Review Article

Clinical Manifestations, Diagnosis, Treatment and Prevention of Dengue Fever

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ABSTRACT

Dengue hemorrhagic fever is a serious of aggressive diseases due to RNA virus which belongs to flaviviridae family. The virus is transmitted by Aedes mosquitoes. Threatening complications like Dengue hemorrhagic fever, Dengue shock syndrome and asymptomatic fever are the manifestation of the diseases. Temperature rises, arthralgia, myalgia, skin rash, and shock in the circulation are the major signs. In some conditions oral characteristic manifestation only present, premature, and intense detection is vital to lower mortality rate. For healing from the diseases, early treatment on some changes in the viral strains, pattern severity of the diseases, and early detection of the virus is very important Population growth, rapid urbanization, global warming, and international travel to the native area contributes a great role in disease distribution. Among the four serotypes (DEN-1, DEN-2, DEN-3, DEN4) one may cause the virus and is transmitted by the bite of an infected Aedes Aegypti mosquito, the virus is also transmitted by Aedes Albopictus. In dengue virus various molecules of protein form virus partied three of them are (PRM, E and C) in addition seven other protein molecules are involved in replication of the virus, these proteins are found in infected host cell and its genome contains 11000 nucleotide bones. The initial host for dengue virus is the human, and after the bite of a person by an infected Mosquito he or she becomes infected with it in 8 to 10 days. The virus has no harmful effect on the mosquito, it also transmitted by infected blood and organ donation.

Introduction

Dengue is a clinical condition of hemorrhagic fever, which is a severe aggressive disease caused by RNA virus which belongs to Flaviviridae family. The virus is transmitted by Aedes mosquitoes. It is also called as Dengue hemorrhagic fever (DHF) and Dengue shock syndrome, sometimes it is asymptomatic fever [1]. The manifestation of the disease is hyperthermia, arthralgia, myalgia, skin rash, and shock. In some conditions non-systemic manifestations can only be observed and it is very important to identify the premature, and intense detection to lower the mortality rate. Dengue fever is a mosquito-borne disease that has four different genotypes/ serotypes. World Health Organization (WHO) recognizes the Dengue fever as a major global public health concern in tropical and sub-tropical areas.

Dengue fever affects individuals of all age groups, which is a hard flu-like infection and transmitted by Aedes Aegypti mosquito mainly seen at the time of rainy season. In this review we will go through the epidemiology, virology, pathogenesis, clinical manifestation, diagnosis, vaccination, treatment, prevention, and control of vector.

Dengue virus is a group of flavivirus genus alongside zika virus, yellow fever, and others. It has infected around 280-550 million people worldwide yearly [2]. WHO approximates that 50 million cases were reported yearly in around hundred countries and most of the infected people continuing with flu-like signs and symptoms, from these nearly 2.5% of the patients acquire DHF manifested by long time fever, hemorrhage at mucous membrane and abnormal hematology which leads to collapse of circulation and death in 2.5-20 % of cases. There is not enough information or literature weather the disease is progressed to dengue fever or dengue hemorrhagic

fever [2, 3]. In various hemorrhagic fever caused by virus involving dengue, cytokines have critical function. Preliminary studies explain the relation between severity of diseases and raised level of various cytokines with prognostic value. Generally, these investigations have explained that cytokine levels affect the coagulation adversely in DHF versus dengue fever. Antibiotics of the tetracycline class of antibiotics have processed immunomodulation characteristics which is used for victims with various sclerosis, rheumatoid arthritis, Huntington's infections by suppressing activity of microglia. Which reversely decreased levels of various pro inflammatory cytokines such as TNF and IL-1. A person who is formerly prone to one DENV serotype is at greater risk for strict symptoms caused by another serotype. Determining the preliminary prone history of a patient is critical as the experiencing symptoms of DENV infection provides perception of the patient's risk of developing severe diseases [4]. There is no particular treatment or vaccine against the virus only supportive care is available.
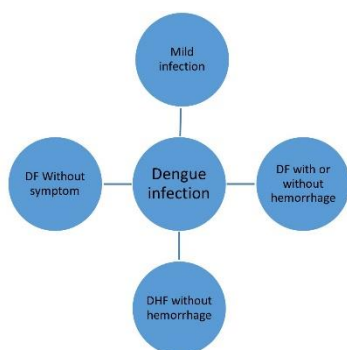

Figure 1. Natural history of dengue syndrome

Epidemiology:

About 50-100 million people infected by Dengue virus globally in each year. The death rate ranges from 1-5% and less than 1% without and with treatment respectively. The mortality rate because of the severe form of dengue fever (DHF) reaches to 26%. The prevalence of dengue rises to 30 folds in the year 1960-2010 due to factors such as rapid urban development, international travel to native areas, growth in population and global warming. Asia and pacific region are the major area affected by the virus and it spreads around the equator [5] About 50-100 million people infected by Dengue virus globally in each year The death rate ranges from 1-5% and less than 1% without and with treatment respectively. The mortality rate because of the severe form of dengue fever (DHF) reaches to 26%. The prevalence of dengue rises to 30 folds in the years 1960 to 2010 due to factors such as rapid urban development, international travel to native areas, growth in population and global warming. Asia and pacific region are the major areas affected by the virus and it spreads around the equator [6].

Virology:

In 1960 an article reported that how the virus is isolated from a collected specimen (12 from sera of human and 2 from infected mosquitoes) in manila were shown Dengue virus [7]. Two studies conducted on monkeys in the Philippines evaluate that possible sylvatic transmission cycle indicates the presence of dengue antibodies [7]. The length of the viral

genome is approximately 11kb and the three parts of the mature virus are membrane associate, core, and envelope. It also contains nonstructural proteins like NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5 [8]. The envelop protein implies the major biological function of the virus and is related to specific form of RBC agglutination called hemagglutination, protective immune response and neutralizing antibody induction [9]. Specialists concerned that earlier dengue virus infection could cause more severe zika disease; however, both are transmitted by Aedes Aegypti mosquitos and cause similar symptoms. Congenital zika syndrome can cause neurological disorder and infection during pregnancy results in birth defect and development problems in babies is termed in some conditions. Dengue is native infectious diseases of the subtropical and tropical area and quickly becomes a global burden. Civilization, increase urbanization, population growth and international travel plays a greater role for the spread of the virus as well as to distribute geographically and demographically. Vaccine development is a demanding work because of presence of 4 marked antigenic serotypes dengue virus.

Pathogenesis:

It has four firmly similar genotypes/serotypes such as DEN-1, DEN-2, DEN-3, and DEN-4. Primary infection with specific serotype is mostly asymptomatic or leads sensitive infection characterization. Although for the virus pathogenesis crossed reactive antibodies and T-cell have a major role. However, those system lonely could not show the immunopathological procedure that result dangerous conditions. But for the occurrence of sever diseases the viral factors, genes of the host and pathology of the immune system play critical role. So further investigation of dengue virus particular immune response in patients with critical, strict, and non-symptomatic dengue fever to find out the resistant correspondence of acute clinical infection and defense is necessary [10]. In general dengue virus is a bleeding characterization related with decrease level of platelet count and raise in circulatory porosity, leakage of plasma into serous space is clear in most of DHF [11].

Thrombocytopenia:

As recommended from the preliminary report the virus found to produces bone marrow repression, low level of platelet production, leads to thrombocytopenia, further coagulation disorder which includes thrombocytopenia as well as fibrinolysis. Yet typical spread into intravascular coagulation in most of the patients who infected with the virus is seen. Diversely study conducted on patient's platelet kinetics who affected with DHF shows raise in platelet demolition as the main cause of thrombocytopenia [11].

Clinical Manifestations:

Undifferentiated fever: this stage often occurs in initial infection and the initial second infection, it is hard to identify clinically from other various viral illnesses and mostly they remain undiagnosed [12] Dengue hemorrhagic fever regularly seen at the time of secondary dengue infection;

although occurs in infants in primary infection due to dengue antibodies attained maternally.

Dengue shock syndrome: It is a form of DHF followed by narrowing of pulse pressure (<20mmHg), restlessness, clammy skin, cold, cyanosis circumorally, shock, unstable pulse , various organ dysfunction and intravascular dissemination of coagulation (disorders in which proteins that control blood clotting become overactive) which narrates the mortality rate associated with DSS. Dengue fever affects individuals of all age groups, which is a hard flu-like infection and transmitted by Aedes Aegypti mosquito mainly seen at the time of rainy season.

The suggested investigation for DENV infection is: -

- Primarily viral replication in macrophage.
- The virus directly infects the skin.
- The host viral infection produces immunological and chemical-mediated mechanism.

The virus is progress as worldwide life terrifying population health threats infecting approximately 2.5 billion individuals over 100 countries. Doctors should be informed about the various clinical characterizations of the situation and certify a prior and sufficient treatment goal. Technique of mosquito prevention, production of vaccine and antiviral agent are the aim to fight this life threatening viral infection [13].

A clinical syndrome caused by infection of the virus are: DHF, DSS, and DF. WHO standard for classification of virus into a spectrum of three categories clinically are shown in the following table 1.

Classification of dengue hemorrhagic fever is depending on severity. Only hemorrhagic characterization has positive tourniquet. Grade-1 constitutional non-specific symptoms and fever. Grade-2 similar to grade 1 but involves unforced hemorrhagic characterization. Grade-3 circulatory failure characterized by narrow pulse pressure, weak and rapid pulse. Grade-4 undetectable pulse and shock profoundly. Grade-3 and grade-4 describes DSS [14].

Diagnosis:

Dengue fever probable diagnosis is cutaneous rash. The blood picture or hematology is also giving valuable insights for the confirmation of the infection. Decreased WBC count such as less than or equal to 5000 cells/mm3, high levels of Hematocrit in the range of 5-10%, lower platelet count of 150,000 cells/mm^3 or lesser than that will be considered as an infectious condition [15-17].

Additionally, any one of the following such as the serology of a single sample of serum, where the titer along inhibition test of hemagglutination and positive testing on the antibodies of immunoglobulin M as confirmed dengue fever cases in the same location as well as time. The affirmed dengue cases will be subjected for dengue virus isolation from CSF, autopsy, and serum sample. There is a significant increase of serum IgG and IgM. Dengue virus detection and tissue in antigen, CSF and serum using ELISA [17].

Laboratory Diagnosis:

Diagnosis of dengue accurately and rapidly is greatly important. Isolation of the virus from clinically provided specimen is done at the time within the illness of first six day and without delay it processed. Specimens for isolation of virus suitably are Serum at the acute phase; Plasma of patient lethal case tissue autopsy particularly spleen, liver, thymus, lymph node and collected mosquito of the affected area; Viral nucleic acid detection; Genome of viral RNA is detected using polymerase chain reaction reverse transcriptase (PCR-RT). The following Immunological response and serological test are performed to confirm the infection: Inhibition of hemagglutination assay, Fixation of complement, Test of neutralization, ELISA-IgG indirectly, Ratio of IgG/IgM, Viral antigen detection [16].

Vaccination:

Due to intense clinical signs as well as broad distribution geographically, the vaccine is essentially needed. But authorized vaccine is not available,

Table 1: The categorization of Dengue infection as per WHO guidelines

DF	DHF	DSS
Sever febrile infection more than two of the below characteristics: Severe headache, high grade fever lasting for 3 days-a week, myalgia and joint pain, metallic test, loss of appetite, diarrhoea, vomiting, stomachache, erythema, and capillary dilation.	Fever or sever fever, for a period of 2-7 days, petechiae, purpura, epistaxis, gingival and mucosal bleeding, splenomegaly, flushing, hematemesis, menorrhagia, bradycardia	Cold clammy skin and unstable pulse, circumoral cyanosis, shock, multi-organ damage, intravascular coagulation
Low level of WBC	Vomiting blood or melena	Restlessness, Rapid and weak pulse
Supportive serology	Lower platelet count (< 100,000 cells/mm3)	Circulatory failure, Hypotension
Occurrence at the same location and time as other confirmed	increased vascular permeability due to plasma leakage characterized by Increase in hematocrit > 20% above average for age,	Plasma leakage, thrombocytopenia,
Laboratory criteria	**Sex and population**	
Isolation of dengue virus > 4-Fold change in antibody titres	Decrease in hematocrit after volume-replacement treatment > 20% of baseline Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia	
Demonstration of dengue virus antigen, ecchymosis		
Detection of dengue virus genomic sequence		

but recently some of the vaccines are progressed to clinical trials for control and prevention of virus infection. The problem with the vaccine is that antibody dependent enhancement, also known as subsequent illness, along with possible serotypes can increase dengue virus severity. One clarification of this event is previous non-neutralizing antibodies could possibly increase the potential of the recently developed dengue virus to attack FcgR carriage cells [18]. Deficiency of antibody cross protection between serotypes of dengue virus infection is common. To develop vaccine for dengue virus, the live attenuated tetravalent vaccine is the most promising candidate with progress clinical trial.

The Sanofi Pasteur's is one vaccine candidate for dengue virus, which is based on yellow fever gene replication and the envelop gene incorporation of the 4 virus serotypes, go in for clinical development in Australia and is in final stage. However, there is an affair about virus replication interference between serotypes, if 4 types of serotypes of virus replication is not balanced, non-dominant serotypes replication can be interfered by dominant serotypes, which can lead to preferential antibody reaction to the controlling strain and results into developing a greater serious disease. Consequently, a perfect dengue vaccine can produce neutralizing antibody reaction simultaneously against all serotypes and should be safe when use to develop safe and effective dengue virus vaccine testing of the recombinant dengue infection vaccine effect is necessary such as virus-like particles (VLPS) [19].

For many viral infection particle vaccines convey significant assurance as vaccine participant. VLPS can be produced by baculovirus, yeast, and mammalian cells, and the recombinant form taken up efficiently, processed and internalized by antigen presenting cells and able to bring out strong cellular and humoral immune reactions against dengue. Vaccination along with tetravalent or monovalent VLPS leads to production of particular cellular reaction, consequently VLPS should be powerful vaccine participant for virus infection prevention [20].

Prevention and Control of Vector:

To control dengue virus the following are preventive measures: Eliminate vector breeding areas, cleaning rooms and roofs, repellent use, environment control, control of patient contact, isolation of case for five days, and finding undiagnosed case, determination of density of vector and eradication. International agreement provision in airplane, land, and ship transport [21].

Therapeutic Development:

Various drug trials were performed in Asia and South America for diseases control since prior to 2000. However, due to insufficient evidence on patient's demography, hire virus severity, and elucidate measurement of end point unhappily the explanation of the results of the previous trail are dumb founded [22, 23]. Spend more time to come to the clinic due to the pathway of finding, small molecular agent. The most current evidenced conception clinical trial for the virus have done using repurposed or off-patent agents, includes prednisolone, chloroquine, balapiravir, lovastatin and celgosivir. All trails have used the ordinary double- blinded, disorganized, inactive drug control pattern with obviously determined initial end points. The agents were established safe in victims with critical or severe dengue but ineffective to reach consequently elucidated end point of trail [24].

Conclusion

Dengue fever is a mosquito-borne disease that has four different genotypes/serotypes. WHO recognize Dengue fever as a major global public health objection in tropical and sub-tropical areas. The virus gains entry together with the saliva of a mosquito carrying DENV when the mosquito bites a person. It reproduces inside WBC while moving all over the body. The signaling protein (interferons) that are produced by WBC are responsible for most of the symptoms like:-increase in temperature, sever pains, flu, in strict infection with raise virus production organ (kidney, liver, bone marrow can affected), less blood circulates and blood pressure decrease due to leakage of fluid from the blood stream via the wall of small blood vessel into body cavities, so that sufficient blood can.t supplied to the vital organ in addition bone marrow impairment leads to low number of platelet count essential for clotting of blood, that rises the chance of hemorrhage. Various diseases in children as well as in healthy babies is caused by dengue virus. Men have less chance to be affected. For the "diabetic", and "Bronchial asthma" patients the virus is terrifying, polymorphism (normal variation) in a specific gene could decrease the risk of severe dengue complication. Creating awareness to the people to eliminate replication areas, standing water and tyers which are not in use. The person should take precautionary measures like wear protective clothes, use mosquito repellents. Take environmental quantifications for the detection and elimination of mosquito replication areas. The virus is progress as worldwide life terrifying population health threats infecting approximately 2.5 billion individuals over 100 countries. Doctors should be informed about the various clinical characterizations of the situation and certify a prior and sufficient treatment goal. Technique of mosquito prevention, production of vaccine and antiviral agent are the aim to fight this life threatening viral infection. For successful victim control prior as well as precise laboratory identification of the virus is analytical. Until date we have no sufficient biological markers in process for strict diseases, prior studies has recommended that raised volume of non-structural protein-1 and viremia have indicative value.

Host reaction gives a powerful indicative marker in addition to dengue virus biological markers for strict infection continuation, many participants came to be recognized, but auguring merit is so far looked for certify. Sero transformation of S1 toS2 as studied by Immuno-serum goblin M, ELISA affirms severe dengue diseases.) Avoiding standing water which provide to the vector breeding habitats, screening of door and window are the fundamental technique of mosquito control.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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