Abstract

Japanese Encephalitis is a major public health challenge due to its high epidemic potential, high case-fatality and neuropsychiatric sequel among survivors, JE was first recognized in Japan in 1924. Japanese Encephalitis, a single stranded RNA virus, is a mosquito-borne endemic disease spreaded over large parts of Asia and Pacific regions. In India, it is found in Karnataka. It infects neurons and causes nausea, vomiting, abdominal pain and may lead to paralysis, seizures and coma. It is transmitted by mosquitoes and the infected pigs. Several diagnostic methods and vaccines are available but till date no drugs has been designed for its treatment.

Introduction

Japanese encephalitis (JE), a vector-borne viral disease, is endemic to large parts of Asia and the Pacific regions (Solomon et al, 2006). It is one of the most important arboviral encephalitis in humans, with an estimated 10 million cases over the last 60 years, with 30% case fatality (Mackenzie et al, 2006). Pigs and wading birds are amplifying hosts of the causative Japanese encephalitis virus (JEV), and do not display clinical signs, except for pregnant sows that may abort or have stillborn piglets (Platt et al, 2006). Humans are not part of the natural transmission cycle, hence cannot pass the virus to other hosts (Endy et al, 2000) Japanese encephalitis virus is transmitted naturally between wild and domestic birds, and pig by Culex mosquitoes—the most important for human infection being Culex tritaeniorrhynchus which breeds in pools of stagnant water (such as rice paddy fields) (Innis et al, 1995). In India, the first human case was reported from North Arcot district of Tamil Nadu in 1955(Webb et al, 1956). Japanese encephalitis virus is a mosquito-borne flavivirus which is divided into five genotypes (Uchil et al, 2001), and the virus has been isolated from more than 25 mosquito species, although not all are equally important in the epidemiology of JEV (Leake C et al, 1995). Japanese encephalitis tends to be endemic, and cases occur sporadically throughout the year with a peak after the start of the rainy season (Vaughn et al, 1992).

Infection by Japanese encephalitis virus (JEV), a member of the family Flaviviridae, may cause acute encephalitis with a high mortality rate in humans and induce severe cytopathic effects in various types of cultured cells (Vaughn et al, 1992). JEV is thought to replicate primarily in the cytoplasm and to mature on the intracellular membranes of infected cells. Employing the intrinsic secretory pathways in cells, JEV buds from the membranes of the endoplasmic reticulum (ER) and Golgi apparatus to release mature virions (Rice et al, 1996).

Japanese encephalitis virus (JEV) belongs to the family flaviviridae and genus Flavivirus (Karabatsos et al., 1987). It is a single stranded, positive-sense polarity RNA genome of approximately 11 kb in length. The 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 (Chamber et al., 1990) JEV exists in a zoonotic cycle between mosquitoes and pigs and/or water birds. This study reviewed JEV literature from 2000 to 2010, outlining the Indian scenario, clinical depictions, diagnosis, and the prevention of this deadly disease.

JEV is active over a vast geographic area that includes India, China, Japan, and virtually all of South-East Asia. Approximately 3 billion people live in the JEV endemic area covering much of Asia with nearly 50 000 cases of Japanese encephalitis (JE) reported each year. Of these, about 10 000 cases results in fatality and a high proportion of survivors have serious neurological and psychiatric squeal (Kaur et al., 2003).
General Overview

JE is a major public health challenge due to its high epidemic potential, high case–fatality and neuropsychiatric squeal among survivors, JE was first recognized in Japan in 1924. Since the late 1960s, the size of epidemics in Japan and the People’s Republic of China has steadily declined. In contrast, new epidemic foci of JE were reported in the parts of tropical south-eastern Asia as late as 1969 (Okuno , 1978). Major epidemics were reported about every 10 years, with more than 6000 cases reported in the 1924 epidemic (Miyake et al., 1964). Over the past decade, there has been a pattern of steadily enlarging recurrent seasonal outbreaks in Vietnam, Thailand, Nepal, and India, with small outbreaks in the Philippines, Indonesia, and the northern tip of Queensland, Australia (Kari et al., 2006). Humans become infected when bitten by an infected mosquito and are a dead-end host because of low viremia, preventing the virus from being transmitted further (Solomon , 2004). In endemic areas, the incidence of JE disease is greater among young persons; attack rates in the 3–15-year age group are 5–10 times higher than among older persons (Burke et al, 2001). More than three thousand million people are currently living in areas affected by Japanese encephalitis; of those, one thousand million children are considered at risk (Kurane et al., 2000). The annual number of human deaths is 10,000–15,000, and the estimated global impact from JE in 2002 was 709,000 disability-adjusted life years (DALYs) (WHO, 2004). Tsai estimated that in the absence of vaccination 175 000 cases of JE would occur annually among Asian children aged 0–14 years living in rural areas (Tsai et al., 2000). 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 (Vaughn et al., 1992). 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 (Kabilan et al., 2004). Severe disease progression is rapid and involves frequent episodes of seizure (especially in children) as well as paralysis and coma (Solomon et al., 2002).

The Japanese encephalitis virus was introduced into mainland Australia as recently as 1998 (Hanna et al., 1999). The disease incidence is mainly influenced by vector abundance, which again is determined by several factors including temperature, rainfall, and agricultural practices (Sunish et al, 2001). Approximately 50,000 cases of Japanese encephalitis are reported each year, yet the true incidence is suspected to be significantly higher as many countries lack adequate disease surveillance and reporting systems (WHO, 1998).

Broadly speaking two epidemiological patterns of Japanese encephalitis are recognised (Vaughn et al., 1992). In northern areas (northern Vietnam, northern Thailand, Korea, Japan, Taiwan, China, Nepal, and northern India) huge epidemics occur during the summer months, whereas in southern areas (southern Vietnam, southern Thailand, Indonesia, Malaysia, Philippines, Sri Lanka, and southern India) Japanese encephalitis tends to be endemic, and cases occur sporadically throughout the year with a peak after the start of the rainy season (Vaughn et al., 1992).

The disease gripped Uttar Pradesh, border areas of Bihar and Nepal. During this interval a total of 6097 JE cases with 1,398 deaths were reported (Saxena et al., 2006). Uttar Pradesh was most affected with 5,737 JE cases and 1,334 deaths (CFR 23.3%) and Bihar experienced 360 cases with 64 deaths (CFR 17.8%) (WHO, 2008). Now approaching newer areas such as Papua New Guinea and Australia, it has been classified as new emerging disease (Umenai et al., 1985). JE incidence during the past few years is given in Table 1 (NVBDC, 2009).

Table 1 - Incidence of Japanese Encephalitis in India

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<td>19/64</td>
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<td>204/45</td>
<td>325/95</td>
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<td>13/3</td>
<td>12/10</td>
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<td>19/5</td>
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<td>19/5</td>
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<td>51/10</td>
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<td>Tamil Nadu</td>
<td>88/9</td>
<td>51/11</td>
<td>181/1</td>
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<td>265/8</td>
<td>262/3</td>
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<td>West Bengal</td>
<td>1090/228</td>
<td>606/150</td>
<td>2320/528</td>
<td>320/645</td>
<td>301/537</td>
<td>3079/556</td>
<td>1065/171</td>
</tr>
<tr>
<td>16</td>
<td>Total</td>
<td>174/367</td>
<td>672/1682</td>
<td>2842/658</td>
<td>4074/963</td>
<td>3839/684</td>
<td>4482/774</td>
<td>1896/251</td>
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C, cases; D, deaths; P, provisionally acute encephalitis syndrome cases.
Transmission of Japanese Encephalitis

Japanese encephalitis virus (JEV) belongs to the family *flaviviridae* and genus *Flavivirus* (Karabatsos, 1985). Viruses from several families can infect neurons in the CNS (Central Nervous System) and the study of gene expression changes in the CNS during virus infection can lead to identification of new genes whose function is essential either for the promotion or prevention of virus infection (Johnston et al., 2001). Japanese encephalitis virus (JEV), a neurotropic one commonly affects children and is a major cause of acute encephalopathy (Chen et al., 2002). In an urban area, the vector *Cx. tritaeniorhynchus* has been shown to increase in number by the presence of pigs, whereas the number of another vector, *Culex quinquefasciatus*, increases by the presence of humans (Lindahl et al, 2012). 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* (Kanojia et al., 2003). In Asia, pigs are considered to be the most important amplifying host, providing a link to humans through their proximity to housing (Kabilan et al., 2004). Among the medically important flaviviruses, JEV infection has the highest mortality rate of 30-50% (Tsai et al., 2000) and remains as a major public health problem in several parts of Asia. The life cycle of the virus is illustrated in Fig. 1 (Tiwari et al., 2012).

Symptoms

Infection due to JEV is most often asymptomatic (Solomon et al., 1997). The initial presentation in children usually begins with gastrointestinal symptoms: nausea, vomiting, and abdominal pains similar to those found in an acute abdominal syndrome (Burke et al., 2001). These may include confusion, paralysis, Parkinsonian movement disorders, abnormal posturing, seizures, and coma (Solomon et al., 2002). A proportion of patients with JE have an acute flaccid paralysis that is easily mistaken for poliomyelitis (Solomon et al., 1998), but the majority present with a reduced level of consciousness, often heralded by generalized convulsions. The duration of the coma is associated with repetitive seizures, peduncular damage, or intracranial hypertension, which are considered poor prognostic factors, leading to fatality (Dung et al., 2002).

JE Virus: Overview and its structure

The JEV genome is single-stranded positive-sense RNA of approximately 11 kb in length and contains both 50 and 30 untranslated regions (Vrati, 2000). The 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 as shown in Fig-2 (Chambers et al., 1990).
The structural proteins constitute the viral particle while the nonstructural proteins are involved in viral RNA replication, virus assembly, and modulation of the host cell responses (Lindenbach et al. 2007). The fusion process is mediated by the Japanese encephalitis virus E protein in a pH-dependent manner (Stiasny et al., 2006). The Japanese encephalitis virus E protein consists of three domains: central domain I, extended fingerlike domain II, and immunoglobulin-like domain III (Luca et al. 2012).

JE predominately affects the thalamus, anterior horn cells of the spinal cord, cerebral cortex, and cerebellum (Tiroumourougane et al., 2002). JEV is thought to replicate primarily in the cytoplasm and to mature on the intracellular membranes of infected cells. Employing the intrinsic secretory pathways in cells, JEV buds from the membranes of the endoplasmic reticulum (ER) and Golgi apparatus to release mature virions (Rice et al., 1996). One of the major morphological changes in JEV-infected cells, as well as in cells infected by other flaviviruses, is proliferation and hypertrophy of the rough endoplasmic reticular (rER) membranes, where virus particles accumulate (Monath et al., 1996). A myriad of factors govern the severity of JEV pathogenesis (King et al., 2007).

Fig 3-Events that lead to the establishment of JE pathogenesis

The failure of the host to produce antibodies against the virus is associated with an increased likelihood of the disease to turn lethal (Burke et al., 1985). Crossing the blood–brain barrier is an important factor in the increased pathogenesis and clinical outcome of the neurotropic viral infection (King, 2007). After entering the body through a mosquito bite, the virus reaches the central nervous system (CNS) via leukocytes (probably T lymphocytes), where JEV virions then bind to the endothelial surface of the CNS and are internalized by endocytosis (Mathur et al., 1989); however, it is still not clear whether macrophages and B lymphocytes can also harbour JEV. In other flaviviral infections, such as WNV, macrophages could serve as a reservoir, spreading the virus from the peripheral areas to the CNS (Rios et al., 2006). Studies have shown that WNV is capable of entering the CNS through anterograde axonal transport (Hunsperger et al., 2006). Because both WNV and JEV belong to the same family of viruses (Mishra et al., 2006), macrophage and axonal transport may play a critical role in JEV pathogenesis; however, convincing evidence is still lacking. T lymphocytes and IgM play a major role in the recovery and clearance of the virus after infection (Burke et al., 1985).

The molecular pathogenesis of JEV infection is still unclear. It is known that JEV causes neuronal cell death in two ways—direct neuronal killing (Raung et al., 2001), wherein viral multiplication within neuronal cells leads to cell death, and the indirect mode of killing, wherein massive inflammatory response causes an up-regulation of reactive oxygen species and cytokines such as tumour necrosis factor a (TNFa), which, in turn, causes neuronal
death (Ghoshal et al., 2007). The key factor in indirect neuronal cell death during JE is the uncontrolled over activation of microglia cells (Ghoshal et al., 2007), which release proinflammatory cytokines such as interleukin 6 (IL-6), TNFα monocyte chemotactic protein 1 (MCP1), and RANTES (regulated upon activation, normal T cell expressed and secreted), promoting massive leukocyte migration and infiltration into the brain (Chen et al., 2004). The production of interferon-c-inducible protein 10 (IP-10) by activated astrocytes also contributes to the infiltration of natural killer cells and monocytes, among others (Bhowmick et al., 2007). Although nitric oxide (NO) plays an important role in inflammation during JE infection, NO itself is a very strong antimicrobial agent, and researchers have shown that it profoundly inhibits viral RNA synthesis, viral protein accumulation, and virus release from infected cells (Lin et al., 1997).

The ability to obtain high-resolution structures of viral components and inhibitory compounds using computational approach suggests that powerful structure-based approaches could rapidly focus the development of highly efficacious compounds (Singh et al. 2013). Plant-derived flavonoids and dietary isoflavones, a large group of naturally occurring phenylchromones found in fruits, vegetables, tea, soy foods, and herbs, have been shown to possess potential therapeutic benefits in a variety of viral infections using both in vitro or in vivo models (Nielsen et al., 2007).

**Diagnosis**

Organization (WHO) has drawn up surveillance standards for the detection of JEV, recommended case definitions of JE, and set up criteria that are to be fulfilled to diagnose a case as JE (Solomon et al., 2008). IgM capture ELISA has been the most widely used diagnostic method for JE detection (Burke et al., 1982). At present, much advancement has been achieved in methods for the early detection of JEV; examples are the dipstick method (Shrivastva et al., 2008), JEVCheX (Ravi et al., 2006), and reverse transcriptase PCR (Swami et al., 2006).

**Treatment**

Interferon therapy has not met with great success (Solomon et al., 2003). A recent clinical trial of oral ribavirin administration was also not encouraging (Kumar et al., 2009). Naturally occurring compounds such as arctigenin, a phenylpropanoid dibenzylbutyrolactone lignan, and rosmarinic acid, a phenolic compound found in various Labiatae herbs, render protection to mice against JEV of the GP78 strain by markedly decreasing JEV-induced neuronal apoptosis, microglial activation, active caspase activity, and induction of proinflammatory mediators in the brains of the infected animals (Swarup et al., 2008). Glucosidase inhibitors of the endoplasmic reticulum, such as N-nonyl- deoxyxojirimycin, which block the trimming step of N-linked glycosylation, have been shown to eliminate the production of several endoplasmic reticulum–budding viruses, including dengue type II (DEN-2) and JEV (Wu et al., 2002).

Currently there is no specific treatment for the disease. In vitro utility of isoquinolone compounds (Takegami et al 1998) and monoclonal antibodies in animal models (Gupta et al 2003) have been demonstrated. Recently treatment with salicylates and non-steroidal anti-inflammatory drugs has been found to suppress the in vitro JEV replication and prevent apoptosis of the virus infected cells (Chen et al., 2002). Treatment with glycoprotein, interferon-α is the most promising anti-viral candidate. It is produced naturally in CSF of the patients with JEV infection (Burke et al 1987). However; in a completed double-blind placebo-controlled trial, no improved outcome in JE patients has been observed with IFNa-2a treatment in 112 Vietnamese children with suspected JE, 87 of whom had serologically confirmed infections (Solomon et al 2003).

There is no cure for JE and treatment is mainly supportive. Patients are not infectious, but should avoid further mosquito bites (Lam et al., 2005). A number of antiviral agents have been investigated, including INF alfa-2a68 and diethyldithiocarbamate (a low molecular weight dithiol) (Solomon et al., 2003). However, none of these have convincingly been shown to improve the outcome of JE. Effective supportive management has been shown to improve the outcome (Tiroumourougane et al., 2002). The standard management of viral encephalitis should be used (Bossi et al., 2004). Mannitol might be used to reduce intracranial pressure. A significant research on minocycline as an anti-JEV drug is an in vivo study that showed that minocycline reduces neuronal apoptosis, microglial activation, active caspase activity, proinflammatory mediators, and viral titre markedly on the ninth day after infection (Mishra et al., 2008). Another compound that has shown inhibition of JEV replication completely in vitro is an N-methyl isatin-b thiosemicarbazone derivative (Sebastian et al., 2008).
Immunization
To prevent JE, it is necessary to implement a large-scale immunization of the susceptible human population. Vaccination provides active immunity against JEV. There are several groups of vaccines which are currently in use: purified, formalin-inactivated mouse-brain derived, cell-culture derived inactivated, and cell-culture derived live attenuated (Diagana et al., 2007) Formalin-inactivated vaccines have been safe and effective against JEV for at least 30 years (Tsai et al., 1998) Of these, the most widely produced and internationally distributed is the mouse-brain derived inactivated vaccine. The efficacy and the strain from which these are produced are given in Table 2(Sarika et al., 2012).

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<tr>
<th>Vaccine</th>
<th>Strain</th>
<th>Efficacy</th>
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<tr>
<td>Inactivated mouse brain</td>
<td>NakayamaBeijing-1</td>
<td>91%</td>
</tr>
<tr>
<td>Inactivated primary hamster kidney cell</td>
<td>P3</td>
<td>85%</td>
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<tr>
<td>Live attenuated primary hamster kidney cell</td>
<td>SA 14-14-12</td>
<td>&gt;95%</td>
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Table 2: Vaccines against Japanese Encephalitis.

Researchers have also constructed the yellow fever virus to express JEV protein, the most promising recombinant vaccine under development. It is widely known as Chemeri-Vax-JE, in which the structural protein (PrM and E) of the JEV SA14-14-2 strain was inserted into YF17D (Monath et al., 2002).

JE Vaccination in India
The JE vaccination campaign was launched during 2006 wherein 11 of the most sensitive districts in Assam, Karnataka and Uttar Pradesh were covered. Altogether, 86 JE endemic districts in the states of Assam, Andhra Pradesh, Bihar, Haryana, Goa, Karnataka, Kerala, Maharashtra, Tamil Nadu, Uttar Pradesh, and West Bengal have been covered. Reorientation training course on AES/JE case management is a continuing process. Such orientating training courses were carried out in Andhra Pradesh, Assam, Haryana, Karnataka, Tamil Nadu, Uttar Pradesh, and West Bengal during 2008 and 2009(NVBDC,2009).

Other JE vaccines under development
Several vaccines are still in various stages of development. These include: recombinant protein based vaccines, recombinant virus based/chimeric vaccine, and DNA vaccines. Second generation recombinant vaccines are in development with the aim of improving immunogenicity and decreasing adverse reactions (Tiroumourougane et al., 2002).

Adverse reactions
There are several side effects of JE vaccination. Local side effects include tenderness, redness, and swelling. Sometimes systematic adverse reactions are also noted after vaccination, such as headache, myalgia, abdominal pain, or skin rash (Diagana et al., 2007). Occasionally local hypersensitivity reactions (erythema or edema at the injection site) can be observed in some children. Other reactions, such as generalized urticaria, facial angioedema, and respiratory distress have been reported in a few people from non-endemic zones after vaccination (Diagana et al., 2007). Some recipients of the vaccine had, very rarely, major neurological side effects (1 to 2.3 per million recipients: encephalitis, seizures, and peripheral neuropathy (Solomon et al., 1997).

Future Prospects
Flaviviral drug research is moving at an expeditious pace. We are hopeful that a dependable chemotherapeutic agent will soon be at hand to abrogate the flaviviral diseases. Fortunately, although JEV is presently under the radar of big, ambitious drug-design projects, owing to the conserved nature of the flaviviral proteins, research that has concentrated on WNV,hepatitis C virus (HCV), dengue virus (DENV), and others could be extrapolated to come up with a JEV-specific drug design. Efforts are being channeled into the design of a future drug against the NS2B and NS3 nonstructural proteins of flaviviruses such as WNV. This design focuses on crucial
physicochemical and biochemical properties of proteases by using crystallography-based models of NS3 substrate interaction compounds (Bessaud et al., 2006). Scientists are also trying to target the flaviviral capping enzyme (Chanprapaph et al., 2005).

The E and NS5 proteins of flaviviruses are also a very promising target for future drug designs. Research has elucidated the crystal structure of the enzymatically active domains of these proteins’ inhibitor to understand its biochemical properties, subcellular localization, and regulation, thereby helping to design specific inhibitors that would alter the kinetics of these proteins and thus viral production (Malet et al., 2007). Finally, studies revealed that different classes of compounds such as flavonoids, alkaloids, polysaccharides, thiophenes, terpenoids, lectins, and lignans, isolated from various plants, have different antiviral properties and target viral inhibition (Jassim et al., 2003).

References


