

## THE ARTHROPOD-BORNE ENCEPHALITIS VIRUSES, THE NEGLECTED SERIOUS DISEASES

By

**MOSTAFA M. ELNAKIB<sup>1</sup>, EMAN EBRAHIM ABDEL FADIL<sup>1</sup>  
And TOSSON A. MORSY<sup>2</sup>**

Military Medical Academy Cairo 11291<sup>1</sup> and Department of Parasitology,  
Faculty of Medicine, Ain Shams University, Cairo 11566<sup>2</sup>, Egypt

### Abstract

Arthropod-borne encephalitis viruses are highly adapted to a particular reservoir host. Viruses spread from animal to animal by an infected specific mosquito or tick species. Mosquito or tick becomes infected when feeding on the viremic animal blood. Virus then replicates in the vector, ultimately infecting the salivary glands, which transmits the virus to a new host with infective saliva while taking a blood meal. Infected patients may become ill; they usually do not develop sufficient viremia to infect feeding vectors, and thus do not contribute to the transmission cycle.

Among mosquito-borne encephalitis, the greatest public health threat in North America and is posed by the West Nile, St. Louis encephalitis, and La Crosse encephalitis viruses. Venezuelan equine encephalitis virus is of concern in Central and South America, while Japanese encephalitis virus affects residents or visitors to parts of Asia. Among the tick-borne encephalitis, tick-borne Encephalitis virus causes the greatest public health threat among residents or visitors to Eastern Europe and Asia.

Eastern equine encephalitis (EEE) virus is widely distributed throughout North, Central, and South America and the Caribbean. EEE virus is the most severe one, with mortality up to 30%. Western equine encephalitis (WEE) virus is found in North and South America and is a potential agent of bioterrorism through the aerosol route. Case fatality rate is 3 to 7%. La Crosse virus (LAC) is the most pathogenic member of California encephalitis serogroup in central and eastern United States, mostly in school-aged children. Most infections are asymptomatic with low mortality rates. Treatment is supportive, with emphasis on control of cerebral edema and seizures. Murray Valley encephalitis (MVE) virus occurs in Australia, New Guinea, and probably islands in the eastern part of the Indonesian archipelago. MVE virus is maintained in a natural cycle involving water birds and *Culex annulirostris*. Only 1 in 1000 to 2000 infections had clinical illness; but, about one-third of patients die and about half the survivors suffered from neurologic deficits. Venezuelan equine encephalitis (VEE) widely spread from Florida to South America, occur periodically, but occasionally, large epidemics occur among equine and humans. VEE is infectious via aerosols, making it an occupational risk to certain laboratory workers and a potential agent of bioterrorism. Effective prevention by immunizing equines, which serve as the primary amplification hosts for the epizootic VEE viruses. Tick-borne encephalitis (TBE) exists over a wide geographical area, including Russia and Europe. Human exposure occurs through work or recreational activities when the ticks are most active. TBE virus is transmitted from the saliva of an infected tick while taking blood meal. Case fatality rates range from 2 to 8%. Treatment is mainly supportive.

In Middle Eastern Countries, no proper reported statistics, although the climatic environment favors the spreading of both the vectors and the viruses. So, it is advisable to make diagnostic techniques readily available and more public health awareness of those risky, potentially fatal infectious diseases. Already Dengue viral hemorrhagic fever is mostly responsible for major worldwide fatalities as well as West Nile Fever already present there from before, without specific treatment or vaccine available.

**Keywords:** Arthropod-borne viral encephalitis, General review, Discussion, Recommendations.

### Introduction

Encephalitis is irritation and swelling (inflammation) of the brain, most often due to infections by a virus, bacterium or fungus (infectious encephalitis, or primary encephalitis), or when the immune system responds to a previous infection; the immune system

mistakenly attacks brain tissue (secondary encephalitis, or post-infectious encephalitis).

The arthropod-borne encephalitis viruses are significant public health problem worldwide, usually highly adapted to specific reservoir hosts and are spread from animal to animal or humans by bite of an infected art-

hropod, usually a specific mosquito species or tick species.

### **Review and Discussion**

The natural animal hosts of these viruses usually remain unaffected and viral circulation generally remains undetected until one of the following occurs: 1- Humans encroach on the natural enzootic focus, 2- Environmental conditions favor substantial amplification in the primary vector-host cycle causing sufficient number of vectors to become infected so human risk is increased, and 3- The virus escapes the primary cycle via a secondary vector or vertebrate host, thereby bringing infected, human-biting vectors in close proximity to human habitation. Although infected humans may become ill, they usually do not develop sufficient viremia to infect feeding vectors. As a result, humans do not usually contribute to the transmission cycle. The mosquito or tick becomes infected when feeding on the blood of the viremic animal. The virus then replicates in the mosquito or tick, then to salivary glands transmitting the virus to a new host as humans while taking a blood meal.

**Geographic Distribution:** Among the mosquito-borne encephalitis viruses, the greatest public health threat in North America is posed by the West Nile, St. Louis encephalitis and La Crosse encephalitis viruses. Venezuelan equine encephalitis virus is of concern in Central and South America, while the Japanese encephalitis virus affects persons living or traveling to parts of Asia. Dengue is a rare cause of encephalitis throughout the tropical world but rather a major illness through viral hemorrhagic fever. Among the tick-borne viruses that cause encephalitis, tick-borne encephalitis virus has the greatest public health impact worldwide and is of concern to residents of or visitors to northern parts of Eastern Europe and Asia. The Powassan virus is a rare, but tick-borne cause of encephalitis in the north central and northeastern parts of the United States, eastern Canada, and Russia.

**Cross-Reactivity:** The close antigenic relationships among the flaviviruses may cause a diagnosis problem. Individuals who have been recently vaccinated with yellow fever, tick borne encephalitis virus, or Japanese encephalitis vaccines or who have been recently infected with a related flavivirus may have a positive serologic test to one or more flaviviruses not causing the current illness. Plaque reduction neutralization test (PRNT), which was the most specific test for the arthropod-borne flaviviruses, may be identified serologic cross-reactions among the flaviviruses. But, some degree of cross-reaction in neutralizing antibody may still cause ambiguous results. Cross re-activities of the bunyaviruses and togaviruses causing encephalitis is not as extensive.

1- West Nile virus encephalitis (WN) virus, a member of the Japanese encephalitis virus antigenic complex, was first isolated in a blood sample in a patient from the West Nile province of Uganda in 1937. This RNA virus was initially considered of minor public health importance (Gubler, 2007). It emerged from obscurity in 1999 when the first incursion of the virus into North America caused 62 cases of encephalitis and seven deaths in New York. Since that time, the virus has dramatically spread, and WN virus activity has now been detected in all 48 continental states, the District of Columbia, and Puerto Rico. WN virus causes both sporadic infection and outbreaks that may be associated with severe neurologic disease (Petersen and Hayes, 2008). WN virus is one of the most widely distributed of all arboviruses with an extensive distribution in the Old World, throughout Africa, the Middle East, parts of Europe and the former Soviet Union, South Asia, and Australia. The virus had not been detected in the Americas before the 1999 New York City outbreak. WN virus strain of United States is nearly genetically identical to a virus identified in Israel, Kuwait, Lebanon, Saudi Arabia, Sudan, and the United Arab Emirates (Gossner *et al*, 2017). Also, transmission was described via

transfused blood, red blood cells, platelets, and fresh frozen plasma but a small residual risk remains from donations with low viremia not detected by nucleic acid detection tests (NAT) tested in the mini-pool format used by blood centers. Transmission was reported by transplanted organs, transplacental transmission, percutaneous occupational transmission, conjunctiva exposure, and in a dialysis center by the unidentified means. The transmission via breast milk was proved (Johnson *et al*, 2006).

In Egypt, more than 110 mosquito species and subspecies (Mikhail *et al*, 2009; El Bahnasawy *et al*, 2013a) and more than 32 tick genera were reported (Hoogstraal, 1954). About 150 migratory birds' species (can act as hosts) visit Egypt annually (Mazyad *et al*, 1999) in addition to 350 resident ones besides WN in man and animals was reported (El-Bahnasawy *et al*, 2013b).

2- St. Louis encephalitis (SLE) is an acute, mosquito-borne viral illness characterized by meningeal and brain parenchymal inflammation and injury. The disease occurs in endemic and epidemic form in North and South America. Epidemics of SLE in the United States have been responsible for at least 1,000,000 mild or subclinical infections, 10,000 clinical cases, and 1000 deaths in the United States since SLE virus was first isolated in 1933 during an outbreak in St. Louis, Missouri (Reisen, 2003). Studies of SLE virus evolution indicate that the virus was introduced into North America from tropical America in the late 19<sup>th</sup> Century (Baillie *et al*, 2008). There is evidence that West Nile virus, which was introduced into the United States in 1999, is displacing SLE in some areas by more efficient transmission and cross-protective immunity in wild birds (Reisen *et al*, 2008). St. Louis encephalitis virus is a member of the family Flaviviridae, a group of small (40 to 60nm), enveloped, positive-sense, single-stranded RNA viruses that replicate in the cytoplasm of infected cells. Other members of this virus family include West Nile virus, Japanese encephali-

tis virus, Murray Valley encephalitis virus, yellow fever virus, and dengue virus (May *et al*, 2008). SLE virus strains from the eastern and western United States and from tropical America are distinguishable at the nucleotide sequence level into at least six lineages and multiple clades (Kramer and Chandler, 2001) and differ with respect to the mosquito vectors responsible for transmission and virulence for animal models (Trent *et al*, 1980). SLE virus Lineage II present east of the Mississippi river has been associated with severe epidemics, has the highest virulence for laboratory animals, and the highest case-fatality rate for humans. While there is evidence for the geographic separation and the local persistence (through overwintering), mainly in California (Lineage I), analyses of SLE virus evolution suggests flow of neotropical strains, particularly from northern Central America, Mexico, and the Caribbean, into the US by migratory birds (Auguste *et al*, 2009).

SLE causes alymphocytic meningitis; pathologic changes in the brain, particularly gray matter, include perivascular lymphocytic infiltrates, cellular nodules, and neuronal degeneration. While lesions are distributed throughout the brain, the most severely affected regions are the hypothalamus, cerebellar and cerebral cortex, basal ganglia, brainstem and cervical spinal cord (Gardner and Reyes, 1980). Rarely, SLE may present as acute demyelinating encephalomyelitis (ADEM) with prominent lesions in white matter, but pathologic changes in extraneural tissues were not reported (Sejvar *et al*, 2004).

Clinically, SLE may be difficult to differentiate from other causes of summer season encephalitis, including West Nile. Flaccid paralysis and polio-like syndrome are more common in West Nile. SLE diagnosis is serology, particularly ELISA-IgM. Presence of IgM antibodies in a single serum provides a presumptive diagnosis, and a significant rise or fall between appropriately timed acute-convalescent or early-late convalescent sera

is diagnostic. But, antigenic cross-reactions with other flaviviruses, particularly West Nile virus, can be a problem, although use of a discriminatory algorithm for analysis of IgM successfully differentiated infections (Martin *et al*, 2004). Non-infectious recombinant virus-like particle antigens are useful as diagnostic reagents.

No specific antiviral therapy was efficacy and corticosteroids are not indicated, except in the rare case of ADEM. Interferon Alfa reduced mortality in mice when it is given either subcutaneously or by aerosol at the time of exposure to the virus (Brooks and Phillpotts, 1999). The potential efficacy of this approach in humans was evaluated in a pilot study in which 15 patients with SLE received interferon alfa-2b were compared to 17 untreated patients with SLE admitted to the same hospital during an outbreak (Rahal *et al*, 2004). There is no available vaccine, although several experimental studies showed promise, including chimeric attenuated virus vectors using yellow fever 17D and vesicular stomatitis viruses. Testing can be done to observe potential virus transmission between birds and mosquitoes and initiate mosquito control measures before appearance of human cases. Mosquito control is also a must.

3- Dengue virus infection: *Aedes*-borne diseases (Dengue, Chikungunya, Yellow Fever and Zika) are an emerging problem worldwide, escalating overall risk and burden of disease worldwide. Dengue viruses are members of the family Flaviviridae, genus flavi-virus with four anti-genically related but distinct viruses; all are mosquito-borne human pathogens. Apart from the *Aedes*, nosocomial transmission via blood donors and needle-stich injury was reported (Morsy, 2018). The four dengue virus serotypes are associated with fever, rash, and the more severe forms, hemorrhagic fever and shock syndrome (Kroeger *et al*, 2004). The symptomatic dengue virus infections can present with a wide range of clinical manifestations, from self-limited dengue fever to

dengue hemorrhagic fever with shock syndrome, which carries a high mortality rate. The risk of severe disease is much higher in sequential rather than primary dengue infection (Deen *et al*, 2008). Classic dengue fever (DF) is an acute febrile illness accompanied by headache, retroorbital pain, and marked muscle and joint pains, which evoked the term break-bone fever (Rigau-Perez, 1998). Fever typically lasts for five to seven days. Hemorrhagic manifestations can also occur in patients with DF. Physical examination is non-specific, but may include a macular or maculo-papular rash in approximately 50% of cases (Halstead, 2007). Dengue hemorrhagic fever (DHF) is the most serious manifestation of dengue virus infection and can be associated with shock. The four cardinal features of DHF include increased vascular permeability, fever, hemorrhage, and marked thrombocytopenia; less than 100,000cells/ mm<sup>3</sup> (WHO, 1997). The plasma leakage is the most specific and life-threatening feature of DHF and usually occurs rapidly over a period of hours and can lead to shock. Severe plasma leakage can occur in patients with minimal hemorrhagic manifestations (Khor *et al*, 2006). Hemorrhagic manifestations of dengue virus infection can range from spontaneous petechiae to profuse bleeding. Severe bleeding sometimes occurs in the absence of plasma leakage (Chhour *et al*, 2002). Diagnosis of acute dengue virus infection is based mainly on clinical signs and symptoms in endemic countries. In countries where serologic assays are available, an acute phase serum plasma sample for use in the IgM immunoassay (MAC-ELISA or equivalent) as a choice procedure was recommended (McBride *et al*, 1998). If the clinical suspicion of dengue infection was high and assay was negative, testing paired acute and convalescent sera by hemagglutination inhibition or ELISA was recommended.

Dengue may be resurging in MENA (middle east-north Africa) (WHO, 2014) with also, outbreaks occurred in Pakistan and the

Arabian Peninsula, Somalia, Sudan (Arya and Agarwal, 2014) and an outbreak in Egypt that occurred following the decades-long absence of reported cases (WHO, 2015). Despite increasing global concern about the *Aedes*-transmitted arboviruses threat, the dengue epidemiology in the MENA region was largely uncharacterized (Humphrey *et al*, 2016).

4- Eastern Equine Encephalitis Virus: Eastern equine encephalitis (EEE) virus (family Togaviridae, genus Alphavirus) is widely distributed throughout North, Central, and South America and the Caribbean. Four genetic lineages exist: Subtype I in North America and the Caribbean, and subtypes II to IV in South and Central America. While subtype I is associated with severe clinical disease, subtypes II to IV are not clearly associated with human disease. In North America, wild birds and *Culiseta melanura*, a mosquito that is found in swamp areas that support cedar, red maple and loblolly bay trees, maintain the virus. The ecology of South American EEE strains is not well described. Laboratory-acquired infections have occurred, and EEE virus is a potential agent of bioterrorism through the aerosol route (Arrigo *et al*, 2010).

Human infections sporadically peak mainly in August and September with small outbreaks each summer, mostly along the Atlantic and Gulf coasts of United States. From 1964 to 2010, 270 cases of EEE were reported, with the largest number of cases identified in Florida, Georgia, Massachusetts, and New Jersey. In 2005, 21 cases were reported, which included an outbreak of 11 cases (with four fatalities) in New Hampshire and Massachusetts. All patients had resided in a wooded area within a half mile of a swamp or cranberry bog (CDC, 2006).

Clinical manifestations: The incubation period usually exceeds one week after the mosquito bite. The illness often begins with a prodrome lasting several days, with fever, headache, nausea and vomiting being com-

mon. Approximately two percent of infected adults and six percent of infected children develop encephalitis. Once neurologic symptoms begin, the clinical condition deteriorates rapidly, with approximately 90% becoming comatose or stuporous. Seizures, and focal neurologic signs, including cranial nerve palsies, develop in approximately one-half the patients. Leukocytosis and hyponatremia are common on laboratory testing.

Cerebrospinal fluid (CSF) analysis typically shows pleocytosis, often with a neutrophilic predominance and elevated protein concentration. An elevated white cell count in initial CSF examination and hyponatremia correlate with a poor prognosis. Electroencephalography revealed generalized slowing and disorganization of the background, and epileptiform discharges was seen. Magnetic resonance imaging (MRI) proved more sensitive than computed tomography (CT). Both were often abnormal early in the course, with focal lesions in the basal ganglia, thalami, and brainstem being particularly common. Cortical lesions, meningeal enhancement, and periventricular white-matter changes were less common (Deresiewicz *et al*, 1997).

EEE diagnosis can be made by demonstration of IgM antibody by capture immune-assay of CSF, a fourfold rise in serum antibody titers against EEE virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Serum IgM antibodies alone should be confirmed by demonstration of IgG antibody by another serologic assay (e.g., neutralization or hemagglutination inhibition (Panzig *et al*, 1978).

Outcome: EEE virus is the most severe of the arboviral encephalitides, with a mortality of at least 30%. Death can occur within three to five days of onset and, among survivors, complete recovery is uncommon. Sequelae include convulsions, paralysis, and mental retardation. EEE in South America is less severe. No specific therapy for EEE. Inactivated vaccines have been successful in hors-

es and an inactivated vaccine has been used in laboratory workers or others at high risk of exposure, but is not commercially available. No specific treatment is available. One patient may have benefited from IVIG therapy (Golomb *et al*, 2001). Prevention focuses on avoidance of mosquito bites and mosquito control in suburban areas.

5- Western Equine Encephalitis Virus: Western equine encephalitis (WEE) virus (family Togaviridae, genus Alphavirus) is a complex of closely related viruses found in North and South America. Flooding, which increases breeding of *Culex* mosquitoes, may precipitate summer outbreaks. Large outbreaks in humans and horses occurred in the western United States in the 1950s & 1960s. But, a declining horse population, equine vaccination, and improved vector control reduced its incidence. WEE is an agent of bioterrorism through the aerosol route (Sewell, 2003). Less than 1 in 1000 infected adults develop encephalitis, but the frequency is greater in children, particularly infants. Following an incubation period of about seven days, headache, vomiting, stiff neck, and backache are typical; restlessness, irritability, and seizures were commonest in children. Although rare in adults and older children, neurologic sequelae are relatively common in infants and case fatality rate was 3 to 7% (Calisher, 1994).

Diagnosis of the WEE can be made by demonstration of IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against WEE virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Serum IgM antibodies alone must be confirmed by detection of IgG antibody by another serologic assay as neutralization or hemagglutination inhibition (Arnold *et al*, 1984). Prevention focuses on mosquito control and avoids mosquito bites. Inactivated vaccine is available for horses. Although inactivated vaccine was used for laboratory staff and others at high risk of

exposure, but it was not commercially available. Specific treatment is not available.

6- Japanese encephalitis virus (JEV), a mosquito-borne flavivirus, is the most important cause of viral encephalitis in Asia based on its frequency and severity and about 50,000 cases of JEV were estimated to occur each year. With the near eradication of poliomyelitis, JEV is now the cause of childhood viral neurological infection and disability in Asia (Halstead, and Jacobson, 2003). JEV is closely related to West Nile, St. Louis encephalitis, and Murray Valley encephalitis viruses. It affects children <15 years of age; by early adulthood the majority of the population has protective immunity following natural exposure to JEV as a result of ongoing environmental transmission. Among immunologically naïve travelers visiting endemic regions, the disease can affect individuals at any age. JEV is transmitted in an enzootic cycle involving mosquitoes and vertebrate amplifying hosts, primarily pigs and wading birds, and man is incidental and dead end hosts in transmission cycle, as they do not develop sufficiently high viremia to infect feeding mosquitoes (MacKenzie *et al*, 2007). The commonest recognized clinical presentation is acute encephalitis. Milder forms of disease such as aseptic meningitis or non-specific febrile illness with headache also occur. Seizures (usually generalized tonic-clonic) are very common, especially among children. JE is diagnosed by serologic detection of JEV-specific IgM antibody in CSF or serum by an antibody capture ELISA. JEV-specific IgM antibodies in CSF proved recent CNS infection. IgM antibody in serum is suggestive of JE but could indicate asymptomatic infection or recent JE. Precautions among travelers to endemic regions include personal protective measures to prevent mosquito bites. For some travelers to a high risk setting based on location, duration, season, and activities, JE vaccine may further minimize the risk of infection vaccination (Sakaguchi *et al*, 2001).

7- La Crosse Encephalitis Virus: La Crosse virus (LAC, family Bunyaviridae, genus Bunyavirus) is the most pathogenic member of the California encephalitis serogroup, which includes the California encephalitis, trivittatus, snowshoe hare, and Jamestown Canyon viruses. LAC is transmitted via *Aedes triseriatus* (eastern tree hole mosquito), and mammalian hosts include the eastern chipmunk, tree squirrels, and foxes. In addition, epidemiologic evidence suggests that the newly introduced *Ae. albopictus* mosquito (Asian tiger mosquito) may be an important vector of man. Human infections occur in the central and eastern United States, mostly in school-aged children from July through September. Most of the infections were asymptomatic (Hotez, 2018)

After an incubation period of three to seven days, were evaluated in a review of 127 patients who required hospitalization. The following findings were noted (Erwin *et al*, 2002): a- All of the patients were school-aged children (range 0.5 to 15 years), b- Headache, fever, and vomiting were each present in at least 70% of patients and disorientation in 42%, c- Seizures occurred in 46%, 62% of which had have a focal component and 24% of which progressed to status epilepticus, d- Approximately 20% had focal neurologic abnormalities. The findings of fever, focal neurologic signs, and focal seizures mimic herpes simplex encephalitis, virus type 1 (HSV-1) encephalitis which is the most common cause of sporadic fatal encephalitis worldwide and is often characterized by rapid onset of fever, headache, seizures, focal neurologic signs, and impaired consciousness and involves all age groups. Beyond the neonatal period, the etiologic agent is herpes simplex virus type 1 (Hjalmarsson *et al*, 2007). In neonates, herpes encephalitis may be caused by either HSV-1 or HSV-2. The clinical syndrome is often characterized by the rapid onset of fever, headache, seizures, focal neurologic signs, and impaired consciousness, f- Aseptic meningitis alone, without evidence of

encephalitis, occurred in 13% of LAC g- Hyponatremia was present in 21% and was present in all 13 patients (11%) whose condition deteriorated in the hospital, and 12% of children had residual focal neurologic, cognitive, and behavioral deficits. Leukocytosis was common, with polymorphonuclear cells predominating. CSF showed pleocytosis with either neutrophilic or lymphocytic predominance. EEG is abnormal in two-thirds of patients, mainly with slowing or epileptic-form discharges. Focal features or periodic lateralizing epileptiform discharges, usually with involvement of the temporal lobe, may suggest herpes simplex encephalitis. CT scan was generally normal, but might show generalized cerebral edema. MRI may show focal areas of gadolinium enhancement (Yahr, 1972).

Diagnosis of LAC can be made by demonstration of IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against LAC virus, or isolation of virus from or detection of viral antigen or genomic sequences in tissue, blood, or CSF. Viral isolation from CSF is rare. Serum IgM antibodies alone must be confirmed by demonstration of IgG antibody by another serologic assay as neutralization (Persijn *et al*, 2011). Treatment is supportive, with emphasis on control of cerebral edema and seizures (McJunkin *et al*, 2001). Ribavirin was used, but efficacy was unproven at least for children (McJunkin *et al*, 1997).

Prevention rests on avoidance of mosquito bites. A case of possible congenital infection has also been reported with IgM antibodies identified in the umbilical cord blood; however, the newborn was asymptomatic and development was normal. No seroconversion was documented in this case because the mother declined further testing (CDC, 2009).

8- Murray Valley Encephalitis: Murray Valley encephalitis (MVE) virus (family Flaviviridae, genus Flavivirus), occurs in Australia, New Guinea, and probably islands in the eastern part of the Indonesian archi-

pelago. MVE virus is believed to be maintained in a natural cycle involving water birds and *Culex annulirostris* mosquitoes. Viremia was not documented in humans, who are likely dead-end hosts (Mackenzie *et al*, 1994).

Only one in 1000 to 2000 infections results in clinical illness, which resembles Japanese encephalitis. There is usually a prodromal illness with headache, fever, nausea and vomiting, anorexia, and myalgias, followed by drowsiness, malaise, irritability, mental confusion, and meningismus. Seizures are more common in children. In severe cases, there may be hyperactive reflexes, spastic paresis, seizures, coma, and death (Burrow *et al*, 1998). CT scan was normal in about two-thirds of patients. Reported abnormalities include mild hydrocephalus, cerebral edema, reduced attenuation extending from the thalami to the brainstem, and cerebral atrophy (Kienzle and Boyes, 2003).

Diagnosis of MVE was made by detection of IgM antibody immunoassay of CSF, a fourfold raised in serum antibody titers against MVE virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Serum IgM antibodies alone should be confirmed by demonstration of IgG antibody by another serologic assay (e.g., neutralization or hemagglutination inhibition (CDC, 1997)).

About one-third of patients with MVE die and about half the survivors have residual neurologic deficits. Children and the elderly are at highest risk as there was no vaccine for MVE virus. Prevention relies on mosquito control and avoidance of mosquito bites.

9- Venezuelan Equine Encephalitis Virus: Six subtypes (I-VI) within the Venezuelan equine encephalitis (VEE) virus (family *Togaviridae*, genus *Alpha virus*) complex. Five antigenic variants exist within subtype I (IAB, IC, ID, IE, IF). These subtypes and variants are classified as epizootic (can produce outbreaks of illness in animals) or enzootic (infects animals in a region, but often produces asymptomatic or sporadic illness in

animals), based upon their apparent virulence and epidemiology: a- Epizootic variants of subtype I (IAB & IC) cause equine epizootics and are associated with more severe human disease, and b- Enzootic strains: ID-F, II [Everglades], III [Mucambo, Tonate], IV [Pixuna], V [Ca-bassou], VI [Rio Negro]) do not cause epizootics in horses, but produce sporadic disease in humans.

Epizootic strains are transmitted by many mosquitoes, and enzootic strains by *Culex* species.

VEE has a widespread geographic distribution from Florida to South America, where it is an important veterinary and public health problem. Focal outbreaks or large regional epidemics occur, with thousands of equine and human infections. VEE is infectious via aerosols, making it an occupational risk to certain laboratory workers and a potential agent of bioterrorism.

After an incubation period of one to six days, there is a brief febrile illness of sudden onset, characterized by malaise, nausea or vomiting, headache, and myalgia. Less than 0.5% of adults and less than 4% of children developed encephalitis, characterized by nuchal rigidity, seizures, coma, and paralysis. Long-term sequelae and fatalities are uncommon. Diagnosis of VEE can be made by demonstration of IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against SLE virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Viremia was usually not detectable in serum. Serum IgM antibodies alone should be confirmed by demonstration of IgG antibody by another serologic assay e.g., neutralization or hemagglutination inhibition (CDC, 1997).

Effective prevention of both human and equine disease can be accomplished by immunizing equines, which serve as the primary amplification hosts for the epizootic VEE viruses and without which there would be little human disease. During the epidemics, mosquito vectors can be controlled by insect-



ticides. Live attenuated and inactivated vaccines have been used for laboratory workers; however, human vaccines are not commercially available.

10- Tick-Borne Encephalitis Virus: Tick-borne encephalitis (TBE) is caused by three closely related viruses (family Flaviviridae, genus Flavivirus): a- The Russian spring-summer encephalitis subtype (also called far eastern subtype), b- The Siberian subtype also called Vasi-lchenko virus, and c- The Central European encephalitis subtype (also called western subtype (Kaiser, 2008).

Vector: These viruses are maintained in natural cycles involving a variety of mammals and ticks. *Ixodes persulcatus* and *Ix. ricinus* are vectors in Russia and Europe, respectively. *Ixodes ovatus* is the vector in Hokkaido. Tick-borne encephalitis exists over a wide geographical area (Süss, 2003).

Transmission: Human exposure occurs through work or recreational activities in the spring and summer months in temperate zones and in fall and winter in the Mediterranean, when the ticks are most active. TBE virus is transmitted from the saliva of an infected tick within minutes of the bite; early removal of the tick may not prevent encephalitis. In Europe, tick activity starts in the spring and declines in the fall. Nymphal forms of *I. ricinus* are most important in human transmission whereas adult ticks are the dominant vector for *I. persulcatus*. Outbreaks occurred occasionally followed ingestion of unpasteurized milk products from infected sheep and goats (Zajkowska, 2010).

Age, severity of illness in the acute stage, and low initial neutralizing antibody titers are associated with illness severity. The CCR5 delta 32 allele may predispose individuals to TBE (Mickienė *et al*, 2014). The CCR5 and CXCR4 are the major chemokine coreceptors used by HIV to enter into human lymphocytes. HIV isolates were classified as CCR5-tropic (R5), CXCR4-tropic (X4), or dual tropic (R5/X4) strains. Some progress from virus transmission to late stage in the AIDS patients within two years. Others are

chronic longterm progresses who maintain low viral loads and normal CD4 counts for >10 years without treatment and there are "elite suppressors" who have VL <50 c/mL without therapy (CDC, 2006). The rate of disease progression appear to be related to the genetic regulation of immunologic control of HIV and medication adherence, besides the rate of progression are older age, viral variants, substance abuse, nutritional status of the host, active tuberculosis. The need for HAART treatment may be life-long once initiated (Williams *et al*, 2006).

Clinical manifestations: The incubation period of TBE generally lasts between 7 and 14 days and approximately two-thirds of patients reported tick bite. The disease is characterized by a biphasic illness. In the first viremic phase, fever, fatigue, malaise, headache, and arth-ralgia predominate (Vili-bić-Čavlek *et al*, 2014). Neurological symptoms hallmark the second phase, ranging from mild meningitis to severe encephalitis, which may be accompanied by myelitis and acute flaccid paralysis (Lessell and Collins, 2003). Reports of chronic and progressive disease were noted primarily with the Siberian subtype; however, this was uncommonly (CDC, 1998).

Diagnosis of the CSF examination generally shows pleocytosis. Although polymorphonuclear cells may predominate at first, the CSF profile is later marked by dominance of mono nuclear cells (Lindquist and Vapalahti, 2008). Diagnosis of TBE can be made by demonstration of IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against TBE virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Serum IgM antibodies alone must be confirmed by detection of IgG antibody by another neutralization test (Hol-zmann, 2003). MRI abnormalities could be noted in approximately 18% of patients with lesions located in the thalamus, cerebellum, brainstem, and caudate nucleus; EEG is abnormal in 77% of patients. Both modalities

gave only non-specific findings (Kindberg *et al*, 2008).

Outcome: Case fatality rates with the Siberian subtype rarely exceed 8% and there is a greater tendency to developing nonparalytic encephalitis and chronic TBE. In comparison, the western European subtype typically produces the biphasic form and tends to be less severe, with case fatality rates of 1 to 2%. Children have a more favorable prognosis than adults. Up to one-half of patients report symptoms 6 to 12 months post-encephalitis, with severe impairment reported in 30% (Haglund and Günther, 2003).

Treatment is mainly supportive. In a large study of 709 patients with TBE in Germany, 12% of patients required intensive care and 5% required assisted ventilation. Of 230 patients who had subsequent examination at a later time, approximately one-quarter had moderate to severe sequelae (Kaiser, 1999).

Effective vaccines are available in Europe and from many travel clinics in Canada; vaccines are not available in the United States. Mass vaccination has been undertaken in Austria, with protection rates of at least 96% (Barrett *et al*, 2003). Between the early 1970s and early 1980s, the average TBE incidence rate was 5.7 per 100,000; it dropped to 0.9 per 100,000 between the mid-1990s & 2005 among vaccinated individuals, but remained high (6 per 100,000) among unvaccinated individuals (Heinz *et al*, 2013).

Travelers with extensive outdoor exposures from camping or related activities in endemic regions during the spring and summer months must be vaccinated. (See CDC, 2017: Travel Book Immunizations section).

11- Powassan virus, a member of the tick-borne encephalitis group of flaviviruses, encompasses 2 lineages with separate enzootic cycles. The prototype lineage of Powassan virus (POWV) is principally maintained between *Ixodes cookei* ticks and the groundhog (*Marmota monax*) or striped skunk (*Mephitis mephitis*), whereas the deer tick virus (DTV) lineage is believed to be maintained between *Ixodes scapularis* ticks and the

white-footed mouse (*Peromyscus leucopus*). It was isolated from four tick species: *Ixodes cookei*, *Ix. narxi*, *Ix. spinipalpus*, and *Dermacentor andersoni* (El Khoury *et al*, 2013).

Powassan virus is a rare cause of encephalitis in eastern Canada and the north central and northeastern United States. There were more than 30 case reports since its discovery in 1958 (Gholam *et al*, 1999). However, serologic surveys have found an antibody prevalence of 1 to 4%, indicating that asymptomatic infection is common. Infection mostly occurs from June to September. The reported incubation periods ranged from eight to 34 days (CDC, 2001). But, few patients recall a tick bite, since Ixodid ticks are small and can be easily overlooked. Symptomatic patients typically present with fever, weakness, somnolence, gastrointestinal complaints, headache, and confusion, and seizures can occur.

Serum and cerebrospinal fluid samples can be tested for IgM and neutralizing antibodies. The diagnosis of Powassan virus infection can be made by demonstration of IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against the virus, or isolation of virus from or the demonstration of viral antigen or genomic sequences in tissue, blood, or CSF. Serum IgM antibodies alone should be confirmed by demonstration of IgG antibody by another serologic assay (e.g., neutralization). The case-fatality rate is 5 to 10%, with a high incidence of residual neurological dysfunction among survivors, which including hemiplegia, headaches, minor memory impairment, and persistent ophthalmoplegia (Hinton *et al*, 2008).

There is no specific treatment or vaccine. Prevention of tick bites by using repellents, avoiding or clearing brushy areas, wearing light colored clothing may be effective. Removing ticks soon after outdoor exposure is advisable.

The so-called deer tick virus is likely an antigenic subtype of Powassan virus and is maintained in *Ix. scapularis* ticks and white-

footed mice. The deer tick virus was reported in 2009 with a fatal outcome in a 62-year-old New York state resident with chronic lymphocytic leukemia who presented with encephalitis (Tavakoli *et al*, 2009).

12- Colorado Tick Fever Virus: Colorado tick fever virus (genus Coltivirus, family Reoviridae) is an acute systemic febrile illness, transmitted to humans in the western United States and Canada, *Dermacentor andersoni*. Colorado tick fever (CTF) is caused by the CTF virus (CTFV). The distribution of human disease corresponds to the wood tick's distribution in the mountainous areas at 4000- to 10,000-foot elevations. Transmission occurs from March to September, but peaks from April to June and transmission by blood transfusion was documented (Yendell *et al*, 2015).

The mean incubation period is three to four days, and 90% of patients reported tick bites or tick exposure. Fever, chills, myalgias, and prostration are common. Headache often occurs during the acute febrile phase. About 15% of patients experience a petechial or maculopapular rash and leukopenia is common. Although the acute symptoms last about a week, fever might recur several days later, fatigue was often prolonged, and 5 to 10% of children developed meningitis or encephalitis (Goodpasture *et al*, 1978).

Serologic tests always not positive for 10 to 14 days after symptom onset. In comparison, reverse transcriptase PCR proved diagnostic from the first day of symptoms (Johnson *et al*, 1997). The virus infects marrow erythrocytic precursors, which accounts for the ability to recover the virus from peripheral blood up to six weeks after illness onset.

The Colorado tick fever virus (from North America), was isolated from patients with flulike syndromes, meningitis, encephalitis, and other severe complications.

13- Another coltivirus, Eyach virus, was isolated from ticks in France and Germany and incriminated in febrile illnesses and neurologic syndromes.

14- Seadornaviruses are endemic in South-

east Asia, particularly Indonesia and China. The prototype virus of the genus, Banna virus (BAV), was isolated from many mosquito species, humans with encephalitis, pigs, and cattle. Two other seadornaviruses, Kadipiro and Liao Ning, were isolated only from mosquitoes (Attoui *et al*, 2005). Serologic tests are often not positive for 10 to 14 days after symptom onset. In comparison, reverse transcriptase polymerase chain reaction (PCR) may be diagnostic from the first day of symptoms. The virus infects marrow erythrocytic precursors, which accounts for the ability to recover the virus from peripheral blood up to six weeks after illness onset (Attoui *et al*, 1998).

15- Chandipura Virus: Since the 1950's, outbreaks of encephalitis of unknown etiology and high mortality have occurred in children in India. In 2003 in Southern India, an outbreak of acute encephalitis in 329 children was associated with Chandipura virus (genus Vesiculovirus, family Rhabdoviridae). The affected children all tested negative for eight other potential viral causes including Japanese encephalitis (which is responsible for many encephalitis outbreaks in India), West Nile virus, dengue, and measles virus. Chandipura virus was identified by electron microscopy, complement fixation, and neutralization tests. Observation that IgM titers directed against this virus were more frequently identified after four days of illness compared to baseline values provided further evidence supporting its pathogenetic role (Jacob, 2010). It may be transmitted by sand-fly bites and has been identified in *Aedes aegypti* mosquitoes. Illness is characterized by the rapid onset of fever followed by vomiting, altered mental status, and seizures. Chandipura virus was isolated from sandflies in India and West Africa (Fontenille *et al*, 1994), which indicated a wide distribution although no human cases have been observed outside India. The mortality rate in the 2003 outbreak was 56%. A similar outbreak occurred in 26 children in western India in 2004, with a