A RECENT REVIEW: JAPANESE ENCEPHALITIS

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ABSTRACT

Japanese encephalitis (JE) is the most common form of viral encephalitis that appears in the form of frequent epidemics of brain fever throughout Southeast Asia, China and India. The disease is caused by a Flavivirus named Japanese encephalitis virus that is spread to humans by mosquitoes., Union health minister Ghulam Nabi Azad launched India’s first indigenously produced vaccine against Japanese Encephalitis (JE), a mosquito-borne viral infection that affects the central nervous system. Bharat Biotech launch of its Vero cell derived purified inactivated JE vaccine “JENVAC™” which received the manufacturing and marketing approvals by Drug Controller General of India (DCGI). It is a fully indigenous vaccine commercialized using strain, identified, characterized, manufactured and tested in India. JENVAC is a purified Inactivated Japanese Encephalitis vaccine produced from an Indian thermally stable strain, 821564-XY. JENVAC® is indicated for the prevention of disease caused by Japanese encephalitis virus (JEV) in persons 1 year of age and older. It is a Vero cell derived, inactivated, and chromatographically purified Japanese encephalitis vaccine and is made from a thermally stable India strain, Kolar, 821564-XY. The vaccine must be administered intramuscularly. JENVAC is the first vaccine to be manufactured in the public-private partnership mode. These new candidate JE vaccines have the potential to generate long-lasting immunity at low cost.

Key Words: Encephalitis, JENVAC, vaccine.

INTRODUCTION

Japanese encephalitis (JE) is a rare disease caused by the Japanese encephalitis virus. It is spread to humans by infected mosquitoes. Japanese encephalitis is an infection of the brain...
caused by a virus. JE virus spreads through the bite of infected mosquitoes. It cannot spread directly from person to person. Japanese encephalitis is mainly a paediatric disease causing acute infection and inflammation of the brain. It is caused by Japanese encephalitis virus which belongs to arthropod-borne virus family and it is transmitted through Culex mosquito. JE was first recognized as a clinical entity in Japan in 1817, but the causative agent (JEV) was later isolated from a fatal human case in 1934. JE was first reported in India in 1955 since than it has taken away thousands of lives. The total numbers of cases reported annually are about 35,000-50,000. Out of them ~30-50 % patients gets affected with neurological squeal and 20-40 % die. The natural cycle of JEV consists of pig-mosquito-pig or bird mosquito-bird circulation of virus. When an infected mosquito bites a healthy individual, it may lead to a nonspecific febrile illness or a severe meningo encephalomyelities illness. In rainy season the incidences of the disease increases. [1]

JEV is a ‘flavivirus’ (family Flaviviridae, genus Flavivirus ).The genus is named for the prototype yellow fever virus (in Latin, yellow is flavus ) and all have positive sense, single-stranded RNA as their genome material, which for JEV is 11,000 base pairs. This genome consists of 5 ′ and 3 ′ non-coding regions flanking a single large open reading frame (ORF) which encodes the three structural and seven non-structural viral proteins [2].

Sources of virus
1) Water birds of the family Ardeidae; herons and egrets (also known as bitterns)
   • effective at geographical dispersal
2) Mosquito vectors
3) Once infected, swine amplify JE virus and high titres in blood, provide more infectious agent to vectors
   • JE virus could be transmitted in boar semen
4) Overwintering of epizootic/epidemic JE virus has not been elucidated
   • introduction of JE virus strains from endemic areas
   • hibernating mosquitoes may maintain virus; also through transovarial passage
   • maintenance in reptiles, amphibians or bats [3].
Japanese encephalitis virus is usually transmitted by mosquitoes in the genus *Culex*. The specific mosquito vectors vary with the region; however, *Culex tritaeniorhynchus* is important in spreading this virus to humans and domesticated animals across a wide geographic range. *C. tritaeniorhynchus* breeds in rice paddies and connecting canals, and is active at twilight. Many other species of *Culex* including *C. vishnui* and *C. fuscocephala* can also transmit Japanese encephalitis virus. In some regions, *Aedes* mosquitoes have been implicated in transmission. The virus has also been isolated from mosquitoes in the genera *Anopheles* and *Mansonia*; however, their role in transmission has not been confirmed.

Most animals are infected when they are bitten by a mosquito. Lizards and bats can also be infected by eating infected mosquitoes. Boars transmit the virus in semen. Birds are the most important reservoir hosts, and usually maintain the virus cycle in nature. Although birds of the family Ardeidae (herons, egrets and bitterns) have been studied the most, other avian species may also be important in transmission. Swine are important amplifying hosts, as they are bitten by the same mosquitoes that bite horses and humans [4].
KEY FACTS ABOUT JAPANESE ENCEPHALITIS

A. PATHOPHYSIOLOGY

On a cellular level, after attachment of the Japanese encephalitis virus (JEV) to a host cell membrane, local membrane disruption may lead to entry of the virus into the cell itself. Subsequently, viremia develops, leading to inflammatory changes in the heart, lungs, liver, and reticuloendothelial system. Most infections are cleared before the virus can invade the central nervous system (CNS), leading to subclinical disease. Subclinical or mild forms of Japanese encephalitis resolve in a few days if the CNS is not involved. In such cases, the infection may not produce symptoms and therefore remains undetected. However, given the neurotropic character of JEV, neurologic invasion can develop, possibly by growth of the virus across vascular endothelial cells, leading to involvement of large areas of the brain, including the thalamus, basal ganglia, brain stem, cerebellum (especially the destruction of the cerebellar Purkinje cells), hippocampus, and cerebral cortex. Persistent infection and congenital transmission may occur. The levels of varying immune response (intrinsic, cellular, humoral) have been characterized. Higher levels of certain cytokines (interferon-alpha, interleukins 6 and 8) have been associated with an increased mortality risk. The types of response implicate impaired T-helper-cell immunity in patients with severe advanced disease. Overall, JEV is believed to result in increased CNS pathology because of its direct neurotoxic effects in brain cells and its ability to prevent the development of new cells from neural stem/progenitor cells (NPCs). JEV likely represents the first mosquito-transmitted viral pathogen to affect neural stem cells. These cells can serve important roles in injury recovery; consequently, Japanese encephalitis–induced disruption of neural stem cell growth may be particularly important to further morbidity and mortality. Recent studies indicate that other CNS cells besides neurons, such as astrocytes and microglial cells, may have replicative viral infection due to JEV, resulting in potential damage to the blood-brain barrier as well [5].

B. ETIOLOGY

Japanese encephalitis virus (JEV) is exemplary of its corresponding antigenic complex. JEV is transmitted to humans via the bite of infected Culex mosquitoes, especially C tritaeniorhynchus. Other Culex vectors include C vishnui (India), C gelidus, and C fuscocephala (Thailand, India, Malaysia). They prefer to bite outdoors and are extremely active in the evening and night, when the risk of infection is greatest. Mosquitoes breed in collections of water (typically rice paddies), increasing the risk of infection in rural areas. Aedes mosquitoes have also been implicated in JEV infection. Humans and other mammals
(eg, horses) are end hosts (low-grade, short-term viremia). Pigs and aquatic birds (eg, egrets, herons) serve as amplifying hosts. They develop persistent, high-grade viremia and represent the main vertebrate hosts as the principal reservoir for the virus. Cattle develop only relatively low-grade viremia or none at all; these animals are not part of the natural transmission cycle of the virus. Horses and piglets (not adult pigs) may develop clinical illness with a symptom spectrum similar to that in humans (eg, fever, locomotion difficulty, confusion).

There are 4 main genotypic variants of JEV, as follows:
- JEV type I isolates have been identified in China, India, Japan, Nepal, Sri Lanka, Taiwan, and Vietnam
- JEV type II isolates have been identified in Cambodia and northern Thailand
- JEV type III isolates have been identified in Indonesia, Malaysia, and southern Thailand; this genotype appears to have had the greatest spread
- JEV type IV isolates were also identified in the Indonesian and Malaysian regions

The virus initially propagates at the site of the bite and in regional lymph nodes. Two cellular characteristics are critical to the pathogenesis: (1) the M protein, which contains hydrophobic domains that help to anchor the virus onto the host cell, and (2) the E protein, which is the principal immunogenic feature and which is expressed on the membrane of infected cells. The E protein mediates membrane fusion of the viral envelope and the cellular membrane, promoting viral entry into the host cell. The JEV replication cycle includes initial host cell receptor interaction of JEV followed by receptor-mediated endocytosis, fusion of the viral and host cell membranes, subsequent cytoplasmic release of viral genome, and several other transcription and pretranslation steps. Maturation of virus particles occurs in the Golgi complex followed by ultimate release of JEV [6].

C. SIGNS AND SYMPTOMS
It usually takes 5 to 15 days between getting bitten and becoming unwell. Symptoms include: headaches, fever, seizures or fits (especially in young children), neck stiffness, drowsiness, confusion and progression to delirium and coma in severe cases.

- Patients with JEV infection have a history of mosquito exposure in an endemic area, with the subsequent occurrence of the following signs and symptoms:
- The prodromal period is characterized by fever, headache, nausea, diarrhea, vomiting, and myalgia, which may last for several days
Altered mental status follows and can range from mild confusion to agitation to overt coma
Seizures develop in 66% of infected persons, most often children
Headache and meningismus occur, but are more common in adults
Mutism has been reported as a presenting symptom
A syndrome of acute flaccid paralysis has been described
Generalized weakness, hypertonia, and hyperreflexia (including the presence of pathologic reflexes) are common
Papilledema occurs, albeit in less than 10% of patients
Cranial nerve findings (eg, disconjugate gaze, cranial nerve palsies) are found in 33% of patients [7,8].

D. DIAGNOSIS
The diagnosis of JE is based upon evidence of a diagnostic rise or decrease in JE virus specific antibody titres taken during the acute and convalescent phases of illness. JE should be suspected in a patient with evidence of a neurologic infection (such as virus-specific antibodies are usually detectable 7 to 10 days after the onset of illness. Viremia in humans is brief and neutralizing antibodies are usually present by the time distinctive clinical symptoms are recognized. (see figure 3)

1) Laboratory studies
Complete blood count (CBC) - Nonspecific, modest leukocytosis is often found in the first week of illness; in one study, 15% of children with Japanese encephalitis had thrombocytopenia
Serum sodium levels - Sodium levels may be depressed secondary to inappropriate antidiuretic hormone secretion
Liver function tests
Viral isolation - Isolation of JEV from clinical specimens or even the identification of positive genetic viral sequences in tissue, blood, or cerebrospinal fluid (CSF) is diagnostic
Immunodiagnostics - Immunoglobulin M (IgM) capture enzyme-linked immunoassay (ELISA) of serum or CSF is the standard diagnostic test for Japanese encephalitis
2) Imaging studies
Magnetic resonance imaging (MRI) and computed tomography (CT) scanning often show bilateral thalamic lesions with haemorrhage, with MRI being more sensitive. The basal ganglia, putamen, pons, spinal cord, and cerebellum may also show abnormalities. Hyperintense lesions may be observed in the areas of the thalamus, cerebrum, and cerebellum on T2-weighted MRI scans.

3) Electroencephalography
Electroencephalography (EEG) often reveals diffuse, continuous delta slowing; a diffuse delta pattern with spikes; theta waves; and burst suppression.

4) Histologic findings
Changes are found in the thalamus, substantia nigra, brainstem, hippocampus, cerebellum, and spinal cord and include focal neuronal degeneration with diffuse and focal microglial proliferation and lymphocytic perivascular cuffing. The diagnosis is made primarily on the basis of the patient’s symptoms and the knowledge of the kinds of illnesses endemic to a particular geographic region.

Most diagnostic techniques for Japanese encephalitis do not yield results very quickly. Immunofluorescence tests, where special viral markers react with human antibodies that have been tagged with a fluorescent chemical, are used to verify the disease. If a doctor suspects encephalitis, he or she will order tests such as a computed tomography (CT) scan or magnetic resonance image (MRI) of the brain. A procedure called a lumbar
puncture or spinal tap may be used to draw fluid from the spine and test it to determine what virus is causing the encephalitis [9,10].

E. TREATMENT & MANAGEMENT

1. Approach Considerations
The most important factor in the appropriate management of intracranial pressure is to identify and initiate appropriate therapeutic interventions. Patients with Japanese encephalitis should be monitored closely for complications, including bacterial infections (eg, pneumonia, urinary tract infections, decubitus ulcers). Be cautious of coinfection with other tropical diseases (eg, tuberculosis, malaria).

2. Supportive care
Therapy for symptomatic Japanese encephalitis virus (JEV) infection is supportive. Patients often require feeding, airway management, and anticonvulsants for seizure control. No clearly effective antiviral agents exist.

3. Management of intracranial pressure
Mannitol is used to decrease intracranial pressure, when needed. In the intensive care unit (ICU) setting, cerebral perfusion pressure (ie, mean arterial pressure minus intracranial pressure) must be maintained through appropriate modulation of systemic blood pressure.

4. Steroid therapy
Based on current studies, steroids (eg, dexamethasone) have not been shown to offer benefit.

5. Experimental therapies
One small study demonstrated some benefit from interferon alfa. However, a randomized trial of interferon alfa-2a in children demonstrated no benefit in overall outcome at discharge or at 3 months after discharge. Suramin, a drug used to treat trypanosomalous disease, and diethyldithiocarbamaten have shown reasonably good antiviral efficacy against Japanese encephalitis virus (JEV) in vitro. A novel intervention using a plant lignan called arctigenin has recently been shown to yield complete protection against experimental Japanese encephalitis in a mouse model. It appears to provide a newer mechanism of action, including decrease in CNS viral replication, decreased neuronal death, and reduction in inflammation and oxidative stress.
6. Invasive monitoring
Patients with evidence of elevated intracranial pressure may require invasive monitoring.

7. Further care
In rare cases, relapses of Japanese encephalitis have been reported several months after recovery. Patients may require long-term care and rehabilitation for residual neurologic deficits, including seizures and movement disorders [11,12].

F. PREVENTION
- Personal protective measures
  Individuals travelling to endemic areas can reduce their risk of vector exposure and infection by use of mosquito repellent and long-sleeved shirts and trousers, by avoiding outdoor activities in the evening, and by sleeping under permethrin-impregnated mosquito nets or in screened or air-conditioned rooms.

- Active vaccination: general principals
  The JE virus is a small (50 nm), enveloped virus containing a 10.7 kb, single stranded RNA genome. The viral envelope protein serves as the cell receptor binding protein and the fusion protein for virus attachment and entry into the host. Antibodies directed against envelope protein neutralize the virus and play an important role in protection. A JE neutralizing antibody titer $\geq 1:10$ is commonly accepted as evidence of protection.

1. First-generation JE vaccines
JE vaccines have been available since the 1950s. For decades, 2 vaccines were routinely used: (1) an inactivated mouse brain-derived vaccine and (2) an inactivated vaccine cultivated on primary hamster kidney cells.

The inactivated mouse brain vaccine containing either Nakayama or Beijing-1 virus strains was developed in Japan. Local production of this vaccine has contributed toward decrease in the incidence of JE in Thailand, India, Korea, Taiwan, Vietnam, and areas of Malaysia and Sri Lanka. For several decades, this JE vaccine has been available in the United States and Europe (The Green Cross JE vaccine, manufactured by Green Cross Vaccine, was not licensed for use in the United Kingdom and was not widely available in Europe but was distributed by MASTA on a named patient basis. Seroconversion rates, quantitative neutralizing antibody titers following vaccination, and efficacy rates varied according to the
population studied (indigenous vs nonindigenous) and number of doses administered (1, 2, or 3 doses in the primary vaccination series). A single efficacy trial showed equivalent protection afforded by either Beijing-1 or Nakayama strains. For travelers, a 3-dose vaccination series has been recommended.

Vaccine reactogenicity was acceptable over years of use, but the occurrence of a single case of acute disseminated encephalomyelitis temporally related to vaccination in Japan prompted the Japanese government (May 2005) to suspend routine childhood JE vaccination. The Global Advisory Committee on Vaccine Safety noted that there was no definite evidence of an increased risk of acute disseminated encephalomyelitis temporally associated with JE vaccine and that a causal link had not been demonstrated.

Acute disseminated encephalomyelitis has been reported as a severe drug reaction following administration of inactivated mouse-brain vaccine in $5\times10^{-4}$ to $1\times10^{-6}$ administered doses. In addition, since 1989, numerous cases of moderate to severe hypersensitivity type reactions temporally associated with JE vaccination have been reported. Adverse events have occasionally resulted in hospitalization requiring supportive care inclusive of parenteral steroids. Data collected on over 99,000 JE (BIKEN) vaccine recipients from Denmark, Sweden, United Kingdom, Australia, Canada, and the United States estimate the rate of hypersensitivity reactions at 0.7–104 reactions per 10,000 vaccines.

The causes of temporally associated neurologic or hypersensitivity reactions are not clearly understood; the presence of murine neural proteins, gelatin, and/or thimerosal in vaccine preparations have all been implicated but none proven as causative. BIKEN ceased production of JE-VAX in 2005; supplies are nearing exhaustion. A second inactivated vaccine has been in wide use. Approximately 70 million doses of the primary hamster kidney cell culture inactivated JE vaccine (Beijing-3, P-3 strain) were administered in China yearly until 2005. This was the country's principal JE vaccine since 1968. Randomized field trials demonstrated vaccine efficacy of 76%–95%.

2. Second-generation JE vaccines

The development and licensure of second-generation, non-mouse brain-derived JE vaccines is important news for nations looking for options to protect travelers, expatriate workers, and military personnel. These vaccines provide new options of benefit to endemic countries because of their improved safety profile and lower dosage requirements. SA14-14-2, a live
attenuated vaccine, has progressively been introduced into China where it has demonstrated an excellent safety profile, effectiveness (88%–96%), and efficacy in large scale trials (involving >200,000 children) and is replacing the inactivate primary hamster kidney cell culture vaccine. Since its licensure in China in 1988, >300 million doses have been produced and administered to >120 million children. Numerous large scale evaluations of vaccine safety demonstrate low rates (0.2%–6%) of short-lived local and systemic (ie, fever) reactogenicity and essentially no neurotoxicity. Case-control studies of a large vaccine trial in Nepal showed rapid onset of protection followed by a 5-year efficacy of 96% after a single dose of vaccine. In a small single study, SA14-14-2 vaccine was co-administered with live measles vaccine in children; normal immune responses were retained to each vaccine. Recently, the vaccine has been licensed for use, and millions of doses have been administered in Nepal, India, Sri Lanka, and South Korea. The Chinese manufacturer, Chengdu Institute of Biological Products, is seeking prequalification by the World Health Organization. PATH has negotiated concessional prices for the use of SA14-14-2 in India, Sri Lanka, and Nepal for public health preventive programs [13-16].

REFERENCES

2. Protection against Japanese encephalitis virus strains representing four genotypes by passive transfer of sera raised against ChimeriVax-JE experimental vaccine. Vaccine 2004; 22 (27-28): 3722-6


