Review Article

Current Progress and Future Perspectives of Controlling Japanese Encephalitis Virus

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Abstract | Japanese encephalitis (JE) is an arthropod-borne disease causing dreadful central nervous system signs and high mortality in adults and children. It is caused by the JE virus (JEV), which belongs to the family Flaviviridae. JEV is endemic to many parts of East Asia, Southeast Asia and Australia, where periodic outbreaks take thousands of lives. With rapid globalisation and climatic shift, JEV has started to emerge in previously unaffected areas. Scientific evidences show that JEV would remain a global pathogen and might cause worldwide pandemics. Currently, more research is required to be applied to JEV pathogenesis and antivirus therapy. This review aims to reveal the exigency of developing a worldwide effort to acknowledge the importance of performing an extensive study of this deadly disease.

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Introduction

JE is one of the most important arboviral encephalitis in the world with high incidence, mortality, and morbidity, which is transmitted to man by culicine mosquitoes. It is a zoonosis and the basic cycles of transmission involve the mosquito, pig, and ardeid water birds, with man acting as an incidental dead-end host, with more than 50,000 new cases and about 15,000 deaths occurring annually in the world (Zheng et al., 2012; Nemeth et al., 2012).The causative agent JEV is a single stranded positive sense RNA virus belonging to family Flaviviridae. It is one of the major causative agents of pediatric encephalitis or viral encephalitis in East Asia, Southeast Asia and Australia (Xu et al., 2013). Since the first epidemic in Japan in the 1930s, the prevalence area of JE has been increasing in the past 80 years and now JE become prevalent across several tropical and temperate regions, including countries in southern, southeastern, and eastern Asia, the Pacific rim, and northern Australia and the Australian mainland. In developed Asian countries such as Japan, Taiwan, South Korea and China, JE incidence has dropped considerably as a result of carry out vaccination campaign, vector control, improved agricultural practices and pork farming, and overall improvement in sanitation. However, there are still more than 10,000 cases being reported annually from China (Zheng et al., 2012). Although the current vaccine can reduce the incidence of JEV infection, the virus is still spreading beyond its traditional boundary (Endy and Nisalak, 2002). There is an utmost need for the development of epidemiology, infection mechanism, novel diagnostic technology

and antiviral therapy to provide effective measure to the patients. Hence, the present review aims to discuss the currently research involving in JEV enzootic cycle, genotypes, infection pathway, clinical manifestation and control, etc. for better preventing and controlling JE disease and its related disorders in the future.

Enzootic cycle of JEV

It has been reported that bats and water birds such as herons, egrets, and other ardeid birds are the most important hosts of JEV, moreover pigs are main reservoir for disseminating JEV and acted as important amplifier hosts because of high-titer viremia during infection. Both pigs and birds are considered main component in the transmission cycle with respect to human infection (Ghosh and Basu, 2009). JEV infection in other domestic animals does not result in high viremia and some of these animals would have low or high level antibodies by natural infection, so they are not expected to transmit the virus to humans. In the same way, man-to-man transmission does not occur because of transient low-level viremia in humans.

JE tends to be endemic, with peak cases appearing during June to Sept each year (Kant Upadhyay, 2013). Human infections are mainly spread by Culex tritaeniorhynchus which breeds in pools of stagnant water. The mosquito salivary gland plays important roles in JEV transmission and JEV could replicate in the salivary glands of the mosquitoes. Mature JE virions remain entrapped in intracellular vacuoles and are later released into the apical cavity of salivary gland cells through the fusion of these vacuoles with the apical plasma membrane. Another way of virus shedding is directly through the apical plasma membrane (Dutta et al., 2010a).

JEV Genotypes

Five JEV genotypes have been identified based on the nucleotide sequence of viral envelope E capsid C, membrane M genes (Li et al., 2011). Genotypes I, II, and III are distributed all over the geographical area of Asia, while genotype IV is restricted to Eastern Indonesia. The genotype V strain of JEV was first isolated in Singapore from a patient who originated from Malaysia (Uchil and Satchidanandam., 2001) and it has most genetically different from other JEV genotypes (Mohammed et al., 2011). Genotype V has isolated form Malaysia, China and the Republic of Korea. As suggested by Solomon et al. (2003), JEV have originated from the oldest JEV lineage (Genotypes IV and V) which have only be found in Indonesia-Malaysia region, and later JEV has spread from this region across Asia. It was classically accepted that Genotypes I, II, and III accounted for 98% of the strains isolated since 1935 (Le Flohic et al., 2013; Chen et al., 2013).

Pathway of JEV invasion

The actual mechanism of JEV reaches the central nervous system (CNS) is not entirely clarified. There a repossibilities that JEV is amplified in dendritic cells (DCs) and Langerhans cells of the skin through a mosquito bite. Then JEV invade the CNS via leukocytes, where JEV virions bind to the endothelial surface of the CNS and are internalized by endocytosis (Johnston et al., 2000; Dutta et al., 2010b).

Clinical manifestations and breaking BBB of JE

JEV infections are mostly asymptomatic or cause mild infection and <1% of people infected with JEV develop clinical disease. 19 The incubation period for JEV infection may be from 5 to 15 days. The manifestations of JE depend on which part of the nervous system is affected. After JEV infection, the clinical course conventionally divided into 3 stages: prodromal phase, encephalitic phase and late stage noticed by recovery or persistence of signs of CNS injury. Apart from the classical presentation, some atypical presentations such as febrile seizures, aseptic meningitis, and acute flaccid paralysis-like illness also have been reported (Solomon et al., 1998; Kimura et al., 2010).

Viruses invade the CNS are prevented by virus-specific and nonspecific host immunity and physical barrier, such as blood-brain barrier (BBB). It has reported that during JEV infection, the structural and functional integrity of BBB has severely being broken, which matrix metalloproteinases (MMPs) has important role in changing the permeability of BBB (Mishra et al., 2009; Gupta et al., 2010). When JEV enter into the CNS, they could spread to the whole CNS, which result in devastating consequences (Liu et al., 2008; Cecilia et al., 2009).

Diagnosis and antivirus therapy

There are no specific signs or symptoms that distinguish JE from other causes of acute encephalitis syn-

drome (AES). Thus, it is very hard to confirm the JE disease based on clinical symptoms in patients. JE disease is currently diagnosed by detecting viral antigens and virus neutralization IgM antibodies in blood serum and CSF by ELISA in laboratory. The laboratory diagnosis of JE is established by measuring (1) a fourfold increase in serum antibody titer, (2) virus isolation, or (3) specific immunoglobulin M (IgM) antibody detection by ELISA in (CSF) or serum, which is most feasible testing methodology than others. JE has no specific treatment at yet and the treatment is symptomatic and supportive. Vaccination of the population at risk is effective method for its prevention (Cecilia et al., 2009).

Although there are currently anti-JEV drugs available today, attempts to develop new antiviral drugs is ongoing. For example, peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) have recently been reported which are antisense agents targeting the 3 cyclization sequence of JEV, they have been shown to significantly inhibit the replication of JEV in cells and in a mice model (Anantpadma et al., 2010). Other therapeutic agents, such as, siRNA (Kumar et al., 2006; Qi et al., 2008) and arctigenin (Swarup et al., 2008), especially NTZ (Shi et al., 2014) are all has distinct effect on against JEV infection in cells and animal model. NTZ is a licensed, safe drug for treating diarrhea due to Cryptosporidium and Giardia in adults and children and there have been no serious toxicities associated with short-term and long-term use of NTZ (Eugene et al., 2010). Thus, NTZ may be a promising candidate for use as an anti-JEV therapeutic agent.

Control

Vector control, and reduction of man-mosquito contact, improving agricultural practices and vaccination are effective measures in the control of JE. Larvicides, insecticides, and ecofriendly methods could be used in controlling mosquitoes in paddy fields. Vaccinating pigs is also a role way to protect human from JEV infection in rural areas by breaking the mosquito-pig-human transmission cycle. People, especially tourists are vaccinated against JEV, is considered to be the most effective control measure. Further, diagnostic facilities, surveillance system and for JEV confirmation should be strengthened in rural areas (Kant Upadhyay., 2013). Moreover, an earlier diagnosis of the disease and medical care is required for patients. Therefore, treatment strategies would be most important before virus spreads into CNS.

Conclusion

JE, as a viral zoonotic disease, has been caused an increasing public health problem in the developing countries of the Asia-Pacific Region. Unfortunately, only a few of laboratories in developing countries actually focused on exploring JEV pathogenesis and anti-virus therapy. Maybe, it is the responsibility of the scientific communities all over the world, governments, and WHO to find drugs that could be provided to the patient infected by JEV (Ghosh and Basu., 2009). We are hopeful that a effective therapeutic drug, such as chemotherapeutic agent or compounds isolated from various plants will soon be identified to abrogate JE diseases.

Conflict of interest

The authors declare that they have no competing interests.

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References

- Anantpadma, M., D.A. Stein, and S. Vrati, 2010: Inhibition of Japanese encephalitis virus replication in cultured cells and mice by a peptide-conjugated morpholino oligomer. J Antimicrob Chemother 65: 953-961. http://dx.doi.org/10.1093/jac/dkq074
- Cecilia Big, MD., A. Lora, M.D. Reineck, M. David, and M.D. Aronoff, 2009: Viral Infections of the Central Nervous System: A Case-Based Review. Clin Med Res 7: 142-146. http://dx.doi.org/10.3121/cmr.2009.864
- Chen, N., and Y.X. Yu, 2013: Progress in the research of phenotype and genotype of Japanese encephalitis virus in China. Bing Du Xue Bao 29:457-464.
- Dutta, K., M.K. Mishra, A. Nazmi, K.L. Kumawat, and A. Basu, 2010a: Minocycline differentially modulates macrophage mediated peripheral

immune response following Japanese encephalitis virus infection. Immunobiology 215:884-893. http://dx.doi.org/10.1016/j.imbio.2009.12.003

- Dutta, K., P.N. Rangarajan, S. Vrati, and A. Basu, 2010b: Japanese encephalitis: pathogenesis, prophylactics and therapeutics. Current Science 98: 326-334.
- Endy, T. P., and A. Nisalak, 2002: Japanese encephalitis virus: ecology and epidemiology. Curr Top Microbiol Immunol 267:11-48. http://dx.doi.org/10.1007/978-3-642-59403-8_2
- Eugene, R., and M.D. Schiff, 2010: Advances in Hepatology. Gastroenterol Hepatol 6: 303-305.
- Ghosh, D., and A. Basu, 2009: Japanese encephalitis-a pathological and clinical perspective. PLoS Negl Trop Dis 3:e437. http://dx.doi.org/10.1371/journal.pntd.0000437
- Gupta, N., V. Lomash, and P. V. Rao, 2010: Expression profile of Japanese encephalitis virus induced neuroinflammation and its implication in disease severity. J Clin Virol 49:4-10. http://dx.doi.org/10.1016/j.jcv.2010.06.009
- Johnston, C., W. Jiang, T. Chu, and B. Levine, 2001: Identification of genes involved in the host response to neurovirulent alphavirus infection. J Virol 75:10431-10445. http://dx.doi.org/10.1128/JVI.75.21.10431-10445.2001
- Kant Upadhyay, R., 2013: Biomarkers in Japanese encephalitis: a review. Biomed Res Int 2013:591290. http://dx.doi.org/10.1155/2013/591290
- Kimura, T., M. Sasaki, M. Okumura, E. Kim, and H. Sawa, 2010: Flavivirus encephalitis: pathological aspects of mouse and other animal models. Vet Pathol 47:806-818. http://dx.doi.org/10.1177/0300985810372507
- Kumar, P., S. K. Lee, P. Shankar, and N. Manjunath, 2006: A single siRNA suppresses fatal encephalitis induced by two different flaviviruses. PLoS Med 3:e96. http://dx.doi.org/10.1371/journal.pmed.0030096
- Le Flohic, G., V. Porphyre, P. Barbazan, and J.P. Gonzalez, 2013: Review of climate, landscape, and viral genetics as drivers of the Japanese encephalitis virus ecology. PLoS Negl Trop Dis 7:e2208. http://dx.doi.org/10.1371/journal.pntd.0002208
- Li, M.H., S.H. Fu, W.X. Chen, H.Y. Wang, Y.H. Guo, Q.Y. Liu, Y.X. Li, H.M. Luo, W. Da, Duo Ji DZ, X.M. Ye, and G.D. Liang, 2011: Genotype V Japanese encephalitis virus is emerging. PLoS Negl Trop Dis 5:e1231. http://dx.doi.org/10.1371/journal.pntd.0001231
- Liu, T.H., L.C. Liang, C.C. Wang, H.C. Liu, and W.J. Chen, 2008: The blood-brain barrier in the cerebrum is the initial site for the Japanese encephalitis virus entering the central nervous system. J Neurovirol 14:514-521. http://dx.doi.org/10.1080/13550280802339643
- Mishra, M.K., K. Dutta, S.K. Saheb, and A. Basu, 2009: Understanding the molecular mechanism of blood-brain barrier damage in an experimental model of Japanese encephalitis: correlation with minocycline administration as a therapeutic agent. Neurochem Int 55:717-723. http://dx.doi.org/10.1016/j.neuint.2009.07.006
- Mohammed, M.A., S.E. Galbraith, A.D. Radford, W. Dove, T. Takasaki, I. Kurane, and T. Solomon, 2011: Molecular phylogenetic and evolutionary analyses of Muar strain of Japanese encephalitis virus reveal it is the missing fifth genotype. Infect Genet Evol 11:885-862. http://dx.doi.org/10.1016/j.meegid.2011.01.020
- Nemeth, N., A. Bosco-Lauth, P. Oesterle, D. Kohler, and R. Bowen, 2010: North American birds as potential amplifying hosts of Japanese encephalitis virus. Am J Trop Med Hyg 87:760-767. http://dx.doi.org/10.4269/ajtmh.2012.12-0141
- Qi, W. B., R. H. Hua, L. P. Yan, G. Z. Tong, G. H. Zhang, T. Ren, D. L. Wu, and M. Liao, 2008: Effective inhibition of Japanese encephalitis virus replication by small interfering RNAs targeting the NS5 gene. Virus Res 132:145-151. http://dx.doi.org/10.1016/j.virusres.2007.11.014
- Shi, Z., J. Wei, X. Deng, S. Li, Y. Qiu, D. Shao, B. Li, K. Zhang, F. Xue, X. Wang, and Z. Ma, 2014: Nitazoxanide inhibits the replication of Japanese encephalitis virus in cultured cells and in a mouse model. Virol J 11:10. http://dx.doi.org/10.1186/1743-422X-11-10
- Solomon, T., H. Ni, D. W. Beasley, M. Ekkelenkamp, M. J. Cardosa, and A. D. Barrett, 2003: Origin and evolution of Japanese encephalitis virus in southeast Asia. J Virol 77:3091-3098. http://dx.doi.org/10.1128/JVI.77.5.3091-3098.2003
- Solomon, T., R. Kneen, N.M. Dung, V.C. Khanh, T.T. Thuy, D.Q. Ha, N.P. Day, A. Nisalak, D.W. Vaughn, and N.J. White, 1998: Poliomyelitis like illness due to Japanese encephalitis virus. Lancet 351:1094-1097. http://dx.doi.org/10.1016/S0140-6736(97)07509-0
- Swarup, V., J, Ghosh., M.K. Mishra, and A. Basu, 2008: Novel strategy for treatment of Japanese encephalitis using arctigenin, a plant lignan. J An-

timicrob Chemother 61: 679-688. http://dx.doi.org/10.1093/jac/dkm503

- Uchil, P.D., and V. Satchidanandam, 2001: Phylogenetic analysis of Japanese encephalitis virus: envelope gene based analysis reveals a fifth genotype, geographic clustering, and multiple introductions of the virus into the Indian subcontinent. Am J Trop Med Hyg 65: 242-251.
- Xu, L. J., R. Liu, S. Ye, H. Ling, and C. M. Zhu, 2013: Genomic analysis of a newly isolated of Japanese encephalitis virus strain, CQ11-66, from a pediatric patient in China. Virol J 10:101. http://dx.doi.org/10.1186/1743-422X-10-101
- Zheng, Y., M. Li, H. Wang, and G. Liang, 2012: Japanese encephalitis and Japanese encephalitis virus in mainland China. Rev Med Virol 22:301-322. http://dx.doi.org/10.1002/rmv.1710