EBOLA VIRUS DISEASE AND ZIKA VIRUS DISEASE: NEUROPSYCHIATRIC SEQUELAE

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SUMMARY
Ebola virus disease (EVD) and Zika virus disease (ZVD) are the two most recent emerging and re-emerging diseases in the world. Due to sudden unexpected surge in the number of cases, a lot of fear and panic had spread all over the world leading to psychological distress. The EVD outbreak in West Africa was the largest and most complex Ebola outbreak since the Ebola virus was first discovered in 1976. Thousands were infected and many lost their lives. The Zika virus epidemic that started in Brazil, spread to >30 countries and territories in Latin America, and led to a rapid rise in the incidence of microcephalic newborns and adults with neurological complications. Neither an effective treatment nor a vaccine is available for both the diseases. The mainstay of the treatment emphasises on physical care and little or no attention has been paid to mental health. Both the diseases left many survivors with psychological distress. Understanding psychological reactions among these survivors may provide relevant information about post-treatment adjustment and possible psychological preventative measures.

KEYWORDS: Ebola virus disease, Zika virus disease, Psychological distress, Neuropsychiatric complications.

INTRODUCTION
During the last few years the world has witnessed 2 unexpected epidemics of Ebola virus disease (EVD) and Zika Virus disease (ZVD). Both these RNA virus belonging to family Filoviridae and Flaviviridae respectively created much panic and havoc in the world. The latest EVD outbreak started in December 2013 in Guinea and later on spread to the neighbouring countries of Liberia and Sierra Leone. This outbreak in West Africa was the largest and most complex Ebola outbreak since the Ebola virus was first discovered in 1976. The Zika virus epidemic that started in Brazil in 2015, spread to >30 countries and territories in Latin America, and led to a rapid rise in the incidence of microcephalic newborns and adults with neurological complications such as Guillain–Barre syndrome, meningitis and meningoencephalitis. Neither an effective treatment nor a vaccine is available for EVD and ZVD. Symptomatic treatment and adequate preventive measures form the mainstay of the treatment. Both the diseases left many survivors with psychological distress. Understanding psychological reactions among these survivors may provide relevant information about post-treatment adjustment and possible psychological preventative measures.

1. EBOLA VIRUS DISEASE (EVD)
1.1. History
Ebola virus disease was first identified in 1976 in Sudan and the Democratic Republic of the Congo (formerly Zaire). It is named after a river in the Democratic Republic of the Congo. Since 1976, there have been several outbreaks in central and West Africa. Outbreaks have been recognised before the 2014 epidemic involving 2,400 cases. The 2014 Ebola epidemic in West Africa has been the largest Ebola outbreak in history. The epidemic started in December 2013 in Guinea and later on spread to the neighbouring countries of Liberia and Sierra Leone. In August 2014, WHO declared this epidemic to be a “public health emergency of international concern”. The Ebola virus (EBOV) has a non-segmented linear negative-sense RNA genome of approximately 19,000 base pairs. It encodes seven structural proteins: nucleoprotein (NP), polymerase cofactor (VP35), (VP40), GP, transcription activator (VP30), VP24, and RNA polymerase (L). Taxonomically, EBOV belongs to the Filoviridae virus family. To date, five species of Ebola viruses have been identified: Zaire, Sudan, Bundibugyo, Reston and Tai Forest. Mostpre-2013 outbreaks were caused by Zaire Ebola virus (EBOV) or Sudan virus (SUDV). Outbreaks caused by Reston virus (RESTV) have occurred in nonhuman primates and pigs, with associated
asymptomatic human infections. The 2014 outbreak was caused by the Zaire species.\[6,7\]

1.2. Transmission

Ebola outbreaks occur when the virus is transmitted first from an infected animal to a human and then between humans. The viral infection is spread from animals to humans through contact with infected wildlife such as fruit bats, chimps, and gorillas.\[8\] Certain fruit bats are believed to be the natural hosts for the Ebola viruses. EVD is transmitted from person to person by direct contact (through broken skin and mucous membrane) via bodily fluids or secretions from infected people, such as: blood, breast milk, semen (up to 61 days after infection), sweat, stool, urine and vomit. Transmission can also occur through contact with objects contaminated with these fluids and the bodies of the deceased with EVD.\[9\] Since the bodies of the deceased can infect those who handle them, safe burial practises are extremely important in containing outbreaks. The infection can be spread further by cultural burial practises such as ritual washings that bring people into close contact with infected bodies. During outbreaks, those at greatest risk of getting the viral infection are health care workers and the family and friends of the infected who have close contact with the patients.

1.3. Clinical features

The length of time between exposure to the virus and the development of symptoms (incubation period) is between 2 and 21 days.\[10\] The symptoms usually begin suddenly with a flu-like stage characterized by fever, headaches, and joint, muscle, and abdominal pain. This is followed by decrease in liver or kidney function. A macular rash may appear on the face and chest on the second or third day in about half the cases. Internal and subcutaneous bleeding may occur in the conjunctiva, and there may be signs of hematemesis, haemoptysis, or melena. Bleeding into the skin may be evident as petechiae, purpura, ecchymoses, and hematomas (especially around needle injection sites). If the infected person does not recover, death due to multiple organ dysfunction syndrome (MODS) usually occurs.\[11\]

1.4. Diagnosis

Due to nonspecific clinical features such as fever, headache, rash, weakness etc. common diseases like malaria, typhoid need to be ruled out. A travel history to country of epidemic and contact history is particularly looked at. People with suspected EVD should be quarantined while waiting for definitive diagnosis by laboratory tests. For early detection of Ebola virus in suspect or probable cases, detection of viral RNA or viral antigen are the recommended tests. Laboratory-confirmed cases must test positive for the presence of the Ebola virus, either by detection of virus RNA by RT-PCR, and/or by detection of Ebola antigen by a specific Antigen detection test, and/or by detection of Immunoglobulin M (IgM) antibodies directed against Ebola.\[12,13\]

1.5. Treatment and Prevention

Due to no definitive cure for EVD at present, supportive treatment forms the mainstay of management.\[14\] Supportive therapy for EVD is directed toward maintaining effective blood volume and pressure, electrolyte balance, and tissue oxygenation since the majority of people with EVD die from severe dehydration. Isolation and strict barrier nursing is necessary to manage EVD patients.\[15\]

Prevention of transmission from animals to humans and between humans is the mainstay in limiting the outbreaks. Identification and isolation of suspected infected individuals from the community, tracing contacts, safe burial practises, wearing personal protective equipment when dealing with infected patients, safe injection practises, regular hand washing and sanitation and sterilization of the environment and instruments are some of the measures which must be taken.\[16,17\]

1.6. EVD and Neuropsychiatric disorders

EVD outbreaks are relatively rare and the emphasis of medical interventions is on physical care, with survival and discharge typically seen as the successful completion of required care. Ebola represents an important global health issue with mental health challenges like depression, anxiety (including post-traumatic stress reactions), and behavioural, mental, psychosomatic and social problems. EVD survivors are significant in number and their illness experience is potentially traumatizing.\[18,19\] They have faced a life threatening event, been exposed to death and extreme suffering and most have witnessed the death of family members and other community members. The survivors suffer from extreme suffering, discrimination, helplessness, fear and grief. It has a huge impact on psychosocial well being such as orphaning of children, discrimination against affected families due to stigma, exposure to extreme traumatic events including mass mortality in addition to loss of healthcare workers and inadequate supplies of medicine, food and resources. In a study done on 117 EVD survivors in Nigeria, the most frequently occurring psychological distress were inability to concentrate (37.6 %) and loss of sleep over worry (33.3 %). Losing a relation to EVD outbreak was significantly associated with feeling unhappy or depressed.\[20\] In another study done in Sierra Leone, 24 survivors were visited at home by psychologist three to four weeks after discharge. All 24 survivors visited at home had lost immediate family members to EVD. Most had also witnessed their deaths. One in three survivors had experienced stigma, and one in five EVD survivors exhibited post trauma reactions similar to those observed in victims of more conventional traumatic events.\[21\]

Previous studies have shown that the level of post traumatic distress following conventional traumas tends to subside once conditions of safety are established as most people recover spontaneously.\[22\] However, the
effects of loss of loved ones, social stigma and the impossibility of performing traditional burials may impact on the recovery of EVD survivors. A study of South Korean defectors found that witnessing trauma events inflicted on family members was more predictive of PTSD severity than personal trauma.\textsuperscript{[23]} Additional research is required to determine the impact of such cultural variables on the trauma experienced by EVD survivors.

2. ZIKA VIRUS DISEASE

2.1. History

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) in the genus Flavivirus and the family Flaviviridae.\textsuperscript{[34]} It is a positive-sense, single-stranded, enveloped RNA virus. Members of the Flavivirus genus within this family cause widespread human diseases, including yellow fever, dengue, Japanese encephalitis, West Nile virus disease, and ZIKV infections. Flaviviruses have a characteristic RNA genomic organization with a capped, 5′RNA followed by a short noncoding region, a single open-reading frame that codes for a polyprotein, and a 3′ noncoding region. The genomic RNA for flaviviruses is typically 10 to 11 kilobases in length, is structured to function in a similar fashion to host messenger RNAs within the host cell, and can quickly undergo translation by host factors.\textsuperscript{[25]} This allows flaviviruses to form replication complexes and create new RNA genomes and viral proteins. ZIKV was first isolated from a nonhuman primate in 1947 and from mosquitoes in 1948 in Africa, and ZIKV infections in humans were sporadic for half a century before emerging in the Pacific and the Americas.\textsuperscript{[30]} The clinical presentation of Zika fever is nonspecific and can be misdiagnosed as other infectious diseases, especially those due to arboviruses such as dengue and chikungunya. ZIKV infection was associated with only mild illness prior to the large French Polynesian outbreak in 2013 and 2014, when severe neurological complications were reported, and the emergence in Brazil of a dramatic increase in severe congenital malformations (microcephaly) suspected to be associated with ZIKV.\textsuperscript{[27]} Laboratory diagnosis of Zika fever relies on the detection of ZIKV-specific RNA. Serological diagnosis is complicated by crossreactivity among members of the Flavivirus genus.\textsuperscript{[28]} Neither an effective treatment nor a vaccine is available for Zika virus; therefore, the public health response primarily focuses on preventing infection particularly in pregnant women.

2.2. Epidemiology

After the first isolation of Zika virus (ZIKV) in 1947 from a rhesus monkey, ZIKV infection in humans was first described in Nigeria (Africa) in 1954 and since then sporadic cases of infection have been reported on the African and Asian continents.\textsuperscript{[26]} In 2007, Yap Island, Micronesia, reported the first large Zika virus epidemic in 2007\textsuperscript{[29]} followed by a larger epidemic in French Polynesia in the South Pacific in 2013 and 2014.\textsuperscript{[30]} They were then followed by sporadic outbreaks in pacific region in 2014 and 2015. In March 2015, ZIKV emerged for the first time in the Americas (Brazil in March) and by January 2016, cases were reported in countries of South, Central, and North America and the Caribbean.\textsuperscript{[31]} The emergence of ZIKV was associated with the description of severe neurological complications: Guillain-Barré syndrome (GBS) in adults in French Polynesia and microcephaly in neonates in Brazil.\textsuperscript{[32]} Imported cases of Zika fever have been reported in travellers returning from areas with endemic/epidemic Zika fever.\textsuperscript{[33,34]} Such cases were reported in European countries such as Denmark, Finland, Austria, Switzerland, Israel, Spain, Ireland, Sweden, England, and Portugal.\textsuperscript{1} This increased the risk of dissemination of ZIKV to areas where potential competent vectors were present, especially Ae. aegypti and Ae. Albopictus such as Spain. Two American scientists developed Zika fever in Colorado a few days after being infected while performing a mosquito-sampling project in south-eastern Senegal in August 2008,\textsuperscript{[35]} a case imported from French Polynesia has been reported in Texas,\textsuperscript{[36]} and another has been reported in New York City.\textsuperscript{[17]} Other imported cases have been reported in Arkansas, Florida, Hawaii, Illinois, New York, Texas, and Virginia. The risk of secondary transmission is highest in states such as Texas and Florida, where both Ae. albopictus and Ae. aegypti are present.\textsuperscript{[38,39]} In addition, five countries in the Americas reported sexually transmitted Zika cases (Argentina, Canada, Chile, Peru, and the United States of America). Additionally, Canada reported 169 travel-related Zika virus disease cases detected by July 2016. State of Florida reported cases caused by bites of local Aedes aegypti mosquitoes.\textsuperscript{[40]}

2.3. Mode of transmission

Zika virus, like other flaviviruses, is transmitted by mosquitoes, primarily of the Aedes (Stegomyia) genus. Several Aedes spp. have been implicated, including Ae. aegypti, Ae. Af. ricanus, Ae. hensilli, and Ae. albopictus. The Ae. aegypti mosquito appears to be the major vector in Asia\textsuperscript{[41]} and was the suspected primary vector for the French Polynesia outbreak.\textsuperscript{[42]} In Africa, the predominant Aedes species vector has not been definitively identified, although viral isolation studies suggest that Ae. albopictus was the likely vector in a 2007 Zika virus outbreak in Gabon.\textsuperscript{[43]} Aedes mosquitoes are widely distributed globally, and native habitats of most species are warm tropical and sub-tropical regions. Other non-vector modes of Zika virus transmission include congenital, perinatal, blood transfusion and sexual.

Vertical transmission of the Zika virus has become a serious risk to pregnancy and fetal development. The detection of Zika virus RNA by reverse transcription PCR (RT-PCR) in amniotic fluid of mothers with symptoms of Zika virus infection during pregnancy support the possibility of intrauterine transmission.\textsuperscript{[44]} Such mothers had delivered babies with microcephaly. Zika virus RNA has also been identified in tissue of fetuses from women infected during pregnancy.\textsuperscript{[45]} The
Transfusion-transmitted Zika virus was proven to be a possible mode of transmission in cases in Brazil. In Brazil, viral RNA was detected in a patient who received blood transfusion from an asymptomatic donor who developed the disease a few days later. The presence of viable Zika virus particles in the blood bags can have serious consequences, especially for pregnant women. The Brazilian Health Surveillance Agency recommended that blood donors with laboratory- or clinically-confirmed Zika virus infections should be ineligible for blood donations for 30 days following complete clinical recovery, and that blood banks should be notified if the donors develop any symptoms a week after donation.

Zika virus can also be sexually transmitted. The initial evidence came from two male American researchers who went to an endemic area in Senegal to collect mosquito samples. Viral RNA has been detected in the semen up to 62 days after the onset of illness, making sexual transmission a serious concern unless condom use is encouraged.

2.4. Clinical Manifestations
In humans, the incubation period from mosquito bite to symptom onset is around 3–12 days. Infection is likely asymptomatic in over 80% of cases and affects all age groups. Zika virus disease typically produces mild and self-limiting symptoms. The clinical features of Zika virus infection may mimic the features of other arbovirus infections (e.g., dengue virus [DEN V] and chikungunya virus [CHIKV]) fever. The common signs and symptoms are fever, rash, joint pain and conjunctivitis. Rash is maculopapular and pruritic in most cases; it begins proximally and spreads to the extremities with spontaneous resolution within 1–4 days of onset. Fever is low grade (37.4°C–38.0°C). The symptoms last for 2 weeks. During the 2015 Brazil outbreak, microcephaly in the new-borns has been the major cause of concern. Some other congenital CNS abnormalities with adverse fetal outcomes and fetal deaths have also been reported. A surge in Guillain-Barre syndrome cases has been observed in Brazil, Colombia, El Salvador, Suriname, Venezuela, and French Polynesia during outbreaks; however, Zika virus has been laboratory confirmed in only some of these cases. Other neurologic sequelae have also been described in adults, including meningitis, meningoencephalitis. non-neurologic sequelae include transient hearing loss, hypotension, and genitourinary symptoms. Hematospermia was reported in 2 cases.

2.5. Diagnosis
The patients with symptoms consistent with Zika virus infection and with a history of travel to Zika affected areas in previous two weeks are tested to confirm the diagnosis. Zika virus can be tested in blood, saliva and urine but mostly blood tests are performed. Nucleic acid detection by reverse transcriptase-polymerase chain reaction targeting the non-structural protein 5 genomic region is the primary means of diagnosis. It is useful in the first 3-5 days after the onset of symptoms. It helps in the direct detection of Zika virus RNA or specific viral antigens in clinical specimens. Standard RT-PCR and quantitative RT-PCR provide a rapid, specific and sensitive method for ZIKV early detection. Viral RNA has been detected in serum up to day 10 after the onset of symptoms. ZIKV RNA also has been detected in urine or saliva samples. The CDC ZIKV assay uses two 1-step real-time reverse transcription–polymerase chain reactions that target the ZIKV premembrane and envelope genes. In convalescent phase (> 5 days) testing IgM antibodies in blood is more useful. However, this is not the main stay of diagnosis as cross reactivity with other flaviviruses is very high. Plaque Reduction Neutralization Test (PRNT) is the confirmatory test. PRNT, however, is done only in highly specialized laboratories, is expensive, and may require regulated laboratories because of the manipulation of live viruses.

2.6. Treatment and prevention
There is no specific treatment or antiviral drug for ZIKV infection. Recommendations are the treatment of symptoms based on acetaminophen for fever and pain, an antihistaminic for pruritic rash, and drinking of fluids. Treatment with acetylsalicylic acid and non-steroidal anti-inflammatory drugs is discouraged because of the reported increased risk of hemorrhagic syndrome with other flaviviruses. The infected child and the family should be counselled by a multidisciplinary team consisting of clinical geneticists or dysmorphologists, paediatric neurologists, pharmacists, infectious disease specialists and other related specialists. Long-term follow-up should also be offered to monitor functional, physical and intellectual progress of the child. There is no vaccine for ZIKV, although several are in the development phase with dengue vaccine technology. Prevention measures are therefore the same as for all Ae. aegypti-borne diseases for which there are no vaccines, including individual protection from mosquito bites and vector control.

2.7. Zika virus disease and Neurological complications
The Brazilian outbreak during 2015 was associated with many proven cases of microcephaly and GB syndrome. Severe neurologic sequelae have also been described in adults, including meningitis, meningoencephalitis, and Guillain-Barre syndrome. A surge in Guillain-Barre syndrome cases has been observed in Brazil, Colombia, El Salvador, Suriname, Venezuela, and French Polynesia during outbreaks; however, Zika virus has been laboratory confirmed in only some of these cases.
**Intrauterine (congenital) infection**

During the 2015 ZIKV outbreak in Brazil, many microcephaly cases were noted in newborns. The affected cases have head circumferences ≥2 standard deviations below the mean for sex and gestational age at birth. During the period from March 2015 to February 2016, a greater than 20-fold increase in microcephaly cases was observed in Brazilian newborns compared to previous years. Numerous reports have proven this association between microcephaly in the newborn and ZIKV infection. The ZIKV genome has also been identified in pathological specimens of first trimester fetal miscarriages, although it has not been confirmed whether ZIKV was the cause of these fetal losses. Typical characteristics of intrauterine ZIKV infection include redundant scalp skin, low birth weight, polyhydrannios, anasarca and arthrogryposis. Neurological deformities include brainstem dysfunction, cerebral lesions, absence of swallowing and polyalformative syndromes. The congenital anomalies or intrauterine death may occur in foetus infected during the first or even second trimesters. The risk of congenital deformities and microcephaly is highest if ZIKV infection occurs in the first trimester. In Brazil, out of the total 35 women having infants born with microcephaly, 57% and 14 % had a rash during the first and second trimesters, respectively. Newborns with possible perinatal ZIKV transmission seem to have mild disease and favorable consequence.

Pathogenesis of microcephaly due to ZIKV infection is still unclear. Some studies have evidenced the pathogenic potential of Brazilian strain of ZIKV during the development of fetus in animal models. These studies concluded that ZIKV first infects the placenta and then the brain of fetus, where it preferentially infects neural progenitor cells and decreases their viability and growth as neurospheres through down-regulation of genes that are involved in cell and organ development, and up-regulation of genes that are involved in immune responses. This results in inhibited cellular proliferation and differentiation, neuronal apoptosis, thinning of the cortex and macroscopic features similar to microcephaly. Hence, a causal link between ZIKV infection and microcephaly could be hypothesized.

**Guillain–Barré syndrome**

Guillain-Barré syndrome is an acute auto-immune polyradiculoneuropathy that may be caused by infections, many of which involve Flavivirus and other arboviruses such as Chikungunya. It is characterized by superior/ inferior limb extremity paresthesia, ascending muscular weakness, and paralysis that can evolve into respiratory and deglutition disorders, and death. The sensorimotor deficits are symmetrical and bilateral. GBS immunopathogenesis is complex, involving Toll-like receptors, production of pro-inflammatory cytokines with myelotoxic activity, cell- mediated immune responses with cytotoxic T cell activation, production of auto-antibodies, and complement activation. In 2013 and 2014, an increase in the number of cases of the Guillain–Barré syndrome was observed during an outbreak of ZIKV infection in French Polynesia. Recently, clusters of the Guillain–Barré syndrome and microcephaly have been spatially and temporally related to the current outbreak of ZIKV infection in the Americas. A surge in Guillain-Barre syndrome cases has been observed in Brazil, Colombia, El Salvador, Suriname, Venezuela, and French Polynesia during outbreaks; however, Zika virus has been laboratory confirmed in only some of these cases. Severe neurologic sequelae have also been described in adults, including meningitis, meningoencephalitis. Meningoencephalitis is characterised by hemiplegia, paresis, Babinski sign, ischemic foci, hypersensitivity of rolandic fissure, coma, spatial delusions with visual and kinesthetic hallucinations, and muscular weakness. Other neurological consequences of Zika virus infection in the adult include a decline in bilateral acuity in hearing, transient dull or metallic hearing, and a delay between the emission and perception of sound.

**Zika virus disease and its effect on mental health**

Women who have contracted Zika virus infection during pregnancy and/or given birth to children with microcephaly or any other congenital deformity are more likely to develop symptoms of distress such as irritability, anger, guilt, shame, insomnia, nightmares. They may also suffer from physical symptoms (shaking, headaches, feeling very tired, loss of appetite, aches and pains), crying, sadness, depressed mood, grief, excessive worries, anxiety, fear. Depression and other mental disorders should be considered in women who are not functioning well in daily activities because of their distress for a prolonged period of time (e.g. more than 2 weeks). Healthcare workers should monitor for depression during antenatal and postnatal visits. Depression in pregnant women can be managed effectively with psychological treatments. Antidepressant medicines should be avoided, especially during the first trimester.

**CONCLUSION**

Survivors and contacts of EVD and ZVD and their relations develop psychological distress. Development of psychological distress could be predicted by loss of family member. It is recommended that psychiatrists and other mental health specialists be part of case management teams. The clinical teams managing EVD patients should be trained on recognition of common psychological distress among patients. A mental health specialist should review contacts being monitored for EVD for psychological distress or disorders.

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