A review on zika virus: clinical aspects and therapeutic responses

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ABSTRACT

The Zika Virus (ZIKV) happens to be one of the recent infections investigated after the Ebola pandemic. It is an arthropod-borne virus (arbovirus) within the family Flaviviridae class. ZIKV is an RNA virus with a single strand, enveloped, icosahedral, non-sectioned, positive sense. It is 40 nm wide and has an outer (E) envelope and a dense inner core. The ZIKV can be transmitted by two methods: human and human-to-human vectors. The vector transmission is by Aedes spp. Mosquitoes and diseases outside Africa are transmitted by Aedes aegypti. Originating in Nigeria in 1947 it was reported as a mild illness and from a rhesus monkey. With a certain passage of time earned significant attention from healthcare organisations for the human population. Many clinical symptoms in adults in French Polynesia have been recorded, ranging from mild illness to severe neurological problems such as Guillain-Barré syndrome. Other symptoms include encephalitis microencephaly, meningoencephalitis, myelitis, paraesthesia, vertigo, facial and ophthalmological paralysis (photophobia and hypertensive iridocyclitis) and auditory manifestations. In this review, the clinical aspects and other therapeutic responses are studied here to understand the approach more treating symptoms arising with the infection of the Zika virus. Various complications have been studied in this review and diagnosis have been performed to identify the presence in the human body and also take clinical measures on alleviating the symptoms of the infected patients.

INTRODUCTION

Zika infection (ZIKV) is the most recent emanant infection after the Ebola pandemic. Before ZIKV was linked to mild disease, perhaps as it may have recently emerged as a significant threat to human well-being after six decades of stifling movement, with apparent foetal anomalies, microcephalus, real neurological complications, and immune system issues, such as Guillain-Barré disorder (GBS). Zika infection is a flavivirus effectively transmitted by an infected Aedes aegypti, Aedes Africanus bite and also from Ae And Albopictus. Mosquitoes Hensilii. ZIKV is a mosquito-borne flavivirus in the positive-abandoned RNA community of Flaviviridae. It is strongly associated with a few different pathogens, including Dengue (DENV), yellow fever (YFV), West Nile (WNV), Japanese encephalitis (JEV), and tick-borne encephalitis (TBEV) infections. Although ZIKV was initially confined from a sentinel monkey at the Zika Forest Research Station in Uganda in 1981. (Singh et al., 2018)

ZIKA Virus/ZIKA Fever

Zika fever, or simply Zika flu, is an infectious disease
caused by the Zika virus. Most cases do not have any side effects but appear to be mild and similar to dengue fever when present. Symptoms can include fever, red eyes, joint pain, cerebral pain, and maculopapular rash. Some propose that dengue fever and Chikungunya fever may recognise zika fever via increasingly noticeable oedema, no severe cerebral pain and discomfort, and a milder level of thrombocytopenia. Zika fever is typically self-constraining with most clinical manifestations resolving fully within 3-7 days. No death, hospitalisation or haemorrhagic complications were recorded during the Yap Island outbreak. Zika fever-related rash usually improves in the first week, but can last up to 14 days and maybe pruritus (Ioos et al., 2014; Gulland, 2016).

Zika infection is an arthropod-borne flavivirus transmitted by mosquitoes. ZIKV is a single-stranded RNA virus, enveloped, icosahedral, non-sectioned, positive sense. The lipid envelope is secured with thick projections which consist of a glycoprotein layer and envelope. Zika virus disease is transmitted by Aedes mosquitoes mainly by bite. When a person is infected with a mosquito bite, the Zika infection can be detected in their blood for a few days or in some individuals for longer.

**Epidemiology**

In 1953, the human disease caused by Zika was first detected in Nigeria, when three sick people were established to have a viral infection. In April 1947, a febrile sentinel rhesus monkey (Rhesus 766) first discovered Zika forests in Uganda. ZIKV was derived from the serum of a 10-year-old Nigerian girl who developed fever and headache in 1954. It is estimated that an epidemic in French Polynesia in 2013 and 2014 involved 32,000 people who had been tested for suspected Zika virus infection. In February 2014, the first occurrence of human ZIKV infection occurred during the annual Tapati Festival in Easter Island, Chile, in the western hemisphere of the globe starting from French Polynesia. In Thailand, East Malaysia, Cambodia, the Philippines and Indonesia, sporadic cases of Zika have been reported.

In April 2007, there was a study of Zika epidemic outside Africa and Asia, on Yap Island in Micronesia. The episode was also reported in 2014 in South and Central America and 2015 in Mexico. The epidemic of Zika was finally revealed in Texas, the United States and Europe. Thus, the World Health Organisation (WHO) pronounced it on “a public health emergency of international concern” 1 February 2016 (Musso et al., 2014; Hasan et al., 2019).

Zika virus first emerged in the Americas in 2015, when Bahia, Brazil, witnessed an exanthematous virus epidemic. Colombia established the most extensive autochthonous transmission of Zika infection outside of Brazil in October 2015, and an estimated 473 suspected cases of Zika infection were reported in that country by 3 March 2016. By September 2015, examiners in Brazil noticed an expansion in the number of newborn children brought into the world with microcephaly in similar territories wherein Zika infection was first announced. In the US in 2016, there was 5168 affirmed non-congenital Zika infection reported. In February 2016, Texas registered the critical instance of sexually transmitted Zika infection in the US. As of March 2017, 24 nations and regions in the Americas had revealed 2767 affirmed cases of microcephaly or central nervous system malformations related to ZIKV infection during pregnancy.

India first announced four cases of ZIKV virus in 2017; three were in Gujarat State (one which had happened in late 2016), and one in Tamil Nadu, in 2018, a ZIKV outbreak was recognised in Rajasthan state. As of December 2018, the India National Center for Disease Control, Ministry of Health and Family Welfare revealed 159 affirmed cases of ZIKV virus from Rajasthan state (include 63 pregnant ladies), 130 cases from Madhya Pradesh, and one case from Gujarat state (Miner and Diamond, 2017), (Table 1).

**Pathogenesis**

ZIKV is an RNA virus with a single strand, enveloped, icosahedral, non-sectioned, positive sense. It is 40 nm wide and has an outer (E) envelope and a dense inner core. The ZIKV can be transmitted by two methods: human and human-to-human vectors. Transmission of vectors is by Aedes spp. The transmission of mosquitoes and infections outside Africa is through Aedes aegypti. ZIKV reproduces the mosquito vector’s midgut and salivary cells in the epithelial coating. It shows up in the currently contagious mosquito saliva with a set period of approximately five days. The vector immunises the infection into the skin of the human host during a blood meal. The infection can contaminate the Langerhans epidermal keratinocytes, fibroblasts and cells. It is predicted that the pathogenesis of the infection continues with drainage to the lymph nodes and bloodstream. Flaviviruses replicate in the cytoplasm, but antigens of Zika have been detected in infected nuclei. ZIKV replication works on an unsusceptible antiviral reaction and produces type I interferon in the cells infected. Autophagosomal production is correlated with upgraded virus
Table 1: The epidemiology of ZIKA virus

<table>
<thead>
<tr>
<th>Year and ZIKV feature</th>
<th>Affected population</th>
</tr>
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<tbody>
<tr>
<td>April 1947, Zikv was first identified from a febrile sentinel rhesus monkey in Uganda's Zika forests (Rhesus 766). 1947-1948 Uganda, The first identification of ZIKV neutralisation antibodies in sentinel rhesus monkeys 1952, ZIKV first human infection in Nigeria 1954 Nigeria, ZIKV is first isolated from human serum. 1964 Uganda, the first well-documented human ZIKV infection study. 2007-2008, First epidemic in Yap Island, Micronesia 2008, First Sexually transmitted case of Zika virus 2009-2012 Africa, Asia, Europe, North America and Australia reported a few cases (including those related to travel). 2013 Second epidemic in French Polynesia 2013, First reported case of Zika virus with Guillain Barré syndrome March 2015, Brazil reported the first autochthonous cases 2015, Third epidemic in South America and October 2015 The first incidence of microcephaly with ZIKV infection 2016 US, Non-congenital Zika infection reported. 2016 February WHO declared ZIKV a public health emergency 2017 March, Americas had cases of microcephaly or central nervous system malformations related to ZIKV infection during pregnancy 2017 first reported India, in Gujrat state and 1 case in Tamil Nadu 2018 December, the India National Center for Disease Control, Ministry of Health and Family Welfare reported zika infection.</td>
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ZIKV=Zikavirus, WHO=World Health Organization

reproduction, the prompted articulation of antiviral antigen clusters (RIG-1, MDA-5, and TLR3) capable of discerning pathogen-associated molecular patterns after skin fibroblast disease was observed. ZIKV caused an autocephalous programme confirmed in the infected fibroblasts by the existence of autophagosome-like vesicles. In the critical process of Zika fever, the lymphocytes are activated. Following viral transmission, E glycoprotein promotes viral connection to the host cell receptors. This is followed by endocytic take-up, nucleocapsid uncoating, and viral RNA discharging into the cytoplasm. The antigen has been expressed in the nucleus of host cells as a noticeable contrast between various flaviviruses. This will explain Zika-related complexities.

Human-to-human transmission of ZIKV by transplacental route, spillage of the infection by a trophoblastic plug, the spread of the infection in an amniotic sac during formation or delivery by an infected mother to her newborn. Sexual methods have been reported in human-to-human transmission, and blood transfusion research has also been carried out in Brazil. Sexual transmission occurs when a person has a severe Zika disease, which is especially significant when the partner is pregnant due to the neurological results on the foetus. Second, placental ZIKV infection causes placental deficiency and restricts growth and microcephalus. (Musso and Gubler, 2016; Foy et al., 2011).

TRANSMISSION

Can transmit the Zika virus to humans by:

1. Infected rodent bites
2. Fetal-maternal transmission
3. Sex (oral, anal, and vaginal)
4. Transfused blood
5. Organ transplant
6. Exposure in laboratory

Zika is transmitted essentially via the Aedes aegypti female mosquito, which is often aggressive during the day. The mosquitoes have to feed into laying
eggs from the blood. The infection has likewise been confined from various arboreal mosquito species in the sort *Aedes*, for example, *A. Africanus*, *A. apicoargenteus*, *A. furcifer*, *A. hensilli*, *A. luteocephalus*, and *A. vittatus*, with an irrelevant time of incubation of about ten days in mosquitoes (Diagne *et al.*, 2015).

Zika can be spread to the sexual partners by individuals; the majority of cases realised include spread from symptomatic men to women. ZIKV may persist in semen for a time, with more than six months of recognised viral RNA. The infection replicates in human testis, where it infects many cell types, including testicular macrophages, peritubular and germ cells, sperm precursors.

Female genital discharges – Zika RNA infection was recognised during symptomatic disease in female genital tract secretions (through endocervical swabs and cervical body fluid). Besides, zika infection RNA was identified in cervical fluid 14 days after the initiation of disease when it was not identifiable in urine or blood for a long time.

Infection with zika can be transmitted via vertical (or mother-to-kid) transmission, during pregnancy or delivery. During pregnancy, an infection was linked to improvements in the neuronal development of the unborn child. Severe disease movements have been related to microcephalus development in the unborn child, although mild infection may trigger adult neurocognitive disorder (Venturi *et al.*, 2016; Murray *et al.*, 2017).

As of April 2016, two cases of blood transmission from Zika were entirely accounted for, both from Brazil, following which the US Food and Drug Administration (FDA) recommended screening for four weeks for blood donors and other high-risk donors.

**CLINICAL FEATURES**

Approximately 80 per cent of ZIKV is asymptomatic. Symptomatic infections are distinguished by a febrile self-constraining disease that usually goes on for 3–12 days and is linked with maculopapular rash, arthralgia, back pain and headache. The skin rash starts blurring precipitously within two days, and fever begins to resolve within three days, and the rash continues. Some less usual clinical highlights include vomiting, diarrhoea, stomach pain, mucous layer ulcerations, uveitis and palatal petechiae.

Following utero infection, extreme ZIKV can be seen leading to neurological complications, especially microcephalus and Guillain-Barre syndrome (GBS), characterised by ascending paralysis and polyneuropathy, multi-organ failure, and thrombocytopenia and purpura. Infection with ZIKV causes encephalitis, meningoencephalitis, myelitis, paraesthesia, vertigo, facial paralysis and ophthalmological symptoms (photophobia and hypertensive iridocyclitis) and auditory. ZIKV can also damage the eye and cause uveitis in adults, which can be blinding. ZIKV disease affects up to 15 per cent of patients with conjunctivitis, possibly because of direct contact with the eye. In people with a variety of eye disorders, including retinal mottling, lens subluxation, and optic neuritis, congenital ZIKV infection can also cause sensory hearing loss and visual impairment. (Fauci and Morens, 2016; Olson *et al.*, 1981).

Other symptoms have been identified in case reports including facial puffiness, uveitis, temporary hearing impairment, myocarditis and pericarditis. Other clinical symptoms widely identified include myalgia, headache, dysesthesia, retro-orbital pain and asthenia. (Chan *et al.*, 2016) (Table 2).

**COMPLICATIONS**

The complications most conspicuous include:

1. Serious dehydration
2. Syndrome with Guillain-barre
3. Congenital malformations, especially microcephalic ones
4. Breastfeeding and stillbirth in pregnant women.
5. Anomalies of the eyes in children with Zika-related microcephalus, such as the retina or optic nerve defects, which in later life can cause blindness that destroys myelin or the protective covering of nerve fibres, gradually leading to loss of vision and weakness to the point of paralysis.

**Guillain-barré syndrome (GBS) in adults**

GBS is a rare, rapid-onset paralysis. It is an immune system syndrome, and its regularly activated by an infection a few days to weeks earlier. The first instance of Zika infection complicated by GBS was accounted for French Polynesia in March 2014. Guillain-Barré disorder (GBS) is the most well-known reason for acute flaccid paralysis in healthy newborn children and kids. GBS happens worldwide with a yearly frequency of 0.34 to 1.34 cases per 100,000 people matured 18 years or less. In all age groups, males are affected about
Table 2: The clinical features of ZIKA virus

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Asymptomatic</td>
<td>&gt; 80% of humans infected person is asymptomatic</td>
</tr>
<tr>
<td>Systemic</td>
<td>Fever, shivering, weakness, pain, anorexia, sore throat, pneumonia, conjunctivitis and hypotension</td>
</tr>
<tr>
<td>Neurological/Ophthalmological</td>
<td>Guillain barre syndrome, encephalitis, paresthesia, photophobia, vertigo, facial paralysis, conjunctivitis, and myelitis</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myalgia, Arthralgia, periaricular oedema (wrists, elbows, ankles and small joints of the hand and foot)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Vomiting, fatigue, diarrhoea, constipation and jaundice</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Haematuria, prostatitis and haematospermia</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Diffuse maculopapular rash, pruritus and inflammation of the gingivitis</td>
</tr>
<tr>
<td>Haematological</td>
<td>Leucopenia, neutropenia, lymphopenia, monocytosis, activated lymphocytes or thrombocytopenia</td>
</tr>
<tr>
<td>Biochemical Changes</td>
<td>Fast serum lactate dehydrogenase, aminotransferase aspartate, g-glutamyltransferase, C-reactive protein, fibrinogen and ferritin levels</td>
</tr>
</tbody>
</table>

1.5 times more frequently than females. Two-thirds develop the neurological symptoms in patients with acute inflammatory demyelinating polyradiculopathy (AIDP), the most common form of GBS, two to four weeks after what initially appears to be a benign respiratory or gastrointestinal infection. The prevalent manifestations of GBS at the presentation in children are pain and gait difficulty. The primary modalities of treatment for Guillain-Barré syndrome incorporate plasmapheresis and administration of intravenous immune globulin. (Barbi et al., 2018; Oehler et al., 2013).

**Congenital Zika syndrome in neonates**

Congenital Zika syndrome is a group of congenital disabilities related to Zika during pregnancy. The congenital anomalies associated with maternal rubella infection during pregnancy include sensorineural hearing loss, eye defects, cardiac anomalies and neurological effects including intellectual disability, ischemic brain damage and microcephalus.

Microcephalus is a small head size clinical finding for gestational age and sex and is indicates the crucial issue with brain development. Guidance Centers for Disease Control and Prevention (CDC) Suggested were microcephalus be identified as an occipitofrontal diameter below the third gestational age and sex percentile. (Coelho and Crovella, 2017; Jaenisch et al., 2015)

**Characterise microcephaly with qualifying terms**

1. Borderline microcephaly – Occipitofrontal circumference (OFC) between 2 and 3 Standard deviations (SD) lower than average for age, sex and gestation
2. Moderate microcephaly – OFC between 3 and 5 SD less than normal for age, sex and gestation
3. Severe microcephaly – OFC ≥5 SD less than mean for age, sex, and gestation

**Microcephaly has two primary mechanisms**

1. Lack of brain growth or irregular brain development associated with a developmental insult during the induction phase and significant cellular migration; this type of microcephaly is thought to result from a reduction in the number of neurons generated during neurogenesis; the forebrain is most severely affected (e.g., holoprosencephaly)
2. Injury or insult to a previously normal brain (sometimes called secondary microcephaly); this type of microcephaly is thought to result from reduced dendritic processes and synaptic interactions.

**ZIKA-Related Death**

In late November, three ZIKV-related deaths were reported in Brazil (two adults with a neurological disorder and one infant,)

1. Adult male with chronic lupus erythematos corticosteroid, rheumatoid arthritis and alcoholism
2. A 15-year-old girl with sickle cell disease who was born with fever, respiratory distress, jaundice and hepatosplenomegaly
3. A neonate microcephalus, foetal anasarca, and polyhydramnios that died within five minutes of birth.

Diagnosis

ZIKV does have two forms of determination. The primary form contains both the infection characteristics as well as the viral sections, to identify ZIKV RNA, viral proteins, and live infection, respectively. RT-PCR, immunoassay, and virus isolation were made. The second diagnostic method is focused on the identification of the antibodies caused by ZIKV infection. RT-PCR and immuno histochemical testing were useful in detecting Zika infection in foetal tissue loss and newborn infants who died after birth. Furthermore, the use of ultrasonography to diagnose microcephalus depends on clinical and technological considerations, and ultrasonography is undoubtedly not a too delicate tool to discern microcephalus (Buckley and Gould, 1988; Foo et al., 2017).

Virus Isolation

Intracerebral mouse immunisation was performed the primary isolation of Zika infection, considered as the reference examine for isolation of arboviruses. Zika infection can be refined from blood, urine, saliva, and semen among human clinical examples.

Molecular Assay

Reverse transcriptase PCR (RT-PCR) is highly sensitive and accurate, and is known as the ZIKV diagnostic "gold standard." For example, the Food and Drug Administration (FDA) has affirmed one assay, Cobas Zika test (Roche), which is a subjective nucleic acid analysis to screen for Zika RNA infection in blood donors.

Serological Assays

The present serology assay is based on the identification of antibodies to structural flaviviral proteins. Antibodies were not routinely explored for serological assays against non-structural viral proteins. The key drawback of the existing serological assays is the cross-reactivity of various antibodies resulting from flavivirus infections. Various serological tests, including complimentary fixation, haemagglutination inhibition, immunofluorescence (IF) assay, ELISA and neutralisation tests, can be used to detect anti-Zika virus antibodies.

Prevention

There are currently no confirmed antibodies/vaccines for four illnesses with flavivirus. On ZIKV may be applied both inactivated and live attenuated virus/vaccine antibodies. These are YFV (live attenuated), TBEV (inactivated), JEV (inactivated and live attenuated) and DENV (recombinant live-attenuated chimeric). For instance, 1 per cent sodium hypochlorite, 2 per cent glutaraldehyde, 70 per cent ethanol, 3 per cent -6 per cent hydrogen peroxide and 3 per cent -8 per cent formaldehyde are known to be susceptible to disinfectants. ZIKV inactivates potassium permanganate and ether. The best form of prevention is avoiding or repelling mosquitoes, preventing bites of mosquitoes by wearing long sleeves and boots, using insect repellents and staying indoors as possible (with air conditioning, window/door screens and mosquito nets to reduce the contact between mosquitoes and humans). Insect repellents that contain N, N-diethyl-m-toluamide should be added for pregnant and lactating women older than two months. At the point outbreak occurs, blood donation should be suspended immediately. At the hour of pregnancy returned men should continue to use condoms with pregnant sex partners anywhere. (Shan et al., 2016; Oster et al., 2016).

Treatment

There is no available ZIKV approved therapeutic or preventive medicine. Patients with asymptomatic or uncomplicated Zika fever frequently do not need medication. Two strategies for antiviral production of ZIKV may be followed. The first is to re-target existing medicinal drugs recently developed for ZIKV treatment for other symptoms of the disease. Few antiviral drugs have shown efficacy in cell culture. When identifying inhibitors, it would be necessary to check if the compound concentration required for the anti-ZIKV effectiveness could be achieved in patients. The second approach is to build actual ZIKV-infection and replication inhibitors. Both viral infection and Viral enzyme assays can also be used to separate inhibitor compound libraries. They may also develop therapeutic antibodies for the treatment of ZIKV disease.

Zika fever treatment is helpful and includes acetaminophen for flu, migraine, or myalgia. Anti-inflammatory drugs (Aspirin) should not be used in children with thrombocytopenia and Reye disease due to the risk of bleeding (Brooks et al., 2016). As a consequence of the increased danger of hemorrhagic disease, non-steroidal anti-inflammatory drugs are likewise not recommended. Enough rehydration should be applied to minimise fluid loss. Neurological complications analysis, particularly GBS, is important for the first remedy of immunoglobulins intravenous.

Virological and foetal ultrasound tests to avoid ZIKV and fetal microcephalus or intracranial calcifica-
tions should be administered to pregnant women with Zika fever-like side effects during or within 14 days of transmission to ZIKV (Gonzalez et al., 2016; Petersen et al., 2016). After delivery, the serum should be collected from the umbilical cord, or directly from the neonate within two days of birth for RT-PCR, IgM, or potentially neutralising antibodies to ZIKV.

CONCLUSION

Zika infection is a mosquito-transmitted flavivirus first detected in monkeys in Uganda in 1947. It was remembered later by citizens in Uganda and the United Republic of Tanzania in 1952. There have been records of an epidemic of Zika infection in Africa, the Americas, Asia and the Pacific etc. The future of the zika epidemic is uncertain, and the ZIKV epidemic has risen as an unprecedented global well-being crisis since the rapidly rising ZIKV epidemic may end up being an extensive and severe impairment in a generation of newborns (microcephaly) in children, including Guillain-barré syndrome in adults. The infection is transmitted through a mosquito vector, even though different non-mosquito methods of spread are also known. Therefore, preventive measures, including vector control, prevention of insect bite, utilisation of condoms, keeping away from travel to ZIKV endemic areas, assume a significant role.

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Conflict of Interest

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