The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Review article

Chikungunya: bending over the Americas and the rest of the world

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ARTICLE INFO

Article history:
Received 9 September 2015
Accepted 16 October 2015
Available online 17 December 2015

Keywords:
Chikungunya
Alphavirus
Epidemics

ABSTRACT

Chikungunya is an arthropod-borne virus transmitted by Aedes mosquito bites. A viral mutation has allowed *Aedes albopictus* to become the preferred vector extending the geographic spread of the condition. The virus causes an acute febrile illness occasionally followed by a chronic rheumatic condition causing severe impairment. The diagnosis is usually confirmed with serology. No specific treatment is currently available. This article reviews the condition with emphasis on his dissemination in the Americas.

Chikungunya virus has disseminated widely and autochthonous cases have already been reported in the Americas. Although the disease tends to be self-limited, a crippling chronic condition with severe joint compromise can affect patients for weeks to months. Health practitioners need to be acquainted with the manifestations, diagnostic methods and treatment options for this formerly "exotic" condition.

Agent

The Chikungunya virus (CHIKV) is an arthropod-borne virus that belongs to the family *Togaviridae*, genus Alphavirus. Its genome is composed by a single stranded positive polarity RNA molecule. The genome codifies four non-structural proteins (NS P 1-4) and three structural proteins (C, E1 and C2). The virus gets destroyed by desiccation and by temperatures above 58 °C.[1] The alphavirus genus includes about 29 species, seven of these viruses can causes joint disorders in humans including CHIKV, O'nyong-nyong (Central Africa), Ross River and Barmah Forest (Australia and the Pacific), Semliki Forest (Africa), Sindbis (Africa, Asia, Australia and Europe), and Mayaro (South America and the French Guyana).[2]

There are three lineages of CHIKV with distinctive genotypic and antigenic characteristics. The virus isolated during the 2004–2006 epidemics in the Indian Ocean belongs to a distinct set within the largest phylogenetic group East/Central/South African (ECSA). However the Asian lineage is the one currently ravaging the Americas. The other group is the West African lineage.[3]

CHIKV persists in nature using two cycles: a sylvatic cycle affecting primates and mosquitoes and an urban cycle affecting humans and mosquitoes (Fig. 1).

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http://dx.doi.org/10.1016/j.bjid.2015.10.004

Virus replication occurs following these steps:

- Early replication of RNA into mRNA and translation of early regulatory proteins
- Late replication of the RNA into mRNA and translation of late structural proteins
- Assembly of structural proteins and single stranded positive RNA, and virion maturation.[4]

Vector

Although there is an ample range of Aedes species that transmit the disease in Africa[5]; in Asia and in the Indian Ocean the main vectors of CHIKV are *Aedes aegypti* and *Aedes albopictus*. *A. albopictus* has a wider geographical distribution, and can survive in both rural and urban environments. Mosquito eggs are quite resistant to dry seasons. *A. albopictus* also has a relatively long life, lasting 4–8 weeks and has a flying range of 400–600 m.[6] All these capabilities have allowed *A. albopictus* to become an important vector not only of CHIKV, but also of dengue and other arbovirosis. A comparison between *A. aegypti* and *A. albopictus* is presented in Table 1.

In Brazil, an extensive DDT campaign eradicated *A. aegypti* from the country in the 1940–50s, however the vector was reintroduced in 1970 and become widespread again. Since 1986 it has been considered endemic in several major Brazilian cities. *A. albopictus* invaded Brazil in the 1980s and a recent survey has detected it in at least 59% of the Brazilian municipalities and in 24 of the 27 federal units[7,8] *A. aegypti* affects predominantly tropical areas of Brazil (North, North-East and Central regions) and is more widespread, whereas *A. albopictus* is more common in the cooler Southern areas of the country. Both vectors combined put 99% of the population of Brazil at risk of acquiring CHIKV.[9] Fig. 2 shows the geographic distribution of Chikungunya virus in the Americas.

In the United States, *A. aegypti* has been established for more than 300 years and since 1985 the Southeast of the United States has been invaded by *A. albopictus*, with a range extending from South Florida to Illinois.[10]

The adaptation of CHIKV to *A. albopictus* is a relatively recent event. During the outbreak in the Indian Ocean in 2005–2006 the virus has acquired a mutation at residue 226 of the membrane fusion glycoprotein-1, which allows it to infest *A. albopictus*. This mutation is likely the cause of the wide spread of the disease.[11]

Table 1 – Comparison between *Aedes aegypti* and *Aedes albopictus*.

Vector	*Aedes aegypti*	*Aedes albopictus*
Local distribution	Predominantly an urban vector, breeds close to households, can bite indoor or outdoors	Predominantly a rural vector, breeds far from households, mostly an outdoor biter
Global distribution	Narrower global distribution	Wider global distribution
Tendency to bite humans	Occasional	Aggressive
Preferred source of blood meals	Prefers humans	Affects humans and a variety of vertebrates
Nickname	Yellow fever mosquito	Asian tiger mosquito

Pathogenesis

CHIKV is transmitted predominantly by female mosquito bites. Alternatively the disease can be transmitted vertically from mother to fetus or theoretically by blood transfusion (although no cases have been reported so far).

After the inoculation, the virus invades endothelial cells and subcutaneous fibroblasts and replicates in a limited fashion. Circulating blood cells may be refractory to invasion. New viruses are transported to local lymph nodes where they further replicate. A significant viremia which can reach up to 10^8 copies/mL then ensues.[12] In the initial phases there is a massive infection of monocyte-derived macrophages which act as "Trojan horses" and transport the virus into target organs including muscle, joints, the liver and the brain.[13]

The innate immune response is activated by the virus via pattern recognition receptors. This triggers the production of type I interferon and activates interferon-stimulated genes which encode more than 300 proteins, with crucial roles in the host defense. In vitro studies have shown that CHIKV can be highly suppressed when interferon α/β is added to cells prior to infection.[14]

Flow cytometry showing CD8+ T lymphocyte response in the early stages of the disease and a CD4+ T lymphocyte-mediated response in the later stages, as well as production of several pro-inflammatory cytokines are evidence of a subsequent adaptive immunity reaction.[15] There is heterogeneity in the cytokines expressed, reflecting the time of the illness in which they are measured and the different genetic backgrounds of the individuals affected. The persistence of a local reservoir of infected monocytes in the joints may potentially explain chronic arthritis in a subset of patients. Patients with chronic joint disease may have high levels of interleukin 6 and granulocyte macrophage colony-stimulating factor, but not of tumor necrosis factor (TNF) or IL-1b (a pattern seen in other inflammatory arthritides). Chronically affected patients also have normal levels of hepatocyte growth factor and eotaxin, as compared with recovered patients, suggesting an inability of the former subjects to maintain an immune mechanism associated with clinical recovery.[16]

Clinical manifestations

The incubation period for CHIKV virus ranges between 1 and 12 days. The disease usually presents abruptly with high fever, rash, back aches and myalgia. The febrile episode lasts 3–4 days. Occasionally there is a second febrile course lasting shortly. Arthralgia and arthritis are extremely common and usually polyarticular and distal, with as many as ten joints involved. Both, small and large joints can be affected. Symmetric inflammation is common, but unilateral compromise is possible. The pain is intense and crippling, preventing patients from sleeping and ambulating properly. Articular