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CLINICAL AND EPIDEMIOLOGICAL STUDY

The clinical differences between dengue and scrub typhus with acute respiratory failure in southern Taiwan

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Abstract
Background For both dengue and scrub typhus, acute respiratory failure (ARF) is a serious complication. The present study was carried out in order to investigate the clinical courses and outcomes of adult dengue and scrub typhus patients with ARF, and to identify the clinical differences between adult dengue and scrub typhus patients with ARF.
Methods We conducted a retrospective study of the serologically confirmed adult dengue or scrub typhus patients admitted between 1998 and 2008 at Kaohsiung Chang Gung Memorial Hospital. A total of 980 dengue and 102 scrub typhus adult patients were included in our study.
Results Eighteen of the 980 adult dengue patients and 8 of the 102 adult scrub typhus patients had ARF. There were significant differences that existed for eschar ($P = 0.001$; dengue 0%; scrub 62.5%), cough ($P = 0.016$; dengue 55.6%; scrub typhus 100%), white blood cell (WBC) count [$P = 0.026$; dengue 7.40 ± 5.74; scrub typhus 11.84 ± 4.95 ($\times 10^3/\mu L$)], platelet count [$P = 0.008$; dengue 42.2 ± 33.9; scrub typhus 104.1 ± 93.3 ($\times 10^9/L$)], prothrombin time (PT) [$P = 0.007$; dengue 12.82 ± 1.36; scrub typhus 10.74 ± 0.98 (s)], activated partial thromboplastin time (APTT) [$P = 0.002$; dengue 50.81 ± 10.08; scrub typhus 37.44 ± 4.06 (s)], blood urea nitrogen (BUN) [$P < 0.001$; dengue 64.6 ± 43.2; scrub typhus 20.9 ± 9.1 (mg/dL)], creatinine [$P < 0.001$; dengue 3.77 ± 3.37; scrub typhus 1.05 ± 0.37 (mg/dL)], admission day (A-day) [$P = 0.027$; dengue 2.9 ± 1.3; scrub typhus 5.4 ± 2.6 (days)], and ventilator duration [$P = 0.022$; dengue 9.4 ± 14.0; scrub typhus 14.8 ± 10.4 (days)] between both groups.
Conclusions This study provides relatively rare data regarding the clinical differences between adult dengue and scrub typhus patients with ARF.

Keywords Dengue · Scrub typhus · Acute respiratory failure · ARDS · Taiwan

Introduction

Both dengue and scrub typhus are major public health issues in tropical and subtropical areas. Dengue is the most important mosquito-borne viral disease affecting humans worldwide. Symptomatic dengue virus infection can present with a wide range of clinical manifestations, from a mild febrile illness to life-threatening shock syndrome [1–7]. Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*. Scrub typhus is an acute febrile disease characterized by a typical primary necrotic lesion (eschar), generalized lymphadenopathy, rash, and non-specific symptoms such as fever, headache, myalgia, and cough. Severe complications include prominent encephalitis, interstitial pneumonia, acute respiratory distress, myocarditis and pericarditis, cardiac arrhythmia, acute renal failure, acute hepatic failure, and acute hearing loss

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[8–13]. For both dengue and scrub typhus, acute respiratory failure (ARF) is a serious complication [14, 15].

Taiwan has been an endemic area for dengue and scrub typhus for many decades. In southern Taiwan, many adult dengue and scrub typhus patients are admitted to Kaohsiung Chang Gung Memorial Hospital, the largest tertiary medical center in southern Taiwan, with a 2,500-bed capacity. This study retrospectively analyzed the medical records of dengue and scrub typhus adult patients admitted to Kaohsiung Chang Gung Memorial Hospital.

The aim of the present study was to investigate the clinical courses and outcomes of adult dengue and scrub typhus patients with ARF, and to identify the clinical differences between adult dengue and scrub typhus patients with ARF. Identification of the clinical differences between adult dengue and scrub typhus patients with ARF may help clinicians in evaluating the clinical differences between adult dengue and scrub typhus patients with ARF.

Materials and methods

The study protocol was reviewed and approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital (No. 97-1560B).

We conducted a retrospective study of the serologically confirmed adult dengue or scrub typhus patients (age $\geq$18 years) admitted between January 1998 and December 2008 at Kaohsiung Chang Gung Memorial Hospital (KCGMH). KCGMH is a 2,500-bed medical facility serving as a primary care and tertiary referral center in Kaohsiung, Taiwan. The medical records of all the included patients were reviewed.

Quality assurance analyses of diagnostic tests for dengue-infected patients were performed by the Centers for Disease Control (CDC) in Taiwan based on at least one of the following criteria: (1) a positive reverse transcriptase polymerase chain reaction (RT-PCR) result, (2) a positive enzyme-linked immunosorbent assay (ELISA) result for specific IgM antibody to the dengue virus in acute-phase serum, or (3) $\geq$4-fold increase in dengue-specific hemagglutination inhibition (HAI) titers in convalescent serum as compared to acute-phase serum. Patients diagnosed by a specific ELISA-IgM antibody to the dengue virus in acute-phase serum had to be serologically concomitantly negative for the specific IgM antibody to Japanese encephalitis [16, 17].

Quality assurance procedures for the diagnostic tests of scrub typhus patients were conducted by the CDC in Taiwan based on PCR or serology of indirect microimmunofluorescent antibody (IFA) for *O. tsutsugamushi*. Diagnostic IFA was deemed positive for *O. tsutsugamushi* if the total antibody titer for Karp, Kato, and Gilliam strains of *O. tsutsugamushi* had a 4-fold or greater increase in paired positive serum samples, or the antibody titer for IgM was 1:80 [16, 18].

A patient with ARF was defined as follows: a patient that was intubated with mechanical ventilation support due to failure to respond to 40% oxygen via a nasal cannula as confirmed by: (1) hypoxemia ($PaO_2 < 60$ mmHg) or hypercapnia ($PaCO_2 > 50$ mmHg), (2) bradypnea (respiratory rate <10/min) or tachypnea (respiratory rate >35/min), and (3) severe chest retraction and nasal flaring [19]. Systemic inflammatory response syndrome (SIRS) is defined by the presence of two or more of the following findings: body temperature <36°C (97°F) or >38°C (100°F) (hypothermia or fever); heart rate >90 beats per min; respiratory rate >20 breaths per min; or, on blood gas, a $PaCO^2$ less than 32 mmHg; white blood cell (WBC) count <4,000 cells/mm^3 or >12,000 cells/mm^3 (<4×10^9 or >12×10^9 cells/L), or greater than 10% band forms. Sepsis is defined as SIRS to a confirmed infectious process. Infection can be suspected or proven [by culture, stain, or polymerase chain reaction (PCR)], or a clinical syndrome pathognomonic for infection.

The demographic characteristics, initial symptoms/signs, and laboratory data [including peripheral WBC count, hematocrit levels, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, alkaline phosphatase (ALP), serum total bilirubin, blood urea nitrogen (BUN), creatinine, and albumin levels] of the included patients were obtained from medical charts for analyses. The initial symptoms/signs and laboratory data of the included patients were defined as those recorded and assayed upon their respiratory failure. The day of admission (Admission-day, A-day) was defined as the day when the patient was admitted to KCGMH after the onset of illness (beginning of fever). The day of respiratory failure (Failure-day, F-day) was defined as the day when the patient experienced respiratory failure after the onset of illness (beginning of fever).

A diagnosis of acute respiratory distress syndrome (ARDS) was based on the American–European Consensus Committee recommended criteria for ARDS: (1) timing: acute onset; (2) chest radiograph: bilateral lung infiltrates; (3) severe hypoxia: partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) of 200 mmHg or less, regardless of the level of positive end-expiratory pressure (PEEP); and (4) no clinical evidence of elevated left atrial pressure: pulmonary arterial wedge pressure (PAWP) $\leq$18 mmHg [20].

Acute renal failure was defined as oliguria with abruptly elevated serum BUN and creatinine after the patient had been hospitalized for dengue or scrub typhus illness. Acute hepatic failure was defined as the development of

encephalopathy or jaundice, prolonged PT [>3 s compared to that of controls (12 s)], and severe liver damage (elevated ALT > 3-fold that of normal values). Combination concomitant bacterial infection was defined as positive bacterial growth from cultures of blood samples after the patient had been hospitalized for dengue or scrub typhus illness and who met the diagnostic criteria for dengue or scrub typhus infection.

Statistical analysis

Data were collected and analyzed by SPSS for Windows version 10.0 (SPSS Inc., Chicago, IL). Some data are presented as summary statistics. Quantitative variables are presented as average ± standard deviation. Statistical significance was determined by the Mann–Whitney *U*-test for continuous variables and Fisher's exact test/Chi-square test for dichotomous variables. A *P*-value of <0.05 was considered to be statistically significant.

Results

A total of 980 dengue and 102 scrub typhus adult patients were included in our study. Eighteen (1.8%) of the 980 adult dengue patients and 8 (7.8%) of the 102 adult scrub typhus patients had ARF. There was a significant difference in the incidence rate of ARF between adult dengue patients and adult scrub typhus patients ($P = 0.002$). All of the 980 dengue and 102 scrub typhus patients were of Chinese ethnicity.

Comparison of characteristics and underlying diseases

Table 1 presents comparisons of the characteristics and underlying diseases between the adult dengue and scrub typhus patients with ARF. No significant differences existed between the two groups regarding age, gender ratio, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, stroke, and end-stage renal disease (ESRD).

Comparison of initial symptoms/signs and initial laboratory findings

Table 2 presents a summary of the initial symptoms/signs between dengue and scrub typhus patients with ARF. Fever was the most common clinical presentation for both dengue and scrub typhus patients with ARF. Furthermore, the initial symptoms and signs of both groups were compared; there were significant differences in eschar ($P = 0.001$) and cough ($P = 0.016$) between both groups.

Table 3 presents a summary of the initial laboratory findings between the dengue and scrub typhus patients with ARF. Table 3 also presents comparisons of the initial laboratory findings between both groups. No significant differences existed between the two groups for hematocrit, AST, ALT, ALP, total bilirubin, and albumin. However, the WBC count ($P = 0.026$), platelet count ($P = 0.008$), PT ($P = 0.007$), APTT ($P = 0.002$), BUN ($P < 0.001$), and creatinine ($P < 0.001$) were significantly different between both groups.

Comparison of associated clinical courses

The three most associated complications in the adult dengue patients with ARF were upper gastrointestinal (UGI) bleeding (10/18, 55.6%), acute renal failure (8/18, 44.4%), and acute hepatic failure (8/18, 44.4%). The three most associated complications in the scrub typhus patients with ARF were ARDS (8/8, 100%), acute hepatic failure (6/8, 75%), and combination bacterial infection (5/8, 62.5%).

The causes of ARF in the adult dengue patients were sepsis (11/18, 61.1%), hypovolemic shock (due to UGI bleeding) (5/18, 27.8%), neurogenic shock (1/18, 5.6%), and bronchospasm (1/18, 5.6%). The cause of ARF in all the scrub typhus patients was sepsis (8/8, 100%).

Table 4 presents comparisons of the associated clinical courses between the dengue and scrub typhus patients with ARF. There were significant differences between both groups in the A-day ($P = 0.027$) and ventilator duration ($P = 0.022$), but there was no significant difference in the

Table 1 Comparative demographic data and underlying disease/condition between adult dengue and scrub typhus patients with acute respiratory failure (ARF)

	Dengue ($n = 18$)	Scrub typhus ($n = 8$)	*P*-value
Sex (M/F)	13/5	3/5	0.189
Age (years)	64.3 ± 11.2	55.4 ± 21.5	0.683
Diabetes mellitus (%)	5 (27.8%)	1 (12.5%)	0.628
Hypertension (%)	9 (50%)	1 (12.5%)	0.099
COPD (%)	6 (33.3%)	3 (37.5%)	1.000
Previous stroke (%)	4 (22.2%)	0	0.277
ESRD (%)	3 (16.7%)	0	0.529
Malignancy (%)	1 (5.6%)	0	1.000

COPD chronic obstructive pulmonary disease, *ESRD* end-stage renal disease

Table 2 Comparative initial symptoms/signs between adult dengue and scrub typhus patients with ARF

Initial symptoms/signs	Dengue ($n = 18$)	Scrub typhus ($n = 8$)	P-value
Fever	17 (94.4%)	8 (100%)	1.000
Eschar	0	6 (62.5%)	**0.001**
Petechiae	8 (44.4%)	3 (37.5%)	1.000
Arthralgia	8 (44.4%)	1 (12.5%)	0.190
Myalgia	8 (44.4%)	1 (12.5%)	0.190
Headache	8 (44.4%)	2 (25%)	0.420
Gum bleeding	3 (16.7%)	1 (12.5%)	1.000
Chest pain	5 (27.8%)	2 (25%)	1.000
Cough	10 (55.6%)	8 (100%)	**0.031**
Dyspnea	10 (55.6%)	7 (41.2%)	0.190
Hemoptysis	2 (11.1%)	1 (12.5%)	1.000
Abdomen pain	11 (61.1%)	3 (37.5%)	0.401
Vomiting	7 (38.9%)	1 (12.5%)	0.360
Diarrhea	3 (16.7%)	1 (12.5%)	1.000
Tarry stool	6 (33.3%)	2 (25%)	1.000

Individual patients may have exhibited more than one symptom and/or sign

Table 3 Comparative initial laboratory data between adult dengue and scrub typhus patients with ARF

	Dengue (n = sample size)	Scrub typhus (n = sample size)	P-value
WBC ($\times 10^3/\mu L$)	7.40 ± 5.74 ($n = 18$)	11.84 ± 4.95 ($n = 8$)	**0.026**
Hematocrit (%)	33.19 ± 8.64 ($n = 18$)	33.13 ± 5.54 ($n = 8$)	0.935
Platelet ($\times 10^9/L$)	42.2 ± 33.9 ($n = 18$)	104.1 ± 93.3 ($n = 8$)	**0.008**
PT (s)	12.82 ± 1.36 ($n = 18$)	10.74 ± 0.98 ($n = 5$)	**0.007**
APTT (s)	50.81 ± 10.08 ($n = 18$)	37.44 ± 4.06 ($n = 5$)	**0.002**
AST (U/L)	709.2 ± 1,381.4 ($n = 18$)	153.9 ± 68.5 ($n = 8$)	0.129
ALT (U/L)	543.8 ± 1,029.6 ($n = 18$)	153.5 ± 78.1 ($n = 8$)	0.461
ALP	115.0 ± 29.4 ($n = 9$)	178.8 ± 100.9 ($n = 8$)	0.114
Total bilirubin (mg/dL)	2.68 ± 1.29 ($n = 12$)	3.72 ± 3.67 ($n = 8$)	0.473
BUN (mg/dL)	64.6 ± 43.2 ($n = 14$)	20.9 ± 9.1 ($n = 8$)	**<0.001**
Creatinine (mg/dL)	3.77 ± 3.37 ($n = 17$)	1.05 ± 0.37 ($n = 8$)	**<0.001**
Albumin (g/dL)	2.47 ± 0.53 ($n = 18$)	2.80 ± 0.92 ($n = 8$)	0.531

Values are shown as the mean ± standard deviation (SD)

WBC white blood cell, *PT* prothrombin time, *APTT* activated partial thromboplastin time, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *BUN* blood urea nitrogen

F-day. No significant differences existed between the two groups for acute renal failure, acute hepatic failure, combination bacterial infection, UGI bleeding, and mortality. However, ARDS ($P < 0.001$) was significantly different between both groups.

Discussion

This 10-year retrospective study showed that 1.8% of 980 adult dengue patients and 7.8% of 102 adult scrub typhus patients had ARF. The mortality rate was 55.6% (10/18)

Table 4 Comparative disease-associated complications and mortality between adult dengue and scrub typhus patients with ARF

	Dengue ($n = 18$)	Scrub typhus ($n = 8$)	P-value
A-day (days)	2.9 ± 1.3	5.4 ± 2.6	**0.027**
F-day (days)	4.6 ± 2.0	6.9 ± 3.6	0.115
Ventilator duration (days)	9.4 ± 14.0	14.8 ± 10.4	**0.022**
Acute renal failure	8 (44.4%)	2 (25%)	0.420
Acute hepatic failure	8 (44.4%)	6 (75%)	0.216
Combination bacterial infection	7 (38.9%)	5 (62.5%)	0.401
ARDS	3 (16.7%)	8 (100%)	**<0.001**
UGI bleeding	10 (55.6%)	4 (50%)	1.000
Mortality	10 (55.6%)	2 (25%)	0.216

A-day the day when the patient was admitted after illness onset (fever beginning)

F-day the day when the patient experienced acute respiratory failure (ARF) after illness onset (fever beginning)

ARDS acute respiratory distress syndrome

UGI bleeding upper gastrointestinal bleeding

Combination bacterial infection was observed in seven dengue patients: bacterial meningitis (B/C, CSF/C: *Klebsiella pneumoniae*); urinary tract infection (U/C: *Acinetobacter baumannii*); pneumonia (S/C: *Klebsiella pneumoniae*); urinary tract infection (U/C: *Citrobacter diversus*); urinary tract infection (B/C, U/C: *Corynebacterium*); bacteremia (B/C: *Klebsiella pneumoniae*); pneumonia (B/C, S/C: *Corynebacterium*)

Combination bacterial infection was observed in five scrub typhus patients: urinary tract infection (*Escherichia coli*); pneumonia (*Pseudomonas aeruginosa*); urinary tract infection (*Escherichia coli*); central venous pressure line infection (*Staphylococcus aureus*); pneumonia (*Acinetobacter baumannii*, *Corynebacterium*)

for adult dengue patients with ARF and 25% (2/8) for adult scrub typhus patients with ARF. Only a few cohort studies on adult dengue patients and adult scrub typhus patients complicated with ARF have been published [14, 15, 21]. Furthermore, no cohort study comparing the clinical differences between adult dengue and scrub typhus patients with ARF has been published. This may have resulted in a lack of wide-spread awareness of ARF in adult dengue and scrub typhus patients. Consequently, clinicians are likely not aware of the potential for ARF when treating adult dengue patients and adult scrub typhus patients. This study provides relatively rare data regarding the clinical differences between the potential for ARF when treating adult dengue patients and adult scrub typhus patients.

Although there were no significant differences in underlying diseases between adult dengue and scrub typhus patients with ARF, other than COPD (37.5%) in the scrub typhus group, the incidence of other underlying diseases was lower (less than 20%) in the current study. Furthermore, no history of stroke was noted in the scrub typhus group. One possible reason for this is that scrub typhus is a mite-borne infectious disease caused by *O. tsutsugamushi*. Almost all subjects had a history of traveling to highly endemic areas, which indicates that most scrub typhus have the resilience to survive extensive travel.

Fever was the major symptom/sign for both ARF groups. Eschar was only observed in scrub typhus patients and was a specific symptom/sign for scrub typhus patients ($P = 0.001$). Incidences of arthralgia, myalgia, headache, and abdomen pain were higher in the dengue group than in the scrub typhus group (there were no significant differences, possibly due to the small sample size). The incidence of cough was significantly higher in the scrub typhus group than in the dengue group ($P = 0.031$). This finding could be explained by the fact that ARDS was the major cause and complication for ARF in the scrub typhus group.

Platelet count ($P = 0.008$), PT ($P = 0.007$), and APTT ($P = 0.002$) were significantly different between both groups. In this study, all 18 adult dengue patients with ARF also presented with dengue hemorrhagic fever (DHF). DHF is the most serious manifestation of dengue. The cardinal features that distinguish DHF from classic dengue are as follows: (1) increased vascular permeability (plasma leakage syndrome); (2) marked thrombocytopenia (<100,000/μL) associated with a bleeding tendency; and (3) hepatomegaly and/or abnormal liver function [22]. Additionally, plasma leakage syndrome is the most specific and life-threatening feature of DHF [23]. Plasma leakage syndrome and extreme depression of the platelet count associated with bleeding tendency frequently occurs between 3 and 7 days after illness onset [24]. In this study, all 18 adult dengue patients with ARF were intubated between day 2 and day 8 (mean 4.6 ± 2.0 days) after illness onset. This finding is similar to the clinical course regarding plasma leakage syndrome occurring in dengue patients with DHF.

The WBC level of the scrub typhus group was significantly higher than that of the dengue group ($P = 0.026$), indicating that the scrub typhus group was more seriously infected than the dengue group. Sepsis complicated with ARDS was the main cause of ARF for the whole scrub

typhus group (8/8, 100%), whereas sepsis complicated with ARDS was only observed in three patients (3/18, 16.7%) in the dengue group.

BUN ($P < 0.001$) and creatinine ($P < 0.001$) were significantly higher in the dengue group than in the scrub typhus group. Renal failure was another important factor in developing ARF for both groups [14, 15]. All cases of acute renal failure were observed before ARF occurred in both groups in our study. Acute renal failure is rare in dengue patients and may result from excessive plasma leakage or a massive active hemorrhage in dengue patients [25, 26].

Although acute renal failure is rare in dengue and scrub typhus patients, it seems to progress to ARF when acute renal failure becomes complicated in dengue and scrub typhus patients. The renal failure of dengue patients was also another important factor to develop ARF. There were significant differences between both groups with regard to the laboratory data (BUN and creatinine) and clinical course (renal insufficiency and acute renal failure). As previously mentioned, all cases of acute renal failure were observed before ARF occurred in our study.

This retrospective study has several limitations. First, it was conducted at a single medical center, and there may be patient population selection bias and referral patterns. Second, this study was a retrospective survey, which not only resulted in incomplete data for some patients, but it also did not control for laboratory examinations and the clinical courses of all adult dengue and scrub typhus patients. Therefore, further prospective investigations should be conducted. Despite these limitations, this study provides relatively rare data regarding the clinical differences between adult dengue and scrub typhus patients with ARF.

Both dengue and scrub typhus are very important and easily neglected diseases in tropical and subtropical areas. Both can present with a life-threatening shock syndrome. We should keep in mind the possibility of dengue and scrub typhus for an early correct differential diagnosis; furthermore, appropriate treatment strategies will be developed eventually in order to avoid ARF in these diseases.

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Conflict of interest The authors declare that they have no conflict of interest.

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