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Review article

Zika virus infection during pregnancy and microcephaly occurrence: a review of literature and Brazilian data

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ABSTRACT

In November of 2015, the Ministry of Health of Brazil published an announcement confirming the relationship between Zika virus and the microcephaly outbreak in the Northeast, suggesting that infected pregnant women might have transmitted the virus to their fetuses. The objectives of this study were to conduct a literature review about Zika virus infection and microcephaly, evaluate national and international epidemiological data, as well as the current recommendations for the health teams. Zika virus is an arbovirus, whose main vector is the *Aedes* sp. The main symptoms of the infection are maculopapular rash, fever, non-purulent conjunctivitis, and arthralgia. Transmission of this pathogen occurs mainly by mosquito bite, but there are also reports via the placenta. Microcephaly is defined as a measure of occipto-frontal circumference being more than two standard deviations below the mean for age and gender. The presence of microcephaly demands evaluation of the patient, in order to diagnose the etiology. Health authorities issued protocols, reports and notes concerning the management of microcephaly caused by Zika virus, but there is still controversy about managing the cases. The Ministry of Health advises notifying any suspected or confirmed cases of children with microcephaly related to the pathogen, which is confirmed by a positive specific laboratory test for the virus. The first choice for imaging exam in children with this malformation is transfontanellar ultrasound. The most effective way to control this outbreak of microcephaly probably caused by this virus is to combat the vector. Since there is still uncertainty about the period of vulnerability of transmission via placenta, the use of repellents is crucial throughout pregnancy. More investigations studying the consequences of this viral infection on the body of newborns and in their development are required.

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Introduction

In November of 2015, the Ministry of Health (MOH) of Brazil issued a bulletin confirming the relationship between Zika virus (ZIKV) infection and the microcephaly outbreak in the northeastern region.[1]

One of the first records of ZIKV disease in the country is from March of 2015, in the state of Bahia, Northeast Brazil, in which patients with "dengue-like syndrome" showed positivity in blood analysis by molecular biology (real time PCR-RT-PCR).[2] Autochthonous transmission by ZIKV was confirmed in Brazil in April 2015[3] and in May of the same year, the Brazilian MOH confirmed the circulation of the virus.[4]

From an obstetric perspective, in October of 2015 there was an unusual increase in the number of newborns with microcephaly in the state of Pernambuco (Northeast). Considering that some of the mothers of these babies had a rash during pregnancy[5] the possibility of ZIKV transmission from mother to child, causing neurological defects in the child, was suggested. After conducting tests in a baby born with microcephaly and other malformations in one of the Northeastern states, the presence of the virus in blood and tissues of the patient was detected, proving that assumption.[4]

Currently, due to the progressive extension of cases of microcephaly, corresponding to 4783 suspected and 404 confirmed cases,[6] this situation became extremely concerning to public health, since only 18% of the infected are symptomatic[4] and there is no treatment for this condition.[7] Therefore, the control of pregnant women who might bear a child with microcephaly is impaired, and consequently, a strict monitoring during prenatal care is needed.

In view of this new and alarming scenery, this study aimed to conduct a literature review about ZIKV and microcephaly, evaluate epidemiological data published until February 5th 2016 in national and international levels, as well as to review the current recommendations for the health teams.

Zika virus

The ZIKV is an arbovirus (arthropod-born virus), since part of its reproductive cycle occurs within the body of hematophagous insets. They belong to the Flaviviridae family, and Flavivirus genus, whose members are composed by a protein capsid involved by a lipid envelope, in which the membrane protein and glycoprotein spikes are inserted. The *Aedes* sp. mosquitoes are the vectors responsible for transmitting this microorganism, as well as Chikungunya virus (CHIKV), dengue virus (DENV), yellow fever virus (YFV), and West Nile fever virus (WNV).[8]

The ZIKV was initially isolated in a Rhesus monkey, at the African Zika forest in Uganda. In the 60s, the first cases of ZIKV infection in humans have been confirmed by serologic evidence in the countries of Uganda, Nigeria, and Senegal.[9] The dissemination was so great that in 2007 the first outbreak outside Africa and Asia was reported, on the Yap Island (Federated States of Micronesia). In October of 2013, the largest ZIKV outbreak affected approximately 28,000 inhabitants of the French Polynesia.[8] After two years, in May 2015 the Brazilian MOH issued a statement confirming the first cases identified in the country: 16 people in the Northeast, at Bahia and Rio Grande do Norte states, were tested positive for the virus.[4]

The condition of ZIKV infection is named "dengue-like syndrome" because it resembles an infection caused by the DENV.[9] The clinical criteria for diagnosing this self-limited disease are pruritic maculopapular rash plus at least two of the following: fever (generally low grade fever lasting 1–2 days), non-purulent conjunctivitis, polyarthralgia, and periarticular swelling.[10] Other signs and symptoms may be present, such as muscle pain, retroocular pain, vomiting, and lymph node hypertrophy.[9] Besides, ZIKV infection can affect the central nervous system (CNS). There are reports of a 20-fold increase in the incidence of Guillain–Barre Syndrome (GBS) in Micronesia during the outbreak of ZIKV, in addition to cases of GBS after infection by this pathogen in French Polynesia.[11] However, about 80% of infections are asymptomatic, what makes the diagnosis and prevention of transmission highly challenging.[12]

The detection of viral RNA in the acute phase – up to 10 days from onset of symptoms – by RT-PCR assay is the method of choice for identification of the virus so far. Fortunately, studies to improve the identification of immunoglobulin (IgM) by ELISA are being carried out, but cross-reaction with the DENV is likely to occur in endemic areas of dengue fever.[5,13] Moreover, another study suggested the possibility of diagnosing the infection from urine samples. Viral RNA was isolated even after 10 days of onset of symptoms, which shows that this technique is suitable for later diagnosis when compared with tests using blood samples.[14]

Transmission

ZIKV is mainly transmitted by the *Aedes aegypti* vector, which resides in tropical and subtropical regions, as well as by the *Aedes albopictus*, inhabitant of the European Mediterranean. After the mosquito's bite, there is an incubation period of about nine days, and then the symptoms ensue.[15,16]

Although there is no evidence of sexual transmission in humans by other arboviruses, some authors hypothesized that this could be possible for ZIKV. Patients exposed to endemic areas showed symptoms of the disease and one atypical signal of hematospermia. In such cases, the presence of virus in semen was confirmed by serological tests or by RT-PCR. In addition, one of the sexual partners of these patients had similar symptoms, strengthening this assumption.[8,16]

During the outbreak in French Polynesia, a study to investigate ZIKV in blood donors was carried out using RT-PCR modified technique. It was noted that 3% of donors were asymptomatic hosts of the virus, but no case of infection was identified after blood transfusion. Still, the results suggest that testing for ZIKV must be implemented in the routine of blood donation.[15,17]

Regarding perinatal transmission, which is the main focus of this review article, on November 17th 2015 investigators of the Oswaldo Cruz Institute (OCI/Fiocruz) detected the presence of ZIKV genome in amniotic fluid samples of two pregnant women in the state of Paraiba (Northeast), in whom ultrasound exams had confirmed microcephalic fetuses.[18] This fact taken in isolation does not confirm transplacental