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Review Article

Dengue: A review on disease symptoms, detection and its management

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KEY WORDS:

ABSTRACT

In recent year's ecological distribution of dengue have significantly increased in tropical areas. Dengue is a deadly viral disease for which the mosquito *Aedes aegypti* serves as a vector. In order to control this disease, the researchers around the world showed their interest and time investment in dengue vaccine development. To achieve this goal, several antiviral drugs were designed to prevent viral genome replication. The present review will provide a detailed overview of the Dengue disease, symptoms, vaccines, antiviral drugs, diagnostic tests, advanced diagnostic tools, bioinformatics work on Dengue virus and home remedies for its control. Vaccines are vital approach to safe community from viral infections. Many antiviral drugs are designed in order to prevent viral genome replication. Home remedies and herbal medicines for dengue are pure and natural with no side effects, are much effective in viral control and stimulating the immune system. Several fruits rich in vitamin C, leaves from various plants like Papaya, Neem, Basil, Amaltas and Coriander are also highly effective in disease control.

Introduction

Dengue fever is a mosquito-borne disease, which originates in sub-tropical and tropical areas around the globe and is also called as “break bone fever” and “dandy fever” [1]. The dengue viruses belonged to genus *Flavivirus*, family Flaviviridae. The genus *Flavivirus* is comprised of yellow fever, tick-borne encephalitis, Japanese encephalitis, West Nile and hepatitis C viruses [2].

The word "dengue" was derived from the Swahili expression Ka-dinga pepo that portrays the disease as being brought on by an evil spirit. The Swahili word dinga have its source from Spanish word dengue which means fastidious or cautious [3]. In West Indies, the slaves who contracted dengue were supposed to have the gait and posture of a dandy and the disease was identified as "dandy fever" [1]. Dengue virus appeared in early nineteenth century and was found common to all tropics and subtropics. Outbreaks have recently happened in the Caribbean, together with Puerto Rico, Costa Rica in Central America, Cuba and South America. In Cambodia, Viet Nam, Philippines and Malaysia, around 1020333 cases were reported from 2001-2008; with highest disease records and deaths in Western Pacific Region countries. In 1994, the first confirmed outbreak of Dengue Hemorrhagic Fever (DHF) occurred in Pakistan [4].

The dengue virus has spherical shape, about 50 nm in diameter, with nucleocapsid made up of viral genome and C proteins. The nucleocapsid is enclosed in a membrane (lipid bilayer viral envelope), encoded from the host. The E and M proteins are embedded in the viral envelope that crosses through the lipid bilayer [4].There are five serotypes of dengue viruses DEN-1, DEN-2, DEN-3 DEN-4 and DEN-5, with similar characters. However genetic variations still exist within these serotypes. These viruses have diverse interaction with the antibodies found within human blood serum and therefore are called as serotypes. Infection by serotype 1 can afford long lasting immunity

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to same serotype, however just heterologous or limited immunity to other serotypes for a short time post-infection. Following this initial partial immunity, the risk of "dengue hemorrhage fever" and "dengue shock syndrome" increases as a result of reinfection by another dengue serotype [5]. The size of Dengue viral genome is almost 11000 bp, which codes for 3 structural proteins i.e. membrane protein M, capsid protein C, 7 nonstructural proteins designated as NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5 and short non-coding sequences on 3' and 5' ends. The non-structural proteins have a vital role in viral replication and assembly [6, 7]. The platelets production system is primarily influenced by dengue virus. A normal person platelet count varies from 150,000 to 250,000 per unit volume. On infection, the patient's platelets are reduced, which mean that the body is not building enough platelets as required. Food, exercise, racial origin and disease are factors influencing individual's platelet count [8].

The dengue epidemic occurs in more than 110 countries [1]. Majority of the patients improve without disease severity. Without disease treatment, the death rate is 1-5%, and with adequate treatment, it is less than 1%. On the other hand severe disease carries a death rate of 26%. This virus infects fifty to hundred million people all over the world in a single year, leading to a half million hospitalizations and around 12,500-25,000 deaths [9].

Indication and symptoms of Dengue fever:

Classical dengue fever does not prompt any complications, also called as simple dengue fever. After 5 to 6 days of infection, symptoms appear as flu in the beginning, then having the "triad" of fever, rash and headache. Dengue hemorrhagic fever (DHF) is most severe, which results in complications in the vascular system like bleeding which appears like small blood spots on the skin, than bigger patches of blood under the skin and minor wounds [10]. Dengue shock syndrome (DSS) is normally seen in young people and children. The mortality rate among patients with DSS is reported to be more than 44%. If a person is already suffering with the attack of one serotype of virus and gets infected with a 2nd type, he experiences dengue hemorrhagic fever with extreme shock [11].

Symptoms of Dengue fever are headache, arthralgia (joint pain), exhaustion, fever, swollen lymph glands (Lymphadenopathy), severe myalgia (muscle pain), abdominal pain, Mucosal bleeding, continuous vomiting, high hematocrit and rash. Other signs are severe pain behind eyes, bleeding gums, severe abdominal pain, red palms and soles, rapid breathing, persistent vomiting, fatigue, bloody vomit, restlessness, petechiae (little purple or red splotches or blisters below the skin), black stools and bleeding from nose [9]. Diagnosis of dengue fever can be hard, since its symptoms and indications can easily be mystified with other diseases like malaria, West Nile virus, typhoid, and chikungunya fever. Both Chikungunya virus (CHIKV) and dengue virus can be transmitted by *Aedes aegypti* and *Ae. Albopictus* [12].

Methods for detection of Dengue virus

Molecular Detection of Dengue virus:

Dengue fever may be diagnosed by microbiological laboratory testing by isolation of virus in cell cultures, viral antigen detection or specific antibodies (serology) and nucleic acid detection by PCR[13]. Virus isolation and nucleic acid findings are more reliable methods than antigen detection, but are not extensively accessible due to their higher cost. PCR and viral antigen identifications are more perfect in the first 7 days [12].

Complement fixation and antibody neutralization tests:

There are some complex tests called complement fixation and neutralizing antibodies which required technicalities, they are only performed in specialized laboratories [11].

MAC-ELISA test:

The MAC-ELISA (IgM Antibody Capture Enzyme Linked Immunosorbent Assay) test is used for rapid confirmation of dengue fever. It needs to be repeated every 10 to 14 days, if initial test was negative [11].

Dengue NS1 Rapid test:

The Dengue NS1 Rapid Test is based on lateral flow technique which detects NS1 antigen, from 1st day of fever, sensitivity and specificity is 92.8% and 98.4%. Quick Dengue Test monitors glycoprotein that is said to be vital for viability of virus, however has no reputable biological action. This NS1 antigen is available at higher amounts in the sera of the patients infected by Dengue virus, so it might be utilized as appropriate marker for quick Dengue Test. Dengue NS1 ELISA Kit for detection of NS1 antigens in human serum, and Dengue ELISA Kit for detection of IgG, IgM, and IgG/IgM antibodies are available [13, 14].

Latest diagnostic tools:

For dengue diagnosis latest nano-diagnostic techniques such as liposomes (complex structures made of phospholipids and small amounts of other molecules), nanowires (that have a lateral size guarded to tens of nanometers or less and unimpeded longitudinal size) and nanopores (a minute hole in a thin membrane, normally sufficiently big to allow passing of only a particular molecule of DNA), coupled to conventional fluorescence (giving out of light by a body that has engrossed light or further electromagnetic radiation), potentiometry (find the concentration of a

solute in solution) and voltammetry (information about an analyte is obtained by measuring the current as the potential is varied) have been described and developed. However these are not available at present in clinical facilities [25]. Furthermore, current instrumental methods like quartz crystal microbalance (QCM measures a mass per unit area by measuring the alteration in frequency of a quartz crystal resonator), surface plasmon resonance (SPR observe label-free biomolecular relations in liquids), photonic crystal (are dielectric structures occurs in periods that contain a band gap that avoids propagation of a light's certain frequency range) plus electrochemical impedance spectroscopy have also shown hopeful results [15].

Management of Dengue:

No specific treatment is available for dengue fever. Fever is treated by anti-pyretics like Paracetamol, Aspirin and Acetaminophen. Aspirin or other non steroidal anti-inflammatory medicines such as ibuprofen and acetylsalicylic acid can increase the bleeding [16]. There are no specific anti-viral injections or tablets that can destroy the dengue virus. Analgesics are used to treat pain in the bones [17]. Hospitalization is required for patients suffered with DHE or DSS. Without proper treatment of the disease, death rate can be up to 50% [18].

Patients who have very low platelet counts or having serious DHF, transfusions of platelets is administered. Transfusion of blood is also requisite in patients with rigorous DHF, but there is no available data on its utilization. In order to avert dengue virus spread, evade being bitten by the mosquitoes (disease carriers), spraying exposed body parts, using mosquito nets at home and wear protective clothing [19].

Vaccines:

Researchers are working for the development of a secure, efficient and less expensive tetravalent vaccine for all the 5 Dengue serotypes. Five type of vaccines are in progress named as live attenuated vaccines, chimeric live attenuated vaccines, inactivated vaccines, subunit vaccines and nucleic acid-based vaccines [20, 21]. These vaccines require multiple doses to provide immunity [22]. A DNA vaccine is developed by the U.S. Naval Medical Research Center [23]. Destroyed virus particles are used in the preparation of inactivated vaccines; moreover subunit vaccines are prepared from dengue virus proteins. An immune response is produce by dengue antigens in both vaccines. Both vaccines comprise elevated level of protection since the virus lacks the ability to replicate. Both need booster vaccinations to grant long lasting immunity, and are extra costly to manufacture than the live attenuated vaccines [24]. In order to design chimeric live attenuated vaccines, genes from various sources are combined to generate a live attenuated virus. The characteristics of ideal chimeric live attenuated vaccines are same like live attenuated vaccines [25].

Antiviral drugs:

There is no specific drug available for the treatment of dengue. Certain antimicrobial compounds from plants are found to be effective to inhibit the replication of dengue virus, but no published record is available for this treatment [26]. Along with Dengue vaccine development, scientists are working to design alternative antiviral drugs [27]. Thousands of potential antiviral compounds are involved in the development of antiviral drugs. Nucleoside analogue blocks a dengue infection; a important example of the antiviral drug. This antiviral drug prevents viral replication in infected cells without having any toxicity or harmful side effects [28].

Currently, vaccination available against dengue infection remains indescribable. There is no particular treatment in opposition to dengue just preventive and supportive care is the treatment. The therapy known as Double-stranded RNA mediated interference (RNAi) is a simple and rapid method of silencing gene expression in a range of organisms, discovered in 1998. The incorporation of dsRNA into the cytoplasm of cell is the first step of this mechanism. Dicer enzyme (DICER) degrades Double stranded RNA, resulting in small interfering RNAs (siRNAs). These siRNAs associates with RNA-Induced Silencing Complex targets and cleaves complementary mRNA. So, the researcher found that siRNAs can be used against several viral diseases, especially ssRNA genome containing viruses. Many of them have been conducted to use siRNA against DENV and siRNA against DENV replication [29].

For predicting protein-protein interaction they developed a novel computational method that captures the essential physical and chemical properties of the interactions between antibody and virus. Scientists achieved important information that made them able to revamp antibody of dengue virus envelope to make progress in its binding by an astonishing 450-folds, when they learn and certify information from various three dimensional structures of interface between antibody and protein complexes. Pan American Health Organization (PHAO) is an international public health agency, who developed the cross-reactive and pan-dengue neutralizing antibody, which was defensive against dengue serotypes in culturing cells and in an animal replica of disease [30]. TV003, one vaccine combination, appeared to stimulate the antibody response against the dengue serotypes. In 45 percent of participants a single dose of TV003 results in an antibody response to all dengue serotypes. It means TV003 stimulate immune response to at least three viruses in 90 percent participants [31].

Home Remedies for Dengue virus control:

Home remedies for dengue are free from side effects

and give relief from various DV symptoms. Herbal medicines allow body to fight against infection, bacteria, viruses and stimulate the immune system by increasing the amount of white blood cells. Herbal anti-viral are advised to patients of dengue infection, as dengue is a viral disease [32]. *Echinacea* and *Astragalus* are popular herbal medicines used against dengue. Fruits rich in vitamin C, like amla are advised to dengue patients. Vitamin C (ascorbic acid) is easily absorbed by body and solved in water, helps immediately to return platelet count [33]. Orange juice is a good natural and effective home remedy to treat dengue fever and also a great source of vitamin C. Drinking orange juice two or three times improves the digestion, immunity of the body, enhances urine output and increases the antibodies for healing. Grape juice is also effective home remedy to treat dengue fever and increase the blood counts in the body [34]. The vitamin C content in guava is five times more than in oranges and effective home remedy to treat dengue fever. Guava leaves are also said to be useful in dengue fever prevention [33]. Papaya may be used as a medicine for dengue fever. Researchers have found that papaya leaf juice is effective in curing dengue. The juice of papaya leaf boosts platelets. A tea made from the leaves of the papaya is also useful in dengue fever prevention [35]. Neem (*Azadirachta indica*) leaves, Neem oil are a great purifying agent and effective for dengue treatment [36]. Ayurvedic medicine Giloy (Guduchi) or Amrita capsules are remedy for dengue. Giloy also increases the platelet count [37]. Jaggery or gurwith Raw Small Onion increase the blood platelets count and also increase the immune power to cure Dengue fever. The tawa–tawa Herbal plant, also known as snake weed is also a cure for dengue fever as it increases the blood platelet count. Boiled Tulsi (basil leaves) is bitter and pungent herb served in a warm drink, like tea. It is said to prevent outbreak of dengue [38]. *Cassia fistula*, also called Amaltas or golden shower tree 'disease killer' is used as a tonic for preventing dengue fever. Herbal tea made with fenugreek leaves (Methi) is good remedy for dengue fever [39].

Bioinformatics analysis:

In bioinformatics, several tools and methods are available to study the variation of E glycoprotein (structural protein). In order to maintain its function and structure, there must be some conservative regions, variation may found by the study of huge number of sequences of E protein which will help in designing sequence and structure of new vaccines for the treatment of dengue virus infection. Hydrophobicity, flexibility, accessibility, antigenicity and exposed surface of polypeptide chains are parameters. In this study Web servers and other software's were also used [40].

A number of scientists are trying to introduce this method for the development of drug for the treatment of dengue fever. It is very difficult to design conserved epitopes for five dengue serotypes because of structural variations in them. As DENV-3 death rate in Pakistan is very high, the researcher chose type 3 of dengue virus (DENV-3) [41]. By analyzing the sequence of individual serotype a better drug can be design. By using computational software, some variable regions and more than 600 E glycoprotein sequences of this protein were analyzed. They found 75.2% conserved bases, approximately 20% mutation rate, large number of conservative sites in the glycoprotein and large number of polar amino acids (Ser, Thr, Asn and Gln). Some methods like hydrophilicity, accessibility, antigenicity and flexibility were selected to predict the epitopes, on the basis of secondary structure prediction. Bioinformatics approaches were used for the development of both B-cell and T-cell epitopes of DENV-3 envelop E glycoprotein. For DENV-3 the sequences at 37-66, 80-121, 183-228 and 242-279 amino acids were predicted as the common epitopes by using several parameters and different softwares. The selected sequences have higher scores and also showed better hydrophilic properties in the average antigen index (AI), which could predict the antigen epitope of envelop glycoprotein E. The predicted antigen epitopes may be used for vaccine development against DHF [40, 42].

The current Dengue status in various countries:

Dengue, a main cause for disease and death in the tropics and subtropics since the 1950′s is quickly spreading in the Western side of the equator. More than 30% of the world's population is at danger for the mosquitoes that transmit any of four related Dengue infections (DENV). Infection induced lifetime assurance to a specific serotype, yet progressive exposure to an alternate DENV improves the probability of extreme manifestation of dengue fever, dengue hemorrhagic fever, or dengue shock syndrome (DF, DHF or DSS) [43].

Simultaneous infection with two agents can bring about an illness having coinciding symptoms making a diagnostic dilemma for the treating doctor. The symptoms of dengue may be similar to different diseases, for example, jungle fever, Japanese encephalitis, leptospirosis, chikungunya, influenza A, and *Salmonella typhi*. There is scarcity of information in regards to dengue and typhoid co-disease both in the developing and developed nations. A study was conducted to discover the recent co-infection rates in North Delhi. Medical records of 659 patients displaying febrile disease (Kasturba Hospital) were contemplated. By using Dengue IgM antibody capture ELISA test, dengue specific IgM antibodies were discovered. Of the 659 febrile sera tests, 141 (21.39%) were found positive for dengue virus. Of these 659 patients, 91 were females, 50 guys and remaining were males. Of these dengue cases, 11 were co-infected with enteric fever

(11/141= 7.8%). Most extreme number of dengue positive cases seen in ages from 0-10 y. Co-infection ought to dependably be remembered while managing cases of dengue or enteric fever with or without atypical peculiarities. To decrease the load of disease, alongside change of sanitation and individual cleanliness, importance ought to be given on vaccination against typhoid [44].

Dengue hemorrhagic fever is also a genuine issue in Indonesia. Since the first cases reported in 1968, frequency rate becomes greater and around 37.3/100.000 cases were observed to be infected with the Dengue in 2012 with case casualty rate of 0.9%. Dengue is a self- limited and systematic viral infection. Struggles to know the range of illness, clinical appearance, pathogenesis, analysis and management were made to reduce disease and mortality [45].

According to dengue control program the spraying of reactive insecticide are preferred around houses of reported cases in order to control the transmission of dengue virus. The researchers performed a prospective study on dengue around households in city of Vietnam Ho Chi Minh (HCMC). The researcher's registered 52 suspected dengue cases and 19 non-dengue controls (71 index cases), 25–35 household members and neighbors who were followed up over 2 weeks were enrolled. The main purpose of spraying insecticide is to reduce mosquito numbers in the houses of reported dengue cases and their neighbors. RT-PCR, NS1-ELISA and/or DENV-IgM/- IgG sero-conversion tests were used for the identification of DENV infections in group participants. The results showed that patients of dengue living close to HCMC were no more likely to be attacked by dengue over a period of two week than controls who did not live near to dengue patients [46].

Conclusion

Dengue is a major global threat common in more than 110 countries. Infection by one of the five DV strains has been revealed to give enduring safety against the homotypic re-infection, but only temporary protection against a secondary heterotypic infection. ELISA, Complement fixation and neutralizing antibody tests, detection by PCR and NS1 Rapid Test are used for diagnosing dengue fever. Advance nano diagnostic tool have also shown hopeful results. For dengue virus infection, no exact anti-viral injections or tablets are available but it is treated by anti-pyretics. Due to dengue-specific complexities, 5 types of vaccines are in progress. For treating dengue infection there is no specific antiviral drug. Scientist used a part of virus (dengue) to produce a therapeutic drug against dengue the envelope protein. Double-stranded RNA mediated interference (RNAi) therapy is also developed against dengue virus. A lot of bioinformatics work is in progress on dengue genome. Home remedies and herbal medicines for dengue are free from side effects and are effective against DV symptoms. The development of new vaccines, antiviral drugs and improved diagnostics tests are important for public health that shows hopeful results against dengue. Extensive research is required to magnify the role of medicinal plants for the treatment Dengue disease.

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