Chapter

108

Chikungunya Fever

ALLADI MOHAN, SK SHARMA

INTRODUCTION

Since time immemorial, human kind has been ravaged by wars, famines, earthquakes and other natural calamities that have caused immeasurable hardship to the human race, often threatening to wipe out our existence from the earth. More recently, there has been a hue and cry about terrorism, and the suffering inflicted by acquired immunodeficiency syndrome (AIDS). But, since time immemorial, the most efficient killer of mankind has been the mosquito, that continues to be a menace to the millions around the globe and remains to be man's deadliest foe. The recent epidemics of Chikungunya fever and the return of dengue fever that India is witnessing are testimonials to the tenacity and survival capability of mosquitoes[1-4].

Chikungunya fever is caused by "Chikungunya virus" (family Togaviridae, genus Alphavirus) that is transmitted by the bite of an infected *Aedes aegypti* and *Aedes albopictus* mosquitoes (that also transmits dengue and yellow fevers)[3-5]. Historical accounts of epidemics of fever, arthralgias/arthritis and rash, resembling what we now call as "Chikungunya fever" have been recorded as early as 1824 in India and elsewhere[6]. In modern times, Chikungunya fever was first described in 1952[7,8], following an outbreak on the Makonde Plateau, along the border between Tanganyika and Mozambique.

The word "Chikungunya" translates to "that which bends up" in reference to the stooped posture developed due to the rheumatological manifestations of the disease. For a long time, it was erroneously reported both in reputed medical journals[9] as well as in lay press and the media that the word "Chikungunya" was derived from the "Swahili" language. However, it has been suggested that the word "Chikungunya" is derived from the *Makonde* language, spoken by an ethnic group in southeast Tanzania and northern Mozambique from the root verb "kungunyala", meaning "to dry up or become contorted, and signifies the cause of a contortion or folding"[8,10]. Literally, "Chikungunya" translates to "that which bends up" in reference to the stooped posture developed due to the rheumatological manifestations of the disease[8,10].

NATURAL HISTORY AND TRANSMISSION

Chikungunya fever epidemics are characterized by explosive outbreaks interspersed by periods of disappearance that may last from several years to a few decades. While the exact reason for this behavior still remains a mystery, a complex interaction between various factors such as the susceptibility of humans and the mosquito vectors to the virus; conditions facilitating mosquito breeding resulting in a high vector density, ability of the vector to efficiently transmit the virus all are thought to play a role. In the jet-age, increasing globalization can facilitate the introduction of the virus from other endemic areas (e.g. international travel) resulting in outbreaks of the illness[11].

The natural cycle of the virus is human-mosquito-human; studies conducted in mosquitoes from Africa suggest the existence of epizootic cycles that may maintain the virus during the inter-epidemic period[3-5]. There is no definitive published evidence available as to if and how virus is maintained in the wild in Asia. Unlike dengue virus, there is no evidence for transovarial transmission of Chikungunya virus in mosquitoes. Variations in the geographical strains of Aedes mosquitoes regarding their susceptibility to infection and ability to transmit the virus may be crucial factors in determining endemicity of Chikungunya virus in a given region[3]. Vertical maternal-fetal transmission has been documented in pregnant women affected by Chikungunya fever[12].

EPIDEMIOLOGY

World

Following the report from Tanganyika in 1952[7,8], globally, Chikungunya fever epidemics have been reported from several countries in Africa, Asia, and other parts of the world. In Asia, epidemics have been documented in India, Sri Lanka, Myanmar, Thailand, Indonesia, the Philippines, Cambodia , Vietnam, Hong Kong and Malaysia[3-5]. Since 2003, there have been outbreaks in the islands of the Pacific Ocean, including Madagascar, Comoros, Mayotte the Seychelles, and Mauritius.[6] The outbreak which began in 2005 in Reunion Island (French overseas district in the Indian Ocean) is currently ongoing[6].

India

Since the first Indian report from Kolkata (Calcutta then) in 1963[13], several outbreaks of Chikungunya fever have been documented from different parts of India including Vellore[14], Chennai (then called Madras) and Pondicherry[15] in Tamil Nadu (1964), Visakhapatnam, Rajahmundry, and Kakinada in Andhra Pradesh[16-18], and Nagpur[19] (1965) and Barsi[20] (1973) in Maharastra. Thereafter, occasional cases were recorded especially in Maharashtra state between 1983 and 2000[21].

The 2006 Epidemic

Keeping with the character of the disease, the disease was silent for nearly 32 years only to re-emerge in October 2005 outbreak[1,17,18]. In the investigation carried out by the National Institute of Virology[18] from several districts in Andhra Pradesh, Karnataka and Maharashtra (n = 1938) the occurrence of Chikungunya epidemic was confirmed. In this report, phylogenic analysis based on partial sequences of NS4 and E1 genes showed that current isolates were African genotype while all earlier isolates (1963–1973) were Asian genotype. The status of the current outbreak in India is shown in Table 1[22]. As per the current release by the Ministry of Health and Family Welfare, Government of India, a general downward trend in Chikungunya fever has been observed beginning from the period June 2006 to 11th October 2006[23].

Table 1: Current status of the Chikungunya epidemic in India*

State	*No. of districts affected*	*No. of cases as suspected Chikungunya fever (as on 28th October, 2006)*	*No. of samples sent to NIV/NICD*	*No. of confirmed cases*
Andhra Pradesh	23	77533	1224	248
Karnataka	27	758531	4953	294
Maharastra	31	263268	5040	679
Tamil Nadu	35	64131	648	116
Madhya Pradesh	21	59777	809	62
Gujarat	25	72073	1056	170
Kerala	8	63093	235	38
A and N Islands	2	4469	0	0
NCT of Delhi	12	356	356	32
Rajasthan	1	102	44	24
Pondicherry	1	542	52	9
Goa	2	260	48	2
Total	*188*	*1364135*	*14465*	*1674*

*Adapted from references 22 and 23

NIV = National Institute of Virology; NICD = National Institute of Communicable Diseases; A and N Islands = Andaman and Nicobar Islands; NCT of Delhi = A National Capital Territory of Delhi

CLINICAL MANIFESTATIONS

Initial Presentation

Chikungunya fever affects all age groups and both sexes are equally affected. The incubation period ranges from 3-12 days (usually 3-7 days)[3-8]. In susceptible populations, Chikungunya fever can have attack rates as high as 40 to 85%. The onset is usually abrupt and sudden with high grade fever (usually 102-105ºF), severe arthralgias, myalgias and skin rash[3-8]. Prodromal symptoms are rarely reported. During the initial few days, patients may also complain of headache, throat discomfort, abdominal pain and constipation are also frequent.

Physical examination reveals conjunctival suffusion, persistent conjunctivitis; and cervical or sometimes generalized lymphadenopathy. Maculopapular or petechial rash may be present usually on the extremities, neck trunk and ear lobes. Swollen tender joints and crippling arthritis is usually evident. The viral polyarthropathy frequently involves the small joints of the hand, wrist and ankles and may also involve the larger joints such as knee and shoulder[3-8]. The pain may be severe enough to immobilize the patient and interfere with sleeping in the night. Joint pain would be exacerbated with movement and back ache may also be present. Rheumatological manifestations are somewhat less frequent in children. Pediatric subjects may also experience febrile seizures, vomiting, abdominal pain and constipation.

Rare Manifestations

Unlike dengue fever, hemorrhagic manifestations are uncommon in Chikungunya fever. When present, they are mild and are more frequently encountered in Asian compared with African patients[3-8]. When present these manifestations include epistaxis, bleeding from the gums, positive Hess test, sub-conjunctival bleed and petechial/purpuric rash. Rarely, meningoencephalitis has also been described.

Course of the Disease

The fever is usually of short duration and usually resolves in three to four days. In some patients, a biphasic pattern of fever has been described with a febrile episode of four to six days, followed by a fever free period of a few days followed by recurrence of fever (usually 101-102ºF) that may last a few days. Chikungunya is a self-limiting disease. In a majority of the patients, the joint pains resolve in one to three weeks. In about 12% of the patients, arthritis persisting for up to three years after the onset of illness has been documented[24,25].

Indiscriminate use of corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), especially aspirin and antibiotics can contribute to thrombocytopenia, gastrointestinal bleeding, nausea, vomiting and gastritis. This may lead to dehydration, pre-renal acute renal failure, dyselectrolytemia, and sometimes hypoglycemia. These can indirectly contribute to the mortality due to Chikungunya fever.

Cardinal Features Observed in the 2006 Epidemic

In our experience at the Sri Venkateswara Institute of Medical Sciences, Tirupati, a tertiary care referral centre, in Andhra Pradesh, (n = 876 Chikungunya suspects) during the period January–September 2006, short abrupt onset fever (100%), severe and crippling arthritis, most frequently involving knees, ankles, wrists, hands, and feet (98%) have been the most significant clinical manifestations. Rare manifestations included meningoencephalitis (1%), fulminant hepatitis (2%). Hemorrhagic manifestations were also relatively uncommon (3%) and have been mild when present (unpublished observations).

DIFFERENTIAL DIAGNOSIS

Various conditions from which Chikungunya fever must be distinguished are listed in Table 2. Twin outbreaks of dengue fever and Chikungunya fever are known to occur frequently, as it is happening in several parts of India presently, especially in Andhra Pradesh and it becomes particularly important to distinguish one from the other. While it is virtually impossible to distinguish one of these conditions from another on clinical grounds, observations published by astute clinicians can be of some help. In a study published from Thailand[26], it was reported that, compared with patients with dengue hemorrhagic fever, subjects with Chikungunya were more likely to manifest arthralgia/arthritis, maculopapular rash and conjunctival injection. However, laboratory testing is essential to distinguish Chikungunya fever from the other conditions.

DIAGNOSIS

In endemic areas, like for example, at our centre at Tirupati, even during the peak of the Chikungunya fever epidemic, and the resurgence of dengue fever, there has been no respite from the load of Falciparum malaria and Leptospirosis. Therefore, the efforts should be directed to carry out the relevant laboratory tests to rule out other mimicks and rule in Chikungunya fever.

Table 2: Differential diagnosis of Chikungunya fever

Other viral fevers
Dengue fever
West Nile fever
O'nyong-nyong fever
Sindbis fever
Crimean-Congo fever
Bussuquara fever
Mayaro fever
Ebola fever
Hanta virus infection
Kysanur Forest disease
Lassa fever
Rubella
Parvovirus B19
Hepatitis B
Mumps
Herpes viruses
Parasitic infections
Falciparum malaria
Bacterial infections
Leptospirosis

The gold standard for the diagnosis of Chikungunya fever is viral culture[3-7]. However, this is seldom routinely carried out as these facilities are available at selected centres only. It has the advantage of detecting a wide range of viruses. Reverse transcription-polymerase chain reaction (RT-PCR) has also been found to be a useful molecular tool for the rapid diagnosis[27]. More frequently, serodiagnostic methods for the detection of IgM and IgG antibodies against Chikungunya virus in acute and convalescent sera are used. These include enzyme linked immunosorbent assay (ELISA) and indirect immunofluorescent method (IgM), and hemagglutination inhibition or neutralization techniques[3-8]. The technical details of these methods are beyond the scope of this paper.

INFORMATION FOR TRAVELLERS: ROLE OF THE INTERNET

Whether it is severe acute respiratory syndrome (SARS) or Avian influenza (Bird flu), or the recent Chikungunya infection, internet surveillance networks, have been useful in monitoring the dynamics of an epidemic in real time. This would facilitate warning international travelers in adequately preparing themselves while traveling to the affected areas. The website of the Directorate of National Vector Borne Disease Control Programme (NVBDCP), one of the Technical Departments of Directorate General of Health Services, Government of India (http://www.namp.gov.in/Chikun-main.html) has been one such site from India that has been providing up-to-date information regarding the status of the epidemic from India. Similarly, the Vector Borne Diseases Division of the Centers for disease Control and Prevention (http://www.cdc.gov/ncidod/dvbid/index.htm), and the World Health Organization (http://www.who.int/csr/en/) provide useful information on Chikungunya fever. Furthermore, websites such as www.fevertravel.ch can provide useful algorithms for the diagnosis of fever in returning travelers or migrants.

MANAGEMENT

Chikungunya is a self limiting disease. Treatment of Chikungunya fever is symptomatic and supportive. Ensuring adequate fluid intake, judicious use of paracetamol or NSAIDs for symptom relief can be helpful. As mentioned earlier, aspirin should be avoided due to its effect on platelets. Some clinicians have used hydroxychloroquine/chloroquine for treating the viral arthropathy of Chikungunya fever[28]. Published evidence does not support the use of corticosteroids, antibiotics or antiviral drugs in the management of Chikungunya fever and indiscriminate use of these agents can be hazardous. Electrolyte imbalance, pre-renal acute renal failure, bleeding manifestations should be watched carefully and managed accordingly.

PREVENTION

Patients with Chikungunya fever should be advised to avoid being bitten by mosquitoes as the disease can be transmitted to others. Educating the community and public health officials, vector control measures such as elimination of breeding sites and spraying of insecticides should be initiated at the individual and community levels as this can be rewarding. Presently no vaccine is available for Chikungunya fever.

CONCLUSIONS

Several issues related to Chikungunya fever merit future research. The reason(s) mysterious behavior of dramatic outbreaks interspersed by periods of prolonged absence needs to be further studied. The quest for an effective vaccine is still on. Affordable, reliable and reproducible indigenously developed, rapid serodiagnostic tests that will be useful in the field setting are

required. With increasing urbanization and lack of hygiene conditions facilitating breeding of the mosquito vector are ever increasing. The amazing audacity with which the mosquito has been successful in overcoming the control measures suggests that the day is not very far away when Yellow fever, hitherto unreported from India will make its entry.

Virology laboratory facilities are available in selected few centres in the country. Given the impending scenario, there is an urgent need for setting up a nationwide network of reliable, high quality of virology laboratories and developing a surveillance system for monitoring outbreaks of Chikungunya, dengue and other diseases. Lastly, mosquito menace cannot be got rid of merely by the machinations of medical profession. A more drastic change in the outlook of the community and public health authorities with regard to hygiene and mosquito control measures is essential to stand a chance in the war against the mosquitoes.

REFERENCES

1. Mohan A. Chikungunya fever strikes in Andhra Pradesh. Natl Med J India 2006;19 (in press).
2. Mohan A. Mosquito wars, Part II: Return of dengue. Natl Med J India 2006;19 (in press).
3. Sam IC, AbuBakar S. Chikungunya virus infection. Med J Malaysia 2006;61:264-9.
4. Mohan A. Chikungunya fever: clinical presentation and principles of management. Indian J Med Res 2006 (in press).
5. Kamath S, Das AK, Parikh FS. Chikungunya. J Assoc Physicians India 2006;54:725-6.
6. World Health Organization. Regional Office for South-East Asia. Chikungunya Fever, a re-emerging Disease in Asia. Available at URL: http://www.searo.who.int/en/Section10/Section2246.htm. Accessed on 28 October 2006.
7. Robinson MC. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53; I. Clinical features. Trans R Soc Trop Med Hyg 1955;49:28-32.
8. Lumsden WHR. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952-53; II. General description and epidemiology. Trans R Soc Trop Med Hyg 1955;49:33-57.
9. Bodenmann P, Genton B. Chikungunya: an epidemic in real time. Lancet 2006;368:258.
10. Benjamin M. The internet living Swahili learning center. Chikungunya is not a Swahili word, it is from the Makonde language! Available at URL: http://research.yale.edu/swahili/learn/?q=en/chikungunya_makonde. Accessed on 28 October 2006.
11. Centers for Disease Control and Prevention (CDC). Chikungunya fever diagnosed among international travelers - United States, 2005-2006. MMWR Morb Mortal Wkly Rep 2006;55:1040-2.
12. Robillard PY, Boumahni B, Gerardin P, Michault A, Fourmaintraux A, Schuffenecker I, et al. Vertical maternal fetal transmission of the chikungunya virus. Ten cases among 84 pregnant women. Presse Med 2006;35:785-8.
13. Shah KV, Gibbs CJ Jr, Banerjee G. Virological investigation of the epidemic of haemorrhagic fever in Calcutta: isolation of three strains of Chikungunya virus. Indian J Med Res 1964;52:676-83.
14. Jadhav M, Namboodripad M, Carman RH, Carey DE, Myers RM. Chikungunya disease in infants and children in Vellore: a report of clinical and haematological features of virologically proved cases. Indian J Med Res 1965;53:764-76.
15. Thiruvengadam KV, Kalyanasundaram V, Rajgopal J. Clinical and pathological studies on chikungunya fever in Madras city. Indian J Med Res 1965;53:729-44.
16. Jupp PG, McIntosh BM. Chikungunya virus disease. In: Monath TP, (Ed). The arboviruses: epidemiology and ecology. Vol. II. Boca Raton (FL): CRC Press; 1988;137-57.
17. Ravi V. Re-emergence of chikungunya virus in India. Indian J Med Microbiol 2006;24:83-4.
18. Yergolkar PN, Tandale BV, Arankalle VA, Sathe PS, Sudeep AB, Gandhe SS, et al. Chikungunya outbreaks caused by African genotype, India. Emerg Infect Dis 2006;12:1580-3.
19. Rodrigues FM, Patankar MR, Banerjee K, et al. Etiology of the 1965 epidemic of febrile illness in Nagpur city, Maharashtra State, India. Bull World Health Organ 1972;46:173-9.
20. Padbidri VS, Gnaneswar TT. Epidemiological investigations of chikungunya epidemic at Barsi, Maharashtra state, India. J Hyg Epidemiol Microbiol Immunol 1979;23:445-51.
21. Mourya DT, Thakare JR, Gokhale MD, Powers AM, Hundekar SL, Jayakumar PC, et al. Isolation of chikungunya virus from Aedes aegypti mosquitoes collected in the town of Yawat, Pune District, Maharashtra State, India. Acta Virol 2001;45:305-9.
22. Directorate of National Vector Borne Disease Control Programme (NVBDCP). Directorate General of Health Services, Government of India. Chikungunya Fever Situation in the Country during 2006 (As on 28.10.2006). Available at URL: http://www.namp.gov.in/Chikun-cases.html. Accessed on 28 October 2006.
23. Government of India, Ministry of Health and Family Welfare. Up date on Chikungunya: 13th October 2006. Available at URL: http://www.namp.gov.in/Doc/Chikungunya %20-%20 Update.pdf. Accessed on 28 October 2006.
24. Brighton SW, Prozesky OW, de la Harpe AL. Chikungunya virus infection. A retrospective study of 107 cases. S Afr Med J 1983;63:313-5.
25. McGill PE. Viral infections: alpha-viral arthropathy. Baillieres Clin Rheumatol 1995;9:145-50.
26. Nimmannitya S, Halstead SB, Cohen SN, Margiotta MR. Dengue and chikungunya virus infection in man in Thailand, 1962-1964. I. Observations on hospitalized patients with hemorrhagic fever. Am J Trop Med Hyg 1969;18:954-71.
27. Pastorino B, Bessaud M, Grandadam M, Murri S, Tolou HJ, Peyrefitte CN. Development of a TaqMan RT-PCR assay without RNA extraction step for the detection and quantification of African Chikungunya viruses. J Virol Methods 2005;124:65-71. Epub 2004 Dec 15.
28. Brighton SW. Chloroquine phosphate treatment of chronic Chikungunya arthritis. An open pilot study. S Afr Med J 1984;66:217-8.