Editorial

Outbreak of Chikungunya Virus Infection with Global Propagation

Received: December 19, 2017 Accepted: December 31, 2017
doi: http://dx.doi.org/10.3329/jemc.v8i1.35428

Chikungunya virus (CHIKV) is a mosquito-borne alpha virus that has precipitated several large outbreaks across the Southern hemisphere in the last decade. It is an arbovirus first described during a 1952 outbreak in Southern Tanganyika (now Tanzania). The name "Chikungunya" derives from a word in the Kimakonde language meaning "to become contorted" or "to walk bent over," an apt description of the appearance of some infected people with arthralgia. Following few outbreaks in the 1960s and 1970s in Asia and Africa, the virus re-emerged in 2005 and spread across the Indian Ocean. Since 2014, over a million cases have been reported in the Americas and the Caribbean, with declining case numbers in 2016. Much of what we currently know about the disease was first published following a large outbreak on the island of La Réunion, affecting 37% of the entire population.[1] The epidemics occur through human–mosquito transmission and was made possible by high-circulating viremia during acute infection. In addition to the *Aedes aegypti*, the genetic variation seen in this RNA virus has allowed mutation of the virus to enable transmission by the *Aedes albopictus*.[2] This has facilitated the outbreaks of the last 10 years around the Indian Ocean and across the Caribbean, with an outbreak in Italy in 2007 and cases in other parts of Europe.[3] Subsequently, there are concerns that the virus may cause further outbreaks across Europe and Northern America. Between 1960 and 1982, outbreaks of CHIKV were reported from Africa and Asia. In Asia, virus strains have been isolated in Bangkok in 1960s, various parts of India including Vellore, Kolkata and Maharashtra in 1964, in Sri Lanka in 1969, Vietnam in 1975, Myanmar in 1975 and in Indonesia in 1982. According to the Institute of Epidemiology, Disease Control and Research (IEDCR) under the Health Ministry, Bangladesh, a total number of suspected Chikungunya patients from across the country was 3200 and the confirmed cases were 791, mostly from the capital city till July 23, 2017. The Director of the IEDCR said the disease virtually swept through over capital Dhaka areas in June and its spread is continuing. Moreover, the prevailing situation may continue or even worsen until the end of September this year as Aedes mosquitoes could breed even after the end of the monsoon season and coordinated efforts by people, the government, and non-government agencies are needed to combat Chikungunya in the capital.[4]

The clinical illness has a relatively short incubation period; typically 2–10 days. Sudden onset high fever is usually the first symptom and can last up to a week and can follow a biphasic course. The onset of fever coincides with viremia, and the viral load can rapidly reach up to 10^9 viral genome copies per milliliter of blood. The intensity of the acute infection correlates with that of viremia, and the acute infection usually lasts one week, until viremia ends when IgM appears.[5] Fever often precedes a maculopapular rash over the trunk and extremities, headache, myalgia, and arthralgia. More severe complications include nephritis, myocarditis, meningo-encephalitis, Guillain–Barré syndrome.[6] It has also been noted that pregnant women infected with the virus in the last few days of pregnancy are able to transmit the virus to the baby, which can lead to severe encephalopathy in the neonate and subsequent neurodisability. After the acute illness, rheumatic sequelae can persist for months to years.

Because of the prolonged joint symptoms, CHIKV-related arthritis can be mistaken as seronegative rheumatoid arthritis (RA), whereas such symptoms are uncommon in dengue. The pathogenesis of CHIKV-related arthritis is poorly understood. CHIKV has not been cultured from synovial fluid, but viral RNA can be detected in the synovium, suggesting that CHIKV may directly invade and persist in joints. Overlapping clinical and immunologic evidence between CHIKV and RA has been reported. In a cohort of CHIKV

infected patients, cytometry analysis revealed that these patients, when compared to RA patients, had similar natural killer and T cell profiles including similar percentages of naive, activated, and effector T killer and helper T cells. Moreover, CHIKV infected and RA patients had greater percentages of activated and effector $CD4^+$ and $CD8^+$ T cells than healthy controls.[7] It is worth mentioning that the musculoskeletal manifestations of disease have been shown to affect 4–75% of those infected with CHIKV.[5] These figures vary widely depending on baseline genetic susceptibility of populations and cultural perceptions. Arthralgia usually affects more than one joint, particularly knees, ankles, hands, and wrists in a bilateral and symmetric distribution.[8]

Molecular tests are most useful in the acute phase of illness. These use reverse transcriptase PCR assays to amplify fragments of the CHIKV genome and can be used to quantify fragments in real time.[7] Serological assays use ELISAs that capture IgM and IgG, immunofluorescence and immunoblot assays for CHIKV proteins. More recently a rapid immunochromatographic test (ICT) has been developed that can detect CHIKV, best used in the first 5 days of illness, and would allow rapid diagnosis at the point of care.

There are currently no licensed treatments for CHIKV infection. Drugs that inhibit viral entry include chloroquine and arbidol. However, arbidol is a licensed antiviral in Russia, and arbidol analogues have been found to have anti-CHIKV activity.[9] Most effective of the antiviral drugs are those that target viral genome replication. Ribavirin has been used most widely as it is licensed for treatment of respiratory syncytial virus in infants. Ribavirin in combination with interferon has been shown to act synergistically in preventing CHIKV replication.[10]An alternative to these antiviral drugs is human poly or monoclonal antibodies. This work suggests the potential for monoclonal neutralizing antibodies in prevention of CHIKV associated arthralgia in endemic areas. Further preventive measures such as vaccines against CHIKV have not yet been licensed but have been a goal animal model. The mainstay of treatment has been with anti-inflammatory drugs, physiotherapy, and short courses of oral steroids; however, clinical withdrawal of these treatments can be difficult. In addition, a number of cases report successful use of biologic immunomodulatory agents such as infliximab or etanercept in patients with severe disease. We should encourage countries to develop and maintain the capacity to detect and confirm cases, manage patients and implement social communication strategies to reduce the presence of the mosquito vector.

There is every reason to speculate that emerging infectious disease outbreaks can quickly become globalized, calling for a global solution. Better coordination of international research efforts taking place sooner could have led to a safe and effective medication that might have been deployed during the epidemic and at the outset of the next one.

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