Chikungunya Virus

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KEYWORDS

• Chikungunya virus • Alphavirus • Arbovirus • Togaviridae

KEY POINTS

- Chikungunya is an arboviral infection that causes debilitating arthritis and arthralgia.
- Chikungunya virus has caused explosive epidemics in the past decade, and has spread rapidly from Africa to Asia to the Americas.
- Improved diagnostic testing and surveillance for chikungunya infection is needed to detect and respond to future outbreaks.
- Further investigation into the pathogenesis of chikungunya infection is needed to understand its long-term sequelae, and to develop effective therapies.

MICROBIOLOGY

Chikungunya virus (CHIKV) belongs to the Semliki Forest antigenic group of the genus *Alphaviridae*, which includes other arthritogenic alphaviruses, such as o'nyong-nyong, Ross River, Barmah Forest, and Mayaro viruses.[1,2] Its genome is closely related to that of o'nyong-nyong virus, and consists of a single 11.8-kbp strand of positive sense RNA, which encodes a 2472 amino acid nonstructural and a 1244 amino acid structural polyprotein.[3] The polyproteins give rise to the four nonstructural proteins (nsP1-4) that make up the viral replication machine, and five structural proteins. Each spherical viral particle is approximately 70 nm in diameter and is comprised of a strand of genomic RNA, encapsidated by capsid (C) proteins, surrounded by a host cell–derived lipid bilayer spiked with heterodimers of envelope proteins E1 and E2.[4] The other two structural proteins, 6K and E3, are leader peptides for E1 and E2, respectively, and are not observed in abundance in the mature virion.[4]

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The envelope proteins, E2 and E1, play important roles in the binding of the virus to the host cell membrane and its subsequent cellular invasion, respectively. Anti-CHIKV antibodies directed against the envelope protein that neutralize the virus in vitro also protect neonatal mice from lethal CHIKV infection in vivo, suggesting that these proteins may be important antigenic lethal targets for development of naturally acquired, or vaccine-elicited protection.[5–7]

EPIDEMIOLOGY

The earliest report of chikungunya fever described an outbreak of a dengue-like illness that occurred in 1952 to 1953, on the Makonde Plateau in the Southern Province of Tanganyika (present day Tanzania).[8] Residents of all ages experienced a febrile illness with rash and arthralgia. However, certain aspects of this outbreak distinguished it from previous reports of dengue fever outbreaks. Most striking was the severity of the arthralgia that "would prevent the sufferer from changing position without help."[8] The local population began to call the disease chikungunya, which is a Makonde (Bantu) term that means "that which bends up," referring to the contorted positions of those who were affected by the sudden and severe onset of arthralgia. Additionally, many individuals affected with the disease continued to experience intermittent joint pains that persisted for months after the acute illness. The attack rate also seemed to be unusually high, often affecting entire households. Between 1952 and 1953, an estimated 60% to 80% of the population in this region developed symptoms of fever, rash, and arthralgia.[8] Attempts to isolate the pathologic agent from symptomatic individuals during the outbreak also diverged from previous experience with dengue virus (DENV): Inoculation of infant mice with serum samples from symptomatic individuals resulted in death of the animals. In contrast, DENV infection is difficult to establish in mice.[9] These data suggested that the cause of the syndrome termed chikungunya indeed was distinct from the cause of dengue fever.

In Africa, CHIKV is transmitted by arboreal *Aedes* mosquitoes (*A furcifer-taylori*, *A africanus*, *A luteocephalus*, and *A neoafricanus*) in an enzootic cycle with nonhuman primates as the principle reservoir (**Fig. 1**).[10–12] Between the 1960s and 1990s, incidental human infection led to numerous, small-scale CHIKV outbreaks in countries throughout Central and Southern Africa, and Senegal, Guinea, and Nigeria in Western Africa (reviewed in Ref.[13]). The outbreaks occurred after periods of large rainfall and associated surges in the arboreal *Aedes* mosquito density. In contrast, CHIKV outbreaks in Southeast Asia occurred in larger cities where *Aedes aegypti* mosquitoes were implicated as the primary transmission vector. *A aegypti* mosquitoes require very small amounts of water to lay eggs, and thrive in human urban environments, particularly in areas where residents store water in open containers or cisterns.

In 2004, a large-scale CHIKV epidemic erupted, sweeping down the coast of Kenya into islands on the Indian Ocean (Comoros, Mayotte, Seychelles, Réunion, Madagascar, Sri Lanka, and the Maldives), India, Southeast Asia (Malaysia, Singapore, Thailand), and China.[14] Although CHIKV infection in travelers returning to Europe had been reported previously, autochthonous transmission of CHIKV was observed for the first time in Italy in 2007,[15] and in France in 2009.[16] An important factor that facilitated the rapid expansion of CHIKV infection was a novel single amino acid substitution of alanine for valine at position 226 (A226V) in the E1 envelope protein that enhanced the ability of the *Aedes albopictus* mosquito to transmit CHIKV to humans.[17] *A albopictus* is an anthropophilic, peridomestic species of mosquito that