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Review Article on Dengue Fever and its Complications

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A B S T R A C T

Dengue is the important mosquito borne disease caused by arbovirus. Clinical manifestations of dengue fever ranges from asymptomatic or mild dengue fever to potentially fatal conditions like Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS), which may result in multiorgan damage. 90% of the DHF patients are of children with <15 years of age. As the incidence & outbreaks of the dengue fever has been increasing worldwide, it is essential to know more about it in order to pervent, early detection and management of it. This review gives the knowledge of causes, mode of transmission, complications, phases, prevention and mangement, which will be helful in prevention and early detection & management of dengue fever and its complications.

Keywords: Dengue fever, mosquito borne disease, arbovirus, dengue hemorrhagic fever, dengue shock syndrome

1. INTRODUCTION:

Dengue is the most important mosquito-borne[1] arbovirus disease of humans[2] in many tropical and sub-tropical areas[1] in terms of both morbidity and mortality[1,2]. Dengue is considered a major global threat by the World Health Organization (WHO)[1]. Since the end of World War II, the incidence of dengue disease has increased greatly[2]. In the past 50 years, its incidence of dengue has increased 30 times with significant outbreaks occurring in five of the World Health Organisation (WHO) regions. At present, dengue is endemic outbreak disease in 112 countries in the world[5].

Dengue virus (DENV) infection results in a broad spectrum of clinical presentations, ranging from asymptomatic or a mild, non-specific fever, to classic dengue fever (DF), and severe presentations such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS)[2,3,4] which is often fatal[2]. Yearly, 100 million cases of dengue fever and 0.5 million cases of Dengue hemorrhagic fever occur worldwide. Ninety percent of DHF subjects are children with <15 years of age. Today DHF is a leading cause of hospitalization and death among children in many countries of Southeast Asia, and in recent years it has become increasingly important in the Pacific Islands and the Americas[2]. There is no specific treatment for DHF or DSS[1,5] although with proper clinical diagnosis and management fatality rates are less than 1%[1].

The clinical course has mainly 3 phases i.e., febrile, critical and recovery phases - plasma leakage[2,3] is the hallmark of DHF, which occurs soon after the end of the febrile phase[3]. The plasma leak in DHF is selective (pleuroperitoneal spaces) and transient usually lasts for 24-48 hours and is dynamic in nature. Use of blood products, immunoglobulin, steroids and N-acetylcysteine is controversial, but some studies show they have lifesaving benefits. Extended and unusual presentations involving heart, kidney, liver, muscle and brain are recognised in dengue[3].

2. MOSQUITO VECTORS IN DENGUE INFECTIONS:

Mosquitoes belonging to the genus aedes play an important part in transmission of dengue whereas the most important vector is A aegypti, but A polynesiensis and A albopictusmay act as vectors depending on the geographic location. For instance, A albopictus is the common dengue causing mosquito in India, Thailand, Singapore, and Mexico regions.

After biting an infected human, dengue viruses enter an adult female mosquito and replicates in its midgut. Then it reaches the haemocoel and haemolymph, and gains access to different tissues of that mosquito. After viral replication in the salivary glands of mosquito, the infected mosquito can transmit the virus to another human through biting. Ultrastructural studies show viral particles within the salivary glands, foregut, midgut, nervous system, epidermal cells, ovary and internal body wall lining cells of the mosquito. In contrast, they are absent from the hindgut, muscle and malphigian tubules[5].

3. ETIOLOGY:

The proposed etiologies for dengue virus infection are:

- Direct skin infection by the virus

- Viral replication, primarily in macrophages
- Chemical-mediated and immunological mechanism induced by host–viral interaction[4].

4. PATHOLOGY:

Dengue virus gains entry into the host organism through the skin following an infected mosquito bite. Humoral, cellular, and innate host immune responses are implicated in the progression of the illness and the more severe clinical signs occur following the rapid clearance of the virus from the host organism. Hence, the most severe clinical presentation during the infection course does not correlate with a high viral load. Alterations in endothelial microvascular permeability and thromboregulatory mechanisms lead to an increased loss of protein and plasma. Proposed theories suggest that endothelial cell activation caused by monocytes, T-cells, the complement system, and various inflammatory molecules mediate plasma leakage. Thrombocytopenia may be related to alterations in megakaryocytopoiesis, manifested by infection of human hematopoietic cells and compromised progenitor cell growth. This may cause platelet dysfunction, damage, or depletion, leading to significant hemorrhages[4].

5. CLINICAL MANIFESTATIONS:

a. **Undifferentiated fever** - most common in primary infection & difficult to differentiate from numerous other viral diseases[4].

b. **Dengue Fever** - seen in both primary and secondary infections, characterized by biphasic & acute-onset high-grade fever lasting for 3 days to 1 week, Severe headache, lassitude, myalgia, joint pains, 50–82% report with a peculiar cutaneous rash, metallic taste, appetite loss, diarrhea, vomiting, and stomachache. Bleeding episodes are infrequently seen in DF, although epistaxis and gingival bleeding, substantial menstruation, petechiae/purpura, and gastrointestinal tract (GIT) hemorrhage can occur[4].

c. **Dengue Hemorrhagic Fever** - seen during secondary infection and may also seen during primary infection in infants. [4]

- Clinical parameters: Acute-onset febrile phase – high-grade fever lasting from 2 days to 1 week. Hemorrhagic episodes (at least one of the following forms): Petechiae, purpura, ecchymosis, epistaxis, gingival and mucosal bleeding, GIT or injection site, hematemesis and/or malena.
- Laboratory parameters: Thrombocytopenia (platelet count <100,000/cu mm)[4]

d. **Dengue shock syndrome:** DSS is defined as DHF accompanied by a unstable pulse, narrow pulse pressure (<20 mmHg), cold, restlessness, clammy skin, and circumoral cyanosis. Progressively worsening shock, disseminated intravascular coagulation and multiorgan damage account for a high mortality rate associated with DSS. The shock persists for a short span of time and the patient can promptly recovers with supportive therapy[4].

6. CLASSIFICATON:

The WHO classifies DF into two groups:

1. Uncomplicated and
2. Severe.

Severe cases are linked to excessive hemorrhage, organ impairement, or severe plasma escape, and the remaining cases are considered uncomplicated.

DHF was further subdivided into grades I–IV.

Grade I: Only mild bruising or a positive tourniquet test

Grade II: Spontaneous bleeding into the skin and elsewhere

Grade III: Clinical sign of shock

Grade IV: Severe shock - feeble pulse, and blood pressure cannot be recorded.

Here, grades III and IV comprise DSS[4].

7. DIAGNOSIS:

- Leucopenia
- Thrombocytopenia
- Metabolic acidosis
- Virus segregation in cell cultures

- Nucleic acid demonstration by PCR
- Serological detection of viral antigens/antibodies[4]

8. DEVELOPMENTAL PHASES OF DENGUE FEVER:

The three phases of dengue includes

- Febrile phase
- Critical phase
- Recovery phase

The **febrile phase** of DF includes a sudden high-grade fever of approximately 40ºc which lasts for about two to seven days. Biphasic fever is seen in about 6% of patients, particularly in patients with DHF or severe dengue. Biphasic fever is described as the fever which sets back for at least one day and the next fever spikes which lasts for one more day. Other symptoms include myalgia, arthralgia, facial flushing, headache, sore throat, nausea, vomiting, lack of appetite, etc[6]. Mild hepatomegaly may be present. CBC shows leukopenia, thrombocytopenia, and increasing haematocrit. Elevation of hepatic transaminases is commonly observed in laboratory findings[3].

Majority of patients recover fully and do not enter the **critical phase** of DF. However patients that do enter the critical phase shows defervescence which is the decrease in body temperature to 37 to 38ºc and plasma leakage[7]. It usually lasts for about two days. The onset of this phase is indicated by rapid fall in platelet count and can progress to shock, organ dysfunction or haemorrhage[6].

In **recovery phase**, the patient shows rapid recovery and the plasma leakage stops. It involves gradual drop in haematocrit, increase in white blood cells followed by platelets and recovery from other symptoms. This phase may be associated with fatigue. Some patients develop "recovery rash" and bradycardia in this phase[3, 6, 7].

9. PATHOPHYSIOLOGY:

After the bite of infected mosquito, the dengue virus enters the body and the primary envelope (E) of virus's glycoprotein is known to aid in binding the host cells and this is followed by viral replication within the cells of macrophages, monocytes and B cells. The incubation period of dengue virus is 7 to 10 days and after the febrile phase follows that leads to increased lymphocytes and decrease in neutrophils and white blood cells. The primary infection brings about life time immunity to that particular viral serotype. However a following infection with another type of serotype may lead to more severe infection[5,8,9].

10. MANAGEMENT:

Symptomatic management:

During the febrile phase, adequate oral fluids is necessary and paracetamol is used as antipyretic. Using other non-steroidal anti-inflammatory medications should be avoided due to increased bleeding risks. The patient can be managed at home in this phase. Patients are advised to seek medical advice if they experience warning symptoms such as excessive vomiting or diarrhoea, early bleeding manifestations, etc.

Fluid management:

The cornerstone for the management of dengue fever is the fluid resuscitation, especially in critical phase. The goal of fluid management is to maintain the intra vascular compartment at an adequate level while preventing patient overload. This can be achieved by careful step-wise fluid administration based on clinical parameters, urine output, and degree of haemoconcentration. The first line of treatment is crystalloids (0.9% saline), colloids (dextran) is the second line of treatment. In addition to fluid management, correction of acidosis, blood sugar and calcium is also important in critical phase of dengue[3,10].

Blood products:

Several factors such as bone marrow suppression, peripheral destruction of platelets, platelet dysfunction, coagulopathy, and vasculopathy can cause thrombocytopenia in dengue patients. Hence platelet transfusion is required to increase the platelet counts[11].

11. PREVENTION:

Control of aedes aegypti mosquito which transmits the dengue virus and development of vaccines are the two potential approaches in preventing dengue virus infection[12].

Mosquito control:

Mosquito control is the most effective approach in preventing the dengue virus. It includes insecticide spraying, community based education to the population to reduce the breeding sites of A. aegypti such as stagnant water or copepods (fish) that feed on mosquito larvae is helpful[12].

Vaccination:

The possibility of a dengue vaccine is supported by the long-lasting protection against the specific serotype that caused the disease that is provided by dengue infection. However, it only offers temporary protection against the other three dengue serotypes. Tetravalent vaccines that induce immunity against all four serotypes is under development[12].

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