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Japanese Encephalitis in Assam: A Sentinel Case

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ABSTRACT

Since times immemorial, mosquito borne diseases have proved to be a great menace to the human population. Their severe clinical manifestations and high mortality contribute to their deadly status. Japanese encephalitis (JE), is one such mosquito borne viral disease mainly prevalent in Southeast Asia including India, particularly in the state of Assam. It mainly affects the central nervous system, resulting in various neurological and locomotor disorders and change in mental status. Seizures are also observed, although they are more common in children. JE is caused by a virus of the *Flaviviridae* family, transmitted by a Culicine mosquito, *Culex tritaeniorynchus*. Pigs are considered to be the amplifier hosts. Throughout the years, JE has become endemic in many districts of Assam affecting many lives in the outbreaks that occur each year, more particularly in the rural and agricultural areas. Assam's climactic conditions, agricultural habits and patterns, and the lifestyle of its population play a major role in the epidemiology of the disease. With the establishment of JE surveillance and vaccination programmes by the government, the JE incidence rate has decreased. However, outbreaks of JE still continue to occur, often with serious complications and a high mortality. This concise review article gives a short summarization of Japanese encephalitis along with its history, epidemiology, vector and host biology, pathology, clinical observations and immunoprophylaxis with respect to the state of Assam, India.

KEYWORDS: Assam, flavivirus, Japanese encephalitis virus, mosquito, pig

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1. INTRODUCTION

Japanese encephalitis (JE) is one of the major mosquito-borne arboviral zoonotic diseases mainly prevalent in Southeast Asia. It is also coincidentally one of the major viral encephalitis prevalent in Asia causing approximately 13600–20400 deaths annually worldwide (Anonymous, 2019a, Yun and Lee, 2014). On an annual basis, it is thought to be the primary factor responsible for the loss of 709,000 disability-adjusted life years (Turtle and Solomon, 2018). The causative agent of JE is the Japanese Encephalitis Virus (JEV). This virus was first isolated in Japan in 1935 from the brain tissue of a fatal encephalitis case (Burke and Leake, 2019). The cycle of transmission of the virus involves pigs as amplifier hosts and wild birds as reservoir hosts (Borah et al., 2013, Lannes et al., 2017, Ricklin et al., 2016). Mosquitoes, mostly of the *Culex* genus, serve as vectors for transmission of the virus between the amplifier hosts and the definitive hosts, i.e. humans, horses and cattle (Lannes et al., 2017, Morita et al., 2015). In horses and cattle, the disease is usually asymptomatic. Like humans, they are also dead-end final hosts of the virus (Mansfield et al., 2017). In India, JE was first recognized in the southern states from 1955, and till the 1970s, it was confined to those states only. Since then, large outbreaks comprising about 2000–7000 cases annually have been reported from the eastern and northeastern states. During these outbreaks, it was observed that both adults and children were equally affected (Griffiths et al., 2014). The first cases in Myanmar and Bangladesh, India's close neighbours sharing common factors favorable for the prevalence of JE, were reported in 1974 and 1977 respectively (Paul et al., 2020, Win et al., 2020).In India, JE is endemic to many areas in the states of Assam, West Bengal, Uttar Pradesh, Jharkhand, Karnataka, Manipur, Kerala, Tamil Nadu, and Haryana (Dev et al., 2015). The hospital-based acute encephalitis syndrome (AES) surveillance in the northeast region of India showed that out of the total positive AES cases registered, approximately25% of cases were found to be positive for JE. Notably, this was found to be prevalent mainly in children (Bandyopadhyay et al., 2013, Sarkar et al., 2012). AES is defined as a clinical condition which manifesting as an acute onset of fever and alteration in mental status including signs and symptoms of confusion, disorientation and delirium and seizures in a person irrespective of the age and time of the year. It may or may not lead to coma (Narain et al., 2017, Tiwari et al., 2017). It is considered that JE is the leading cause of AES in Asia including India (Anonymous, 2019b, Jain et al.,2017). Over the years, since the first outbreak, JE has proved itself to be having a devastating impact on the Assamese population, particularly for the people living in rural areas and those occupationally dependent on agriculture. In 2014, more than 50% of the JE caseload of India was from Assam (Ahmad et al., 2015). The 2010–2014 period saw Assam experience a fivefold increase in the total JE cases. During the last ten years, more than 1200 people in Assam died due to JE. This disease is of great concern regarding public health due to its high fatality rate and its menacing ability to cause permanent neurological conditions even after recovery from infection (Cheng et al., 2022, Turtle et al., 2019, Yin et al., 2015). Although vaccination programmes against the disease are proving to be useful, the primary comprehensive measures like mosquito control, improvement of the vulnerable population's living conditions, and education on health especially during a JE outbreak, still remain the most effective ways of keeping the disease at bay (Tiwari et al., 2012, Wang and Liang, 2015).

2. GENERAL CHARACTERISTICS OF JEV

JEV falls under the genus *Flavivirus* of the *Flaviviridae* family. It is considered the type virus of a serocomplex of viruses which includes the West Nile virus, Kunjin virus, St. Louis encephalitis virus, and the Murray Valley encephalitis virus (Maclachlan and Dubovi, 2010). The virions are about 50 nm in diameter, spherical, and enveloped. The genome is composed of a positive sense single-stranded RNA with a 5' terminal cap structure encased in an icosahedral capsid. The RNA genome encodes three structural proteins namely C (nucleocapsid protein), prM (precursor protein to M, the transmembrane protein) and E (major spike protein) (Mukhopadhyay et al., 2005). The genome also encodes for seven non-structural proteins which are- NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS (Chambers et al., 1990). The viruses are unstable at room temperature and are sensitive to ether, chloroform and other lipid solvents. They are usually cultivated in BHK-21, Vero and PK-15 cell lines and duck and chicken embryo fibroblasts.

2.1. *Hosts*

Susceptible vertebrate hosts of the virus are horses, pigs, cattle and water birds. Invertebrate hosts include mosquitoes and ticks. Naturally, the virus exists in a cycle between mosquitoes, water birds and pigs (Anonymous, 2019a). Ardeid wading birds act as the natural enzootic reservoirs of the virus and pigs are considered the potential major amplifier hosts (van den Hurk et al., 2009). Humans are the accidental and terminal hosts. The viraemia occurring post JEV infection in humans is thought to be insufficient to infect mosquitoes for further transmission from humans (Ricklin et al., 2016).

2.2. *Historical perspective*

India recognized and reported its first JE case from Vellore, Tamil Nadu in 1955 (Webb and Pereira, 1956). The first major epidemic in India occurred in Bankura and Burdwan districts of West Bengal in 1973. After a few years, major epidemics took place between 1977–1979 in Uttar Pradesh, Assam, Andhra Pradesh, Karnataka, Bihar, Tamil Nadu and West Bengal (Reuben & Gajanana, 1997). Coming to the state of Assam, the earliest recorded case of a positive JE infection was reported in 1978 from an outbreak that took place in Lakhimpur, a district in upper Assam (Dev et al., 2015). Since then, sporadic outbreaks of JE have been reported consecutively from Assam between the years of 1985–1988. During July–August 1989, a major outbreak of JE took place in the Lakhimpur district again, affecting about 90 villages housing approximately a population of 36000 at that time. The case fatality rate was 50% (Vajpayee et al., 1992). Major outbreaks also took place consecutively from 2000–2002. 34.2% of the positive cases were children between the ages of 7–12 (Phukan et al., 2004). This disease has now become endemic to this northeastern state of India, recording outbreaks every year. Till 2015, JE was prevalent mainly in the upper Assam districts like Dibrugarh, Lakhimpur, Golaghat, etc. but nowadays cases are reported from almost every district in Assam.

3. EPIDEMIOLOGY

3.1. Pattern and climactic perspective

Globally, two epidemiological patterns of JE, i.e., endemic (in southern India, Singapore, southern Vietnam, Sri Lanka, southern Thailand, Malaysia, Cambodia, Laos, Indonesia, Myanmar, Papua New Guinea, Philippines and Australia) and epidemic (in northern and northeastern India, Bangladesh, Japan, South Korea, North Korea, Bhutan, Taiwan, People's Republic of China, northern Vietnam, northern Thailand, Pakistan and Russia) are recognized (Wang and Liang, 2015). Approximately 3 billion people are at risk globally from this deadly disease and it is still spreading to new territories (Erlanger et al., 2009). China and India bear approximately about 95% of the total JE global caseload. Assam, being a part of northeastern India, falls under the region of the epidemic pattern of JE around the globe. The state experiences a tropical monsoon type of climate, with heavy rainfall and high levels of humidity (Anonymous, 2022a). Floods occur every year during monsoon and the post-monsoon period, proving an abundant breeding ground for mosquitoes. In today's scenario, JE outbreaks in Assam are reported from July–October every year. It is to be noted here that Assam is also subjected to a high number of Acute Encephalitis Syndrome (AES) cases which are caused by a wide variety of bacterial, viral, fungal, parasitic and chemical agents including JEV. All AES cases were reported as JE cases till 2005. AES with other etiological agents' clinical signs often correlates to that of JE. Only after proper clinical diagnosis with detection of IgM antibody against JEV antigen, it can be confirmed that a patient is infected with JEV. JE accounts for 5–35% of the AES cases in India (Kamble & Raghvendra, 2016, Kumar et al., 2016).

3.2. Distribution

Until recently, upper Assam districts, namely Dibrugarh, Dhemaji, Golaghat, Lakhimpur, Sibsagar, Jorhat and Tinsukia had relatively reported more cases and deaths due to JE than other districts. But now lower Assam districts like Barpeta, Nalbari and Bongaigaon have also become endemic. Government authorities have identified ten highly endemic districts to be included under the multi-pronged plan constituted for the prevention and control of JE. These districts are: Sivasagar, Barpeta, Nagaon, Sonitpur, Darrang, Udalguri, Bongaigaon, Cachar, Morigaon and Nalbari (Desk, 2019). These districts are also covered by the vaccination programme against JE for adults. The typical tropical climate, the agricultural practices particularly rice cultivation and pig rearing, an abundance of mosquito vectors and the socio-cultural behavior of the population are important factors that make JE conducive in those areas.

3.3. Vectors and transmission

JEV is one of the many arboviruses, which are a group of viruses that are transmitted by arthropod vectors like mosquitoes and ticks. In many parts of India and Southeast Asia, *Culex tritaeniorynchus*is considered the major vector of JE. In Assam, the principal vector mosquito species carrying the JEV are the *Culex vishnui* and *Culex gelidus*, which are found to be highly prevalent in the region during the peak JE period (Khan et al., 2021). In the overall Indian scenario, many secondary vectors like *Culex pseudovishnui*, *Cx. whitmorei*, *Cx. gelidus*, *Cx. bitaeniorynchus, Cx. epidesmus, Anopheles subpictus*, *An. peditaeniatus, Mansonia indiana* and *Ma. annulifera* have also been found to be harboring the JEV (Anonymous, 2022b, Kanojia et al., 2003). Globally, JEV has been isolated from over 30 mosquito species, 19 of which are found in India (Pearce et al., 2018). Under natural conditions, the life cycle of the virus generally involves the *Culex* mosquitoes and the water birds (enzootic cycle) or the *Culex* mosquitoes and pigs (infection cycle). Interestingly, the *Culex* spp. is also involved in the transmission of the West Nile Virus (WNV), another flavivirus in Assam which causes AES in humans (Chowdhury et al., 2014, Chowdhury and Khan, 2021). The emergence of WNV Assam is also a great cause for concern for public health as Assam is already a JE endemic region. There are many factors as to why mosquito-prone diseases like JE, malaria, dengue, WNV infection and lymphatic filariasis are high in Assam. Assam has a tropical climate and vast paddy fields. The state also experiences heavy rainfall and floods in the monsoon season which provides a favourable environment and breeding ground for the mosquitoes. Aggressive deforestation and urbanization also have a role in it (Burkett-Cadena and Vittor, 2018)

3.4. Role of the pig

In JE endemic regions of northeast India, where human JE infection is prevalent, pigs enter the life cycle of JEV as the major amplifier hosts. In nature, the mosquito vector, after carrying the virus from water birds like egrets and herons, bite the pigs which are found near the water bodies, thus infecting the pig population in that area. Measurable viraemia in pigs has been observed after infection with JEV (Mansfield et al., 2017). In the majority of the rural households in Assam, domestic pigs stay near human housing. This provides an easy route for the *Culex* mosquitoes to bite the pigs and then bite humans near them, thus transmitting the virus to humans. Recent years have indicated that pig rearing in Assam has increased manifold which also correlates to the trend of JE cases in the state (Borah et al., 2013). Assam has the highest domestic pig population with a figure of 2.1 million (Anonymous, 2019b). And it has also been seen that the pig population has been the highest in JE endemic districts like Dhemaji and Lakhimpur (Anonymous, 2019c). It is observed that tea garden labourers and the people of the Mising community of Assam were at high risk of getting infected with JEV. Cases in tea garden-rich areas are attributed mainly to poor hygiene and a general lack of awareness. People of the Mising community, particularly in villages, rear pigs very close to their living quarters, thereby increasing the chances of getting infected (Ladreyt et al., 2019). Person-to-person transmission of JE has not yet been reported. The cycle of disease is depicted in Figure 1.

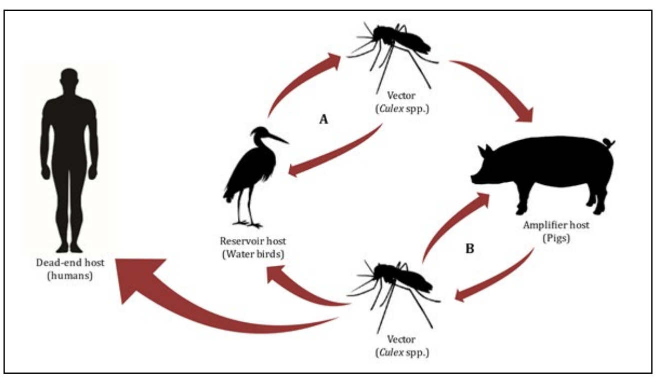

Figure 1: Transmission cycle of Japanese Encephalitis

3.5. Target population

JE Prime susceptible age group in humans is 3–15 years. They are more likely to get infected and present clinical manifestations.

4. PATHOGENESIS

JEV is a neurotropic virus. Its incubation period in humans ranges from six to fourteen days. After the infected mosquito takes a bite, the virus travels to the regional lymph nodes after replicating in the skin. It is reported that Langerhans dendritic cells, which are a special subset of dendritic cells present in the skin support this viral replication (Tiwari et al., 2012). Now the virus multiplies in the body, causing viraemia before it enters the central nervous system (CNS) (Monath et al., 1983). The virus primarily enters the brain through the blood-brain barrier (Hsieh and John, 2020). It is believed that certain neurotransmitter receptors have a role in the binding of the virions to the cells of the CNS tissue (Kabilan et al., 2004). Encephalitic clinical manifestation only occurs when the virus invades the neural tissues. Infection of organs and tissues outside the nervous system generally causes mild or asymptomatic infection.

4.1. Clinical signs and pathology

JE presents as an asymptomatic infection in the majority of the cases, mainly in adults. The common clinical signs found in positive JE cases in the global and Assamese scenarios are fever, rigidity in the neck and headache in the first 2–4 days, vomiting, nausea, diffuse abdominal pain and diarrhea (gastrointestinal), abnormal behaviour, seizures, unconsciousness, confusion, a neurological deficit in form of hemiplegia and quadriplegia, sensory alteration, paralysis, and coma (neurological) (Misra and Kalita, 2010). The prominent gross pathological findings are mainly found in the thalamus, the cerebral cortex, the cerebellum and the anterior horn cells of the spinal cord (Tiroumourougane et al., 2002). Autopsy involving the brain of fatal cases reveals severe vascular congestion, cerebral edema and necrotic foci in the brain parenchyma (Ghosh and Basu, 2009). Microscopic examination reveals meningitis, perivascular cuffing with lymphocytic infiltration, gliosis and neuronophagia. Case fatality rate ranges from about 25% to 30% and about 50% of the recovered patients are left with permanent neuropsychiatric complications (Yun and Lee, 2014). During a study conducted by Patgiri et al. (2014) in Assam during 2011–12, there was a case of JE-induced abortion in an infected pregnant woman who was at 30 weeks of gestation. The patient also reportedly died a week after she was hospitalized (Patgiri et al., 2014).

5. DISTRIBUTION OF JE IN INDIA AND ITS RECENT TRENDS IN ASSAM

The figures for cases and deaths that occurred during 2010–2021 are given in Figure 2. The case fatality ratio (CFR) is also shown here in Figure 3.

6. DIAGNOSIS

Clinical diagnosis is mainly done based on the presence of clinical features representing encephalitis within the context of an ongoing outbreak or epidemic mostly during monsoon and post-monsoon season in JE endemic areas (Kumar, 2014). Laboratory tests used to detect JE

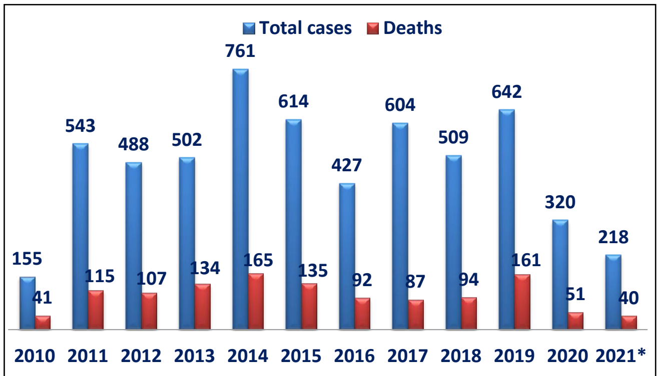

Figure 2: JE trends in Assam during 2010–2021. Compiled and updated from(Anonymous,2022; Anonymous, 2022)

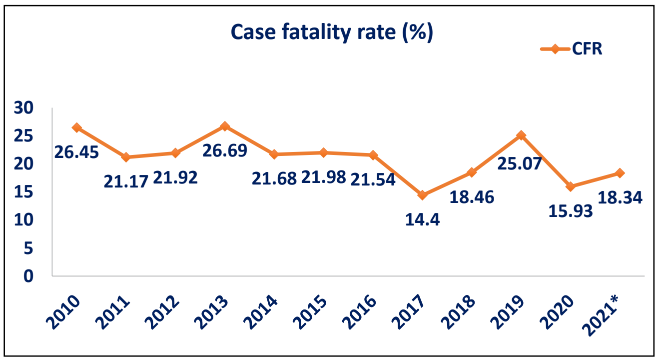

Figure 3: CFR of JE in Assam during 2010–2021

include serological tests like virus neutralization test, complement fixation test, haemagglutination inhibition test and molecular diagnostic tests like RT-PCR. Blood (serum) and cerebrospinal fluid (CSF) are the preferred samples for JE diagnosis.

7. TREATMENT AND PREVENTION

At present, there is no definitive cure for JE. All the treatments currently focus on supportive care and the prevention of secondary infection during hospitalization. The first step towards the prevention of JE would be vector control. Effective irrigation, thermal fogging, insecticidal and larvicidal measures in the endemic areas may inhibit mosquito breeding to a certain extent but due to the vastness of breeding places, some of those measures may seem ineffective. Vaccines stand as another method of prevention. There are presently 15 WHO-qualified vaccines available used worldwide. However, the most common one used in Asian countries including India is the live attenuated SA-14-14-2 JE vaccine (LAJEV) manufactured by the Chengdu Institute of Biological Products, China (Khan et al., 2021). It has been reported that the single dose effectiveness of the LAJEV vaccine among children was found to be 94.5% after six months in India (Kumar et al., 2009).

8. CONCLUSION

Despite all the measures taken by the government including vaccination and vector control, JE continues to wreak havoc in India, particularly in Assam. Although there are vaccines available against the virus, there are currently no efficient antiviral medications. The only effective preventive strategies are vaccination and mosquito control. The current demand is for the creation of fresh data for building a holistic strategy with integrated engagement of scientists, molecular biologists, medical and veterinary practitioners, medication developers, policy makers, and local community.

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