Travel Medicine and Infectious Disease (2016) 14, 39–44

Available online at www.sciencedirect.com

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journal homepage: www.elsevierhealth.com/journals/tmid

Clinical features and laboratory findings of dengue fever in German travellers: A single-centre, retrospective analysis

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Received 7 December 2015; received in revised form 21 January 2016; accepted 22 January 2016
Available online 29 January 2016

KEYWORDS
Dengue;
Travel-associated infection;
Vector-borne disease;
Arthropod-borne disease;
Arboviral infection

Summary *Background:* Dengue fever (DF) is one of the most relevant human arboviral infections worldwide and has become a frequent cause of fever in the returning traveller. This retrospective study aimed to characterize epidemiological and clinical features and laboratory findings of dengue fever in German travellers.
Methods: This descriptive study analyzed medical records of patients diagnosed with DF presenting at the Section of Tropical Medicine of the University Medical Centre Hamburg-Eppendorf from 2007 to 2011. Data were collected and analyzed retrospectively.
Results: In total, data of 119 DF patients (52 female, 67 male) were included in this study. The median age of the patients was 35 (range 15–75 years). DF was most frequently acquired in South-East Asia (n = 65; 54.7%), and in particular in Thailand (n = 23; 19.7%). A considerable percentage of DF infections (n = 14; 11.8%) was imported from Africa. Patients predominantly presented with fever, headache, rash, myalgia and arthralgia but also with gastrointestinal symptoms, i.e. diarrhoea. Nine patients showed signs of minor haemorrhagic manifestations. Neurological complications occurred in 13 patients. Low platelet count, leukopenia and elevated liver enzymes were the most relevant laboratory findings. Twenty patients (17.8%) had to be hospitalized. Overall, the clinical course was mostly mild to moderate, 13 patients (10.9%) showed DF warnings signs, no fatalities occurred.

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http://dx.doi.org/10.1016/j.tmaid.2016.01.007

Conclusions: DF presented as a mostly mild to moderate disease in this study cohort. Outpatient treatment was adequate for the majority of patients. Still, detailed knowledge of clinical symptoms and laboratory features is essential for appropriate triage.

1. Introduction

Around 3.5 billion people are living in dengue virus (DENV) countries with the major disease burden in South East Asia, South Asia and Latin America. There has been a 30-fold growth of the worldwide incidence of DENV in the last 50 years and DENV has become a great severe public health concern in many countries around the world [1—3]. DENV is not only relevant for DENV-endemic countries but has become a matter of significance for non-endemic areas i.e. Europe, Australia and Northern America. Dengue Fever (DF) is the most frequent arboviral infection among travellers and was shown to be the second most common reason for fever among returning travellers only second to malaria [4,5]. The main factors for the worldwide increase of the incidence of DF are rising international travel, urbanization, overpopulation and climate changes [6,7].

DF is an acute febrile illness caused by one of the four antigenically distinct DENV serotypes (DENV-1, DENV-2, DENV-3, DENV-4). The primary vector is the day biting and highly anthropophilic *Aedes* (*Ae*.) *aegypti*. *Ae*. *aegypti* mosquitos are effective vectors and their global distribution is matching the distribution of DENV [8,9].

The clinical presentation of DF ranges from asymptomatic infection or mild self-limiting febrile illness to a potentially fatal illness with haemorrhage or shock syndrome resulting in multiple organ failure, formerly classified as dengue haemorrhagic fever (DHF) and dengue shock syndrome [10]. Symptomatic patients typically present with one or more of the following symptoms: high fever, headache, retro-orbital pain, myalgia, arthralgia, rash or nausea/vomiting [11]. The clinical course of the infection can be divided into three phases: an initial febrile phase lasting 3—7 days, a 24—48 h lasting critical phase around defervescence and the recovery phase. In the critical phase, a small number of patients develop symptoms of plasma leakage, coagulation derangement and organ impairment. Severe dengue also includes patients with hepatitis, neurological disorders, myocarditis or severe bleeding without plasma leakage or shock. The febrile phase is often associated with leukopenia. An increase in haematocrit and rapid decrease of platelet count are associated with complications in the critical phase [10,12]. Severe cases of dengue fever with case fatality rates ranging from $<$1—5% are associated with secondary infections. Children living in endemic regions have the highest risk of acquiring these secondary infections [13]. The pathogenesis of dengue is likely to be a complex interplay of host immunity and genetic predisposition as well as viral virulence factors [14]. A revised WHO case classification was introduced in 2009, replacing the traditional dengue fever and dengue haemorrhagic fever/dengue shock syndrome with dengue with and without warning signs and severe dengue. The revised guidelines aimed to facilitate early risk stratification and improve clinical management of patients with DF [15].

The increasing numbers of imported DF to Europe resulted in a rising number of autochthonous DF cases in several European countries where the potential vectors *Ae*. *albopictus* and *Ae*. *aegypti* are present. Since 2010 several cases have been reported from Croatia, Italy, Spain and France [16]. The so far largest outbreak of autochthonous DF in Europe occurred in Madeira, Portugal in October 2012 to February 2013 with more than 2000 local infections and with 81 cases imported to continental Europe. About 100 patients were hospitalized due to DF during the outbreak. No fatalities occurred [17,18]. Severe infections seem to be less common in travellers than in endemic populations but still there are reports of fatal cases [19—21].

Since there is an increasing number of returning travellers with DF, acquisition of detailed knowledge of symptoms of the disease, potential risk factors for severe disease and disease management is becoming important not only to infectious disease specialists in non-endemic countries but as well for general practitioners. Our study aimed to identify epidemiological and clinical characteristics as well as laboratory findings of a real life cohort of outpatients and hospitalized patients with acute DF in a tertiary care centre in Germany.

2. Material and methods

For this retrospective single centre analysis, case records of patients presenting at the Section of Tropical Medicine at the University Hospital Hamburg-Eppendorf from January 2007 to April 2011 and were undergoing serological testing for DENV infection were revised. Potential cases were identified from laboratory records held at the Bernhard Nocht Institute for Tropical Medicine, which serves as a reference laboratory for tropical diseases in Germany and is the WHO Collaborating Centre for Arbovirus and Hemorrhagic Fever Reference and Research. The Section of Tropical Medicine serves as a tertiary care centre for infectious diseases in Hamburg and is a referral centre for imported tropical diseases in Germany. All patients gave written consent for the use of pseudonymized personal and medical data for research purposes.

2.1. Study subjects

DENV IgM and IgG antibody tests and DENV real-time RT-PCR were performed as previously described [22]. In addition, the presence of DENV nonstructural protein-1 (NS1) antigen in serum samples was tested by ELISA (Bio-Rad Platelia