Chikungunya Fever in Travelers: Clinical Presentation and Course

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Background. An outbreak of chikungunya virus infection emerged in the southwest Indian Ocean islands in 2005, spread out to India, and resulted in an ongoing outbreak that has involved >1.5 million patients, including travelers who have visited these areas.

Methods. Our study investigated 69 travelers who developed signs and symptoms compatible with chikungunya fever after returning home from countries involved in the epidemic. Twenty cases of infection that were confirmed by serological analysis, polymerase chain reaction, and/or cell culture were investigated.

Results. All patients experienced flulike symptoms with fever and joint pain. No serious complications were observed, but 69% of the patients had persistent arthralgia for >2 months, and 13% had it for >6 months. Viral RNA could be detected in blood samples using reverse-transcriptase polymerase chain reaction in 4 of 4 patients who presented to a health care facility during their first week of illness, and the virus was successfully isolated from blood samples obtained from 2 of these patients. Chikungunya virus–specific immunoglobulin M and/or immunoglobulin G antibodies were detected in all patients. However, initial testing of serum samples yielded negative results for 3 of 5 patients during the first week.

Conclusions. Chikungunya fever must be considered in travelers who develop fever and arthritis after traveling to areas affected by an ongoing epidemic. Related arthritis mainly affects smaller joints and often persists for extended periods. Serological testing may have negative results during the first week of the disease; diagnosis using polymerase chain reaction appears to be more reliable during this time. Travelers to areas of epidemicity should be informed of the risk of infection and of adequate preventive measures, such as protection against mosquitos.

Chikungunya fever is caused by the chikungunya virus (CHIKV), a single stranded (+) RNA virus that belongs to the genus *Alphavirus* of the Togaviridae family. Chikungunya, a word from the Bantu language (often misattributed to Swahili) of the Makonde people of northern Mozambique and southeast Tanzania, means "that which bends up," referring to the stooped posture that develops in an individual as a result of arthritic symptoms [1]. CHIKV was first isolated 1953 in Tanzania during an epidemic outbreak in East Africa [2]. It is transmitted by mosquitoes, predominantly *Aedes aegypti* and *Aedes albopictus*; however, in some areas, transmission by *Culex, Mansonia,* and *Anopheles* species has also been observed. Outside of its involvement in humans, CHIKV circulates in natural sylvatic pools and has primates and probably rodents as its hosts and reservoirs. Incidental infection and disease in humans have been reported in many regions of tropical Africa and Asia. Under conditions of vector abundance and nonimmune populations, CHIKV has been the cause of several epidemics [3].

Since early 2005, the largest outbreak of chikungunya fever ever recorded has been occurring in the islands of the southwest Indian Ocean and in India. The first cases were reported from the Comoro Islands, and the epidemic spread to Mauritius, Réunion, the Seychelles, and India. Between March 2005 and April 2006, ~255,000 cases were reported in Réunion, a French territory in the Indian Ocean with a population of

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~770,000. Most cases occurred after mid-December 2005, with a maximum of 45,000 cases during the week of 29 January to 4 February 2006 [4]. At the end of 2006, it was estimated that >1.5 million cases have occurred in 7 countries, with ~1.25 million suspected cases in India alone [5]. Since early 2005, the importation of cases to Europe has been reported [6, 7].

METHODS

Patients returning between January and October 2006 from travel to the islands of the western Indian Ocean and to India and Southeast Asia who experienced fever and/or joint pain and a history of fever starting during travel or up to 12 days after return, and who were treated within the clinical departments of the Institutes of Tropical Medicine at Hamburg, Heidelberg, and Munich (Germany), were retrospectively analyzed. The following data were collected from each patient: age, sex, destination and duration of travel, date of onset of disease, clinical symptoms, course and persistence of symptoms, results of CHIKV-specific serologic testing, and PCR and cell culture findings, as well as leukocyte count, platelet count, and liver enzyme levels at the first presentation to a health care facility.

Specific IgG and IgM antibodies against CHIKV were detected using an indirect immunofluorescence technique [8]. CHIKV RNA was detected using real-time RT-PCR [9]. For cultural virus isolation, Vero B4 cells were used.

RESULTS

From January to October 2006, a total of 69 travelers who exhibited symptoms and reported a history compatible with CHIKV infection were investigated; 41 of these patients were female, and 48 experienced joint pain. A diagnosis of chikungunya fever was made in 20 patients; 14 of these patients were women, and the mean patient age was 44.6 years (range, 12–64 years). Nine patients (45%) returned from travel to Mauritius; 3 (15%) from India; 2 (10%) each from Réunion, Malaysia, and the Seychelles; 1 (5%) from Madagascar; and 1 (5%) from Indonesia. Nineteen of these patients were German tourists on holiday, and 1 patient was in Réunion on a student exchange. The median duration of travel was 3 weeks (range, 2–26 weeks).

Flulike symptoms started during travel (in 14 patients) or 1–3 days after return (in 6 patients), including fever, fatigue, headache, and myalgia (table 1). Patients presented to our clinical departments 2–73 days (median, 12 days; mean, 15.8 days) after onset of symptoms. All patients experienced severe joint pain. In 18 patients (90%), mainly the peripheral joints (wrists, ankles, and phalanges) were affected. Two patients presented with pain in the proximal joints of the shoulder, hips, and knees. Nineteen patients (95%) had visible and/or palpable swelling of joints, with a limited range of motion. One patient displayed redness and hyperthermia of the ankles and phalanges.

Table 1. Signs and symptoms in 20 travelers with chikungunya fever.

Symptom	Value
Flu-like symptoms	20
Fever	
No. of patients	20
Mean duration, days	4.9
Arthralgia	20
Involving peripheral joints	18
Involving proximal joints	2
Proportion of patients with arthralgia for >2 months	11/16[a]
Proportion of patients with arthralgia for >6 months	2/16[a]
Exanthema (macular or maculopapular)	11
Erythema	4
Nausea	6
Vomiting	3
Pruritus	5
Conjunctivitis	4
Abdominal pain	2
Diarrhea	2
Edema	2
Bleeding	1

NOTE. Data are no. of patients, unless otherwise indicated.

[a] 16 patients were available for follow-up.

A rash manifesting as macular or maculopapular exanthema and/or erythema was observed in 15 patients (75%). Generalized pruritus occurred in 5 patients (25%) and conjunctivitis occurred in 4 patients (20%). Nonsevere bleeding from the nose and gums was reported by 1 patient who had slight thrombocytopenia (thrombocyte count, 104,000 cells/μL) but normal prothrombin and partial thromboplastin times. Severe complications in terms of significant hemorrhage, meningoencephalitis, or acute renal failure were not observed. Blood test anomalies consisting of leukopenia (leukocyte count, 1900–3800 cells/μL), thrombocytopenia (thrombocyte count, 70,000–141,000 cells/μL), and elevated aminotransferase levels (aspartate transaminase level, 49–264 U/L; alanine transaminase level, 58–311 U/L) were detected in 5 patients at an early stage of their disease. When patients presented to a health care facility >14 days after the symptoms started, no anomalous blood test results were observed.

The median duration of fever was 4.9 days (range, 3–7 days). Sixteen patients were available for follow-up, and the duration of arthralgia was assessed. The median duration of arthralgia at assessment in October 2006 was 8.5 weeks (range, 1–30 weeks). Joint pain lasted >2 months in 11 patients (69%) and >6 months in 2 patients (13%). Because of ongoing persistence of arthralgia in 7 patients at the time of data collection, a final evaluation was not yet possible.

Table 2. Alphavirus infections causing persistent arthritis.

Pathogen	Distribution	Major symptoms
Barmah-Forest	Australia	Fever, rash
Chikungunya	Africa, Asia	Fever, rash, hemorrhage,[a] paresthesia[a]
Mayaro	South America	Fever, rash, hemorrhage[a]
O'nyong-nyong	Africa	Fever, rash, lymphadenopathy, hemorrhage,[a] paresthesia[a]
Ross River	Australia, Oceania	Fever, rash, paresthesia[a]
Semliki Forest	Africa	Fever, rash
Sindbis; Sindbis–like[b]	Africa, Asia; Scandinavia, Russia	Fever, rash, paresthesia[a]

[a] Noted occasionally.
[b] Including Ockelbo, Pogosta, and Karelian fever.

PCR detection of viral RNA in blood samples was successful in 4 of 4 patients who presented during their first week of illness, and results were negative for 3 patients who presented later. CHIKV isolation from blood was successful in 2 of the patients with positive PCR results. Chikungunya-specific IgM and/or IgG antibodies were detected in all patients. However, initial serum sample tests yielded negative results in 3 of 5 patients when performed during the first week of the disease, with IgM antibodies detectable not earlier than 3 days after symptoms started and not earlier than day 6 for IgG antibodies. Serological tests for the detection of dengue virus were performed for all patients. Antibodies to dengue virus (IgM and IgG) were detected in only 1 patient, with no change in titer results at reexamination after 10 and 22 days. This patient had traveled several times to Southeast Asia during recent years and had experienced at least 1 episode of a travel-related febrile disease with symptoms that were compatible with dengue fever.

All patients required symptomatic treatment with cyclooxygenase inhibitors, mostly diclofenac or ibuprofen, for various periods. Prednisolone (up to 40 mg/day) was administered to 1 patient, without evidence of significant efficacy. Chloroquine therapy (150 mg of base/day) was effectively used in 1 of the patients who had persistent and incapacitating arthralgia and who had experienced failure of cyclooxygenase inhibitor treatment.

DISCUSSION

Among travelers returning from the tropics, febrile systemic illness is common. In a recent study [10], fever was the most frequent symptom among persons who required medical care after return from travel, with malaria and dengue fever being the most common specific diagnoses. However, the etiologic spectrum largely depends on destination-specific epidemiologic variations, and travelers may serve as sentinels for the emergence and dissemination of pathogens that affect local populations. As an example, the chikungunya fever epidemic that originated in the southwest Indian Ocean islands in 2005 led to the importation of cases into Europe and the United States [6, 7, 11, 12]. Beyond the diagnostic and therapeutic challenge that this infection presents in the individual patient, there is a risk of further transmission and spread in some areas of Europe and the United States where *A. albopictus,* a competent vector of CHIKV in the current epidemic, has been introduced and has become established in recent years [11, 13, 14].

Most of our patients with CHIKV infection returned to Germany after a 2–3-week holiday trip to typical tourist destinations, such as Mauritius, India, Réunion, or the Seychelles. Currently, the disease is a relevant differential diagnosis in travelers who are returning from countries of epidemicity and who present with such symptoms as fever and joint pain. However, most of the symptoms described by patients were nonspecific and are also observed in dengue fever, a disease that shares endemicity with chikungunya fever in many areas affected by the epidemic. Because of similar incubation periods (2–12 days), overlapping clinical signs and symptoms, and lack of awareness of CHIV infection and limited availability of appropriate diagnostic procedures for CHIKV infection, it is likely that chikungunya fever is underdiagnosed in travelers or is misinterpreted as dengue fever.

Serodiagnosis has been the most reliable method to confirm the diagnosis of CHIKV infection in our patients. However, serological findings may be normal during the first week of the disease, and we were not able to detect specific antibodies $\leqslant$3 days after the onset of symptoms; in some patients, these antibodies could be detected only after >1 week. In this situation, repeated antibody testing is warranted. At an early stage of infection, detection of viral RNA from blood samples using RT-PCR appears to be a more sensitive method for diagnosis.

Long-lasting peripheral joint pain, with a preference for such smaller joints as the wrists and ankles, is a typical feature of chikungunya fever [15]. However, persistent arthralgia is also observed in cases of infection with other alphaviruses (table 2). The pathogenesis of persistent arthritis is not clear, but in experimental models with other alphaviruses, persistent infection of synovial macrophages and chronic inflammation due to activation of innate and adaptive immune responses have been

described [16, 17]. Despite the frequent persistence of arthralgia for months (and sometimes for >1 year), symptoms usually resolve completely. Progressive and destructive arthritis has been described only rarely and with questionable relationship to chikungunya virus infection [18]. Cyclooxygenase inhibitors were administered to all of our patients; high doses may be required to effectively control arthralgia in some cases. Treatment with chloroquine has been reported to be effective during a previous epidemic [19], but controlled studies are lacking.

Although we did not observe severe complications, severe and fatal cases of chikungunya fever have been observed during the current epidemic: >250 fatalities have been reported thus far. However, only a minority of these seem to be directly associated with CHIKV infection [20]. Complete genomic sequencing of the current epidemic strain has revealed a new CHIKV variant of the East/Central African evolutionary lineage. This strain is considered to have emerged only recently [14, 21, 22], and it seems to be associated with higher initial viral load, a greater number of severe complications, transplacental transmission, and a number of fatalities not reported from previous epidemics [3, 4, 14, 20].

None of our patients had been aware of the risk of CHIKV infection or the need for personal protective measures. They did not receive any information about the disease from their travel agencies or from local authorities during their stay. This shows the importance of adequate pretravel health advice, including dissemination of information about high-risk areas and consequent protection from mosquito bites.

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