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Review Article

CURRENT REVIEW ON DENGUE : LIFE CYCLE OF DENGUE, PATHOPHYSIOLOGY AND DIAGNOSIS

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ABSTRACT

Dengue is the major health concern in developing countries. Dengue is mainly caused by four serotypes of dengue virus (DENV). Based on the symptoms dengue is classified into febrile fever, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). It had become endemic to 128 countries that may occur throughout the year. Dengue virus has two life cycles – sylvatic and urban cycle. These both life cycles occur in primates, mosquitoes and humans. This disease is transmitted generally by *Aedes* species mosquitoes. *Aedes aegypti* and *Aedes albopictus* are the primary carriers for the dengue transmission. The majorly used diagnostic assays are serology, virus RNA (RiboNucleic Acid) detection, antigen detection and virus detection. In endemic countries dengue is uncontrollable due to unavailability of vaccines and particular antivirals. Protective measures such as larvicide spraying and wearing suitable clothes to prevent mosquito bites can reduce the diseased population. Government, stakeholders and public health system can contribute for awareness programmes to public in endemic countries. Sanofi Pasteur invented dengvaxia used for 9 to 45 years age people can help to reduce the severity of dengue.

Keywords : Dengue, dengue virus (DENV), *Aedes* mosquito, diagnosis, dengvaxia.

INTRODUCTION

Dengue is the arthropod borne disease caused by Dengue Virus (DENV). It is commonly seen in the tropical and sub-tropical countries which is endemic in those areas. [1] According to World Health Organisation (WHO), it is internationally major health problem affecting 3.97 billion people with 400 million cases. [1,2] There exist four serotypes of dengue virus are DENV-1, DENV-2, DENV-3, DENV-4. [3,4] In 2013, a fifth serotype that causes a mild disease was isolated in Malaysia. [5] From the past few years dengue virus (DENV) has spread from not more than nine endemic countries to 128 countries. [6,7] The rapid spread of the DENV to other places in the world is due to a wide international travel and trade, urbanisation, global warming, virus and vector evolution. [8]

The transmission of DENVs is through arthropod vectors like *Aedes aegypti, Aedes albopictus* mosquitoes. These are mostly seen in tropical and sub-tropical regions.[9,10] Recently, the WHO and Special Programme for Research and Training in Tropical Diseases (TDR) had revised the guidelines for the classification of the cases of dengue as:

1) Mild self-limiting illness.
2) Dengue with broad range of signs such as – accumulation of fluid, pain in abdomen, persistent vomiting, bleeding of mucosa, lethargy, increase in haematocrit and decrease in platelets.
3) Severe dengue which show signs such as – leakage of plasma, heavy bleeding, failure of organ. [11]

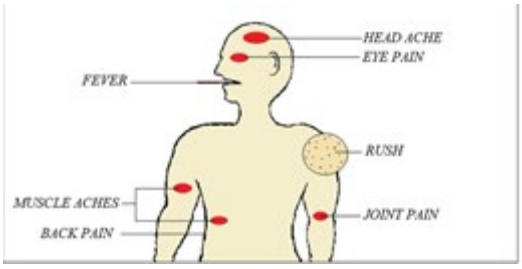

Figure 1: Symptoms of Dengue

Previously, dengue infection was classified as a mild fever known as dengue fever (DV), a complicated condition- dengue hemorrhagic fever (DHF) and a dengue shock syndrome (DSS). After the mosquito infected blood meal, the incubation time is 3-15 days. The transmission of virus from human to human by injury due to needle sticks, contamination of blood products, organ donating and transmission to an unborn child from infected mother. [12] Dengue is endemic in 128 countries that may occur throughout the year. Dengue has highest prevalence during the rainy season due to the environment is suitable for the

vector breeding.[13] The epidemic of dengue occur mostly during the rainy season because of more vector population and exposure of humans to mosquito bites is high. [14] Due to the lack of vaccine and antivirals the dengue epidemic can be controlled by taking appropriate measures. The measures can be taken to control the vector population like awareness programmes to educate the people about insecticide spraying and protective clothes wearing to avoid mosquito bites. [7,8,15] Sometimes dengue fever is similar to malaria and considered as presumptive malaria in the endemic countries. The regular and distinctive diagnosis of dengue may provide accurate treatment and can avoid antibiotic and antimalarial drugs. In endemic countries dengue burden can be estimated by regular screening of the public. [16]

World Health Organisation proposed the severity level and classification of dengue as mentioned in figure 2 and table 1 [17]:

FIGURE 2 : WHO DENGUE CLASSIFICATION AND LEVELS OF SEVERITY

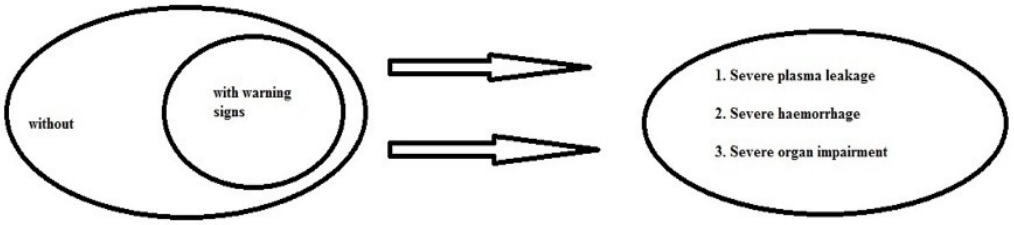

Figure 2 : WHO Dengue classification and levels of severity

TABLE 1 : WHO DENGUE CLASSIFICATION AND LEVELS OF SEVERITY

CRITERIA FOR DENGUE ± WARNIING SIGNS		CRITERIA FOR SEVERE DENGUE
Probable dengue Travel to/ live in dengue endemic area	Warning signs*	Severe plasma leakage leads to:
Fever and two of the following criteria: Rash Nausea, vomiting Torniquet test positive Pains, aches Leukopenia Any warning sign Laboratory-confirmed dengue (This is important when there is no sign of plasma leakage.)	Abdominal pain or tenderness Persistent vomiting Clinical fluid accumulation Mucosal bleed Lethargy, restlessness Liver enlargement > 2cm Laboratory: Rise in HCT concurrent with rapid fall in platelet count. *(needed strict observation and medical intervention)	Shock (DSS) Fluid accumulation with respiratory distress Severe bleeding is evaluated by clinician. Severe organ involvement. Liver: ASTor ALT >= 1000 CNS: Impaired consciousness Heart and other organs

EPIDEMIOLOGY

Among the mosquito spreading infections dengue is becoming a most common arboviral disease. In the past fifty years dengue epidemic has increased 30-fold. [18] At present dengue is endemic to 128 countries and attacking 3.97 billion people in the developing countries per year. Recently, there is an estimation of dengue causing infections to 390 million and in which 96 million cases have apparent occurrence. [19,20] The epicentre for dengue is the Indian sub-continent [21] where the cases are largely underestimated. [22] So, the importance for serosurveillance can enhance the government to be ready for the epidemic. [23]

DENGUE VECTOR

The virus of the dengue is generally transmitted to humans through the *Aedes(Ae.)* mosquito that belongs to the subgenius *Stegomyia.* The most common vector in tropical and subtropical regions is *Aedes aegypt. Aedes scutellaris* complex consist of species *Aedes albopictus, Aedes polynesiensis. Aedes scutellaris* complex and *Aedes niveus* are the secondary vectors. [21] *Aedes niveus* is a sylvatic vector. *Aedes* mosquito life cycle may last for 8-10 days that depends on the feeding at room temperature. *Aedes* mosquito have life cycle of two phases. First phase is aquatic consist of larvae and pupae stage. Second phase is terrestrial having egg and adult stage. *Aedes albopictus* vector can be modified to any temperatures including mild climates. *Aedes albopictus* spread DENV to new regions free of *Aedes aegypti.* [24] But its contribution to causing infections is low. [23]

DENGUE VIRUS

Dengue virus belongs to the family *Flaviviridae* and can cause West Nile Encephalities, yellow fever and Japanese Encephalitis. Dengue virus exist in four serotypes (DENV 1-4). The fifth serotype has to be justified. [25] In Malaysia, fifth

serotype is identified during an outbreak in 2007 by virus samples screening. [25] The genome of the four serotypes have 65% homology [26] but the fifth serotype is different phylogenetically. [25]

The virus consist of single stranded positive sense RNA of diameter 50nm. [27] The capsid (C) surrounds the genome. Inturn, the capsid is covered by lipid bilayer inside and glycoprotein shell outside. The envelope (E) and membrane glycoproteins (prM/M) are present as projections on the surface of the lipid membrane. The size of the genome is 11 kb. It encodes C, E and prM structural genes and NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 non-structural genes (NS). Non-structural genes encodes the proteins. These proteins have role in viral assembly and replication. [27] The structure of dengue virus is shown as in figure 3.

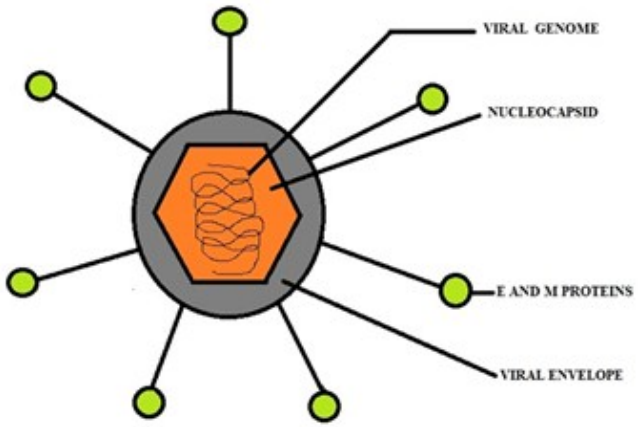

Figure 3: Structure of Dengue virus.

LIFE CYCLE OF DENGUE

The life cycle of dengue is between mosquitoes and humans. The two life cycles of DENV are separate. They are sylvatic and urban cycles occur in primates, mosquitoes and humans.[28] The mammals like lower primates and humans act as reservoirs for transmission of dengue. The infection to humans is caused by four serotypes DENV (1-4) through mosquito transmission in the urban cycle. If the mosquito feeds on an infected human it acquire viruses.Then the midgut epithelial cells of the mosquito are infected by the viruses. The viruses systematically spread to the tissues and salivary glands through the hemocoel. The virus transmission occurs in an uninfected human is through the bites of infected mosquitoes. [29]*Aedes aegypti* and *Aedes albopictus* mosquitoes are the primary carriers for DENV transmission to humans by their bites in the urban cycle. In sub-tropical and tropical areas, *Aedes aegypti* is the primary vector that transmits viruses. *Aedes albopictus* is the secondary vector for DENV that can survive in both tropical and temperate regions. It has spread to all continents excluding Antarctica. *Aedes albopictus* can cause the diseases that are presently absent in these areas. In Europe and China, DENV is majorly transmitted by *Aedes albopictus* vector. [30, 31, 32]

PATHOPHYSIOLOGY

Dengue pathogenesis is not fully known. In the pathogenesis of dengue virus the intracellular events occur in a successive way. The intracellular events are response of unfolded proteins then succeeded by lipid bodies, lipophagy, endoplasmic reticulum, autophagy. [33] The present-day research is concentrated upon dengue viral infection on dendritic cells (DCs) in the skin. After the infected mosquito bite, the virus enters into the dendritic cells and interacts with the main factors of immune system in the human body. [34] While the host immune system tries to clear the virus, then the DV shows strong phenotypes. In this way, dengue infection pathogenesis is connected to immune response. Macrophages, dendritic cells and monocytes are the important targets for DV infection in humans. The infected mosquitoes after injecting DV its foremost target is Langerhans cells in the epidermis and dermis. [35] The inflammatory response and damage to these cells is due to platelet and endothelial cross reaction with DV non-structural protein (NS1). It is concluded that in DV infection anti-dengue viral NS1 is related. [36]

Increase in viral infection depends on improvement in antibody which also inhibit IFN (Interferons) type-1 mediated antiviral responses. Vascular permeability increases due to soluble factors uncontrolled production and abnormal activated T- cells. Plasma leakage process includes activated immune system or complement system activated by cytokine production. The complement fragments like C5a (Complement factor 5a) and C3a (Complement factor 3a) proteins are involved in vascular permeability. [37] Induced autoantibodies production results abnormal activation of coagulators, platelets and endothelial cells. [38] Cytokines mediated vascular permeability in DHF produces plasma leakage in peritoneal and pulmonary chambers. In DHF there is no damage to vessels wall due to absence of vasculitis. [39]

The dengue infected various organ lesions are examined by Pove'aet al. [40] In this study haemorrhages and oedema of all organs were observed. In liver, micro and macrosteatosis, necrotic areas were observed. The majorly damaged organ is liver. Destructed fibers in myocarditis are seen in cardiac lesions. In spleen, there is germinal centres loss and lymphoid follicles atrophy. Respiratory distress increases by megakaryocytes in alveolar spaces. Autopsies of six patients died due to acute dengue infection was done by Rathiet. al [41] and conclude that the causes for death were hypotension, acute renal failure, hepatic failure, bleeding diathesis and acute respiratory distress.

TYPES OF DIAGNOSTIC METHODS

Diagnosis of dengue is useful in controlling the outbreak, regular diagnosis and epidemiological surveillance. Regular diagnosis can be done in people suffering from febrile diseases and travellers in endemic countries. The diagnostic assays are serology, virus detection, antigen detection and virus RNA detection. They differ with sensitivity, specifity, advantages and limitations.

VIRUS CULTURE

The samples of plasma, serum or buffy coat are inoculated into either mammalian cell lines like LLC-MK2 (Rhesus Monkey Epithelial Kidney Cells), Vero cell lines or mosquito cell lines of AP61 (clone of *Aedes pseudoscutellaris* cell line), C6/36 (*Aedes albopictus* cell line). [42] The DENV isolation can also be done in sucking mice by intra-cerebrally. [43] From fatal cases the virus isolation is by autopsy of liver, spleen, lymph nodes and thymus. [3] By using monoclonal antibodies specific to serotype in immunofluorescence the identification of serotypes is done.

More copies of virus is available during the acute phase of dengue infection. The cultures are prepared from the samples collected from patients during the acute phase. Before the onset of symptoms acute phase has fast replication and elevated load of virus. [3] For accurate results the samples must be collected at right time.

ANTIGEN DETECTION

Non- structural protein (NS1) is the chief target antigen. During the replication of virus NS1 is produced. After the disease onset upto nine days, from the secondary and primary infection patients the detection of this protein can be done. [44] In acute phase infection the infected cells secrete NS1. Stimulation of humoral response is due to NS1 in blood. DHF progression is linked to increased levels of NS1. Dengue prognostic marker is NS1 quantification. [45]

METHOD OF SEROLOGY

Screening of dengue IgG (Immuno globulin G)/ IgM (Immuno globulin M) antibodies is done by serology method. Production of IgM antibodies starts from the four to eight days of fever onset and continue for 2 weeks. After the primary infection the production of IgG is decreased and maturation occurs in weeks, months and continues for years. [46] Surveillance of dengue is performed by IgM assays based on ELISA (Enzyme Linked Immuno Sorbent Assay). IgM-based assays act as tools for diagnosis. Test results must be interpreted carefully. Flaviviruses like St. Louis encephalitis virus (SLE), yellow fever virus (YFV), West Nile virus (WNV), Japanese encephalitis virus (JEV) involves in cross-rectivity. At the time of results interpretation to determine the acute febrile illness is DENV infection the patient's record of vaccination, history of recent travelling, medical history are reviewed. Extended sero-conversion period makes the results false-negative. [47] Recent infection is identified by anti-dengue IgM presence. The secondary and primary infection classification is by detection of IgG. [48] If IgM/ IgG ratio is lower than 1.78 assures secondary infection while more than 1.78 shows primary infection. [47] The IgA diagnostic value is identified. The levels of IgA antibodies are more in DHF/ DSS than in DF. [49] The antigen quality used in the IgM based assays gives specificity and sensitivity.

DETECTION OF VIRUS RNA

Polymerase chain reaction is used to detect the dengue RNA. This is done during infection at acute phase from blood, tissues or sera samples by primers. The specific regions of genome serotype are directed by primers. [50, 51] NS1, E, prM/ E, E/ NS1, NS5/ 3 and NS5 are the regularly used regions of genome for PCR (Polymerase Chain Reaction). RT-PCR (Reverse Transcriptase PCR) is used to quantify the load of virus. Phylogenetic analysis and nucleotide sequencing are required to perform strain typing. [52]Due to contamination in nested PCR false positive results may occur in lab. This can be prevented by proper precautions. [43] Real time PCR has developed to give easy and rapid assay even exposure to contamination in detection and typing of dengue. DENV serotypes detection by *in-vitro* qualitative method needs hydrolysis of dual labelled and primers of oligonucleotide in multiplex or singleplex reactions. Delayed collection of sample impedes this method. The diagnosis of dengue is not hindered by negative result. For infection confirmation anti-IgM ELISA is performed. [53]

DENGUE DISEASE CONTROL AND PREVENTION

Mostly diseases can be prohibited by medicines and vaccines. Due to deficiency of vaccines and medicines like antivirals some measures are needed to control this disease. In endemic countries the travellers and people living in these areas can be educated on basic measures. Spraying of insecticides and protective cloths to wear is the most preferred method.

The responsibility and involvement of public, stakeholder and government in endemic countries is needed for successful control. The policies can be established for considering dengue as notifiable disease. Spraying of larvicide and sustained environment are used as measures to decrease vector population. Most countries in tropical regions dosen't have indicator measurements to control vector population. In vulnerable countries dengue disease is controlled by awareness programmes in public and regular disease surveillance – response information. [54] Management of water supply and effective disposal of waste helps in reduction of breeding vectors. Innovative policies by operational research are laid for providing cost-effective and evidence based knowledge to prohibit dengue. Mosquitoes are genetically modified to interrupt their transmission and to decrease their population. Dengvaxia is a dengue vaccine invented by Sanofi Pasteur used in 9 to 45 years people. In hotspot regions new drug discovery and treatment availability for dengue are accelerated. [53]

CONCLUSION

This review article gives brief information about dengue disease classification, vectors, DENV and diagnosis. In developing countries the dengue is mainly due to DENV and underreporting, misdiagnosis of dengue has made it occurrence more. Lack of prioritization of public health and regular surveillance also contributed in endemic countries. In these countries dengue can be considered as notifiable disease by training personally, commitment to public health and regular diagnosis. Diagnosis of dengue by IgM antibody tests must be provided in all primary health care centres. In endemic countries the travellers must be provided knowledge on dengue symptoms, uses of dengue tests before the departure or later going to their countries. This is to decrease the spreading of the disease in their countries .

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