

JAPANESE ENCEPHALITIS: MEDICAL EMERGENCY IN INDIA

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ABSTRACT

Encephalitis or Brain fever is one of the most epidemic diseases all over the world, affecting children and adolescents in the tropics. The disease progresses through prodromal, encephalitic and convalescent stages. It is difficult to diagnose in early stage. According to the World Health Organization statistics, about 1 in 300 infection results in symptomatic illness and about 30 percent of these cases may cause death or life long disability like long term neuro-psychiatry sequelae. Epidemic of Japanese encephalitis has become dreadly in India, around 1500-4000 peoples are being affected every year. It has become a medical emergency for us. In spite of great efforts there is no any specific and effective drug against brain fever; vaccination is the only way to prevent brain fever. But it's high cost and medical complications make it far away from the reach of Asian people. Recently, in India, an outbreak of this fever led to number of children death in Bihar and Uttar Pradesh. In spite of extensive research all over world, till now, we have not been able to get any significant treatment of this fever. So discovery of new targets and cost effective drugs against brain fever are much needed in present scenarios. We hope that this review will attract attention of the researchers all over the globe to find out probable targets and drugs against this dreadly bug (Japanese encephalitis).

Keywords: Encephalitis, epidemic, Drugs, Vaccine, India

INTRODUCTION

Encephalitis is one of the leading causes of acute encephalopathy affecting children and adolescents in the tropics^{1,2}. It is the acute inflammation of brain tissue leading to acute onset of fever, headache, confusion, and sometimes seizures. The disease is caused by bacteria, viruses, fungi and protozoans, among them virally associated encephalitis, Japanese encephalitis is the leading cause of death in newborns in India and other countries³. Among viruses, flaviviruses is the main cause of viral encephalitis. It is estimated that around 35,000 cases of encephalitis and 10,000 deaths in humans are taking place each year in southern and eastern Asia⁴. It is transmitted to human beings by insects, such as mosquitoes and ticks^{5,6}. Although viruses are the most common source of infection, bacteria, fungi, and parasites can also be responsible for encephalitis. Mosquitoes that proliferate in close association with pigs & other animal reservoirs are found to spread virus of Japanese encephalitis in malnourished children of poor families from rural areas (areas of intensive rice farming). Extensive research to develop specific vaccine against Japanese encephalitis has been carried out in the Asian continent, where the virus causes encephalitis in human beings. The WHO has consigned the authorities of developing countries for the development of effective vaccine for the prevention of Japanese encephalitis in the affected areas. Some countries in Asia (Japan, South Korea, North Korea, Taiwan, Vietnam, Thailand) had developed vaccines to immunize the children⁷. In Indian perspective the disease is still a deadly bug and needs great attention of the scientific community to solve the problematic scenario.

Occurrence and Prevalence

The first case of encephalitis was recognized in the Japan during 1871. First Outbreak was observed in Tokyo metropolitan, affecting many people⁶. The causative agent of the disease was mosquitoes *Culex tritaeniorhynchus*^{8,9}. Due to changes in agricultural and pig-rearing practices, increased use of pesticides, and widespread immunization, the incidence of Japanese encephalitis decreased to 100 cases pr year in Japan¹⁰. Recently, in Republic of Korea *Culex bitaeniorhynchus* was reported to cause virus encephalitis in local civilian¹¹. At that time, the incidence of encephalitis has been also reported in other countries like China, affected mainly children of 2-5-year age group. It is rapidly increasing and spreading to other part of world. Now, it has become the most epidemic disease worldwide¹². The life cycle of Japanese encephalitis virus is very complex. It shares life cycle with birds and pigs, animals become infectious by infected mosquito bites¹³ (Figure 1). Birds and pigs are the

amplifying host of encephalitis virus, where virus proliferate and increase their number but they don't manifest the disease. Mosquitoes become infectious vector after sucking blood from infected amplified host. Japanese encephalitis is occasionally transmitted to human being through infected *Culex mosquitoes*¹⁴. Japanese encephalitis is not a communicable disease. It can't be spread from infected human to normal human, they are the dead end hosts. Climate change may also play an important role in the incidence of encephalitis outbreak. Rainy season support the rapid growth and proliferation of mosquitoes, that can transmits the virus from infected host to human being, leading to outbreak¹⁵.

Major outbreak in Indiapathogenesis

In India, the first endemic case of Japanese encephalitis was identified in the state of Tamilnadu in 1955. A total of about 65 cases were reported between 1955 and 1966 in South-India¹⁶. Japanese encephalitis is severe disease and its epidemics are reported from many parts of India¹⁷. The first outbreak of encephalitis was observed in West Bengal in 1973, where 325 cases of deaths were reported out of 763 cases of encephalitis¹⁸. In 1976 and 1978 encephalitis outbreak dominated again in West Bengal where 1500 cases was recognized out of which 700 patients died¹⁹. During 20th century extensive outbreaks of encephalitis was recognized in north-eastern India with 7463 cases reported. In the north region, Uttar Pradesh experienced its first epidemic in 1979 and the disease has continued there with 1716-3894 cases per year. The outbreak of encephalitis have been reported from different parts of india, predominantly in the rural areas of Bihar, Uttar Pradesh, Assam, Manipur, Andhra Pradesh, Karnataka, Madhya Pradesh, Maharashtra, Tamil Nadu, Haryana, Kerala, West Bengal, Orissa and union territories of Goa and Pondicherry¹⁷. Occurrence of Epidemic of Japanese encephalitis in Andhra Pradesh, during 1999, caused 178 deaths out of 873 affected peoples²⁰. In Northern states, the disease was reported between 1997 and 1981²¹. Gorakhpur region (UP) experienced the most serious outbreak in 1988 with 875 cases²². An epidemic of viral encephalitis was reported in 2005, First encephalitis outbreak was in Utter Pradesh state of India, as estimated more than 400 people, mainly children, have died in an outbreak of viral encephalitis. In northern India, nearly 6,000 children have died of encephalitis, since the first case was detected in 1978. From time to time this disease dominated again and again in Utter Pradesh and Bihar causing death of newborn children. In year 2011, around 891 people, including 508 in Uttar Pradesh alone and 200 in Bihar, died due to encephalitis. So it is still an important endemic disease in India.

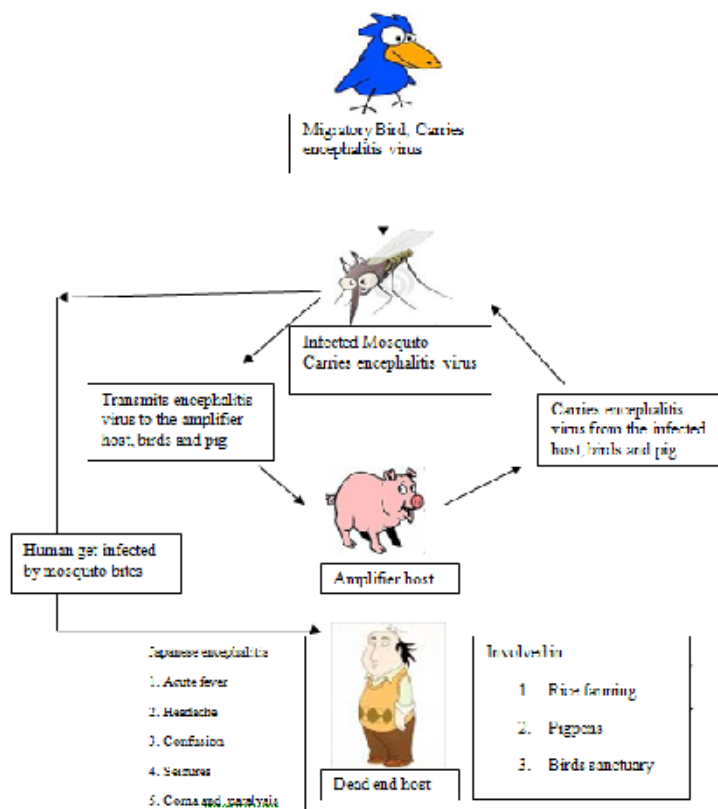


Figure.1: Mode of transmission of Japanese encephalitis Virus

Problems in diagnosis and treatment

Diagnosis of early Japanese encephalitis is difficult, as its present symptoms are also shared by other Flaviviruses. Sometimes viruses responsible for causing cold sores, mumps, measles, and chickenpox can also share encephalitis symptoms. RT-PCR and virus isolation from brain tissues have been developed for the detection of Japanese encephalitis. But it has to be limited by the specific requirements of laboratory operations, skilled technicians and special equipments and difficult to isolate Japanese encephalitis virus from clinical specimens because of low circulating viral numbers and rapid removal of transient viremia by neutralizing antibodies²⁴. The serological tests used, or surveys performed, to detect existing immunoglobulin G antibodies cannot specifically distinguish antibodies to Japanese encephalitis virus²⁵. Recently, antigen capture ELISA method to detect highly conserved E gene in different Japanese encephalitis virus genotypes was developed by Mie et al., 2012, is found to be very sensitive diagnostic test against Japanese encephalitis²⁶. Vaccine against Japanese encephalitis was developed in India but it has some significant limitation, also not routinely immunization of vaccine into remote area of country which is severely affected with this disease led to outbreak. The control of vector and shared host like pigs and birds in the rural areas is practically not possible, because control of Japanese encephalitis through vector and host control methods have some limitations owing to sustainability and cost effectiveness of the programs. Both inactivated²⁷ and live-attenuated²⁸ vaccines have been used in Asian continent against Japanese encephalitis virus with considerable success. Earlier Vaccines derived from Mouse-brain and hamster kidney cell-lines were used, but, they have some significant medical complication²⁹. Recent research identified that a natural compound, sulfated polysaccharide extracts isolated from *Ulva lactuca* is able to obstruct virus absorption and stop the virus to infect the healthy cells³⁰.

Disease Managements

Disease managements are the combination of preventive measures that provide better health of human beings. It includes screening, monitoring, and education that provide the use of best medical

practices and reducing the progression of Japanese encephalitis, results in quick recovery and effective treatment. Better disease managements are quiet helpful in eradication of Japanese encephalitis virus form the environment. The belief is that better care today will mean better health and, perhaps, less expensive care tomorrow.

Vector Management

Control of vector and host of Japanese encephalitis is important to prevent the proliferation of Japanese encephalitis virus. Seasonal epidemics occur during the rainy seasons, when mosquito populations are maximal¹². Insecticide and pesticide are initially used to eradicate the encephalitis larvae of mosquito from the rice field but it require multiple round of spraying of pesticide in one season. It may be responsible for the development of insecticidal resistant of pathogens³¹. Alternating irrigation of rice field also reduce vector breeding³². Use of protective mosquito nets and repellents are also valuable protective tools for the encephalitis.

Host Management

Amplified host pigs to be grown in localized piggens away form housing may be attractive procedure for disease control purposes. Immunization of the pigs and birds of affected area against Japanese encephalitis is also an important step to eradicate it from the environment. Preventive measures which provide in-door facility to animals will be helpful in protection from mosquitoes.

Vaccination

A number of vaccines had been developed against Japanese encephalitis, among them, WHO had approved, only mouse-brain derived inactivated vaccine. But it has to be improved, because administration of mouse-brain derived inactivated vaccine in patients leads to some common allergic reaction like erythema, swelling, tenderness, fever, headache, malaise and dizziness³³. Vaccine developed from primary hamster kidney (PHK) cell culture has relatively less side effects and is easy to manufacture. But its efficacy was found to range between 76-90%³⁴. Application of vero cell-culture derived formaldehyde inactivated JE vaccine generated

high quantity of anti-JEV antibodies in mice and sera from immunized mice efficiently neutralized different JEV strains with different efficacies^{35,36}. Administration of cell culture derived live attenuated vaccine can also evoke sufficient immune response against Japanese encephalitis, which makes it effective and cheaper vaccine against the disease³⁷. Clinical trials on administration of this vaccine are under process. Recent day's development of recombinant Japanese encephalitis vaccine is under process. Recently, identification of the role of E-protein in Japanese encephalitis provides a strong base to develop recombinant protein vaccine against JE. E-protein of JE was expressed in *E.coli*, recombinant fusion protein with glutathione-S-transferase was found to be eliciting the immune response in mice^{38,39,40}. It was also reported that oral administration of recombinant E-protein with adjuvants provoked immune system to develop virus-specific antibody response against it, in mice. But, but it unable to neutralize JEV in vitro and did not provide any protection against lethal virus challenge⁴¹. E protein of JE was also expressed in Baculovirus system^{42,43} and immunogenic properties are tested in animal models. But due to lack of suitable adjuvants and delivery systems to strongly immunize the infected person, obstruct the development of an effective subunit of protein-based vaccine^[44,45,46].

CONCLUSION

Increasing incidence and recent outbreak of Japanese encephalitis in India, indicates the failure of present vaccination and immunization program, controlled by Indian government. In India immunization of children has been carried out in different regions but reoccurrence of Japanese encephalitis in those area and lack of surveillance system in other parts of country has been showing where we are and what we have done to protect from this endemic disease. Researches for the effective treatment of Japanese encephalitis are being carried out all over the world. Products of natural resources have been found to be effective remedy against JE. But the therapeutic perspective of some of these agents is being evaluated in clinical trials. Recombinant vaccines are found to be promising agent to cure and immunize people against Japanese encephalitis but, their use is presently limited by significant limitation.

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