

CARDIAC MANIFESTATIONS IN DENGUE FEVER: A CROSS SECTIONAL STUDY FROM A TERTIARY CARE CENTRE OF NORTH INDIA

Mansi Singh¹, Ajay Kumar², Sanjay Mehrotra³, Virendra Atam⁴, Ravi Mishra⁵, Arvind Mishra⁶, Sudhir Kumar Verma⁷, Satish Kumar⁸

¹Junior Resident, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

²Associate Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

³Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

⁴Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

⁵Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

⁶Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

⁷Assistant Professor, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

⁸Senior Resident, Department of General Medicine, King George's Medical University, Lucknow, Uttar Pradesh, India.

ABSTRACT

BACKGROUND

Dengue fever is caused by any of the four closely related serotypes: dengue 1 to 4. Dengue is transmitted between people by mosquitoes- *Aedes aegypti* and *Aedes albopictus*, which are found throughout the world. We tried to describe the outcome and parameters of clinical and subclinical cardiac involvement in dengue fever (DF) and compared them without cardiac involvement.

METHODS

We included patients of age group of ≥ 18 years, fulfilling the WHO criteria for DF, and confirmed dengue serology NS1 antigen, IgM and IgG antibodies against dengue. Clinical data along with plasma leakage and abnormalities in ECG, 2-D Echo and cardiac biomarkers were recorded.

RESULTS

Out of a total of 75 patients, 48 (64.00%) had DF. 52 (17.33%) had abnormal ECG and 13 (17.33%) had abnormal 2-D echo but all the changes were transient. Abnormal 2-D echo findings were grade I diastolic dysfunction in 13.33% patients, one with grade II diastolic dysfunction and 2 with pericardial effusion.

CONCLUSIONS

Dengue affects endocardium, myocardium, pericardium as well as electrical conduction system of the heart. But the outcome remains unaffected by the transient cardiac involvement in different clinical types of dengue fever.

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BACKGROUND

Dengue fever is caused by any of four closely related serotypes: dengue 1 to 4. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue haemorrhagic fever and dengue shock syndrome. Dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *Aedes albopictus*, which are found throughout the world.¹

Over the past two decades, there has been global increase in the frequency of dengue fever, dengue haemorrhagic fever and its epidemics, with a concomitant increase in disease incidence. Considering this great burden of disease, vigorous research is going on to better

understand the pathophysiology especially the involvement of other organs being the cause of high morbidity. It is postulated that, dengue rarely affects the heart. Cardiac manifestations ranged from elevated biomarkers such as CK-MB and Troponin I to abnormal electrocardiography and echocardiography. 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 haemorrhagic fever has been described by several authors and is probably under diagnosed in clinical practice. Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the haemorrhagic form of the disease or in the associated shock.

Aim of the Study

To evaluate abnormalities in electrocardiographic, echocardiographic and cardiac biomarkers in patients with or without plasma leak (evident by pedal oedema/ascites/pleural effusion) among dengue patients.

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Corresponding Author:

Dr. Ajay Kumar,

Department of General Medicine,

King George's Medical University,

Lucknow- 226003, Uttar Pradesh.

E-mail: drajaymd12345@gmail.com

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METHODS

The study was conducted in patients admitted in the indoors of our institute during year 2016-2017. It was a cross sectional observational study. All the patients having fever with thrombocytopenia were admitted and detailed clinical symptoms and signs along with investigations were done in all dengue serology positive patients. Those less than 12 years of age, pregnant females, known diabetic, hypertensive or cardiac disease patients were excluded. In our study various cardiac parameters were compared between three clinical classes of dengue fever and outcome of patients with and without cardiac involvement was compared. All the patients with signs and symptoms of dengue fever were investigated for dengue viral serology along with other routine parameters including total leucocyte count (TLC). The patients included in this study were of age group of ≥ 18 years, fulfilling the WHO criteria for dengue fever, and positive dengue serology i.e. NS1 Antigen (by RT-PCR), IgM dengue antibody (MAC ELISA) and IgG (MAC ELISA) dengue. Patients who were having pre-existing cardiac illness, diabetes mellitus, hypertension and other coinfection were excluded from the study.

The patients were classified according to WHO classification of dengue,² dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). The cardiac parameters evaluated were electrocardiography (ECG), cardiac biomarkers in the form of Troponin-T (Trop T), Creatine Kinase - Muscle/Brain (CPK-MB) and N-Terminal Pro B-Type Natriuretic Peptide (NT-PROBNP) and echocardiography. The parameters studied in echocardiography were systolic function by calculating left ventricular ejection fraction using M mode³ and diastolic function by using mitral flow pattern on pulsed wave and tissue doppler imaging and calculating (mitral inflow pattern $-E/A$, isovolumic relaxation time, E-wave deceleration time and Tissue Doppler Imaging (TDI) findings: E/e ratio).⁴ Echocardiography was performed by a single cardiologist using Mylabseven e HD crystalline (serial no. 2747) of Ferginius. Routine 2-D echocardiogram and colour flow Doppler were obtained in subcostal and apical 4-chamber and epigastric views. Left ventricular ejection fraction was measured in M-mode scan of the LV obtained from a standard parasternal long-axis view, at the level of the mitral valve (MV) tip, which was recorded simultaneously with the electrocardiogram. Measurements of LV walls and dimensions were performed in accordance with published guidelines.^{3,4} Left ventricular ejection fraction (LVEF) was calculated and normal values were taken as $67 \pm 12\%$.

Transmitral pulsed-wave Doppler velocities (peak E- and A-wave velocities) were measured in the apical four chamber view with the sample volume positioned at the MV. E wave deceleration time and isovolemic relaxation time were also calculated. TDI of the LV was performed using pulsed wave Doppler assessment of the medial and lateral MV annulus. Peak tissue medial and lateral S-wave (S) and E-wave (e') velocities were measured. TDI parameters were

assessed using published age-specific normal values. Values below the 5th or above the 95th percentile normal values were deemed abnormal. The recommended variables for identifying diastolic dysfunction and their abnormal cut off values are septal e' < 7 cm/sec, lateral e' < 10 cm/sec and average E/e' ratio > 14 . LV diastolic function is normal if more than half of the available variables do not meet the cut off values for identifying abnormal function. LV diastolic dysfunction is present if more than half of the available parameters meet these cut off values. The study is inconclusive if half of the parameters do not meet the cutoff values. Plasma leakage was diagnosed by presence of any one of four: subcutaneous oedema (pedal oedema, facial puffiness) or pleural effusion or pericardial effusion or ascites. Pleural effusion and ascites were detected by ultrasonography while pericardial effusion was detected by echocardiography.

Statistical Analysis

The data was analysed using Statistical Package for Social Sciences (SPSS) version 21.0. Continuous data were presented as Mean \pm SD. Frequency data were presented as percentages. Chi-square test and independent 't'-test was used to find the significant differences among frequencies and continuous data respectively. A 'p' value less than 0.05 was considered to indicate a significant association.

RESULTS

A total of 75 patients of dengue fever were admitted during the period of study. Out of these, majority were diagnosed as DF 48 (64.00%), only 2 (2.67%) were diagnosed as DSS and rest 25 (33.33%) were diagnosed as DHF (Figure 1).

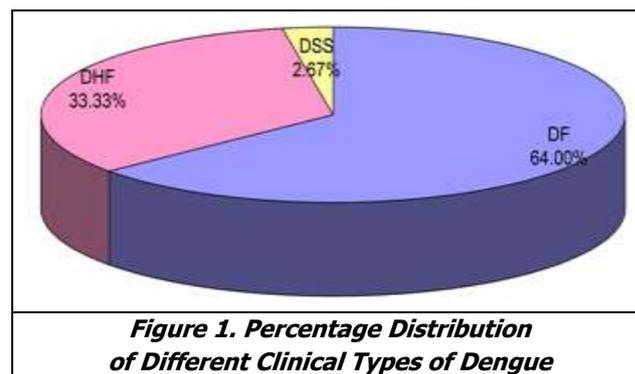


Figure 1. Percentage Distribution of Different Clinical Types of Dengue

ECG findings in the majority of the patients (52 (69.3%)) were found to be normal. Relative bradycardia was found in 6, ST depression in 11, left ventricular hypertrophy in 3, tall t waves in 2 and ventricular ectopics in 1 patient. Though incidence of ECG abnormalities was higher among DHF as compared to DF patients (68.00% vs. 41.67%) but this difference was not found to be statistically significant (Table 1).

Electrocardiography Finding	Total (N=75)	Dengue Fever (n=48)	Dengue Haemorrhagic Fever (n=25)	Dengue Shock Syndrome (n=2)
Left Ventricular Hypertrophy	3	1	2	0
Normal	52	37	14	1
ST Depression	6	5	1	0
Relative Bradycardia	11	5	6	0
Tall T Waves	2	0	2	0
Ventricular Ectopics	1	0	0	1

Table 1. Comparison of Electrocardiography Findings of Patients with Different Clinical Types of Dengue
 $\chi^2=46.6$ (dengue fever=10); $p<0.001$

Thirteen (17.33%) patients had abnormal echocardiography findings in the form of grade I diastolic dysfunction in 10 (13.33%) patients, one patient with grade II diastolic dysfunction and two patients with pericardial effusion. Echocardiography findings of majority of overall patients (n=62; 82.67%) as well as DF (n=38, 79.17%), DHF (n=22, 88.00%) and DSS (n=2, 100.00%) were normal. No echocardiography abnormality was observed in

any of the patients of dengue shock syndrome. Proportion of DF patients with echocardiography abnormalities was found to be higher as compared to DHF i.e. grade 1 diastolic dysfunction (14.58% vs. 12.00%), grade 2 diastolic dysfunction (2.08% vs. 0.00%) and pericardial effusion (4.17% vs. 0.00%) (Table 2).

Echocardiography Findings	Total (N=75)	Dengue Fever (n=48)		Dengue Haemorrhagic Fever (n=25)		Dengue Shock Syndrome (n=2)
		No.	%	No.	%	
Normal	62	38	79.17	22	88.00	2
Grade I Diastolic Dysfunction	10	7	14.58	3	12.00	0
Grade II Diastolic Dysfunction	1	1	2.08	0	0.00	0
Pericardial Effusion	2	2	4.17	0	0.00	0

$\chi^2=2.276$ (dengue fever=6); $p=0.893$

Table 2. Comparison of Echocardiography Findings of Patients with Different Clinical Types of Dengue

Sixteen (21.33%) patients had elevated NT-PROBNP (values were adjusted to age and kidney function). Eight (10.616%) had elevated levels of Trop-T and 6 (8%) patients had elevated CK-MB levels. Four (8.7%) of dengue fever, 2 (8%) of DHF and none of DSS were having elevated values of CPK-MB but the difference amongst the three clinical types was not found to be significant. For NT-PRO-BNP values 11 (23.4%) of DF, 5 (20%) of DHF and none of DSS were having significantly raised values. Five (10.8%) of DF, 3 (12%) of DHF and none amongst DSS were having raised values for Trop T but significant difference was not noticed amongst different clinical types (Figure 2).

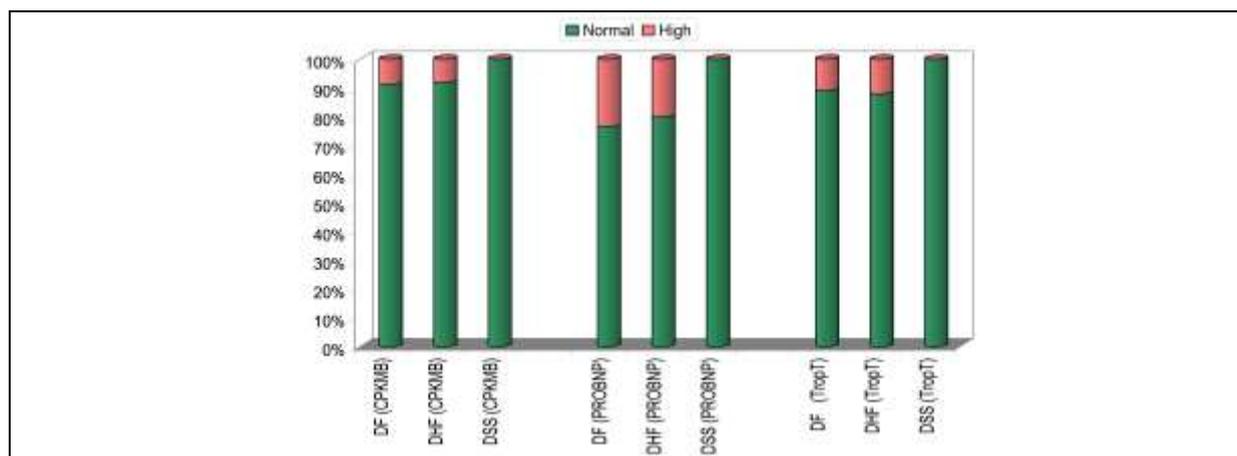


Figure 2. Comparison of Cardiac Markers (CPKMB, PROBNP and Trop-T) in Different Clinical Types of Dengue

Seventy-two (96%) patients were screened for the presence of plasma leakage. Proportion of echocardiography abnormalities were higher among patients with plasma leak 5 (29.41%) as compared to without plasma leak 8 (14.55%), this difference was not found to be statistically significant (Table 3).

	Total (N=72)	Plasma Leak Present (n=17)		Plasma Leak Absent (n=55)		Statistical Significance	
		No.	%	No.	%	z	p
Echocardiography Abnormalities	13	5	29.41	8	14.55	1.940	0.164

Table 3. Association of Echocardiography Abnormalities with Plasma Leak

For day 1-3 evaluation, mean TLC levels of those with increased cardiac markers were significantly higher as compared to those having all cardiac markers in normal range (p=0.05). For Day 4-6 and Day 10-12 assessment too, mean TLC levels of those with raised cardiac markers were higher as compared to those with all cardiac markers in normal range yet this difference was not significant statistically. However, for day 7-9 assessment, mean TLC levels of those with increased cardiac markers were lower as compared to those having all cardiac markers in normal range yet this difference was not significant statistically (p>0.05) (Table 4).

Time Period	Any Raised Cardiac Markers			All Cardiac Markers Normal			Statistical Significance	
	n	Mean	SD	n	Mean	SD	t'	p'
Day 1-3	18	9235.56	5550.94	48	6825.83	3851.89	1.996	0.050
Day 4-6	19	8105.26	3975.83	54	7096.30	3201.90	1.108	0.272
Day 7-9	9	6267.78	3162.77	28	6417.14	3451.86	-0.115	0.909
Day 10-12	9	8544.44	2411.49	39	8230.77	2697.77	0.320	0.750

Table 4. Association of Raised Cardiac Markers (CPKMB, PROBNP or Trop-T) with TLC Levels

Statistically, no significant difference could be seen in total duration of illness between cases showing cardiac involvement (11.64±2.38 days) as compared to those not having cardiac involvement (10.67±3.32 days) (p=0.262) (Table 5).

	Cardiac Involvement	Non-Cardiac Involvement
Average Duration of Illness	11.64±2.38	10.67±3.32

Table 5. Comparison of Duration of Illness in Patients With and Without Cardiac Involvement

t'=1.133; p=0.262 (NS)

DISCUSSION

The present study is an attempt to describe the cardiac evaluation of serologically confirmed hospitalized cases of dengue fever and also the outcome of patients. The cardiac involvement was studied in the form of electrocardiography changes, cardiac biomarkers and echocardiography changes. In a previous study from our centre DF was seen in 74.5%, DHF in 22% and DSS in 3.45% of patients which is almost similar to our study.⁵

Out of 75 patients, 52 (69.33%) patients had normal and 23 (30.67%) had abnormal electrocardiography. Abnormal ECG were also noticed in other studies like Tarique et al, but incidence was slightly higher than our study (67.24%).⁶ In our study, 26 (34.6%) had tachycardia on day of admission when they presented with fever. Out of which 11 patients had relative bradycardia during defervescence period. Similar incidence of relative bradycardia was found in study done by Aisha lateef et al.⁷ Similar to our study, abnormal ECG findings e.g. tachycardia, bradycardia, supraventricular tachycardia, left bundle branch block, ST depression, poor progression of R wave were noted in the study done by Tarique et al.⁶

No relationship was demonstrated between the clinical severity of dengue and the incidence of rhythm abnormalities. Tarique et al showed that T wave inversion was not the sole manifestation. In their study patients had other arrhythmias like bundle branch block but no atrial fibrillation was noted.⁶ During Dengue outbreak in Srilanka in 2005, electrocardiography manifestations such as T wave inversion, bundle branch block, tachycardia and bradycardia were noted.⁸ Similar findings were noted in Indian study by Wali et al 5/17 (29%) patients of dengue haemorrhagic fever had electrocardiography changes.⁹ Literature review by Gulati revealed that rhythm disturbances such as atrial fibrillation, sinus node dysfunction, atrioventricular blocks and ectopic ventricular beats have been documented in dengue haemorrhagic fever.¹⁰ In our study though the incidence of ECG abnormalities was higher among DHF as compared to DF (68.00% vs. 41.67%) but this difference was not found to be statistically significant.

In the current study we found that 40% of the dengue population had elevated cardiac biomarkers in the form of Trop-T, NT-PROBNP or CPK-MB. High levels of biomarker were found in patient with ECG changes. In Sri Lanka,

Wichmann et al¹¹ showed that only 1 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 which was same as incidence noted in our study. We found similar study by Miranda Ch et al,¹² in which 1997 WHO guidelines were used whereas in our study recent 2009 WHO guidelines were used. The number of patients were almost same in both the studies (75 patients in our study and 81 in theirs). For diagnosis of dengue patients Miranda Ch et al also used RT-PCR. We could not use RT-PCR due to resource constraints. For assessment of cardiac involvement, they screened the patients with raised biomarkers with echocardiography which could have missed significant number of patients with mild cardiac abnormality only presenting as echocardiographic abnormalities. Whereas in our study all dengue patients were screened for echocardiographic abnormalities and that is why we got higher proportion of population with cardiac abnormalities (17.33% in our study and 4.9% in their study). Moreover, Miranda Ch et al included procedures like MRI and cardiac tissue histology which makes it less cost effective and more complicated to replicate. Whereas our study had less economic burden and is simple to replicate for further research. The results are similar in both the studies. They observed Troponin I elevation in 6(7%) patients and important elevation of NT-PROBNP in 10 (10%) patients. In their study patients with elevated biomarkers showed a more intense inflammatory activity confirmed by a higher leukocyte count and C-reactive protein levels and similar correlation was seen in our study. Thus, it is possible that the inflammatory activity secondary to dengue virus has a pivotal role in the pathophysiology of the cardiac disease, and the myocardial injury could be an immune-mediated event. Although dengue complications are described to be more frequent during secondary infection, in our study, cardiac involvement was in dengue patients with primary infection.

Cardiac performance and hemodynamic status are affected by intravascular volume, cardiac functions and autonomic response. We obtained echocardiography studies during the critical phase of illness in a cohort that included both milder and more severe illness, and analysed cardiac function data in conjunction with assessments of plasma leakage. The data show that cardiac functional abnormalities are common in dengue and correlate with disease severity (Table 5). However, these abnormalities were transient, did not require specific treatment, and were not accompanied by evidence of structural damage to the myocardium. In our study 29.4% of patients with plasma leakage and 13.7% of patients without plasma leakage had cardiac involvement. Similar results were seen in Kirawitaya Tawachai et al.¹³ Vishal Gupta et al also observed diastolic dysfunction in 14% patients and pericardial effusion in 3% of patients.¹⁴ Unlike others in Khongphatthanayothin A et al,¹⁵ LVEF <50% was observed in 6.7%, 13.8%, and 36% of patients with DF, DHF, and DSS, respectively. Wail et al also concluded the same. Myocarditis and regional wall motion abnormalities were the main findings in many studies,¹⁶⁻²¹ Satarasinghe et

al⁸ and Yacoub et al.¹⁸ So we concluded that cardiac functional abnormalities were related to the severity of plasma leakage. This was most evident in decreased LV wall movement during early diastole indicating a relaxation defect. However, the correlation between abnormal LV diastolic movement and the extent of plasma leakage among dengue cases suggests that plasma leakage may also directly contribute to this functional abnormality by reducing intravascular volume. Alternatively, plasma leakage may be a correlate of the disease mechanism that affects cardiac function. The pathology underlying this finding is unknown. Nevertheless, the abnormal LV relaxation may further compromise LV filling. Decreased LV relaxation may also contribute to high LV filling pressure when intravascular volume has been restored by intravenous fluid treatment and by reabsorption of effusion fluid, and may lead to the pulmonary oedema observed in some dengue haemorrhagic fever cases. The prevalence of subclinical diastolic dysfunction has been reported to increase with age, in individuals with hypertension, LV hypertrophy, and diabetes so these were already excluded from the study.²²⁻²⁶ This has important implications for clinical care considering the shift in the demographics of dengue cases to adults who may have these common co-morbidities.

There was no change in disease outcome in patients with cardiac involvement as the duration of illness was almost same as that of noncardiac patients and there was no incidence of myocardial infarction or heart failure or any other cardiac illness in the follow up. Thus, it was observed that the outcome remained unaffected by the transient cardiac involvement. Still one has to be cautious in patient with cardiac involvement during fluid management.

CONCLUSIONS

Incidence of cardiac involvement was quite high in all type of Dengue infections. However, it was unrelated with different clinical types of dengue infection, TLC levels and duration of hospital stay. Incidence of abnormal echocardiography may be associated with the plasma leakage suggesting the possible role of plasma leakage in cardiac abnormalities. Cardiac involvement did not change the duration of illness significantly, so the outcome remains unaffected by the transient cardiac involvement. Further studies to assess impact of management following cardiac abnormality detection are warranted.

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