Review Article

Zika virus: An overview

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Abstract

The Zika virus has been in the news for quite some time due to the ongoing recent outbreak in the Southern America, which started in December 2015. It has been declared a public health emergency by the World Health Organization in February 2016 owing to its association with the congenital deformities, particularly microcephaly in infants borne to the infected mothers. The rapid spread of the virus throughout the United States of America and subsequently to Asia has raised serious international concerns. Its spread to countries neighboring India is a serious threat to the Indian population. This review article gives an overview about the virus, its diagnosis, clinical features, and the management.

Keywords: *Aedes*, arbovirus, *Flavivirus*, microcephaly, virus, Zika

Introduction

A number of emerging and re-emerging infections have taken a heavy toll on the public health around the globe.[1] Some of these infections that have been in the news recently include the swine influenza, severe acute respiratory syndrome, Middle East respiratory syndrome (MERS), Ebola virus disease, and the Zika virus (ZIKV) infection.[1,2] The situation in resource-limited countries is really grave due to growing panic and fear, especially in the absence of clear management guidelines and definitive treatment.[1] Although initially some of these infections have been confined to particular geographical areas such as the MERS-Corona virus infection in the middle-east, ZIKV in South America, and Ebola virus disease in the Western Africa, but the situation may become really serious due to rapid globalization, international migration, and relatively easy travel to and from these afflicted countries resulting in the dissemination of these infections to newer countries.[3] The affected cases may travel to other countries where the infection may not have been present and eventually lead to the spread of the pandemic.[3] Most remarkable among all these infections is the infection by ZIKV that has crossed all international borders and has been reported from various corners of the globe.[4]

ZIKV was first identified, almost 70 years ago, in rhesus monkeys during a yellow fever surveillance in the Zika Forest in Uganda (hence its name) and was initially reported in humans in 1952.[3] Seldom was imagined that this virus will become a major international public health concern in the 21st century. Its rapid spread throughout the American continent in 2016 and its potential to cause congenital abnormalities in infants have raised serious concerns. This led to the World Health Organization declaring the ZIKV infection as a global health emergency on February 1, 2016.[5]

About Zika Virus

ZIKV is one of the re-emerging arboviruses (arthropod borne) which is transmitted by *Aedes* mosquito.[3,4] It is a single-stranded RNA virus belonging to the genus *Flavivirus* of the *Flaviviridae* family and has been related to the other Flaviviruses including yellow fever virus, dengue virus (DENV), chikungunya virus, and West Nile virus.[6,7] ZIKV virus has two major geographically different lineages: Asian and African.[6] ZIKV in Africa is

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maintained in a life cycle (sylvatic transmission) that mainly includes monkeys and apes with humans as occasional hosts, but on the other hand, the Asian lineage of ZIKV includes humans as the main host.[6,8]

Epidemiology

Since its isolation from Uganda, it has been reported to be associated with sporadic human infections in Africa and Asia.[3] The most remarkable details are available from the epidemic that occurred in Yap Island, Micronesia (2007), in French Polynesia (2013), and in New Caledonia (2014).[3] ZIKV infection in Brazil was confirmed in May 2015 and by January 2016 the ZIKV epidemic had spread to many countries of Americas, including Bolivia, Brazil, Cape Verde, Colombia, Dominican Republic, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Saint Martin, Samoa, Suriname, and Venezuela.[5,9-11]

Transmission

ZIKV transmission to human takes place mostly via the bite of an infected *Aedes aegypti* mosquito which breeds in fresh standing water and usually bite during the daytime (both indoors and outdoors).[11] *Aedes albopictus* and other species of *Aedes* mosquito (A. africanus, A. luteocephalus, A. furcifer, and A. taylori) also have the potential to spread the virus.[12]

Few cases of person to person presumptive sexual transmission of ZIKV have been reported in women who had sexual intercourse with the partners suffering from the ZIKV illness.[13,14] Researchers have also confirmed the presence of the ZIKV RNA in semen of the affected male giving the hypothesis of sexual spread of the ZIKV illness.[13]

ZIKV RNA has also been detected in blood, urine, saliva, cerebrospinal fluid (CSF), amniotic fluid, and breast milk.[15-17] Maternal to fetal transmission can occur, as the virus can cross the placental barrier resulting in congenital (intrauterine) infection and also intrapartum transmission can occur.[18-20] ZIKV transmission through breastfeeding has not yet been described, and thus it is recommended that the affected mothers continue to breastfeed their babies.[21]

Clinical Manifestations

Symptoms and signs of ZIKV infection occur only in about 20% cases infected with the majority of the patients being asymptomatic.[4,22] The common symptoms are similar to those of DENV and chikungunya virus infections and include the acute onset of low-grade fever with maculopapular rash, arthralgia (involves the small joints of hands and feet), and conjunctivitis (non-purulent).[10,11,23] Other symptoms include headache, retro-orbital pain, myalgia, asthenia, peripheral edema, and gastrointestinal disturbance (abdominal pain, nausea, diarrhea).[10,11,23] Symptoms and signs typically occur approximately 2–12 days after the *Aedes* mosquito bite and usually resolve within 2–7 days.[22,23] The patients with clinical signs and symptoms along with a history of travel to ZIKV endemic areas should raise a suspicion for its diagnosis.

Postnatal ZIKV infection in infants and children present with similar signs and symptoms as that of adults.[24] Arthralgia in infants (also young children) usually manifests as the child being irritable, walking with a limp, having difficulty in moving or refusing to move an extremity, or pain with active or passive movement of the affected joint or on palpation of the joint.[24]

Complications

ZIKV infection has been associated with various complications, including congenital microcephaly, Guillain–Barré syndrome, and even fetal losses in women infected during pregnancy.[25,26]

Congenital (intrauterine) infection: ZIKV infection in pregnant mothers can occur in any trimester and is reported to cause microcephaly in infants with many confirmed reports coming from Brazil showing the association of the virus infection with microcephaly in the newborn and even infant death (mostly if the infection is acquired during the first trimester).[25,27] The cases of muscular atrophy have also been observed in children with microcephaly born after the onset of the ZIKV outbreak in Brazil.[27]

ZIKV infection acquired during pregnancy is associated with poor outcomes of the fetus, which includes central nervous system injury, placental insufficiency, *in vitro* fetal growth restriction (with or without microcephaly), and also fetal death.[28]

Neurological complications: Few cases have been reported showing the association of ZIKV infection with the Guillain–Barré syndrome.[26,29] About 90% of the patients had reported to have symptoms of ZIKV infection about 6 days prior to neurological symptoms.[26] The other neurological manifestations include the reports of acute myelitis and meningoencephalitis associated with detection of ZIKV in the CSF.[30,31]

Moreover, there is a report of ankle edema, axillary and/or inguinal lymphadenopathy, leukopenia with monocytosis, and thrombocytopenia from the cases of ZIKV infection in travelers from Italy.[32]

Diagnosis

The ZIKV infection should be suspected in patients having clinical symptomology of acute viremia during an ongoing epidemic in an area of the prevalence of *Aedes* mosquito or a history of recent travel to a ZIKV endemic area or if the person has had an unprotected sexual contact with an infected partner.

The diagnosis of ZIKV infection is established by serum reverse transcription polymerase chain reaction (RT-PCR) for detection of ZIKV RNA or ZIKV serology (IgM antibodies).[33,34]

Serum RT-PCR is positive if done in the acute phase of the viremia, i.e., the first 3–7 days of the onset of illness.[34] The specific antibodies against ZIKV in serum (IgM antibodies) are detectable after 4 days of symptom onset, but its diagnostic value is limited due to cross-reactivity with other Flaviviruses (DENV and chikungunya virus). In ZIKV infection, the serum titers of the IgM antibody are ≥4-fold greater than DENV antibody titers, thus helping in the diagnosis.[32,34]

The medical literature has studies suggesting that the ZIKV RNA can be detected in urine, and saliva of the patients for a longer duration than the serum by the RT-PCR method.[34]

Prenatal fetal evaluation of the pregnant females suspected or confirmed to have a ZIKV infection (also exposed to ZIKV) is done by regular fetal ultrasound examination, which can detect abnormalities at as early as 18–20 weeks of gestation, but is also operator dependent.[34] The main ultrasound findings pointing toward fetal ZIKV infection are microcephaly (head circumference more than two standard deviations below the mean for gestational age), intracranial calcifications (cerebellum, intraocular, brain), hydranencephaly, ventricular dilatation, brain atrophy, anhydramnios, hydrops fetalis, and intrauterine growth retardation.[34]

Management

There is no specific treatment option available for ZIKV infection.[1,3,4] The course of the disease is mostly self-limiting and the management is primarily bed rest and supportive care, including increased intake of fluids to prevent dehydration and administration of acetaminophen for relief of fever and pain.[33,34] There is no vaccine or antiviral therapy available presently for ZIKV.[33,34] The preventive measures involve the control of the vector (*Aedes* mosquito) growth and its elimination and prevention of mosquito bites. The sexual mode of transmission can be avoided by the use of barrier methods (condoms) or abstinence from sexual intercourse.

Mosquito bites can be prevented by wearing long sleeve shirt and pants, use of insect repellent, and being indoors as much as possible (with air conditioning, window/door screens, and/or mosquito nets).[35]

Aedes mosquitoes breed in stagnant water, thus found in abundance in places of on-going construction (making it a disease more prominent in urban areas). Moreover, these mosquitoes are commonly found in tropical and sub-tropical areas, making Asian countries (including Indian subcontinent) an endemic zone for growth of *Aedes*. Environmental control measures include the identification and elimination of the potential breeding sites of water stagnation.[35]

So far the cases of ZIKV in India have not been reported, but a study conducted in six states of India in the year 1952–1953 reported the neutralizing antibodies in the sera to certain viruses including ZIKV in the Indians.[36,37] This detection could well be due to cross reactivity among different *Flavivirus* antibody assays. However, the recent reports from Bangladesh are alarming where the first case of ZIKV infection in a 67-year-old male has been detected.[38] The problem of ZIKV could become really grave in Asian countries due to warm and humid conditions which are ideal for the mosquito vector breeding.[37] In these resources-strained countries where the per capita income is low and there is a meagre contribution from the government's annual health budget, the emergence of ZIKV could only add to the woes.[39-41] Moreover, in the absence of clear guidelines, management strategies, and cure, the proper dissemination of the healthcare information about the ZIKV is imperative, and thus the role of all the stakeholders, including clinicians, healthcare workers, the general public, government agencies, NGO's such as the HIFA2015 is very important.[42-44]

Zika Virus Epidemic Concerns

The outbreak of ZIKV infection in 2013 in the French Polynesia is considered to be the largest and is postulated to have spread to Brazil during the major sport events of 2014, the World Cup Soccer and the Va'a World Sprint Championship canoe race, which were hosted by Brazil.[45] Now with the upcoming Summer Olympics in August 2016 to be again hosted in Brazil, the spread of this virus to a massive scale remains a global concern.[11]

The rapid spread of the zoonotic diseases such as ZIKV is due to the urbanization of the forest areas for the ever expanding human population. Moreover, the speed and the ease of transport (airways, roadways, railways, and water travel) not only for humans, but also for disease vectors, lead to the rapid and widespread dissemination of the disease.[11]

India carries a potential threat of outbreak of ZIKV infection, being an endemic country for the vector (*Aedes aegypti*) and thus realizing the same, the Indian government has issued guidelines for tackling this problem.[46,47]

Conclusions

The recent outbreaks of ZIKV infection in the Americas have brought this emerging arbovirus disease into the limelight as a cause of congenital anomaly (microcephaly) in infants born to infected mothers. The rapid spread of ZIKV is an international cause of concern with the virus reaching the Asian countries, including the neighboring countries of India. The other issue of the epidemic control in future to be addressed is the spreading menace of the mosquito borne diseases due to the inadequate control of breeding of this vector. Furthermore, there is a need for large scale animal and human studies from various corners of the globe so that the clear management guidelines can be developed against ZIKV. Furthermore, efforts to control the emerging menace due to obscure and new virus should be given prime importance.

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Conflicts of interest

There are no conflicts of interest.

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