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Review Article

Japanese Encephalitis: A Clinical Review

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Abstract:

Japanese encephalitis (JE) is a severe disease caused by the Japanese encephalitis virus of the genus Flavivirus and the family Flaviviridae. Mosquitoes of the Culex Vishnu subgroup, particularly Culex tritaeniorhynchus, are the main vectors of JEV. This zoophilic mosquito species is sustained in an enzootic cycle with pigs and wading birds as amplifying hosts. JE is endemic to rural Asia, the Western Pacific, and northern Australia, with three billion people at risk. Globally, an estimated 68,000 clinical cases occur annually, and over 13,000 deaths. Most JEV infections are subclinical; symptomatic infection can cause a spectrum of clinical manifestations ranging from undifferentiated febrile illness and aseptic meningitis to acute encephalitis. One-third of JE infections are fatal, and half of the survivors develop permanent neurological sequelae. Because of the frequent neurological sequelae of the condition, JEV causes loss of more disability-adjusted life years than any other arthropod-borne virus. WHO recommends incorporating the JE vaccine into the routine childhood immunization program in all JE-endemic areas. However, not all JEV-affected countries, including Bangladesh, have the vaccine implemented in their routine immunization programs. Introducing a childhood vaccination program can significantly reduce the number of JE cases in Bangladesh.

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Introduction:

Japanese encephalitis virus (JEV), a mosquito-borne flavivirus closely related to dengue, yellow fever, West Nile, Zika, St. Louis åxòephàliti¾ viruses.[1] It affects around 3 billion people in 25 countries across Asia, the Western Pacific, and northern Australia.[2] JE virus infection and encephalitis were first described in Japan in 1871, but the first large epidemic involving over 6,000 cases occurred in 1924.[3] Globally, an estimated 68,000 clinical cases occur annually, and over 13,000 deaths.[4]

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Although vaccination against JEV is ongoing in many Asian countries, a substantial number of new cases occur every year, resulting in either death or residual neurological disability.[5] One-third of JE infections are fatal, and half of the survivors develop permanent neurological sequelae.[6] Because of the frequent neurological sequelae, JEV causes the loss of more disability-adjusted life years than any other arthropod-borne virus.[7] AM Khan et al. first described a focus of Japanese encephalitis in the Modhupur Forest area, Bangladesh, in 1981.[8]

Virology:

Japanese encephalitis virus (JEV) belongs to the family Flaviviridae.[7] Like other flaviviruses, JEV is a single-stranded, positive-sense RNA virus. The virion is spherical, around 50 nm in diameter, and contains a central nucleocapsid core of viral RNA and core protein. In the mature virion, this core is surrounded by a lipid bilayer envelope where the viral membrane and envelope proteins are embedded. At the five 2 end of the open reading frame

is the core (C); encoding the capsid), membrane (M), and envelope (E) proteins, which are referred to as structural proteins.[9] The M protein's hydrophobic domains likely act as a transmission anchor. The E protein is a key immunogen and is expressed during plasma membrane fusion and cell entry. It plays an important role in determining the virulence phenotype, and single amino acid changes can result in neurovirulence or neuroinvasiveness. The protein is the main target of the host's antiviral immune response.[10]

Genetic and antigenic diversity of the JE virus:

Based on the nucleotide sequence of the viral genome, JEV is classified into five genotypes, GI-GV. All of the genotypes may be traced back to a common ancestor, who most likely evolved in the vicinity of modern-day Indonesia and Malaysia. Geographically, they are distributed as follows: (1) all five genotypes were isolated in the Indonesia-Malaysia region; (2) GI and GII were isolated in the Australia-New Guinea region; (3) GII and GIII were isolated in the Taiwan-Philippines region; (4) GI, GII, and GIII were isolated in the Thailand-Cambodia-Vietnam region; (5) GI and GIII were isolated in the Japan-Korea-China region; and (6) GIII were isolated from the India-Sri Lanka-Nepal region.[11]

Different immunological assays distinguish at least five antigenic groups despite the fact that all JEV genotypes comprise a single serotype. This indicates that there is some antigenic heterogeneity among circulating JEVs. The genetic and antigenic heterogeneity of JEV may, therefore, significantly impact the prevention and control of JE.[12]

Epidemiology:

Two epidemiological patterns of JE are recognized: epidemic and endemic (Table 1).[13,14,15] Epidemic patterns observed mainly in northern areas (Bangladesh, Bhutan, People's Republic of China, Taiwan, Japan, South Korea, North Korea, Nepal, northern Vietnam, northern India, northern Thailand, Pakistan, and Russia) demonstrate typical seasonal characteristics with occasional outbreaks. Endemic patterns found in southern areas (Australia, Myanmar, Brunei, Cambodia, Indonesia, Laos, Malaysia, Papua New Guinea, the Philippines, Singapore, southern Vietnam, southern Thailand, southern India, Sri Lanka, and Timor-Leste) occur sporadically throughout the year (figure 1).[13,16]

Figure-1. Areas at Risk for Japanese encephalitis.
[Source: https://www.cdc.gov/japanese-encephalitis/data-maps/index.html]

In most of the endemic areas, JE typically affects children <15 years of age; by early adulthood, most of the population has protective immunity following natural exposure to JEV as a result of ongoing environmental transmission. However, when the virus enters new geographic areas with no immunity, it affects both adults and children. Among immunologically naïve travelers visiting JEV-endemic regions, the disease can occur in individuals of any age.[17] But, Bangladesh has a different age distribution for JE. Hospital-based surveillance in four government hospitals in Bangladesh was done between the years 2007 and 2016.

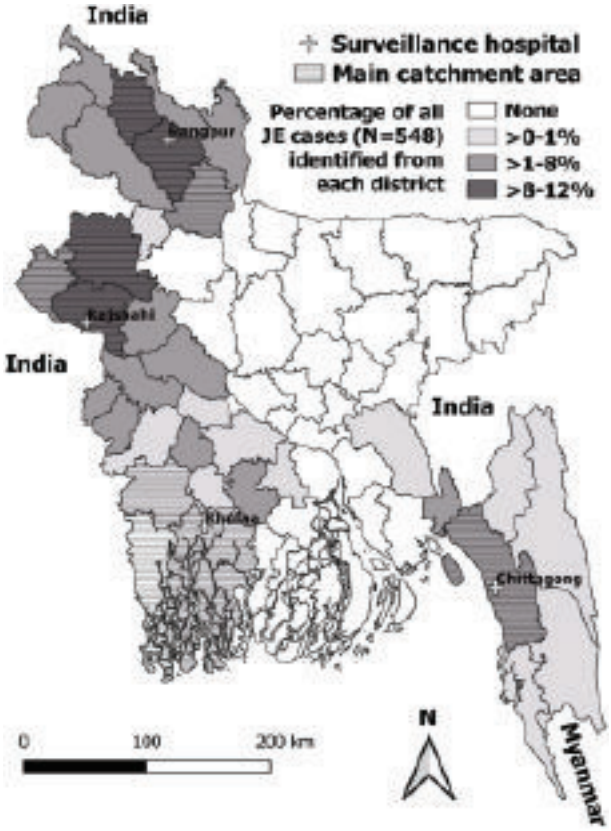

Figure 2. *Japanese encephalitis surveillance sites, main catchment areas, and case locations in Bangladesh, 2007–2016.*

In Bangladesh, both children and adults are affected by JE, and the median age of JE cases is 30 years. About two-thirds of cases in Rajshahi, Rangpur, and Khulna regions were in persons aged >15 years; only in the Chittagong region, the majority (64%) of cases were aged d”15 years. This was similar to another hospital-based surveillance in Bangladesh between 2003–2005, in which 55% of cases were also >15 years of age.[15]

KK Paul et al. reported results of hospital-based surveillance of acute meningoencephalitis syndrome (AMES) conducted in four government medical college hospitals, namely Rajshahi, Rangpur, Khulna, and Chittagong medical colleges (figure 2).[14] Between 2007 and 2016, 6543 AMES patients were detected at four tertiary hospitals. Of the 6525 patients screened, 548 (8%) were categorized as JE patients. These 548 individuals lived in 36 (56%) of Bangladesh’s 64 districts. The majority of JE cases among AMES patients (12% and 7%) occurred at two hospitals in the country’s northwest region.[16] JE incidences were higher in Rajshahi than in Khulna or Chittagong. This is possibly associated with a higher concentration of pigs, a major vertebrate host in the JEV transmission cycle, in the northwestern areas of Bangladesh.[14]

Most JE cases in Bangladesh (80%) occurred during July–November, corresponding to the monsoon and post-monsoon months. This is likely related to the abundance of Culex tritaeniorhynchus in these months due to prolific breeding in the paddy fields and other water bodies.[16] In India, 83% of clinically suspected cases of Japanese encephalitis occurred between September and November.[18]

Table-1. Epidemiological characteristics of Japanese Encephalitis

Region	Epidemiological pattern	Seasonality	Affected Age Group	Unique Characteristics
Northern Asia & Others	Epidemic	Seasonal	Children<15 years	Outbreaks with high mortality and morbidity
Southern Asia & Others	Endemic	Year-round	Adults & children <15 years	Sporadic cases, ongoing environmental transmission
Bangladesh (Specific data)	Mixed	July-November	Median age: 30 years	Adults > 15 years more affected in some regions

Transmission:

Mosquitoes of the Culex Vishnu subgroup, particularly Culex tritaeniorhynchus, are the main vectors of JEV, while JEV has been isolated from about 30 mosquito species.[19] This zoophilic mosquito species is sustained in an enzootic cycle with pigs and wading birds as amplifying hosts.

Wading water birds (e.g., herons and egrets) serve as virus reservoirs. However, the virus regularly spills over into pigs, members of the family of Equidae (e.g., horses and donkeys), and humans.[20] Pigs are a key host as they develop high levels of viremia and have subclinical infection. Large numbers of pigs are frequently kept near human dwellings in many Asian countries. The risk for JEV infection is highest in rural, agricultural areas of Asia, as all the elements of the enzootic transmission cycle are in close proximity to humans.[21]

Culex tritaeniorhynchus mosquitoes, one of the main vectors of JEV, breed in wet paddy fields. Wading birds, another known vertebrate host of JEV, are also frequently found in paddy fields.[22] Some authors challenged the idea of dominance of pigs as amplifying hosts , as countries such as Bangladesh, which have predominantly Muslim populations and very little pig rearing, still have a significant burden of JE in humans.[23] Ducks and chickens can produce sufficient viremia if infected at an early age to act as amplifying hosts, and their number and density in Bangladesh are quite high (figure 3).[24] Non-avian vertebrates such as humans and horses are considered unintentional dead-end hosts as they do not generate enough viremia to infect new mosquitoes.[25] Besides its natural transmission, JEV is also considered to be transmissible through blood transfusion and organ transplantation.[26]

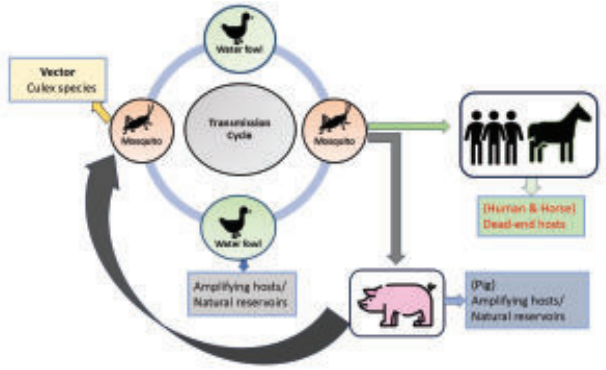

Figure-3: Transmission cycle of Japanese Encephalitis

Pathogenesis:

The pathogenesis of JEV infection has been studied in animal models: following peripheral JEV inoculation, replication occurs in the local lymph nodes, and the virus may be identified peripherally in monocytes and certain T cells. After the initial replication, viremia occurs, and the infection spreads to the CNS.[27]

The exact process by which JEV enters the brain remains unknown. The observations of peripheral replication and viremia in animal models, as well as the distribution of lesions in the brain, clearly suggest that JEV penetrates the CNS via the bloodstream. Patients with JE have substantial inflammation in their brains; inflammation is dominated by T cells, with monocytes and macrophages playing a minor role. Finally, neurons are likely to die as a result of a combination of direct viral-mediated damage, immune-mediated damage, and apoptosis, all of which contribute to the clinical signs of the disease.[28]

Clinical features:

Most JEV infections are subclinical, with a symptomatic-to-asymptomatic ratio of 1:25–1000.[29] About 1% of infections induce clinical illness with a 20%–30 % mortality risk, and another 30 %–50 % of recovered persons may have long-term neuropsychiatric consequences.[30]

Symptomatic JEV infection can induce a spectrum of clinical manifestations ranging from undifferentiated febrile illness and aseptic meningitis to acute encephalitis. After an incubation period of 5 to 15 days, initial symptoms are usually nonspecific and may include fever, diarrhea, and rigors followed by headache, vomiting, and generalized weakness. The acute encephalitic phase, which follows this mild febrile illness, is characterized by changes in mental status, focal neurologic abnormalities, and movement disorders. A very distinctive clinical presentation of JE is a Parkinsonian syndrome resulting from extrapyramidal involvement; findings include dull, flat, mask-like facies with unblinking eyes, tremîr, and cogwheel rigidity. Other possible movement disorders include choreoathetosis, hemiballismus, lip-smacking, and bruxism. In some patients, the initial presentation may consist of abnormal behavior or acute psychosis, leading to potential misdiagnosis (table 2).[18,31,32]

Table-2: Clinical Features and Complications of Japanese Encephalitis

Clinical Feature	Percentage	Comment
Altered sensorium	96%	Most common symptom
Seizures	86%	Includes generalized and motor seizures
Hyperkinetic involuntary movements	46%	Includes Parkinsonian syndrome
Paralytic features	17%	Poliomyelitis-like flaccid paralysis
Neuropsychiatric sequelae	(30-50) %	Includes chronic motor and cognitive disabilities

Seizures (usually generalized tonic-clonic) are very common, especially among children. In some children, subtle motor seizures occur and may present with twitching of a digit, eye deviation, or irregular breathing.[31] Some individuals with JEV infection may present with poliomyelitis-like acute flaccid paralysis caused by anterior horn cell destruction without any alteration of consciousness. Following a brief febrile illness, paralysis occurs in one or more limbs, frequently asymmetric and more common in the lower than upper limbs.[33] JEV has occasionally been associated with Guillain–Barré syndrome (GBS).[34]

In a large Indian cohort of 1282 cases, altered sensorium was present in 96%, convulsions in 86%, headache in 85%, hyperkinetic involuntary in 46%, seizures in 30%, and paralytic features in 17% of cases.[18] Multiple protracted seizures and elevated intracranial pressure are clinical indications of a bad prognosis. Changes in breathing patterns, flexor and extensor posture, and abnormalities of the pupillary and oculocephalic reflexes are poor prognostic indicators and may suggest brainstem encephalitis.[35] The differential diagnosis of JE includes various viral encephalitides, central nervous system infections, para- or postinfectious causes, and non-infectious illnesses, including autoimmune encephalitis or acute disseminated encephalomyelitis.[36]

Diagnosis of Japanese encephalitis:

The laboratory-confirmed cases of JE were defined as cases that met both clinical criteria for acute encephalitis syndrome (AES) and laboratory criteria for JE, according to the World Health Organization recommendation.[37]

Clinically, AES refers to the acute onset of fever and at least one of altered mental status and newly developed seizures. Laboratory confirmation of JEV infection requires one of the following: 1) the presence of JEV-specific IgM antibody in serum or cerebrospinal fluid (CSF) samples in the absence of IgM to other flaviviruses; 2) the detection of a more than 4-fold increase in JEV-neutralizing antibody between acute and convalescent stages.[38]

The presence of JEV-specific IgM antibodies in CSF confirms JE. IgM antibodies in serum are suggestive of JE but can also be due to asymptomatic JEV illness or recent JEV immunization. CSF antibodies are detectable in 70 to 90 percent of JE patients during admission of the patient to the hospital (Table 3).[39-41] JEV IgM can be detected in most CSF samples collected five to eight days after symptom onset. Serum antibodies are detectable in about 60 to 70 percent of patients on admission to the hospital; in nearly all serum samples collected at least nine days after symptom onset, serum antibodies are detectable. If JE is suspected and acute samples are negative, a convalescent serum sample should be collected.[39]

A nucleic acid amplification test (NAAT) can provide a definitive diagnosis, but positive results from CSF or blood are rare. This is because humans have low levels of transient viremia, and by the time clinical symptoms develop, the patient already has high levels of neutralizing antibodies.[40] Routine blood tests of patients with Japanese encephalitis are nonspecific; neutrophilia is common, and hyponatremia can be present. In around 50% of patients, the cerebrospinal fluid (CSF) opening pressure is increased. CSF results often show a mild to moderate pleocytosis of 10 to several hundred white blood cells/mm^3, with lymphocytic predominance, slightly increased protein, and a normal CSF to plasma glucose ratio. Early in the disease, there may be no pleocytosis, or neutrophils may be predominant.[42]

An MRI of the brain might be an important tool for diagnosing Japanese encephalitis. It may help to differentiate JE from other types of encephalitis in the initial days while microbiological reports are pending. In an Indian cohort of 54 JE patients, the majority of JE patients exhibited aberrant signal changes in bilateral thalami and substantia nigra. Other less commonly involved areas include the brainstem, cerebral cortex, cerebellum, cerebral white matter, and spinal cord. T2 weighted image (T2WI) hyperintensities in thalami have high specificity for JE in the endemic area. Diffusion-weighted imaging with ADC mapping can assess the stage of JE. In herpes simplex encephalitis, involvement of medial temporal lobes, insular cortex, and orbitofrontal lobes was observed.[41] Whereas in Nipah encephalitis, discrete high-signal-intensity lesions, measuring 2-7 mm, are found throughout the brain, mostly in the subcortical and deep white matter of the cerebral hemispheres.[43]

Table-3. Diagnostic Criteria and Tests for Japanese Encephalitis

Diagnostic test	Specimen	Sensitivity	Comments
JEV- specific IgM antibody	CSF	(70-90) % sensitivity	Highly specific diagnostic of JE
JEV- specific IgM antibody	Serum	(60-70) % sensitivity	Can indicate recent infection or immunization
Nucleic acid amplification	CSF/Blood	Low sensitivity due to transient viremia	Useful if performed early in infection
MRI (Thalami T2WI hyperintensities)	Brain Imaging	High specificity for JE in endemic regions	Distinguished JE from other encephalitis

Treatment:

Treatment is mostly supportive, as there is no specific antiviral treatment for JE. Supportive measures should focus on control of intracranial pressure, maintenance of adequate cerebral perfusion pressure, seizure control, and prevention of secondary complications.[44] In randomized clinical trials, dexamethasone, interferon-alfa-2a, and ribavirin did not show any benefit compared to placebo.[45,46,47] When given on day 5 after infection, at which time JEV is detectable in the brain, anti-JEV monoclonal antibody was partially protective in mouse models.[48] Although, a preliminary trial of intravenous immunoglobulin given for virus-neutralizing and anti-inflammatory effects found this safe and feasible; the study was not powered enough to find an improvement in outcome.[49]

Vaccine for JE:

The most used JE vaccines now are based on the attenuated strain SA14-14-2, which was generated from the JEV SA14 strain (which has relatively low pathogenicity) and grown from larvae of Culex pipiens from Xi'an in 1954.[50] The live attenuated vaccine SA14-14-2 produces neutralizing antibodies against wild genotype III strains (Beijing1 and SA14) in humans.[51] Inactivated, adjuvanted SA14-14-2 vaccine generates neutralizing antibodies against JEV genotypes I-IV and provides equivalent seroconversion rates for genotype I and III viruses.[52]

In India, after a single dose of live attenuated JE vaccine SA 14-14-2, vaccine effectiveness dropped from 91% (95% CI: 73.0-97.0) in the first year of vaccination to 71% (95% CI: 21.0-90.0) at six years post-vaccination. The incidence of adult JE cases declined from 10.5 per 100,000 in the pre-vaccination period to 5.7 per 100,000 in the years following vaccination.[53]

The case for JE vaccine in Bangladesh:

The World Health Organization (WHO) advocates human immunization as the most effective method of controlling JE. Several WHO-prequalified vaccinations are available to prevent JE, but no vaccination program has been established in Bangladesh. JEV antibodies were found in 19.0% of the Bangladeshi population [95% confidence interval (CI): 17.1 to 21.1]. On average, 0.7% (95% CI: 0.2 to 2.0) of the susceptible population becomes infected each year, with proximity to pigs being the primary human infection risk. It is believed that 1 in 1000 infections causes severe disease, 1 in 10,000 causes death, and hospital surveillance misses 76% of severe cases.[26]

There is a compelling human vaccine against JEV, with vaccine efficacies of more than 95%.[54] WHO recommends the incorporation of the JE vaccine into the routine childhood immunization program in all JE-endemic areas.[55] However, not all JEV-affected countries, including Bangladesh, have the vaccine implemented in their routine immunization programs. As the median age of JE cases in Bangladesh is 30 years, the introduction of a childhood vaccination program can significantly reduce the number of JE cases in the endemic areas.

Conclusion:

Bangladesh is an endemic area for Japanese encephalitis (JE). Although WHO recommends incorporating the JE vaccine in all endemic areas, Bangladesh does not have a JE immunization program. Because JE has a high fatality rate and survivors develop long-term neurological sequelae, we should consider implementing a childhood JE vaccine program.

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