

Chikungunya Virus Infection

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Summary

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus which causes epidemic fever, rash and polyarthralgia in Africa and Asia. Two outbreaks have been reported in Malaysia, in Klang, Selangor (1998) and Bagan Panchor, Perak (2006). It is not known if the outbreaks were caused by the recent introduction of CHIKV, or if the virus was already circulating in Malaysia. Seroprevalence studies from the 1960s suggested previous disease activity in certain parts of the country. In Asia, CHIKV is thought to be transmitted by the same mosquitoes as dengue, *Aedes aegypti* and *Ae. albopictus*. Due to similarities in clinical presentation with dengue, limited awareness, and a lack of laboratory diagnostic capability, CHIKV is probably often underdiagnosed or misdiagnosed as dengue. Treatment is supportive. The prognosis is generally good, although some patients experience chronic arthritis. With no vaccine or antiviral available, prevention and control depends on surveillance, early identification of outbreaks, and vector control. CHIKV should be borne in mind in sporadic cases, and in patients epidemiologically linked to ongoing local or international outbreaks or endemic areas.

Key Words: Chikungunya virus, Infectious arthritis, Outbreaks, Malaysia

Introduction

Between March and April 2006, a Chikungunya (CHIKV) outbreak affected over 200 people in Bagan Panchor, Perak¹. This is the second outbreak reported in Malaysia, after 51 infections were reported in Klang between December 1998 and February 1999². The Bagan Panchor outbreak coincides with ongoing CHIKV outbreaks in the Indian Ocean (including Mauritius, La Réunion, and Seychelles) and India, which have reportedly affected several hundred thousand people, including imported cases into Europe³.

Virology

CHIKV is a re-emerging, mosquito-borne viral infection causing epidemic fever, rash and arthralgia. Historical descriptions of outbreaks characteristic of CHIKV date from the 18th Century⁴, but the virus was only first isolated in Tanzania in 1952⁵. CHIKV is a single-stranded RNA alphavirus, from the family *Togaviridae*.

Other alphaviruses also cause fever, rash and arthralgia, including O'nyong-nyong, Mayaro, Barmah Forest, Ross River and Sindbis viruses⁶. CHIKV is most closely related to O'nyong-nyong, but remains genetically distinct⁷.

Transmission and Epidemiology

CHIKV disease occurs in Africa and Asia, including India^{3,8}, Sri Lanka⁹, Myanmar¹⁰, Thailand^{4,11}, Indonesia^{12,13}, the Philippines¹⁴, and Malaysia¹². There is historical evidence that CHIKV originated in Africa, and subsequently spread to Asia⁴. Phylogenetic studies support this theory, with CHIKV strains falling into three distinct genotypes based on origin from West Africa, Central/East Africa or Asia, the latter group including Malaysian isolates from the Klang outbreak^{7,15}.

A distinctive feature of CHIKV is that it causes explosive outbreaks, before apparently disappearing for a period of several years to decades^{13,16}. This is in

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contrast to the endemic nature of dengue, which shares with CHIKV the same mosquito vectors of *Aedes aegypti* and *Ae. albopictus*. CHIKV is also known to be transmitted by several other mosquito species. In Africa, it is transmitted mainly by the *Ae. furcifer-taylori* group, which feed on humans and other primates¹⁷. The isolation of virus from non-human primates, other vertebrates such as squirrels and bats, and zoophilic mosquito species (that feed on animals) supports the existence of sylvatic transmission cycles in Africa, which may maintain the virus in the wild during inter-epidemic years¹⁷.

In Asia, transmission appears to be mainly from *Ae. aegypti* and *Ae. albopictus* to man in urban settings. It is not known if and how virus is maintained in the wild in Asia. No animal reservoirs have been definitively identified yet, although the presence of neutralising antibodies to CHIKV in Malaysian monkeys suggests that these primates may be hosts¹⁸. Unlike dengue, transovarial transmission of CHIKV in mosquitoes has not been demonstrated¹⁹. Different geographical strains of *Aedes* mosquitoes vary in their susceptibility to infection and ability to transmit the virus, which may be critical in determining CHIKV endemicity in a given area²⁰. The episodic nature of CHIKV outbreaks still cannot be explained, but likely depends on an interplay of factors, including human²¹ and vector susceptibility to infection, high density of mosquito vectors^{2,8,11} and the introduction of virus from other endemic areas. The latter has become increasingly likely in this age of increased travel by, for example, immigrants and tourists.

As with other arboviruses, factors such as urbanisation, global warming, travel and transportation may lead to increasing numbers of mosquito vectors, or the introduction of vectors into new geographical areas²². In the future, therefore, the epidemiology of CHIKV may change, just as it apparently spread from Africa into Asia.

Chikungunya in Malaysia

The Klang outbreak was the first time that CHIKV was isolated and reported to cause clinical disease in Malaysia. Earlier studies in Malaysia showed only the presence of CHIKV antibodies in the human population in northern and eastern states bordering Thailand, where CHIKV is known to be present²¹. Seropositivity has also been found in people in East Malaysia²³, especially among immigrants from neighbouring countries²⁴. This suggests that CHIKV has been in existence in certain parts of Malaysia, and that

transmission was probably low-level, sporadic, and undiagnosed. Interestingly, Marchette *et al.* predicted in 1980 that if an outbreak were to happen in Malaysia, it would most likely occur in urban centers of west-central states (including Selangor and Perak), which have almost no population immunity and widespread *Ae. aegypti*²¹. In both recent CHIKV outbreaks, it is speculated that a viraemic migrant worker introduced the virus into the antibody-naive population¹².

Clinical Findings

It has been reported that attack rates in susceptible populations maybe as high as 40-85%, and the ratio of symptomatic to asymptomatic patients is about 1.2:1². The incubation period may be up to ten days, but is usually between two to four days. The classical symptoms are fever, myalgia, arthralgia and rash (Table I). Onset of fever and arthralgia is usually abrupt. The small joints of the hands and feet, wrists and ankles are most commonly involved, but larger joints such as knees and shoulders may be affected. Arthralgia is more common than overt arthritis. In the first few days there may be accompanying headache, pharyngitis and conjunctivitis. After 3-5 days, a maculopapular rash (which may be itchy) appears on the trunk and limbs, along with cervical or generalised lymphadenopathy. Fever may show a biphasic pattern, with a febrile period of 1 to 6 days followed by an afebrile interval, and then a shorter second bout of fever. Children are less likely to experience joint pain, but may have other features such as febrile fits, vomiting, abdominal pain and constipation⁴. Mild haemorrhagic symptoms such as a positive tourniquet test, epistaxis and a petechial rash, are sometimes seen in Asia^{4,8-10,12,13}. Very rarely, severe haemorrhage and deaths have occurred in CHIKV-infected patients during outbreaks in India and Sri Lanka, but it is unclear if CHIKV was directly responsible or coincidentally present^{8,9}. In the ongoing Indian Ocean outbreaks, some CHIKV-infected patients have reportedly developed severe neurological disease or fulminant hepatitis³. In uncomplicated infections, acute symptoms generally last no more than ten days, but arthralgia may persist for weeks to months. The majority of patients recover completely. However, one retrospective study from South Africa found that some patients had continued joint pain, stiffness and effusions 3-5 years after infection²⁵.

Differential Diagnosis

As they share the same vectors, CHIKV and dengue are often found in the same areas, and dual infections in a single patient have been reported¹⁰. It is likely, however, that CHIKV is undiagnosed or mistaken for

dengue as the clinical presentations overlap, especially in children, who more frequently have haemorrhagic symptoms with CHIKV^{4,10}. Furthermore, awareness of CHIKV and laboratory diagnostic capabilities are generally lacking due to the relative rarity of the disease. The presence of a rash, conjunctivitis, arthralgia and myalgia are more common in CHIKV, and should aid in differentiation from dengue⁴.

There are many other viruses that cause polyarthritis. The most well-known are rubella (also a *togavirus*) and *parvovirus* B19, which cause joint symptoms particularly in women. Rarer causes include hepatitis B, mumps, herpesviruses (VZV, EBV, CMV) and retroviruses (HTLV-1, HIV). As outbreaks of febrile polyarthralgia are characteristic of alphaviruses (Table II)⁶ with similar clinical features, diagnosis of the causative agent depends on knowledge of the geographical distribution of each virus, and the patient's history of contact with the affected areas. Up-to-date outbreak reports may be obtained from websites run by the World Health Organisation (<http://www.who.int/csr/en/>) or the International Society for Infectious Diseases (<http://www.promedmail.org>).

Laboratory Diagnosis

CHIKV can be diagnosed by serology, virus isolation or nucleic acid amplification, depending on the timing of the patient's blood specimen in relation to onset of symptoms. The gold standard and most specific test is viral culture in Vero (monkey kidney) or C6/36 (*Ae. albopictus*) cells, or newborn mice. Isolation is most likely to be successful if the sample is collected in the first three days of illness. Cell culture also allows potential isolation of a wide range of viruses, and is therefore useful for isolation of novel or unexpected agents. Reverse transcription-PCR¹⁵ is a powerful tool that can detect nucleic acid from non-viable viruses, and thus may be used for blood samples obtained beyond three days. However, once the patient starts producing antibodies, the probability of a positive

culture or PCR decrease. IgM is detectable from 3-5 days by ELISA^{10,12} or indirect immunofluorescent assay², and declines within three months¹¹. Convalescent sera may be tested for IgG by ELISA¹², haemagglutination inhibition or neutralisation test¹⁸. Serological detection of IgM and IgG is most useful in retrospective diagnosis, particularly if a significant rise in antibody titre can be demonstrated.

Treatment and Prevention

Treatment for CHIKV is mainly supportive, with analgesics and rehydration as necessary. No antivirals have been used clinically. In an open trial, chloroquine was found to improve symptoms of patients with chronic arthritis following CHIKV infection, but controlled studies are needed²⁶. A live CHIKV vaccine, developed by the United States Army, was found to be safe and immunogenic in Phase II studies, but has not been tested further²⁷. Like dengue, prevention and control of outbreaks has been focused on community education and vector control methods, such as spraying of insecticides and elimination of breeding sites³. Surveillance is also important for early identification of outbreaks.

Conclusion

Global changes in human activities and ecological factors have led to many emerging and re-emerging infectious diseases in recent years²². CHIKV, a relatively rare disease in Malaysia, has now caused a second outbreak seven years after it was described here for the first time². The re-emergence of CHIKV in Malaysia raises many questions. It is not known why the outbreaks occurred; whether the virus is endemic here (as it is in neighbouring countries), and if so, how it is maintained; and what the true burden of CHIKV disease is. A clearer understanding of the disease may help with prevention of the disease becoming endemic, and better preparation towards early detection and limitation of future outbreaks.

Table 1: Signs and symptoms of Chikungunya infection during outbreaks in different countries

Location and year of outbreak	Malaysia		Thailand		Indonesia		Sri Lanka	India
	Klang (1998-9)	Khon Kaen (1991), Nakhon Si Thammarat (1995), Nong Khai (1995)	Bangkok (1962-4)	Yogyakarta (1998-9)	West Java (2001-2)	Colombo (1965)	Maharashtra (1973)	
Reference	5	11	1	12	13	9	8	
No. of patients with clinical data	22	1001	49 (children)	161	179	106	1424	
Fever	100%	92-100%	100%	60%	76-78%	100%	99%	
Arthralgia (arthritis)	82%	80-98% (29%)	40%	76%	81-89%	88%	99%	
Myalgia	50%	-	59%	52%	(20-25%)	15%	-	
Rash	50%	21-72%	42%	30%	69-72%	28%	"up to 70"	
Headache	50%	56%	-	71%	38-49%	83%	"characteristic"	
Backache	50%	-	31%	-	70-71%	54%	-	
Lymphadenopathy	-	15-30%	16%	-	-	-	"most"	
Cough	-	-	83%	34%	-	-	-	
Sore throat	9%	-	-	-	-	-	-	
Haemorrhagic manifestations	0%	-	Positive tourniquet test (56%), petechiae (31%), epistaxis (13%)	Bleeding gums (5%)	Epistaxis, bleeding gums (8%)	Petechiae (3%)	Epistaxis, gingivitis ("occasionally")	
Other	Retro-orbital pain (14%)	Vomiting (28%), abdominal pain (13%)	Conjunctivitis (56%), vomiting (59%), abdominal pain (32%)	Chills (34%),	Pruritus (48%)	Vomiting, diarrhoea (0.4%)		

--Not stated

Table II: Geographic distribution of alphaviruses causing fever, rash and arthralgia

Virus	Distribution
Chikungunya	Africa, India, Southeast Asia, Philippines
O'nyong-nyong	Africa
Mayaro	South America, Trinidad
Barmah Forest	Australia
Ross River	Australia, Melanesia, South Pacific
Sindbis	Europe, Africa, Asia, Australia

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Multiple Choice Questions (MCQs)

T=True **F=False**

1. The following are common features of Chikungunya infection:
 - A. Arthralgia.
 - B. Purpuric rash.
 - C. Headache.
 - D. Lymphadenopathy.
 - E. Melaena.

2. Which of the following are important in the management of a patient with acute Chikungunya infection?
 - A. Aciclovir.
 - B. Chloroquine.
 - C. Notification to Public Health.
 - D. Mosquito vector control.
 - E. Vaccination of household contacts.

3. Which of the following are true concerning Chikungunya:
 - A. It is a DNA virus.
 - B. In Asia, the main vectors are *Aedes albopictus* and *Aedes aegypti*.
 - C. There is a well recognised sylvatic cycle in Malaysia.
 - D. Chikungunya is in the same virus family as rubella.
 - E. Non-human primates are thought to be important reservoirs in Africa.

4. The following tests are appropriate for a patient suspected of acute Chikungunya infection:
 - A. Chikungunya PCR (serum sample).
 - B. Dengue IgM (serum sample).
 - C. Viral culture (serum sample).
 - D. Viral culture (throat swab).
 - E. Haemagglutination-inhibition assay (acute and convalescent sera).

5. Which of the following is true about Chikungunya in Asia?
 - A. Haemorrhagic symptoms occur more frequently in children.
 - B. Chikungunya probably originated in Asia.
 - C. Some patients suspected of dengue infection may in fact have Chikungunya.
 - D. Prior to 1998, Chikungunya seropositivity was most frequently found in populations on the Malaysian-Thai border.
 - E. Deaths have been directly attributable to Chikungunya.