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Virology & Immunology Journal
ISSN: 2577-4379

Dengue- A Global Threat; Need to be Halted with Sound Scientific Measures to Stop its Rapid Devastation throughout the World

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Review Article
Volume 7 Issue 1
Received Date: February 22, 2023
Published Date: March 13, 2023
DOI: 10.23880/vij-16000309

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Abstract

Dengue virus belongs to family Flaviviridae and genus Flavivirus, transmitted primarly in a cycle through human beings and mosquito vector. The rate of incidence of dengue fever epidemics has reached to the highest, since past few years. Over a geologically expanding area, the level of hyperendemic transmission has been established. The person with sequential dengue infection is also victim of dengue hemorrhagic fever (DHF) which is the most severs disease. The rate of incidence of DHF and the possibility of sequential infections has increased intensely, first of all in Asian countries and currently in America. The wide spreading of mosquito Aedes aegypti is even more alarming. As a consequence of insufficiency of antiviral drugs and potential vaccine, a large number of individuals are infected with severe dengue virus every year which causes huge death cases.

Conclusion: Effective vector control measures are the only weapon against dengue these days, however effective potential drugs and vaccine are expected in future.

Keywords: Dengue Virus; Aedes Aegypti; Dengue Hemorrhagic Fever; Vaccine

Introduction

Dengue is a mosquito-borne single stranded RNA virus (40-60 nm in size) in the genus Flavivirus and family Flaviviridae, responsible for causing fever and dengue hemorrhagic fever (DHF), both are universally severe diseases [1]. The total four antigenically different serotypes of the virus have been found i-e DENV1, DENV2, DENV3, and DENV4 which are liable for causing the full spectrum of infection [2]. The more severe infection leads to DHF, which can be life threatening. There are numerous viral and host factors that have been linked with the severity of dengue infections. Generally, the secondary dengue infection is profoundly associated with DHF as compare to primary infections [3]. Generally, dengue virus has a globular shape having diameter of 50 nm and has a single-stranded, positive-sense RNA genome of about 11 kb encoding three structural proteins i.e. capsid, envelope, and membrane and seven non-structural proteins i.e. NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. For virion assembly, virus replication

and evasion of the host immune response, the non-structural proteins are prime essential [4]. Genetically linked all types of dengue virus from DENV1 to DENV4 occur in nature that belong to the genus Flavivirus and family Flaviviridae. Each of them is further classified into various genotypes according to their nucleotide order. Presently, DENV1 consists of five genotypes (I) Southeast Asia, China, and East Africa; (II) Thailand; (III) Sylvatic (Malaysia) (IV) the Western Pacific islands and Australia; and (V) America, West America, and Asia. DENV3 also contains five genotypes (I) Indonesia, Malaysia, Thailand, the South Pacific, the Philippines, and East Timor; (II) Thailand, Myanmar, Singapore, Indonesia, Malaysia, Bangladesh, and Vietnam; (III) Sri Lanka, India, Samoa, Somalia, Japan, Singapore, and Taiwan; (IV) Puerto Rico; and (V) the Philippines and Asia [2].

The main symptoms of dengue virus infection are high-grade fever, headache, myalgia, pain in joints fever, muscle and joint or retro-orbital pain. About 50-100 million dengue cases have been reported so far caused dengue vector in approximately 100 common countries including America, South-East Asia, Pacific Asia; however, countries in South Asia, including India, Bangladesh and most recently in Pakistan [5].

In china during 2005-2015, a total of 59334 dengue cases were documented. The cases were higher in humans aged between 21 years and 50 years. In September and October of 2012–2015, the rates of cases were higher than in 2005–2011 [6].

In Pakistan the first dengue epidemic was reported in 1994. Later then, in different age groups, epidemics of dengue infection have been documented from various region of Pakistan. In the year of 2011 major dengue epidemic in Lahore, Peshawar, Islamabad and Multan, affected thousands of people and resulted hundreds of deaths. Some deaths arised due to co-morbidities such diabetes and lack of effective awareness among the physicians for its management. It has been documented that dengue infection has caused so for 133.76 disability adjusted life years lost per million population [7].

Mode of Transmission

Dengue fever is found to be wide-ranging spread mosquito-borne infection around the world. Universal visitors having dengue virus infection are the common means of virus transmission from destination to another destination. Dengue virus is a vector-borne pathogen that is transferred by interaction amongst vectors and hosts. Dengue, the most severe universal viral pathogen that has established itself around the world in endemic and epidemic transmission cycles [8]. In human population, Dengue virus infection is normally unapparent but can cause clinical manifestations in a wide range, from mild fever to potentially fatal dengue shock syndrome. The main vector of dengue virus is Aedes. Aegypti and Aedes. Albopictus mosquitoes. Through the bites of infected female mosquitoes, the virus gets transmitted to human population with the incubation period of 8 to 12 days [9]. Aedes aegypti and Aedes albopictus mosquitoes do play a key role in the spreading of infection, mainly in the tropical and subtropical districts of the whole world. The vertical transmission of the dengue virus in populations of Aedes aegypti and Aedes albopictus is found to be of great significance [10] Seasonal transmission of dengue virus was verified by the indication of virus in fetal tissue, newborn serum, and placenta of pregnant women [11].

Male Aedes albopictus mosquitos were infected experimentally with dengue virus types 1, 2, 3, and 4 that transferred their infection sexually to female Aedes Albopictus mosquito. Such transmission was boosted if the female's mosquito had taken a blood meal 2 to 7 days prior to mating. Male Aedes albopictus also spread dengue virus vertically to their female offspring. Interestingly it was also reported that male mosquitoes acquired their infection vertically as they are infected naturally with dengue virus [12]. Transovarial transmission of all four types of dengue serotypes was verified in Aedes albopictus mosquitoes. Overall, the supreme rates of causing infection were detected with strains of dengue type 1 and the lowermost with dengue type 3 [13].

In community, transmission of virus take place by social interaction due to routine activities amongst the same places, such as friends gathering and homes of the family are usually similar for the infected individual and their contacts. The locomotion of human beings in society plays distinctive impact in spreading this vector-borne pathogen at fine spatial scales [14].

Mechanism of Pathogenesis of Dengue Virus

Although dengue is an ancient disease but recently an unexpected increase was seen in different geographical range, laterally with the severity of infection. The Aedes aegypti mosquito inserts the virus into the blood stream after feeding on human being and spread infection all over the body. The virus primarly targets the immature Langerhans cells and keratinocytes. The infectious cells move towards lymph nodes, and attacks monocytes and macrophages. Thereby, the infection replicates and the virus move towards many parts of the body through the lymphatic system. The viral occurrence in the blood stream is known as viremia. That results infecting many other cells including blood-derived

monocytes cells [15]. Both Macrophages and lymphocytes are mainly infected with the virus. Within two to six days of infection, viremia appears. As compared to DF patients, the level of viremia is found to be high in DHF patients. Plasma leakage into the abdominal and pleural cavities, is the most distinguishing feature causes low platelet counts that is below 100,000/mm3 within 1–2 days of infection and which remains low almost for 3–5 days in most cases while there is no plasma leakage found in case of DF [16]. Dengue virus initially interact with the specific receptor(s) of the host cell. The provision of surface recepetors facilitates the entery of vires to the target cell thus triggers signals for penetration, intracellular transport and cause infection in the host cell. The role of protein evcelop of the virus (E-protein) plays a crucial role in the attachment and ultimately the interaction with cellular responses [17].

Proteomic Analysis of Dengue Virus

The NS1 protein of dengue virus is usually consisted of about 352 amino acids with variable size of 40–55 kDa, depending on its glycosylation degree and is normally produced initially in viral infection, before the beginning of antibodies production in the infected host. Hence, dengue NS1 protein discovery in the patient's blood is seemed to be a suitable sign for detection in the early days of the fever [18]. Flavivirus, the non-structural protein NS2A is one of the main integral of the viral replication complex that utilized in virion assembly and alienates the host immune response. The detailed topology of this protein has not been determined while it was known to be associated with the endoplasmic reticulum (ER) membrane [19]. In the non-structural protein (NS) region, most of the proteolytic cleavages of the flavivirus polyprotein are affected due to virus-encoded protease which is comprised of two viral proteins i-e NS2B and NS3 [20].

NS4B, The highly hydrophobic transmembrane protein of the dengue virus, responsible for viral replication complexes formation which are typically necessary for the viral life cycle. DENV NS4A and NS4B are the main non-structural hydrophobic proteins, if solely, engaged in this task [21]. Their purposes and therefore their properties should be comparable to other non–structural proteins of other enveloped viruses which is involved in same functions such as NS4B from hepatitis C virus [22]. The most conserved protein in dengue virus known as NS5 protein has RNA-dependent RNA polymerase activity at its C-terminal domain and methyltransferase activity at its N-terminal domains and also having essential functions for capping of the mRN [23]. Cellular proteins also play significant roles throughout the life cycle of all viruses. In addition to, host cell nucleic acid-binding proteins make interaction with viral components of positive-stranded RNA viruses and regulate viral translation as well as RNA replication [24] (Table 1).

Protein Name	Function of Protein
NS1	Immune evasion
NS2A	RNA synthesis, viral assembly
NS2B	Viral replication
NS3	Enzymatic activities
NS4A	RNA synthesis and assembly
NS4B	Formation of the viral replication complex
NS5	Enzymatic activities
E	Envelope protein

Table 1: Proteins of the DENV2 and their function.

Discovery of Vaccine Against Dengue Virus

The spreading of dengue virus-transmitting mosquitoes is one of the main reasons for the wide spread of dengue disease since the past 50 years, and in recent times outbreaks have also detected in the United States. Development of drugs and vaccine against dengue virus is the most important worldwide health priority. The potential vaccine discovery is challenging because of the presence of all four serotypes of the dengue virus, which a vaccine must defend against [25]. The first vaccine against dengue virus has been approved in December of 2015 in several Asian countries and Latin American countries for protection against all four serotypes of the virus. The vaccine is a tetravalent, recombinant, live-attenuated with a yellow fever 17D vaccine virus backbone and is administered in a 3-dose plan at 6-month intervals [26]. In dengue endemic areas, the vaccine has been permitted to patients between 9-45 years of age though the age limit might vary by license. This vaccine is not intended as a routine vaccination for travellers [27]. Presently, CYD-TDV is primarily accessible in private market nut in Brazil and Philippines. The vaccine has been presented in subnationionl community based programs [28]. The vaccine has not been examined as mediation for dengue epidemic control however the 3-dose vaccine might be presented during an epidemic as part of worldwide dengue control strategy [29].

Dengue virus might be treated by virus isolation and serology i-e MAC-ELISA, IgG ELISA, NS1 ELISA, and PRNT, or by following molecular basis approaches (RT-PCR. PCR) which are taken as standard for dengue as serological tests suffer from cross-reactivity, variable sensitivity by timing of specimen collection, and the need for multiple samples which are IgG acute and convalescent samples [30] (Table 2).

Vaccine Name	Type of Vaccine	Stage	Earliest Licensure
CYD-TDV	Live attenuated chimeric vaccine	Complete	2015
TV003/TV005	Live attenuated chimeric vaccine	Phase III	2018–2019
TDV	Live attenuated chimeric vaccine	Phase III	2017–2018
TDEN	Purified inactivated whole virus vaccine	Phase II	2018
V180	Subunit protein vaccine	Phase I	
D1ME100	DNA vaccine	Phase I	...

Table 2: Modern dengue potential vaccine candidates that are being examined in various stages of clinical trials.

Prevention and Control

The development of dengue virus control tools urgently need, which include potent vaccines and vector control, in order to effectively the harm of dengue virus. The dengue virus infected population in more than 120 countries and has expanded since past decades [31]. The large-scale global forces will continue to contribute in the spreading of dengue virus, comprising population growth, unexpected urbanisation, and suboptimal mosquito control in urban centres [32]. Dengue prevention depends upon control of the mosquito vector, while several novel potential vaccine candidates and new tools for vector elimination are under assessment and will be presented in the near future. A novel approaches for dengue virus control and prevention is being employed for the period 2012–20, [33]. In the absence of effective tetravalent vaccine for dengue viruses, the vector control is the only approach to prevent viral infection. Besides this, reducing the area of skin exposed by wearing long pants, shirts with long sleeves, socks, and wearing a hat might be helpful to reduce the risk of infection. By applying pesticides on nets could be more effectible as the mosquito can bite the person right beside to the net. The insctide will either repel or kill the mosquito from biting human inside the net. Clean and stagent water is most favourable habitat for breeding of Aedes mosquito. By covering clean water, we can avoid the possible damage caused by dengue virus [34].

Conclusion

Almost 40% population of the world is under the risk of infection. Elimination of dengue virus signifies a missionary battle of the 21st century. Presently, to prevent epidemics, controlling the dengue mosquito is the only available method. On the other hand, new investigation for discovery of potential vaccine, evaluation of vector control tools and approaches are desirable. In conclusion, the modern research progresses on the prevention and treatment of dengue comprises different methods to control vector, vaccine identification and novel antiviral drugs discovery, since there are several under diagnosed cases of dengue virus infection due to these unusual modes of transmission.

Author Contributions

All the authors have accepted responsibility for the entire content of this submitted manuscript and have approved its submission.

Conflict of Interest

This study has no conflict of interest to be declared by any author.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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