Dengue fever in Czech travellers: A 10-year retrospective study in a tertiary care centre

Milan Trojánek a,b,*, Jan Maixner c, Naděžda Sojková c, Jan Kyncl d,e, Hana Roháčová a,b, Vilma Marešová a,b, František Stejskal a,b,f,g

a 1st Department of Infectious Diseases, 2nd Medical Faculty, Charles University in Prague, Budínova 2, 180 81 Prague, Czech Republic
b Department of Infectious, Parasitic and Tropical Diseases, Hospital Na Bulovce, Budínova 2, 180 81 Prague, Czech Republic
c Department of Virology, Institute of Public Health in Ústí nad Labem, Budínova 2, 180 81 Prague, Czech Republic
d Department of Epidemiology of Infectious Diseases, National Institute of Public Health, Šrobarová 48, 100 42 Prague, Czech Republic
e Department of Epidemiology, 3rd Medical Faculty, Charles University in Prague, Ruská 87, 100 00 Prague, Czech Republic
f Institute of Immunology and Microbiology, 1st Medical Faculty, Charles University in Prague, Studnickova 7, 128 00 Prague, Czech Republic
g Department of Infectious Diseases, Regional Hospital Liberec, Husova 10, 460 63 Liberec, Czech Republic

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Summary  Background: Dengue fever is a frequent cause of morbidity in travellers. The objective was to describe the epidemiological and clinical characteristics of dengue fever in Czech travellers.
Method: This descriptive study includes patients with acute dengue fever diagnosed at Hospital Na Bulovce during 2004—2013. Data were collected and analysed retrospectively.
Results: A total of 132 patients (83 males and 49 females) of median age 33 years (IQR 29–40) were included. Diagnosis was established by NS1 antigen detection in 87/107 cases (81.3%) and/or RT-PCR in 50/72 (69.4%) and by serology in 25 cases (18.9%). Dengue was acquired in South-East Asia in 69 cases (52.3%), followed by South Asia (48 cases; 36.3%), Latin America (14; 10.6%) and Sub-Saharan Africa (1; 0.8%). The most frequent symptoms included fever, rash and headache. Initial leucocyte and lymphocyte counts were lower in patients who presented in the early phase (0–4 days), however, platelet count was lower and AST, ALT and LDH activity

* Corresponding author. Department of Infectious Diseases, 2nd 8 Medical Faculty, Charles University in Prague, Budínova 2, 9 180 81 Prague, Czech Republic. Tel.: +420 266 083 197; fax: +420 283 840 504.
E-mail address: milan.trojanek@bulovka.cz (M. Trojánek).

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1. Introduction

Dengue fever is the most common arthropod-borne viral infection in the world and is becoming increasingly recognized as an emerging public health issue. The disease is endemic in more than 100 tropical and subtropical countries and 2.5 billion people live in areas with risk of transmission. According to recent estimates, there are 390 million infections every year. Severe dengue develops in approximately 500,000 patients resulting in 22,000 deaths annually [1]. The major disease burden is reported in Southeast Asia, South Asia and Latin America [1,2].

Dengue fever is a viral infection caused by five closely related single-stranded RNA viruses that belong to the family Flaviviridae. New virus dengue 5 has been recently identified during an outbreak in Sarawak state in Borneo in Malaysia in 2007 [3]. The principal vectors of infection are Aedes mosquitoes, especially the species Ae. aegypti [2].

The spectrum of clinical manifestation ranges from asymptomatic infection or mild self-limiting febrile illness to a potentially fatal disease with the development of shock and multiple organ failure. The clinical symptoms usually include fever, frontal or retro-orbital headache, arthralgia, myalgia and rash. Only 1–3% of infected people develop severe dengue with case-fatality rates ranging from <1 to 5%. The risk of severe clinical course is associated with secondary dengue infection and the greatest burden occurs in children living in endemic areas [2,4].

Dengue is recognized as a frequent cause of morbidity in travellers. The presence of the virus in the most popular tourist destinations and the steady increase in people visiting endemic areas increases the risk of exposure [5]. In recent years an increasing number of imported cases of dengue fever has been reported in many European countries with the majority of cases imported from South-East and South Asia [6–12]. At present, the import of dengue fever to continental Europe is associated with the risk of autochthonous transmission due to the presence of the potential vector Ae. albopictus. There have already been reported cases of autochthonous dengue fever acquired in France and Croatia [13].

The last outbreak of dengue fever in continental Europe occurred in Greece in the years 1927–8, in which more than 1 million cases and 1500 deaths were reported. The vector of the infection was Ae. aegypti [14]. A recent outbreak of dengue fever occurred in Madeira in 2012–13, in which there were more than 2100 infections and 81 cases exported to continental Europe [15,16].

The objective of this study was to describe the epidemiological and clinical characteristics of acute dengue fever diagnosed at the Department of Infectious, Parasitic and Tropical Diseases of Hospital Na Bulovce in Prague, Czech Republic.

2. Material and methods

This retrospective hospital-based descriptive study includes imported cases of dengue fever diagnosed at the Department of Infectious, Parasitic and Tropical Diseases of Hospital Na Bulovce in Prague from January 2004 to December 2013. This university-affiliated department serves as a tertiary care centre for infectious diseases in Prague and the Central Bohemian Region (catchment area of 2.5 million people) and is a referral centre for the management of imported tropical infections in the Czech Republic. At our centre, we investigated and treated 614 patients (524 outpatients and 90 inpatients) after return from tropical or high-risk regions in 2012 and 717 (614 outpatients and 103 inpatients) in 2013, respectively.

2.1. Study subjects

The study includes patients with laboratory-confirmed acute dengue infection. A case was defined as acute onset of illness with clinical symptoms corresponding to dengue fever in people who had recently stayed in endemic areas and in whom there were detected dengue virus-specific IgM and subsequently IgG antibodies and/or NS1 antigen and/or viral RNA. The cases were identified from medical records using the hospital computer-based information system. The study has been approved by the Ethical Committee of Hospital Na Bulovce (EK NNB 14.7.2014/7273/EK-Z).

Laboratory investigations were performed at the Department of Virology, Institute of Public Health in Usti nad Labem (Prague branch). Dengue-virus specific IgM and IgG antibodies in serum samples were detected using IgM capture ELISA (Dengue Fever Virus IgM Capture ELISA, PanBio, Brisbane, Australia) and Dengue indirect IgG ELISA (PanBio, Brisbane, Australia). Methods of direct detection were used since 2008. The detection of NS1 antigen was performed using a one-step sandwich-format Platelia Dengue NS1 Antigen EIA test (Bio-Rad Laboratories). Viral RNA was detected using commercially available Dengue Virus General-type real-time RT-PCR (Shanghai ZJ, Bio-Tech Co.) on ABI 7300 detection system (Applied Biosystems). Testing was performed according to the manufacturers’ instructions.

2.2. Clinical data

Clinical data were taken from medical records and subsequently anonymously retrospectively studied. Recorded
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2.3. Statistical methods

Continuous variables are described as medians with interquartile ranges (IQR). Mann–Whitney tests were used for comparison of continuous variables between two groups.

Categorical variables are described as absolute frequencies and proportions and compared using the Fisher's exact test. Poisson logistic regression was used for evaluation of association of number of cases with year. A p-value of 0.05 was considered statistically significant. Data were analysed using GraphPad PRISM 5.03 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) and STATISTICA 9.1 software (StatSoft Inc., USA).

3. Results

During the study period, 132 cases were diagnosed with acute dengue fever. The median age was 33 years (IQR 29–40) with a male to female ratio of 1.69:1. Males were significantly older (median 35 years, IQR 31–40) than females (median 30 years, IQR 27–38, p = 0.001). The infection was acquired in South-East Asia in 69 cases (52.3%), in South Asia in 48 (36.3%), in Latin America in 14 (10.6%) and in Sub-Saharan Africa in 1 case (0.8%). The countries of acquisition are listed in Table 1. The median duration of stay abroad was 21 days (IQR 14–30). Dengue fever was diagnosed in 127 (96.2%) Czech citizens who travelled for reasons of tourism (54 M and 40 F, in total 94 cases; 71.2%) or for work (26 M and 7 F; in total 33 cases; 25%). Five cases (3.8%) of dengue fever were identified in people visiting friends or relatives (Vietnam in 4 cases and the Philippines in 1 case). Thirty-four patients (25.8%) reported a previous stay in dengue-endemic areas. The number of imported dengue cases increased in July with a peak in October (17 cases) and remained relatively high by December (July–December: 77 cases; 58.3%). The number of cases per year is presented in Fig. 1. During the study period a significant increase in the number of cases occurred (p = 0.003), with the highest number of cases occurring in the years 2012 (30 patients) and 2013 (46 patients). The proportion of dengue cases among travellers treated at our centre was 30/614 (4.9%) in 2012 and 46/717 (6.4) in 2013, p = 0.239. Thirty (39.5%) out of the 76 cases diagnosed in 2012–2013 were acquired during occupational trips in the Maldives.

One hundred and three patients (78.0%) presented to our department in less than 7 days after return, 23 (17.4%) in 8–14 days, and 6 (4.6%) patients in more than 15 days. The median period from onset of symptoms to clinical examination was 4 days (IQR 3–7). A total of 67 patients (50.8%) developed clinical symptoms before return (median 4 days, IQR 2–6). Sixty-five patients (49.2%) reported onset of symptoms after return (median 2 days, IQR 1–4). The most frequent symptoms and signs are presented in Table 2. All patients were febrile (>38 °C) and the median duration of fever was 5 days (IQR 3–6). Other symptoms included rash, headache, joint and muscle pain, skin itching and dyspepsia. Forty-two (31.8%) patients presented with a sore throat, 32 (24.2%) with cervical lymphadenopathy, 23 (17.4%) with conjunctival injection, 14 (10.6%) with hepatomegaly and 12 (9.1%) with splenomegaly.

The laboratory findings are presented in Table 3. A white blood cell count less than 2.0 × 10^9/l was detected in 19 patients (14.4%) and a platelet count less than 50 × 10^9/l in 17 patients (12.9%). Serum activity of AST and ALT was more than 3 μkat/l in 23 (17.4%) and 29 (22%) patients, respectively; and more than 10 μkat/l in 4 (3%) and 2 (1.5%)
patients, respectively. Laboratory parameters were compared with respect to the duration of symptoms. Patients who presented within 0–4 days from the onset of symptoms had lower initial red blood cell, white blood cell, absolute lymphocyte and monocyte counts. However, platelet counts were significantly lower in patients who presented in 5 or more days from onset of symptoms. Serum activity of AST, ALT and LDH was significantly increased in patients who presented with longer durations of symptoms.

The diagnosis was established solely by serology in 25 cases (18.9%). However, the majority of cases were diagnosed by detection of NS1 antigen and/or RT-PCR after the implementation of direct diagnostic methods in 2008. NS1 antigen was detected in 87/107 (81.3%) and viral RNA in 50/72 cases (69.4%).

Fifty-one patients (38.6%) were treated as inpatients and 81 (61.4%) were treated on an outpatient basis. Admission to hospital was based solely on the clinician’s decision and was influenced by disease severity (clinical or laboratory parameters), the need for further investigations and/or the social circumstances.

The median length of hospitalisation was 5 days (IQR 4–8). The clinical course was mostly uncomplicated and there were no fatalities in our study group. The clinical course was complicated in one 21-year old patient by the development of hypotension and multiple serous effusions and fulfilled the criteria of severe dengue. She required intensive care for 22 days. However, the outcome was favourable.

4. Discussion

Our study presents epidemiological and clinical characteristics of imported cases of dengue fever diagnosed in the Czech Republic. During the study period a significant increasing trend in the number of imported dengue cases was detected. This study is one of the first such studies to originate from a Central or Eastern European country contributing to the description of the epidemiological trends in these countries. The significant asset of clinical importance is the comparison of clinical and laboratory findings in travellers with dengue fever according to the symptoms duration.

This retrospective study analysed a total of 132 cases of dengue fever, which have been diagnosed at Hospital Na Bulovce in Prague. During the study period a total of 195 cases of dengue fever were reported in the Czech national surveillance system EPIDAT, thus our study group represents 67.7% of all dengue cases reported in the Czech Republic in the years 2004–2013. In this period a total of 62 cases of enteric fever and 199 cases of malaria were diagnosed, thus dengue ranges among the most frequently imported diseases.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Laboratory findings in patients with acute dengue fever by duration of symptoms.</th>
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<tr>
<td></td>
<td>All patients</td>
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<tr>
<td>Number of patients</td>
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<tr>
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<tr>
<td>Absolute neutrophil count (×10³/l)</td>
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<tr>
<td>Absolute lymphocyte count (×10³/l)</td>
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<td>Absolute monocyte count (×10³/l)</td>
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<td>Platelet count (×10⁹/l)</td>
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<td>Red blood cell count (×10¹²/l)</td>
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<td>Haematocrit (1/1)</td>
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<tr>
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<td>APTT-R (1)</td>
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tropical infections in the Czech Republic [17]. The increasing number of cases could be partially attributed to the introduction of direct detection methods and increased awareness of the medical personnel.

Dengue fever is the most common arthropod-borne viral infection in the world and it is endemic in more than 100 countries in tropical and subtropical region. There has been a dramatic increase in the number of dengue cases worldwide with an estimated 30-fold increase in the last 50 years [2]. Furthermore, dengue virus is a significant cause of illness in international travellers [1, 5]. The risk of dengue acquisition in travellers to endemic countries was described in four recently published prospective studies and it was demonstrated that the incidence varies from 10.2 to 30 per 1000 person-months according to the travel destination and duration of stay [5, 18–21]. In the recent GeoSentinel study, dengue fever was found to be the third most common confirmed diagnosis. The majority of infections arise from visits to South-East and South Asia, followed by Latin America [22]. In a Canadian study by Boggild et al., dengue fever was diagnosed in 7.1% of patients presenting with fever and was imported most frequently from Latin America [23]. Similar findings were reported in a study by Mohammad et al. who found the most common geographical regions of acquisition in U.S. travellers to be the Caribbean with Central America in second place [24]. In the EuroTravNet study dengue fever represented 5% of cases and was the second most frequent cause of fever among ill returned travellers and the authors recorded a significant increase in the number of cases in the investigated period [25].

The majority of cases in our study have been diagnosed in patients who stayed in South-East Asia, followed by South Asia and Latin America. There was only one case of acute dengue fever in a patient who returned from Sub-Saharan Africa. According to data available from the Czech epidemiological surveillance system EPIDAT, 94 (48.2%) and 73 (37.4%) out of the total 195 reported dengue cases were imported from South-East and South Asia, respectively. The Latin American region accounted for 14 cases (7.2%). This is in contrast to the destinations of patients with malaria, as the majority of cases was imported from Sub-Saharan Africa (132/199, 66.3%), followed by South and South-East Asia accounting for only 45 cases (22.6%) [17]. Similar results have been published by other European study groups [6–12].

The absolute number of cases and the proportion of travel destinations reflects the global activity of dengue virus in endemic countries and the preferences of travellers as well [6, 26]. As previously mentioned in terms of absolute numbers, the most frequently reported destinations in our study group were Thailand and the Maldives, followed by Indonesia and India. Similarly to Rocklöv et al., we calculated the attack rates for the most frequent destinations using data from the Czech epidemiological surveillance system (EPIDAT) and tourism data published by the United Nations World Tourism Organisation [6]. The highest attack rates per 100,000 travellers were found for the Maldives (109.4, 95% CI 81.5, 147.0), India (33.5, 95% CI 22.8, 49.2), Cambodia (18.2, 95% CI 6.8, 48.3), Costa Rica (16.6, 95% CI 4.1, 66.2), Thailand (16.2, 95% CI 11.0, 24.0) and Sri Lanka (15.7, 95% CI 6.6, 37.8). Unfortunately, this calculation was limited by the lack of availability to tourism data for the four major destinations in our study group, which were Indonesia, Vietnam, Myanmar and the Philippines. When compared to the results published by Rocklöv similarly the attack rates were relatively high in travellers to India and Sri Lanka [6]. In contrast, high attack rate in the Maldives can be explained by the fact that in 2012–2013 a Czech investment group financed a construction of a new tourist resort in the Maldives (Fushivelavaru island) and a group of Czech engineers and construction workers stayed there for several months during dengue outbreak. In our study group a total of 30 cases of acute dengue fever were diagnosed in patients who worked on the construction site of this tourist resort.

In this study there were five cases of infection (3.8%) in patients who visited their relatives. All of these cases were diagnosed in patients of Vietnamese origin, as there is a large community of migrants from Vietnam living in the Czech Republic. The vast majority of patients presented to our department in less than 7 days after return and the onset of symptoms was reported in a half of our patients before return and in additional 49.2% patients shortly after return. This could be explained by the incubation period, which is usually 4–7 days (range 3–14). It can be presumed that due to the short incubation period many travellers experience dengue fever during their stay abroad and this subsequently leads to an underestimation of the true incidence of dengue incidence travellers [18]. In addition, in the prospective study published by Baatren et al. the majority of travel-related dengue infections were asymptomatic [20].

The most frequent clinical symptoms included fever, rash, frontal or retro-orbital headache, myalgia, arthralgia, and pruritus. The clinical manifestation in this group was similar to previously published studies [10–12]. Interestingly, a significant proportion of patients presented with gastrointestinal or respiratory signs or symptoms such as diarrhea, vomiting, cough or sore throat, which can lead to misdiagnosis of dengue fever (see Table 2).

Laboratory findings in this study are presented according to the duration of symptoms, thus the study group has been divided into two subgroups: patients who presented within 0–4 days from the onset of symptoms (the febrile phase), and those who presented after more than 5 days (after defervescence), as the identified median duration of fever was five days. Interestingly, laboratory findings between these two subgroups differed significantly which is important for clinicians who should consider these differences in biochemical and haematological parameters during initial assessment of a traveller with fever. Patients with dengue fever usually present with leukocytopenia and lymphocytopenia in the early acute (febrile) phase, followed by the development of thrombocytopenia during defervescence. Similar findings were published by Itoda et al. [27] and our results support these observations that are significant for the clinical practice. The activity of LDH and serum aminotransferases can be significantly increased in the convalescent phase and the activity of aminotransferases can even achieve the levels typical for acute viral hepatitis. However, dengue fever is a self-limiting infection and the long-term hepatic injuries have not been described. These results are consistent with previously published studies.
[28]. Dengue fever, unlike malaria or enteric fever, is not accompanied by an increase of C-reactive protein in the serum [29].

Despite the fact that serology has remained the mainstay in the diagnostics of dengue fever for many decades, it is limited by the fact that IgM antibodies usually arise in the later stage of acute illness. Additional problems may be posed by the cross reactivity with other flaviviruses and after vaccination against yellow fever, tick-borne encephalitis and Japanese encephalitis [30]. This issue should be taken into consideration, especially in countries where these diseases are occurring or where these vaccinations are used more frequently. For early diagnosis there have been recently introduced novel commercially available kits for detection of viral RNA and NS1 antigen. It was confirmed that these methods are more sensitive in the early phase of acute dengue fever [31]. We have been using the NS1 antigen and RT-PCR in the diagnosis of dengue fever in our centre since 2008. The majority of dengue fever cases included in this study have been diagnosed by either NS1 antigen and/or RT-PCR. We assume that the increasing trend in the incidence of reported dengue fever in the Czech Republic might be influenced by the inclusion of these more sensitive diagnostic methods into routine work-up in patients with a suspicion of dengue fever.

Severe dengue appears to be less common in travellers than in endemic population. Secondary dengue infection is considered to be a significant risk factor for severe clinical course as non-neutralizing cross-reactive antibodies enhance the infecting ability of the viral particles. Another contributory factor for the lower incidence of severe dengue in travellers is that the vast majority are adults who are at a lower risk of development of severe dengue [4]. Nevertheless, several cases with fatal outcomes in European tourists have been reported [32,33]. In our study there were no fatalities. In one patient the clinical course was complicated by severe plasma leakage, development of ascites and pleural effusion, which required clinical management in the ICU. The clinical outcome, however, was favourable.

Dengue fever represents a significant cause of illness in returned travellers. The incidence of this infection has been recently increasing, most likely and notably due to the enhancement of diagnostic methods and due to the increasing international travel. Even in the Czech Republic, there was a significant proportion of acquired infections among people who travelled for work or who were visiting their friends or relatives in endemic countries. As dengue fever represents an important cause of febrile illness in travellers, physicians should be familiar with the clinical and laboratory findings and should implement novel diagnostic methods of direct detection.

Conflict of interest statement

This study was not supported from either commercial or non-commercial resources and the authors declare that there are no conflicts of interests.

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