Chikungunya Outbreak in Southern Thailand, December 2008 to October 2009

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ABSTRACT

In recent years there have been an increase number of reports describing the clinical manifestations of chikungunya infection. The 2004-2009 global outbreaks included an unprecedentedly large chikungunya epidemic in Southern Thailand during 2008-2009 with 31,786 cases reported. During this period, we studied 256 serologically confirmed and 45 virologically confirmed patients. This report presents the demographics and clinical manifestations of these patients, including the characteristics of arthritis, rashes, gastrointestinal symptoms and neurological symptoms. We also reported routine laboratory findings including complete blood count, renal function and liver enzymes of patients who were diagnosed with chikungunya infection. (J Infect Dis Antimicrob Agents 2011;28:25-34.)

INTRODUCTION

Chikungunya (CHIK) is an Aedes mosquito-transmitted infection caused by the Chikungunya virus (CHIKV), an RNA virus in the genus Alpha virus of the Togaviridae family. The disease characteristically consists of a triad of fever, rashes and incapacitating arthralgia. An unprecedentedly large outbreak of this disease began in Kenya in 2004, swept eastward over many islands in the Indian Ocean (the Comoros, Mauritius, the Seychelles, Madagascar, Mayotte, and Reunion) and spread to India by early 2006. Estimated cases for India alone were in the order of 1.6 to 6 million. In addition, more than one thousand cases were reported from at least 11 countries in Europe and the Americas, mostly imported by returning travelers. This further led to a locally transmitted outbreak of Aedes albopictus-borne chikungunya in Italy in the summer of 2007, the first indigenous outbreak ever recorded on the European Continent. This transmission beyond the tropical region into a temperate area demonstrated for the first time that chikungunya could be a health threat to Europe and the United States of America where Aedes albopictus was known to exist in at least 13 countries and 28 states, respectively.
Meanwhile, the domino effect of the chikungunya epidemic reached southeast Asia where outbreaks occurred in late 2006 in Malaysia and in Singapore in early 2008. And then finally, in August 2008, chikungunya emerged in Narathiwat, a border province between Thailand and Malaysia, and spread northwards to involve the entire 14 southern provinces of Thailand with 31,786 cases reported by the end of June 2009.

MATERIALS AND METHODS

The following 3 hospitals located in Songkhla province in southern Thailand participated in our study from December 2008 through October 2009. Songklanagarind Hospital, the major tertiary care hospital in southern Thailand, Thepa Hospital, a primary care hospital located in Thepa district, and Sikarin Hospital, a private hospital in Hat Yai, the largest city in southern Thailand.

Our study was undertaken in two parts. First was a prospective study (Figure 1), in which we examined patients aged ≥ 18 years who presented at our institution, Songklanagarind Hospital, with acute fever (defined by core body temperature ≥ 38.3°C), and polyarthralgia or oligoarthralgia during the 4 days preceding the referrals to our institution from Thepa and Sikarin Hospitals, and all of whom had had virological confirmation with RT-PCR for chikungunya virus. We serially examined the core body temperature, rashes, characteristic of polyarthralgia or oligoarthralgia and did blood testing for complete blood cell count, renal function test and liver function test at first visit. None of the enrolled patients in this study were hospitalized.

The second part of our study was a retrospective study (Figure 2) in which we reviewed patients aged > 18 years clinically diagnosed with chikungunya (based on serological Chikungunya HI results ≥ 1:80) from December 2008 through October 2009 in Songklanagarind Hospital, our home institution. We reviewed the data of these patients including demographic and clinical manifestations from the electronic health records of Songklanagarind Hospital.

![Figure 1. Enrollment of virologically confirmed patients.](image-url)
and the medical records of Thepa and Sikarin Hospitals. We excluded patients who were serologically diagnosed with dengue fever, leptospirosis or rickettsial disease, or whose records were insufficient. We used SPSS for windows for data collection. Mean and standard deviation (SD) were used for quantitative data and frequency and percentage were used for qualitative data.

RESULTS

In our institution, Songklanagarind Hospital, during the study period December 2008 through October 2009 there were 1,018 patients who presented with a clinical condition which suggested possible chikungunya infection. Of whom 1,018 patients, 256 subsequently had a positive serologic test for chikungunya viral infection and were defined as serologically confirmed (SC) group. Of all, only 45 cases had a viral study that fulfilled the definition for acute chikungunya infection, defined as virologically confirmed (VC) group. The majority of patients were referred to our institution during the period from December 2008 through October 2009, a time period which closely corresponded to the peak chikungunya outbreak in Songkhla Province. The demographic and clinical data for these 45 patients are presented in Table 1.

The mean age of the patients was 49 years in VC group and 57 years in SC group, with ratios of male to female patients of 1:1.4 and 1:1.8, respectively. Two hundred and ten patients (82.0%) in the SC group and 35 patients (77.8%) in the VC group were gardeners and most of them were rubber plantation workers. Only fifty-one patients (19.9%) of the SC group and 17.8 percent of the VC group had no underlying illness. The most common underlying disease was hypertension. Almost all of the patients (99.4%) were initially treated as outpatients, and only forty-one patients (4.0%) were ever hospitalized. The

![Diagram showing the enrollment of serologically confirmed patients.](image-url)
indications for admission were other conditions not related to chikungunya in 10 of the 41 patients (24.3%), with the most common conditions being congestive heart failure, community acquired pneumonia, volume overload from renal failure resulting from another condition and infection in pregnancy (2 patients). Eight of the 41 (19.5%) were hospitalized due to misdiagnosed dengue hemorrhagic fever, leptospirosis, or septic arthritis. Twenty-three (56.1%) were hospitalized due to chikungunya infection; the most common indication for admission was for pain control. Only 4 patients were admitted due to complications related to Chikungunya; all of which were neurological complications related to the chikungunya. The average times from onset of illness to visiting a doctor or hospital were 1.2 and 1.8 days in the VC and SC patients respectively.

The main clinical manifestations of all patients are described in Table 2. A total of 240 SC patients (93.6%) experienced arthralgia and 210 (82.0%)
experienced fever. Due to the inclusion criteria of this study, all VC patients had fever and the rashes were not different at trunk and extremities. Almost all patients reported the rashes were itchy. Headache was found in 39 VC patients (86.7%) and 187 SC patients (73.0%). Only 112 (43.8%) patients had gastrointestinal symptoms including nausea, vomiting and only 10 (4.0%) patients had a history of diarrhea. Only two patients had a history of bleeding (one with bleeding per gums and one with purpura). We had only two pregnant patients, both in the SC group; one of the two aborted and fetal autopsy and serologic study was done. Two hundred and fifty (84.0%) patients with arthralgia had polyarthralgia but only 35.1

Table 2. Clinical features for serologically and virologically confirmed patients with Chikungunya.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Serologically Confirmed Patients (n = 256)</th>
<th>Virologically Confirmed Patients (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>210 (82)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>240 (94)</td>
<td>45 (100)</td>
</tr>
<tr>
<td>Polyarthralgia</td>
<td>215 (84)</td>
<td>42 (93)</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>90 (35)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Interphalangeal</td>
<td>212 (82)</td>
<td>41 (91)</td>
</tr>
<tr>
<td>Metacarpophalangeal</td>
<td>130 (51)</td>
<td>25 (56)</td>
</tr>
<tr>
<td>Metatarsophalangeal</td>
<td>56 (22)</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Wrist</td>
<td>156 (61)</td>
<td>25 (56)</td>
</tr>
<tr>
<td>Knee</td>
<td>178 (70)</td>
<td>32 (71)</td>
</tr>
<tr>
<td>Ankle</td>
<td>134 (52)</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Shoulder</td>
<td>68 (27)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Elbow</td>
<td>119 (47)</td>
<td>30 (67)</td>
</tr>
<tr>
<td>Sternoclavicular</td>
<td>10 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Hip</td>
<td>8 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Unidentified</td>
<td>37 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Rashes</td>
<td>190 (74)</td>
<td>37 (82)</td>
</tr>
<tr>
<td>Limbs</td>
<td>124 (48)</td>
<td>23 (51)</td>
</tr>
<tr>
<td>Trunk</td>
<td>146 (57)</td>
<td>24 (53)</td>
</tr>
<tr>
<td>Face</td>
<td>38 (15)</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Itching</td>
<td>110 (43)</td>
<td>30 (67)</td>
</tr>
</tbody>
</table>
percent were symmetrical. The most common arthralgia site was the interphalangeal joint (82.8% in SC patients and 91.1% in VC patients), followed by the metacarpophalangeal joints, wrists, knees, ankles and elbows. We did not find any significant differences between male and female patients or patients ≥ or < 60 years of age. Laboratory results broken down by SC and VC patients are shown in Table 3.

**DISCUSSION**

The first record of chikungunya outside of Africa was in Bangkok during the dengue hemorrhagic fever epidemic in 1958. Since then, there have been 8 sporadic outbreaks of this disease in Thailand before the recent epidemic we describe in this paper, which was the largest outbreak ever recorded in the country. To our knowledge, the only clinical study that included a considerable number of patients (86 patients) with serologically confirmed diagnoses of chikungunya was the 1,965 study by Thiruvengadam et al about the Madras City outbreak. One reason we undertook this current study was to help to fill this striking gap in clinical and laboratory reports about chikungunya.

As previously reported, fever and polyarthralgia were the two major clinical manifestations of chikungunya in our study. The average age of patients in our study was quite higher than in previous studies. Most of our patients were rubber planters and sappers, which is not surprising in that their work exposes them to contact with the *Aedes* mosquito which is the main vector of this disease. The ratio of males to females in our study was different from previous studies. A fact that would seem to be related to their rubber plantation work-rubber tapping is normally done by males in the very early morning, 4-5 AM, while tapping, primarily done by females, is done about 6-7 AM, the time when *Aedes* mosquito is most active.

Time from onset of illness to the first doctor or hospital visit was earlier than with other common
diseases that present with acute undifferentiated fever in this region.\textsuperscript{14,16,17} The severe joint pain, which is more frequent in chikungunya than in dengue fever, scrub typhus or leptospirosis,\textsuperscript{16,17} might be the cause of such earlier visits. In our study, joint pain was present in almost all SC patients (not in VC patients due to the inclusion criteria). Effusion was also rare, as noted in previous reports.\textsuperscript{1,4-16} We did not evaluate the intensity of arthralgia in these articles as observation was made by patients in the 1964 study by D Ranitzetal during the Madras city epidemic and the description made by Robinson in 1955.\textsuperscript{16} It is known that polyarthralgia is particularly important in differentiating chikungunya from dengue fever, and getting accurate information on this symptom, and understanding it correctly, is a problem that clinicians encounter when they work in countries suffering co-epidemics from both infections, as in Taiwan during the 2002 outbreak of dengue fever.\textsuperscript{17} The frequency of arthralgia was reported at 93.6 percent in serological confirmed patients. Moreover, some appearance of arthralgia was noticed before onset of fever. The characteristics of arthralgia in our study were not different from previous reports. Only one third experience symmetrical arthralgia, and almost all was polyarthralgia.\textsuperscript{15,16} The notable difference between the arthralgia in our patients and patients from previous reports was location. In our study the most common site was the interphalangeal joints (91\% in VC and 82\% in SC group), while the metacarpophalangeal joints, wrists, knees, ankles and elbows were less common than in previous reports.\textsuperscript{1-3,15} The frequency of skin rashes, which was reported in 82 percent in VC patients and 71 percent in SC patients was different than found in a previous study, although the rate was probably underestimated in the Thiruvengadam et al study done in Madras, the capital city of the Indian state of Tamil Nadu.\textsuperscript{15} In our study, which was similar

\begin{table}
\centering
\caption{Laboratory findings of serologically confirmed and virologically confirmed patients with Chikungunya.}
\begin{tabular}{llll}
\hline
Characteristics & Normal range & Serologically Confirmed Patients & Virologically Confirmed Patients \\
& & (n = 256) & (n = 45) \\
\hline
WBC count, cells/mm\(^3\) & 4,000-10,000 & 6,789 ± 2,456* & 5,987 ± 1,734 \\
PMN count, cells/mm\(^3\) & 1,500-7,500 & 3,988 ± 1,654* & 4,098 ± 1,945 \\
Lymphocyte count, cells/mm\(^3\) & 1,000-4,000 & 842 ± 523* & 725 ± 455 \\
Platelet count x10\(^3\), cells/mm\(^3\) & 150-500 & 189 ± 87* & 196 ± 72 \\
Creatinine level, mg/dL & 0.8-1.2 & 1.1 ± 0.7** & 1.1 ± 0.8 \\
SGOT level, U/L & 10-40 & 32 ± 28*** & 29 ± 18 \\
SGPT level, U/L & 10-40 & 34 ± 17*** & 35 ± 11 \\
ALP level, U/L & 10-100 & 65 ± 43*** & 75 ± 24 \\
\hline
\end{tabular}
\*N=132, \**N=118, \***N=87
\end{table}
to previous studies, rashes generally appeared the second to third day after onset of illness, and about half of the rash patients complained of itching. The location of rashes in our study was also similar to the previous studies in that there was no significant difference between rashes at the trunk and extremities, and only about one-third of the patients had facial rashes. There were only three cases that had blisters and/or vesicles following an erythematous rash (not shown in the Table). Bulbous lesions, which occurred in three patients, had previously been associated with chikungunya in the study from the Reunion Island outbreak. Gastrointestinal symptoms were a quite common complaint among the patients in our study, as in other studies. The main symptoms our patients reported, mainly nausea and vomiting (63%) abdominal pain (42%) and diarrhea (2%) (not described in the Table), were the same as the main symptoms complained of in dengue fever patients during the 2002 outbreak in Taiwan, India and Thailand. It is interesting that only two patients in our study had a history of minor bleeding disorder and no patients had a history of major bleeding, which correlated with the routine laboratory findings that no patient in our study had thrombocytopenia. The only complications in our study were four cases of neurological complications, of whom one was a child and the rest were described above. There were also two cases of pregnant women, one of whom aborted.

In our study, there were no routine laboratory findings that would have enabled us to differentiate the chikungunya cases from other viral infections. Lymphopenia and thrombocytopenia, both of which were present in the study of Borgherini G et al, and are typical findings in dengue fever, were not found in our study. The mean platelet counts in serological and virological confirmed patients were 180,000/mm$^3$ and 190,000/mm$^3$, and no patients had a platelet count of less than 100,000/mm$^3$. As described earlier, there were no patients with any major bleeding disorder and only two patients with minor bleeding (bleeding per gum and purpura), who had platelet counts of 110,000/mm$^3$ and 115,000/mm$^3$. Although most patients had a history of acetaminophen and/or NSAID sue, aspartate aminotransferase, alanine aminotransferase and serum creatinine levels were all in normal ranges.

The main limitation of our study was that we had no definite single cutoff serological titer point beyond which a definite diagnosis of acute chikungunya infection was considered proven. Three earlier studies used a serological titer with HI $\geq 1:80$ plus clinical suspicions for diagnosis, and only 1.8 percent of our SC patients had a convalescent serological titer. However in our prospective study in which we enrolled 47 patients who came to the hospital with fever and arthralgia, up to 45 patients (95.7%) had a positive viral PCR assay, which all had seroconversion for their convalescent serum. The other common causes of acute febrile illness were excluded with only a single titer serological study, but in our second study, all of the 45 patients had negative convalescent serological titers for dengue fever, rickettsial disease and leptospirosis. Only 70-80 percent of the SC patients were able to be reviewed for characteristics and clinical manifestations and only 45-50 percent in routine laboratory from electrical medical record.

Although chikungunya is considered as benign disease with rare mortality, it has a demonstrated ability to spread through large proportions of a population, and the severe joint pain which it can cause can result in socioeconomic problems. Early diagnosis and differentiation from common acute undifferentiated fever can play an important role in management and control of a potential outbreak. Although Chikungunya viral detection and seroconversion of viral antibodies can provide a definite diagnosis, the limitations of
virological studies and the difficulty of collecting convalescent serum are major obstacles to definite diagnoses in large groups of people. We propose that chikungunya IgM and single antibody titer should be used to screen patients suspected of chikungunya in areas that have never had an outbreak of this disease before, or for screening suspected patients who have a history of travelling in an endemic area. Further studies are required to obtain more complete information about changing levels of antibodies, including copies of the virus during the disease, to manage and control future outbreaks.

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