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Dengue Viral Infection: Focus on Epidemiology, Laboratory Diagnosis, Management and Control Measures

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Abstract Among the various seasonal infections, Dengue virus infection has become a potential public health threat contributing to severe morbidity and mortality both in developed and developing nations. With no specific prophylactic treatment options and no vaccine available for prevention of infection, thousands of deaths and severe economic burden are attributed to the dengue viral infection worldwide. The condition is most severe in the low-socioeconomic nations which are ill equipped to control the vector *Aedes aegypti* responsible for spread of infection. Health awareness among the public regarding the potential nature of dengue virus, measures required in controlling the spread of infection and effective management of infected patients during Dengue epidemics and endemics is the need of the hour.

Keywords: *dengue fever, Aedes aegypti, diagnosis and management of Dengue, control and prevention of Dengue*

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1. Introduction

Dengue fever is an arthropod-borne viral infection caused by Dengue virus, belonging to the genus Flavivirus group also consisting of other vector borne viral infections like the yellow fever, Japanese encephalitis, St. Louis encephalitis and others. Many of these flaviviral infections are distributed throughout the world causing significant morbidity and mortality. Individual cases, isolated outbreaks and limited geographical impact have undermined the serious nature of these viral infections. Although vaccines are available for the control and prevention of few of these viruses (yellow fever virus, Japanese B encephalitis), globally these viruses are responsible for considerable mortality and have been difficult to prevent. Dengue virus is transmitted to human predominantly by mosquito *Aedes aegypti*. *Aedes albopictus*, *Aedes scutelleris complex* and *Aedes polynesiensis* have also been identified as potential vectors of dengue viral transmission in various geographical regions. Dengue virus is a RNA virus possessing positive sense single-stranded RNA genome made of approx. 11,000 base pairs consisting of three structural and seven non-structural proteins. Important antigens include the capsid (C), precursor of membrane (prM) and envelope antigen (E). Non-structural antigens include NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5 [1,2,3].

2. Historical Significance

Early descriptions of dengue viral infection as a 'water poison' caused by flying insects' dates back to 265-420 AD during the Chin dynasty. Modern era description of dengue viral infection dates back to 1780, when an epidemic struck Philadelphia which was described by Benjamin Rush as break bone fever. Complicated dengue viral infection clinically appearing as haemorrhage, shock and death was first described in 1897 in an outbreak in Australia. In 1903, dengue viral transmission was experimentally proved to be caused by mosquito *Aedes aegypti*. The dengue virus was first cultured in laboratory in 1944 and later in 1956 it was described to have four serotypes. Dengue virus may persist in various amplifying hosts including mammals, birds, reptiles and arthropods by maintaining a non destructive life cycle before being responsible for vertebrate infection [2,4] Figure 1.

3. Epidemiology

It has been noted that reports of incidences of dengue viral infection have increased thirty- fold over the last half-a-century throughout the world. It is estimated that more than 390 million cases are reported annually with five lakh patients developing severe dengue (DHF/DSS) and 20,000 deaths throughout the world. Dengue viral infection globally has been observed to be present as endemic in many parts of world and few regions identified as hyperendemic where all the dengue serotypes are in circulation as noted in Brazil. From the Indian perspective dengue, which was previously presenting as a classic

epidemic pattern with initial outbreak and later sporadic small outbreaks mostly in urban areas and spreading geographically towards semi-urban regions has now changed the pattern causing large scale outbreaks involving both urban and rural areas. World health organization (WHO) has recently recognized Dengue virus as the most important vector-borne viral infection in the world considering the increase in the geographic areas (spreading through previously unaffected areas) affected by the virus and the economic burden of the disease. It has also been noted that the environmental factors (weather/climate) influence the spread of dengue virus. Long gaps between rainfalls leading to increased temperatures could be another facilitating factor for the survival and breeding of vectors. From our own experiences it was noted that the incidences of dengue virus infections peak through July and decline near November (Figure 2). This trend may change in case of late or early rainfall patterns, which is directly proportional to vector breeding times and virus transmission [4-10].

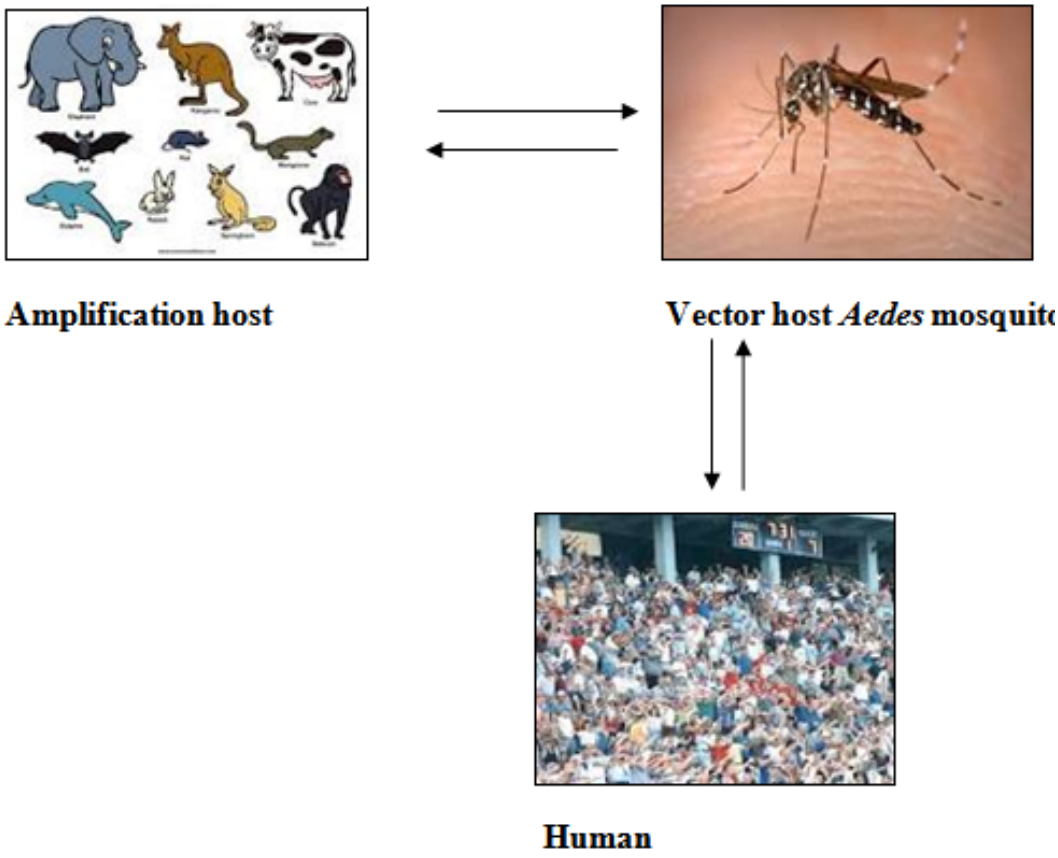

Figure 1. Non destructive life cycle of Dengue virus and hunan transmission

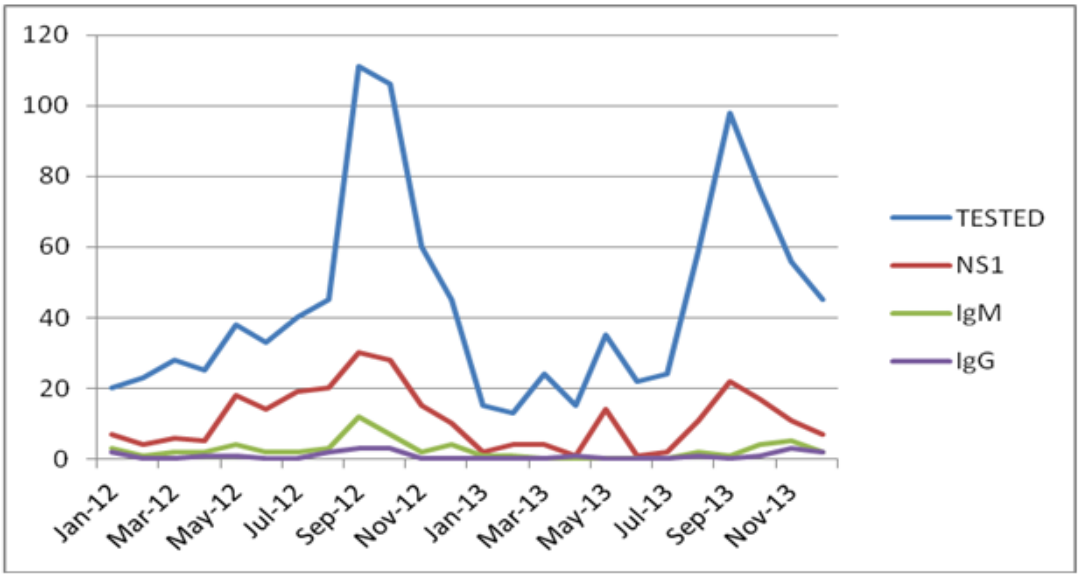

Figure 2. A two year trend of dengue viral infection showing seasonal prevalence at a tertiary care center at Prathima Institute of Medical Sciences, Karimnagar, India (Unpublished data)

4. Dengue Virus Disease

Dengue virus circulates in four serotypes (DENV 1-4) and endemic parts of the world simultaneously harbour all the four serotypes. Although infection with dengue virus is self limiting and that infection with single serotypes results in lifelong immunity to the specific serotype, the cause of concern is that there is only limited cross protection against other serotypes. Dengue viral infection presents usually as a three phase disease, the febrile phase, critical phase and recovery phase. During the first stage, patients develop fever with or without chills which may last for up to one week, head ache, sore throat, anorexia, retro-orbital pain, musculoskeletal pain, myalgia, macular skin rash, mild hemorrhagic manifestations (pitechiae, nose and gum bleeding) and leucopoenia. The second phase, critical phase, termed as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) is considered as a serious consequence leading to severe internal organ haemorrhage, plasma leakage, ascitis, pleural effusion, organ failure and shock. The patients also complain of abdominal pain, vomiting and severe thrombocytopenia. Clinical diagnosis of dengue remains complicated due to varied and similar symptoms resembling other seasonal infections. Although infection is self limited in most of the infected population, the risk of developing severe dengue (DHF/DSS) increases in secondary dengue infection with a different serotype. Differential diagnosis of dengue with other illnesses including chickungunya, influenza, measles, rubella, infectious mononucleosis, meningococcal infection must be carefully evaluated [5,6].

5. Laboratory Diagnosis

Laboratory diagnosis of dengue viral infection depends on the detection of NS1 antigen and dengue specific IgM and IgG antibodies in the patient's serum. Neutralizing and haemagglutination inhibition antibodies can be detected during the first week of infection. Serological and molecular methods available for the diagnosis of dengue viral infection include rapid immunochromatographic tests that can detect NS1 antigen and IgM and IgG antibodies, Enzyme linked immunosorbent assay (ELISA), IgM antibody capture ELISA (MAC-ELISA) and dengue specific reverse transcriptase polymerase chain reaction (RT-PCR). Viral isolation, fluorescent antibody techniques and nucleic acid sequence based amplification methods (NASBA) are also available for the diagnosis of Dengue [11,12,13].

6. Management of Dengue

Dengue viral infection has no specific treatment as yet apart from the management of patients for associated complications. Oral/intravenous rehydration is indicated to replace the loss of body fluid due to high fever, vomiting and capillary leak. A careful clinical evaluation based on the patients history and critical monitoring of vitals (pulse, blood pressure, urine output and hematocrit) for possible symptoms of shock may be beneficial in initiating measures for better patient management. Whole blood, platelets and fresh frozen plasma transfusions may be administered in severe cases of haemorrhage. Investigations for secondary infections must be simultaneously done. It is also advised that prophylactic platelet transfusion may not be necessary in patients who are haemodynamiccally stable. Avoiding acetyl salicylic acid (Aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDS) is necessary which may otherwise contribute to complications of internal bleeding. Fluid overload must be avoided as this may result in pulmonary oedema, pleural effusion, ascitis and acute respiratory distress syndrome (ARDS). Electrolyte and acid-base imbalances, hypo/hyperglycaemia and serum calcium levels must be carefully monitored for better patient management [14].

7. Control and Prevention

As there is no specific treatment available for dengue viral infection, and most vaccines are currently under trials, the only way to prevent dengue viral transmission is by controlling the vector responsible for its spread. World health organization has proposed guidelines for vector control called as integrated vector control measures (IVM) to effectively control mosquito vector throughout the world. Public health awareness programmes must be initiated and community based activities should be undertaken to remove and destroy mosquito-breeding sites. Fogging of the house-hold environments with insecticides in regular intervals during the mosquito breeding season may help in control of vector. Mosquito repellents and insecticide coated mosquito nets may help in avoiding potential infective mosquito bite. Use of chemical larvicides (Organophosphorous/Pyrethroid (methoprene, pyriproxyfen and temephos) and biological agents (larvivorous fish, predatory copepods and *Bacillus thuringiensis* serovar *israelensis*) have been successful in the control of vector but their use in treating potable water is still in debate. The only way to prevent dengue viral infection is by vaccination. Currently there is no licensed vaccine available for Dengue, apart from few candidate vaccines that are still under trials. Recently a live attenuated tetravalent chimeric Yellow fever-Dengue virus vaccine (CYD-TDV) has progressed to phase III trials. Several other candidate vaccines including the live-attenuated, sub-unit, DNA and purified protein vaccines are also undergoing clinical trials [15,16].

8. Conclusion

Dengue infection, though is a self limiting seasonal viral infection, spread throughout the world, prompt clinical and laboratory diagnosis combined with appropriate patient management strategies are necessary to reduce the morbidity and mortality of dengue viral infection. Regular surveillance (epidemiological, clinical and laboratory surveillance) of dengue viral infections is required to understand the factors responsible for the spread of the disease, serotypes in circulation and severity of the infection, which may be helpful to prepare ourselves during the subsequent seasonal infections.

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