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JAPANESE ENCEPHALITIS

***Jiji Alfred, Bincy Charley, Bini Ann Koshy, Christy Merin Mathew**

Nazareth College of Pharmacy, Othera, Thiruvalla, Kerala, India.

ABSTRACT

Japanese encephalitis (JE) is a serious public health problem in several parts of world, because of its threatening morbidity and mortality outcome, particularly among children. In India, there are 3 known mosquito vector species widely present in all the endemic areas. The ecology of JE is a multidimensional issue involving several macro- to- micro level factors influencing the spatio- temporal dynamics of transmission. There is a need to understand the ecological linkage and interface of the reservoir (bird) - amplifier (pig) - the vector (mosquito) as a crucial aspect of the biologic route in the maintenance of the JEV in nature. Risk factor identification based on micro analysis of diverse factors ranging from local ecology to socio-economic well being of people living in endemic areas, is of utmost importance for JE prevention and control. The scarcity of specific information and importance of socioeconomic and cultural aspects in relation to JE epidemiology has been emphasized and reviewed in the article. All these aspects of JE ecosystem have been grossly reviewed highlighting specific areas of interest for disease prevention/ control programme in order to provoke ecological thinking among various specialists like epidemiologists, medical entomologists, molecular epidemiologists and public health decision makers.

Keywords: Japanese encephalitis, mosquito vector, flavivirus.

INTRODUCTION

Japanese encephalitis (JE) is a viral disease caused by a type of virus called a flavivirus. It is spread through the bite of an infected mosquito. In most cases, the illness is mild, with symptoms including headaches and a high temperature (fever). Although severely under-reported, 50,000 cases are annually recorded throughout Asia, with 15,000 deaths (5-35% case fatality rate) and a 75% JE-related disability rate. JE virus was isolated from wild caught mosquitoes in the same year, followed by isolations from patients from the same area in 1958. JE continues to be endemic in these states. Since 1972, JE has spread to newer areas and outbreaks have been reported from West Bengal, Uttar Pradesh, Assam, Manipur, Bihar, Andhra Pradesh, Pondicherry, Karnataka, and Goa and recently from Kerala and Maharashtra. The disease in southern India affects children below 15 years, while in north India all age groups are affectedThe virion of JEV contains three structural proteins – nucleocapsid or core protein (C), non-glycosylated membrane protein (M) and glycosylated envelope protein (E), as well as seven non-structural (NS) proteins – NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS.7 JEV exists in a zoonotic cycle between mosquitoes and pigs and/or water birds. WHO recommends JE immunization in all regions where the disease is a recognized public health problem, and for travelers to endemic regions. Several vaccines have been available for decades with proven ability to control the disease [1,2].

HISTORICAL PERSPECTIVE

The first outbreak of encephalitis attributed to JEV was reported in Japan in 1871. Major epidemics have been reported about every ten years; in 1924, over 6,000 cases were documented in a severe epidemic in Japan. In 1935, the prototype Nakayama strain was isolated from the brain of a patient suffering from encephalitis. Thereafter, the virus has been classified with other flaviviruses as a group B parvovirus in the family Togaviridae, Originally the term “type B” encephalitis was used to distinguish this summer epidemic from von Economy’s lethargic/sleepy

Corresponding Author:- **Jiji Alfred** Email: jijialfred89@gmail.com

sickness, commonly known as type A encephalitis, which occurs in winter with a different clinical presentation. Later on, the designation "type B" was abandoned, and in 1985, JEV was designated under a separate family Flaviviridae, as a member of genus Flavivirus.The genus Flavivirus has been named after the prototype yellow fever virus (from the Latin word flavi,), and is comprised of 70 small, enveloped viruses with single stranded positive-sense RNA [3,4].

VECTORS AND TRANSMISSION

The JEV is transmitted to vertebrates by mosquitoes. Many species of Culet mosquitoes can transmit JE. For Southern Asia, Eastern Asia, and Southeastern Asia, the main vector of JE is C. tritaeniorhynchus. For Northern Australia, the main vector is C. annulirostris. However, various other secondary vectors may be important. Indian studies in particular have revealed a number of secondary vectors, including Mansonia indiana, C. pseudovishnui, C. whitmorei, C. gelidus, C. epidesmus, Anopheles subpictus, A. peditaeniatus, and M. uniform.The natural cycle of JE virus in Asia involves water birds and Culet mosquitoes. Unlike many other mosquito-borne diseases, an amplifying host is important in the epidemiology of human JE. In Asia, pigs are considered to be the most important amplifying host, providing a link to humans through their proximity to housing. The life cycle of the virus is illustrated in below Fig 1. There are two epidemiological patterns of transmission: an endemic pattern in tropical areas with viral circulation in most months of the year, but with a broad seasonal peak, probably resulting from irrigation practices; and an epidemic pattern in more temperate areas with clear summer seasonality. Besides mosquitos, birds also spread the virus into new geographical areas [5,6,7].

PREVELANCE OF THE DISEASE

Almost half of the human population now lives in countries where the disease is endemic. The annual incidence of the disease is of 30,000 to 50,000 cases and the annual number of deaths reported is 10,000 to 15,000.33,36. The disease can cause irreversible neurological damage. A fatality rate of 30% to 50% has been attributed to JE in Southern and Eastern Asia. A large proportion of survivors, 30% to 60% of the cases, suffer from long-term neurological manifestations in the form of convulsions, tremors, paralysis, ataxia, and other such symptoms. Annual incidence ranged between 1,765 and 3,428 cases and deaths ranged between 466 and 707 in India, according to the National Vector Borne Disease Control Programme of the Ministry of Health and Family Welfare [8,9].

PATHOPHYSIOLOGY

Only about 1 in 25 to 1 in 1000 humans infected with Japanese encephalitis virus develop clinical features of infection. These may range from a mild flu-like illness to a fatal meningoencephalomyelitis. The factors determining which of all the humans infected develop disease are unknown, but could include viral factors such as route of entry, titre and neurovirulence of the inoculums and host factors such as age, genetic makeup, general health and pre-existing immunity. After the bite of an infected mosquito, the virus is thought to amplify peripherally, causing a transient viraemia before invading the CNS. Based on data from mice and macaque monkeys, the site of peripheral amplification is thought to be dermal tissue and then lymph nodes. The means by which Japanese encephalitis virus crosses the blood-brain barrier is unknown. However, immunohistochemical staining of human postmortem material has shown diverse infection throughout the brain, indicating a haematogenous route of entry. Although experimental evidence suggests that replication within endothelial cells may be an important means of crossing the blood-brain barrier in some flaviviruses, for Japanese encephalitis virus passive transfer across the endothelial cells seems a more likely mechanism. Other factors which compromise the integrity of the blood-brain barrier have also been implicated as risk factors for neuroinvasion. In several studies a disproportionate number of fatal cases had neurocysticercosis at necropsy. It has also been suggested that head trauma during the transient viraemia could facilitate viral entry into the CNS. Electron microscopic studies of the brains of infected mice show that the virus replicates in the rough endoplasmic reticulum and Golgi apparatus. There is hypertrophy of the endoplasmic reticulum and degeneration into cystic structures causing extensive dysfunction [10,11].

HISTOPATHOLOGY

At necropsy, CNS findings in Japanese encephalitis reflect the inflammatory response to widespread neuronal infection with virus. The leptomeninges are normal or hazy. The brain parenchyma is congested with focal petechiae or hemorrhage in the grey matter. When survival is prolonged beyond 7 days blotchy necrolytic zones are seen. The white matter usually appears normal. In some patients, the grey matter of the spinal cord is confluent discolored, resembling that of poliomyelitis. The thalamus, basal ganglia, and midbrain are heavily affected, providing anatomical correlates for the tremor and dystopias which characterize Japanese encephalitis. At the histological level, invasion of neurons by Japanese encephalitis virus is followed by per vascular cuffing, infiltration of inflammatory cells (T cells and macrophages) into the parenchyma, and phagocytosis of infected cells. T cells in the brains of fatal cases stained with monoclonal antibodies are CD8+ and CD8- (presumed to be CD4+) and are localized at the per vascular cuff. Both cell types are found in the CSF in acute

infection, though the predominant cell type is CD4+. In patients that die rapidly, there may be no histological signs of inflammation, but immunohistochemical studies disclose viral antigen in morphologically normal neurons. This may explain the normal CSF findings in a proportion of patients with Japanese encephalitis [12,13].

CELLULAR IMMUNITY

In animal models of Japanese encephalitis, the cellular immune response seems to contribute to the prevention of disease during acute infection by restricting virus replication before the CNS is invaded: athymic nude mice have increased susceptibility to experimental infection with Japanese encephalitis virus; transfer of spleen cells from mice immunized with live attenuated virus conveys immunity to infection. Spider monkeys, which are normally unaffected by intracerebrally inoculated virus develop rapidly progressive encephalitis when T cell function has been impaired by cyclophosphamide. In humans infected with St Louis encephalitis virus (a flavivirus in the same antigenic complex as Japanese encephalitis virus) impairment of T cell function by human immunodeficiency virus (HIV) seems to increase the risk of developing encephalitis. By analogy with other human viral infections, including influenza, HIV, Epstein-Barr virus, and dengue, cytotoxic T lymphocytes might be important in the control and possibly clearance of Japanese encephalitis virus. Preliminary experimental evidence is in agreement with this: T lymphocyte responses were characterized in seven convalescent patients with Japanese encephalitis and 10 vaccine recipients. Japanese encephalitis virus specific T cell proliferation (including CD4+ and CD8+ T lymphocyte responses) was demonstrated in both groups. Japanese encephalitis virus specific and flavivirus cross reactive CD4+ T lymphocytes which recognize E protein in an HLA restricted manner were recently demonstrated in two vaccine recipients [14,15].

MORTALITY

Children and elderly are at highest risk for mortality which ranges from 5%-40% with the highest frequency usually associated with poor medical care and the most severe cases (2%-11% in US military personnel) JE's mortality rate is approximately 25% to 30%.Although intensive care support can reduce the mortality rate, patients often suffer significant long-term morbidity. Some effects, such as learning difficulties and behavioral problems, can be subtle and may remain undetected for several years. 50% of those who recover suffer from neurological deficit. Over the past 60 years, it has been estimated that JEV has infected more than ten million people, of whom three million died [8].

RECURRING PATTERN

Generally, two epidemiological patterns of JE are recognized. In northern temperate areas (Japan, Taiwan, China, Korea, Northern Vietnam, Northern Thailand, Nepal, and Northern India), large epidemics occur during the summer months, roughly from May to October. In southern tropical areas (Southern Vietnam, Southern Thailand, Indonesia, Malaysia, Philippines, Sri Lanka, and Southern India), JE tends to be endemic; cases occur sporadically throughout the year, with a peak after the start of the rainy season (July to September). In India, the state of Karnataka experiences two epidemics each year, with a severe form from April to July and a milder one from September to December along with the rest of India [8,16].

TARGET POPULATION

JE is mostly a disease of children and young adults. Rates of infection in the 3 to 15 year age group are five to ten times higher than in older individuals, because of high background immunity in older individuals. Epidemics in non-endemic regions have affected all age groups, but a bimodal age distribution (young children and elderly) has appeared, indicating an increased risk in elderly people. In endemic areas, nearly all residents have sustained infection by young adulthood. The ratio of unapparent to apparent infections is 200:1 to 300:1. An excess of cases has been noted in males in many outbreaks; presumably because of increased exposure in areas of rice cultivation [7,17].

CLINICAL MANIFESTATIONS

The incubation period in man, following mosquito bite varies from 5 to 15 days. The clinical features of JE are those of encephalitis. Majority of the cases are in younger age groups, although all age groups are affected. In areas where disease has become endemic, cases are mainly reported from age groups below 15 years. Various epidemiological studies conducted during investigation of outbreaks, observed that though both sexes are affected, males outnumber females. The patient will give history of acute onset with fever with altered sensorium. Some of the patients may show change in behavior. There may be history of convulsions. Febrile seizures may mimic a case of JE but the sensorium is not altered. The focal neurological deficits may or may not be present. Disturbances of sensorium are refl ected as lethargy, somnolence, irritability, apathy or loss of consciousness. The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, tremor and ataxia. There may also be loss of bladder and bowel control. The focal neurological signs may be stationary or progressive. 5% to 70% patients who recover from the acute episode may have neurological sequelae depending upon the age and severity of the disease viz. mental impairment, severe emotional instability, personality changes, paralysis etc. In majority of the cases, however, the infection is mild with no overt clinical symptoms or mild fever with headache. Clinical laboratory finding in

acute encephalitic stage - CSF is clear and may show variable findings: fluid pressure is normal to mildly elevated, CSF glucose is normal and proteins are mildly elevated. Case fatality rate is high i.e. 20 to 40% in severe cases [8,9].

DIAGNOSIS

Attempts to isolate Japanese encephalitis virus from clinical specimens are usually unsuccessful, probably because of low viral titres and the rapid production of neutralizing antibodies. Isolates may sometimes be obtained from CSF (in which case it is associated with a failure of antibody production and a high mortality rate) or from brain tissue (either at necropsy or postmortem needle biopsy). Immunohistochemical staining of CSF cells or necropsy tissue with anti- Japanese encephalitis virus polyclonal antibodies may be positive. However, for most practical purposes Japanese encephalitis is diagnosed serologically. The haemoglutination inhibition test was used for many years, but it had various practical limitations, and as it required paired serum, could not give an early diagnosis. In the 1980s IgM and IgG capture enzyme linked immunosorbant assays (ELISAs) were developed which has become the accepted standard for diagnosis of Japanese encephalitis. After the first few days of illness, the presence of anti-Japanese encephalitis virus IgM in the CSF has a sensitivity and specificity of >95% for CNS infection with the virus (before this false negatives may occur). However, because ELISAs require complex equipment, their use has been confined largely to a few academic or referral centres, rather than the rural areas where Japanese encephalitis occurs. Recently the IgM ELISA has been modified to a simple nitrocellulose membrane based format in which the result is a colour change visible to the naked eye. This test, which is rapid, simple to use, and requires no specialised equipment should prove useful for diagnosis of the disease in rural hospitals. Japanese encephalitis virus RNA has been detected in human CSF samples using the reverse transcriptase polymerase chain reaction; however, its reliability as a routine diagnostic test has yet to be shown [18,19].

LABORATORY DIAGNOSIS

Detection/isolation of antigen/virus

(i) Demonstration of viral antigen in the autopsied brain tissue by the fl uorescent antibody test

(ii) Isolation and identification of the virus from CSF, occasionally from peripheral blood (within 3 to 4 days after onset of symptoms) or autopsied brain tissue [18].

DETECTION OF ANTIBODY

The diagnosis of JE is supported by serological tests. The tests include detection of IgM antibodies which appear after the first week of onset of symptoms and are detectable for one to three months after the acute episode. A fourfold rise in IgG antibody titre in paired sera taken at an interval of 10 days or more is confi rmatory. IgG antibodies indicate previous infection and are useful for conducting seroepidemiological studies to determine the extent of silent infection and immunity levels in the local population. The detection of antibodies to JE virus can be done routinely by Haemoglutination Inhibition Test (HI) test to demonstrate fourfold rise in total antibodies and IgM Capture ELISA test for demonstration of IgM antibodies. National Institute of Virology may be contacted for antigens and reagents [18,20].

CULTURE

Japanese encephalitis virus can be isolated by intracerebral inoculation of clinical specimens in the suckling mouse brain. Various cell cultures that have been used more recently include primary chick, duck embryo cells, and lines of Vero, LLCMK2, C6/36, PK, and AP61 cells. The virus can be isolated from the blood of patients in the preneuroinvasive and neuroinvasive phases of the illness, usually not later than six or seven days after the onset of symptoms [19].

PCR DIAGNOSIS

Real-time polymerase chain reaction (PCR) assays provide sensitivity and specificity equivalent to that of conventional PCR combined with Southern blot analysis, and since amplification and detection steps are performed in the same closed vessel, the risk of releasing amplified nucleic acids into the environment is negligible. In general, both PCR and ampli- fied product detection are completed within an hour and less, which is considerably faster than conventional PCR detection methods. By reverse transcriptase PCR, the viral genome can be amplified directly from tissue or blood. A novel nested reverse transcription-polymerase chain reaction (RTPCR)-based kit is described for detecting JEV, in which all reagents are lyophilized in reaction tubes and control RNA is included in each reaction to monitor false negative results. Another study described and evaluated a reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay for detecting JEV. The sensitivity of the JEV RT-LAMP assay was in concordance with that real-time RT-PCR, and it was more sensitive than that of conventional RT-PCR. The JEV RTLAMP was highly specific; no cross-reactivity was found with dengue-2 virus, rabies virus, norovirus, astrovirus, and human enterovirus. The JEV RT-LAMP assay was simpler and less time-consuming compared to the conventional RT-PCR and real-time RT-PCR. The results suggest that the RT-LAMP assay can be applied as a practical molecular diagnostic tool for JEV infection and surveillance [18,19].

MANAGEMENT

Treatment for Japanese encephalitis is supportive, and involves controlling convulsions and raised

intracranial pressure when they occur. For many years corticosteroids were given, but a double blind randomized placebo controlled trial of dexamethasone failed to show any benefit. Careful nursing care and physiotherapy are needed to reduce the risk of bed sores, malnutrition, and contractures. Aspiration pneumonia is a common occurrence in patients with a reduced gag reflex. There is currently no specific treatment for Japanese encephalitis. Isoquinolone compounds are effective in vitro, and monoclonal antibodies are apparently effective in animal models. Interferon-a is currently the most promising potential treatment. It is produced naturally in the CSF in response to infection with Japanese encephalitis virus and in vitro it has activity against the virus. Recombinant interferon-á has been given in open trials to a few patients with encouraging results, and is currently being assessed in a placebo controlled double blind trial [21,22].

TREATMENT

There is no cure for JE and treatment is mainly supportive. Patients are not infectious, but should avoid further mosquito bites. A number of antiviral agents have been investigated, including INF alfa-2a68 and diethyldithiocarbamate (a low molecular weight dithiol).However, none of these has convincingly been shown to improve the outcome of JE. Effective supportive management has been shown to improve the outcome. The standard management of viral encephalitis should be used. Mannitol might be used to reduce intracranial pressure. Another compound that has shown inhibition of JEV replication completely in vitro is an N-methyl isatin -b thiosemicarbazone derivative. Supportive. Nursing care and prevention of infection during hospitalization are important. Close monitoring is necessary for the physiological disturbances during hospitalization and for sequelae after discharge [23].

Formalin inactivated vaccine

Formalin inactivated vaccines against Japanese encephalitis were produced in Russia, Japan and in the United States by Albert Sabin (later of polio fame) during the second world war to protect American troops in Asia. A similar formalin inactivated vaccine has been manufactured in Japan since 1954. It is produced by Osaka University and is available internationally under the BIKEN label. Similar vaccines are made by other manufacturers in India, Japan, Korea, Taiwan, Thailand, and Vietnam. The vaccine's efficacy was shown in large double blind randomized tetanus toxoid controlled trials in Taiwan and Thailand involving more than 300 000 children. In western subjects three doses of vaccine are required to give protective antibody levels to a suitably high number of recipients (80%- 100%); It is given at 0, 7, and 30 days, with a booster immunization recommended at 1 year. In Asian subjects two doses may be sufficient because of prior or subsequent exposure to Japanese encephalitis or other flaviviruses. A booster vaccination has been recommended at 1–2 years for those with continued exposure [11,23].

Live attenuated vaccine

In 1988 the Chinese authorities licensed a new live attenuated Japanese encephalitis vaccine. This strain (SA 14–14–2) was produced by passing the virus through weanling mice, then culturing in primary baby hamster kidney cells. The vaccine has been shown to be safe and immunogenic, and has been given to over 100 million children in China. Its efficacy was recently demonstrated in a relatively simple and inexpensive case-control study in which the prevalence of immunization was compared between 56 cases of Japanese encephalitis and age and village matched controls. The effectiveness of one dose was 80% (95% confidence intervals 44%-93%) and of two doses 1 year apart 97.5% (86%-99.6%). The vaccine's short term safety was recently confirmed in a randomized trial of 26 000 children, and it has been shown to be immunogenic at the shorter dosage interval of 1 and 2.5 months, which might facilitate its incorporation into existing immunizations programmes [11,23].

PREVENTION

Broadly speaking, measures to control Japanese encephalitis include those which interfere with the enzootic cycle of the virus, and those which prevent disease in humans. Measures to control breeding of Culet mosquitoes, such as the application of larvicides to rice fields, and insecticide spraying have proved ineffectual. Inactivated and live attenuated vaccines (described below) have been used to protect swine against the virus; however, widespread vaccination is not feasible in most settings. Residents and travelers to endemic areas should take personal protection to reduce the number of Culet bites. These include minimizing outdoor exposure at dusk and dawn, wearing clothing that leaves a minimum of exposed skin, using insect repellents containing at least 30% DEET [24].

CONTROL OF JE

Prevention of transmission is possible through vector control. For effective control of vectors, residual insecticidal spraying has been suggested in all animal dwellings with appropriate insecticide before the onset of transmission season. The detailed guidelines for vector control formulated by Directorate of NVBDCP are annexed [18].

Three types of vaccine against JE is presently produced and used worldwide. Inactivated mouse brain (Japan, Korea, Taiwan, Thailand, Vietnam, PR China, and India), inactivated and live attenuated primary hamster kidney cells are manufactured in China [18,19].

In most areas of Asia, the mouse brain vaccine produced from the Nakayama strain is given

subcutaneously in 2 doses of 0.5 ml (1.0 ml for people > 3 years) 1 to 4 weeks apart with a booster dose at 1 year and additional booster doses thereafter at 1 to 3 year intervals. Vaccination should be carried out during inter-epidemic period in the age group of 1 to 15 years. In India, the vaccine is being produced at Central Research Institute, Kasauli. The live attenuated (SA-14-14-2) vaccine is produced and has been licensed and used in China since 1988. Recently countries like Nepal, South Korea and Sri Lanka have licensed this vaccine for use in their countries. The live vaccine when given in single dose and has a high efficacy (data reported from several countries have shown efficacy to be between 80 – 99% following a single dose vaccination and 98% or greater with two doses of vaccination). The live vaccine has excellent safety record and no severe adverse effects have been reported. However, live attenuated vaccine requires 'field testing' in Indian context, especially in known endemic areas [19].

Fig 1. Life cycle of Japanese Encephalitis Virus [28]

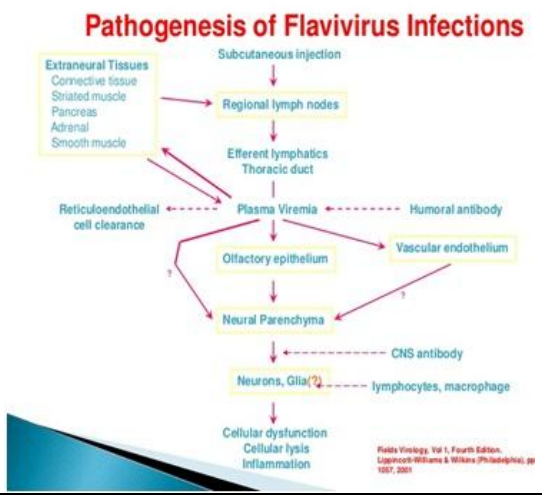
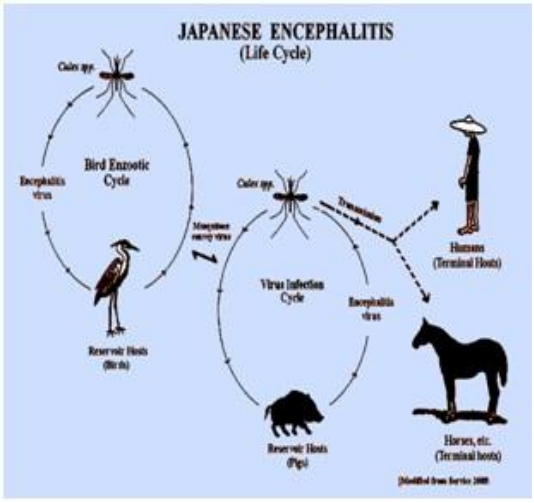


Fig 2. Pathogenesis of Flavivirus Infections [29]



CURRENT SCENARIO OF DRUGS FOR JE

There are many promising candidates against JE infection which need further assessment and increased availability to the needful.

❖ Nitazoxanide (NTZ) is a thiazolide anti-infective which is validated to have antiviral properties and is used for the treatment of parasitic gastroenteritis. Combination of N-methylisatin -β-thiosemicarbazone derivative (SCH16) with ribavirin and mycophenolic acid demonstrates the antiviral activity of SCH16 against JE in vitro [25].

❖ Griffithsin (GRFT) is a broad spectrum antiviral protein that is effective against several glycosylated viruses which may be used for therapeutic development against JEV or other flaviviruses [26].

❖ Bispidine, an amino acid conjugate of 3,7-diazabicyclo[3.3.1]nonane acts as a molecular scaffold for the development of potent antiviral against encephalitic viruses [27].

❖ Tilapia hepcidin (TH) 1-5, an antimicrobial peptide can control JEV viral infection and could be a promising antiviral candidate [26].

❖ Mycophenolic acid is reported to inhibit the replication of JEV in mouse model experiments, therefore could be used against JEV infection [27].

❖ Minocycline acts as neuroprotective agent in various animal studies of a number of acute CNS injuries, neurodegenerative disorders and CNS infection. It is reported to reduce the neuronal damage by JEV in cell culture models by inhibiting oxidative stress [25].

❖ Pentoxifylline acts as antiviral against several RNA and DNA viruses. In vivo studies have shown that pentoxifylline at a concentration of 100mg/kg body weight can protect mice introduced to LD (50) of JEV [26].

❖ Rosmarinic acid is to reduce mortality infected with JEV. Short interfering RNA (siRNA) can be used as a broad spectrum antiviral agent for treating encephalitis caused by multiple flaviviruses like JEV, West Nile virus, tick-borne encephalitis virus [27].

❖ Dehydroepiandrosterone (DHEA) is an adrenal derived steroid which involves in protection against neurotoxicity and viral induced encephalitis, resulting in a better survival rate of the animals. A low molecular weight dithiol, Diethyldithiocaramate (DDTC) is an immunomodulator and modifier of different biological actions in animal and human models. It is also effective in several disease conditions. Many experiments have shown that DDTC have a possible therapeutic role during JEV infection. It has been studied that macrophage derived neutrophil chemotactic factor (MDF) induces production of nitric oxide (NO) during JEV infection, which has an antiviral effect [27].

❖ NO may play a crucial role in the innate immunity of the host to restrict the initial stage of JEV infection in the

central nervous system. Several kinds of furanonaphthoquinone (FNQ) derivatives have antiviral activity against JEV [25].

- ❖ FNQ3 inhibits JEV replication through attacking viral RNA and protein synthesis [26].
- ❖ Aloe-emodin is a potential interferon inducer produced from Chinese herbal medicines and is reported for antiviral activity against JE [26].
- ❖ Kaempferol is a natural flavonol which acts as antiviral agent as it inactivates virus by binding with JEV frame shift site RNA (fsRNA) .

Lactoferrin is a natural anti-microbial protein which attaches to cell surface expressed heparan sulfate, one potential receptor for JEV, and has anti-JEV activity.

CONCLUSION

Japanese encephalitis is a public health problem for the entire world. However, JE is rising throughout Asia, because epidemics are typically noticed only after outbreaks, and because the disease may go largely unobserved in endemic regions. Environmental and ecological factors are responsible for the spread of JEV. There is no specific treatment for JE; only prevention can control the disease. Control may be possible only after developing a strong surveillance system together with a high-quality immunization program. Implementation of a vaccination program for young children, as well as modified agricultural practices, pig vaccination, rigorous monitoring, vector control, and improved living standards can reduce the number of JE case.

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None

CONFLICT OF INTEREST

None declared.

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