CHAPTER

2

Cardiac Manifestations in Dengue Fever

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ABSTRACT

Dengue fever, also known as "break bone" fever is a mosquito borne infection caused by Dengue virus. The disease can have a self-limiting febrile course or can range to severe forms like dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). Cardiac involvement in dengue fever in not uncommon. The involvement is more in severe forms of the disease. Although most of them are transient and self-limiting but a proper diagnosis is a must and aggressive management should be given to avoid hemodynamic collapse. Treatment involves supportive care with antipyretics and IV fluids to replenish intravascular fluid compartment.

INTRODUCTION

Dengue fever has emerged as one of the most important viral disease in the world. It is transmitted by the bite of female Aedes aegypti mosquito infected with the dengue virus. There are 4 known strains of the dengue virus (DEN1, DEN2, DEN3 and DEN4) and all the 4 strains are known to cause disease. The disease can range from mild dengue fever to the severe forms like dengue hemorrhagic fever and dengue shock syndrome[1]. Although the disease is not new and humans have been trying to curb it since many decades but there has been an endemic in the tropical areas of the world where the environmental factors favors breeding of the Aedes aegypti mosquito. Dengue fever emerged from Africa almost 500 to 600 years ago, and the first outbreaks reached different parts of world such as Asia and South America concurrently in the 1780 [2]. India faced first outbreak in 1780 in madras and the condition is worsening every year. In 2012, WHO classified Dengue Fever "the most important mosquito borne viral disease in the world"[3]. DF has been the major cause of hospitalization and mortality after acute respiratory and diarrhea infections among children. Cases of dengue related deaths have increased significantly. In 2015, 99913 cases were reported from all over the county (Figure 1).[4] The numbers quote only the reported number of cases and many more cases that are not diagnosed or not reported.

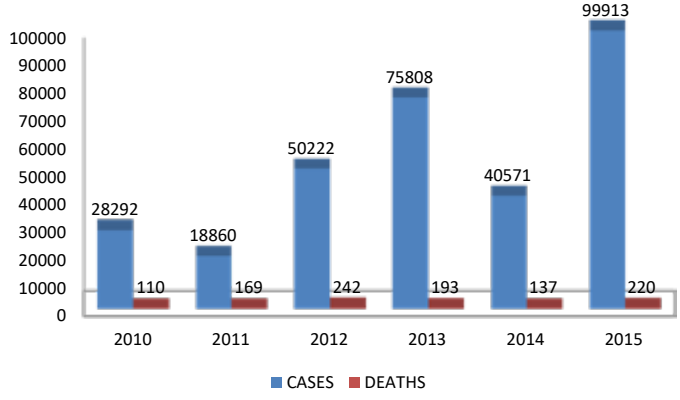

Fig. 1: Number of Dengue Cases and Deaths in India (since 2010[4])

The mosquito, Aedes aegypti breeds in clean water bodies and bite during the daytime. The peak biting hours range from early morning to evening before dawn. After incubation period of 4 – 10 days the viremia ensues producing clinical signs and symptoms of the disease. People infected with the dengue virus serve as source of infection by transmitting it to the non-infected Aedes aegypti mosquito during their bite.

PATHOPHYSIOLOGY

The exact mechanism of the cardiac injury in dengue fever remains unknown, however it is proposed that the direct invasion of the cardiac myocyte by the virus and damage to the cardiac cells by the ongoing inflammatory damage are the major mechanism of the cardiac manifestations. Dengue virus upon its entry in the body is taken up by the macrophages which causes activation of the T cells. These activated T cells cause release of various inflammatory cytokines, interleukins (IL1, IL2, IL6 etc), tumor necrosis factors (and activation of the complement pathway(C3a, C5a) and histamine.[5] This leads to the inflammation and necrosis of the endothelial cells leading to their dysfunction and plasma leakage. Leakage of the plasma in the interstitial space cause myocardial interstitial edema leading to impairment of myocardial function. Decreased fluid in the intravascular compartment secondary to plasma leakage leads to alteration in the coronary circulation(Figure 2). Various inflammatory markers released cause direct suppression of the cardiac contractility and alteration in the electrical conduction of heart leading to various conduction blocks and ventricular arrhythmia. The release of these inflammatory markers is more in severe form of the disease that correlates with the higher incidence of cardiac manifestations in patients with severe form of the disease.

CLINICAL FEATURES

The disease has an incubation period of 4 – 10 days before the symptoms starts appearing. The characteristic symptoms include fever, headache, body ache, multiple joint pain including both small and large joints of body, retro orbital pain, myalgia, itching and rash.

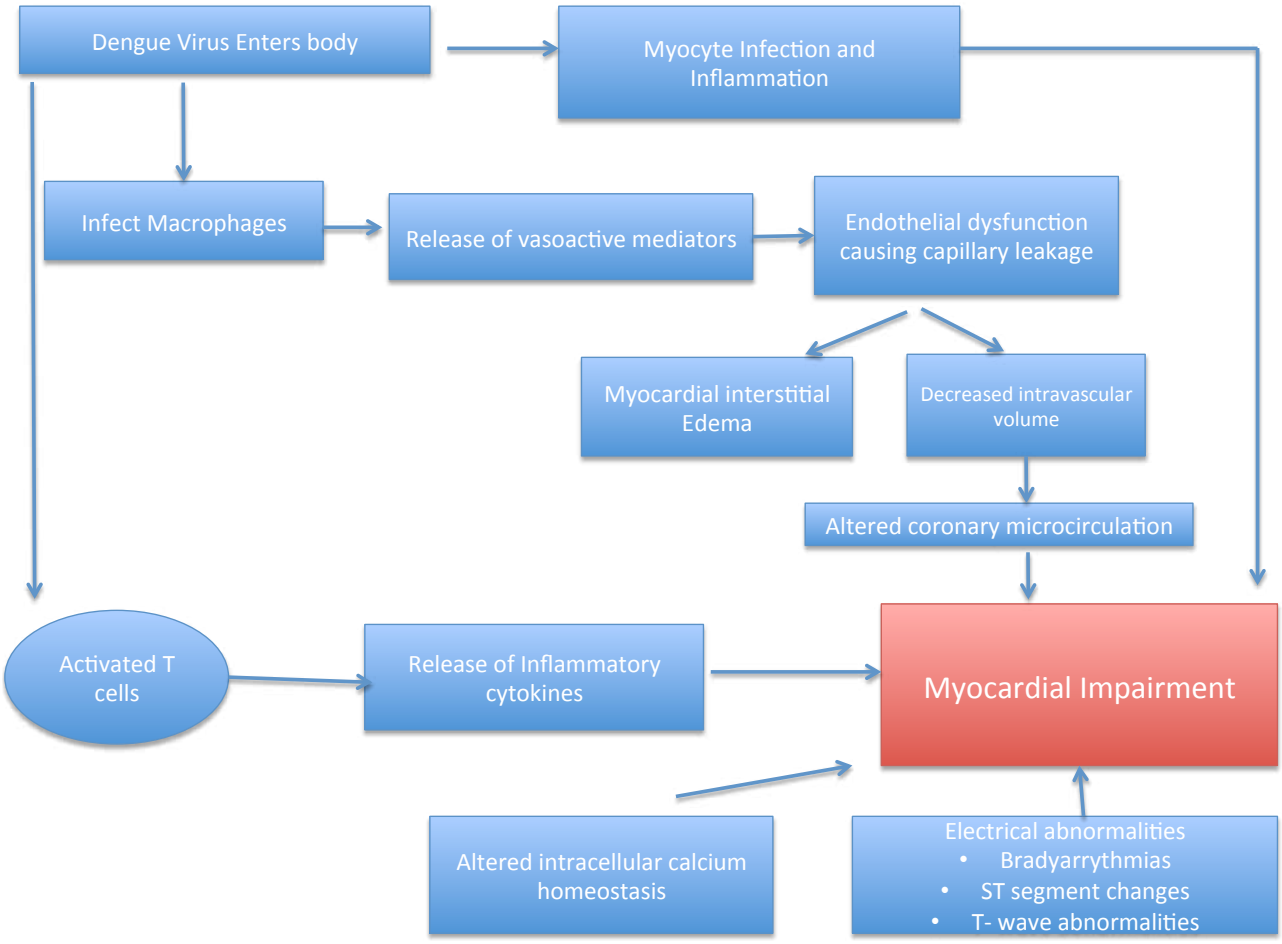

Fig. 2: Proposed Viral and Immune Mechanisms for Cardiac & Vascular Manifestations in dengue[5]

Table 1: Grading the severity of Dengue infection

DF/DHF	Grade	Symptoms/signs	Laboratory findings
DF		Fever with two or more of following - Headache - Retro-orbital pain - Myalgia - Arthralgia	Leucopenia, thrombocytopenia
DHF	I	Above criteria for DF plus positive tourniquet test, evidence of plasma leakage	Thrombocytopenia: Platelet count less than 100,000/cu.mm Haematocrit rise 20% or more
DHF	II	Above signs and symptoms plus some evidence of spontaneous bleeding in skin or other organs (black tarry stools, epistaxis, bleeding from gums, etc) and abdominal pain	Thrombocytopenia platelet count less than 100,000/cumm Haematocrit rise 20% or more
DHF	III	Above signs and symptoms plus circulating failure (weak rapid pulse, pulse pressure ≤20 mm Hg or high diastolic pressure, hypotension with the presence of cold clammy skin and restlessness)	Thrombocytopenia: Platelet count less than 100,000/cumm Haematocrit rise more than 20%
DHF	IV	Profound shock with undetectable blood pressure or pulse Haematocrit rise more than20%	Thrombocytopenia: Platelet count less than 100,000/cumm Haemotocrit rise more than 20%

Depending upon the severity, it can be classified into – Dengue Fever, Dengue Hemorrhagic Fever and Dengue Shock Syndrome (Table 1).

Cardiac symptoms in dengue fever can range from

Table 2: Holliday and Segar Formula[6]

Maintenance Fluid Requirement Holliday and Segar formula[6]	
Body weight (kg)	**Maintenance fluid requirement for 24 hours**
Less than 10 kg	100 ml / kg
10 – 20 kg	1000 ml + 50 ml per kg
More than 20 kg	1500 ml + 20 ml per kg

asymptomatic bradycardia to life threatening myocarditis and pericardial effusion. Most of the manifestations are self limiting and tend to settle with other symptoms of the disease.

These include

- Sinus tachycardia
- Sinus bradycardia
- Non specific ST T changes
- SA node dysfunction
- AV dissociation with variable degree of heart block
- Tachyarrhythmia – Atrial fibrillation, ventricular tachycardia
- Pericardial effusion
- Wall hypokinesia
- Elevation of cardiac enzymes

The incidence of these cardiac manifestations has been co related with the severity of the disease. Patients with more severe forms of disease like DHF or DSS are more at risk of developing cardiac manifestations. Among severe dengue, fluid accumulation causing respiratory distress was found to have a significant correlation with the cardiac manifestations.

DIAGNOSIS[6]

A high suspicion of dengue fever should be kept in mind in endemic areas with patients complaining of symptoms of the dengue fever. All the patients with suspected dengue fever must go under routine hematological examination including – Hb, TLC, Platelet count, hematocrit and peripheral smear. A tourniquet test should be performed to exclude DHF. Blood tests for diagnosis of Dengue infection include:

- NS1 ANTIGEN detection – usually comes detectable before 5 days of fever
- IgM capture Enzyme linked immunosorbent assay (MAC- ELISA)-becomes positive after 5 days and persist detectable levels upto 90 days.
- IgG ELISA – it is used to differentiate primary and secondary dengue infection.

A detailed blood workup including LFT, KFT and cardiac enzymes level should be done to rule out any hepatic, renal or cardiac damage.

Investigations for cardiac monitoring:

- BP charting
- ECG monitoring – if the admission ECG shows any abnormality a repeat ECG should be conducted daily to monitor the ongoing cardiac insult and pulse chart to be maintained to know the rate and rhythm abnormality.
- Cardiac enzymes
  - CK MB
  - Troponin I
  - Troponin T
- Echocardiography – to rule out wall hypokinesia or pericardial effusion

MANAGEMENT[6]

Till date no anti viral drug has been licensed for treatment. Dengue vaccine has been developed and is in Phase 3 trial[7]. No vaccine has been liscenced till date. The mainstay for prevention of the disease personal protection and environmental management of mosquitos. Some of the personal preventive methods include

- Maintaining cleanliness and avoid stagnation of the water in and around homes and office to reduce mosquito habitat. The mosquito typically breed in stagnant water bodies. Reduce the habitat to lower the mosquito population.
- Avoiding mosquito bite by wearing protective clothes like long sleeve shirts, socks and shoes.
- Using mosquito repellent sprays, creams

Once the symptoms appear no casual attitude should be adopted and urgent medical help must be sought.

Symptomatic care

- Bed rest
- Antipyretics – Use Paracetamol. NO ASPIRIN/ NSAIDS

IV Paracetamol can be used in case of high-grade fever

- Tepid sponging
- I.V. Fluids
- Watch for bleeding manifestations
- Look for signs of DHF/DSS

Criteria for admission[6]

- DF with warning signs or symptoms
- Significant bleeding from any site
- Hypotension
- Persistent high grade fever
- Rapid fall of platelet count
- Sudden drop in temperature
- Evidence of organ dysfunction

Management of DHF I and II [6]

- General symptomatic care
- Volume replacement therapy
- Careful monitoring for development of shock

Management of DHF III and IV [6]

- Rapid assessment of vital signs, hematocrit and platelet count
- Initiation of IV fluids
- Blood transfusion if hematocrit falls suddenly indicating suspected concealed bleeding
- Platelet transfusion if indicated
- Testing for PT, aPTT and LFT

Requirement of IV fluids[6]

The amount of fluid replaced should be sufficient to maintain effective circulation during the period of plasma leakage. To ensure adequate fluid replacement and avoid over-fluid infusion, the rate of intravenous fluid should be adjusted throughout the 24 to 48 hour period of plasma leakage by periodic hematocrit determination. The amount of fluid correction in 24 hours should be calculated as double the amount of maintance fluid. The maintanance fluid should be calculated with Holliday and Segar formula (Table 2):

Therefore for a 60 kg individual, 24 hour fluid requirement would be = 1500 +(20 x 40) = 4600 ml.

Choice of IV fluid

- There is no clear advantage of colloid over crystalloids in terms of the overall outcome.
- Colloids restore BP quickly and reduce the hematocrit faster than crystalloid in patients with intractable shock and pulse pressure les than 10 mm Hg.
- Side effects of colloid include allergic reaction, impact on coagulation and osmotic renal injury in hypovolemic patients.
- Crystalloids – start with 0.9 % NS. However plenty of the same can cause hyperchloremic acidosis. So follow with Ringer Lactate.

Indications of red cell transfusion[6]

- Loss of blood (overt blood loss) -10% or more of total blood volume -Preferably whole blood/ component to be used.
- Refractory shock despite adequate fluid administration and declining hematocrit.
- Replacement volume should be 10 ml/kg body wt. at a time and coagulogram should be done.
- If fluid overload is present PCV is to be given.

Indications of Platelet transfusion[6]

- In general there is no need to give prophylactic platelets even at < 20,000/mm^3
- Prophylactic platelet transfusion may be given at level of <10,000/mm^3 in absence of bleeding manifestations.
- Prolonged shock; with coagulopathy and abnormal coagulogram
- In case of Systemic massive bleeding, platelet transfusion may be needed in addition to red cell transfusion.
- Compatibility testing is not required for platelet transfusion.

Management of cardiac manifestation per se

The cardiac insult in dengue fever is acute and transient and no specific guidelines are available for its management. The treatment is to provide symptomatic support and maintain hemodynamic stability. The role of anti arrythmics is not clearly defined. Atrial fibrillation, the most commonly clinically encountered arrhythmia. However viral dengue causing AF is extremely rare and thus the treatment of AF caused by dengue fever is not well established. Role of drugs like calcium channel blockers and beta-blocker in management of AF secondary to DF is controversial in view of impending hypotension. However some of the studies have shown use of anti arrythmics for non self limiting AF[8].AV dissociation, premature ventricular complexes, wall hypokinesia, nonspecific ST – T changes are transient and subside within 4 – 8 weeks of follow up. However such patients should be kept under strict monitoring and any event of hemodynamic instability should be managed aggressively.

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