We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

6,600
Open access books available

177,000
International authors and editors

195M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter

The Global Distribution and Burden of Dengue and Japanese Encephalitis Co-Infection in Acute Encephalitis Syndrome

Shailendra K. Saxena, Swatantra Kumar, Vimal K. Maurya and Madan L.B. Bhatt

Abstract

Dengue is widespread throughout the tropics globally in more than hundred countries and coincides with various climatic factors for co-infection with other flaviviral infections of the central nervous system (CNS). Dengue and Japanese encephalitis virus co-infection are highly prevalent, with diagnosis dilemma including significant mortality and morbidity in Southeast Asia. Both dengue and Japanese encephalitis transmissions intensify during the rainy season, during which the vector population increases. CNS involvement during dengue and Japanese encephalitis co-infection-associated acute encephalitis syndrome (AES) is still poorly understood, and therefore, there is a desperate need to understand the etiology, therapeutics, clinical management, and prevention of these tropically neglected diseases. AES can be differentiated from other etiologies of encephalopathy through considering its essential features: sudden onset of fever, cerebrospinal fluid (CSF) comprising inflammatory cells, magnetic resonance imaging (MRI)-based confirmation, and presence of pathogen or pathogen-specific antibodies. Complementary and alternative medicine is progressively being used globally and can be effective for the overall management of this co-infection.

Keywords: dengue, Japanese encephalitis, co-infection, encephalitis, acute encephalitis syndrome (AES), differential diagnosis, treatment, management, prevention, complementary and alternative medicine

1. Introduction

Neglected tropical diseases (NTDs) are the diverse group of communicable diseases which exist in tropical and subtropical settings affecting more than one billion people worldwide [1]. Populations inhabiting places with poor sanitation are in close contact with infected vectors, and domestic animals are principally affected. Arthropod-borne or arboviruses such as dengue, Zika, and Chikungunya have been recently included in the list of NTDs by the World Health Organization [2].

Human infection of flavivirus may cause severe clinical manifestations and can be broadly subdivided into two groups as neurological diseases caused by Japanese encephalitis virus (JEV), West Nile virus, and Zika virus (ZIKV) and hemorrhagic and viscerotropic diseases caused by dengue virus (DENV), ZIKV, and yellow fever
virus (YFV) [3]. More than half of the global population is now at the risk of getting flavivirus infections where the majority of areas are endemic for more than one flaviviruses which results in the phenomenon of co-infection [4]. The worldwide incident of dengue has extensively grown in few decades [5]. Majority of the dengue cases are asymptomatic, and therefore, it is hard to anticipate the accurate burden of the disease. The rise in number of cases from 2.2 million in the year 2010 to 3.34 million cases in 2016 suggests the sharp increase in the disease burden. The 2016 year is characterized as the largest outbreak for dengue where 2.38 million cases were reported from the region of the Americas where 1.5 million cases were contributed by Brazil alone. Currently 3.9 billion in 128 countries people are at risk of DENV infection [6]. Unlike dengue, Japanese encephalitis (JE) is confined to Southeast Asia and Western Pacific regions. Approximately 68,000 clinical cases of JE are reported annually with 13,000 to 24,000 deaths. Currently more than 3 billion in 24 countries are at risk of JEV infection [7]. The epidemiology of dengue and JE has been depicted in Figure 1.

DENV and JEV belongs to the Flaviviridae family, which consists of more than 70 viruses, comprising of single-stranded positive-sense RNA genome protected by envelope protein [8]. Viruses from this family belong to the genus Flavivirus, which are transmitted by mosquitoes or ticks and are characterized as arthropod-borne infections. The transmission cycle of Flavivirus involves animals including human which are considered to be the dead-end hosts [9]. Hematophagous mosquitoes are the transmission vector for these diseases. Aedes albopictus and Aedes aegypti mosquitoes are known to transmit the dengue virus, whereas Culex tritaeniorhynchus is predominantly involve in the transmission of JEV [10]. These viruses have been shown to be transmitted via transplacental route as well [11].

Pathogen-associated acute encephalitis syndrome (PA-AES) may result from diverse pathogenic infections including DENV and JEV. PA-AES shows a wide range of symptoms including headache, vomiting and severe illness, reduced consciousness, altered sensorium, convulsions, and tremors [12]. Flaviviruses share substantial sequence similarities to stimulate sero-cross-reactivity which results in the antibody-dependent enhancement (ADE) of infection with other flaviviruses [13].

Figure 1. Dengue and Japanese encephalitis epidemiology. The worldwide epidemiology of dengue and Japanese encephalitis has been depicted in this map. More than 100 countries are endemic for dengue where America, Western Pacific regions, and Southeast Asia are mostly affected. The Japanese encephalitis is confined to mostly in Southeast Asia and Western Pacific regions which include approximately 24 countries. The dengue-affected regions are highlighted in red color, JE-affected regions are highlighted in yellow color, and regions where both viruses are circulating have been highlighted in orange color.
Outbreaks of DENV co-infection are predominantly associated with the JEV endemic area or areas of JE immunization [14]. Although DENV-induced encephalitis is rare, the co-infection may increase the severity of encephalitis. DENV infection causes dengue hemorrhagic fever (DHF), whereas JEV infection may result in neurological complications [15]. Intermittently, DENV has been reported to cause encephalitis, and JEV infection may cause extraneural hemorrhage [16, 17]. However, this may not be the case in co-infection with both the flaviviruses. Simultaneous detection of both the viruses is not unusual; nevertheless we need to be attentive in the diagnosis of the etiology of PA-AES.

2. Molecular mechanism of DENV and JEV co-infection

Co-infection with both viruses may occur in the single-cell types or different cells in the infected individuals. Simultaneous infection of target cells or different cell types by DENV and JEV defines the phenomenon of co-infection [18]. Both the viruses share common cell surface receptors expressed on target cell types such as DC-SIGN, mannose receptors, and CLEC5A [19]. On the other hand, virus can be internalized in the presence of non-neutralizing antibodies via Fcγ receptor-mediated endocytosis [20]. Clathrin-mediated endocytosis has been shown to be involved in the internalization of flaviviruses [21]. After internalization, the virus from the endocytic vesicles is delivered to the early endosomes [22]. Acidification of the endosomal

Figure 2.
DENV and JEV co-infection. The mechanism of co-infection has not been completely understood. Co-infection with DENV and JEV may occur in the single-cell types or different cells in the infected individuals. Co-infection results in the generation of antibodies against both viruses. However, detection of nucleic acids and antigens may confirm the phenomenon of co-infection (A). Upon infection, JEV is internalized by receptor-mediated endocytosis. The decrease in pH causes the fusion of viral and endosomal membrane which results in the release of viral RNA into the cytosol. The released viral genome is then translated prior to the commencement of replication. Virus maturation occurs at the Golgi complex and mature virus is released via the egress process. JEV infection in the hyperendemic area may result in false-positive diagnosis due to presence of pre-existing sero-cross-reactive antibody (B). Pre-existing sero-cross-reactive antibodies may bind to the viral particles upon infection which results in antibody-dependent enhancement of infection (C).
compartments causes trimerization of the envelope protein that results in the fusion of endosomes to the viral membrane and release of nucleocapsid in the cytosol [23]. The released viral genome is then translated prior to the commencement of replication [24]. The backbone of flaviviral genome is invariable which are of ~10 kb that codes for three structural capsid (C), premembrane (prM), and envelope (E) and seven nonstructural proteins NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. The viral genome encodes for 3400 amino acid long polyprotein which is arranged in the lumen endoplasmic reticulum where the replication takes place by the RNA-dependent RNA polymerase [25]. Replicated copies of the genome interact with viral proteins to form nucleocapsid. Immature virions enter into the secretory pathway where furin-mediated cleavage of prM results in the maturation of virus [26]. Mature virus is then released from the infected cells via the egress process [27]. The conventional mechanism of pathogenesis and viral replication may not be followed in case of co-infection and may involve distinct process. In order to effectively control and treat the co-infection of DENV and JEV, we need to first understand the immunopathogenesis of dual infection in various cell and animal models. The probable phenomenon of DENV and JEV co-infection has been demonstrated in Figure 2.

3. Diagnostic schemes for dengue and Japanese encephalitis co-infection

JEV is the most documented causative agent of acute encephalitis syndrome (AES) [28]. DENV has also been considered among the top three etiological agents causing...
AES [29]. Broad spectrum of clinical features in the endemic areas of both viruses may dilute the encephalitis-like clinical presentation. Therefore, laboratory based diagnosis and discrimination of pathogenesis is crucial to understand. Detection of IgG antibodies against both viruses may be considered as the previous exposure of the viruses, whereas detection of IgM suggests the recent or current infectious conditions. However, this should be further validated based on the nucleic acid-based tests where detection of DENV and JEV nucleic acids defines the co-infectious condition.

Nucleic acid-based detection by RT-PCR for other probable arboviral infections such as Zika and Chikungunya can also be included which may overlap with the clinical manifestations of dengue or JE [30]. Although the clinical manifestations presented in the individual cases of DENV and JEV infections are distinct, the co-infection might be a complex situation to diagnose. Co-detection of serum antibodies against both viruses may not be the evidence of co-infection. Surveillance programs conducted in the hyperendemic areas of flaviviruses have reported at least 9% of co-infections cases [31]. Moreover, the MRI findings of DENV-infected patients may show the characteristic features of encephalitis as in case of JEV where the basal ganglia, thalamus, and midbrain are predominantly affected [32]. Considering the sero-cross-reactivity among flaviviruses, the dependence of serum-based diagnosis may give false-positive results. However, simultaneous detection of nucleic acid or viral-specific antigens in blood or CSF samples may define the incident of co-infection. The laboratory diagnostic algorithms during DENV and JEV co-infection have been depicted in Figure 3.

4. Treatments regimes for dengue and Japanese encephalitis co-infection

Viral infections have always been a global threat to mankind due to scarcity of effective antiviral drugs. Flaviviral infections are not the exception since there is no specific treatment available for both DENV and JEV [33]. The overall treatment relies on the symptomatic relief of the patients. Due to the complex and unclear pathogenesis of dual infection, the potential candidate drugs may not effective. Therefore, we need to look for the complementary and alternative medicine (CAM) in alliance with conventional medicines as the choice of treatment during co-infection.

In case of DENV infection, various forms of CAM have been used such as Carica papaya leaf extracts is the most accepted one. Platelet-activating factor receptor (PTAFR) gene has been shown to be upregulated upon consumption of Carica papaya leaf extracts or its juices [34]. In case of sever dengue infection, maintenance of body fluids volume of the patients is critical [35]. However, this may or may not be effective in case of co-infections. Recently, andrographolide has been shown to exhibit anti-DENV activity [36]. Eupatorium perfoliatum which is a homeopathic medicine has been shown to exhibit anti-DENV activity [37]. Luteolin has been shown to be effective during JEV infection which also exhibits direct virucidal activity [38]. Similarly, belladonna has been shown to be effective in chick embryos infected with JEV [39]. Several of the CAM-based therapies have been shown to be effective in case of JEV infection, but these have to be validated in case of co-infection.

5. Preventive strategies for dengue and Japanese encephalitis co-infection

To prevent the worldwide burden of DENV infection, the WHO has recently approved a tetravalent vaccine, Dengvaxia (CYD-TDV) in 20 countries. This has
been designed by using the yellow fever vaccine backbone expressing the prM and envelope protein of DENV 1–4 serotypes [40]. In case of JEV, a live attenuated vaccine based on SA 14–14–2 has been used in China, India, Sri Lanka, Republic of Korea, and Thailand. Due to higher sero-cross-reactivity, the one vaccine may induce the other infection due to the antibody-dependent enhancement [41]. Therefore, to design an effective vaccine for co-infection, there is a need to understand the mechanism and probability of sero-cross-reactivity among the viruses. Apart from the vaccination, the personal preventive measures are always paramount to prevent any vector-borne infections [42]. To prevent the mosquito biting, several protective measures include mosquito repellents, mosquito nets, and use of full sleeves cloths [43].

6. Conclusions

Genomic and proteomic sequence similarity among the flaviviruses causes the sero-cross-reactivity that leads to the phenomenon of antibody-dependent enhancement of infections. Incidence of DENV and JEV co-infection in the hyperendemic areas may be frequently reported. The diagnosis of co-infection should not rely on the presence of serum antibodies. However, simultaneous detection of nucleic acids or antigens may define the condition of co-infection. Clinical features may overlap in the patients infected with both viruses, and therefore we need to precisely distinguish the patients’ clinical reports. Development of effective antivirals targeting both the viruses is the most imperative therapeutic strategy.

7. Future perspectives

Due to the similarity in the structural domains of the viral proteins, molecules may be designed to inhibit the action of viral proteins or enzymes. Similarly, vaccines may be designed to target the population living in the hyperendemic areas of flaviviruses. Peptide-based vaccines may be designed by using various immunoinformatics approaches by considering the consensus peptide sequences among the viruses. Apart from the vaccination, personal preventive measures are always recommended the best practice to reduce the chances of infections.

Acknowledgements

The authors are grateful to the Vice Chancellor, King George's Medical University (KGMU), Lucknow, India, for the encouragement and support for this work. SK Saxena is also supported by CCRH, Government of India, and US NIH grants: R37DA025576 and R01MH085259. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
Author details

Shailendra K. Saxena*, Swatantra Kumar, Vimal K. Maurya and Madan L.B. Bhatt
Center for Advanced Research (CFAR)-Stem Cell/Cell Culture Unit, Faculty of Medicine, King George’s Medical University, Lucknow, India

*Address all correspondence to: myedrsaxena@gmail.com
References

[1] Molyneux DH, Savioli L, Engels D. Neglected tropical diseases: Progress towards addressing the chronic pandemic. Lancet. 2017;389(10066):312-325

[2] Mitra AK, Mawson AR. Neglected tropical diseases: Epidemiology and global burden. Tropical Medicine and Infectious Disease. 2017;2(3):pii. E36

[3] Holbrook MR. Historical perspectives on Flavivirus research. Viruses. 2017;9(5):pii. E97

[4] Vogels CBF, Rückert C, Cavany SM, Perkins TA, Ebel GD, Grubaugh ND. Arbovirus coinfection and co-transmission: A neglected public health concern? PLoS Biology. 2019;17(1):e3000130

[5] Guo C, Zhou Z, Wen Z, Liu Y, Zeng C, Xiao D, et al. Global epidemiology of dengue outbreaks in 1990-2015: A systematic review and meta-analysis. Frontiers in Cellular and Infection Microbiology. 2017;7:317

[6] World Health Organization. Dengue and severe dengue. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue [Accessed: June 01, 2019]

[7] World Health Organization. Japanese encephalitis. https://www.who.int/news-room/fact-sheets/detail/japanese-encephalitis [Accessed: June 01, 2019]

[8] Daep CA, Muñoz-Jordán JL, Eugenin EA. Flaviviruses, an expanding threat in public health: Focus on dengue, west Nile, and Japanese encephalitis virus. Journal of Neurovirology. 2014;20(6):539-560

[9] Neufeldt CJ, Cortese M, Acosta EG, Bartenschlager R. Rewiring cellular networks by members of the Flaviviridae family. Nature Reviews. Microbiology. 2018;16(3):125-142

[10] Huang YJ, Higgs S, Horne KM, Vanlandingham DL. Flavivirus-mosquito interactions. Viruses. 2014;6(11):4703-4730

[11] Raj Y, Kumar S, Haikerwal A, Goel MM, Bhatt ML, Saxena SK. Current advances in Zika virus transmission: Urgency for effective therapeutics and prevention. American Journal of Infectious Diseases. 2017;13(2):13-20

[12] Saxena SK, Kumar S, Maurya VK. Pathogen-associated acute encephalitis syndrome: Therapeutics and management. Future Microbiology. 2019;14:259-262

[13] Saron WAA, Rathore APS, Ting L, Ooi EE, Low J, Abraham SN, et al. Flavivirus serocomplex cross-reactive immunity is protective by activating heterologous memory CD4 T cells. Science Advances. 2018;4(7):eaar4297

[14] Saito Y, Moi ML, Takeshita N, Lim CK, Shiba H, Hosono K, et al. Japanese encephalitis vaccine-facilitated dengue virus infection-enhancement antibody in adults. BMC Infectious Diseases. 2016;16(1):578

[15] Garg RK, Malhotra HS, Gupta A, Kumar N, Jain A. Concurrent dengue virus and Japanese encephalitis virus infection of the brain: Is it co-infection or co-detection? Infection. 2012;40(5):589-593

[16] Aggarwal A, Kumar P, Faridi MM. Neurological manifestation as presenting feature of dengue infection. Journal of Pediatric Neurosciences. 2015;10(1):76-77

[17] Tiroumourougane SV, Raghava P, Srinivasan S. Japanese viral encephalitis.
Salas-Benito JS, De Nova-Ocampo M. Viral interference and persistence in mosquito borne flaviviruses. Journal of Immunology Research. 2015;2015:873404

Laureti M, Narayanan D, Rodriguez-Andres J, Fazakerley JK, Kedzierski L. Flavivirus receptors: Diversity, identity, and cell entry. Frontiers in Immunology. 2018;9:2180

Slon Campos JL, Mongkolsapaya J, Screaton GR. The immune response against flaviviruses. Nature Immunology. 2018;19(11):1189-1198

Piccini LE, Castilla V, Damonte EB. Dengue-3 virus entry into vero cells: Role of clathrin-mediated endocytosis in the outcome of infection. PLoS One. 2015;10(10):e0140824

Hackett BA, Cherry S. Flavivirus internalization is regulated by a size-dependent endocytic pathway. Proceedings of the National Academy of Sciences of the United States of America. 2018;115(16):4246-4251

Bressanelli S, Stiasny K, Allison SL, Stura EA, Duquerroy S, Lescar J, et al. Structure of a flavivirus envelope glycoprotein in its low-pH-induced membrane fusion conformation. The EMBO Journal. 2004;23(4):728-738

Nour AM, Li Y, Wolenski J, Modis Y. Viral membrane fusion and nucleocapsid delivery into the cytoplasm are distinct events in some flaviviruses. PLoS Pathogens. 2013;9(9):e1003585

Mazeaud C, Freppel W, Chatel-Chaix L. The multiples fates of the flavivirus RNA genome during pathogenesis. Frontiers in Genetics. 2018;9:595

Plevka P, Battisti AJ, Junjhon J, Winkler DC, Holdaway HA, Keelapang P, et al. Maturation of flaviviruses starts from one or more icosahedrally independent nucleation centres. EMBO Reports. 2011;12(6):602-606

Plevka P, Battisti AJ, Sheng J, Rossmann MG. Mechanism for maturation-related reorganization of flavivirus glycoproteins. Journal of Structural Biology. 2014;185(1):27-31

Ghosh S, Basu A. Acute encephalitis syndrome in India: The changing scenario. Annals of Neurosciences. 2016;23(3):131-133

Vasanthapuram R, Shahul Hameed SK, Desai A, Mani RS, Reddy V, Velayudhan A, et al. Dengue virus is an under-recognised causative agent of acute encephalitis syndrome (AES): Results from a four year AES surveillance study of Japanese encephalitis in selected states of India. International Journal Infectious Diseases. 2019;84S(2019):S19-S24

Paixão ES, Teixeira MG, Rodrigues LC. Zika, chikungunya and dengue: The causes and threats of new and re-emerging arboviral diseases. BMJ Global Health. 2018;3(Suppl 1):e000530

Singh KP, Mishra G, Jain P, Pandey N, Nagar R, Gupta S, et al. Co-positivity of anti-dengue virus and anti-Japanese encephalitis virus IgM in endemic area: co-infection or cross reactivity? Asian Pacific Journal of Tropical Medicine. 2014;7(2):124-129

Verma R. MRI features of Japanese encephalitis. BML Case Reports. 2012;2012. pii: bcr0320126088

Wang S, Liu Y, Guo J, Wang P, Zhang L, Xiao G, Wang W. Screening of FDA-approved drugs for inhibitors of Japanese encephalitis virus infection.
[34] Sarala N, Paknikar S. Papaya extract to treat dengue: A novel therapeutic option? Annals of Medical and Health Sciences Research. 2014;4(3):320-324

[35] Hung NT. Fluid management for dengue in children. Paediatrics and International Child Health. 2012;32(Suppl 1):39-42

[36] Panraksa P, Ramphan S, Khongwichit S, Smith DR. Activity of andrographolide against dengue virus. Antiviral Research. 2017;139:69-78

[37] Saxena SK, Haikerwal A, Gadugu S, Bhatt ML. Complementary and alternative medicine in alliance with conventional medicine for dengue therapeutics and prevention. Future Virology. 2017;12(8):399-402

[38] Fan W, Qian S, Qian P, Li X. Antiviral activity of luteolin against Japanese encephalitis virus. Virus Research. 2016;220:112-116

[39] Chakraborty U, Katoch S, Sinha M, Nayak D, Khurana A, Manchanda RK, et al. Changes in viral load in different organs of Japanese encephalitis virus-infected chick embryo under the influence of belladonna 200C. Indian Journal of Research in Homoeopathy. 2018;12(2):75

[40] Clapham H, Wills B. Implementing a dengue vaccination programme-who, where and how? Transactions of the Royal Society of Tropical Medicine and Hygiene. 2018;112(8):367-368

[41] Ginsburg AS, Meghani A, Halstead SB, Yaich M. Use of the live attenuated Japanese encephalitis vaccine SA 14-14-2 in children: A review of safety and tolerability studies. Human Vaccines & Immunotherapeutics. 2017;13(10):2222-2231

[42] Demers J, Bewick S, Calabrese J, Fagan WF. Dynamic modelling of personal protection control strategies for vector-borne disease limits the role of diversity amplification. Journal of the Royal Society Interface. 2018;15(145):pii. 20180166

[43] Tangena JA, Thammavong P, Chonephetsarath S, Logan JG, Brey PT, Lindsay SW. Field evaluation of personal protection methods against outdoor-biting mosquitoes in Lao PDR. Parasites & Vectors. 2018;11(1):661