

[ ORIGINAL ARTICLE ]

## A Retrospective Single-center Analysis of 16 Cases of Imported Chikungunya Fever in Japan

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### Abstract:

**Objective** Chikungunya fever (CHIK) is a re-emerging arboviral disease that is transmitted through the bite of infected *Aedes* mosquitoes. There is limited information regarding the epidemiology and clinical information of imported CHIK in Japan. The objective of this study was to review the epidemiology and clinical information of imported CHIK patients treated at the National Center for Global Health and Medicine (NCGM).

**Methods** We evaluated all patients (n=16) who were diagnosed with imported CHIK and treated at the NCGM between October 1, 2005 and March 31, 2016.

**Results** The primary complaint of 7 patients who presented to the NCGM after 31 days from disease onset was persistent arthritis, and the primary complaints of 9 patients who presented within 30 days after disease onset were a fever, headache, arthralgia, and rash. Eleven patients experienced a rash during the first week of illness. The median duration of the arthralgia was 75 days, and the joint pain lasted for >2 months in 8 patients and >6 months in 3 patients. Persistent arthralgia was not significantly associated with an age of >35 years (p=0.13) or patient sex (p=0.69). All 16 patients exhibited positive results for CHIK IgM, although only 4 exhibited positive real-time polymerase chain reaction results.

**Conclusion** Physicians should consider CHIK in patients with a fever who have returned from areas where CHIK is endemic.

**Key words:** Chikungunya fever, Japan, imported disease, arbovirus, mosquito-borne disease

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### Introduction

Chikungunya fever (CHIK) is a re-emerging infectious arboviral disease that is transmitted through the bite of infected *Aedes aegypti* and *Aedes albopictus* mosquitoes (1). In Japan, CHIK has been a notifiable infectious disease since February 2011, although only 50 imported cases have been reported in Japan since 2011, according to the National Institute of Infectious Diseases (2). Thus, there is limited information regarding the epidemiology and clinical information of imported CHIK in Japan.

The present study aimed to provide additional information based on cases of imported CHIK that were treated at the National Center for Global Health and Medicine (NCGM).

### Materials and Methods

This study's retrospective design was reviewed and approved by our institutional ethics review board. This study included all patients who were diagnosed with CHIK between October 1, 2005, and March 31, 2016, at the Disease Control and Prevention Center, NCGM. The NCGM is a tertiary-care general hospital in Tokyo, Japan, with approximately 750 inpatient beds and a travel clinic that is also a GeoSentinel Network site, participating in a global surveillance network of travel and tropical medicine clinicians. The NCGM is a referral hospital for travelers who have returned from abroad.

A laboratory diagnosis of CHIK was made using real-

**Table 1. Demographic Characteristics of 16 Patients with Chikungunya Fever.**

Age	38.4±11.7 years
Sex	6 men (37.5%), 10 women (62.5%)
Nationality	Japanese (12), Colombian (2), Philippine (1), Indian (1)
Place disease was contracted	Southeast Asia (8), Latin America (5), South Asia (2), Pacific region (1)
Reason for travel	Business (6), leisure (5), visiting friends or relatives (4), research (1)
Duration of stay	14 days (interquartile range: 9.3-41.3 days)

**Table 2. Clinical Characteristics of 16 Patients with Chikungunya Fever.**

Fever (both measured and subjective fever)	16 (100%)
Median duration of fever	3.0 days (interquartile range: 2-4 days)
Arthralgia	15 (93.7%)
Affected region(s)*	Ankle (9/15, 60%), knee (9/15, 60%), DIP/PIP/MP (7/15, 46.7%), shoulder (5/15, 33.3%), spine (4/15, 26.7%), interphalangeal joint (2/15, 13.3%), elbow (1/15, 6.7%)
Arthritis**	11 (68.7%)
Arthritis for >2 months	8/11 (72.7%)
Arthralgia for >6 months	3/11 (27.2%)
Rash	11 (68.8%)
Headache	7 (43.7%)

DIP/PIP/MP: distal interphalangeal/proximal interphalangeal/metacarpophalangeal joints

\*All regions with arthralgia and arthritis were symmetrically affected.

\*\*Arthritis is defined as arthralgia with redness, tenderness, and swelling at the joint.

time polymerase chain reaction (RT-PCR; TaqMan RT-PCR) and/or an IgM-capture enzyme-linked immunosorbent assay, and was performed at the National Institute of Infectious Diseases in Tokyo, Japan. The patients' records were also evaluated to retrieve data regarding their demographic characteristics (age, sex, nationality, reason for travel, country in which the patients were infected with CHIKV, and length of stay), background and comorbid conditions, days between the onset of the fever and first presentation at the NCGM, clinical manifestations (fever, rash, headache, myalgia, arthralgia, arthritis, and affected joints), and diagnostic methods. We performed phone follow-ups for all patients during March 2016 to obtain accurate information regarding the duration of their arthralgia.

All statistical analyses were performed using the IBM SPSS software program (version 20; IBM, Armonk, USA). The chi-squared test was used to evaluate the differences between patients with and without persistent arthralgia (arthralgia that persisted for >1 month). The Mann-Whitney U test was used to compare continuous variables. A two-sided *p* value of <0.05 was considered statistically significant.

## Results

There were 16 confirmed cases of CHIK during the study period (6 men and 10 women), and the mean patient age was 38.4±11.7 years (Table 1). Among these 16 cases, 1 case had been reported as the first case of imported CHIK in Japan (3), and the clinical and radiological features of 6 cases had been reported by Mizuno et al. (4). None of the

patients had underlying diseases. The countries where the patients were infected with CHIKV were South Asia, Southeast Asia, the Pacific region, and Latin America. All of the CHIK cases diagnosed before December 2013 had been infected in South and Southeast Asia, while all of the cases diagnosed after January 2014 had been infected in Oceania and Latin America. The median duration of staying abroad was 14 days (interquartile range: 9.3-41.3 days).

The median duration between the onset of fever and presentation was 8.5 days (interquartile range: 3.0-40.5 days). The primary complaints of 7 patients who presented at >30 days after disease onset were persistent arthralgia, and the primary complaints of 9 patients who presented within 30 days from onset were fever, headache, arthralgia, and rash. The patients' clinical findings are shown in Table 2. Eleven patients experienced a rash during the first week of illness, which was typically located on their face, trunk, and extremities. The median duration of the arthralgia (including arthritis) was 75 days (range: 1-360 days). The arthritis lasted for >2 months in 8 patients (72.7%) and for >6 months in 3 patients (27.2%). The duration was unknown for 2 patients because we could not reach them by phone to obtain accurate information. Persistent arthralgia (arthralgia that lasted for >2 months) was not significantly associated with an age of >35 years (*p*=0.13, 95% confidence interval: 0.94-207.6) or patient sex (*p*=0.69, 95% confidence interval: 0.13-11.5). None of the patients required hospitalization, and all of the patients survived.

We divided the cases into 2 groups: those that presented ≤30 days after the disease onset and those that presented

**Table 3. Laboratory Findings from 16 Patients with Chikungunya Fever.**

	All cases (n=16)	Cases presented within 30 days after disease onset (n=7)	Cases presented at >30 days after disease onset (n=9)	p value
WBC (/mm <sup>3</sup> )	4,393 (5,190-7,275)	5,190 (4,020-7,770)	5,745 (5,175-6,660)	0.529
Lymphocytes (/mm <sup>3</sup> )	1,642 (1,145-2,036)	1,582 (1,030-1,695)	2,034 (1,600-2,042)	0.343
RBC (×10 <sup>4</sup> /μL)	459 (433-484)	460 (441-483)	442 (427-577)	0.388
Hb (g/dL)	14.1 (13.1-14.2)	14.1 (13.6-14.2)	13.6 (12.9-14.1)	0.328
Plt (/mm <sup>3</sup> )	22.0 (18.6-24.2)	22.0 (18.7-23)	21.3 (18.8-26)	0.776
AST (IU/L)	23 (19-30)	23 (19-34)	22.0 (16.7-25)	0.388
ALT (IU/L)	25 (15.5-29.5)	25 (19-26)	22.5 (12.5-30.3)	0.689
LDH (IU/L)	198 (176-257)	256 (187-269)	194 (152-210)	0.181
CRP (mg/dL)	0.12 (0.048-0.58)	0.14 (0.09-0.87)	0.09 (0.04-0.12)	0.224
BUN (mg/dL)	12.0 (10.0-13.9)	10.6 (9.95-12.2)	13.6 (12.6-14.6)	0.343
Cre (mg/dL)	0.75 (0.54-0.83)	0.77 (0.68-0.84)	0.64 (0.53-0.76)	0.181

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Plt: platelets, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein, BUN: blood urea nitrogen, Cre: creatinine

>30 days after the onset. We compared the laboratory findings between these two groups but found no significant differences (Table 3). All 16 patients exhibited positive results for CHIK IgM, whereas only 4 (25%) exhibited positive RT-PCR results. These four patients had presented to the NCGM within three days from the onset of their symptoms, although two other patients who had presented within two days exhibited negative RT-PCR results.

## Discussion

CHIK is an acute febrile illness caused by an arthropod-borne *alphavirus* (CHIKV) (5). Since CHIKV was identified in Tanzania in 1952, multiple outbreaks have occurred near the Indian Ocean (6), in South Asia (7), and in Southeast Asia (8). However, GeoSentinel surveillance did not detect any reported cases of CHIK between June 1996 and August 2004 (9), although CHIK was the fifth most common febrile disease from 2007-2011 (10). Since 2013, CHIK has also become endemic in the Pacific region (11) and in Latin America (12). The CHIKV is currently thought to be circulating in most tropical and sub-tropical countries, and co-circulation with the dengue and Zika viruses has been reported in some regions (11). The present 16 cases and other cases that were reported by the National Institute of Infectious Diseases (2) therefore reflect CHIK's recent epidemiology, as all patients who were diagnosed before December 2013 were infected in Asia, and all patients who were diagnosed after January 2014 were infected in the Pacific region or Latin America.

A fever was the most common symptom in cases of imported CHIK, although arthralgia and arthritis were the second-most common symptoms. Similarly, Borgherini et al. reported the clinical features of 157 patients with CHIK (13), and polyarthralgia was observed in 151 patients (96.1%), typically affecting the ankle (66.2%), knee (60.9%), and metacarpophalangeal (49.6%) joints. Our cases validate these findings, as we observed symmetrical arthral-

gia in 15 of our cases, although this rate is slightly higher than the rate of 73.2% from Borgherini et al.'s report. In addition, persistent arthralgia is a characteristic feature of CHIK, and >50% of our patients had arthralgia for >2 months, with 20% of our patients having arthralgia for >6 months. Taubitz et al. reported the signs and symptoms from 20 travelers with CHIK (14); 11 of 16 patients (68.8%) had arthralgia for >2 months and 2 of 11 patients (12.5%) had arthralgia for >6 months. Schilte et al. also reported that an age of >35 years was a significant risk factor for persistent arthralgia (15), although we did not observe this association in the present study. Nevertheless, persistent arthralgia is not commonly associated with infectious disease in Japan and is more frequently associated with rheumatism, connective tissue disease, or osteoarthritis. Therefore, it is important for physicians to consider CHIK in the differential diagnosis of patients who present with persistent arthralgia.

The clinical manifestation of CHIK is similar to that of dengue fever (16) and Zika fever (17), which are also *Aedes* mosquito-borne infectious diseases. The shared symptoms of these three diseases are a fever, headache, arthralgia, myalgia, and rash. Furthermore, the three diseases share overlapping endemic regions, and physicians should consider the other two diseases as differential diagnoses when one of these diseases is suspected. This diagnosis may be aided by the higher frequency of arthralgia in patients with CHIK (vs. dengue or Zika fever) and the fact that arthritis is a characteristic clinical manifestation of CHIK but only rarely observed in dengue and Zika cases.

None of the patients in the present study required hospitalization, which agrees with the historical belief that CHIK is associated with a good prognosis. However, a recent outbreak that involved hundreds of thousands of people suggests that the prognosis of CHIK is not necessarily good (18). In this context, the risk factors for more severe disease include hypertension, underlying respiratory or cardiovascular conditions, and older age. Therefore, the good prognosis in the present study may be related to the fact that

the patients were not very old (mean patient age 38.4±11.7 years) and did not have any underlying diseases.

A definitive CHIK diagnosis requires a positive RT-PCR result during the viremic phase (the first week of the infection) and IgM antibody detection (from day 5 or earlier) (19). Although 8 patients presented to our hospital within 7 days from the onset of symptoms, only 4 (50%) exhibited positive RT-PCR results. Panning et al. reported that the sensitivity of RT-PCR is 100% until 4 days after the symptom onset, although its sensitivity subsequently decreases to 40% at 7 days (20). Our results match these findings, as all 4 patients with positive RT-PCR results presented within 4 days after symptom onset, and the 4 patients with negative RT-PCR results presented at 5-7 days after symptom onset.

Several limitations associated with the present study warrant mention. First, this study used a retrospective design to collect patient data (e.g., demographic characteristics, background and comorbid conditions, and clinical manifestations) from the patients' medical records. However, the attending physicians did not always describe the clinical manifestations in detail, which limits the accuracy of our related analyses. Second, the duration of arthralgia was obtained using phone follow-up for all patients, and the patients' self-reported durations might not be correct.

In conclusion, physicians should consider CHIK in patients with an unspecific fever who have returned from areas where dengue or Zika are endemic. Although these diseases have similar clinical manifestations, persistent arthralgia and arthritis are characteristic of CHIK.

**The authors state that they have no Conflict of Interest (COI).**

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