PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

http://dx.doi.org/10.17058/reci.v6i1.6959

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ARTIGO DE REVISÃO

Relato sobre o *Zika* vírus no Brasil

A report about Zika virus in Brazil

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Recebido em: 10/12/2015
Aceito em: 15/12/2015
Disponível online: 24/03/16

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DESCRITORES
Zika Vírus.

KEYWORDS
Zika Virus.

RESUMO

Zika vírus, um Flavivirus isolado pela primeira vez NA África, se espalhou para muitos países do mundo, incluindo o Brasil. Neste país, sete meses após a Copa do Mundo de futebol, foi registrada a ocorrência de uma epidemia, posteriormente associada a casos de microcefalia e síndrome de Guillain-Barre. O vírus é transmitido por mosquitos do gênero *Aedes*, frequenctemente aapós uma picada de um vetor infectado. A doença febril é auto-limitada e não há nenhum tratamento específico. Poucos meses após este surto no Brasil, as autoridades reconheceram a associação entre o Zika vírus e a ocorrência de síndrome de Guillain-Barre e microcefalia em recém-nascidos, o que corresponde a malformações cerebrais fetais ou lesões cerebrais. Esta descoberta é um alerta mundial para o fortalecimento de medidas preventivas, restrito a prevenção de picadas de insetos e cuidado com o meio ambiente.

ABSTRACT

*Z*ika vírus, a Flavivirus first isolated in Africa, has spread to many countries worldwide including Brazil. In this country, seven months after the World Football Cup, the occurrence of an epidemic was recorded, subsequently associated to cases of microcephaly and Guillain-Barre syndrome. The virus is transmitted by mosquitoes of the *Aedes* genus, often following a bite from an infected vector. The febrile disease is self-limited and there is no specific treatment. Few months after this outbreak in Brazil, the authorities acknowledged the association between the Zika virus and the occurrence of Guillain-Barre syndrome and microcephaly in newborns, corresponding to fetal cerebral malformation or brain lesions. This finding is a worldwide alert for the strengthening of preventive measures, restricted to preventing insect bites and caring for the environment.

Please cite this article in press as: *CIPRIANO, Rosangela. A report about Zika virus in Brazil. Revista de Epidemiologia e Controle de Infecção, Santa Cruz do Sul, v. 6, n. 1, jan. 2016. ISSN 2238-3360. Disponível em: <http://online.unisc.br/seer/index.php/epidemiologia/article/view/6959>. Acesso em: 18 abr. 2016. doi: http://dx.doi.org/10.17058/reci.v6i1.6959.*

INTRODUCTION

In the past three years, several emergent diseases - including vector-transmitted diseases, such as arboviruses - were noticed as increasing around the world, especially because of climate changes as well as globalization of travel and trade. These diseases include those caused by the *Flaviviridae* Family, which comprises over 70 different members and includes the Dengue virus, the Japanese Encephalitis virus and the Yellow Fever virus.[1-3] There are serological evidences that the *Zika* virus first isolated in Africa, has spread to Asia since 1966.[3] Few human cases were reported until 2007, when a *Zika* fever epidemic took place in Micronesia. Some major outbreaks were then described in Thailand in 2012-2014. In that country, it is now considered widespread.[4] In December 2013, there was a *Zika* virus outbreak in the French Polynesia and the New Caledonia, when 396 laboratory-confirmed cases occurred and an estimated 29,000 people sought medical care for suspected *Zika* illness. In that outbreak, 70 cases presented neurological or auto-immune complications.[5] In 2013, the *Zika* virus had its complete coding sequenced.[6] However, at that time, *Zika* virus was not described as a particular problem in Brazil.

According to the *World Tourism Organization*, over 1,1 billion tourists travelled abroad in 2014. In Brazil, there were several international events with the arrival of large numbers of people from various parts of the world.[3,7] In February 2015, seven months after the football world cup was held in the country, the Ministry of Health in Brazil registered the occurrence of a new viral febrile syndrome, affecting mainly people between 20 and 40 years old. This situation worsened, becoming a major public health problem, mostly due to the suspected correlation between *Zika* and the microcephaly in newly born children, as well as cases of the Guillain-Barre syndrome.

The virus and the vector

Zika is a mosquito-borne viral disease caused by the *Zika* virus (ZIKAV), a flavivirus from the *Flaviviridae* Family. Flaviviruses are RNA viruses that circulate in cycles involving vertebrate hosts and insect vectors. It includes multiple long known human, animal and zoonotic pathogens such as the *Dengue* virus, the Yellow fever virus, the West Nilo virus and the Japanese encephalitis virus.[2] The *Zika* virus was first isolated in 1947 from monkeys in the *Zika* forest of Uganda.[8]

The transmission occurs via mosquito vectors from the *Aedes* genus of the Culicidae Family in a sylvatic cycle involving nonhuman primates. Many species of *Aedes* can be involved in the transmission, such as *A. africanus, A. aegypti, A. albopictus* and some other insects like *Anopheles* and *Culex*. The potential emergence of arboviruses in a region depends on the mosquito vector presence and the entry of people with the virus, often in an asymptomatic form. Human infection almost always follow the bite of an infected tick or mosquito vectors.[1,2,5]

The virus was identified in urine, breast milk, saliva and semen, but the potential transmission by these routes was not confirmed.[3] In 2008 and 2013, some cases probably associating prostatitis, with blood in semen and sexual transmission by ZIKAV were related.[9,10] Neonatal infection is probably transmitted via the placenta or during the delivery.[7]

According to latest studies, the epidermal keratinocytes and dendritic immature cells are susceptible to the infection by ZIKV. The cutaneous fibroblastes infection is associated to the production of viral particles and the formation of autophagosomes.[7] After the infection, the virus invades the human cells and promotes an interaction with the endoplasmatic reticulum like a replication platform, inducing a profound remodeling of its architecture and composition. It includes the activation and rearrangement of cellular pathways related to this organelle which are connected with other relevant pathways as apoptosis and innate immunity.[2] Pioneering studies indicate the flaviviral replication complex as a promising target for the development of antiviral compounds.[11] Various members of the flavivirus have ability to gain entry to the central nervous system - a process known as viral neuroinvasiveness - and to infect neural cells - a phenomenon known as neurovirulence. Both abilities seem to be widely dispersed among various members of the Flavivirus genes, which have a global distribution range and suggest the existence of potential emergence or more neurovirulent dengue strains.[12] In a study held in the 1970s, the neurotropism of the virus has been demonstrated in experimental studies in mices.[13]

The disease

A substantial proportion of ZIKAV infections are subclinical, and even the vast majority of patients are asymptomatic. There are no pathognomonic signs. The viruses generally cause a self-limiting illness, which most common symptoms are the same reported to other arboviral infections like *dengue* and *chikungunya*: low grade fever, maculopapular rash, headache, non purulent conjunctival suffusion, myalgia and joint pains.[4,7] These symptoms appear after an incubation period lasting about four days. Until recently the disease was known as not causing serious complications, rarely leading to hospitalization or death. Rare cough and gastrointestinal disorders like vomiting may occur. When compared to other arboviruses - such as *dengue* fever, *Zika* causes more rash and conjunctival hyperemia, and less laboratorial changes. Although the joint pain could persist for a month, other symptoms may disappear after three to seven days of its beginning.[3]

The laboratory alterations are mild and similar to those found in other viruses. They are leucopenia, thrombocytopenia, elevation of serum lactic dehydrogenase and inflammatory markers as C-reactive protein, fibrinogen and ferritin. The specific laboratory diagnosis is based on detection of viral RNA from clinical specimens. The viral isolation is only possible during the first four to

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seven days from the onset of the symptoms, when the viruses are circulating. After this period, the production of IgM antibodies begin followed by the production of IgG antibodies two weeks later.[14,15]

There is no specific treatment for ZIKAV infection. For symptomatic patients it is recommended the use of acetaminophen to control the fever and pain. Anti histamines can help to relieve itching. Anti-inflammatory and acetylsalicylic acid should not be used, as well as in all the infections caused by flaviviruses, due to the increased risk of bleeding.[3]

The current outbreak in Brazil

Neurological and auto-immune complications were reported in the outbreak occurred in the French Polynesia in 2013.[16] On 24 November 2015, the health authorities of the French Polynesia reported an unusual increase of at least 17 cases of central nervous system malformations in fetuses and infants during 2014-2015, coinciding with the *Zika* outbreaks on the island, including fetal cerebral malformations or brain lesions, brainstem dysfunction and absence of swallowing. None of the pregnant women described clinical signs of ZIKV infections, but the four of them tested were found positive for flavivirus, suggesting a possible asymptomatic ZIKV infection. It was hypothesized that ZIKV infection may be associated with these abnormalities if mothers are infected during the first or second trimester of pregnancy.[16]

In Brazil, the introduction of the *Zika* virus was supposed to be started in the second half of 2014.[3] And it was confirmed in May 2015. Its spread was laboratory confirmed in 18 states, distributed in the five regions of the country, featuring an outbreak.[17] The outbreak peaked in May with overall attack rate 5.5 cases/10,000 inhabitants. In January 2016 there are laboratorial confirmed cases in 20 states, involving almost all the country.[18] Between January and July 2015, 121 cases of neurological manifestations of the Guillain-Barré syndrome were notified in several northeastern states with the record of previous rash illness, raising the hypothesis of possible association with ZIKAV infection.[1,7]

During the current outbreak in Brazil, the authorities recognized the relationship between the *Zika* virus and the occurrence of microcephaly outbreaks and deaths.[19] 3530 suspected cases of microcephaly identified in 724 municipalities of twenty-one states were reported in Brazil until January 2016.[18] The state of Pernambuco, the first one to identify the rise of microcephaly, has held the larger number of cases.[19] This fact is unpublished in the world medical literature and began a series of discussions among experts to identify causes and define diagnosis criteria. It was recorded an alteration in the pattern of occurrence of microcephaly with clear excess in the number of cases in various parts of the northeast. The patterns of suspected cases distribution of post infectious microcephaly presented dispersion characteristics. The first three months of pregnancy of women with microcephalic children correspond to a higher virus circulation period in the Northeast region in Brazil. More than 60 women that referred rash during the pregnancy had affected babies without familiar genetic diseases. The *Zika* virus RNA was identified in the amniotic fluid of two pregnant women whose fetuses had microcephaly. Newly born children that had had the diagnosis of microcephaly during the pregnancy with positive results to *Zika* virus who died five minutes after birth were also identified. It is known that congenital malformations have complex and multifactorial etiology, but the current evidences strongly indicate the relationship between *Zika* virus and microcephaly.[20]

From these observations, the health authorities have drawn protocols standardizing care, surveillance, diagnostic criteria both clinical and laboratorial and routine care to pregnant women with probable *Zika* virus infection. It also includes routine investigations for fetus with central nervous system alterations probably related to Zika virus during the pregnancy and spontaneous

From: National Program of Dengue Control (CGPNCD/DEVIT/SVS)[18]

Figure 1. States in Brazil with laboratorial confirmation of ZIKAV infection. 2015-2016.

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abortion and stillbirth or newborn presenting microcephaly, probably related to *Zika* virus infection during the pregnancy. This protocol also describes the occurrence of the neurological syndrome related to ZIKAV, causing Guillain-Barré or acute disseminated encephalomyelitis. The objective of this protocol is to optimize the care of affected persons and the prevention of new cases, in an attempt to minimize damage and control this outbreak which represents a serious public health problem in Brazil.[20]

The prevention is another challenge in this disease. There is no vacccine to prevent ZIKAV disease. The most importante form to prevent is by avoiding mosquito bites. It is recommended the use of repellents, the wearing of long-sleeved shirts and long pants and air conditioning or window/door screens to keep mosquitoes outside. Although mosquitoes may bite at any time of day, peak biting activity for the vector is during daylight hours. It is also very important to take care of the environment to prevent the proliferation of mosquitoes by emptying standing water from containers such as flowerpots or buckets.[21] It is really a new moment to an old virus.

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