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Japanese encephalitis: A review

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Abstract
Flavivirus which is produced in mosquitoes is responsible for infection in humans and horses. Pregnant infected sow shows no symptoms and signs of infection in pregnancy, while pigs demonstrate abortions and stillbirths. In nature JEV is amplified in wild creatures like pigs, birds and mosquitoes. *Culex tritaeniorhynchus* species, a mosquito vector of JEV is wide spread in various parts of Asia. Horses and humans are called as dead-end hosts because they do not transmit virus to mosquitoes by its bite. Japanese Encephalitis virus is most commonly found in south-eastern and southern countries of Asia, Northern Australia, Papua New Guinea and Indonesian Archipelago.

Keywords: Japanese encephalitis, *Culex tritaeniorhynchus*

Introduction
In Asia encephalitis is caused by Japanese Encephalitis virus which belongs to family Flaviviridae. Decades ago Poliomyelitis causing polio in children was the major disease but now a day's JEV has replaced it and the major cause of disabilities during childhood in Asia (Halstead and Jacobson, 2003). Each year about 68,000 people are affected with this virus. It is the endemic disease of Pacific and Asian regions. For travelers to Asia the risk of the disease is less than 1 case from 1 million but it can vary according to season and duration of travelling (Fischer *et al.* 2010) [7].

Virology
The structure of JEV is like other viruses as St.louis and west Nile virus,belongs to genus flavivirus. This is RNA virus in which 11Kb single stranded RNA of 3800 KD is enveloped inside of the lipoprotein made capsid. The capsid protects virus, acts as an antigen and helps in injecting the RNA into the host cell. Non-structural proteins or enzymes are also encoded by inner RNA core (He B, 2006) [14].
Non-structural protein includes helicase enzyme and polymerase enzyme which are produced by NS3 and NS5 regions. By JEV endoplasmic reticulum's lumen is infected and filled with viral proteins (Su *et al*., 2002) [36]. There are five types of JEV based on the type of gene forming its envelope.

Geographical Distribution of virus
Disease of Japanese encephalitis is spreading on large scale from last 50 years. The presence of disease in an area can be diagnosed from its first time impression in particular area. Diagnosis of disease for the first in different countries is given below.

Table 1

Country Name	First time diagnosis/ Isolation Date
China	1935 and 1940 (Vaughn and Hook, 1992) [41]
Eastern Russian States	1938
South Korea	1949
Northern Vietnam	1965
Northern Thailand	1969
Southern India	1955
Bangladesh and Burma and Southwestern Nepal	1970s (Khan et al., 1981) [23]
Sri Lanka	1985 (75 deaths out of 410 cases)
Pakistan	1980s (Igarashi *et al.*, 1994) [19]
Katmandu Valley of Nepal	1990s (Zimmerman *et al.*, 1997) [41]
Pacific Islands (Guam)	1947 (Hammon *et al.*, 1958) [11]
Saipan	1990 (Paul *et al.*, 1990) [32]
New Guinea and Philippines	1995 (Hanna *et al.*, 1993) [12]
Australia	1998 (Anonymous, 1998) [2]

Identification of Virus
Like other zoonotic viruses like kunjin virus, Murray Valley encephalitis virus and St Louis encephalitis virus Japanese encephalitis serocomplex is found in japanese encephalitis virus. By the use of different techniques like fingerprints of viral RNA (Banerjee & Ranadive, 1989; Hori *et al.*, 1986) [4, 17] haemagglutination inhibition, complement fixation and neutralization tests using monoclonal and polyclonal antibodies the genetic and antigenic differences among Japanese encephalitis virus have been identified (Ali &

Igarashi 1997; Banerjee, 1986; Hale & Lee, 1954; Hasegawa *et al.,* 1994; Kimura-Kuroda & Yasui, 1986) [1, 5, 9, 13, 24]. The phylogeny of virus can be studied through the gene analysis of viral envelope. The envelope analysis is representative of JEV's phylogenetic analysis. Based on envelope gene five different kinds of Japanese encephalitis virus have been identified (Solomon *et al.,* 2003; Uchil & Sachidanandam, 2001; Williams *et al.,* 2000) [34, 39].

Analysis of disease

The disease can be identified by the separation of virus from horse body. As the virus is highly unstable under some environmental conditions like antibody presence, so virus is isolated in least in dead or infected horses. Pathology and serology has also assisted in analysis of disease. ELISA technique is also used in diagnosis of antibodies in cerebrospinal fluid (Burke *et al.,* 1985) [6]. Reverse transcription Polymerase chain reaction is also helpful in nucleic acid detection of virus in the brains of diseased horses (Lian *et al.,* 2002) [26, 27, 36].

Thalamus or Cortex of brain, spinal cord, blood and some parts of corpus striatum of horses are used for virus collection. After collection the specimen is cooled at -80°C for about 48 hours. The material should be handled safely to reduce the risk of human infection. Human infectious materials are mucous membranes, aerosol and broken skin. Vaccines are also available against JEV. Presence of antibodies (IgM) in cerebrospinal fluid and serum are the representatives of this virus and detection is possible by ELIZA or indirect fluorescent antibody staining. (Shrivastva *et al.,* 2008) [33].

Symptoms of the disease

Symptoms of the disease may range from severe to mild and non-specific to specific. Severe headache with vomiting, nausea, diarrhea, coryza, gastrointestinal illness, chills, fever, muscle aches are the initial non-specific symptoms of the disease. In some people recovery is possible after this non-specific stage while in others neurological disorders are also seen which grow gradually after the first exposure to that viral antigen. Neurological symptoms of disease are coma, lack of consciousness, changes in behavior, hemiplegia, and cerebellar disorders quadriplegia, Parkinson's disease like symptoms, severe convulsions, and stiffness of neck which is very painful. Flaccid paralysis like polio, behavioral psychiatric disorders is also seen rarely. In some cases upper gastrointestinal hemorrhage and pulmonary edema is also seen. Recovery from the disease is time consuming though some patients show rapid recovery response still about 50% survivors suffer from syndromes like Parkinson and epileptic seizures, language, behavioral and cognitive destruction. Pregnant women who are first time exposed to this virus have shown miscarriage cases (Thomas *et al.,* 2010) [37].

Vaccines against Japanese encephalitis virus

The first vaccine formed against JEV was developed by china named as SA14-14-2. This vaccine approved to be safe cheap and efficacious (Xin *et al.,* 1988) [40]. This vaccine showed no side effects in about 600,000 children vaccinated by this (Ma *et al.,* 1993) [28]. In the people of affected village 1300 cases were observed and vaccinated, in 80% cases the vaccine showed positive effect with single dose while in 98% cases the vaccine showed positive effects with two doses (Hennessy *et al.,* 1996) [15]. Now days a chimeric vaccine is under development in which E genes and PrM of Japanese encephalitis virus SA14-14-2 stain were inserted into 17D yellow fever infectious clone of vaccine strain. Chimeric virus was found to be safe in primates except humans and mice because they can grow resourcefully *In vitro* (Monath *et al.,* 2000).

For any reduction in vaccine activity at least three amino acids of E proteins should be changed (Arroyo *et al.,* 2001). To deliver Japanese encephalitis virus structural genes vaccinia virus strain can also be used. The humans who are already vaccinated with vaccinia will not show the symptoms of JEV because their immune system has developed vaccines against that pathogen JEV (Kanesa-thasan *et al.,* 2000) [21].

Pathogenecity of Virus

Serum studies of Patients blood from the Asia which is endemic to that disease have shown that 1 person from 300 is affected by this virus during their childhood (Aaughn and Hoke, 1992) [42]. Japanese Encephalitis strains are different from each other due to neurovirulence and neuroinvasiveness in model animals. Some are more virulent than others. Japanese encephalitis strains neurovirulence is directly proportional to viremia (Huang and Wong, 1963; Ni and Barrett, 1996) [18, 29]. The change in virulence is due to the changes in non-coding, nonstructural and structural regions of amino acid and nucleotide sequences. The deletion of even a single amino acid from E protein can cause loss of virulence (Ni *et al.,* 1994, 1995). Pathogenesis is possible either through attachment of virus to its receptors or through fusion of host and viral cell membranes. Receptor for binding is present on the domain III of envelope protein having the residues of aspartate, glysine and arginine which enhance their sensitivity and virulence after attachment (Holzmann *et al.,* 1990; Lee and Lobigs, 2000; Ni and Barrett, 1996) [16, 25, 29].

Latest Trends of Japanese Encephalitis Virus

There are two factors involved in the emergence or spreading of the disease.

1. The population of countries where this disease is endemic is increasing day by day. Southeast, South-central and Eastern Asia is its endemic region and the population size has been increased from 1.7billion in 1950s to 3.5 billion in 2000 (UN 2005) [38].
2. Pig and irrigated rice production has been increased. These are two important factors involved in the growth and production of disease. Pork production in china has been doubled from 1990 to 2005, the production of rice is increased 22 %(226 million tons to 529 million tons) in 40 years and area of rice fields is 1,345,000 km^2 (Keiser *et al.,* 2005).

This disease can be controlled by controlling world population, rice irrigated areas and pork production. The rice irrigated areas are India, Bangladesh, Thailand, Myanmar, Cambodia and China. Pork oroducing areas are Vietnam, China and Myanmar while it is produced in least quantity in Japan, North Korea and Malaysia (FAO, 2008).

Conclusion

Japanese Encephalitis is the most common disease of childhood, found in countries where the season is rainier and rice is cultivated in large quantities. Vaccines are the best

remedy to get rid of disease. Its emerging rate is increasing day by day through rice paddies and pigs.

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