Zika virus: A current review of literature

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Abstract

Zika virus is a mosquito-transmitted flavivirus belonging to the family Flaviviridae. Its spread has been an ongoing pandemic and the focus of a public health emergency since 2007. Though Zika virus was first detected in 1947, its rapid spread, newfound modes of transmission, and the absence of adequate treatments have recently brought this virus into the public eye. After an outbreak of Zika virus in Brazil in 2007, many complications were suspected to be linked with to its infection. These complications include Guillain-Barré syndrome, several congenital malformations, microcephaly, and some neurological complications. There is no effective treatment nor vaccine for Zika virus. Ongoing research focusses largely on preventing infection in regions where transmission is most common, especially in populations of pregnant women. It is advisable for clinicians working in non-endemic areas to maintain a full awareness of Zika virus in order to properly manage this infection when it spreads into their catchment areas. This review aims to summarize what is currently known about the epidemiology, transmission, pathogenesis, clinical presentation, diagnosis, treatment, and prevention methods of the Zika virus.

Introduction

Zika virus is an arbovirus of the genus flavivirus. It was first isolated from a febrile rhesus macaque monkey in Uganda and subsequently in Aedes africanus mosquitoes from the same region.[1] Since 2007, Zika virus infection has spread quickly in many countries around the world. In 2015 the Brazillian government described relationships between infections of Zika virus and both Guillain-Barré syndrome and microcephaly.[2]

A public health emergency of international concern (PHEIC) was declared with regard to Zika virus by The World Health Organization (WHO) in 2016. Over 4,000 neurological disorders and cases of microcephaly have been linked to the virus in affected areas.[3] However, Zika virus infections remain incompletely understood, because Zika causes self-limiting and benign illnesses in most people. Therefore, infection may possibly be underreported in endemic areas.[4]

In this article, we review the literature available to clinicians for obtaining the necessary information regarding Zika virus infection.

Epidemiology

Zika virus (strain MR 766) was first isolated in 1947 at Yellow Fever Research Institute, in Zika Forest, Uganda.[1] The first three cases of human infection were reported in Nigeria, in 1954.[5] In Brazil, Zika virus was first detected in the northeast and was then recognized in other South American countries, including Ecuador, Colombia, Suriname, French, Venezuela, Guyana, and Paraguay. Symptomatic infections of Zika virus were restricted to small, sporadic clusters of cases. Transmission has been documented in Central America, Mexico, and the Caribbean, and has also occurred in travelers returning from infected regions to non-endemic areas, including Japan, the United States, Canada, and Western Europe.[6] Until 2007, only 14 human cases had been identified, and these came from exclusively Africa and Southeast Asia.[7] The first major outbreak of the virus infection was in Yap (Federated States of Micronesia) in 2007. Approximately 73% of Yap's population was infected in this outbreak. A reported 18% of the infected individuals developed symptomatic clinical conditions.[8] Outbreaks subsequently occurred in French Polynesia, New Caledonia, the Cook Islands, Easter Island, and the Americas, with sporadic exportations to Europe. Since January 2016, 20 countries including the Americas have reported Zika virus infections (Figure 1).

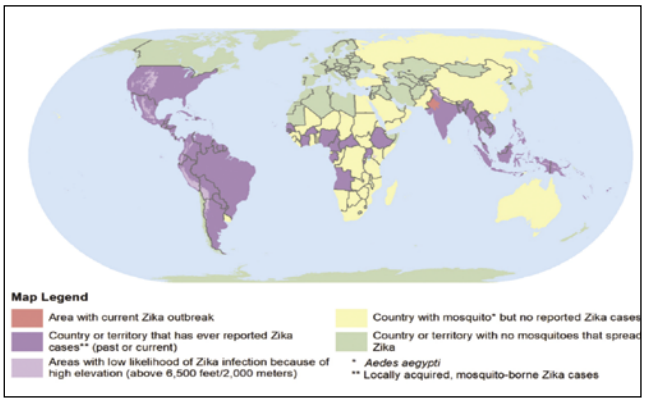

Figure 1. World Map of Areas with Zika Virus, 2019 (source: https://ww-wnc.cdc.gov/travel/page/zika-travel-information)

Virology

Zika virus is an RNA virus which is approximately 11kb in size. It belongs to the family Flaviviridae.[9] This virus is like other viruses in the Flaviviridae family, including yellow fever virus, dengue virus, and West Nile virus. It also has similar characteristics to the

Spondweni virus.[10] The Zika virus is composed of single-stranded RNA, containing 10794 nucleotides encoding 3419 amino acids, and this RNA is contained within a capsid, an envelope (E), a precursor of membrane, and 7 non-structural proteins (Figure 2).[11] This virus is 50 nm in diameter, and its envelope is structured in an icosahedral composition of surface proteins.[12] The E protein is an important protein on the surface of the virus and plays a role in both membrane fusion and receptor binding.[8]

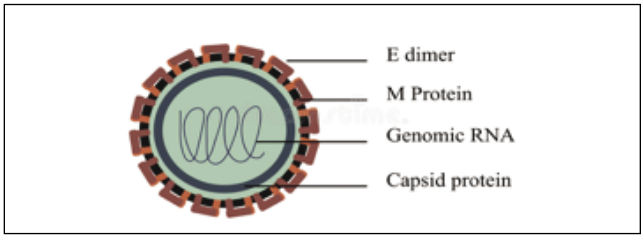

Figure 2. Structure of Zika virus (source: www.dreamstime.com)

Pathogenesis

Cellular entry for the Zika virus follows the same steps as with other flaviviruses. The virus enters skin cells via cellular receptors, and goes on to access lymph nodes and the bloodstream. According to some studies, human skin fibroblasts, keratinocytes, and immature dendritic cells allow the virus entry. Several adhesion factors (e.g. AXL receptor tyrosine kinase) enable viral infection, and increase the virus's replication in skin fibroblasts.[13] Most flaviviruses replicate within endoplasmic reticulum-derived vesicles following cellular entry, but Zika virus antigens have only been found in the nuclei of infected cells, demonstrating that the Zika virus replication process differs from other flaviviruses.[14] Further research should be done in this area.

The pathogenesis of congenital infections and neurological complications is explained by two different mechanisms. The first is direct viral damage, and the second is an immune-mediated mechanism of pathogenicity.[15] According to studies on animal models (rats), the Zika virus is extremely neurotropic and can be transmitted through the placenta, causing growth retardation, apoptosis of neural progenitor cells, placental damage, fetal death, impaired neural proliferation, and development in an affected fetus.[16,17]

Transmission

Infected rhesus monkeys in their natural habitats can become a source for human infection, transmitted through the bites of *Aedes aegypti* and *Ae. Albopictus*, which subsequently pass the infection to vulnerable human hosts.[18] The most likely non-human animal reservoirs are *Cercopithecus denti*, *Cercopithecus aethiops*, *Macaca mulatta*, *Chlorocebus sabaeus*, *Erythrocebus patas*, *Cercopithecus ascanius schmidti*, *Pongo pygmaeus*, *Lophocebus albigena*, and *Colobus abyssinicus*, as well as other mammals, such as rodents, zebras, and elephants.[19] Zika virus has been transmitted mainly by the bite of female *Aedes* mosquitoes.[20] Risk of infection is also present in the settings of blood transfusion, pregnancy, and sexual contact.[20-22] Sexual transmission is particularly common in patients who have blood in their semen. Transmission of the Zika virus from mother to infant can occur perinatally or in utero.[23-24] Transmission via breastfeeding has not yet been observed.[23] Other routes of Zika virus transmission include organ transplantation, mucocutaneous exposure, hemodialysis, and monkey bites.[25] It is as yet undetermined whether Zika virus can spread through respiratory droplets.[26]

Clinical Presentations

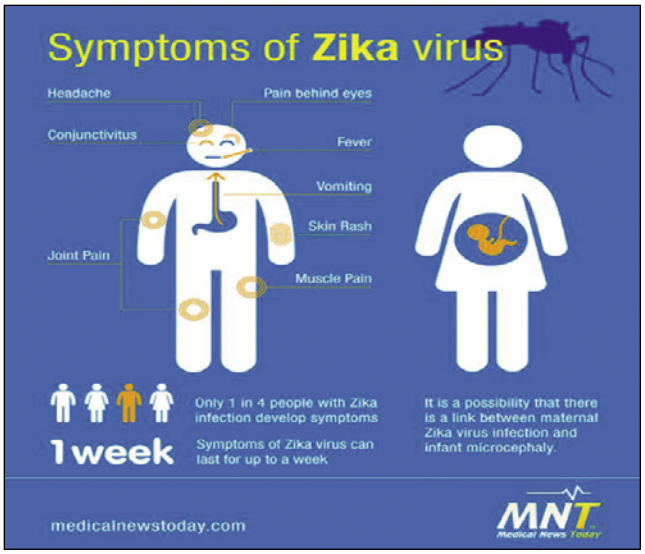

Figure 3. Symptoms of Zika virus (source: medicalnewstoday.com)

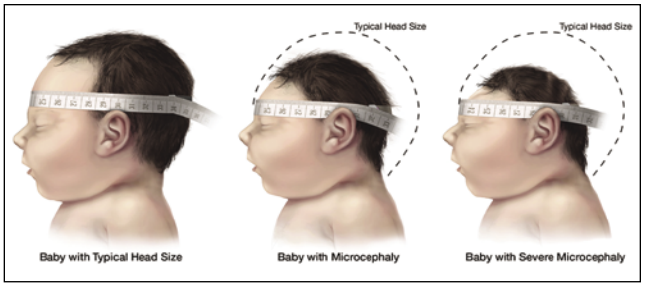

Figure 4. Baby with Microcephaly in Zika virus disease (source: https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-syndrome-birth-defects.html)

The incubation period of the Zika virus is not yet known. Most cases present 3-12 days after the mosquito bites.[2] Case fatalities and severe illness are rare consequences of infection, and 80% of cases are asymptomatic.[27] Symptoms tend to be non-specific, mild, and self-limiting. In almost all cases who acquire the virus via vector or sexual contact, the infection has a benign course without complications. Symptoms of the infection include dermatologic rashes, mild fever, myalgia, conjunctivitis, joint pain, malaise, and headache (Figure 3).[28] The most common manifestation is skin rash, seen in 90% of cases. The skin rash is typically macular or maculopapular, often itchy, and with centrifugal evolution from the trunk to the extremities that usually lasts 4-5 days.[2] In 65-70% of cases, the rashes may be preceded by 1-4 days of fatigue and fever (typically <38°C) for a maximum of 7 days.[29-39] The next most frequent symptom is arthralgia, seen in 65% of cases. Arthralgia is associated in 20-45% of cases with periarticular edema of the hands and feet, and less frequently also the knees and wrists. This edema

may persist for a long duration, on the order of weeks to months.[31] Nonpurulent and bilateral conjunctival infections may also occur in 55-60% of cases and resolve in 1-2 weeks.[2,31] In a case series of pregnant women with Zika virus infections, lymphadenopathy was found to be a common clinical manifestation in approximately 40% of cases, however, it was found in only 15% of cases during the French Polynesia outbreak.[31] It is rare to be hospitalized for Zika virus infection. The Zika virus fever can be distinguished from chikungunya and dengue fever by more significant edema in the extremities, thrombocytopenia (rarely), and less severe malaise and headaches.[29] Furthermore, arthralgia in chikungunya fever tends to be more severe than in Zika virus fever. In comparison to dengue fever, there are no hemorrhagic complications in Zika virus fever.[32]

Autoimmune and neurological complications of Zika virus have been reported. The major complications associated with Zika virus infection are congenital microcephaly and Guillain-Barré syndrome (Figure 4). The incidence rate of Guillain-Barré syndrome was 20-fold higher than otherwise expected in regions of the Zika epidemic.[8] The risk of microcephaly is greatest in the first trimester of pregnancy.[33] The clinical presentation of Zika infection is similar in pregnant and non-pregnant women. Congenital infections are possible even in asymptomatic women.[34] Persistent maternal viraemia may be a significant prognostic factor, as viral RNA was detected in maternal blood up to 107 days after symptom onset. This may be the result of viral replication in either the fetus or placenta.[35-36]

Heart complications and immune thrombocytopenic purpura have been reported in a few cases of Zika infection. Clinical symptoms of this infection are similar in children and adults, however, it should be considered that arthralgia may be difficult to detect in children and Zika can manifest instead as pain on palpation, irritability, impaired walking, refusal to move, and difficulty with movement.[37]

Diagnosis

Clinical evaluations are not reliable for the diagnosis of Zika virus infection, and laboratory profiles are often normal. Clinic manifestations are often insidous and include non-specific symptoms. When a clinician suspects Zika infection, viral RNA can be detected through reverse transcription polymerase chain reaction (RT-PCR). Also, antiviral antibodies can be detected by serologic tests such as IgM enzyme-linked immunosorbent assays (ELISAs) and plaque reduction neutralization tests (PRNTs).[38] The plaque reduction neutralization test is used to quantify the titer of neutralization antibody for the virus. To date, there is no definite consensus as to which test is superior. The Centers for Disease Control and Prevention (CDC) recommends performing both serological tests and RT-PCR to in order to diagnose Zika virus infection.[38] RT-PCR is the preferred testing method during the acute phase of the disease. In contrast, serologic tests are not recommended during the acute phase due to the fact that Zika virus IgM may be undetectable.[10] IgM antibodies only appear in the blood toward end of first week of the disease.[38] RT-PCR must be performed during the viremic period, which is about 3-5 days after onset of the illness.[39] RT-PCR tests can be performed on the serum of infants or the umbilical cord tissue within 2 days of birth. In addition, placental tissue, cerebrospinal fluid, and amniotic fluid can be used for RT-PCR. The virus can be isolated from saliva, however this does not shorten the diagnostic period.[26] Persistence of the virus in urine has been observed up to 10-20 days after manifestation.[40-41] As the precise timing of infection is difficult to establish, a negative RT-PCR does not exclude the possibility of Zika infection.[42] Both symptomatic and asymptomatic pregnant women with a risk of infection should undergo a laboratory test for Zika virus.

Flaviviral cross-reactivity can be problematic, especially for patients infected with another flavivirus or previously immunized (e.g. against yellow fever or Japanese encephalitis virus). These conditions can cause false-positive results in serologic tests. Hence, positive results should be confirmed by a plaque reduction neutralization test. Virus neutralization tests are the most specific tests for flavivirus. A complicated diagnosis may be considered the presence of potential co-infection with chikungunya or proven co-infection with dengue.[43] Clinicians must therefore be careful to correctly diagnose Zika virus infection.

Treatment

An effective treatment for Zika virus infection is not yet known.[38] Supportive treatments may help patients, and this includes taking rest, maintaining adequate hydration, and ensuring appropriate nutrition. Aspirin and other nonsteroidal anti-inflammatory drugs are potentially dangerous until dengue infection is excluded, because of the risk of hemorrhage associated with dengue. There is no antiviral drug against the Zika virus in vivo either.[44] Antibiotics like Duramycin have been reported to decrease the ability of the Zika virus to infect cells, but this is not strongly evidenced.[45] To date, no vaccine for the Zika virus is available, although research currently is underway on various pre-vaccine candidates.[38,51,52] Nevertheless, phase 3 efficacy trials are difficult to conduct due to the unpredictability of Zika virus epidemics, the broad clinical manifestations of infection, inadequately sensitive and specific diagnostic assays, and the need for inclusion of a vulnarable target population. Clarification of immune correlates and surrogates is a current priorty in the development of vaccines and drugs for prophylactic treatment.

Prevention

At the present time, the most important prevention methods against the Zika virus are the reduction of the mosquito population and the removal of potential breeding sites of mosquitoes. Mosquito control measures should be strictly applied to reduce infection risk in endemic regions, because appropriate preventive methods can break the chain of transmission. Individuals who live in or travel to endemic areas should protect themselves against infection using appropriate personal protections such as insect repellents, mosquito nets, and wearing clothes that cover as much of the body's surface area as possible.[24] Using condoms is also an important step in preventing viral transmission.

Scientists are still working on CRISPR/Cas9 genome editing technology directed at preventing the transmission of various diseases by mosquitos. Genetically-engineered insects which are less threatening to humans have been designed to compete with wild-type populations. However, this is the source of several ethical and social problems in some countries. Furthermore, there is significant uncertainty around the long-term effects of these interventions on the ecosystem.

Conclusion

Zika virus has been declared a public health emergency by the WHO. As many as 1.3 million persons have been affected from the virus in Brazil alone. In addition, more than 20 countries have reported local transmission of the virus, which spreads with air travel and international trade into regions where the virus is not endemic. Transmission is most common in locations with mosquito vectors.

In non-endemic areas, Zika virus infection may not be correctly diagnosed due to its mild clinical course. Clinicians working in non-endemic areas should maintain a full awareness of Zika virus infections and should consider it as a part of any relevant differential diagnosis. There is not enough knowledge about immune correlates, transmission mechanisms, pathogenesis, diagnostic tests, prevention methods, and effective treatments for Zika virus, despite its ability to cause very severe and irreversible sequelae such as microcephaly. This virus can be transmitted by both animal and human vectors. A robust, multifaceted response to Zika virus involving public health authorities, government agencies, medical practitioners, and researchers is currently underway, and it is anticipated that this will increase the support for research on the Zika virus.

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