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Original article

Comparison of clinical characteristics and laboratory findings of malaria, dengue, and enteric fever in returning travelers: 8-year experience at a referral center in Tokyo, Japan

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ABSTRACT

Background: Without specific symptoms, diagnosis of febrile illness in returning travelers is challenging. Dengue, malaria, and enteric fever are common causes of fever in returning travelers and timely and appropriate treatment is important. However, differentiation is difficult without specific diagnostic tests.
Methods: A retrospective study was conducted at the National Centre for Global Health and Medicine (NCGM) from April 2005 to March 2013. Febrile travelers returning from overseas who were diagnosed with dengue, malaria, or enteric fever were included in this study. Clinical characteristics and laboratory findings were compared for each diagnosis.
Results: During the study period, 86 malaria, 85 dengue, and 31 enteric fever cases were identified. The mean age of the study cohort was 33.1 ± 12 years and 134 (66.3%) study participants were male. Asia was the most common area visited by returning travelers with fevers (89% of dengue, 18.6% of malaria, and 100% of enteric fever cases), followed by Africa (1.2% of dengue and 70.9% of malaria cases). Clinical characteristics and laboratory findings were significantly different among each group with each diagnosis. Decision tree models revealed that returning from Africa and CRP levels <10 mg/L were factors specific for diagnosis of malaria and dengue fever, respectively.
Conclusion: Clinical manifestations, simple laboratory test results, and regions of travel are helpful to distinguish between dengue, malaria, and enteric fever in febrile returning travelers with non-specific symptoms.

1. Introduction

A GeoSentinel review of over 42,000 ill-returned travelers highlighted that malaria, dengue fever (DF), and enteric fever (EF) were the most common causes of febrile illness in returning travelers during 2007–2011, accounting for 28.7%, 14.6%, and 4.6% fever cases, respectively [1]. The clinical manifestations of these diseases, including fever, headache, arthralgia, myalgia, and gastrointestinal symptoms, are non-specific and overlapping. Therefore, it is challenging to diagnose these diseases without specific tests. In Japan, a limited number of clinics perform specific tests to differentiate these diseases, such as malaria smear tests or rapid diagnostic tests for DF. The number of people who travel abroad is increasing due to the globalization of economy and tourism [2]; thus, early disease diagnosis is important.

We have previously reported the clinical characteristics of DF and malaria cases in our institute from 2005 to 2010 [3], and differences in laboratory findings between DF and malaria cases from 2005 to 2013 [4]. The current study included the same sample set of patients with DF and malaria, and extended the observations of our previous studies. The sample set was used to assess differences in clinical characteristics, including the location where the disease (DF, malaria, or EF) was contracted, duration of stay at the location, and clinical manifestations of the diseases in travelers. These characteristics were used to design a flow chart to distinguish between DF, malaria, and EF.

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Table 1
Countries where patients with dengue fever were infected. 13 patients who visited more than one endemic country were excluded.

Country	Number of patients	Country	Number of patients	Country	Number of patients
Southeast Asia		**South Asia**		**Africa**	
Philippines	19	India	9	Benin	1
Indonesia	16	Bangladesh	3	**Oceania**	
Thailand	4	Pakistan	2	Papua New Guinea	1
Cambodia	3	Sri Lanka	2	Tahiti	1
Malaysia	2			Solomon Islands	1
Myanmar	2			Tonga	1
East Timor	2			**Latin America**	
Viet Nam	1			Mexico	1
				Brazil	1

To our knowledge, no other study has compared the usefulness of clinical characteristics and general laboratory findings to differentiate these diseases. The aim of this study was to describe differences in clinical characteristics and laboratory findings and to design decision tree models to diagnose DF, malaria, and EF at the first hospital presentation.

2. Patients and methods

This retrospective study was conducted at the National Centre for Global Health and Medicine (NCGM), a tertiary care governmental general hospital in Tokyo, Japan with about 900 inpatient beds which houses a travel clinic that is also a GeoSentinel Network site. NCGM functions as a referral hospital for returned travelers. Febrile returned travelers who visited NCGM during the period (April 2005 through March 2013) and were diagnosed with malaria, dengue, or EF were included in the study. Patients without fever at the first presentation were excluded. Demographic information including age, sex, nationality, and possible source of infection as well as reasons for travel, including business, leisure, visiting friends or relatives (VFR), volunteering, resease, expatriation or other reasons, were analyzed. Each country was classified according to geographical region, including Asia, Africa, Oceania, and South America. If 2 or more countries were visited, then all visited countries were included in the data. Clinical manifestations (rash, diarrhea, nausea/vomiting, headache, arthralgia, and myalgia) and laboratory data (white blood cell, WBC; hematocrit, Ht; platelet, Plt; total bilirubin, T-bil; aspartate aminotransferase, GOT; glutamate oxaloacetate transaminase, GPT; glutamate pyruvate transaminase, LDH; and C-reactive protein; CRP) at the first presentation were collected.

Dengue was confirmed by real-time polymerase chain reaction (PCR) (TaqMan RT-PCR), IgM-capture ELISA, IgG ELISA performed at the National Institute of Infectious Diseases in Tokyo, Japan, and a rapid diagnostic test that detected the viral non-structural 1 antigen (Standard Diagnostics Inc., Korea) performed at NCGM.

Malaria was confirmed by combined conventional microscope examination of Giemsa-stained thin blood films and rapid diagnostic tests (BinaxNOW Malaria Test, Binax, Inc. Maine, USA); *Plasmodium* species were confirmed by PCR if parasite morphology was not diagnostic. Laboratory diagnoses were performed at the Research Institute of the National Centre for Global Health and Medicine.

EF was confirmed by blood or stool culture of *Salmonella enterica* serotype Typhi or paratyphi A in the setting of a compatible clinical illness.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20 (2011, IBM Corp., Armonk, NY, USA). The sensitivity and specificity of the decision trees were calculated using a diagnostic test calculator (MedCalc Software; http://www.medcalc.org/calc/diagnostic_test.php). The Mann–Whitney U test was used to compare continuous variables. A two-sided P value <0.05 was considered statistically significant. The study protocol was approved by the Ethics Committee at National Center for Global Health and Medicine (approved number: NCGM-G-001648-00).

Table 2
Countries where patients with malaria were infected. Of confirmed cases, 56 were due to *Plasmodium falciparum* (*Pf*), 20 were *P. vivax* (*Pv*), 8 were *P. ovale* (*Po*), 1 was *P. malariae* (*Pm*), and 1 was *P. knowlesi* (*Pk*) infection. 8 patients (5*Pf*, 2*Pv*, 1*Po*) who visited more than one endemic country were excluded.

Country	Number of patients	Country	Number of patients	Country	Number of patients
Oceania		**South Asia**		**Africa**	
Papua New Guinea	4 (1 *Pf*, 3 *Pv*)	India	6 (6 *Pv*)	Ghana	13 (11 *Pf*, 2 *Po*)
Solomon islands	1 (1 *Pf*)	Pakistan	2 (2 *Pv*)	Nigeria	9 (9 *Pf*)
Latin America				Uganda	7 (3 *Pf*, 4 *Po*)
Brazil	2 (2 *Pv*)			Benin	4 (4 *Pf*)
French Guiana	1 (1 *Pv*)	**Southeast Asia**		Sierra Leone	3 (3 *Pf*)
Ecuador	1 (1 *Pv*)	Indonesia	3 (2 *Pf*, 1 *Pv*)	Guinea	3 (3 *Pf*)
		Malaysia	2 (1 *Pv*, 1 *Pk*)	Cameroon	3 (2 *Pf*, 1 *Po*)
		Myanmar	1 (1 *Pf*)	Zambia	2 (2 *Pf*)
				Burkina Faso	2 (2 *Pf*)
				Malawi	2 (2 *Pf*)
				Kenya	1 (1 *Pf*)
				Rwanda	1 (1 *Pv*)
				Togo	1 (1 *Pf*)
				Senegal	1 (1 *Pf*)
				Cote d'Ivoire	1 (1 *Pf*)
				Mali	1 (1 *Pf*)
				Mozambique	1 (1 *Pm*)

3. Results

Characteristics of DF, malaria, and EF are shown in Tables 1–4. Clinical manifestations of these diseases were compared and odds ratios calculated (Table 5). Laboratory findings were compared using the Mann–Whitney U-test for each diagnosis group (Table 6).

The flow chart for determining DF, malaria, and EF at the first hospital presentation are shown in Fig. 1. "Returning from Africa" had a sensitivity of 72.09% (95% confidence interval [95% CI] = 61.38–81.23%) and specificity of 99.14% (95% CI = 95.27–99.86%) to predict malaria as opposed to the other 2 diseases (Box A). "Returning from elsewhere than Africa" combined with "CRP < 10 mg/L" had a sensitivity of 76.47% (95% CI = 66.02–84.99%) and specificity of 98.29% (95% CI = 93.95–99.74%) to predict DF as opposed to the other 2 diseases (BOX B). "Returning from elsewhere than Africa" combined with "CRP > 10 mg/L" had a sensitivity of 96.77% (95% CI = 83.24–99.46%) and specificity of 75.44% (95% CI = 68.28–81.69%) to predict EF as opposed to the other 2 diseases (BOX C). "Returning from Africa" or "Returning from elsewhere than Africa" with "CRP >10 mg/L" had a sensitivity of 98.84% (95% CI = 93.67–99.81%) and specificity of 57.76% (95% CI = 48.24–66.87%) to predict malaria as opposed to the other 2 diseases (BOX A + C). The combination of "Returning from elsewhere than Africa," "CRP > 10 mg/L," "Returned from South Asia," and "Platelet count < 15 cells/mm^3" had a sensitivity of 51.61% (95% CI = 33.07–69.83%) and specificity of 99.42% (95%