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REVIEW ARTICLE

Immunology of viral infections with a high impact in Mexico: Dengue, Chikungunya, and Zika

A. Castillo-Macías[a], M.C. Salinas-Carmona[b], E. Torres-López[b,*]

[a] *Departamento de Patología Clínica de la Facultad de Medicina y Hospital Universitario ''Dr. José Eleuterio González'', Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico*
[b] *Departamento de Inmunología de la Facultad de Medicina y Hospital Universitario ''Dr. José Eleuterio González'', Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico*

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Abstract High-impact viral infections have become more relevant in recent years, with arthropods as a vector of particular interest. Among these, the most important are those caused by the Dengue virus (DENV), the Chikungunya virus (CHIKV) and the Zika virus (ZIKV). The objective of this review is to make known the immune response of the organism to these infections. When clinical characteristics are similar to each other, it is difficult to differentiate them clinically, which is why the role of the laboratory plays a crucial role in its diagnosis. At present, there is no specific treatment for these infections, so the role of health services should be focused on prevention campaigns, with critical importance placed on the reduction and control of new cases.

Introduction

In the last decade, high-impact viral infectious have become more relevant, especially those transmitted by arthropods to humans, the most important of these infections being DENV, CHIKV, and ZIKV, the latter presenting a rise in fetal mortality.[1] These viruses share transmission through the same vectors, these being *Aedes aegypti* or *Aedes albopictus*.[2] Infection by the DENV virus is caused by one of these four serological types: DENV-1, DENV-2, DENV-3, and DENV-4.[3] It is usually asymptomatic, but can manifest a wide range of clinical manifestations. Today, estimations suggest that there are 390 million infections by the DENV virus a year worldwide, significantly impacting public health programs across the world.[4] In the case of CHIKV, its name derives from an African language and means ''*the one who folds*''

* Corresponding author at: Avenida Gonzalitos #235 Mitras Centro, C.P. 64000 Monterrey, Nuevo León, Mexico.
E-mail address: ernesto.torreslp@uanl.edu.mx (E. Torres-López).

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because of its manifested clinical characteristics. Among the multiple symptoms presented by the CHIKV virus infection, joint and muscle pain are particularly relevant.

The ZIKV virus kindles a particular interest due to the alterations caused by the products of infected mothers.[1] Currently, there is an outbreak caused by this infection in America, the Caribbean, and the Pacific, and it had been declared a public health emergency of international interest by the WHO. Clinical manifestations caused by this virus are seen in approximately 20% of infected patients, with various signs and symptoms.[6]

Classification

The word *Arbovirus* is an acronym of Arthropod-Borne Viruses, with particular interest attached to the *Flaviviridae* family, of the *Flavivirus* genre, where the DENV and ZIKV viruses belong, while the CHIKV virus is classified within the *Togaviridae* family, of the *Alphavirus* genre.[7] The DENV virus is of the positive-stranded RNA type, with four serotypes, which are composed of a genome of 11,000 bp (base pairs), coded for seven non-structural proteins and three structural proteins.[8] On the other hand, the CHIKV is a positive-stranded RNA type virus with 11,600 bp, which codifies four non-structural and three structural proteins.[9] Lastly, the ZIKV virus consists of an RNA positive-strand with a genome of 10,749 bp, all distributed in a polyprotein which is coded for three structural and seven non-structural proteins, giving them their biological characteristics.[10]

Epidemiology

Dengue (DENV)

Currently, there are about 2.5 billion people (40% of the world's population) living in hazardous areas at risk of becoming infected by dengue.[4] This infection is endemic in at least 100 countries in Asia, the Pacific, America, Africa, and the Caribbean. The World Health Organization estimates that between 50 and 100 new cases are reported each year.[4] In Mexico, there were 17,795 confirmed cases reported in 2016 (including dengue with and without severe or significant alert symptoms),[11] and there have been 541 confirmed cases in the first ten weeks of 2017; out of these 541, 76 are from Nuevo Leon.[12]

Chikungunya (CHIKV)

Up until 2013, there had been outbreaks identified in Africa, Asia, Europe and the Pacific and Indian oceans.[5] By the end of that same year, the first infection by local transmission in America was identified in the Caribbean countries, spreading to 45 countries all throughout the continent.[13] In Mexico, there were 168 registered confirmed cases during 2016, and eight confirmed cases up to week 9 of 2017, from which only one case was reported in our state, Nuevo Leon.[14]

Zika (ZIKV)

Initially identified in Africa during the 1940s-1950s with few reports of infection in humans up until recent years. In the year 2007, an outbreak was detected in the Pacific's Yap island, in Micronesia, resulting in the infection of 70% of their population in 3 years. Between 2013 and 2014, there were reports of 4 countries in the Pacific islands where outbreaks of this infection were detected. By the year 2015, the arrival of the Zika virus to the Americas was confirmed by the Brazilian Health Ministry.[15] This led to a dissemination throughout the entire continent and was linked to an increase in the number of newborns with microcephalia, as well as an increase in cases of Guillian-Barré syndrome. In Mexico, there are 8033 confirmed cases of ZIKV, and 40,607 confirmed autoctonous ZIKV cases in pregnant women between 2015 and 2016. During the year 2017, by epidemiological week 9, there have been 94 confirmed cases reported, and 43 confirmed autoctonous ZIKV cases in pregnant women, 6 of which are in Nuevo Leon.[16]

Pathophysiology

Dengue (DENV)

The DENV virus contains a single positive-stranded RNA. For the incorporation of the virions to the cells to occur, the interaction of the primary glycoprotein (E) with the receptors on the cellular surface is critical; these include heparan sulfate or lectins (DC SIGN and GLEC5A). Moreover, they can also bind to immunoglobin-type surface receptors in the presence of antibodies against glycoprotein-E or membrane precursor protein (pre-M)[8] (Fig. 1). After the fusion of the viral and cell membranes through acidified endocytic vesicles, the viral RNA enters the cytoplasm along the other viral proteins. Non-structural NS5 proteins are the polymerase of RNA dependent of RNA, which fits viral proteins as well as cell proteins to form the replication complex, transcribing viral RNA to produce the RNA template, beginning the replication of viral genetic material. The DENV virus enters the organism through a mosquito bite, infecting the Langerhans cells and fibroblasts.[17] The viremia starts three days after the vector bite, is detectable 6–18 hours before the onset of the signs and symptoms, and concludes at the moment of solving the fever.[18] The immunological response of the organism to the virus is complex, with elevated levels of interferon (IFN) α and β, which are part of the type-I IFN group contributing to the elimination of viral particles. However, viral proteins are capable of inhibiting the production of interferons as well as the infected cells' antiviral function.[19] The antibody answer is mainly directed at specific determinants of each serotype, from these, the primary targets are protein E, membrane precursor protein (pre-M) and NS1 protein. When there is a primary infection with one of the four serotypes of the DENV virus, it will generally provide long-term immunity to infections with viruses of the same serotype. Nevertheless, it does not work for a virus of a different serotype, which may result in a secondary infection.

Once an immunological answer is assembled, this will cause most of the symptoms in the patient, hence the

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