	62.7	D for 2 d (before admission), D for 11 d	10 d
6/55/F	320/2048 1280/4096	Duodenal ulcer	Yes	Yes	3	2	0 d	295 (5/95)	87.7	71.2	D for 2d (before admission) D for 11d	4 d
7/69/M	640/2048 640/4096	Pneumonitis Shock	No	Yes	2	5	2 d	37 (30/70)	107.9	48	D for 2 d (before admission) D for 14 d, then R for 5 d	15 d
8/72/F	0/2048 80/4096		Yes	No	1	7	0 d	20 (73/27)	54.2	62	D for 3 d (before admission) D for 7 d	
9/72/F	0/2048 0/512	Pneumonitis, Myocarditis Shock	Yes	Yes	3	10	1 d	79 (70/30)	97.4	39	D for 2 d (before admission) Doxy for 6 d	5 d
1076/M	0/16384 80/8192	Pneumonitis, ARF Shock	Yes	Yes	3	7	1 d	6	23.8	57	D for 3 d (before admission) R for 11 d	10 d
11/77/F	80/16384.		Yes	No	4	14	4 d	16 (40/60)	48.4	191	D for 11 d	7 d
12/66/F	1280/2048.	Pneumonitis	Yes	No	1	3	3 d	38 (63/37)	107	56	D for 5 d	–
13/76/F	640/4096 1280/4096	Pneumonitis	Yes	No	1	5	1 d	8	54	93	D for 7 d	–
14/65/F	0/0 1280/4096		Yes	No	1	5	0 d	7	65.9	76.4	D for 8 d	–
15/60/F	80/32 80/2048	Pneumonitis CN palsy	Yes	.	1	4	1 d	5	47	47	D for 5 d	–
16/43/F	160/1024 1280/8192		Yes	Yes	1	7	2 d	28 (75/25)	41.8	92	D for 5 d	–
17/88/F	0/1024 0/8192		Yes	Yes	2	8	1 d	6	33.8	96.9	D for 5 d	1 d
18/70/M	320/128 2560/512	Pneumonitis Deep vein thrombosis	Yes	Yes	2	14		13 (70/30)	60.2	47.7	R for 11 d	4 d
19/70/M	0/512 1280/2048	Meningitis, Gastric ulcer, Duodenal ulcer	Yes	Yes	2	7		126 (46/54)	132.6	140.6	R for 5 d	2 d
20/67/M	0/32 0/0	Meningitis	No	No	2	5		8	68.1	42.6	R for 4 d	1 d
21/65/M	0/32 40/128	Pneumonitis CN palsy	No	Yes	3	7	2 d	111 (45/55)	122	50	R for 7 d	4 d
22/70/F	40/512 80/512	Pneumonitis	Yes	Yes	1	10	0 d	10 (20/80)	35	53	T for 5 d	–

Mental state: 1. alert, 2. confusion, 3. obtunded, 4. stupor, 5. coma.
R: rifampin, D: doxycycline, T: telithromycin, P: pneumonia
CSF = cerebrospinal fluid; WBC = white blood cell; ARF = acute renal failure; GI bleeding = gastrointestinal bleeding; CN palsy = cranial nerve palsy.

only four of seven patients (57.1%) who died of scrub typhus meningoencephalitis complained of headaches, whereas 29 of 43 (67.4%) survivors did so. This result may be in part explained by the loss of pain sensation in patients with meningitis or meningoencephalitis. However, the time to resolve headache was significantly prolonged in the case group.

Age and occupation (farmer) were significant risk factors for the occurrence of meningitis or meningoencephalitis. Of all the enrolled patients, 166 were farmers, and 135 were not. The mean age of the patients who were farmers was 67 years, whereas the mean age of those who were not was 57 years, and the difference was statistically significant. Because there

are more farmers in the rural population, as a result of the aging of rural communities, it is conceivable that being a farmer by occupation is a risk factor for the occurrence of meningitis or meningoencephalitis.

We identified the presence of pneumonitis as an independent predictive variable by multivariate analysis. Song and others[22] reported that interstitial pneumonitis is closely associated with the morbidity and severity of scrub typhus. Similarly, in our case pneumonitis was frequently associated with meningitis or meningoencephalitis, and moreover, meningitis or meningoencephalitis was 7.7 times more frequent in the patients with pneumonitis than in those free of pnuemonitis suggesting that severe cases of scrub typhus caused by *O. tsutsugamushi* are frequently associated with interstitial pneumonitis as well as meningitis or meningoencephalitis. To confirm that pneumonitis is a significant prognositic factor of meningitis and meningoencephalitis, the chronology of the occurrence of CNS complications should be investigated. However, many of the patients in our study were diagnosed as having both pneumonitis and meningitis or meningoencephalitis at the same time on admission. For this reason, it was difficult to find the chronological tendency. However, in patient 1, pneumonitis was diagnosed on admission, and meningitis obviously occurred thereafter in our hospital.

Six of the nine patients who were transferred from a local clinic to our department had pneumonitis. Pneumonitis preceded meningoencephalitis in two of these six patients, but the sequence was not identified in the remaining four patients. Considering that meningitis or meningoencephalitis usually develops at a late stage, this result might indicate that pneumonitis is a prognostic factor of meningitis or meningoencephalitis. Physicians should be aware of the possibility that patients with scrub typhus pneumonitis may have current meningitis or meningoencephalitis and future CNS complications may arise.

In conclusion, physicians should be aware of the possible development of meningitis or meningoencephalitis during appropriate drug therapy for scrub typhus, including the use of doxycycline, the drug of choice. Moreover, because the frequency of meningitis or meningoencephalitis is relatively high, close observation and intensive care are essential for patients with risk factors, particularly those with pneumonitis. Increasing the doxycycline dosage or administration of antimicrobial agents such as rifampin, with good penetration to the CNS, might be considered in such cases.

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REFERENCES

1. Kim SJ, Chung IK, Chung IS, Song DH, Park SH, Kim HS, Lee MH, 2000. The clinical significance of upper gastrointestinal endoscopy in gastrointestinal vasculitis related to scrub typhus. *Endoscopy 32:* 950–955.
2. Ogawa M, Hagiwara T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y, Kaiho I, Ito T, Nemoto H, Yamamoto N, Masukawa K, 2002. Scrub typhus in Japan: epidemiology and clinical features of cases reported in 1998. *Am J Trop Med Hyg 67:* 162–165.
3. Thap LC, Supanaranond W, Treeprasertsuk S, Kitvatanachai S, Chinprasatsak S, Phonrat B, 2002. Septic shock secondary to scrub typhus: characteristics and complications. *Southeast Asian J Trop Med Public Health 33:* 780–786.
4. Elsom KA, Beebe GW, Sayen JJ, Scheie HG, Gammon GD, Wood FC, 1961. Scrub typhus: a follow-up study. *Ann Intern Med 55:* 784–795.
5. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K, 1991. Rickettsial meningitis and encephalitis. *Arch Intern Med 151:* 1753–1757.
6. Kim DM, Yun NR, Yang TY, Lee JH, Yang JT, Shim SK, Choi EN, Park MY, Lee SH, 2006. Usefulness of nested PCR for the diagnosis of scrub typhus in clinical practice: a prospective study. *Am J Trop Med Hyg 75:* 542.
7. Kim DM, Kim SW, Choi SH, Yun NR, 2010. Clinical and laboratory findings associated with severe scrub typhus. *BMC Infect Dis 10:* 108.
8. Lee J, Kim DM, Yun NR, Byeon YM, Kim YD, Park CG, Kim MW, Han MA, 2011. A comparative study of hepatitis caused by scrub typhus and viral hepatitis A in South Korea. *Am J Trop Med Hyg 85:* 873–877.
9. World Health Organization (WHO), 2004. *WHO Recommended Surveillance Standards.* Second edition. Available at: http://www.who.int/emcdocuments/surveillance/docs/whocdscsrisr992.pdf. Accessed June 19, 2004.
10. Ko AI, Galvao Reis M, Ribeiro Dourado CM, Johnson WD Jr, Riley LW, 1999. Urban epidemic of severe leptospirosis in Brazil. Salvador Leptospirosis Study Group. *Lancet 354:* 820–825.
11. Yu M, Nardella A, Pechet L, 2000. Screening tests of disseminated intravascular coagulation: guidelines for rapid and specific laboratory diagnosis. *Crit Care Med 28:* 1777–1780.
12. Pai H, Sohn S, Seong Y, Kee S, Chang WH, Choe KW, 1997. Central nervous system involvement in patients with scrub typhus. *Clin Infect Dis 24:* 436–440.
13. Vallejo-Maroto I, Garcia-Morillo S, Wittel MB, Stiefel P, Miranda M, Pamies E, Aparicio R, Carneado J, 2002. Aseptic meningitis as a delayed neurologic complication of murine typhus. *Clin Microbiol Infect 8:* 826–827.
14. Dotevall L, Hagberg L, 1989. Penetration of doxycycline into cerebrospinal fluid in patients treated for suspected Lyme neuroborreliosis. *Antimicrob Agents Chemother 33:* 1078–1080.
15. Raoult D, Drancourt M, 1991. Antimicrobial therapy of rickettsial diseases. *Antimicrob Agents Chemother 35:* 2457–2462.
16. Yim CW, Flynn NM, Fitzgerald FT, 1985. Penetration of oral doxycycline into the cerebrospinal fluid of patients with latent or neurosyphilis. *Antimicrob Agents Chemother 28:* 347–348.
17. Strickman D, Sheer T, Salata K, Hershey J, Dasch G, Kelly D, Kuschner R, 1995. *In vitro* effectiveness of azithromycin against doxycycline-resistant and - susceptible strains of *Rickettsia tsutsugamushi*, etiologic agent of scrub typhus. *Antimicrob Agents Chemother 39:* 2406–2410.
18. Mindermann T, Zimmerli W, Gratzl O, 1998. Rifampin concentrations in various compartments of the human brain: a novel method for determining drug levels in the cerebral extracellular space. *Antimicrob Agents Chemother 42:* 2626–2629.

19. Nau R, Prange HW, Menck S, Kolenda H, Visser K, Seydel JK, 1992. Penetration of rifampicin into the cerebrospinal fluid of adults with uninflamed meninges. *J Antimicrob Chemother 29:* 719–724.
20. Cho BA, Ko Y, Kim YS, Kim S, Choi MS, Kim IS, Kim HR, Cho NH, 2012. Phenotypic characterization of peripheral T cells and their dynamics in scrub typhus patients. *PLoS Negl Trop Dis 6:* e1789.
21. Varghese GM, Abraham OC, Mathai D, Thomas K, Aaron R, Kavitha ML, Mathai E, 2006. Scrub typhus among hospitalized patients with febrile illness in South India: magnitude and clinical predictors. *J Infect 52:* 56–60.
22. Song SW, Kim KT, Ku YM, Park SH, Kim YS, Lee DG, Yoon SA, Kim YO, 2004. Clinical role of interstitial pneumonia in patients with scrub typhus: a possible marker of disease severity. *J Korean Med Sci 19:* 668–673.