PACIFIC JOURNAL OF MEDICAL SCIENCES

{Formerly: Medical Sciences Bulletin}

ISSN: 2072 – 1625

Pac. J. Med. Sci. (PJMS)

www.pacjmedsci.com. Email: pacjmedsci@gmail.com.

DENGUE FEVER: AN OVERVIEW

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Submitted April 2016; Accepted May 2016

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INTRODUCTION:

Dengue Fever is caused by one of the arthropod –borne viruses of the genus *Flavivirus* in the family *Flaviviridae* [1]. They are also called arboviruses. The genus includes a number of other viruses transmitted by mosquitoes and ticks that cause diseases in humans; these are yellow fever, West Nile, Japanese encephalitis, and tick-borne encephalitis viruses [1].

Aedes aegypti is the main vector for the dengue virus (DENV) worldwide. In nature, infection by the DENV involves mainly humans and *Aedes* mosquitoes, although in Malaysia and West Africa dengue transmission have been reported in monkeys and forest *Aedes* spp [1]. The vector as well as the less common species have been reported to live around homes biting humans mainly during the day and breed where there are small collections of fresh water, such as in cisterns and even in backyard litters. For example, surveys in Texas revealed that up to 25% of premises had *A. aegypti* breeding in their water containers [1]. It has been reported that humans are uniformly susceptible and that age, race and gender do not appear to influence this susceptibility [1, 2].

In 1943, Ren Kimura and Susumu Hotta first isolated the dengue virus [3]. These two scientists were studying blood samples of patients taken during the 1943 dengue epidemic in Nagasaki, Japan. A year later, Albert B. Sabin and Walter Schlesinger independently isolated the dengue virus. These scientists working in different countries isolated the virus now referred to as dengue virus 1 (DEN-1) [3].

Dengue Virus (DENV) Genome and Structure:

The genome of DENV is a single strand positive-sense RNA (ss RNA) of approximately 11 kilobase. The positive-sense implies that the RNA can be translated directly into polypeptide. The RNA genome of DENV encodes 10 genes. During translation the DENV genome produces a single long polypeptide chain, which is later fragmented into 10 separate proteins [4].

The 10 proteins are made up of 3 structural proteins and 7 non-structural proteins. The

structural proteins are the Capsid (C), Envelope (E) and Membrane (M). The non-structural proteins are NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5. They are involved in viral replication and assembly [4].

The DENV is roughly spherical in shape. The Nucleocapsid that forms the viral core is made up of the viral genome and the Capsid (C) proteins. The viral envelope is the lipid bilayer (membrane) that surrounds the Nucleocapsid. There are about 180 copies of proteins E and M embedded in the viral envelope and span the lipid bilayer. These proteins form the protective outer layer that regulates the entry of the DENV into the host cells [4]. The glycoprotein E contains most of the antigenic determinants of the DENV and is essential for viral attachment and entry into the host cell.

During infection, the DENV attaches to the surface of the host cell and enters the cell via Endocytosis. Inside the cell, the DENV fuses with the endosomal membrane and is released into the cytoplasm. The DENV particle comes apart, releasing the viral genome. The positive-strand viral RNA is then translated into a single polypeptide, which is fragmented into 10 proteins. The viral RNA is replicated by using the genetic materials of the host [4]. When production of the structural proteins and RNA genome are completed, the assembly of new DENV occurs on the endoplasmic reticulum. The immature viral particles are transported through the trans-Golgi network (TGN), where they mature and are converted to their infectious form. When the mature DENV are released they then infect new cells [4].

Infected white blood cells respond by producing cytokines, such as interferon that are responsible for most of the symptoms characteristics of dengue fever, the flulike symptoms and severe pains [4, 5]. In severe infection, large amount of the DENV are produced and many more tissues and organs (such as the liver and the bone marrow) are affected. Dysfunction of the bone marrow can cause thrombocytopenia that increases the risk of bleeding, which is one of the major complications of severe dengue [4, 5].

Dengue Serotypes:

Four closely related dengue viruses named DEN-1, DEN-2, DEN-3, and DEN-4 are known to cause dengue infections [1, 4 – 7]. Each of the four viruses has different interactions with antibodies in the human host serum, thus they are called Serotypes. Genetically, the four dengue viruses are similar because they share about 65% of their genomes; however, within a single serotype, there is some genetic variation. Despite these variations, infection with each of the dengue serotypes results in the same disease and range of clinical symptoms.

Infection with one serotype provides life-time protection only against that particular serotype. However, it is still possible to become infected

by other serotypes, which may develop into severe dengue [4 – 7].

According to the WHO expert consensus groups, dengue is a single entity with different clinical presentations [6, 7]. Infected patients may present with a range of clinical symptoms that vary according to severity and age. Infection by any of the four dengue serotypes may be asymptomatic or may lead to classic dengue fever (DF), or to more severe forms of the disease, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [6, 7]. In 1997 the dengue case definition was limited in terms of its complexity and applicability. This recognition of the limitations led to a multicenter study in seven countries in Asia and Latin America. A new case definition emerged from this study. The new WHO classification for dengue severity was divided into Dengue without Warning Signs, Dengue with Warning Signs, and Severe Dengue (DHF) [6, 7].

Epidemiology of dengue and severe dengue:

The DENV is endemic in many areas of the tropics and subtropics, Asia, Oceania, Africa and parts of North and South America. Outbreaks have been known to occur in the Caribbean and the USA (Rio Grande Valley of Texas). In 1981, 350,000 cases of dengue were recorded in Cuba of which 158 died [8]. According to the current WHO database, only 9 countries had experienced severe dengue epidemics before 1970. However, the disease is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific [9,10]. The America, South-East Asia and Western Pacific regions are the most seriously affected [9 – 11]. In 2008 the cases across the Americas, South-East Asia and Western Pacific exceeded 1.2 million and over 3 million in 2013 [9 – 11]. The threat of a possible outbreak of dengue fever in Europe was raised because local transmission was reported in France and Croatia in 2010 and imported cases were detected in 3 other European countries. In 2012, an outbreak of dengue on the Madeira Islands of Portugal resulted in over 2000 cases and imported cases were detected in mainland Portugal and 10 other countries in Europe. In 2013, severe dengue cases occurred in Florida (USA) and Yunnan province of China. Dengue also continues to affect several South American countries, notably Costa Rica, Honduras and Mexico. In Asia, Singapore has reported an increase in cases after a lapse of several years and outbreaks have also been reported in Laos. In 2014, trends indicate increases in the number of cases in China, the Cook Islands, Fiji, Malaysia and Vanuatu, with DEN-3 affecting the Pacific Island countries after a lapse of over 10 years. Dengue was also reported in Japan after a lapse of over 70 years. A total of 2.35 million cases of dengue

were reported in the Americas alone in 2015, of which 10200 cases were diagnosed as severe dengue causing 1181 deaths [10 – 11]. The year 2015 was characterized by large dengue outbreaks worldwide, with the Philippines reporting more than 169000 cases and Malaysia exceeding 111000 suspected cases of dengue, representing a 59.5% and 16% increase in case numbers to the previous year, respectively. Brazil alone reported over 1.5 million cases in 2015, approximately 3 times higher than in 2014. Delhi, India in 2015 recorded its worst outbreak since 2006 with over 15000 cases. The Island of Hawaii USA was affected by an outbreak with 181 cases reported in 2015 and ongoing transmission in 2016. The Pacific island countries of Fiji, Tonga and French Polynesia have continued to record cases. An estimated 500000 people with severe dengue require hospitalization each year, a large proportion of which are children. About 2.5% of those affected died [10 – 11].

In the recent and ongoing outbreak in Papua New Guinea (PNG) a total of 170 cases were seen at the Daru Hospital Outpatient Department, Daru Western Province from 4 November 2015 to 8 January 2016 [12]. There were a total of 126 clinical cases and 44 confirmed cases (2 confirmed by PCR as DENV-2). Age of cases ranged between 6 to 35 years with children less than 5 years representing 12% of the cases. Seven severe clinical cases were hospitalised; all of them recovered and discharged. Several other cases have been reported in Port Moresby General Hospital with no fatalities reported [12].

Clinical Manifestations of dengue:

Infections by the DENV may not be apparent or may be subclinical. When symptoms are obvious, three classes may be recognized: Classic dengue (dengue with warning signs), dengue haemorrhagic fever (DHF, also known as Severe Dengue) and an atypical form (dengue without warning signs) [6, 7, 13]. Classic dengue is also known as “break bone fever” (because of the associated muscle and joint pains) and it occurs mainly in non immune people. The usual incubation period is 5 to 8 days. These patients may have mild conjunctivitis and coryza which may be followed a few hours later by a sudden onset of severe headache with pain in the back of their eyes as well as in the lower back. About three quarters of these patients may have sore eyes with some photophobia. Rigors are commonly seen later. Patients in this category may have some difficulty sleeping, anorexia and a bitter taste. Quite a few of them may experience some weakness at this stage [6, 7, 13]. About a quarter of these patients may have a sore throat with some rhinitis. Cough is hardly seen in this group. Some patients may present with bleeding noses and gums, haematuria and black stool (melaena). In one study where 26 patients were recruited, 13% had bleeding peptic ulcers on endoscopy. Ninety percent

have red eyes which were tender upon pressing [1, 14]. Some of these patients may present with non tender palpable lymph nodes in the posterior cervical, the epitroclear and the inguinal groups. Over half of these patients may have small vesicles in the posterior part of the soft palate. The tongue is often coated in these patients and they have skin rash which vary from diffuse flushing over the thorax and inner aspect of the arms. Later these give way to a more definite maculopapular rash on the trunk on the third to the fifth day and spreads peripherally. This rash may be pruritic and ends with drying or scaling.

Extreme bradycardia is rare in this group of patients. About 2 to 3 days after the onset of the illness, the fever as well as the other symptoms may almost subside completely. This remission however may last for 2 days only to be followed by the return of fever and the other symptoms, although they are usually not as severe as during the initial attack. This is described as a saddleback diphasic phase of the illness although it may not occur in some patients [1, 6, 7, 13, 14]. This febrile illness may last 5 to 6 days and terminates abruptly. Some patients may experience fatigue for several months after the attack of dengue fever.

The atypical mild illness may be seen in some patients. Symptoms include fever, anorexia, headache and muscle aches. Clinical examination may reveal skin rashes but involvement of lymph nodes is usually absent. The course of the illness is usually less than 3 days [1, 6, 7].

In both the classic and mild dengue, the leukocyte count may be low or normal. By the third to the fifth day the leukocyte counts of less than 5000 per microliter and neutropenia are common. Sometimes albuminuria of moderate degree may be seen [14].

Severe Dengue {Dengue Haemorrhagic fever (DHF)}:

This is the third category of Dengue infection. Severe dengue (also known as Dengue Haemorrhagic Fever DHF) was first recognized in the 1950s during dengue epidemics in the Philippines and Thailand. Today, severe dengue affects most Asian and Latin American countries and has become a leading cause of hospitalization and death among children in these regions [6, 7, 13].

All the 4 dengue serotypes can cause Severe Dengue and Dengue Shock Syndrome (DSS). This may occur in about 5% of patients, especially in patients who have previously been infected with another serotype of DENV. This is referred to as “Secondary Infection”. The major reason why secondary infection with a different serotype of DENV places individuals at risk of developing Severe Dengue Fever and DSS is not clear. However, the most widely accepted hypothesis is that of antibody-dependent enhancement (ADE). Severe dengue and DSS

are the most serious clinical manifestations of DENV infection. Some researchers have suggested that ADE and immunopathological mechanisms are implicated in such complications [6, 7, 13].

In Asia, children suffer more from severe dengue, with one peak occurring under the age of 1 and a second in older children aged 3 to 5. In infants, the disease is associated with primary infection in the presence of maternal antibodies. Studies in Thailand have estimated the frequency of DSS as 11 per 1000 secondary dengue infections with the disease being more common in girls. DSS tends to occur more frequently in the indigenous populations. It seems to be rare in people of European descent [6, 7, 13, 14].

Clinical Manifestations of Severe Dengue:

The illness begins abruptly and is characterized by fever, cough, pharyngitis, headache, anorexia, nausea, vomiting and abdominal pain which is often severe. This usually lasts for 2 to 4 days. Muscle pain, joint pain and bone pains are unusual compared to the classical disease [1, 6, 7].

Physical signs include fever ranging from 38.3 to 40.6^{o}C, redness or inflammation of tonsils and pharynx, palpable lymph nodes and liver. The initial stage is usually followed by sudden deterioration, with rapid onset of weakness and lassitude. On examination, the patient (usually a child), may be found to be restless, with cold clammy hands and feet, a warm trunk and with cyanosis. Petechiae, caused by broken capillaries, are often found on the forehead and extremities in 50% of cases [1, 6, 7]. There may be a macular or maculopapular rash. The extremities are often cyanotic. Hypotension with narrowing of the pulse pressure, and tachycardia are often noted. Pathologic reflexes may be present. Most fatalities occur in the fourth or fifth day of the illness. Poor prognostic signs include melaena, haematemesis, coma, or unresponsive shock.

Laboratory findings:

Haemo-concentration may be present in 20% of affected children. The majority of children may develop leukocyte count between 5000 and 10,000 per microliter with about one third showing leukocytosis. Usually about 10% of children may have true leukopenia. The most characteristic findings are thrombocytopenia, rarely with blood platelets under 75,000 cells per microliter, positive tourniquet test and prolonged bleeding time. Prothrombin time and Partial Thromboplastin Times (PTT) are usually near the normal values [6, 7]. Depression of clotting factors V, Vll, IX and X may be present. Bone marrow examination may reveal maturation arrest of megakaryocytes.

In a case study in Manila and in Bankok, haematuria was frequent even with other bleeding signs; however in Tahiti gross haematuria was common [14]. The cerebrospinal fluid (CSF) examinations are

usually normal in most patients. Other abnormal laboratory findings may include hyponatremia, acidosis, elevated blood urea and nitrogen levels, elevation of Aspartate Transaminase (AST) level, mild hyperblirubinaemia and hypoproteinaemia [14]. ECG may reveal diffuse myocardial abnormalities. Two thirds of patients may have radiological evidence of pneumonia; many of them may show pleural effusions. Ultrasonography is useful in detecting pleural effusions, ascites and thickening of the bladder wall.

Diagnosis of severe dengue:

The WHO has established criteria for the diagnosis of severe dengue (DHF). Acute onset high fever continuous and lasting for 2 – 7days; haemorrhagic manifestations, including at least a positive tourniquet test and any of the following: petechiae, purpura, ehymoses, epistaxis, bleeding gums, haematemesis or melaena, enlargement of the liver, thrombocytopenia of less than 100,000 cells per microliter, haemoconcentration, haematocrit increased by more than 20% [1, 6, 7].

Criteria for DSS: rapid weak pulse with narrowing of the pulse pressure of less than 20%, or hypotension with cold, clammy skin and restlessness. The WHO classification includes grading of severity (table 1). Minor haemorrhagic manifestations may be seen during the course of Classic Dengue fever without meeting WHO criteria for severe dengue [1, 6, 7].

Table 1: (Modified) World Health Organisation's clinical classification of Severe Dengue or Haemorrhagic fever (DHF)

Grades	Clinical Features	Laboratory findings
I	Fever, constitutional symptoms, positive tourniquet test	Haemoconcentration, Thrombocytopenia
II	Grade 1 plus spontaneous bleeding (eg. Skin, gums, git)	Haemoconcentratiion, Thrombocytopenia
III	Grade ll plus circulatory failure, agitation	Haemoconcentration, Thrombocytopenia
IV	Grade ll plus profound shock (BP =0)	Haemoconcentration, Thrombocytopenia

NB: Grades I – IV = DHF (Dengue Haemorrhagic Fever)
III & IV =DSS (Dengue Shock Syndrome)
Git = Gastrointestinal tract

Treatment for Severe Dengue:

The mainstay is correction of circulatory collapse while avoiding fluid overload. Administration of 5% glucose in 0.5N saline at a rate of 40ml/kg will restore blood pressure within 1 to 2 hours in most of the patients. When stable, the rate of administration of IV fluids can be reduced to 10ml/kg per hour. If improvement does not occur, plasma or plasma expander (20ml/kg) may be administered. Transfusion of whole blood is not recommended. Oxygen should be administered. Glucocorticoids have been used but doses of 25mg/kg have not resulted in significant improvement. Since the evidence for severe disseminated intravascular coagulation is questionable, the use of heparin is not clear-cut, although in a group of Philipino children with DEN 3, administration of heparin (1.0mg Sodium Heparin per kilogram) was associated with a dramatic rise in number of platelets and level of plasma fibrinogen. Antibiotics are not indicated; sympathomimetic amines and Salicylates are contraindicated [1, 6, 7]. Paracetamol can be taken to bring down fever and reduce joint pains. However, aspirin or ibuprofen should not be taken since they can increase the risk of bleeding.

Recovery from vascular collapse usually occurs within 24 to 48 hours at which time diuretics and digitalis may be necessary. An uncontrolled trial of interferon was conducted during the 1981 epidemic in Cuba with some indication of efficacy [1].

Prognosis:

Mortality has varied from 1- 23%. Deaths have been most common in infants under 1 year of age [6, 7].

Prevention:

At present there is no specific dengue therapeutics; vector control is the only preventive method available. As a precautionary approach, patients can adopt measures to reduce transmission by sleeping under treated bed nets especially during the period of illness with fever. However, the growing global epidemic of dengue is of mounting concern, thus a safe and effective vaccine is urgently needed [6, 7, 15].

Status of dengue vaccine development:

According to the WHO [15], the first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was registered in Mexico in December, 2015. CYD-TDV is a live recombinant tetravalent dengue vaccine that has been evaluated as a 3-dose series on zero / six / twelve month schedule in Phase III clinical studies. The vaccine has been registered for use in individuals 9-45 years of age living in endemic areas. There are approximately five additional vaccine candidates under evaluation in clinical trials,

including other live-attenuated vaccines, as well as subunit, DNA and purified inactivated vaccine candidates. Additional technological approaches, such as virus-vectored and VLP-based vaccines, are under evaluation in preclinical studies [15].

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