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An Epidemiological Review on Japanese Encephalitis

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Abstract Japanese encephalitis (JE) is one of the most deadliest metazoonotic diseases world wide, specially in South East Asia. In WHO's report, high mortality has been recorded for JE, specially for children of age group 3 to 6 years. Flavivirus causes the disease with vector *Culex tritaeniorhynchus* mosquito. In rainy season , this disease show hink. Animals also suffer in this disease and swine act as reservoir host and facilate the zoonotic cycle. Besides detection of viral antibody, cell culture technique, virus neutralization test (VNT) and other molecular technique can be followed for diagnosis. Vector control is the main preventive measures along with vaccination in endemic regions. To combat JE multidisciplinary approach is needed.

Keywords JE, Metazoonosis, Culex, VNT, Vector control.

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Introduction

Japanese encephalitis (JE) is a common Flaviviral metazoonotic disease. It is one of the leading forms of viral encephalitis worldwide, mostly prevalent in Eastern and South Eastern Asia, covering a region with a population of over three billion. Although under reported, an annual estimates of JE are 50, 000 cases with 15, 000 deaths approximately through Asia Tsai (1997) with 5-35% case fatality rate and a 75% JE related disability rate (767,000 DALYs, WHO 2002). The disease bears significant public health importance due to high epidemic potential and high fatality rate. Children of 3 to 6 years of age, are the most targeted victims in the endemic areas Hoke et al. (1992) and neuropsychiatic sequelae becomes companion to helf of the survivors from the disease (Solomon et al. 2000).

History, Worldwide Scenario and Indian Perspective

After first recognition of JE from Japan in 1871, the first outbreak was occurred in Tokyo metropolitan (Buescher 1956). However, three epidemiological regions can be distinguished namely the endemic region (Southern India, Southern Vietnam, Southern Thailand, Philippines, Malaysia and Indonesia), the intermediary subtropical region (Northern India, Nepal, North and Central Burma, Northern Thailand, Northern Vietnam, Southern China and Bangladesh) and the temperate epidemic region (spanning Northern China, Korea, Japan, Taiwan and Southern extre-

mities of Russia) (Tiwari et al. 2012).

In India, the first case of JE was reported from North Arcot district of Tamil Nadu in 1955 followed by 65 cases from South India in between 1955-56 (Carey et al.1968). Whereas in Northern India, 6,000 children died of encephalitis since the first detection of JE in 1978. In the year 2005, a massive outbreak of JE was reported from Eastern Uttar Pradesh resulting approximately 6000 cases and 1500 deaths which led to a major decision to introduce vaccine in highly endemic areas in very next year (Chakraborty et al. 2015).

In recent time, major outbreaks of encephalitis were reported in North-Eastern India with 7463 cases reported by Kaur et al. (2012). The Eastern India with North Eastern states and WB, the disease is epidemic, since 1972. The first outbreak of encephalitis was observed in West Bengal in 1973, where 325 numbers of deaths out of 763 cases of encephalitis (Chakravarty et al. 1975). The disease is endemic in Assam, Manipur and Nagaland.

Epidemiology

Agent

Japanese encephalitis virus belongs to the family : *Flaviviridae* and genus : *Flavivirus* (Karabatsos 1985). It is a single-strand positive sense polarity RNA virus with approximately 11kb genome length (Tiwari et al. 2012). Japanese encephalitis virus is a member of a viral complex containing three other viruses : St. Louis encephalitis virus, Murray Valley encephalitis virus and West Nile virus (Mackenzie et al. 2004). It contains three structural protein—nucleocapcid or core protein (C), non-glycosylated membrane protein (M) and glycosylated envelope protein (E). There are 7 non-structural (NS) proteins-NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS 7 (Weaver and Barrett 2004). These are translated as a single ORF and co-or post-translationally cleaved.

Host

A number of animals such as cattle, sheep, dogs, cat, chickens, ducks and and reptiles are infected by JEV in natures subclinical and do not contribute in the transmission cycle (Pant et al. 2006). Human gets infection accidentally when bitten by infected mosquitoes (Acha and Szyfres 2003). Pigs are the key reservoir hosts due to high viraemia and their close proximity with people of low socio-economic groups facilitates the disease to be a zoonotic one particularly in Asia (Kabilan et al. 2004). Seroconversion in pigs generally produces human cases. Cattle do not develop enough viraemic state to infect mosquitoes and act as damper to infection and reduce risk to humans. Horse and human beings is the deadend host with a very low titre during viraemia (Solomon 2006). Bats are also found to be seropositive for JEV (WHO 2006).

Vector

The JEV is transmitted by mosquitoes to different vertebrate hosts. The virus is transmitted by mosquitoe species *Culex tritaeniorhynchus* (Mitamura et al. 1938, Ishii 1986). However, other secondary vectors may also play an important role in the transmission. Indian studies in particular revealed a number of secondary mosquito vectors including *Mansonia indiana*, *C. pseudovishnui, C. whitmorei, C. gelidus, C. epidesmus, Anopheles subpictus, A. peditaeniatus* and *M. uniform* (Kanojia et al. 2003). In recent time, *C. bitaeniorhynchus* was reported to cause viral encephalitis in republic of Korea (Kim et al. 2011). The female mosquitoes feeding on infected viraemic patient, remain infected lifelong (WHO 2006).

Environment and Ecology

The transmission of JE involves a complex epidemiological triad which includes host, agent and vector with ecological balance. In Northern temperate areas, large epidemics occur during the summer moonths (May to October) (Tsai et al. 1999). In Southern tropical areas, JE tends to be endemic; though cases occur sporadically throughout the year, a peak is generally observed just after the starting of the rainy season (July to September) (Vaughn and Hoke 1992). The araeid birds like cattle egrets and pond herons are the natural reservoir of the virus and play a definite role in maintenance of JEV in nature (WHO 20006). The

vertical transmission of JEV in mosquito vectors have been well documented (Rosen et al. 1989). However, person to person transmission has not been reported (Park 2005). The JEV can also be transmitted through infected boar semen (Guerin and Pozzi 2005).

In Asian countries, the paddy field ecology influences the complete cycle of JEV with suitable temperature and humidity (Diagana et al. 2007) for breeding of mosquitoes and farmers are the most vulnerable group of people. Close proximity of pigs to human community under unhygienic environment results in zoonotic transmission of JE in poor Asian countries.

Diagnosis

For diagnosis of JE, laboratory detection of viral antibody coupled with history and clinical features are required (WHO 2007). Virus isolation is the best diagnostic technique, however it needs equipped laboratory. Most desirable sample for virus isolation is CSF for live patients while blood, serum, CSF, brain and spinal cord for equines and blood and aborted foetus in pigs can also be useful (Himani et al. 2014). In case of human, blood of the patient who is in the preneuroinvasive and neuroinvasivephase (within one week from the onset of symptoms) can be used for virus isolation (Tiroumourougane et al. 2002). Culture of the virus can be done in primary chick duck embryo cells and other cell lines like Vero, LLCMK2, C6/36 (insect cell line), PK and AP61 (Tiwari et al. 2012).

Different serological tests viz., plaque reduction neutralization test (PRNT), hemagglutination inhibition test, virus neutralization test (VNT), enzyme linked immunosorbent assay and latex agglutination assay can be employed for diagnosis of JE in animals (OIE 2010). However, PRNT/VNT is gold standard and is recommended over ELISA as to avoid any confusing cross reactions (WHO 2007). Now-a-days, lateral flow assay is also used for quick diagnosis (Peter 2012). Modified techniques like detection of antigen in mononuclear cells from CSF or peripheral blood of patients can be used (Deng et al. 1994). Staphylococcal coagglutination test using polyclonal or monoclonal antibody is also another rapid diagnostic technique (Raghava and Badrinath 1998).

Molecular detection is the most effective method for diagnosis. RT-PCR is unique method to detect viral genome from tissue (brain), CSF or blood (Lian et al. 2002, Swami et al. 2008). For large sample size, the method is very useful and time saving . For surveillance study of JEV , RT-LAMP assay can be applied (Chen et al. 2011). Recent researches revealed that the rRT-PCR on peripheral blood mononuclear cells can detect the recent and latent infections more accurately than IgM MAC-ELISA (Kakkar et al. 2014).

Prevention

To prevent and control this vector borne viral encephalitis, prevention strategies such as vector control, controlling ecology by limiting the amplifier host and immunization of human and amplifier hosts and surveillance program may be employed. Proper immunization among young children, modified agricultural practice, vaccination of pigs and intense monitoring are needed for effective control of JE (Tiwari et al. 2012). In India, National Vector Borne Disease Control Program (NVBDCP) has developed surveillance and case management guidelines for syndromic reporting of Acute Encephalitis Syndrome (AES) including JE (Operational Guideline, NVBDCP 2014).

Vector control is the key preventive measure for JE. The vector (mosquitoes) of JE is widely scattered and not easy to control. An effective way to control the mosquitoes is to aerial or ground fogging with ultra-low-volume (ULV) insecticides (e. g. fenitrothion, malathion). Insecticide and use of bed net is widely accepted to get protection from mosquitoes in endemic areas (Tiroumourougane et al. 2002). However, unscientific abuse of insecticides has been leading to the resistance developed by the mosquitoes. Rotational irrigation of rice field is very helpful to reduce the mosquito population (Keiser et al. 2005). Uninfected villages falling within 2-3 km radius of the infected villages should also receive insecticide spraying as a preventive measure.

Different types of vaccines are available which are currently in use : Purified, formalin-inactivated mouse-brain derived, cell-culture derived inactivat-

ed and cell-culture derived live attenuated vaccines (Diagana et al. 2007). Efficacy of the vaccines is dependent on epidemiological aspect of different geographical areas along with economic aspects of the JE control program.

(a) The mouse brain-derived, purified and inactivated vaccine is used in Asian countries, which is made by Nakayama or Beijing-1 strain, the only vaccine approved by WHO (Tiwari et al. 2012) with high seroconversion rate of 80-90% and protective efficacy of 90%. The Central Research Institute, Kasauli, Himachal Pradesh manufactures the vaccine in lyophilized form in India (Bharati and Vrati 2006). (b) Inactivated hamster kidney cell-culture-derived JE vaccine is made by Beijing P-3 strain (Diagana et al. 2007) and protective efficacy is 76-90% (Tsai et al. 1999). (c) The cell culture derived live attenuated vaccine named SA 14-14-2 strain of JE virusis prepared by passaging the SA 14 strain of JEV in PHK cells (Tiwari et al. 2012) and has shown an efficacy of 98% in Nepal (Ohrr et al. 2005).

Conclusion

Japanese encephalitis is a public health concern which cannot be managed by only medical practioners. A multidisciplinary approach is much needed with contributions of physicians, veterinarians, epidemiologists, sanitary experts, agricultural specialist and meteorologist. According to the one health concept, welfare of animals and human being has to be done with proper balance in environment and JE is such a kind of infections vector borne disease, that all of us have to combat it.

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