Journal of Microbiology, Immunology and Infection (2017) 50, 104–111

Available online at www.sciencedirect.com

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ORIGINAL ARTICLE

Identification of factors for physicians to facilitate early differential diagnosis of scrub typhus, murine typhus, and Q fever from dengue fever in Taiwan

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Received 5 January 2014; received in revised form 30 September 2014; accepted 9 December 2014
Available online 26 December 2014

KEYWORDS
dengue fever;
murine typhus;
Q fever;
rainfall;
scrub typhus;
temperature

Background: Dengue fever, rickettsial diseases, and Q fever are acute febrile illnesses with similar manifestations in tropical areas. Early differential diagnosis of scrub typhus, murine typhus, and Q fever from dengue fever may be made by understanding the distinguishing clinical characteristics and the significance of demographic and weather factors.
Methods: We conducted a retrospective study to identify clinical, demographic, and meteorological characteristics of 454 dengue fever, 178 scrub typhus, 143 Q fever, and 81 murine typhus cases in three Taiwan hospitals.

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http://dx.doi.org/10.1016/j.jmii.2014.12.001

Results: Case numbers of murine typhus and Q fever correlated significantly with temperature and rainfall; the scrub typhus case number was only significantly related with temperature. Neither temperature nor rainfall correlated with the case number of dengue fever. The rarity of dengue fever cases from January to June in Taiwan may be a helpful clue for diagnosis in the area. A male predominance was observed, as the male-to-female rate was 2.1 for murine typhus and 7.4 for Q fever. Multivariate analysis revealed the following six important factors for differentiating the rickettsial diseases and Q fever group from the dengue fever group: fever $\geq$8 days, alanine aminotransferase $>$ aspartate aminotransferase, platelets $>$63,000/mL, C-reactive protein $>$31.9 mg/L, absence of bone pain, and absence of a bleeding syndrome.
Conclusion: Understanding the rarity of dengue in the first half of a year in Taiwan and the six differentiating factors may help facilitate the early differential diagnosis of rickettsial diseases and Q fever from dengue fever, permitting early antibiotic treatment.

Introduction

Dengue fever, scrub typhus, murine typhus, and Q fever are common infections in tropical Asia and often present initially as acute febrile illnesses of unclear etiology.[1,2] Many clinical manifestations and laboratory results of dengue fever[2–4] resemble those of rickettsial diseases (such as scrub typhus and murine typhus) and Q fever,[5–9] which makes an early diagnosis difficult. The local data revealed the mortality rate of scrub typhus cases to be 1.5–3%[10,11] and that of murine typhus to be 1.2%.[12] The limited data with regard to Q fever in Taiwan revealed no mortality.[13] The mortality rate of dengue fever is 0.4%, but that of dengue hemorrhagic fever is 8.7%.[14] For suspected cases of scrub typhus, murine typhus, and Q fever, empirical doxycycline is indicated to save lives. In cases of dengue fever, careful observation for the occurrence of dengue hemorrhagic fever is warranted. Therefore, establishing an early differential diagnosis of these diseases is important for providing the appropriate antimicrobial therapy and carefully monitoring anticipated complications.

We retrospectively evaluated cases of dengue fever, rickettsial diseases (scrub typhus and murine typhus), and Q fever from three Taiwan hospitals located south of the Tropic of Cancer. This tropical area has the highest case numbers of dengue fever, rickettsial diseases, and Q fever in Taiwan. In Taiwan, there are case series reports of Q fever, scrub typhus, murine typhus, and dengue fever.[15–17] Our aim was to compare the demographics and clinical characteristics of dengue fever with those of rickettsial diseases and Q fever in order to help with the establishment of an early differential diagnosis. The associated incidence of the four diseases each month and weather factors (i.e., temperature and rainfall) were also analyzed.

Methods

We retrospectively reviewed the charts of all the patients with dengue fever, scrub typhus, murine typhus, or Q fever in three Taiwan hospitals KMUH (Kaohsiung Medical University Hospital), KMHKH (Kaohsiung Municipal Hsaio-Kang Hospital), and NCKUH (National Cheng Kung University Hospital) from 1995 to 2009. The three hospitals that provide about 20% of the hospital beds in the Kaohsiung and Tainan regions are located in a region that is home to about 4,643,000 persons in an area of 5138 km^2. This work was approved by the Institute Ethics Committee of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (KMUH-IRB-960195 and KMUH-IRB-970216). The Institute Ethics Committee of Kaohsiung Medical University Hospital waived the need for written informed consent from the participants because of the nature of the study and the retrospective collection of routine medical practice data. We collected data including demographic characteristics (including age, gender, and location), clinical manifestations, and laboratory results. All data analyzed were anonymized. The characteristics of murine typhus cases in the study have already been reported.[12] Relative bradycardia was defined as an increase in heart rate by $<$10 beats/min/°C increase in temperature in the absence of cardiac arrhythmia, a pacemaker, or administration of beta-blockers.[18]

Case definitions

All the laboratory diagnostic methods were performed at the laboratories of the Center for Disease Control and Prevention, Taiwan. The diagnosis of dengue fever was confirmed if one of the following criteria was met: (1) virus isolation; (2) positive result of real-time polymerase chain reaction; (3) positive result of higher-titer dengue-specific immunoglobulin (Ig)M and IgG antibodies in a single serum specimen, in which cross-reaction to Japanese encephalitis had been excluded; or (4) positive seroconversion or $\geq$4-fold rise in dengue-specific IgM or IgG antibody from the acute phase compared with the convalescent phase.[19] The diagnosis of Q fever was made based on the presence of fever and a compatible serologic profile, which included at least a 4-fold increase in Phase II IgG titers between the acute and convalescent sera or the presence of a significant titer of Phase II IgM ($\geq$1:50) by indirect immunofluorescence assay at the Centers for Disease Control, Taiwan.[6,20] Scrub typhus was diagnosed from patients' blood samples based on a polymerase chain reaction analysis[21] or the serology result of an indirect microimmunofluorescence assay for *Orientia tsutsugamushi*. Diagnostic immunofluorescence assay must have met the following criteria: the total antibody titer for