"TO STUDY THE CARDIAC MANIFESTATIONS IN DENGUE FEVER IN PATIENTS ADMITTED IN KLES DR PRABHAKAR KORE HOSPITAL & M.R.C., BELGAUM – A ONE YEAR HOSPITAL BASED DESCRIPTIVE STUDY"

REG NO. BG0112006

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"TO STUDY THE CARDIAC MANIFESTATIONS IN DENGUE FEVER IN PATIENTS ADMITTED IN KLES DR PRABHAKAR KORE HOSPITAL & M.R.C., BELGAUM – A ONE YEAR HOSPITAL BASED DESCRIPTIVE STUDY"** is a bonafide research work done by **CANDIDATE REG NO. BG0112006.**

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LIST OF ABBREVIATIONS USED

A.D.	-	Anno domini
AIIMS	-	All India Institute of Medical Sciences
ALT	-	Alanine aminotransferase
APC	-	Antigen presenting cell
ARDS	-	Acute respiratory distress syndrome
ASA	-	Acetylsalicylic acid
AST	-	Aspartate aminotransferase
AV	-	Atrioventricular
BP	-	Blood pressure
CAF	-	Chronic atrial fibrillation
CAR	-	Coxsackie adenoviral receptor
CK-MB	-	Serum creatine kinase MB
CPK-MB	-	Serum creatine kinase MB
cTnl	-	Quantitative determination of cardiac troponin I
Cumm	-	Cubic millimeter
CVA	-	Cerebrovascular accidents
CVS	-	Cardiovascular system
DAF	-	Decay accelerating factor
DALY	-	Disability adjusted life year
DENV	-	Dengue virus
DF	-	Dengue fever
DFB	-	Dengue Fever with unusual bleed
DHF	-	Dengue hemorrhagic fever
DIC	-	Disseminated intravascular coagulation

DSS	-	Dengue shock syndrome
ECG	-	Electrocardiography
ECHO	-	Echocardiography
EF	-	Ejection fraction
ELISA	-	Enzyme linked immunosorbent assay
ESS	-	Endsystolic meridional stress
FDP	-	Fibrin degradation products
GGT	-	Gamma-glutamyl transpeptidase
h-FABP	-	Heart-type fatty acid binding protein levels
HR	-	Heart rate
IFN	-	Interferon
IgG	-	Immunoglobulin G
IgM	-	Immunoglobulin M
IL	-	Interleukin
M.I.	-	Myocardial infarction
MEIA	-	Microparticle Enzyme Immunoassay
MHC	-	Major histoconipatibility complex
mm Hg	-	Millimeters of mercury
MRD	-	Medical Records Department
n	-	Total number
NSST-T	-	Nonspecific ST-segment and T-wave
NT-proBNP	-	N-terminal of the prohormone brain natriuretic peptide
p	-	Probability
PAHO	-	The Pan American Health Organization
PAI-1	-	Plasminogen activator inhibitor-1

PT	-	Prothrombin time
RBBB	-	Right bundle branch block
RNA	-	Ribonucleic acid
RT-PCR	-	Reverse transcription polymerase chain reaction
SEA	-	South East Asia
TF	-	Tissue factor
TNF	-	Tumor necrosis factor
tPA	-	Tissue plasminogen activator
uPA	-	Urokinase plasminogen activator
US	-	United States
VCFc	-	Velocity of circumferential fiber shortening
WHO	-	World Health Organization

ABSTRACT

Background and objectives

Dengue fever is a serious public health problem. Though dengue rarely affects heart, cardiac dysfunction with dengue fever has been described by several authors. The present study was aimed to assess the cardiac manifestations of dengue fever.

Methodology

This one year descriptive study was undertaken at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum under the Department of Medicine. A total of 120 patients with either dengue IgM or IgM and IgG and NS1 positive patients admitted between January 2013 to December 2013 were studied. The assessment of cardiac manifestations was done based on electrocardiogram, 2D echocardiography and cardiac enzymes.

Results

Total 120 patients were enrolled in the study of which, 85 (70.83%) were males and the male to female ratio was 2.4:1. The mean age of the patients was 33.02 ± 12.71 years. The commonest clinical presentation was myalgia (97.5%). On clinical examination, 33.33% had petechiae followed by hepatomegaly and shock signs (21.6% each), pulmonary crepitations, oedema (13.33% each), hypotension (12.5%), splenomegaly (10.83%), narrow pulse pressure (10%), tachycardia (7.5%) and tachypnoea (1.67%).

Cardiac manifestations was present in 36.66% patients. It was high (53.33%) in patients with dengue shock syndrome compared to the patients with dengue haemorrhagic fever (35.29%) and dengue fever (30%).

A wide range of cardiac manifestations were observed in this study. CK-MB and troponin I at admission were raised in 23.3% of the patients while only CK MB and only troponin I was raised in 10% and 3.3% of the patients respectively. On ECG, at admission, 95% of the patients had normal rhythm with 84.21% with normal heart rate, 8.77% with sinus bradycardia 3.51% of the patients each with sinus tachycardia and NSST-T changes. In patient with abnormal rhythm the abnormalities noted were first degree AV block (66.67%) and RBBB (33.33%). ECG on day seven (or day of discharge whichever was earlier) showed normal rhythm and normal heart rate for all the patients. None of the patient was detected with abnormal echocardiograph.

In patients with sinus tachycardia and first degree AV block all the patients (100%) had raised CK MB levels and 75% of the patients had raised troponin I levels. In those with sinus bradycardia, NSST-T changes, RBBB all the patients were found to have raised CK MB level (100%). However, Troponin I was raised in all the patients with NSST-T changes, 90% in patients with bradycardia and none of the patient with RBBB.

Based on WHO criteria Dengue fever was present in 16.66%, dengue haemorrhagic fever in 70.83% and dengue shock syndrome in 12.5%.

Conclusion and interpretation

Transient cardiac abnormality can be an important presentation and this should guide the treating physician to look for cardiac involvement.

Keywords

Cardiac manifestations; Dengue fever; Dengue Haemorrhagic fever; Dengue shock syndrome;

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INTRODUCTION

Arboviruses represent a serious public health problem and are associated with epidemics have great economic and social impact in tropical and subtropical regions of the world. Dengue virus (DENV) causes a highly infectious illness and it is transmitted to humans by mosquitos of the *Aedes* family.[1]

Dengue virus (DENV) infection is a global health threat affecting at least 3.6 billion people living in more than 125 countries in the tropics and subtropics. It is among the most important arthropod-borne diseases. All four dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) can cause dengue. The disease can present as a mild self-limiting illness, dengue fever (DF), or as the more severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[2]

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 1780s.[3] Now, worldwide, an estimated 2.5 billion people are at risk of infection, approximately 975 million of whom live in urban areas of tropical and sub-tropical countries like Southeast Asia, the Pacific and the Americas.[4] The rural areas are also being increasingly affected in regions of Africa and the eastern Mediterranean. It is estimated that more than 50 million infections occur each year, of which 500,000 hospitalizations are of dengue haemorrhagic fever, mainly among children, with the case fatality rate exceeding 5% in some areas.[4,5]

The first outbreak of dengue fever in India was recorded in 1812.[6] In spite of preventive measures taken by the respective governments since then, recurrent outbreaks have occurred, and over the last 10 to 15 years DF has been the major cause of hospitalization and mortality after acute respiratory and diarrhoeal infections among children.[7] New Delhi, the capital of India located in the northern region of the country, experienced seven major outbreaks between 1967 and 2003.[8,9]

Dengue virus (DENV) belongs to the genus *Flavivirus* and the *Flaviviridae* family. It is an enveloped virus and contains a single stranded positive sense RNA of about 11kb and is classified in four serotypes designated as DENV-1, DENV-2, DENV-3 and DENV-4, based on its antigenic characteristics. The genome of DENV contains 10 genes in an open reading frame (ORF), the translation of the ORF results in a polyprotein that is processed by a signal-peptidase of the host cell into 3 structural proteins (C, E and pr M) and 7 nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5). Infection by any of the above serotypes causes clinical manifestations that vary and are both nonspecific and benign, until more serious stages which sometimes have fatal consequences in the form of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).[10] The World Health Organization (WHO) 2009 guidelines classify patients into three groups; dengue without warning signs, dengue with warning signs and severe dengue.[11]

Early laboratory confirmation of dengue infection is crucial. Among the methods available for dengue diagnosis, virus isolation provides the most specific test result. Detection of IgM or IgG antibodies is the standard for serologically confirming a dengue infection. The presence of IgM or high levels of IgG in acute serum collected from a suspected dengue case suggests a probable dengue

infection.[12] An up-to-date test for early diagnosis of dengue infection is dengue NS1 antigen detection.[13]

Most cases of dengue are self-limited, and the course of the disease is a nonspecific febrile state, general malaise and weakness. Patients may feel severe muscle pain and retro-orbital pain, with or without skin rash. Laboratory tests may reveal increased hepatic enzyme levels, leukopenia and thrombocytopenia, which are abnormalities consistent with but nonspecific for dengue fever.[1]

The most severe forms of the disease are dengue shock syndrome and dengue hemorrhagic fever. The shock syndrome is due to an important alteration in capillary permeability and significant capillary leakage of plasma into extra-vascular spaces, and is associated with immune activation and high serum levels of tumor necrosis factor-a (TNF) receptor, interleukin (IL)-8, and other factors.

Dengue hemorrhagic fever typically develops together with shock and occurs 2 to 7 days after defervescence. From a clinical point of view, it is not possible to distinguish those patients who will progress to the hemorrhagic form of the disease from those with the self-limited illness.[14]

It is postulated that, dengue rarely affects the heart. Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis. On the other hand, the ventricular dysfunction associated with the acute phase of dengue hemorrhagic fever has been described by several authors and is probably underdiagnosed in clinical practice.[14]

Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the hemorrhagic form of the disease or in the associated shock. The "dengue-related shock syndrome" is due to the increased vascular permeability and hypovolemic pattern.[14]

To-date very few studies have addressed the issues of cardiac manifestation in dengue fever and to our knowledge no such study was undertaken in this region. Hence the present study was planned to assess the cardiac manifestations of dengue fever.

OBJECTIVES

Objectives of the present study were to assess the cardiac manifestations of dengue fever.

REVIEW OF LITERATURE

Historical Aspects

The term "Dengue" was coined in the English medical literature from the West Indies during the 1827–1828 Caribbean epidemic that presented as exanthema with arthralgia. Dengue is a Spanish synonym for the Swahili "Ki denga Pepo" (a sudden cramp like seizure caused by an evil spirit). The term "Break bone fever" for the modern dengue was proposed in Philadelphia in 1780.[15] *Aedes aegypti* mosquito as a vector of dengue virus was first discovered by Bancroft in 1906.[16]

Isolation and detection of dengue virus dates back to World War II and further characterization led to postulation of dengue virus as an agent involved in various past outbreaks which were exhibiting dengue-like symptoms. Dengue-like disease was mentioned in ancient Chinese manuscripts dates back to 992 A.D. and to the 1600s A.D. in the West Indies.[16]

The first historical account of DSS was reported by Benjamin Rush during an outbreak (1780) in Philadelphia among people living at Delaware River.[17] North America had similar outbreaks in the 18th and 19th centuries along the Atlantic coast, on the Caribbean Islands, and also in the Mississippi basin.

Shock and death cases were documented in a dengue epidemic in Queens land, Australia in 1897, while nearly 1250 persons died during the explosive Greek dengue epidemic of 1928. Another epidemic was related to substandard living conditions among refugees who moved from Turkey following the Greco-Turkish

war of 1922. Dengue viruses for the first time were adapted to laboratory animals in the 1940's (Dengue type 1 and 2) and 1950's (Dengue type 3 and 4).[15]

However, it was only in 1943-44 that the modern chapter of dengue research started. This was when for the first time dengue virus was cultured and later isolated from suckling mice brain.[16]

Dengue fever was first observed in Africa, but later with the increase in trade DF reached all parts of the world including Asia, South America and the Indian subcontinent that includes India, Pakistan, Bangladesh and Sri Lanka. These countries experience epidemics every year with cases reaching several thousands in numbers.[16]

Hammon et al in 1956 mentioned that DHF/DSS were associated with dengue virus.[15]

The first case of dengue hemorrhagic fever in Southeast Asia was noted in Manila in 1953 to 1954 and outbreaks have since then been reported throughout the Indo-China Peninsula and the Indian sub-continent.[18]

Dengue virus belongs to the Arbovirus group of viruses that are transmitted through insect vectors most commomly Aedes Aegypti mosquito. Virions are 40-50 nm in diameter and spherical in shape with 11kb single-stranded RNA containing a single open reading frame. Dengue virus consists of ten proteins, three of which are structural and seven non structural, and it has four serotypes, namely DENV1, DENV2, DENV3 and DENV4.[16]

The Indian subcontinent is mainly affected by DENV2 and DENV3 serotypes. DENV1 and DENV4 were identified by studying neutralizing antibodies in the blood of volunteers in 1973 while DENV1 and DENV2 were isolated as a consequence of the failure of viral strains to cross-protect human volunteers.[19]

All four virus serotypes cause similar illness, but severe and fatal hemorrhagic disease is more often associated with DENV2 and DENV3 infections.[16] DENV2 (genotype IV) and DENV3 (genotype III) are the most commonly isolated genotypes.[16]

Epidemic and pandemic of dengue virus infections[20]

Benjamin Rush identified the tip of the 18th century pandemic from the classic description of dengue fever in Philadelphia in 1780. The causal virus and mosquito were introduced into Philadelphia by ship, an unwelcome consequence of the sugar, rum and slave trade between African, colonial American and Caribbean ports. This first pandemic produced reports of sporadic dengue outbreaks in the United States of America, Caribbean and South American coastal cities during the 19th century and first three decades of 20th century. Second pandemic occurred in semitropical Northern Queensland.

The 20th century pandemic increased after World War II in which soldiers from South East Asia to Japan and Pacific Islands carried dengue strains. Destruction of city water supplies, temporary housing for refugees, the explosive post – war growth of populations through high fertility, rural to urban migration and the steady decline of urban environments, have led to steady growth in density and

the area occupied by Aedes aegypti. Together these factors have resulted in the endemic transmission of all four dengue serotypes in most of the Asian tropics.

Mean while, the remarkable gains achieved towards the eradication of Aedes aegypti in the American tropics have been eroded and reversed. This was followed by the introduction and spread of dengue viruses beginning in the 1960s. Dengue viruses have invaded Cuba, Caribbean Islands, Mexico, the United States, Central America, Colombia, Ecuador, Peru, Paraguay, Bolivia, Argentina and Brazil. By the 1990s dengue had spread to China, Taiwan, south to Australia and eastward to nearly all of the Pacific Islands. In Africa and the Middle East, areas of epidemic activity include outbreaks in Kenya. Mozambique, Somalia and Yemen. Major recent outbreaks occurred in Cuba (1981), Southern China, Sri Lanka, India, Maldives, Tahiti and Venezuela in mid to late 1980s.

Epidemics of dengue fever in India[21]

Dengue fever is endemic in many parts of India barring the Himalayan and other mountainous regions where conditions are not conductive to the propagation of its vector. Outbreaks of dengue fever occur mostly in India, during or after the rainy season, but outbreaks during summer season have also been reported due to storage of water for domestic purposes causing a rise in vector population.

Some of the epidemics of DHF/DSS which occurred in India are as follows:[22]

Year	Region	Type of dengue virus
1964	Vellore, Tamil Nadu	DV-2
1966	Vellore, Tamil Nadu	DV-3
1968	Vellore, Tamil Nadu	DV- 1,2,3 & 4
1968	Kanpur, Uttar Pradesh	DV-4
1969	Kanpur, Uttar Pradesh	DV-4 and DV-2
1970	Hardoi, Uttar Pradesh	DV-2
NA	NA	DV- 1,2,3 & 4
1983	Kolkata, West Bengal	DV-3
1985	Jalore town, South-West Rajasthan	DV-3
1988	Delhi	DV-2
1990	Calcutta, West Bengal	DV-3
1988	Rural and urban areas of Gujarat	DV-2
1993	Mangalore, Karnataka	DV-2
1996	Ludhiana, Punjab	DV- 1,2,3 & 4
1996	Lucknow	DV-2
1996	Delhi	DV-2
1996	Delhi	DV-2
1997	Delhi	DV-1
1996	Delhi	DV-2 (Genotype IV)
1997	Delhi	DV-1
1996	Rural areas of Haryana	DV-2
2001	Dharmapuri district, Tamil Nadu	DV-2
NA	Andaman and Nicobar Islands	DV-2
2001	Gwalior, Madhya Pradesh	DV-2
2001	Chennai, Tamil Nadu	DV-3
2003	Northern India (Delhi & Gwalior)	DV-3
2005	Kolkata, West Bengal	DV-3
2003	Kanyakumari district, Tamil Nadu	DV-3
2003-04	Delhi	DV-3 (subtype III)
2003-05	Delhi	DV-1,2,3 & 4
2006	Delhi	DV-3
2006	Delhi	DV-1 & 3
2001-07	North India (Delhi and Gwalior region)	DV-1 (Genotype III)
2006	Delhi	DV-1,3 & 4
2008	Delhi region	DV-1,2 & 3
1956-2005	Entire country	DV-2
2002-06	Delhi	DV-1, 2, 3 & 4
2003	Delhi	DV-3 (Genotype III)
2008	Ernakulam, Kerala	DV-2 & 3
2007	Rural areas of Madurai, Tamil Nadu	DV-3 (Genotype III)
2007	Andhra Pradesh	DV-1 & 4 (Genotype I)
2003-08	Different parts of the country	DV-3 (Genotype III)
2007-09	Delhi	DV 1, 2, 3 & 4
2009-10	Pune, Maharashtra	DV-4 (Genotype I)

Epidemiology

Worldwide

Up to 3.6 billion people are estimated to now live in tropical and subtropical areas where the dengue viruses have the potential to be transmitted. Global estimates vary, but regularly approximate 50 million to 200 million dengue infections, 500,000 episodes of severe dengue (DHF/DSS), and over 20,000 dengue related deaths occur annually.[23,24] Figure 1 shows the geographic distribution of dengue cases reported in 2011.[24]

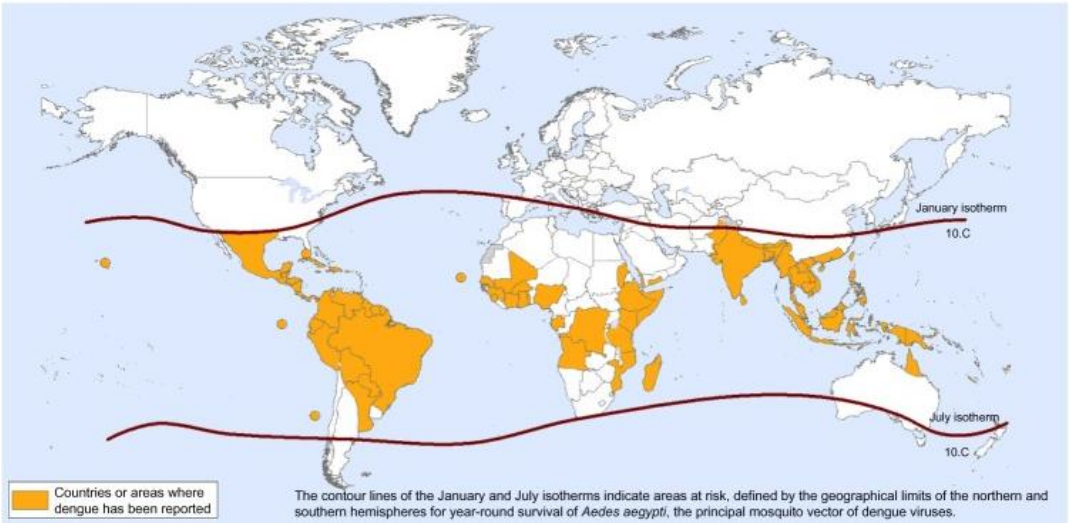


Figure 1. Countries or areas of the world where dengue was reported in 2011, as per data collected by the World Health Organization[24]

In 2012, dengue was once again classified by the World Health Organization (WHO) as the 'most important mosquito-borne viral disease in the world'[25] due to significant geographic spread of the virus and its vector into previously unaffected areas and the subsequent costly burden of disease it brings. Disability adjusted life year (DALY) estimates differ, but a 2009 estimate of DALYs lost due to dengue

globally was 700,000 per year. In most countries, the main burden of this morbidity and mortality lies with children.[23,24]

Dıaz-Quijano and Waldman[26] conducted an ecological study investigating the determinants of the dengue mortality burden. Length of recognized endemicity, rainfall, and population density were all shown to be associated with dengue mortality in Latin America and the Caribbean.

A study which reviewed all nations in the Americas (with available data from the PAHO, 2000–2007) estimated an aggregate annual cost of dengue for the Americas at US$2.1 billion. Approximately 60% of this cost related to indirect or 'productivity' losses, and the figure notably excluded prevention costs.[27]

A study of twelve countries in South East Asia (using available data from 2001–2010) showed an aggregate annual economic burden of US$950 million amongst the studied nations, with approximately 52% of these costs coming from productivity loss. This figure again excluded necessary prevention and vector control costs.[28]

Due to poor disease surveillance, low level of reporting, low case fatality rate, difficulties in diagnosis, and inconsistent comparative analyses, the true incidence and impact of dengue is likely significantly higher than that which is currently reported. Thus, the true global burden of disease and associated economic impact is unknown.[23]

However, Brady et al[29] have conducted the first of a series of steps in evidence consensus mapping of global dengue incidence to better determine the population at risk. Their 2012 publication suggested an 'upper bound' total of 3.97

billion people living in 128 countries are at risk of dengue globally, 824 million in urban residences, and 763 in peri-urban residences.

The same group published again in April 2013 using cartographic approaches. These data suggested 390 million dengue infections occur annually worldwide, including both apparent and inapparent infections, almost double the highest figure regularly reported to date.[30]

Despite the level of uncertainty on total numbers, we have evidence today that every WHO region now has dengue transmission and that there are more than 125 dengue endemic countries globally.[23,24]

WHO Southeast Asia (SEA) region

It is evident that dengue is now a worldwide concern; however, almost 75% of the global population exposed to dengue live in Asia-Pacific.[23,24,31] 1.3 billion of these at-risk individuals live in ten dengue endemic countries in SEA, and dengue is a leading cause of hospitalization and death in children from the region.[31] The rates of disease reported in each of the SEA countries varies as they include either laboratory confirmed, probable, or suspected cases.[28]

However, it is clearly evident from data collated by WHO that, in SEA, an overall expansion of dengue has occurred over the last decade. In 2003, eight countries in SEA had reported cases of dengue and, by 2009, all SEA member countries excluding the Democratic People's Republic of Korea reported indigenous cases.[31] Epidemics continue to persist on regular 3–5 year cycles throughout SEA, and the number of reported cases continues to increase along with the severity of cases in many member countries.[28] 187,333 dengue cases were reported to WHO in

2010 from the region.[32] Eight SEA countries are now also classified as hyperendemic with all four of the dengue virus serotypes present.[31] Severe dengue is endemic in most SEA countries, with rates of severe dengue being 18 times higher in this region compared with the Americas.[23,28,31]

Indian scenario

The first outbreak of dengue fever in India was recorded in 1812.[6] In spite of preventive measures taken by the respective governments since then, recurrent outbreaks have occurred, and over the last 10 to 15 years DF has been the major cause of hospitalization and mortality after acute respiratory and diarrheal infections among children.[7]

New Delhi, the capital of India located in the northern region of the country, experienced seven major outbreaks between 1967 and 2003.[8,9]

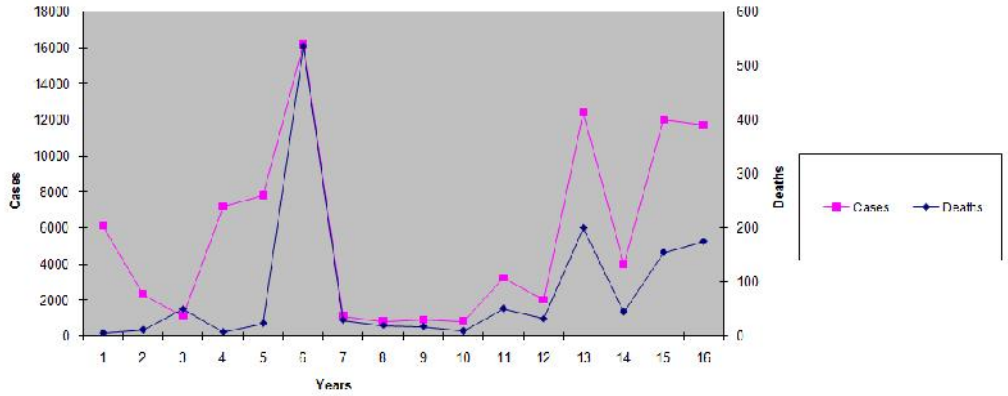


Figure 2. DF reported cases and deaths in India from 1991 till 2008[16]

Then in 2006 another major outbreak occurred with more than 11,000 reported cases and 165 reported fatal cases. Figure 2 shows data obtained from the World Health Organization (WHO) exhibiting the number of DF cases reported in

India from 1991 to 2008 as well as the annual reported fatality rate during this period.[33]

Samples isolated from Gujarat state showed that the epidemics of 1988-89 were dominated by DENV2. As time passed, dengue virus outbreaks reached different states of India. In 1992 Jammu also saw an outbreak of DENV2 followed by an outbreak in Haryana. DENV2 outbreaks were seen in Northern India in Delhi, Lucknow and Gwalior. However, DENV1 was the predominant serotype in the outbreak of 1997 in New Delhi. The Gwalior outbreaks of 2003-04 were dominated by DENV3, and DENV3 was also prominent in 2004-05 at Delhi. This co-circulation of serotypes in the same area might be the reason behind the large number of DHF cases reported that year.[22]

Rapid growth of the population and sudden climatic changes contributed to the increase in cases of DF/DHF in India. During 1997 until 2004, DENV1 was seen as the causative agent of most DF/DHF cases but later in 2005, DENV3 became the leading source of dengue outbreaks. According to the WHO in 2006, the total number of reported cases reached 12,317, while in 2007 fewer cases occurred 5,534 owing greatly to preventive measures taken by both the public and private sectors. In 2009, however, DF cases again reached 11,476 by November. Initial cases were reported in July 2009 with the greatest number of cases seen in October. These trends demonstrate that DENV has penetrated deep into India, with DENV2 and DENV3 predominating among different DENV serotypes.[16]

Etiology

Arboviruses (Arthropod borne viruses) are viruses of vertebrates, biologically transmitted by hematophagous insect vector. They multiply in blood sucking insects and are transmitted by bite to vertebrate hosts. Taxonomically, Arboviruses belong to families as diverse as Togaviridae, Bunyaviridae, Reoviridae, Arenaviridae and Rhabdoviridae.

Togaviruses are spherical viruses, 40-70 nm in diameter with lipoprotein envelope and single stranded RNA genome. The Togavirus family contains three genera of medically important viruses.[34]

Alphavirus	:	Arbovirus Group A
Flavivirus	:	Arbovirus Group B. The name being derived from flavi meaning yellow
Rubivirus	:	Rubella virus. It is antigenically and epidemiologically unrelated to arboviruses

Dengue virus, a species of flavivirus genus belonging to Togaviridae family, is a single stranded RNA virus. There are four serotypes of dengue virus, which are 1, 2, 3 and 4, and all serotypes can cause DF and DHF. All four types of dengue viruses have been isolated in this country and occasionally more than one type of dengue virus have been isolated from the same patient. The virus can survive at 4°C for several weeks and at 70°C for years.

Transmission and vector

The mosquitoes of "Stegomyia family" transmit dengue viruses. Aedes aegypti is the principal vector. Other vectors, which are also responsible for outbreaks of dengue infections are Aedes albopictus, Aedes polynesiensis and Aedes scutellaris complex.[35]

These are domestic mosquitoes and are most abundant during the rainy season. Females are fearless biters and bite during daytime. Two peak biting activity periods being two to three hours after dawn and in the afternoon few hours before dark. They do not fly over long distances and epidemic transmission of dengue requires a favorable temperature (>20°C).

The reservoir of infection is both man and mosquito. The transmission cycle is "man-mosquito-man", although in jungle setting, probably the monkeys are also responsible for maintaining this infection cycle. The Aedes mosquito becomes infective by feeding on a patient during viremia i.e. from a day before onset to the fifth day of illness. The virus multiplies in its salivary glands. After an incubation period of 8 to 10 days the mosquito becomes infective and is able to transmit the disease. Once the mosquito become infective, it remains so for life.

Pathology and Pathogenesis

Certain terms, which are come across during the pathogenesis of dengue fever are;

Homotypic infection

Refers to the infection caused by dengue virus strains of a single serotype.

Heterotypic infection

Refers to the infection caused by different virus serotype.

Primary infection

Is infection caused by any serotype in non-immune individual.

Secondary infection

Is heterotypic infection in a monotype immune individual.

Tertiary infection

Is heterotypic infection in a multitypic immune individual (two infection).

The most significant pathophysiologic changes among DV infections are seen in DHF/DSS, due to plasma leakage from intravascular to extravascular compartments. The leakage of plasma leads to hemoconcentration, hypotension, hypoproteinemia and collection of fluid in serious cavities. The plasma leakage occurs as a result of acute increase in vascular permeability, which is attributed to transient functional disturbance due to action of short acting chemical mediators as no significant inflammatory or destructive vascular lesions are seen on histological examination.

Most accepted hypothesis explaining the pathogenesis of DHF/DSS is immune enhancement hypothesis. According to this hypothesis presence of non-neutralizing heterologus antibody is necessary for occurrence of serious manifestations due to vessel wall dysfunction. This heterologous antibody acquired either transplacentally from mothers or as a result of first infection binds to DV and

facilitate the entry of virus into the cells of monocyte macrophage lineage. Within these cells, rapid viral replication occurs through a process called antibody dependent enhancement. These cells produce various vasoactive mediators e.g. tumour necrosis factor, interleukins (IL-1, IL-2, IL-6 etc.), platelet activating factor, complement activation products (C3a, C5a) and histamine. Simultaneously CD4 + T-Lymphocytes are also induced to produce gamma interferon, lymphotoxins and various interleukins. These cytokines have a complex interplay and act synergistically on vessel wall to produce increased vascular permeability.[36]

Though immunopathogenesis is important in the severity of DHF/DSS, certain viral factors may also be important determinant of severity, genetic changes might be occurring in the virus leading to variation in virulence and epidemic potential. Certain host factors like age, state of nutrition, sequence of infection for example serotype 1 followed by serotype 2 is more dangerous than serotype 4 followed by serotype 2 are also important in determining the severity of disease.[37]

There are four serologically related dengue viruses that parenterally enter human hosts. After a short period of cross protection, individuals infected with one serotype are fully susceptible to infection with other types; in contrast there is life long immunity to reinfection by the homologus serotype. Primary and heterologous infections can be distinguished by their characteristic serological responses. In primary dengue infections antibody responses are largely of IgM class and predominantly directed against type specific determinant. In secondary infections antibodies are largely of IgG class and directed against the antigens of flavivirus group on the dengue virus complex or sub complex.[38] Three major hemostatic factors appear to be involved in the bleeding diathesis in DHF/DSS, which are; [39]

Vascular injury

Vasculopathy is manifested by petechiae, positive tourniquet test and leakage of fluid and protein into extravascular spaces. This cause an acute increase in vascular permeability leading to loss of plasma from the vascular compartment, clinically producing pleural effusion, ascites, hemoconcentration, hypoproteinemia and shock. It is said that chemical mediators, histamine and not endothelial infection generate vascular permeability.

Coagulopathy

Weiss and Halstead et al observed a moderate prolongation of the prothrombin time due to decrease in factors II, V, VII and X.

In WHO collaborative study, platelet counts and average minimum fibrinogen level fell in correlation with severity of illness, while fibrin degradation products (FDP) rose correspondingly.

Suratte et al, Bokish et al and Srichaikul et al confirmed the mild increase in FDP but since euglobulin clot lysis times were normal, the authors concluded that there is evidence of mild to moderate consumptive coagulopahty, but no DIC, also it contributes neither to shock nor to bleeding nor was therapy with heparin justified.

Thrombocytopenia

The cause of thrombocytopenia is controversial, but the possibilities include impaired megakaryocyte production earlier in the disease, platelet injury by virus itself, platelet specific antibodies, immune complexes or DIC.

Hematological abnormalities[39]

In DF, leukopenia begins on day two of infection, reaching low point on fourth to sixth day along with early absolute neutropenia and lymphopenia, gradually returning to normal by ninth to tenth day with lymphocyte count returning to normal before neutrophils. Contrast to it in DHF/DSS cases where early absolute leukopenia was observed, in a few cases moderate leukocytosis between days four to nine along with early relative lymphocytosis is observed. In both syndromes there occurred marked degeneration of mature neutrophils and "shift to left" during febrile phases of illness. Atypical or transformed lymphocytes were seen on day fifth of illness, which have large nuclei with fine, homogenous nuclear chromatin and azurophilic cytoplasm. A bone marrow biopsies on fourth day of fever in dengue fever found that the bone marrow was hypocellular with diminished megakaryocytes, diminished erythropoiesis and totally absent granulocytopoiesis, on day seven and ten the bone marrow cellularity returns to normal. In DHF/DSS, early in febrile course, the bone marrow is hypocellular with maturation arrest of all elements. At the time of shock or defervescence marrow are usually normocellular or hyper-cellular with an unusual incidence of phagocytic reticulum cells.

Clinical features

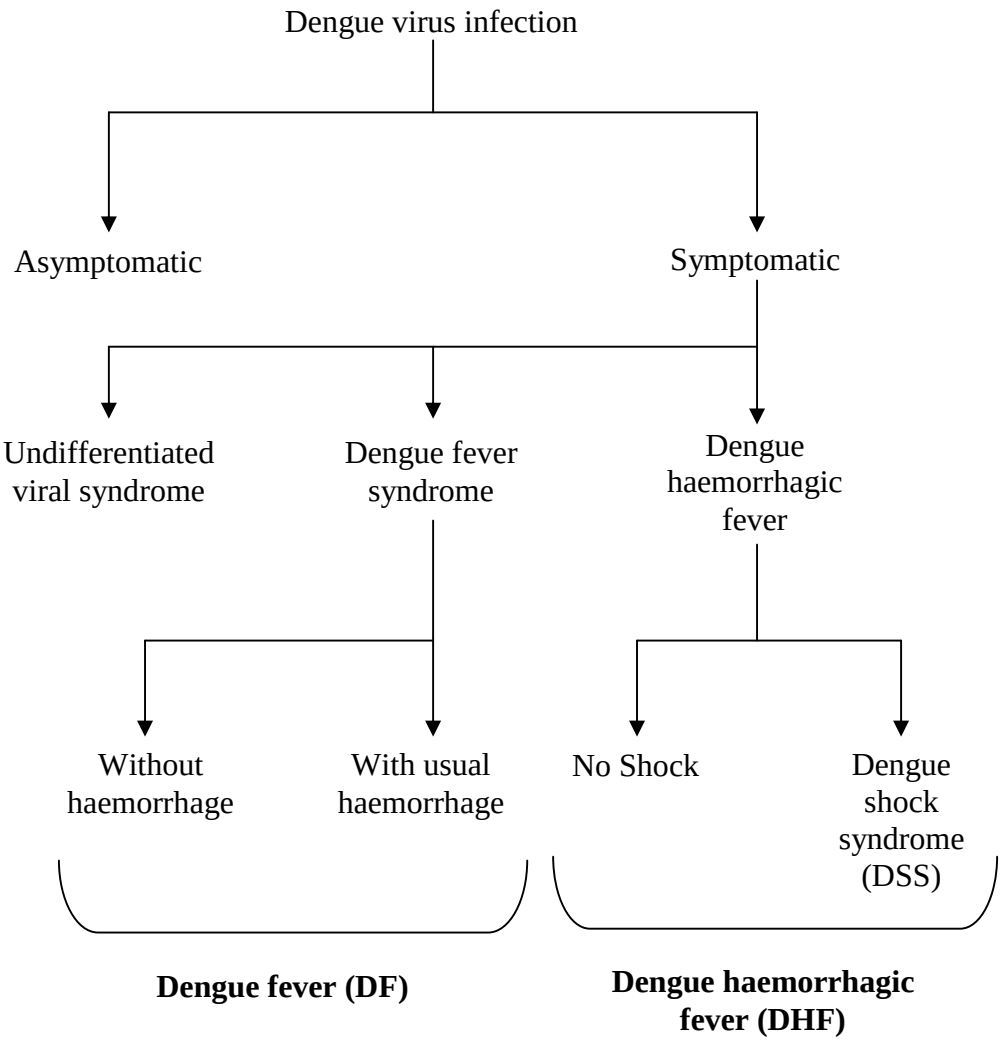
The dengue virus infection may be manifested as asymptomatic to symptomatic disease as classical dengue fever, dengue hemorrhagic fever/dengue shock syndrome.

Dengue fever

Dengue fever is an acute viral infection caused by at least one of the four serotypes (1,2,3 and 4) of dengue virus. All ages and both sexes are susceptible to dengue fever. The illness is characterized by an incubation period of three to ten days. The onset is sudden with chills and high fever, intense headache, muscle pain, joint or bony pain (Break bone fever), retro orbital pain and photophobia. Other common symptoms include weakness, abdominal pain, sore throat and general depression. Fever is usually between 39°C and 40°C, followed by a remission of a few hours to two days (biphasic fever or saddle back fever).

The skin eruptions in 80 percent of case appear during the remission or during second febrile phase, which lasts for one to two days. The rash may be diffuse flushing, mottling or fleeting pinpoint eruptions or the rash may be maculopapular or scarlatiniform.

Figure 3. Spectrum of clinical features of dengue virus infection[35]



Some patients with dengue fever have evidence of mucosal or cutaneous bleeding without other evidence of DHF/DSS like hemoconcentration or fluid leak; such patients are classified as dengue fever with unusual bleeding.[40]

Fever lasts for about five to seven days after which recovery is usually complete although convalescence may be protracted.

Dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS)

DHF/DSS is a severe form of dengue fever, caused by infection with more than one dengue virus and may be fatal in 40-50% of untreated patients. The disease is confined exclusively to children less than 15 years of age, but due to change in epidemiological trend the disease may occur in adult population.

After an incubation period of four to six days the patient develops clinical features of dengue fever. There may be varying degree of tender hepatomegaly or less commonly splenomegaly. All patients have some degree of haemorrhagic phenomenon like positive tourniquet test, petechial spots, bruising at venepuncture site, bleeding from gums, epistaxis, hemetemesis or melena, muscle hematoma, hematuria and rarely intracranial haemorrhage may occur.

Fever may subside after two to seven days. At this stage patient may develop varying degree of peripheral circulatory failure. With progressive peripheral circulatory failure, patient may have sweating, restlessness, cold extremities, pulse pressure gets narrow, blood pressure starts falling ultimately leading to unrecordable blood pressure and irreversible shock.

Unusual manifestations of DHF/DSS include hepatitis, encephalitis and glomerulopnephritis.[40]

Several studies[6,22,41-51] have reported different clinical features and complications of dengue fever. Thrombocytopenia is a very important indicator of prognosis in DHF as was shown by the study conducted in Philippines by Chua MN, et al.[42] in 1992.

Sharma S et al.[43] from AIIMS, New Delhi studied 98 adult patients diagnosed to have dengue haemorrhagic fever (DHF) (n=75) and dengue shock syndrome (DS) (n=23) during an epidemic of dengue fever in the middle of August 1996. Fever (100%), body aches (45.9%), abdominal pain (38.7%), purpura (33.6%), epistaxis (32.6%), malena (26.5%), haematemesis (22.4%) and ecchymoses (20%) were commonly present symptoms. ELISA IgM antibodies for serodiagnosis of dengue virus infection was positive in 23 of the 27 patients tested. At the time of admission, 94 patients had a platelet count below 100,000/mm3. Four patients with haemorrhagic manifestations had an initial platelet count of >100,000/mm3. Severe thrombocytopenia (platelet count <20,000 /mm^3) was present in 43.8% of the patients. The ultrasound tests showed pleural effusion in 10 of the 12 patients and ascites in five patients tested when they were not clinically evident.

Wali JP et al.[44] studied 17 consecutive patients of DHF/DSS in New Delhi to assess cardiac function by radionuclide ventriculography, echocardiography and electrocardiography (ECG) during the epidemic of Dengue virus type-2 (DENV-2) in Delhi, India (1996). Fourteen patients were seropositive for Dengue infection. In radionuclide ventriculography study, the mean left-ventricular ejection fraction was 41.69 (5.04% (range 33-49%) and 7 patients had an ejection fraction less than 40%, global hypokinesia was detected in 12 (70.59%) patients. In echocardiography, the mean ejection fraction was 47.06 (3.8%). Eight patients had Dengue Shock Syndrome and the mean ejection fraction was 39.63%. Authors concluded that, acute reversible cardiac insult may be noticed in DHF and DSS could be responsible for hypotension/shock.

Kuo CH et al.[45] studied the impact of dengue on liver function by biochemical tests on 125 male and 145 female patients diagnosed with this disease during an outbreak that extended from November 1987 to December 1988 in Taiwan. Abnormal levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase (GGT) were observed in 93.3%, 82.2%, 7.2%, 16.3% and 83.0% of the patients, respectively. Study concluded that, dengue fever might cause hepatic injury and transaminase elevation similar to that in patients with conventional viral hepatitis. In epidemic or endemic areas, dengue fever infection should be considered in the differential diagnosis of hepatitis.

Mohan B et al.[46] prospectively studied hepatic functions of 61 children, diagnosed to have dengue infection, aged 2 months to 12 years comprising 37 cases of dengue fever (DF), 16 with dengue hemorrhagic fever (DHF), and eight with dengue shock syndrome (DSS) during the acute attack. Hepatomegaly (74%), epistaxis (26%), jaundice (25%), and petechial rashes (18%) were the common clinical manifestations of dengue infection. On admission, levels of serum aspartate transaminase (AST), serum alanine transaminase (ALT) and serum alkaline phosphatase were raised in 80-87% of children with hepatomegaly (group I) and 81% of cases without hepatomegaly (group II). During the second week of hospitalization the proportion of cases with raised levels of AST, ALT, alkaline phosphatase and serum bilirubin increased and the mean levels were significantly higher ($p<0.05$) in both the groups. Authors suggested that, transient derangement of liver functions in childhood dengue infection, more so in DSS and DHF, with or without hepatomegaly.

In a study by Shivbalan S et al.[47] during 2004 on the predictors of spontaneous bleeding in dengue, a platelet count of less than 50,000 was found to be significantly associated with increased risk of bleeding. The other associated predictors of bleeding in the study conducted were prolonged PT, raised AST/ALT and haemoconcentration.

Shah I et al.[48] conducted prospective study in the pediatric wards and pediatric intensive care unit of B. J. Wadia Hospital, Mumbai for Children between 27 August 2003 and 10 October 2003 to determine the clinical features of children affected with dengue. Fever, hepatomegaly, vomiting, bleeding tendencies, erythematous rash, thrombocytopenia, elevated liver enzymes, and deranged PT and PTT were the predominant clinical and laboratory features. Predictive markers for DSS were younger age at onset, altered sensorium, paralytic ileus, and significantly deranged PT.

In a study by Venkat Sai PM et al.[49] on the role of USG in dengue fever, 100% of the patients showed gall bladder thickening and pericholecystic fluid, 21% had hepatomegaly, 6.25% had spleenomegaly and minimal right pleural effusion. In a follow up USG on the 5th day in the same patients, 53% had ascites. Study concluded that, in an epidemic of dengue, ultrasound features of thickened gall bladder wall, pleural effusion and ascites should strongly favour the diagnosis of dengue fever.

Recently, Kumar A et al.[50] in his record-based study conducted in a coastal district of Karnataka to study the clinical manifestations, trend and outcome of all confirmed dengue cases admitted in a tertiary care hospital assessed the laboratory

confirmed cases from 2002 to 2008 from Medical Records Department (MRD). Of the 466 patients, the most common presentation was fever 462 (99.1%), followed by myalgia 301 (64.6%), vomiting 222 (47.6%), headache 222 (47.6%) and abdominal pain 175 (37.6%). The most common hemorrhagic manifestation was petechiae (67.2%). Of the 66 (14.1%) patients who developed clinical complications, 22 (33.3%) had ARDS and 20 (30.3%) had pleural effusion.

More recently Karoli R et al.[51] in their cross-sectional study at Lucknow during the monsoon and post-monsoon seasons in the year 2010 on 356 patients with suspected dengue fever found 138 (39%) had serologically confirmed dengue infection. Out of this Ninety-six (70%) patients had classical dengue fever while 42 (30%) had dengue hemorrhagic fever. The most common symptoms were headache (105, 76%), abdominal pain (87, 63%), vomiting (80, 58%), rash (36, 26%) and cutaneous hypersensitivity (22, 16%). Hemorrhagic manifestations were present in 55 (40%) patients. Notably, 14% of patients had neurological involvement and 4% had acute hepatic failure. Study concluded that, dengue infection had varied and multi-systemic manifestations that can go unrecognized.

Also there is high index of suspicion of the various atypical clinical presentations involving various organs / systems which include; [22]

- Neurological manifestations - Encephalopathy, acute motor weakness, seizures, neuritis, Guillain Barre syndrome, hypokalemic paralysis acute viral myositis, acute encephalitis;
- Hepatic involvement - Acute liver failure, hepatic encephalopathy, hepatomegaly, jaundice and petechial rashes;

- Myositis - Acute myositis, pure motor quadriplegia;
- Cardiac involvement - Acute reversible cardiac insult, sinoatrial block and atrioventricular dissociation;
- Lupus erythematosus (systemic) - Abnormal immune response leading to systemic lupus erythematosus;
- Occlar complications & uveitis - Unilateral blurring of inferior visual field;
- Acute renal dysfunction - Renal dysfunction, acute kidney injury; Acute inflammatory colitis such as Lower gastrointestinal bleeding and acute inflammatory colitis;
- Cutaneous manifestations - Maculopapular/morbilliform eruption followed by ecchymotic, petechial, and macular/scarlatiniform eruption, Confluent erythema, morbilliform eruptions, and haemorrhagic lesions;
- Kawasaki disease - Young child developed Kawasaki disease later in disease and Bone marrow haemophagocytosis associated with nasal bleeding and pancytopenia

Physiopathology of dengue hemorrhagic fever[14]

The hemorrhagic form of dengue is rare and affects almost exclusively patients with a prior episode, suggesting a physiopathology associated with an exacerbated immune response mediated by heterologous antibodies. Increases in TNF, IL-2, and soluble CD8 are suggestive of hyperactivation of memory CD4 and CD8 cells. There is evidence of overexpression of Fc receptors and class I and II MHC antigens, as well as a serum increase of several inflammatory mediators, as a result of endothelial and mononuclear cell lysis. The result of the immune over-response is a combination of vasculopathy and consumption coagulopathy. The

hemorrhagic diathesis in dengue is caused by vasculopathy, thrombocytopenia, and mild coagulopathy, which are responsible for skin and mucous membrane bleeding[3]. The greater vascular fragility is probably a result of the direct action of the virus, which would occur as early as the viremic or initial febrile phases.

Thrombocytopenia and platelet disorders

As to platelets, there may be thrombocytopenia and platelet disorders. Thrombocytopenia may be secondary to decreased platelet production by the bone marrow, as well as increased peripheral destruction of platelets. It has already been observed that during the acute febrile phase of dengue hemorrhagic fever, bone marrow is markedly hypocellular, with a drop in the production of all cell lines. These findings were later shown to result from direct action of the virus on the medullary stroma and on the hematopoietic progenitor cells. Two days before the defervescence phase, bone marrow hypercellularity is noted, with an enhanced production of precursor cells of the three medullary cell lines. Hemophagocytosis is another possible explanation for the reduced platelet count, which can also occur due to immune destruction (IgM class antiplatelet antibodies and dengue-specific antibodies). Platelet counts return to normal within 7 to 10 days after the defervescence phase.[14]

Alterations in platelet function are also described; these are evidenced by ADP-induced platelet hypoaggregation, a drop in the secretion of intra-platelet ADP, and a rise in plasma concentrations of b-thromboglobulin and platelet factor-4. These findings are consistent with *in vivo* platelet activation resulting from

activation by immune complexes. Platelet function resumes its normal conditions 2 to 3 weeks after the initial convalescence period.[14]

Alterations in coagulation

During the febrile period, variable reductions are observed in the different coagulation factors, such as fibrinogen, factor V, factor VIII, factor IX and factor X, besides antithrombin and a_2-antiplasmin. These changes explain the discreet prolongation in prothrombin time and activated partial thromboplastin time. Elevations in the concentrations of fibrinogen/fibrin (FDP) degradation products and D5-dimer have also been described.[14]

Due to these alterations in hemostasis, the use of acetylsalicylic acid, non-hormonal anti-inflammatory agents, and large quantities of volume expanders (Dextran 40 and Haemacel) is considered as risk factors for bleeding.[14]

Immunity and inflammation

The mechanisms involved in the development of severe dengue hemorrhagic disease are not fully understood, but it is suggested that a secondary infection induced by another dengue serotype is the main risk factor for dengue hemorrhagic fever and dengue shock syndrome. Cross-reactive non-neutralizing antibodies from a previous infection bind to the new serotype, increasing capture by monocytes and macrophages, thus resulting in the amplification of the cytokine cascade and activation of the complement. However, as only 2% to 4% of individuals with a second infection develop the severe form of the disease, the antibody-dependent increase alone can not explain the whole process. Significant differences in

antibody, cytokine, and T-cell responses are observed between patients with the non-complicated form of the disease and those with the complicated forms.[14]

Monocytes, B lymphocytes, and mastocytes infected by the dengue virus produce different cytokines, and some authors show that the largest increases in concentrations of TFN-a, IL-2, IL-6, and interferon (IFN)-g take place during the first 3 days of the disease, followed by the appearance of IL-10, IL-5 and IL-4. Patients with the hemorrhagic form of the disease present larger concentrations of TNF-a, IL-6, IL-13, IL-18, and cytotoxic factor, and these cytokines are involved in the increased vascular permeability and shock that occur during the infection. Additionally, by producing T CD4+ cells, the cytotoxic factor induces macrophages to produce IL-1a, TNF-a, and IL-8. Concentrations of IL-6 (of endothelial and mastocyte origin) are higher in patients with shock and dengue hemorrhagic fever. The highest levels of TNF-a and IL-10 correlate with hemorrhagic manifestations and thrombocytopenia, respectively. IL-10 also reduces platelet function and contributes to dengue platelet defects.[14]

There is much evidence linking inflammation and coagulation, and the main interfaces for this are the tissue factor (TF) pathway, the C-protein system, and the fibrinolytic system. Proinflammatory cytokines can affect all these coagulation mechanisms, whereas activated coagulation proteases, physiological anticoagulants, or components of the fibrinolytic system can modulate inflammation through specific cell receptors.[14]

The main inflammatory mediators involved are IL-6, in coagulation activation, and TNF-a and IL-1 in physiological anticoagulant regulation. Several

studies demonstrate the importance of IL-6 in the induction of TF expression in many cells, such as mononuclear cells, leading to systemic activation of coagulation. Once TF is expressed, the coagulation cascade is triggered, as well as the formation of enzymatic complexes on a phospholipid surface which, ideally, is presented by the platelets. During the inflammatory process, platelets can be directly activated by endotoxins, thrombin, and inflammatory mediators, such as the platelet activating factor. By expressing P-selectin, the activated platelets mediate platelet adhesion to the endothelium and leukocytes. The binding of activated platelets to neutrophils and mononuclear cells induces activation of nuclear factor kB, thus increasing the expression of TF in monocytes. During the acute inflammatory process, concentrations of antithrombin are significantly decreased due to the reduced synthesis, degradation by neutrophil elastase released from activated neutrophils, and consumption. The C-protein system is also blocked, as the endothelial expression of thrombomodulin is reduced by the action of TNF-a and IL-1b. TNF-a and IL-1b also have a role in regulating plasminogen inhibitors and activators. Cytokines induce secretion of tPA and uPA from their storage sites in endothelial cells. However, this increase in fibrinolytic activation is counterbalanced by a delayed and sustained rise in PAI-1.[14]

Atypical manifestations of dengue

The endothelium is the target of the immunopathological mechanisms in dengue and DHF. The hallmark is vascular permeability and coagulation disorders. These mechanisms can explain varied systemic involvement.

Cardiac manifestations of dengue

Cardiac manifestations of dengue are uncommon but cardiac rhythm disorders such as atrioventricular blocks, atrial fibrillation, sinus node dysfunction and ectopic ventricular beats have been reported during episodes of DHF. Most are asymptomatic and have a benign self limiting course with resolution of infection. These arrythmias have been attributed to viral myocarditis, but an exact mechanism has not been elucidated. In most of the reported cases there were no documented electrolyte disturbances or significant Chest X ray or echocardiography findings. Pericardial involvement has also been attributed to dengue infection along with myocarditis.[52]

Dengue rarely affects the heart. In 1996, during an epidemic outbreak of dengue in India, 206 patients were evaluated and only one had cardiac symptoms.[42] Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis.[53]

On the other hand, the ventricular dysfunction associated with the acute phase of dengue hemorrhagic fever has been described by several authors and is probably underdiagnosed in clinical practice. During the 1996 epidemic, 54 children with dengue of varied degrees of severity underwent evaluation of the ventricular function. Approximately 16% had ejection fractions under 50%.[54] In that same period, 17 subjects with dengue hemorrhagic fever or dengue shock syndrome underwent myocardial scintigraphy, which showed that 70% of them had diffuse hypokinesia, with a mean ejection fraction of 40%.[46] After three weeks, the

myocardial function of all patients had normalized. More recently, 24 patients with dengue hemorrhagic fever were evaluated and underwent serial echocardiograms during the acute phase of the infection and convalescence. In the study, a transient reduction in ventricular ejection fraction and in cardiac index during the infection was observed.[56]

Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the hemorrhagic form of the disease or in the associated shock. The "dengue-related shock syndrome" is due to the increased vascular permeability and hypovolemic pattern.[57] However, an adequate approach to the hemodynamic instability associated with dengue requires not only a significant volemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction, as in the current treatment of sepsis.

Clinical features of cardiac involvement by dengue

1. *Subclinical presentation:* This is most common as myocarditis in dengue remains asymptomatic and myocardial involvement in dengue runs a benign course without long term complications.[58]

2. *Persistent shock despite fluid resuscitation:* This is one of the commonest cardiovascular complication of Dengue Hemorrhagic fever. This can be due to diastolic dysfunction, systolic dysfunction or arrhythmias.[59] The left ventricular failure may contribute to hypotension seen in DHF/DSS and may have implications in fluid management as fluid overload may worsen the condition.[58] Similarly children with diastolic dysfunction are at a higher

risk of elevated left ventricular filling pressures and resultant pulmonary edema with fluid challenges.[59]

3. *ECG changes*[46,58,60,61] These are asymptomatic and most are transient among patients with DF/DHF.

    a. Evidence of Pericardial effusion

        i. Low voltage QRS complex- QRS < 5 mm in limb leads and < 10 mm in chest leads

        ii. Widespread ST segment elevation

        iii. Total electrical alternans

    b. Evidence of Pericarditis

        i. ST elevation with concavity upwards

        ii. T wave inversion in V5 and V6

    c. Evidence of Myocarditis

        i. Sinus tachycardia

        ii. Low voltage QRS complex

        iii. Prolonged PR interval

        iv. Low amplitude T waves

    d. Evidence of AV block

    e. Relative bradycardia

4. ECHO changes[46,61]

    a. Pericardial effusion -usually tends to be small and located only posteriorly.

b. Decreased left ventricular ejection sfraction -may contribute to hypotension seen in DHF/DSS and may have implications in fluid management as fluid overload may worsen the condition.

c. Diastolic dysfunction

d. Global hypokinesia

e. Left ventricular dilatation

f. Tricuspid regurgitation.

5. Elevated cardiac enzymes[58]

   a. CPK- CPK MB isoform which is heart specific can be elevated.

   b. Serum troponin T:Specific for myocardial injury.

Pathogenesis of cardiac involvement[62]

Vigorous infection of heart tissues in vivo and striated skeletal cells in vitro has been observed. Derangements of Calcium storage in the infected cells may directly contribute to the presentation of myocarditis in pediatric patients. The following are the pathogenetic mechanisms of cardiac involvement in dengue,

1. The direct invasion of heart muscle cells and their damage by Dengue virus- as suggested by increase in CK-MB which is an independent marker of myocardial damage.

2. DENV directly infects and alters the Ca+2 storage of cardiac & skeletal muscle cells in vitro.

3. An increase in resting ionized calcium was one of the consequences of DENV infection-it is probable that increased resting (diastolic) Ca2+ is

present in infected myocardium and may be responsible for the arrhythmias and altered contractile function of the myocardium documented in vivo.

4. Ca2+ release from intracellular stores has been identified as one of the major signals that can induce the mitochondrion-dependent pathway of apoptotic cell death. Increased Ca2+ has been shown to produce mitochondrial pore opening, cytochrome c release, caspase activation, and nuclear apoptosis in cells exposed to apoptotic signals.

Pericardial effusion

Pericardial effusion in DHF and DSS results from capillary leakage of intravascular fluids, electrolytes, and small proteins into perivascular tissues.[63] The increased production of cytokines, including TNF-α and IFN-α, and other chemical mediators release is responsible for this increased vascular permeability and abnormal leakage of plasma leading to pericardial effusion.[64]

Several viral infections, other than Dengue are known to cause Myocarditis and Cardiomyopathy. Cardiac dysfunction may have a contributing role in the pathogenesis of shock and could also influence the outcome of the disease.

A viral infection of the heart follows a standard progression. Most viral pathogens enter the body through the upper respiratory or gastrointestinal tract. Susceptibility to viral infection in humans is increased by malnutrition, exercise, age (young and old), stress and hormones.[65,66] There are undoubtedly genetic susceptibilities that alter the autoimmune response to viral infections.

The typical viral infection produces a systemic viremia and associated vascular response on days 0 to 3. During this interval, the pathogenic virus can invade the myocardium and replicate in the myocyte, causing myocytolysis. In day 5 to 10 there is a generalized macrophage and IgM antibody response associated with a histological inflammatory infiltrate.[67] An antigen specific IgG antibody response peaks by day 14 and is associated with histological evidence of myofiber dropout and interstitial fibrosis.

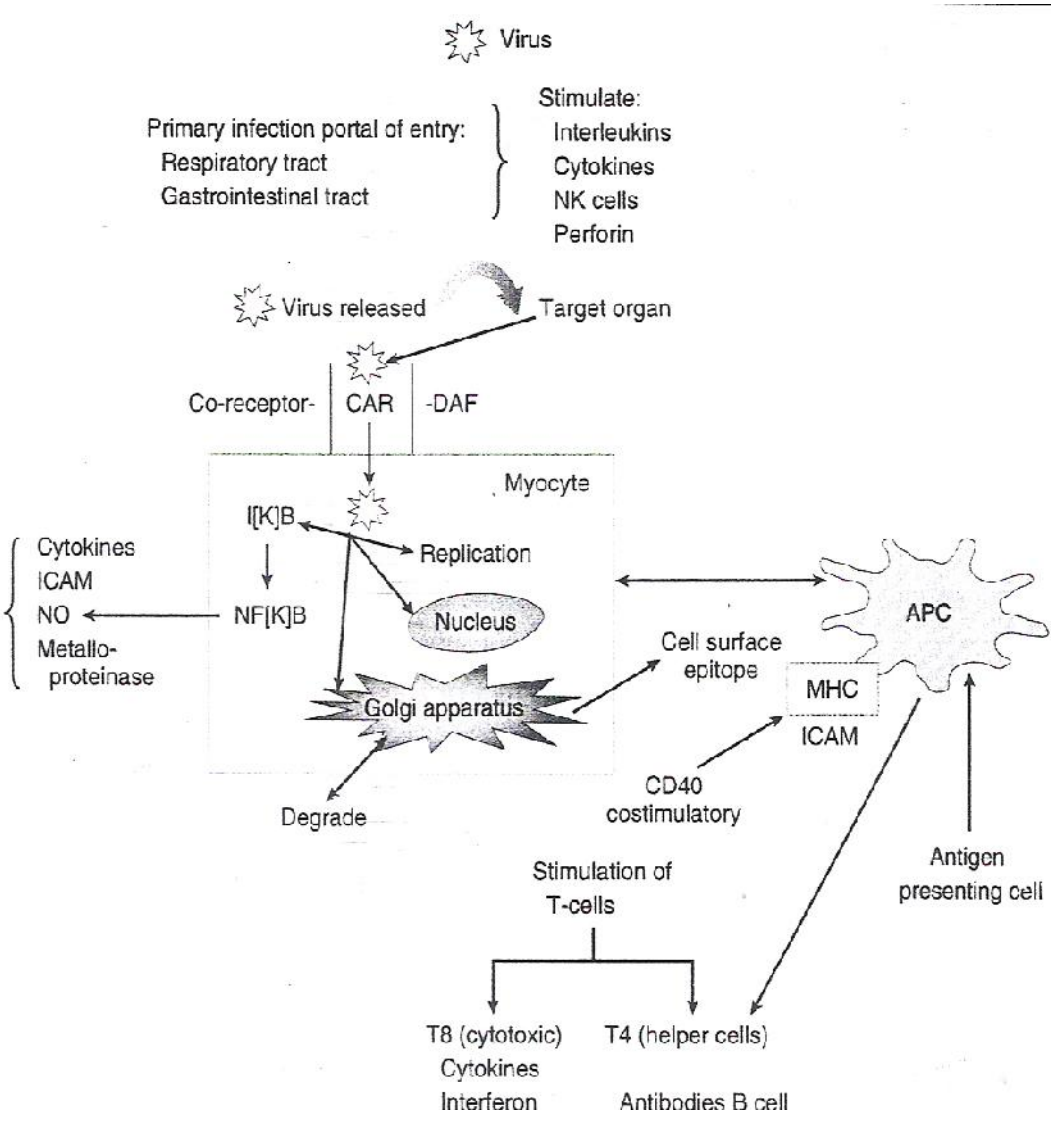


Figure 4. Pathophysiology of viral myocarditis[68]

The virus enters the body through the respiratory or gastrointestinal tract stimulating a systemic immune response. The virus enters the myocytes through the CAR (Coxsackie adenoviral receptor) with coreceptors including DAF (decay accelerating factor). Once in the myocyte, the virus replicates and is transmitted to the nucleus, where it redirects cell activity and is released to the cell surface, where the virus can escape to infect additional cells. Dendritic cells and macrophages ingest foreign elements, including viruses causing further enhancement of the immune response. Antigen- presenting cells expressing MHC (major histoconipatibility complex) and associated with coreceptors CAM and CD40 couple with infected myocytes displaying antigen (epitope). On their surface, The APC (antigen presenting cell) then stimulates Cytotoxic cells capable of ingesting the myocyte surface or antibody-producing cells, which affect cell function or enhance membrane damage by cytotovic cells.

The underlying mechanisms were postulated to be immune in origin, although myocarditis may be a contributory factor. Fever production in response to exogenous pyrogens is believed to be mediated mostly by cytokine prostaglandin pathways, and neural input is important in the early phases of fever.[69] Concentrations of cytokines, including tumor necrosis factor, interferon- γ, interleukin-8 (IL-8)**,** IL-10, and IL-12, are substantially increased during dengue infection. Their levels likely correlate with specific clinical manifestations and illness severity.[70] The relationship of cytokines to relative bradycardia is unknown. Further studies could consider the relative importance of immune and neural mechanisms and also any direct cardiac pathology in the etiology of dengue-associated relative bradycardia.

Myocardial involvement may be a result of the direct effect of the dengue virus in susceptible individuals or due to the effects of cytokine mediators and / or cellular components of the immune response. The possibility of IgM antibodies produced against the dengue virus cross reacting with a myocardial antigen is unlikely as echocardiographic improvement was seen within three weeks of the illness, when these antibodies were still in circulation. Dengue viral antigen associating with a myocardial receptor site, thereby triggering off an immunological response in also another possibility in susceptible individuals. This myocardial inflammation ceases when the viral antigen disappears from the circulation. Dengue haemorrhagic fever patients have higher levels of TNF-α, IL-6, 13 and 18 and cytotoxic factor. These cytokines are implicated in causing increased vascular permeability and shock during dengue infection but their contribution towards development of myocarditis remain undefined.[71-73]

Dengue virus can infect both CD-4 and CD-8 T cells.[74] Following primary infections both serotype specific and serotype cross reactive memory T cells are formed and the latter, on secondary exposure to the virus, augment infection by producing various cytokines.[75] These mechanisms may have a role in the pathogenesis dengue associated myocarditis, although the exact pathophysiology is undefined. Liver injury during dengue infection could also be due to a T cell immune response.

Pathology[76]

Primary cardiac failure due to myocarditis in dengue infection is very often overlooked. There is histopathological evidence to support myocarditis in dengue

infection. The presence of interstitial oedema, infiltration of inflammatory cells and necrosis of myocardial fibers in the myocardium suggests severe myocarditis.

There are few studies done on myocardial involvement in dengue fever.

In 1996, a study of 17 patients of Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) the mean left-ventricular ejection fraction was 41.69 (5.04% (range 33–49%) and 7 patients had an ejection fraction less than 40%, global hypokinesia was detected in 12 (70.59%) patients. In echocardiography, the mean ejection fraction was 47.06 (3.8%). Eight patients had Dengue Shock Syndrome and the mean ejection fraction was 39.63% (4.97%). 5 patients had ST and T changes in the electrocardiogram, and echocardiography revealed no abnormalities after 3 weeks of follow up and the ejection fraction was more than 50% in all cases. Global hypokinesia also improved and ECG changes reverted back to normal within 3 weeks.[46]

Sri Lanka experienced a dramatic increase in dengue cases (15,400) in the 2004 - 2005 season. A prospective study investigated cardiac involvement in dengue virus infected patients during the 2004 - 2005 season in Peradeniya, Central Province, Sri Lanka. Cardiac involvement was defined as elevated levels of myoglobin, creatine kinase-muscle brain-type, N-terminal pro-brain natriuretic peptide, heart-type fatty acid-binding protein and troponin T. Twenty-five percent of dengue virus infected patients had one or more of the above tests with abnormal results.[77]

A similar study done in 1998 took 54 patients with Dengue Hemorrhagic Fever. Ejection fraction was reduced (<50%) in 9 children (16.7%), 2 of which had EF<35%.[29]

Another study done in 2011, showed cardiac rhythm abnormalities were found in ten patients (29%), including sinus pause, first-degree and Mobitz type I second-degree AV block (Wenckebach) and atrial and ventricular ectopic beats. However, there was no relationship between the clinical severity of dengue virus infection (DF, DHF without shock and DSS) and the incidence of cardiac arrhythmia.[78]

Another study done in 2009 included 319 cases of dengue fever, 166(52%) had severe infection. Of them, 149 patients (90%) had secondary dengue infection and in 5 patients, DEN-1 was identified as the causative serotype. The clinical diagnosis of myocarditis was considered in 45(27%) patients. The autopsies were done in 5 patients who succumbed to shock (3 females and 2 males) aged 13- 31 years. All had pleural effusions, ascites, bleeding patches in tissue planes and histological evidence of myocarditis. One patient had pericarditis.[76]

A high incidence of cardiac complications was observed in an outbreak of dengue fever at General Hospital, Peradeniya, Sri Lanka, in 2005. This report described 120 serologically confirmed dengue fever patients who presented during the outbreak. Seventy-five (62.5%) of these patients had electrocardiogram changes (T inversion, ST depression, bundle branch blocks) and were assigned to the 'cardiac group' (50 females, 25 males; median age 34 years, range 13-76). These patients were more susceptible to fatigue, dyspnoea, low peripheral oxygen saturation in

room air (P=0.001), chest pain (P=0.001) and flushing of skin (P=0.05) than 45 (37.5%) patients who had normal electrocardiograms and made up the 'non-cardiac group'. In the cardiac group there were 31 primary and 44 secondary dengue patients. In the cardiac group, 17 (23%) patients had hypotension and 58 (77%) developed tachycardia and bradycardia (P<0.001) compared to four (9%) in the non-cardiac group, suggestive of significant cardiac dysfunction. There was no correlation between pulse rate and body temperature: cardiac group (r=0.05; P=0.63); non-cardiac group (r=0.11, P=0.46). RT-PCR detected DEN-3 in three cardiac patients.[79]

In a study conducted by Weerakoon KGAD et al at General hospital, Peradeniya out of 319 cases of dengue fever, clinical diagnosis of myocarditis was considered in 45 patients. Autopsies done in 5 patients who succumbed to shock revealed histological evidence of myocarditis. It was concluded that primary cardiac failure due to myocarditis in dengue infection is very often overlooked and emphasis is needed to consider myocarditis in severly ill patients with dengue infection.[76]

In a study conducted by Yusoff K. and others in Institute of Medical Research, Kaula Lumpur, Malaysia ECG and ECHO were prospectively performed on 23 consecutive adult patients with a clinical diagnosis of dengue infection.20 out of 23 patients had abnormal ECG in the form of conduction abnormalities, ST segment elevation, T wave inversion and sinus bradycardia. Abnormal ECHO were present in 12 patients and these were pericardial effusion, abnormal systolic and diastolic functions, left ventricular dilatation and tricuspid regurgitation. It was concluded that cardiac involvement in the pathogenesis of severe forms of dengue remains to be defined.[61]

A study done by Wali JP et al[44] conducted on 17 consecutive adult patients of Dengue Haemorrhagic Fever/Dengue Shock Syndrome, assessed cardiac function by radionuclide ventriculography, echo-cardiography and electrocardiography during the epidemic of Dengue virus type-2 (DEN-2) in Delhi, India which showed global hypokinesia in 70.6%. TC99 pyrophosphate imaging carried out in four patients showed no myocardial necrosis. Five percent patients showed ST and T wave changes. Electrocardiogram changes, echo-cardiographic and radionuclide ventriculography all returning to normal within three weeks.

Another Indian study done by Kabra et al[55] at AIIMS, New Delhi conducted on 54 children with dengue fever studied myocardial dysfunction in children with dengue haemorrhagic fever, found no correlation between myocardial involvement and clinical severity. The echo showed ejection fraction < 50 in nine out of 54 (16.7%) children and two of these had significant reductions (less than 35%). Three of these nine children who had a repeat echo with in two months of illness had an improved ejection fraction.

A cohort study from Sri Lanka done by Satarasinghe RL et al[80] in adults revealed that, myocardial involvement of dengue infection run a benign course without long term complications, contrary to what was believed in past. The dengue shock syndrome in severe dengue infections is most likely to be due to hypovolemia and internal fluid extravasation than due to cardiogenic shock.

A study conducted by Khongphatthanayothin A et al[81] in Sri Lanka to determine prevalence of myocardial depression and its effect on clinical severity in patients with dengue hemorrhagic fever showed that, transient myocardial

depression is not uncommon in patients with DSS. Cardiac dysfunction in children with DSS may contribute to the clinical severity and the degree of fluid overload in the patients.

Another observational study was done by Khongphatthanayothin A et al[56] in Sri Lanka to assess hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage by echocardiography on 24 patients. Results of the study showed that, ejection fraction and VCFC / ESS were significantly lower during the toxic stage than after recovery. Cardiac index was low during the toxic stage due to decreased preload (low end diastolic volume) and depressed left ventricular ejection fraction. Cardiac index remained subnormal during convalescence due to sinus bradycardia.

In another study by Gupta VK et al[58] in PGI Chandigarh on, nine of the 11 myocarditis patients' electrocardiogram indicated sinus bradycardia while two had tachycardia. Seven myocarditis patients showed T-wave inversions. Of the seven echocardiograms studied, pericardial effusion and diastolic function impairment was present in five and two patients, respectively. In addition, pathologically elevated concentrations of creatine phosphokinase myocardial band (muscle specific) (CPK-MB) levels were found in six patients with symptoms of myocarditis.

Implications of the interruption of antithrombotic agents used in cardiac patients with dengue

The decision to interrupt the use of platelet antiaggregants and anticoagulants in patients with dengue depends on a complex assessment of the risks and benefits of these treatments. The risk of interrupting the use of antithrombotics in different

clinical conditions and the risk of hemorrhage in an acute virus infection should also be taken in consideration.[14]

Patients who have recently undergone angioplasty, with chronic atrial fibrillation (CAF) and those with metal valvar prostheses are the ones who benefit most from the use of antiaggregants and anticoagulants in the long run. Treatment interruption increases the risk of thrombosis in different ways in each of the clinical conditions described below.

After stent implantation, treatment with acetylsalicylic acid (ASA) and thienopyridines (ticlopidine or clopidogrel) is mandatory, as it significantly reduces the risk of acute and subacute stent thrombosis, as well as adverse cardiovascular events.[14]

A study conducted with 1,653 patients who had undergone stent angioplasty revealed a reduction from 3.6% to 0.5% in the risk of adverse events within 30 days, with the use of thienopyridines combined with aspirin.[82] Besides the use of aspirin, current recommendations are to add clopidogrel for at least one month after the implantation of non drug-eluting stents, three months after the implantation of sirolimus-coated stents, six months for plaxitaxel and, ideally, 12 months for all of them, provided they do not represent a high risk of hemorrhage.[14]

Recently, the occurrence of late (after one year) drug-eluting stent thrombosis raised a discussion about the possibility of long-term treatment with clopidogrel for an unlimited time. On the other hand, early interruption of treatment with platelet antiaggregants during the first month after stent implantation can be

devastating, with an incidence as high as 30% of acute or subacute stent thrombosis.[14]

Patients with CAF must be treated with platelet antiaggregants or anticoagulants to prevent atrial thrombosis and cardioembolic cerebrovascular accidents (CVA) Anticoagulants should be preferred for patients at a higher risk of embolism (patients with ventricular dysfunction, who are elderly, hypertensive, diabetic, have valvar disorders or a prior CVA). Depending on the number of risk factors, the annual risk of CVA in patients who have not undergone treatment with anticoagulants may vary from 3% to 20%.[14] A meta-analysis demonstrated that patients with CAF had a 62% reduction in the risk of CVA with the use of anticoagulants.[83]

Patients with metal valvar prostheses may benefit from the use of anticoagulants to prevent valvar thrombosis. Patients with mitral prostheses are at higher risk than those with aortic prostheses. Patients with implanted Starr-Edwards prostheses, prior CAF or thromboembolism, more than one mechanical valve, and tricuspid involvement are also at a higher risk of thromboembolism. However, even in patients with mechanical valves, the annual risk of thrombosis without warfarin protection is approximately 20%. Therefore, interrupting the use of warfarin for a few days does not represent a significant risk of thrombosis.[14]

METHODOLOGY

This study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on patients presenting with dengue fever from January 2013 to December 2013.

Study design

The study design was one year descriptive study.

Study period and duration

The present study was conducted for the period of one year from January 2013 to December 2013.

Place

This study was done under the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients with dengue fever admitted in the wards of Medicine Department were studied.

Sample size

A total of 120 patients with dengue fever were studied.

Sampling procedure

Based on average 80% of the past three year hospital admission satisfying selection criteria the sample size was calculated as below.

Admission during 2010	166
Admission in 2011	151
Admissions in 2012	132
Total	449
Average admission during three years	149.66
80% of the average	119.2 ≈ 120

Selection criteria

Inclusion

- Age > 18 years.
- Patients admitted in KLE Hospital with either one of the following.
    - Dengue IgM Positive.
    - Dengue IgG & IgM positive.
    - Dengue NS-1 antigen positive.

Exclusion

- Previously Diagnosed cases of any cardiac disease.
- Mixed infections (Malaria, leptospira).
- E.C.G. showing features of old M.I.
- No laboratory confirmation.
- Medication affecting heart rate, e.g., β-blockers, β-agonists, calcium channel blockers, or xanthine derivatives

Ethical clearance

The ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belgaum prior to the commencement.

Informed Consent

Patients presenting with dengue fever and fulfilling the selection criteria were explained about the nature of study and a written informed consent was taken prior to the enrollment (Annexure I).

Method of collection of data

Demographic data such as age and sex were noted. Patients were interviewed for the present illness and presenting complaints were recorded. Further the patients underwent general physical examination and systemic examination. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The selected patients underwent the following investigations.

- Complete blood count
- Platelet count
- Electrocardiography
- 2D Echocardiography
- Cardiac enzymes – CK-MB and Troponin I

Procedure

Cardiac involvement[55]

Electrocardiography

The ECG was done on 12 lead surface ECG machine. Three serial ECGs were taken on;

- Day one
- Day three
- Day Seven or day of discharge (Whichever was earlier)

Echocardiography

All the patients were evaluated using two dimensional echocardiography.

CK MB

The CKMB method used on the dimension clinical chemistry system is an in vitro diagnostic test intended for the quantitative determination of creatinine kinase MB isoenzyme activity in human serum and heparinized (Siemen's Dimension Clinical Chemistry System). Values were interpreted as normal between 0 to 25 IU.[84] In patients with raised CK MB levels at the time of admission, it was repeated at discharge.

Troponin I

AxSYM Troponin – I ADV is an microparticle Enzyme Immunoassay (MEIA) for the quantitative determination of cardiac troponin I (cTnl) in human

serum or plasma on the AxSYM system (Abbott AxSYM System). Values were interpreted as normal between 0.00 to 0.04 IU.[84] In patients with raised troponin I levels at the time of admission, it was repeated at discharge.

Clinical features suggestive of cardiac involvement

Dengue patients positive for one of the following investigations with or without clinical features were considered as cardiac involvement. Features suggestive of rhythm disturbance, heart rate changes like sinus tachycardia or bradycardia, raised CKMB and/or troponin I and abnormal ECG and ECHO were considered for cardiac manifestations.

ECG changes included sinus tachycardia, sinus bradycardia, non specific ST-T wave changes, inverted T waves, First degree heart block, right bundle branch block

Echocardiography changes were interpreted as;

Systolic dysfunction – Refers to impaired ventricular contraction.

Diastolic dysfunction – Refers to an abnormality in the filling during diastole.

Ejection fraction – The fraction of the blood pumped out of a ventricle with each heart beat (Normal value – 67 ± 12%)

Pericardial effusion – An abnormal accumulation of fluid in the pericardial cavity.

Severity of dengue fever

Patients who were seropositive for Dengue were classified on the basis of WHO Criteria[85,86] as follows:

- Dengue Fever (DF)
- Dengue Fever with unusual bleed (DFB) - bleeding tendencies not satisfying WHO criteria for DHF.
- Dengue Hemorrhagic Fever (DHF)

  Four cardinal features of DHF as defined by WHO are as follows:

  1. Fever or history of fever lasting 2–7 days, occasionally biphasic
  2. A hemorrhagic tendency shown by at least one of the following: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or hematemesis or melena
  3. Thrombocytopenia [≤ 100,000 cells/mm^3 (100×10^9/L)]
  4. Evidence of plasma leakage owing to increased vascular permeability shown by: an increase in hematocrit ≥20% above the average for age, sex and population; a decrease in the hematocrit after intervention ≥ 20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypoproteinaemia.
- Dengue Shock Syndrome (DSS) - For a case of DSS, all four criteria for DHF must be met, in addition to evidence of circulatory failure manifested by:
  - Rapid and weak pulse *and* narrow pulse pressure (<20 mmHg or 2.7 kPa) *manifested by* Hypotension for age a*nd* Cold, clammy skin and restlessness or lethargy.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test and Fisher's exact test. The continuous data was expressed as mean ± standard deviation (SD). A probability value ('p' value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

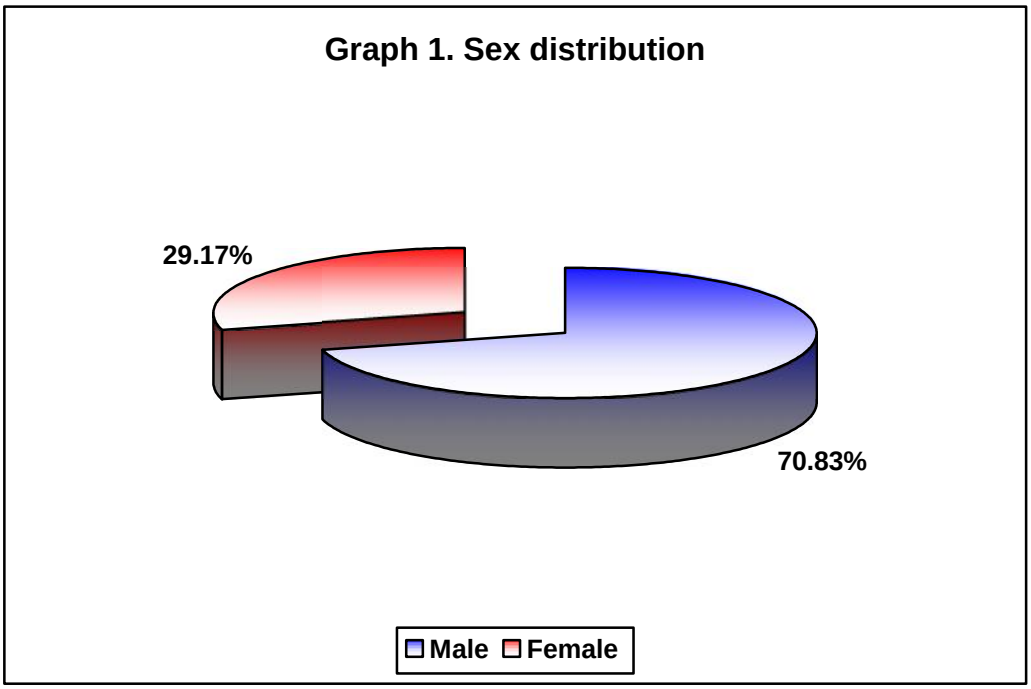
RESULTS

The present one year descriptive study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 120 patients who presented with dengue fever from January 2013 to December 2013 were enrolled.

The data was analysed and the final results and observations were tabulated as below.

Table 1. Sex distribution

Sex	Distribution (n=120)	
	Number	**Percentage**
Male	85	70.83
Female	35	29.17
Total	**120**	**100.00**



In the present study 70.83% of the patients were males and 29.17% were females. The male to female ratio was 2.4:1.

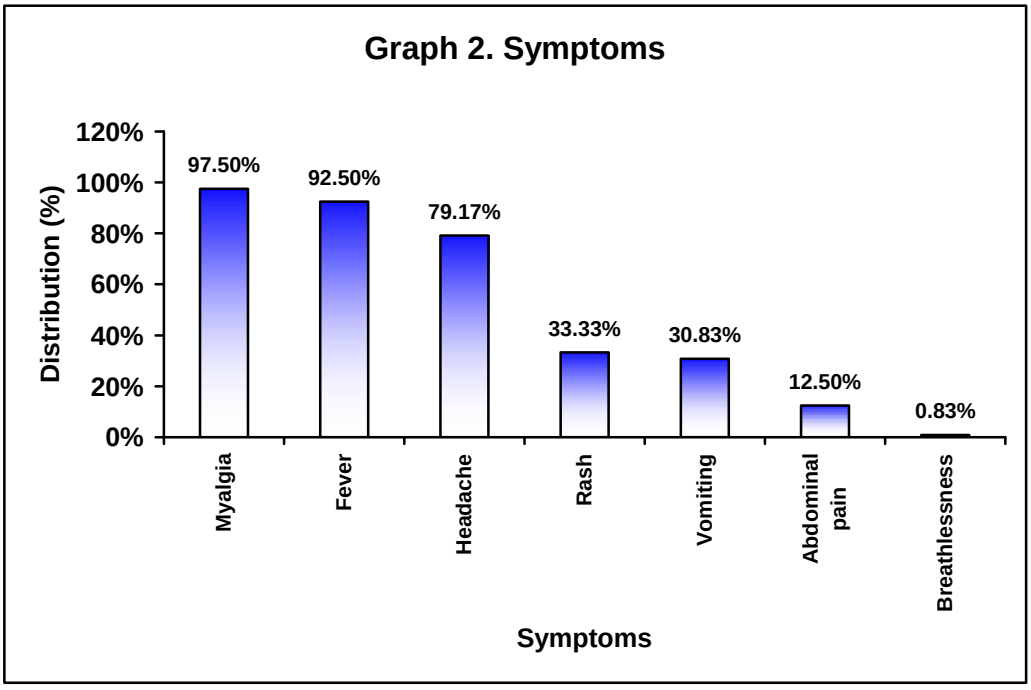
Table 2. Mean and Median Age

Sex	Mean		Median		
	Mean	**SD**	**Median**	**Min**	**Max**
Male	32.43	12.71	27.5	18	74
Female	34.45	12.77	33	18	64
Overall	**33.02**	**12.71**	**29**	**18**	**74**

The mean and median age among males was 32.43 ± 12.71 years and 27.5 (range 18 to 74) years. In females the same was 34.45 ± 12.77 years and 33 (range 18 to 64 years) years respectively.

Table 3. Symptoms

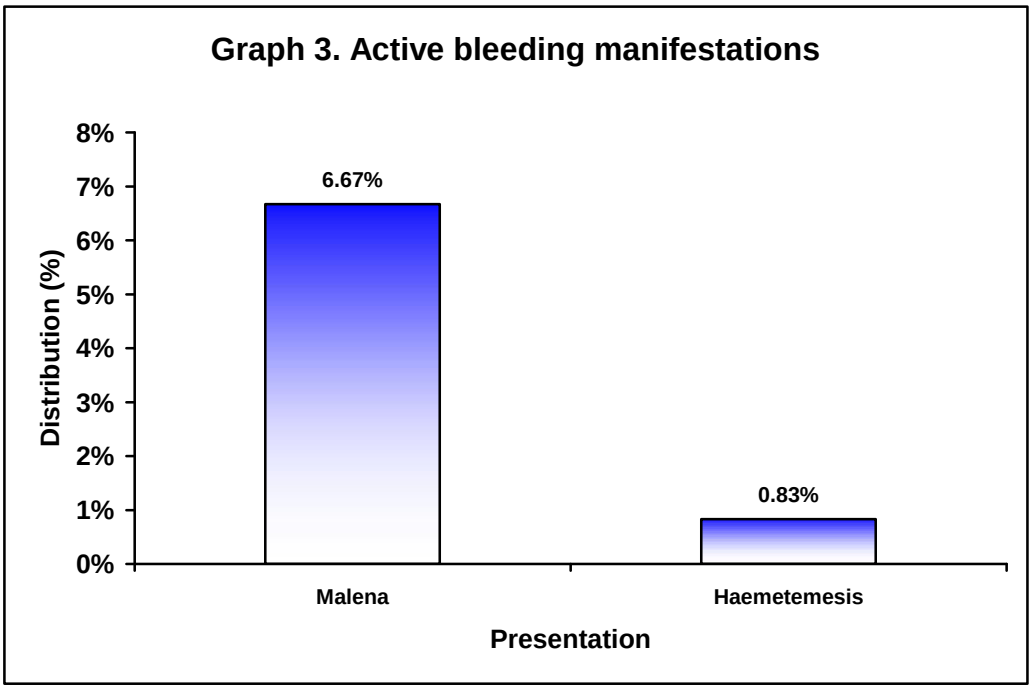
Symptoms	Distribution (n=120)	
	Number	Percentage
Myalgia	117	97.50
Fever	111	92.50
Headache	95	79.17
Rash	40	33.33
Vomiting	37	30.83
Abdominal pain	15	12.50
Breathlessness	1	0.83



In the present study myalgia was the commonest clinical presentation noted in 97.5% of the patients. The next common presentation was fever (92.5%). The other presentations included headache, rash, vomiting, abdominal pain and breathlessness as shown in table 3 and graph 2.

Table 4. Active bleeding manifestations

Presentation	Distribution (n=120)	
	Number	Percentage
Malena	8	6.67
Haemetemesis	1	0.83



In this study active bleeding manifestations of malena was noted in 7.5% of the patients with 6.67% having malena and 0.83% of the patients had haemetemesis at presentation.

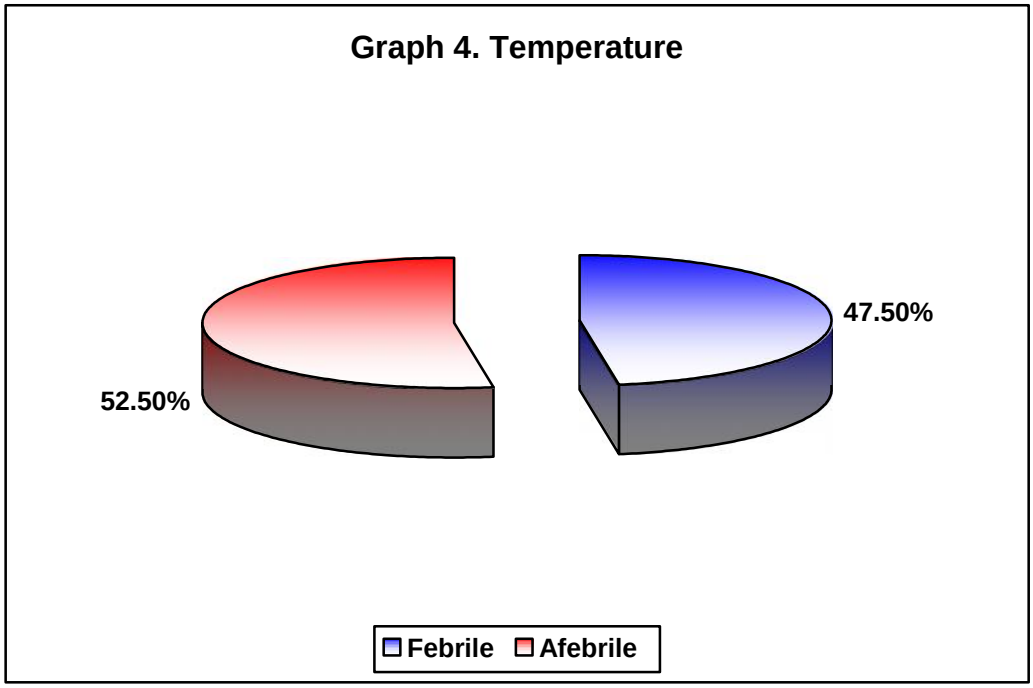
Table 5. Vitals

Vitals	Mean		Median		
	Mean	**SD**	**Median**	**Min**	**Max**
Pulse pressure (/Minute)	38.66	9.76	40	10	64
Systolic BP (mm Hg)	114.51	14.48	118	70	140
Diastolic BP (mm Hg)	75.6	10.79	78	30	90
Heart rate (/Minute)	77.04	15.12	78	40	118

The mean pulse pressure, systolic and diastolic blood pressure, and heart rate are as shown in table 5.

Table 6. Temperature

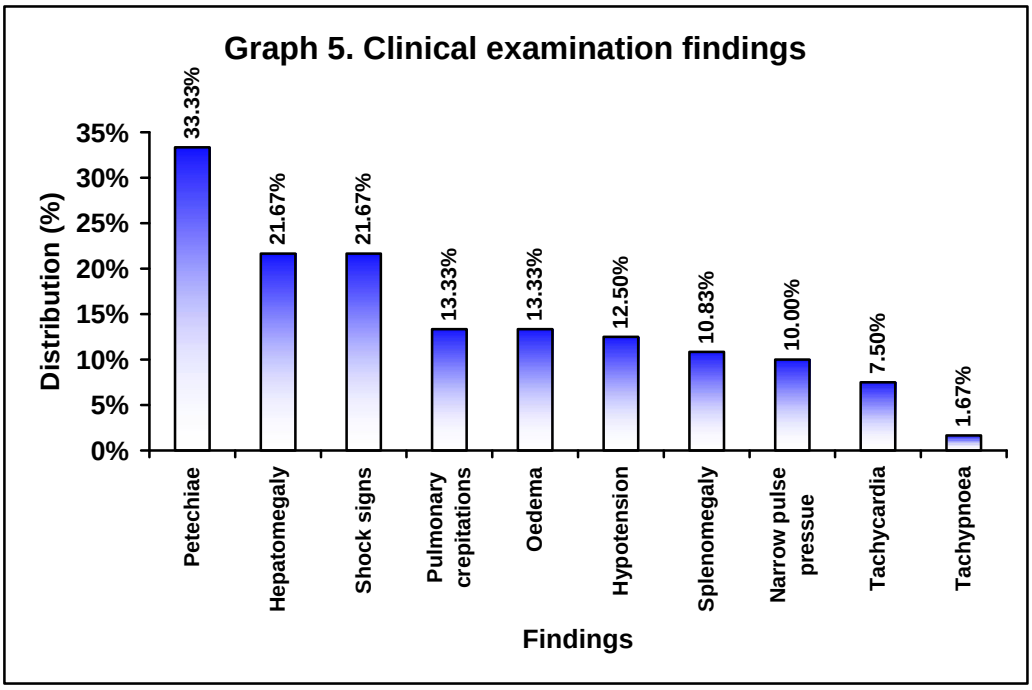
Temperature	Distribution (n=120)	
	Number	**Percentage**
Febrile	57	47.50
Afebrile	63	52.50
Total	**120**	**100.00**



In the present study on clinical examination 52.5% of the patients were found to be afebrile and 47.5% were febrile.

Table 7. Clinical examination findings

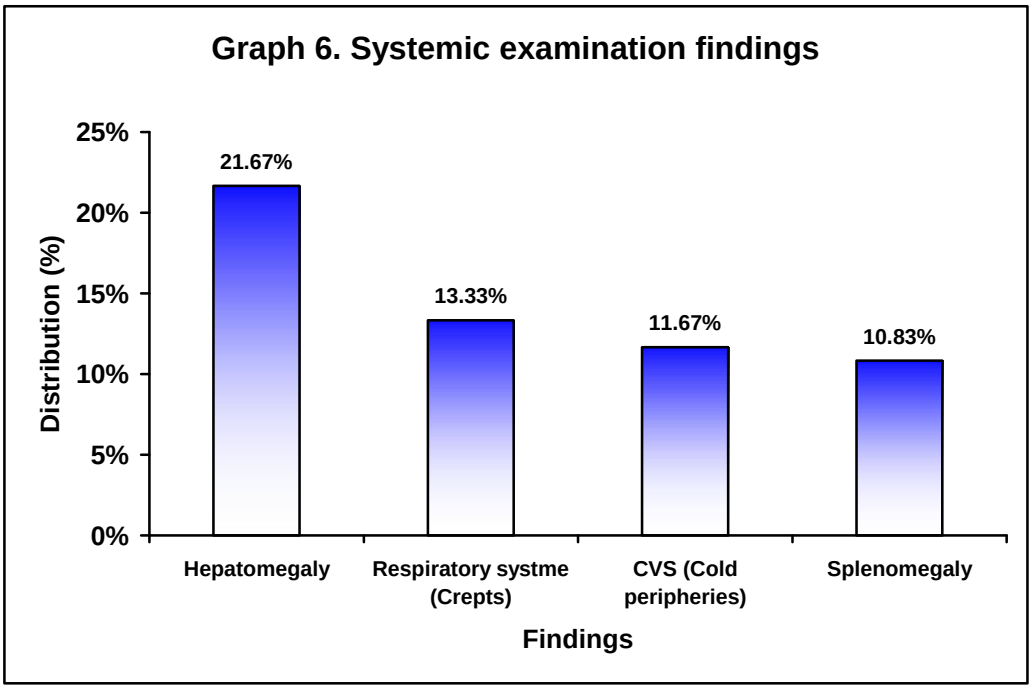
Findings	Distribution (n=120)	
	Number	Percentage
Petechiae	40	33.33
Hepatomegaly	26	21.67
Shock signs	26	21.67
Pulmonary crepitations	16	13.33
Oedema	16	13.33
Hypotension	15	12.50
Splenomegaly	13	10.83
Narrow pulse pressure	12	10.00
Tachycardia	9	7.50
Tachypnoea	2	1.67



Petechiae was the most common sign observed in 33.3% of the patients followed by hepatomegaly and shock signs in 21.67% of the patients each.

Table 8. Systemic examination findings

Findings	Distribution (n=120)	
	Number	Percentage
Hepatomegaly	26	21.67
Respiratory system (Crepts)	16	13.33
CVS (Cold peripheries)	14	11.67
Splenomegaly	13	10.83



In the present study systemic examination findings revealed hepatomgealy in 21.67%, crepts in 13.33%, cold peripherals in (11.67%) and splenomegaly in 10.83% of the patients.

Table 9. Platelet count

	Mean		Median		
	Mean	**SD**	**Median**	**Min**	**Max**
Platelet (x 1000 /cumm)	68.95	74.11	45	1	411

In this study mean platelet count was found to be 68.95 ± 74.11 x 1000 cumm.

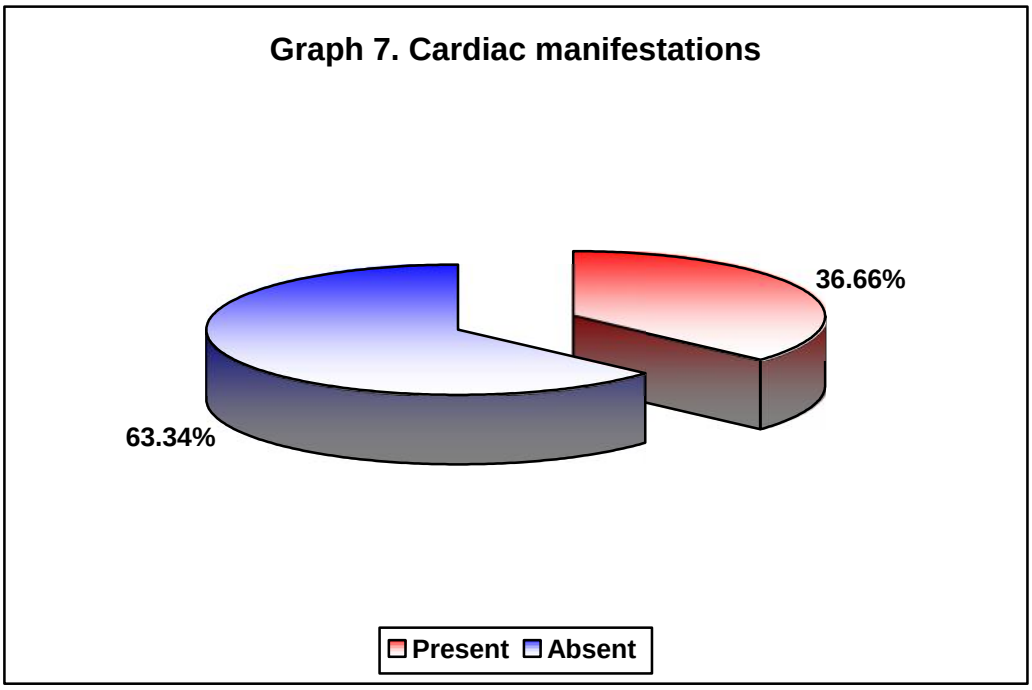
Table 10. Dengue serological test

Tests	**Distribution (n=120)**	
	Number	**Percentage**
IGM	120	100.00
IGG	109	90.83

In the present study IgM and IGG were positive in 100% and 90.83% of the patients respectively.

Table 11. Cardiac manifestations

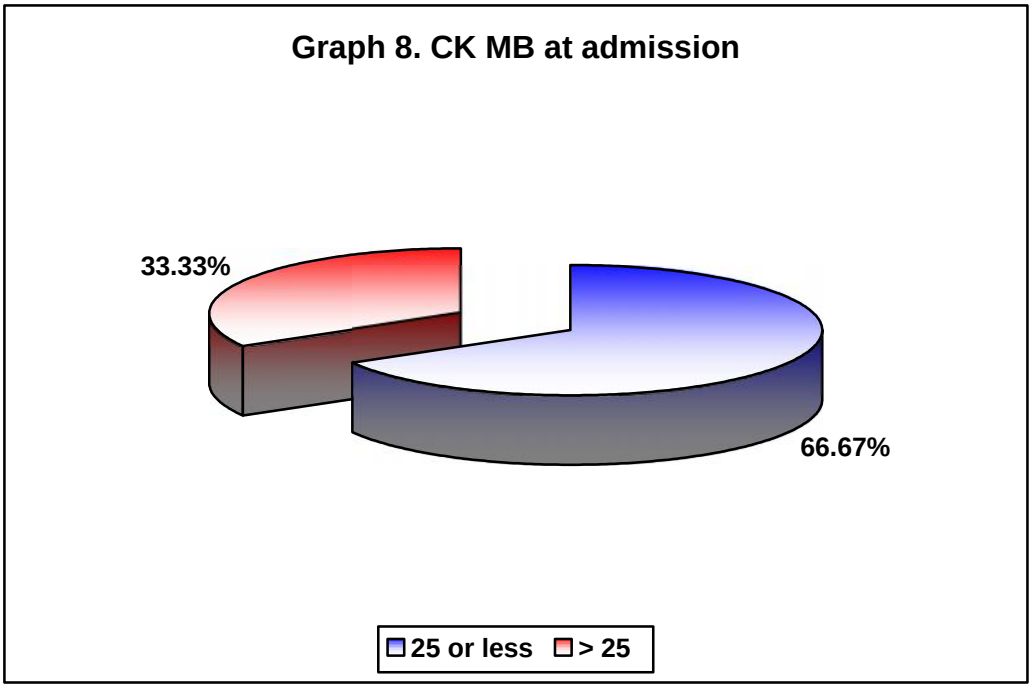
Cardiac manifestations	Distribution (n=120)	
	Number	**Percentage**
Present	44	36.66
Absent	76	63.34
Total	**120**	**100.00**



In the present study based on abnormal cardiac enzymes and ECG 36.66% of the patients were found to have cardiac manifestations.

Table 12. CKMB at admission

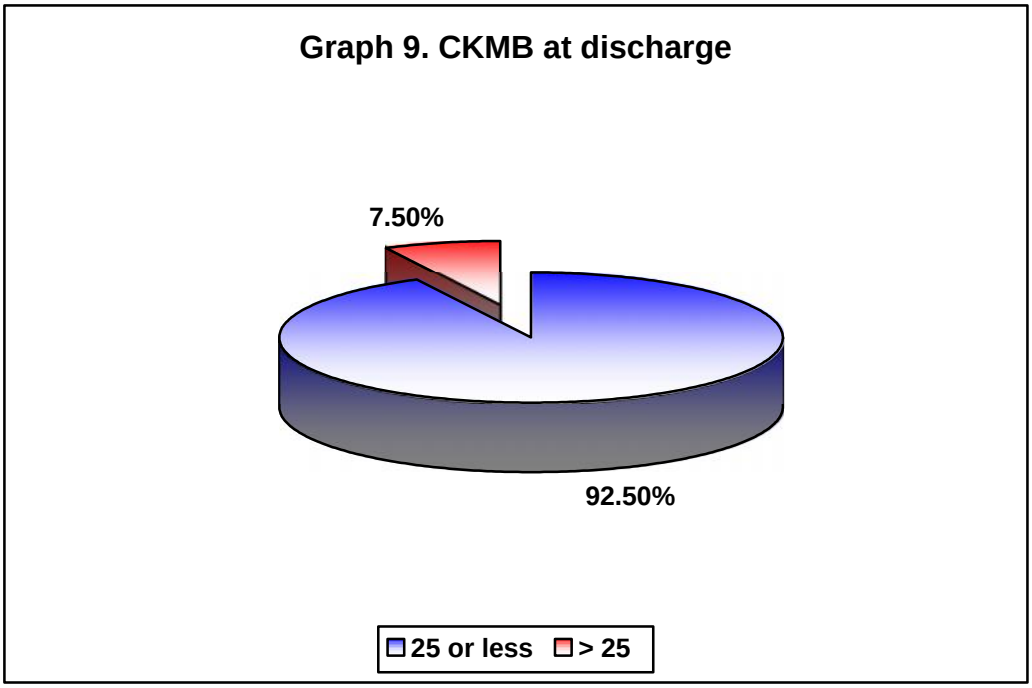
CK MB	Distribution (n=120)	
	Number	**Percentage**
25 or less	80	66.67
> 25	40	33.33
Total	**120**	**100.00**



In this study CK-MB at admission was ≥ 25 in 33.33% of the patients.

Table 13. CK MB at discharge

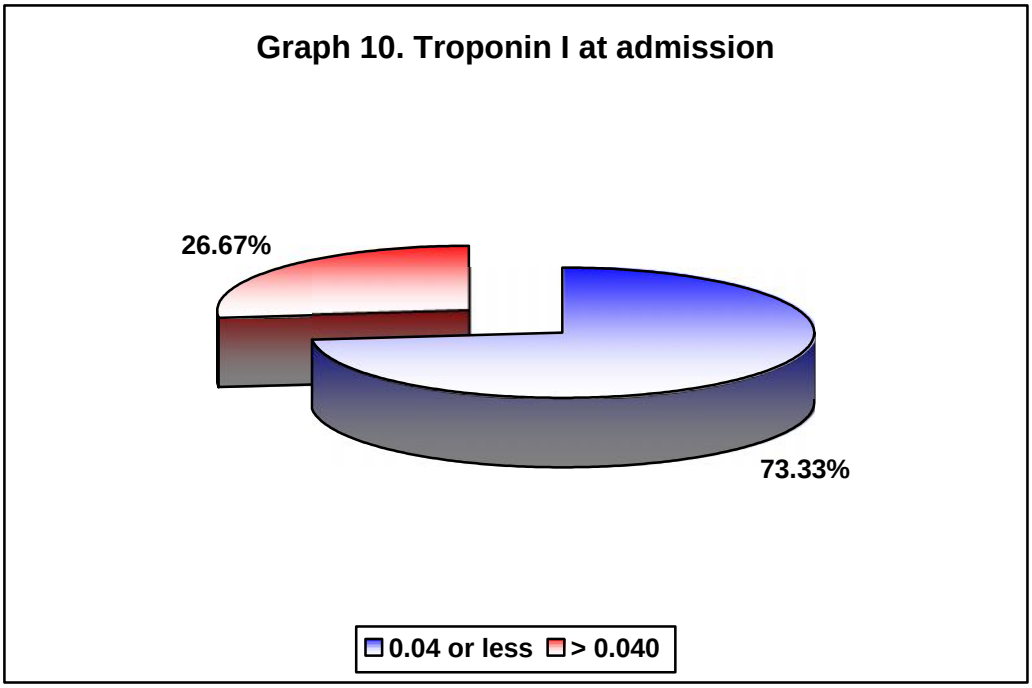
CK MB	Distribution (n=40)	
	Number	**Percentage**
25 or less	37	92.50
> 25	3	7.50
Total	**40**	**100.00**



In this study of the 40 patients with abnormal CK-MB levels at admission, 37 (92.5%) patients were found to have normal CK-MB levels at the time of discharge.

Table 14. Troponin I at admission

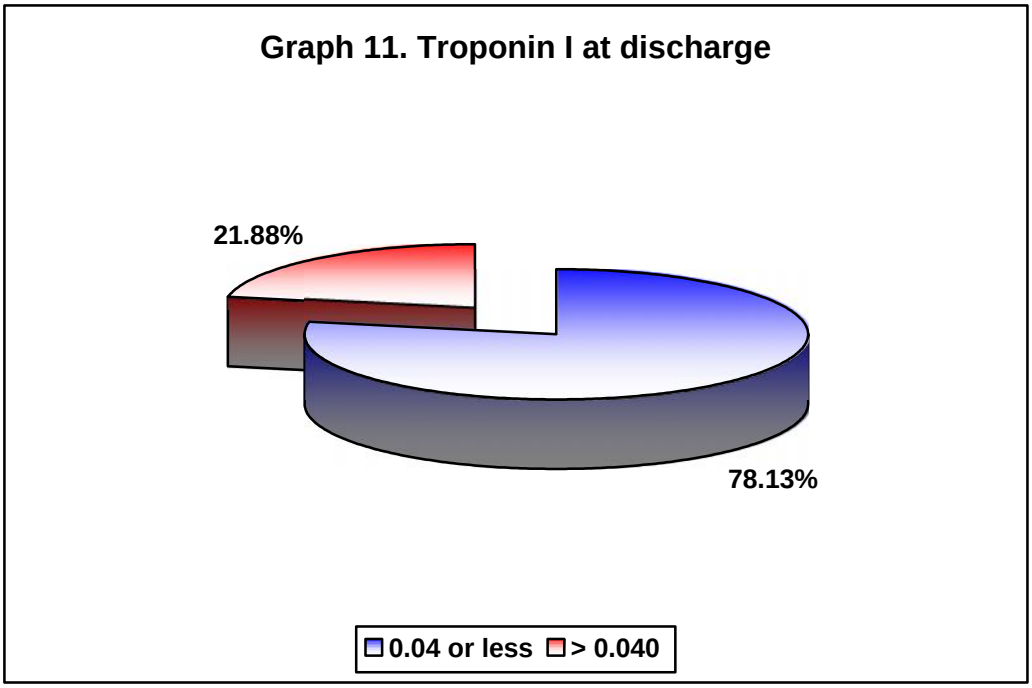
Troponin I	Distribution (n=120)	
	Number	**Percentage**
0.04 or less	88	73.33
> 0.040	32	26.67
Total	**120**	**100.00**



In this study, troponin I at admission was raised (≥ 0.04) in 26.67% of the patients.

Table 15. Troponin I at discharge

Troponin I	Distribution (n=32)	
	Number	**Percentage**
0.04 or less	25	78.13
> 0.040	7	21.88
Total	**120**	**100.00**



In this study, of the 32 patients with raised troponin I at admission, 78.13% of the patients had troponin I levels within the normal limits at discharge.

Table 16. ECG findings in patients with normal and abnormal rhythm at admission

Rhythm	ECG findings	Distribution (n=120)	
		Number	**Percentage**
Sinus rhythm	Normal heart rate	96	84.21
	Sinus bradycardia	10	8.77
	Sinus tachycardia	4	3.51
	NSST-T	4	3.51
	Total	**114**	**100.00**
Abnormal rhythm	1st degree AV block	4	66.67
	RBBB	2	33.33
	Total	**6**	**100.00**

In this study of the 114 patients with sinus rhythm 84.21% had normal heart rate, 8.77% had sinus bradycardia and 3.51% of the patients each had sinus tachycardia and NSST-T changes. Among the six patients with abnormal rhythm 66.67% had first degree AV block and RBBB was noted in 33.33%.

Table 17. Serial ECG findings

ECG	Findings	Distribution (n=120)	
		Number	**Percentage**
At admission	Normal rhythm	114	95.00
	Abnormal Rhythm	6	5.00
	Total	**120**	**100.00**
Second	Normal rhythm	120	100
	Abnormal Rhythm	0	0.00
	Total	**120**	**100.00**
At discharge	Normal rhythm	120	100.00
	Abnormal Rhythm	0	0.00
	Total	**120**	**100.00**

In the present study ECG at admission revealed normal rhythm in 95% of the patients while abnormal rhythm was noted among 5%. The second and third ECG done on day three and day seven (or at the time of discharge whichever was earlier) showed normal rhythm in all the patients (100%) indicating transient rhythm abnormality in patients with dengue fever.

Table 18. Serial heart rate monitoring according to ECG

Interval	Findings	Distribution (n=120)	
		Number	**Percentage**
At admission	< 60	15	12.50
	60 to 100	96	80.00
	> 100	9	7.50
	Total	**120**	**100.00**
Second	< 60	0	0.00
	60 to 100	117	97.50
	> 100	3	2.50
	Total	**120**	**100.00**
At discharge	< 60	0	0.00
	60 to 100	120	100.00
	> 100	0	0.00
	Total	**120**	**100.00**

In the present study 20% of the patients (12.5% had heart rate < 60 per minutes and 7.5% had > 100 per minute) had abnormal heart rate at the time of admission, on day three 2.5% of the patients had abnormal heart rate (HR > 100 per minute), while at discharge all the patients had normal heart rate. This indicates transient heart rate variability in patients with dengue fever.

Table 19. Correlation of CKMB and troponin I

CKMB	Troponin I				Total (n=120)	
	> 0.04		0.04 or less			
	No.	**%**	**No.**	**%**	**No.**	**%**
> 25	28	70.00	12	30.00	40	100.00
25 or less	4	5.00	76	95.00	80	100.00
Total	**32**	**26.67**	**88**	**73.33**	**120**	**100.00**

p<0.001

In this study of 120 patients, 23.3% of the patients had both CK MB and troponin I levels elevated and 10% had only CK MB elevated. 3.3% had only troponin I elevated while 63.3% had both CK MB and troponin I had normal ($p<0.001$).

Table 20. Comparison of CKMB and Troponin I in patients with and without sinus tachycardia

Variables	Findings	Sinus Tachycardia				Total (n=120)		p value
		Present		Absent				
		No.	%	No.	%	No.	%	
CKMB	< 25	0	0.00	80	100.00	80	100.00	0.011
	≥ 25	4	10.00	36	90.00	40	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	
Troponin I	< 0.04	1	1.14	87	98.86	88	100.00	0.058
	≥ 0.04	3	9.38	29	90.63	32	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	

In the present study four patients with sinus tachycardia, all four had abnormally higher levels of CK MB at admission (p=0.011) and three had raised troponin I (p=0.058).

Table 21. Comparison of CKMB and Troponin I in patients with and without sinus bradycardia

Variables	Findings	Sinus bradycardia				Total (n=120)		p value
		Present		Absent				
		No.	%	No.	%	No.	%	
CKMB	< 25	0	0.00	80	100.00	80	100.00	<0.001
	≥ 25	10	25.00	30	75.00	40	100.00	
	Total	**10**	**8.33**	**110**	**91.67**	**120**	**100.00**	
Troponin I	< 0.04	1	1.14	87	98.86	88	100.00	<0.001
	≥ 0.04	9	28.13	23	71.88	32	100.00	
	Total	**10**	**8.33**	**110**	**91.67**	**120**	**100.00**	

In the present study of the 10 patients with sinus bradycardia all had abnormally higher levels of CK MB at admission and nine had higher levels of troponin I ($p<0.001$).

Table 22. Comparison of CKMB and Troponin I in patients with and without NS ST-T

Variables	Findings	NS ST-T changes				Total (n=120)		p value
		Present		Absent				
		No.	%	No.	%	No.	%	
CKMB	< 25	0	0.00	80	100.00	80	100.00	0.011
	≥ 25	4	10.00	36	90.00	40	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	
Troponin I	< 0.04	0	0.00	88	100.00	88	100.00	0.004
	≥ 0.04	4	12.50	28	87.50	32	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	

In the present study of the 4 patients with NS ST-T changes in ECG all had higher levels of CK MB and troponin I ($p<0.050$).

Table 23. Comparison of CKMB and Troponin in patients with and without First degree AV block

Variables	Findings	First degree AV block				Total (n=120)		p value
		Present		Absent				
		No.	%	No.	%	No.	%	
CKMB	< 25	0	0.00	80	100.00	80	100.00	0.011
	≥ 25	4	10.00	36	90.00	40	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	
Troponin I	< 0.04	1	1.14	87	98.86	88	100.00	0.058
	≥ 0.04	3	9.38	29	90.63	32	100.00	
	Total	**4**	**3.33**	**116**	**96.67**	**120**	**100.00**	

In this study of the four patients with first degree AV block all the patients (10%) had CK MB ≥ 25 ($p<0.011$) while troponin I was found to be elevated in three (9.38%) of the patients ($p=0.058$).

Table 24. Comparison of vitals and cardiac enzymes in patients with and without RBBB

Variables	Findings	RBBB				Total (n=120)		p value
		Present		Absent				
		No.	%	No.	%	No.	%	
Heart rate (/Minute)	< 60	0	0.00	15	100.00	15	100.00	0.776
	60 - 100	2	2.08	94	97.92	96	100.00	
	> 100	0	0.00	9	100.00	9	100.00	
	Total	**2**	**1.67**	**118**	**98.33**	**120**	**100.00**	
SBP (mm Hg)	< 90	0	0.00	6	100.00	6	100.00	0.902
	90 - 140	2	1.75	112	98.25	114	100.00	
	Total	**2**	**1.67**	**118**	**98.33**	**120**	**100.00**	
DBP (mm Hg)	< 60	0	0.00	9	100.00	9	100.00	0.855
	60 - 90	2	1.80	109	98.20	111	100.00	
	Total	**2**	**1.67**	**118**	**98.33**	**120**	**100.00**	
CKMB	< 25	0	0.00	80	100.00	80	100.00	0.109
	≥ 25	2	5.00	38	95.00	40	100.00	
	Total	**2**	**1.67**	**118**	**98.33**	**120**	**100.00**	
Troponin I	< 0.04	2	2.27	86	97.73	88	100.00	0.536
	≥ 0.04	0	0.00	32	100.00	32	100.00	
	Total	**2**	**1.67**	**118**	**98.33**	**120**	**100.00**	

In the present study two patients with RBBB had raised CK MB levels while other parameters like troponin I, heart rate, systolic blood pressure and diastolic blood pressure were normal ($p>0.050$).

Table 25. Comparison of vitals and cardiac enzymes in patients with normal and abnormal rhythm

Variables	Findings	Rhythm				Total (n=120)		p value
		Normal		Abnormal				
		No.	%	No.	%	No.	%	
Heart rate (/Minute)	< 60	15	100.00	0	0.00	15	100.00	0.454
	60 - 100	90	93.75	6	6.25	96	100.00	
	> 100	9	100.00	0	0.00	9	100.00	
	Total	**114**	**95.00**	**6**	**5.00**	**120**	**100.00**	
SBP (mm Hg)	< 90	6	100.00	0	0.00	6	100.00	0.730
	90 - 140	108	94.74	6	5.26	114	100.00	
	Total	**114**	**95.00**	**6**	**5.00**	**120**	**100.00**	
DBP (mm Hg)	< 60	9	100.00	0	0.00	9	100.00	0.620
	60 - 90	105	94.59	6	5.41	111	100.00	
	Total	**114**	**95.00**	**6**	**5.00**	**120**	**100.00**	
CKMB	< 25	80	100.00	0	0.00	80	100.00	0.001
	≥ 25	34	85.00	6	15.00	40	100.00	
	Total	**114**	**95.00**	**6**	**5.00**	**120**	**100.00**	
Troponin I	< 0.04	85	96.59	3	3.41	88	100.00	0.340
	≥ 0.04	29	90.63	3	9.38	32	100.00	
	Total	**114**	**95.00**	**6**	**5.00**	**120**	**100.00**	

In this study six patients with abnormal rhythm all had raised CK MB, three had raised troponin I but all having normal heart rate, systolic and diastolic blood pressure.

Table 26. Comparison of CKMB with dengue grades

Dengue severity	CK MB				Total (n=120)	
	> 25		25 or less			
	No.	%	No.	%	No.	%
Dengue fever	5	25.00	15	75.00	20	100.00
Dengue haemorrhagic fever	29	34.12	56	65.88	85	100.00
Dengue shock syndrome	6	40.00	9	60.00	15	100.00
Total	**40**	**33.33**	**80**	**66.67**	**120**	**100.00**

p=0.622

In the present study 15 patients were found to have dengue shock syndrome with 40% of them having raised CK MB levels compared to 34.12% and 25% in dengue haemorrhagic fever and dengue fever. This indicates the percentage of dengue patients having abnormal CK MB correlates with severity of dengue fever. However, the difference was statistically not significant (p=0.622).

Table 27. Comparison of Troponin I with dengue grades

Dengue severity	Troponin I				Total (n=120)	
	> 0.040		< 0.040			
	No.	%	No.	%	No.	%
Dengue fever	5	25.00	15	75.00	20	100.00
Dengue haemorrhagic fever	21	24.71	64	75.29	85	100.00
Dengue shock syndrome	6	40.00	9	60.00	15	100.00
Total	**32**	**26.67**	**88**	**73.33**	**120**	**100.00**

p=0.459

In this study of the 15 patients were found to have dengue shock syndrome of which 40% had raised levels of troponin I compared to 24.71% and 25% in dengue haemorrhagic fever and dengue fever. This indicates the percentage of dengue patients having abnormal troponin I correlates with severity of dengue fever. However, the difference was statistically not significant (p=0.459).

Table 28. Comparison of cardiac abnormalities in dengue grades

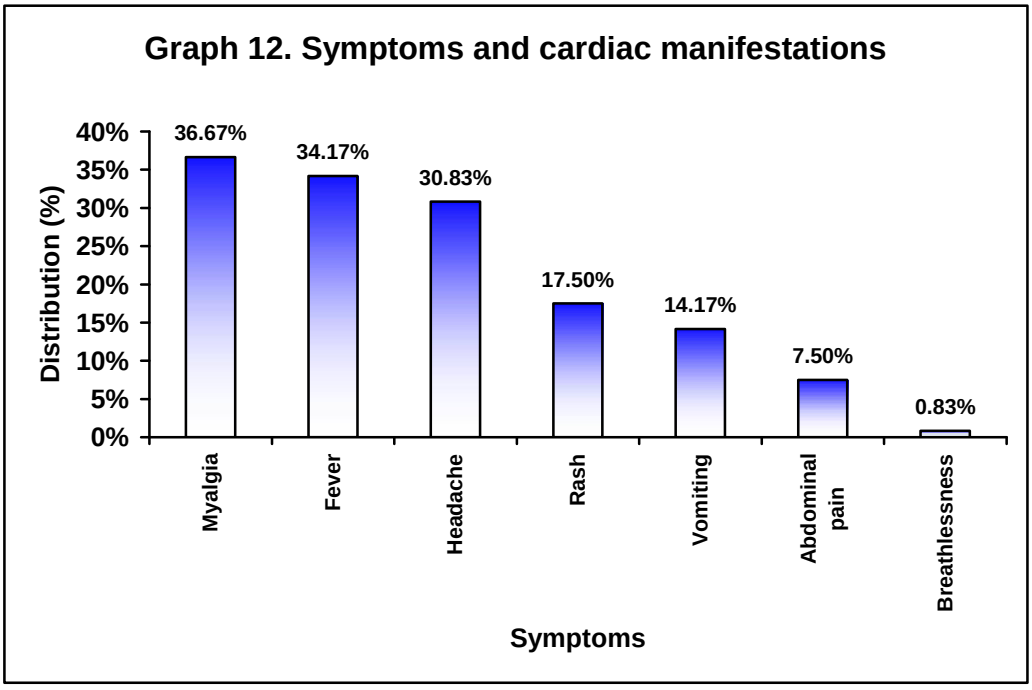
Dengue severity	Cardiac abnormalities				Total (n=120)	
	Present		Absent			
	No.	%	No.	%	No.	%
Dengue fever	6	30.00	14	70.00	20	100.00
Dengue haemorrhagic fever	30	35.29	55	64.71	85	100.00
Dengue shock syndrome	8	53.33	7	46.67	15	100.00
Total	**44**	**36.67**	**76**	**63.33**	**120**	**100.00**

p=0.325

In this study when compared the incidence of cardiac manifestations it was observed that, cardiac manifestation was present in 53.33% of the patients with dengue shock syndrome compared to 35.29% of the patients with dengue haemorrhagic fever and 30% with dengue fever. However, this difference was statistically not significant (p=0.325).

Table 29. Symptoms and cardiac manifestations

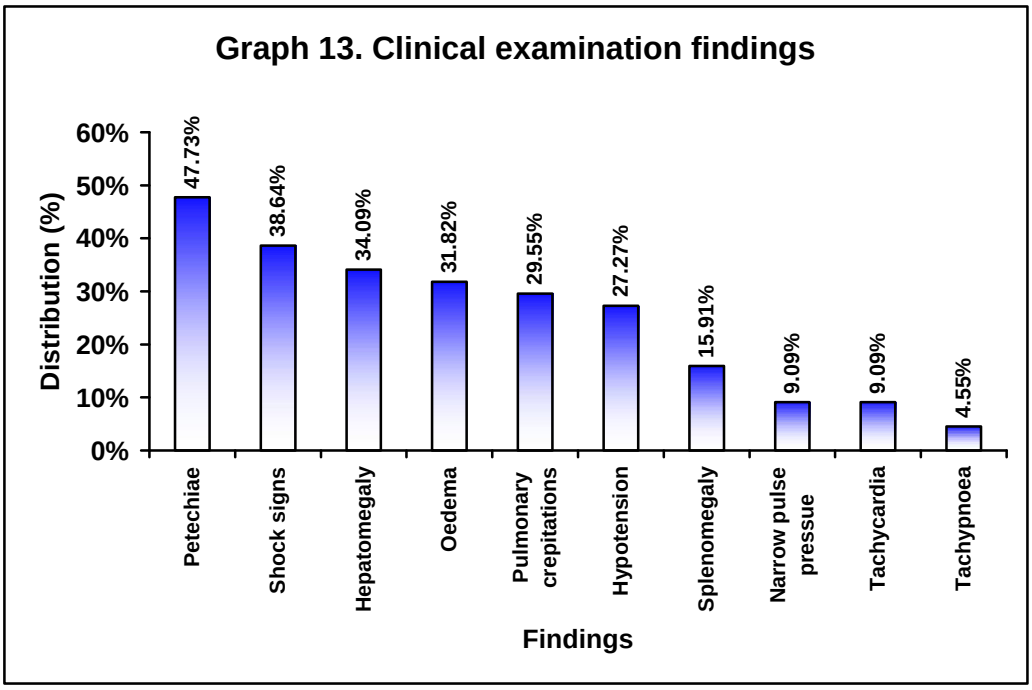
Symptoms	Distribution (n=44)	
	Number	Percentage
Myalgia	44	36.67
Fever	41	34.17
Headache	37	30.83
Rash	21	17.50
Vomiting	17	14.17
Abdominal pain	9	7.50
Breathlessness	1	0.83



In the present study patients with cardiac manifestations commonly presented with myalgia (36.67%), fever (34.17%), headache (30.83%), rash (17.5%), vomiting (14.17%), abdominal pain (7.5%) and breathlessness (0.83%).

Table 30. Clinical examination findings in patients with cardiac manifestations

Findings	Distribution (n=44)	
	Number	Percentage
Petechiae	21	47.73
Shock signs	17	38.64
Hepatomegaly	15	34.09
Oedema	14	31.82
Pulmonary crepitations	13	29.55
Hypotension	12	27.27
Splenomegaly	7	15.91
Narrow pulse pressure	4	9.09
Tachycardia	4	9.09
Tachypnoea	2	4.55



In this study petechiae was the commonest clinical sign (47.73%) noted in patients with cardiac manifestations. The signs are as shown in table 28 and graph 10.

DISCUSSION

Dengue is one of the most important emerging viral diseases globally. The majority of symptomatic infections result in a relatively benign disease course. However, a small proportion of patients develop severe clinical manifestations, including bleeding, organ impairment, and endothelial dysfunction with increased capillary permeability causing hypovolemic shock that can lead to cardiovascular collapse. Evidence is increasing that dengue can also cause myocardial impairment, arrhythmias and occasionally fulminant myocarditis. No antiviral agents or vaccines are licensed for dengue, and treatment remains supportive with judicious fluid replacement for patients with severe disease. Defining the role of cardiac dysfunction in the haemodynamic compromise of severe dengue has potentially important management implications.[87]

Myocarditis is the most common documented cardiac pathology in dengue, however, only a few cases are reported in the world literature. To-date little is known about cardiac manifestation in dengue fever. The present study was an attempt to assess the cardiac manifestations of dengue fever.

This one year descriptive study was carried out on a total of 120 patients who presented with dengue fever in the Department of Medicine at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. The dengue fever was confirmed by either IgM or IGG which were positive in 100% and 90.83% of the patients respectively.

In the present study majority of the patients were males (70.83%) with male to female ratio of 2.4:1 suggesting male preponderance. The sex distribution observed in the present study was comparable with a study conducted by Agarwal et al[21] in which male to female ratio was 1.9:1. Another study conducted by Sharma et al[18] showed that male to female ratio was 3:1. However, fewer cases of dengue hemorrhagic fever and dengue shock syndrome have been reported in men than in women.

In this study mean age of the study population was 33.02 ± 12.71 years and the median age was 27.5 years. The youngest patient was 18 year old and the oldest patient was aged 74 years. These findings were comparable with a recent study from Brazil which reported mean age of the patients as 32±21 years.[88]

In this study majority of the patients presented with myalgia (97.5%) followed by fever (92.5%). Other presentations like headache, rash, vomiting, abdominal pain and breathlessness were noted among 79.17%, 33.33%, 30.83%, 12.5% and 0.83%. In this study few patients present with bleeding manifestations viz. malena was present in 6.67% and haemetemesis in 0.83% of the patients. The clinical examination revealed, fever in 47.5%, petechiae in 33.3%, hepatomegaly and shock signs in 21.67% of the patients each. On systemic examination, hepatomgealy was present in 21.67%, crepts in 13.33%, cold peripherals in 11.67% and splenomegaly in 10.83% of the patients. Several studies[22,41-51] have reported different clinical features and complications of dengue fever.

A study from Singapore by Low JGH et al reported headache in 80%, myalgia in 69.2%, retro-orbital pain in 26% and pain abdomen in 11.6% of patients as early clinical symptoms in dengue infection.[89]

Recently, Kumar A et al.[50] in his record-based study conducted in a coastal district of Karnataka to assess the clinical manifestations, trend and outcome of all confirmed dengue cases admitted in a tertiary care hospital assessed the laboratory confirmed cases from 2002 to 2008 from Medical Records Department (MRD). Of the 466 patients, the most common presentation was fever 462 (99.1%), followed by myalgia 301 (64.6%), vomiting 222 (47.6%), headache 222 (47.6%) and abdominal pain 175 (37.6%). The most common hemorrhagic manifestation was petechiae (67.2%). Of the 66 (14.1%) patients who developed clinical complications, 22 (33.3%) had ARDS and 20 (30.3%) had pleural effusion.

Another study[90] from Mumbai, to study the clinical profile of dengue fever reported fever as the major presenting complaint in all these cases (100%). The other common presenting symptoms were icterus in 25.8%, myalgia in 25.0%, and headache in 13.9%.

In this study raised CK-MB and troponin I at admission were noted in 33.33% and 26.67% of the patients. At admission ECG findings revealed normal rhythm in 95% of the patients while abnormal rhythm was noted among 5%. Among the patients with normal rhythm, 84.21% had normal heart rate, 8.77% had sinus bradycardia and 3.51% of the patients each had sinus tachycardia and NSST-T changes. In those with abnormal rhythm, 66.67% had first degree AV block and RBBB was noted in 33.33%. None of the patient was detected with abnormal

echocardiograph. Based on these findings 36.66% of the patients were found to have cardiac manifestations. The incidence of cardiac manifestations was present in 53.33% of the patients with dengue shock syndrome compared to 35.29% of the patients with dengue haemorrhagic fever and 30% with dengue fever but the difference was statistically not significant (p=0.325).

Dengue rarely affects the heart. In 1996, during an epidemic outbreak of dengue in India, 206 patients were evaluated and only one had cardiac symptoms.[53] Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis.[54]

Recently, a study[58] from New Delhi to assess cardiac involvement in dengue haemorrhagic fever estimated cardiac enzymes, and found significant level of CPK-MB was raised in 22 patients (78.55%), serum troponin T (Rapid card test) was weakly positive in 12 patients (42.8%). In electrocardiography, sinus bradycardia (HR < 60) was present in 4 patients (14.28%), and sinus tachycardia in 6 patients (21.4%). No QRS and ST changes were seen in any patient. 2D-Echo showed mean left ventricular ejection fraction 59% (range 52 - 66%); systolic dysfunction was absent in all patients; mild diastolic dysfunction was present in 4 patients (14.28%). Global hypokinesia was absent in all patients. Echocardiography was repeated after 4 weeks and was found to be normal in all patients.

A study[91] conducted in southern Taiwan in 2006, showed that cardiac complications are not uncommon in dengue illness. Acute myocarditis in dengue may be clinically severe to such an extent that it has a fatal outcome.

In a study[79] conducted during the outbreak of dengue fever in 2005 in Sri Lanka, 75 patients and ECG changes. (T wave inversion, ST depression and bundle branch blocks). These patients were more susceptible to dyspnoea, fatigue and flushing of skin than 45 patients who had normal ECG.

In a study[56] conducted in Thailand, 24 patients with serologically confirmed dengue fever were subjected to ECHO. Ejection fraction was significantly lower in these patients.

Cardiac dysfunction associated with the acute phase of dengue fever has been described by several authors and is underdiagnosed in clinical practice. Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in dengue haemorrhagic fever and dengue shock syndrome.[14]

A recent study[88] from Brazil reported that, 15% of the dengue patients showed increased levels of at least one cardiac biomarkers, and four patients, of both. Troponin I level was increased in 7% patients. Cardiac involvement was observed in 15% of patients requiring hospitalization, with clinical manifestation ranging from mild elevation of cardiac biomarkers to myocarditis and/or pericarditis and death.

In Sri Lanka, Wichmann et al.[77] showed that 25% of dengue patients presented with one or more elevated markers of myocardial injury, such as myoglobin, CK-MB, troponin T, NT-proBNP, and/or heart-type fatty acid binding protein levels (h-FABP). However, the majority of patients had elevation of myoglobin or CK-MB that are nonspecific biomarkers of myocardial injury. Furthermore, only one patient (0.8%) had elevation of troponin and 25 patients

(18.9%) had elevation of NT-proBNP; however distinct NT-proBNP cut-off levels were used (14) and observed troponin I elevation in six (7%) patients and important elevation of NT-proBNP in 10 (10%) patients.

Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the hemorrhagic form of the disease or in the associated shock.[88] The "dengue-related shock syndrome" is due to the increased vascular permeability and hypovolemic pattern.[92] However, an adequate approach to the hemodynamic instability associated with dengue requires not only a significant volemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction, as in the current treatment of sepsis. Similarly in this study the second and third ECG done on day three and day seven showed normal rhythm in all the patients (100%) indicating transient rhythm abnormality in patients with dengue fever. Further, majority of the patients were found to have normal CK MB and troponin I (>95%) levels at discharge.[88]

Although shock in dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) has been attributed largely to decreased intravascular volume due to capillary leakage of plasma into the interstitial space, a few recent studies have reported that it may be due to cardiac involvement.[58] Acute reversible myocarditis has been reported in patients with dengue infections. ST segment and T wave changes in the electrocardiogram together with low ejection fraction and global hypokinesia on radionuclide ventriculography have been found.[58]

It is widely agreed that dengue haemorrhagic fever is an immunologically mediated disease, a mechanism similar to those involved in causing viral

myocarditis, may play a role in the development of dengue virus related myocarditis.[58] Myocardial dysfunction can be seen in patients with DHF. Approximately 20% of those who developed DHF have a LV ejection fraction of less than 50% and are likely to return to normal within a few weeks.[46] Electrocardiographic abnormalities have been reported in 44 - 75% of patients with viral haemorrhagic fever, and prolongation of the PR interval or sinus bradycardia commonly occurs.[58] Some have reported atrioventricular block in variable degrees.[54]

CONCLUSION

The incidence of cardiac manifestations was present in 36.66% of the patients It was high (53.33%) in patients with dengue shock syndrome compared to the patients with dengue haemorrhagic fever (35.29%) and dengue fever (30%).

A wide range of cardiac manifestations were observed in this study. CK-MB and troponin I at admission were raised in 23.3% of the patients while only CK MB and only troponin I was raised in 10% and 3.3% of the patients respectively. On ECG, at admission, 95% of the patients had normal rhythm with 84.21% with normal heart rate, 8.77% with sinus bradycardia 3.51% of the patients each with sinus tachycardia and NSST-T changes. In patient with abnormal rhythm the abnormalities noted were first degree AV block (66.67%) and RBBB (33.33%). The subsequent ECG on day seven (or day of discharge whichever was earlier) showed normal rhythm and normal heart rate for all the patients. None of the patient was detected with abnormal echocardiograph.

In patients with sinus tachycardia and first degree AV block all the patients (100%) had raised CK MB levels and 75% of the patients had raised troponin I levels. In those with sinus bradycardia, NSST-T changes, RBBB all the patients were found to have raised CK MB level (100%). However, Troponin I was raised in all the patients with NSST-T changes, 90% in patients with bradycardia and none of the patient with RBBB.

The study shows transient changes in heart rate, rhythm and raised CK MB and troponin I levels in patients with dengue fever. All the patients were followed

till the day of discharge and rate and rhythm reverted back to normal in all the patients suggesting transient reversible cardiac abnormality.

Transient cardiac abnormality can be an important presentation and this should guide the treating physician to look for cardiac involvement.

SUMMARY

Though dengue rarely affects heart, cardiac dysfunction with dengue fever has been described by several authors. The present study was aimed to assess the cardiac manifestations of dengue fever.

This one year descriptive study was undertaken at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum under the Department of Medicine. A total of 120 patients with either dengue IgM or IgM and IgG and NS1 positive patients admitted between January 2013 to December 2013 were studied. The assessment of cardiac manifestations was done based on electrocardiogram, 2D echocardiography and cardiac enzymes.

Of the 120 patients, 85 (70.83%) were males and the male to female ratio was 2.4:1. The mean age of the patients was 33.02 ± 12.71 years. The commonest clinical presentation was myalgia (97.5%) followed by fever (92.5%). On clinical examination 33.33% of the patients had petechiae and systemic examination revealed hepatomegaly in 21.67%. Investigations revealed mean platelet count of 68950 ± 74110 /cumm. Based on WHO criteria Dengue fever was present in 16.66%, dengue haemorrhagic fever in 70.83% and dengue shock syndrome in 12.5%. Cardiac enzymes that is, CKMB and troponin I were found to be high in 33.33% and 26.67% of the patients. ECG findings revealed normal rhythm among 95% and abnormal rhythm in 5%. In patients with abnormal rhythm, first degree AV block was present in 66.67%, and RBBB in 33.3%. The commonest clinical presentation in patients with cardiac manifestations was myalgia (36.67%) and petechiae was the

commonest sign (17.5%). Most of the patients with dengue shock syndrome had cardiac manifestations (53.33%) but the difference was statistically not significant (p=0.325).

Patients with dengue fever are at high risk of developing cardiac manifestations and should be monitored carefully for the same.Transient cardiac abnormality can be an important presentation and this should guide the treating physician to look for cardiac involvement.

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ANNEXURE I – CONSENT FORM

"TO STUDY THE INCIDENCE OF CARDIAC MANIFESTSTIONS OF DEGUE FEVER - A ONE YEAR HOSPITAL BASED DESCRIPTIVE STUDY**"**

Objective and purpose of the study:

This research is intended to study the cardiac complications in patients of dengue fever. The principal investigator of the study is Dr. **** ****** under the guidance of Dr. **** ******.

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part now, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

Queries & Contact

In case of the queries during study or in future you may contact following person

Principal investigator : Dr. ***** ****** - ***** *****

Guide : Dr. ***** ******

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____

Signature / Thumb print _____

Name of the Witness _____

Signature _____

Name of the investigator _____

Signature _____

Date: Place:

ANNEXURE II – PROFORMA

Case No :

Name : Sex :

Age : In patient No. : Address

:

Date of admission: Date of discharge:

Occupation:

Chief complaints

Fever :

Rash :

Headache :

Retroorbital pain :

Vomiting :

Abdominal pain :

Breathlessness :

Myalgia :

Haemetemesis :

Malena :

Epistaxis :

Past history

- History of any cardiac disease-
- History of use of drugs affecting the heart rate (e.g.- β-blockers, β-agonists, calcium channel blockers, or xanthine derivatives)

On examination:

Pulse rate (/Min) :

Temperature :

Heart rate (/Min) :

Blood pressure

Systolic : mm Hg

Diastolic : mm Hg

SPO2 :

Oedema :

Petechiae :

Bleeding :

Narrow pulses :

Hepatomegaly :

Shock signs :

Pulmonary oedema :

Pulmonary crepitations:

Systolic murmur :

Tachypnoea :

Tachycardia :

Systemic examination

Cerebrovascular system:

Peripheral :

Central :

Respiratory system :

Per abdomen :

Central nervous system:

Investigations

Platelet count :

Dengue serology

NS1 :

IGM :

IGG :

Cardiac enzymes

CKMB

At admission :

At Discharge :

Troponin I

At admission :

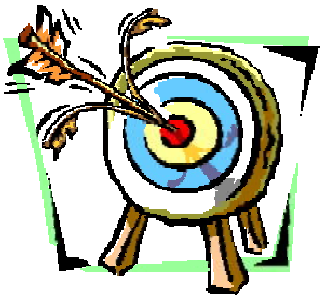
At Discharge :

	Day 1	**Day 3**	**Day Of Discharge**
E.C.G.			
E.C.H.O.			

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
AF	-	Atrial fibrillation
AF	-	Afebrile
BL	-	Bilateral
CK MB	-	Serum creatinine kinase MB
CPF	-	Cold peripheries
DF	-	Dengue fever
DHF	-	Dengue haemorrhagic fever
DSS	-	Dengue shock syndrome
F	-	Female
FB	-	Febrile
LT	-	Left
M	-	Male
mm Hg	-	Millimeters of mercury
N	-	Normal
ng/L	-	Nano grams per litre
RT	-	Right
U/L	-	Units per liter

Introduction



Objectives

Review of Literature

Methodology

Results

Discussion

Conclusion

Summary

Bibliography

Annexure-I

Annexure-II

Annexure-III