



A Study on Cardiac Manifestations of Dengue Fever

Authors

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Abstract

Aims and Objectives: *To study the cardiac manifestations of the dengue fever.*

Method: *This two year descriptive study was undertaken at Darbhanga Medical College and Hospital, department of medicine, Darbhanga, Bihar. 50 patients admitted with dengue NSI Ag, dengue IgM or IgM and IgG positivity were studied. Grading of severity and management were done following WHO guidelines. Electrocardiogram, 2D echocardiography and cardiac enzymes assay were done to find out cardiac manifestation. Other major organ involvements were also assessed.*

Results: *Of the 50 patients, 32(64%) were males and 18(36%) were female. The mean age of the patients was 30 ± 8.5 years. The commonest clinical presentation was fever (94%). On clinical examination 54% of the patients had petecheia. Rhythm disturbance was noted in 8% of the patients. with AV block being the most common (66.67%). Cardiac manifestation in the form of changes in ECG and echocardiography were observed in 52% of the patients with a positive correlation with the severity of the dengue fever as defined by W.H.O. criteria. Cardiac manifestation was also found to be significantly related to other organ involvement.*

Conclusion: *Patients with dengue fever are at high risk of developing cardiac involvement and therefore require a close cardiac monitoring.*

Introduction

Dengue fever (DF) and its severe forms dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) have become major international public health concerns. Over the past three decades, there has been a dramatic global increase in the frequency of dengue fever (DF), DHF and DSS and their epidemics, with a concomitant increase in disease incidence. Dengue is found in tropical and subtropical regions around the world, predominantly in urban and semi-urban areas. The name dengue is derived from the Swahili word 'ki

denga pepo' which means 'sudden seizure by the demon'. The term 'break bone fever' was coined following the Philadelphia epidemic in 1780. The earliest description of dengue fever was made in the same year by Benjamin Rush. The other names for dengue fever are dandy fever, denga, dunga fever and coupd-barre. Humans and mosquitoes are the principal hosts of dengue virus; the mosquito remains infected for life but the viruses are only known to cause illness in humans. There is no specific treatment for dengue, but appropriate medical care frequently saves the lives

of patients. The first confirmed epidemic of DHF was recorded in the Philippines in 1953–1954 and in Thailand in 1958. Since then, Member countries of the WHO South-East Asia (SEA) and Western Pacific (WP) regions have reported major dengue outbreaks at regular frequencies. In India, first confirmed DHF outbreak occurred in 1963. Due to the high disease burden, dengue has become a priority area for several global organizations other than WHO, including the United Nations Children's Fund (UNICEF), United Nations Environment Programme (UNEP), the World Bank, and the WHO Special Programme for Research and Training in Tropical Diseases (TDR), among others.

The dengue viruses form a distinct complex within the genus *Flavivirus* based on antigenic and biological characteristics. There are four virus serotypes, which are designated as DENV-1, DENV-2, DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that virus serotype. Although all four serotypes are antigenically similar, they are different enough to elicit cross-protection for only a few months after infection by any one of them. Secondary infection with another serotype or multiple infections with different serotypes leads to severe form of dengue (DHF/DSS). Unusual manifestations of patients with severe organ involvement such as liver, kidneys, brain or heart associated with dengue infection have been increasingly reported in DHF even in dengue patients who do not have evidence of plasma leakage.

Cardiac manifestations in dengue virus infection can range from asymptomatic bradycardia to life threatening myocarditis. Various studies have quoted several cardiac manifestations of dengue infection like sinus bradycardia, transient AV blocks, ventricular arrhythmias, myocarditis and pericardial effusion. We performed this study with the objective of studying the cardiac manifestations of dengue and to study the correlation of the cardiac manifestations to the severity of dengue.

Objectives of the Study

1. To study the prevalence of cardiac manifestation of dengue patients in our hospital.
2. To find out the correlation of cardiac manifestations to severe forms of dengue; DHF and DSS.

Materials and Methods

The present study, a two year observational study was conducted in the Department of Medicine, DMCH, Bihar on 50 patients presenting with dengue fever from July 2014 to July 2016.

Inclusion Criteria

Age group of ≥ 13 years fulfilling the WHO criteria for dengue who Confirmed dengue serology (NS1Ag/Ig M antibody for dengue/IgM and Ig G antibody for dengue)

Exclusion criteria

- Patients on medications affecting the heart rate / rhythm (calcium channel blocker, B blocker, xanthine derivative, B agonist)
- Patients with history of preexisting heart disease
- Patients with electrolyte abnormalities which may affect the heart rate/rhythm
- Patients not willing to give consent for the study.
- Patients with mixed infection.

Ethical clearance was obtained prior to the study and written informed consent was obtained from the participating patients. The patients underwent general physical examination, systemic examination and a group of tests that included: Complete blood count, Platelet count, liver function test, renal function test, electrocardiography, 2D Echocardiography, cardiac enzymes – Troponin T and Troponin I test by commercial ELISA kit available. Serial ECGs were taken on everyday during hospital stay. All the patients were evaluated using two-dimensional echocardiography on day one and day three, and day seven or day of discharge (whichever is earlier). 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, and abnormal ECG and ECHO. 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 – $67 \pm 12\%$) Pericardial effusion– An abnormal accumulation of fluid in the pericardial cavity. Additional investigations were done as appropriate if signs suggestive of any other system involvement found in clinical examination.

Severity of Dengue Fever in patients who were seropositive for Dengue were classified as follows:

- Dengue Fever (DF) (without or with unusual bleed)
- 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, gastrointestinal tract, injection sites or other locations; or hematemesis or melena
 3. Thrombocytopenia [$\leq 100,000$ cells/mm³ (100×10^9 /L)]
 4. Evidence of plasma leakage owing to increased vascular permeability shown by: an increase in hematocrit $\geq 20\%$ above the average for age, sex and population; a decrease in the hematocrit after intervention $\geq 20\%$ 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 as

-Rapid and weak pulse and narrow pulse pressure (< 20 mmHg or 2.7 kPa) manifested by Hypotension for age and Cold, clammy skin and restlessness or lethargy.

All patients were managed according to WHO guideline and with intravenous fluid and transfusion as required.

Statistical Analysis: The categorical data was expressed as rates, ratios and proportions and comparison was done using chisquare test and Fisher's exact test. The continuous data was expressed as mean \pm 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 mean age of our study group was 30 ± 8.5 years. The youngest patient was 13 years old and the oldest patient was 67 years old. There were 32(64%) males and 18(36%) females in our study. 44(88%) patients presented to us within the first week of fever. Forty-seven(94%) were febrile at admission Of the 50 patients studied, 32 patients were dengue NS1 positive (ELISA), 12 were positive for IgM and IgG dengue (ELISA) both, and 6 patients with IgM dengue (ELISA) only. 50 (100%) patients were with platelet count $< 100,000$ /cumm with 28(56%) patients having platelet count $< 20,000$ /cumm. Fever was the most common clinical presentation (94%) followed by myalgia (76%) and others. (figure 1)

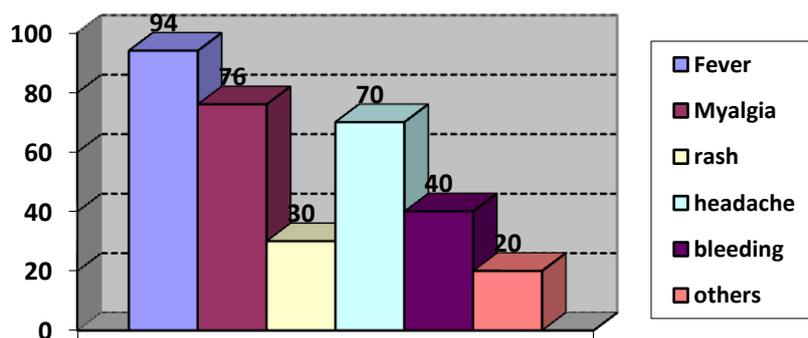


Figure 1

Petechiae was commonest sign (54%) followed by others. (figure 2) Shock signs included-tachycardia (HR>100 beats/min), narrow pulse

pressure (<30mm of Hg), tachypnea (>20 cycles/min), low blood pressure and cold peripheries narrow pulse pressure.

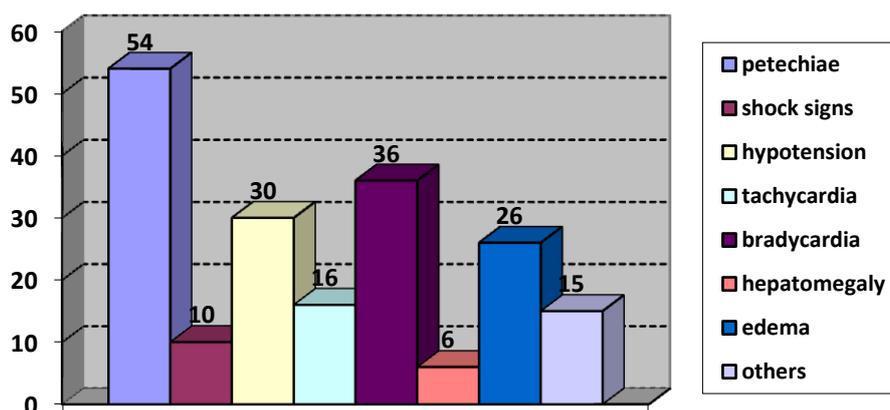


Figure 2

At the time of admission, 30(60%) patients had dengue fever,15(30%)had DHF and 5(10%) had DSS. Based on ECG and echocardiography

26(52%) patients had cardiac manifestations. Cardiac enzyme assay was done qualitatively (by kit test) and all results were negative.

Table 1: ECG finding at admission (figure:3)

Sinus rhythm	46(90%)	
	Sinus bradycardia	14(28%)
	Sinus tachycardia	6(12%)
	ST-Tchanges	2(4%)
AV block(1 st degree)		3(6%)
AV block(2 nd degree)		1(2%)

ECG findings of patients

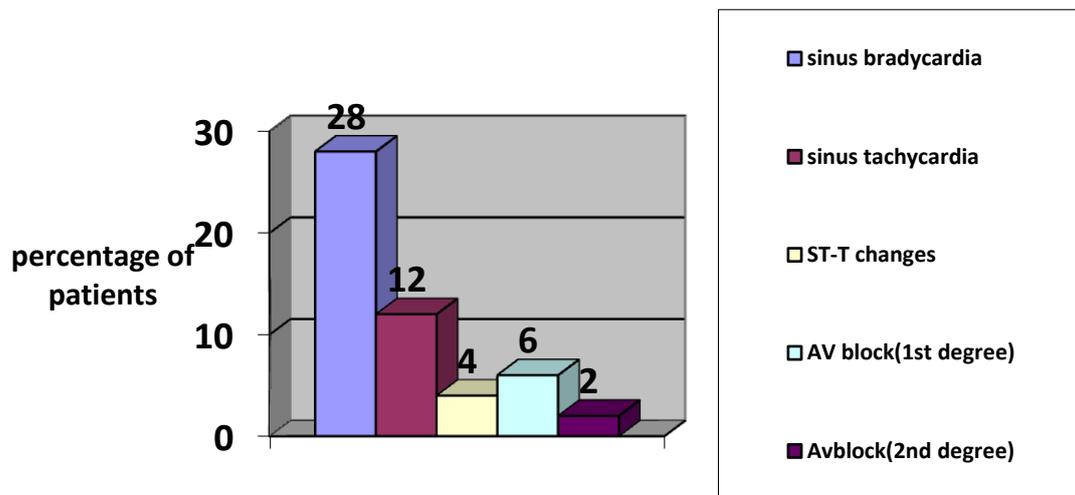


Figure 3

Table 2 : echo cardiographic finding at admission

Normal	45(90%)
Reduced LVEF	3(6%)
Pericardial effusion	2(4%)
LV hypokinesia	1(2%)

ECHO findings of patients

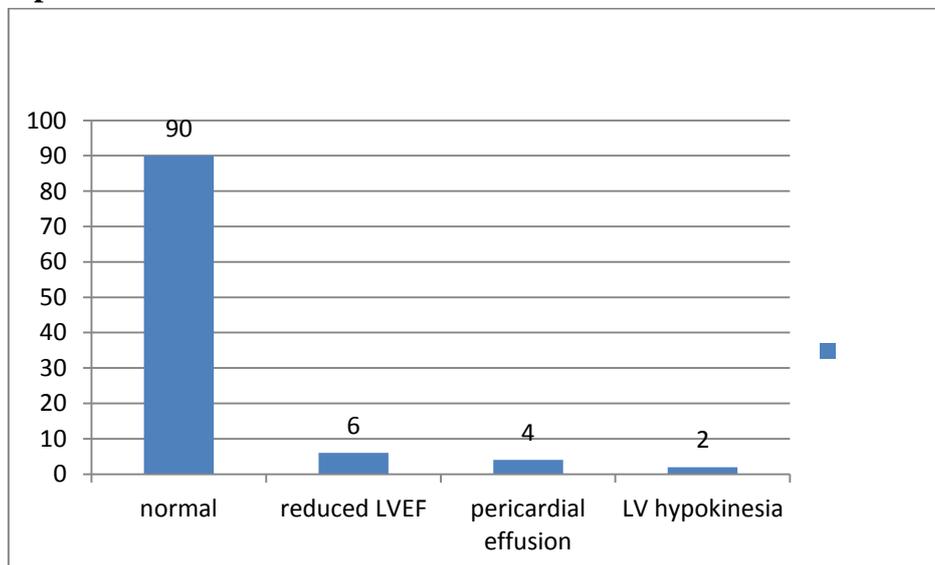


Figure 4

3rd day onwards all ECG and echocardiography were normal. Hence all cardiac manifestations were transient and reversible.

Other organ involvement also recorded in 20(40%) patients.(table 3)

Table: 3

Neurological involvement	8(16%)	
	Encephalitis/aseptic meningitis	7(14%)
	Transverse myelitis	(1%)
Gastrointestinal	15(30%)	
	Hepatitis	9(18%)
	Acalculous cholecystitis	1(2%)
	Pancreatitis	1(2%)
	Gastrointestinal bleeding	5(10%)
Renal	12(24%)	
	Acute kidney injury	7(14%)
	Haemolytic uremic syndrome	5(10%)
	Haematuria	7(14%)
Respiratory	4(8%)	
	ALI/ARDS	3(6%)
	Pulmonary haemorrhage	1(2%)
Musculoskeletal	4(8%)	
	Myositis with raised CPK	4(8%)
Others	2(4%)	

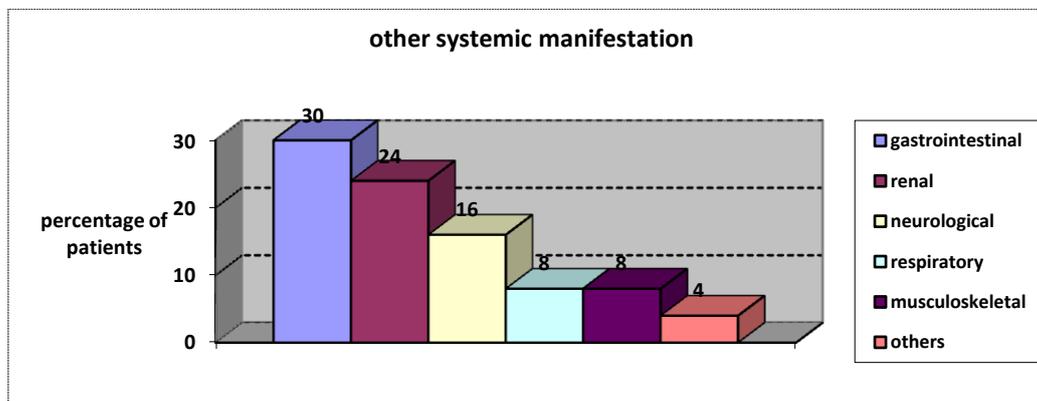


Figure :4

Cardiologic manifestation were significantly higher in DHF and DSS. (table 5) Cardiologic manifestations were also observed to be

associated with involvement of other system involvement.(table6)Both results were statistically significant.

Table 5:

	Dengue fever(n=30)	DHF(n=15)	DSS(n=5)	P value
ECG abnormality	10(33.33%)	12(80%)	4(80%)	0.004
Echocardiographic abnormality	1(3.33%)	2(13.33%)	2(40%)	0.018

Table 6:

Other organ involvement	With Cardiac Manifestation(n=26)	Without cardiac Manifestation(n=24)	P value
Present(n=20)	14	6	0.03
Absent(n=30)	12	18	

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. Cardiac dysfunction associated with the acute phase of dengue fever has been under diagnosed in clinical practice. Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in dengue hemorrhagic fever and dengue shock syndrome. Cardiac involvement in dengue fever is often under diagnosed due to low index of clinical suspicion and its overlapping clinical manifestations such as hypotension, tachycardia, pulmonary edema and capillary leak associated with dengue virus infection.

The mean pulse rate of the study population was 66/minute. The minimum pulse rate was 48/minute and the maximum pulse rate was 120/minute with a standard deviation 15.86. In the study by Latheef et al mean heart rates were significantly lower in the dengue group 87.6 (± 12.5) beats/min (dengue) compared to the control group. The commonest rhythm abnormality noted was sinus bradycardia, found in 32%. Three patients had unexplained sinus tachycardia. In the study by Gupta et al, sinus bradycardia was found in 14.28%, and sinus tachycardia in 21.4% patients. AV dissociation with sinus node dysfunction was observed in one patient, which resolved in 24 hours. Kaushik et al have described atrioventricular dissociation and sino atrial exit block in a child with dengue fever. All these changes reverted back to sinus rhythm in 24 hours. Chuah et al and Veloso et al have described transient ventricular arrhythmias as a cardiac manifestation of dengue fever. Troponin T testing was done in all patients and it was found to be negative in all. Kularatne et al in their study in

2007 found 62.5% of 120 adult dengue patients had ECG changes. They divided patients into "Cardiac group" or "Non-cardiac group" based on presence or absence of ECG changes. Higher incidence of tachycardia, bradycardia and hypotension in "Cardiac group" were found with statistical significance.

Satarasinghe et al in 2007 found that 24% out of 217 patients had echocardiographic abnormality while none had clinical features of overt myocarditis (such as significant sinus tachycardia, raised jugular venous pressure, triple rhythm, bilateral pulmonary crepitations) All patients showed improvement at three months. A study by Carlos Henrique Miranda et al found 2 patients had reduced LV function, two had LV segmental hypokinesia and one had pericardial effusion. In our study 52% patients showed cardiac manifestation with sinus bradycardia (28%) commonest. 10% had echocardiographic evidence of cardiac involvement. In our study both ECG and ECHO findings were reversible and improved before discharge.

It is widely accepted that dengue haemorrhagic fever is an immunologically mediated disease, a mechanism similar to those involved in viral myocarditis. In a study conducted by Wali et al in 1998, 17 patients with DHF/DSS were studied. 12 (70.59%) patients had global hypokinesia in echocardiography. 7 patients had an ejection fraction less than 40%. 8 patients had DSS with a mean ejection fraction 39.63%, out of which 5 had an ejection fraction less than 40. They opined that acute reversible cardiac insult may be responsible for hypotension or shock in these patients. Though Carlos Henrique Miranda et al found no significant difference of cardiac manifestation in different grades of severity in dengue, they stated two deaths of patients from cardiogenic shock. A study of hemodynamic profiles in DHF from Thailand reported lowered cardiac index due to decreased ejection fraction and lowered preload. The incidence of cardiac manifestations was stated to be high (53.33%) in patients with dengue shock syndrome compared to the patients with

dengue hemorrhagic fever (35.29%) and dengue fever (30%) in study of Mohit Arora, Rekha S Patil in 2016. In our study prevalence of cardiac manifestation was found to be significantly higher in patients with DHF and DSS. Hence an adequate approach to the hemodynamic instability associated with dengue requires not only a significant volume expansion, but also evaluation and treatment of the accompanying ventricular dysfunction.

Dengue may have varied and multisystem presentations. Encephalopathy by Kho et al. (1981), Row et al. (1996), Thakare et al. (1996), Cam et al. (2001); Encephalitis/ aseptic meningitis by Lum et al. (1996), Hommel et al. (1998); Intracranial haemorrhages/ thrombosis by Luiz Jose de Souza et al.; Mononeuropathies/ polyneuropathies/ Guillane–Barre Syndrome by Soares et al. (2006) were reported as neurological manifestation. Gastrointestinal manifestation was reported as Hepatitis/ fulminant hepatic failure by Lawn et al (2003), Acalculous cholecystitis by Sharma et al. (2006), Goh & Tan (2006), Wu et al. (2003); Acute pancreatitis by Jusuf et al. (1998), Chen et al. (2004); Febrile diarrhea Helbok et al. (2004); Acute parotitis Torres et al. (2000) Renal involvement as Hemolytic uremic syndrome by Wiersinga et al (2006); Renal failure by Hommel et al (1999), Wiwanitkit (2005a,b); pulmonary involvement as ARDS by Sen et al. (1999), Thong (1998), Lum et al. (1995) Pulmonary hemorrhage by Setlik et al. (2004), Liam et al. (1993); Musculoskeletal involvement as Myositis by Kalita et al. (2005) Rhabdomyolysis by Gunasekera et al. (2000), Davis & Bourke (2004) were reported. Multisystem involvement also noted in our study and interestingly had a significant association with cardiac manifestation. Not all cases of myocardial dysfunction are due to direct or indirect myocardial structural damage. Possible reasons include Plasma leakage, Cytokine response associated with the infection (TNF- α and IL -6, IL -13, IL -18) as stated by Hober et al in 1993. 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. Further studies are needed to understand the interrelation of different system involvement manifestations.

Limitation

- 1) Quantitative assay of cardiac biomarkers were not done in this study.
- 2) Corelation of cardiac manifestation with biochemical marker liked platelet count was not done.
- 3) Difference of cardiac manifestation between primary and secondary infection of dengue were not assessed.
- 4) central venous pressure was not measured or correlated with cardiac manifestation.
- 5) Correlation of clinical finding and investigational findings were not assessed.

Conclusion

Simultaneous evaluation of all included patients with biomarkers, ECG and 2D-echo was done on a reasonable sample size in the present study. 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. Each patient were stable with treatment and discharged home finally. Transient cardiac abnormality can be an important presentation and this should guide the treating physician to look for cardiac involvement. There was statistically significant correlation between cardiac manifestations and severe forms of dengue, i.e. DHF and DSS. Hence, awareness regarding cardiac manifestation in dengue can help in the early recognition of dengue complications and reduction of death associated with dengue virus infection.

Abbreviation

ECG=electrocardiogram, ELISA=Enzyme linked immune sorbent assay; DHF=Dengue haemorrhagic fever, DSS=Dengue shock

syndrome; A-V=atrio ventricular; NS1=non structural protein 1

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