

# Japanese B Encephalitis

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## ABSTRACT

RNA viruses are not only reported for viral pandemics but also as important agents for emerging/re-emerging diseases. **Japanese encephalitis virus (JEV)** is reported to cause epidemics of encephalitis in Southeast Asia, India, Korea, China, and Indonesia. In addition, several reports show that JEV has spread to new populations beyond these geographical regions. The disease mostly affects children with a mortality rate up to 30%. In peridomestic settings, pigs are reported as amplifiers of JEV transmission and aquatic birds as maintenance hosts of the virus. The *Culex* mosquito is the vector for transmission of JEV. This virus is a member of the family Flaviviridae and has a single-stranded positive-sense RNA virus. Five different genotypes (G-I to G-V) of JEV have been reported. Four different kinds of vaccines have been produced to prevent JEV infection. However, there is no FDA-approved antiviral drug available for JEV.

**Keywords:** Acute disseminated encephalomyelitis; Extrapyramidal sequelae; Flavivirus; IgM ELISA test; Japanese encephalitis; Minocycline.

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## INTRODUCTION

Encephalitis is an acute inflammation (swelling and irritation) of the brain. Viral infection is an important cause of encephalitis, one of them is the Japanese encephalitis virus (JEV). Japanese encephalitis (JE) is endemic in different parts of the world especially in South and Southeast Asia.<sup>1</sup> According to the latest report, JE affects 50,000 to 175,000 cases per year.<sup>2</sup> JEV along with West Nile virus, Zika viruses, and dengue virus belongs to the genus *Flavivirus*, family *Flaviviridae*.<sup>3</sup>

JEV is approximately 50 nm in size and spherical in shape containing a single-stranded RNA.<sup>3</sup> It is enclosed by a lipid envelope, and the length of the RNA is approximately 11 kb. Initially, the genome of JEV encodes a single polypeptide which is cleaved into three structural proteins and seven nonstructural proteins by viral proteases and host signalases. Three structural proteins are envelope E, precursor to membrane (prM), and capsid (C). The nonstructural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.<sup>4</sup>

Transmission of JEV occurs through a zoonotic cycle among arthropod vector (mosquitoes), amplifying host (pigs), and maintenance host (water birds).<sup>5-7</sup> Humans are infected by JEV accidentally and because of the low level of viremia further transmission does not occur.<sup>8</sup> JEV causes encephalitis in adults as well as in children; however, in endemic regions, it is regarded as a disease of children.<sup>9</sup> Symptomatic JEV infection starts with acute high fever with altered consciousness, convulsions, and focal neurological deficit.<sup>10,11</sup> In some cases, acute flaccid paralysis may also occur.<sup>12</sup> The affected parts of the brain in JE are thalamus, corpus striatum, brainstem, and spinal cord.

## EPIDEMIOLOGY OF JE

The mosquito of genus *Culex* is the transmission vector for JEV.<sup>13</sup> Although JEV has been isolated from more than 30 species of mosquitoes (genera *Aedes*, *Anopheles*, *Armigeres*, *Culex*, and *Mansonia*), but *Culex tritaeniorhynchus* is the primary vector in most endemic areas.<sup>14-19</sup> There is a direct association between *Culex tritaeniorhynchus* and wetland rice fields and similar irrigation systems,<sup>20-22</sup> which provide an optimal habitat for larval development.

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According to epidemiological studies by the Japanese group, the pig was established as the amplifying host.<sup>14</sup> Wild wading birds act as a maintenance host for JEV in Asia. Transmission of JEV between pigs via respiratory secretions has been reported, but more evidence is required to claim as the natural cycle.<sup>15</sup> Although mild viremia can be detected in a number of vertebrate hosts like cattle, horses, and humans, high level of blood viremia to enable transmission to mosquitoes is seen only in porcine and avian hosts. In experimental studies chickens, ducks and pigeons have also shown high blood viremia as seen in pigs<sup>16</sup> and could be important alternative amplifying vectors.

Traditionally, JEV is linked to rice agriculture and pig rearing and is therefore considered a disease of rural areas. Because of the wide genetic variation of JEV and its ability to infect a large number of potential vector species, now it is considered a disease of urban and periurban areas. Children are affected most often in endemic areas, but JE also occurs in adults in nonendemic areas.<sup>17</sup> JEV has two types of transmission patterns: seasonal epidemic transmission (in temperate region) and low endemic transmission throughout the year (in tropical region).<sup>18</sup> Asymptomatic cases of JEV infection are most common. Symptomatic cases are rare and reported to occur in 1 in 250 subclinical infections.<sup>19</sup> In symptomatic cases, however, the case fatality rate may be up to 30%.<sup>1</sup>

## Genotype and Geographic Spread

After complete nucleotide sequencing and molecular characterization of the JEV genome, five different genotypes (G-I to G-V) have been identified.<sup>20</sup> All five genotypes have originated from a common ancestor from Southeast Asian countries, i.e., Indonesia and Malaysia. Genotypes Ib and III are commonly seen in temperate Asia, but Genotype III has also been reported from various tropical areas. The genotypes Ia, II, and IV are seen in tropical Asia.<sup>21</sup>

## CLINICAL SIGNS AND SYMPTOMS

The clinical features associated with the JEV varies from asymptomatic infection to a fulminant encephalitic syndrome with high mortality and morbidity. The incubation period varies between 6 and 14 days. Most patients have a subclinical infection with low-grade fever, anorexia, diarrhea, coryza, and malaise. Some children may present with abdominal pain, diarrhea, and vomiting.<sup>22</sup>

The disease course may be divided into four phases. In the prodromal phase, the patient has a high-grade fever with headache with/without vomiting, malaise, and anorexia. The second stage is the "acute stage" with alteration in sensorium, convulsion, and focal deficit. During this stage, features of raised intracranial pressure are often seen. Nearly 45 to 50% of patients have convulsions during the acute illness, which are more common in children (85%). Lower Glasgow Coma Scale (GCS) scores, focal weakness, EEG slowing, and cortical and thalamic lesions on MRI are significantly associated with convulsion occurrence.<sup>23,24</sup> Cheyne Stokes respiration, abnormal pupillary response, oculocephalic reflexes, and flexor or extensor posturing are predictors of poor prognosis.<sup>25</sup> In some patients, however, this phase presents with behavioral abnormality alone, seen in some American soldiers with JE, and it was diagnosed as "war neurosis." Others only have aseptic meningitis without encephalopathy.<sup>5</sup> The "defervescence phase" is the third phase, where the acute features subside and transient extrapyramidal features become prominent in 20 to 60% of patients with mask-like facies, rigidity, tremor, dystonia, and other movement disorders. Opisthotonic posturing is associated with poor prognosis, which is seen in 15% of JE patients. Patients may have focal pyramidal weakness and asymmetric flaccid weakness with areflexia, seen in 5 to 20% of patients because of anterior horn cell involvement.<sup>25,26</sup> The last phase is the "sequelae phase" which is described subsequently.

The case fatality rate ranges between 20 and 30% and is most common during the acute phase of the illness due to raised intracranial pressure or neurogenic pulmonary edema. Nearly 50% of survivors have neurological sequelae. Sequelae are again more common in children than adults. Nearly 30% of survivors have extrapyramidal sequelae, pyramidal weakness, or convulsions. Cognitive and language dysfunction is seen in nearly 20% of patients, and children often have persistent mental retardation. Another 20% of patients persist with convulsions. A few patients show spontaneous rapid recovery, or "abortive encephalitis."<sup>25</sup> Even those children who have an apparent "good recovery" have subtle neurologic signs and learning disabilities.<sup>23,24,26</sup>

## DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

Most of the patients with acute encephalitis syndrome present with a short history of high fever, altered level of consciousness, with or without convulsion, or focal neurological deficit. The differential

diagnosis is therefore broad and includes other causes of encephalitis like herpes simplex encephalitis (HSE), cerebral malaria, dengue, and other arboviral encephalitides, West Nile encephalitis, untreated bacterial meningitis, and tuberculous meningitis.<sup>26,27</sup>

The blood counts and biochemical parameters are usually unremarkable, except for a mild elevation in liver enzymes.<sup>26,27</sup> The cerebro spinal fluid (CSF) opening pressure may be elevated in half the patients and is associated with a poorer prognosis. CSF studies reveal a moderate lymphocytic pleocytosis (10–100 cells/mm<sup>3</sup>), normal glucose, and mild elevation in protein (50–200 mg%). However, this is not the rule, and some patients may show a neutrophilic pleocytosis early in the course of illness, and others may not have any CSF cells.<sup>24</sup>

Electroencephalography may show theta delta slowing, burst suppression pattern, epileptiform discharges, and alpha coma during the acute stage. Electrophysiological tests reveal signs of focal anterior horn cell damage with fibrillations, fasciculations, positive sharp waves, and neurogenic motor unit potentials.<sup>26</sup>

Neuroimaging findings on CT reveal unilateral or bilateral thalamic and basal ganglia hypodensities, which are nonenhancing with contrast. Diffuse cerebral edema may be seen. MRI studies are more sensitive and reveal unilateral or bilateral T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities in thalami, basal ganglia, midbrain substantia nigra, and less commonly in the pons, medulla, and cerebellum. Occasionally temporal lobe (hippocampal) involvement may also be seen in extensive disease, causing confusion with HSE. However, in HSE, thalamic and basal ganglia involvement is not seen. Focal T2 and FLAIR hyperintensities may be seen in the spinal cord as well who present with flaccid paralysis.<sup>27</sup> Some of the lesions may be hemorrhagic, as seen by mixed intensities on T1 and T2 weighted scans and gradient recalled echo (GRE) images.<sup>25</sup> Diffusion restriction may also be seen in the lesions during the acute phase.<sup>27</sup> Acute disseminated encephalomyelitis (ADEM) has also been reported with JE. Single photon emission tomography studies during the acute stage have shown hyperperfusion in the thalami and basal ganglia, and occasionally frontal lobes.

Similar neuroimaging findings with thalamic, basal ganglia, and midbrain lesions are also seen in West Nile encephalitis and eastern equine encephalitis from the USA.<sup>27,28</sup> However thalamic lesions are less common, and white matter lesions are more commonly seen with West Nile encephalitis than JE. Some Indian studies have reported coinfection of neurocysticercosis with JE. Predominant brainstem lesions are seen in brainstem encephalitis with listeria monocytogenes, cytomegalovirus, rabies, mycoplasma, and St. Louis encephalitis.

The JE cases are diagnosed by detection of viral RNA in CSF by reverse transcription polymerase chain reaction in the early stages of the disease. However, JE IgM ELISA in the CSF is commonly used to diagnose JE. By the end of the first week of illness, it has a sensitivity and specificity >95%.<sup>22</sup> Newer and faster diagnostic techniques are being developed such as the use of immunosensors with lateral flow-based assays and electrochemical assays, and nanotechnology-based biosensors.

## CURRENT TREATMENT OPTIONS

In present time for JEV, no FDA-approved antiviral drug is available. Oral/enteral minocycline has shown some promise and needs further investigation.<sup>29</sup> Supportive care in the form

of management of raised intracranial pressure and control of convulsions important measures to minimize poor neurological outcomes. Nutrition and good nursing care for unconscious patient improve the prognosis.

### Currently Available Vaccine and Other Preventive Measures

At present, there is no antiviral drug available for JE; therefore, vaccination is the only way for long-term control. Four types of safe vaccines are available for JEV. World Health Organization also recommended vaccination of at-risk population through the national immunization program.<sup>30</sup> In India, JE vaccine is recommended only for individuals living in endemic areas. Other measures for the prevention of JE are the use of mosquito repellents, mosquito nets, and to wear shirts of long sleeves and trousers.

In addition, environmental hygiene is an important preventive measure. Stagnant water that allows breeding of mosquitoes and unsanitary conditions that encourage pigs to breed and roam freely near human habitation are important in maintaining the endemicity of this disease in countries like ours.

### Inactivated Mouse Brain-derived Vaccines

This inactivated mouse-brain-derived vaccine was prepared from wild-type Nakayama or Beijing-1 strains in Japan (1930s). In 2005, the production of this vaccine was stopped because of infrequent reports of ADEM. In 2006, the WHO has declared to gradually replace this vaccine by new generation JE vaccines.<sup>31</sup>

### Inactivated Vero Cell Vaccines

This vaccine was developed from different strains (Beijing, Beijing P-3, and SA 14-14-2) of JEV. The dosing and schedules are different for vaccines derived from different strains. For primary immunization of Vero cell culture-derived JE vaccine (SA 14-14-2), two intramuscular doses should be given 4 weeks apart with a booster after 1 year of age.

### Live Attenuated Vaccines

This vaccine is based on a neuro-attenuated and genetically stable strain of JE virus (SA-14-14-2). Two doses are recommended, first at 9 months and second at 16 to 18 months of age.<sup>32</sup> It is immunogenic, effective, safe, and elicits broad protective immunity for children.

### Chimeric Vaccines (JE-CV)

This novel, live, attenuated chimeric vaccine (JE-CV) is prepared by insertion of genes of SA 14-14-2 into yellow fever 17D virus, and it lacks neurotropic properties. Two doses are given subcutaneously around the age of 9 months which confer 5 years of protection against clinical JE disease.<sup>33</sup> But single dose is recommended by WHO in preference to the two-dose schedule.

### CONCLUSION

JE is an endemic disease in India and affects children more often than adults. The disease is maintained in water birds and transmitted by the Culex mosquito. Pigs are the amplifying host. The disease results in nonspecific encephalitis which can be fatal or leave the patient with long-term neurological sequelae. There are no specific drugs available to treat JE. Prophylactic options (vaccines) are the

key to handle outbreaks of JE. We need to find more promising vaccines/antivirals to prevent mortality and sequelae because of JE. Attention to environmental sanitation and newer vaccines would go a long way in preventing this disease.

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