



CARDIAC MANIFESTATIONS OF DENGUE FEVER IN CHILDREN

Pediatrics

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ABSTRACT

Introduction: Dengue fever represents a significant public health problem in tropical and subtropical regions. 70% of total cases are from Asia, especially India. Caused by 4 dengue virus serotypes(DENV-1, DENV-2 DENV-3 and DENV-4), DENV-2 being the most prevalent in India. Incidence and range of cardiac manifestations in dengue fever vary widely. **Aims & objectives:** To study the incidence and range of cardiac manifestations of dengue fever in children. **Material & methods:** This is an observational study, conducted in department of pediatrics at National Institute of Medical Sciences & Research, Jaipur in study period of 18 months. A total of 94 patients were included in the study fulfilling the inclusion criteria. **Results:** The overall incidence of cardiac manifestations was found to be 31.9%. The incidence of cardiac manifestations in dengue without warning signs was 4.4%, in dengue with warning signs was 52.5% and in severe dengue was 77.7%. **Conclusion:** Incidence of cardiac manifestations increases with increase in disease severity

KEYWORDS

Severe dengue, cardiac manifestations, ECG changes, ECHO, Troponin I, CPK-MB

INTRODUCTION

Dengue fever represents a significant public health problem in tropical and subtropical regions. A study on the prevalence of dengue estimates that 3.9 billion people are at risk of infection with dengue viruses. 70% of the total cases are from Asia, especially India.¹ The largest number of dengue cases ever reported globally was in 2019, India has reported 16,439 cases as of 20 September 2020 including twelve deaths which is higher than previous year.² This indicates that dengue is on a rising trend worldwide.

Caused by 4 dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4), it can vary from mild self-limiting illness to severe forms like, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).³ DENV-2 is the most widespread serotype causing dengue in India, especially North India.⁴ It's transmitted to humans by mosquitos of the Aedes family.⁵

Dengue is characterized by cytokine mediated increase in capillary permeability (high serum levels of interferon-G, interleukin (IL-2), tumor necrosis factor (TNF)- α and other factors), without vasculitis or any injury to the vessel walls. Significant capillary leakage of plasma occurs into the extravascular compartment due to immune activation, is responsible for the clinical manifestations of dengue.⁶⁻⁹

Plasma leakage can even cause various atypical manifestations which does not fall into either dengue shock syndrome or dengue hemorrhagic fever, WHO coined the term Expanded dengue syndrome in 2012 to describe such cases, with a multisystemic and multifaceted approach involving organs such as liver, brain, heart, kidney and CNS.¹⁰

Cardiac involvement is one such atypical manifestation of dengue fever. Main factors thought to be the cause are reduced preload, altered coronary microcirculation, and myocardial interstitial oedema.¹¹

Other factors like direct viral invasion, immune mechanisms, electrolyte imbalance, derangement of intracellular Ca⁺ ion storage, lactic acidosis, and ischemia caused by hypotension may additionally play a role in causing cardiac injury, the main pathogenic mechanism is not yet clear.¹²

In patients with shock unresponsive to fluid resuscitation, likelihood of concurrent myocarditis should be considered. Thus an appropriate

approach to the hemodynamic instability related to dengue requires not only volemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction.¹³

Clinical manifestations of cardiac involvement can vary widely, from silent disease to severe myocarditis causing death. Rhythm abnormalities, hypotension, pericarditis, myocarditis, myocardial depression with symptoms of heart-failure & shock all have been reported in various studies.¹⁴⁻¹⁷

The purpose of this study is to detect various cardiac manifestations of Dengue with help of clinical features, electrocardiographic abnormalities, echocardiographic findings, abnormal cardiac biomarkers (CPK-MB and Troponin I) and cardiac MRI, and to look for their incidence to decrease mortality and morbidity caused by them.

AIM & OBJECTIVES

To study the incidence and range of cardiac manifestations of dengue fever in children.

STUDY DESIGN

Observational study.

SELECTION CRITERIA OF PATIENTS:

Inclusion Criteria

Serologically confirmed (NS1 or IgM ELISA positive) dengue patients in pediatric age group 1-18 years by

- Demonstration of IgM antibody titre by ELISA positive in single serum sample.¹⁸
- Demonstration of dengue virus antigen in serum sample by NS1-ELISA.¹⁸

Exclusion Criteria

1. Age <1 or >18 years.
2. Children with pre-existing congenital or acquired heart diseases.
3. IgM or NS1 negative dengue like illnesses.
4. Those patients who refused to provide consent to be included in the study.

METHODOLOGY

98 consecutive IgM or NS 1 ELISA Positive dengue fever patients of

age 1 to 18 years were admitted to National Institute of Medical Sciences and Research Hospital, Jaipur, Rajasthan, from 1st January 2019 to 30th June 2020.

2 patients went LAMA (Left Against Medical Advice), 1 refused to be included in the study and 1 patient had Rheumatic heart disease. The remaining 94 patients were included in our study.

TECHNIQUE

All children admitted with clinical suspicion of dengue were subjected to Urine routine microscopy and culture sensitivity, Complete blood counts, Liver Function Test, Renal Function Test, Peripheral Blood Film for Malarial Parasite, Rapid diagnostic test for malaria, Widal test, Blood culture, IgM for Scrub Typhus, NS1 and Ig M Dengue serology.

Those positive for Dengue NS1 and IgM by ELISA¹⁸ were included in our study.

Purpose of the study was explained to attendants in their own language and written consent was taken.

Clinical examination was done at Department of Paediatrics, National Institute of Medical Sciences & Research, Jaipur. Routine investigations were sent including investigations for cardiac involvement like CPK MB, Troponin I, ECG, ECHO, Serum Electrolyte, Chest Xray, USG Whole abdomen.

Torniquet test was performed in all patients daily to look for hemorrhagic tendencies by inflating appropriately sized BP cuff on upper arm midway between systolic BP & diastolic BP for five minutes. The result was considered Positive if resulting petechiae below antecubital fossa per square inch was 10 or more.¹⁸

DHF (Dengue Hemorrhagic Fever) & DSS (Dengue Shock Syndrome) were diagnosed as per WHO definition and criteria.¹⁸

Heart rate, BP, platelet count & haematocrit were monitored as indicated. Heart rate¹⁹ and blood pressure²⁰ were compared with age specific limits and labelled as bradycardia, tachycardia and hypotension accordingly. ECG was done every alternate day. CPK-MB and Troponin I were done on day of admission and values were interpreted as normal between 0 to 25 IU and 0.00 to 0.04 IU respectively.²¹ Patients having increased value for one or both cardiac biomarkers (CPK-MB & TROPONIN I) were further subjected to Cardiac MRI to confirm myocarditis.

The study subjects were classified as per WHO classification¹⁸ as Dengue without warning sign (D), Dengue with warning signs (DW) and Severe Dengue (SD) following which treatment was commenced as per standard WHO Guidelines.¹⁸

The clinical, laboratory and radiological investigations of all the study subjects were recorded in a specially designed pretested proforma.

Dengue patients positive for one or more of these investigations were considered as cardiac involvement.

- Rhythm disturbance, pulse rate changes like sinus tachycardia or bradycardia, raised CPK-MB and/or Troponin I and abnormal ECG and ECHO.
- ECG changes- sinus tachycardia, sinus bradycardia, non-specific ST-T wave changes, inverted T waves, 1ST degree heart block and right bundle branch block.
- Echocardiography changes-
 - a) Systolic dysfunction – impaired ventricular contraction.
 - b) Diastolic dysfunction – abnormality in filling ventricles during diastole.
 - c) Ventricular Ejection fraction – Fraction of the blood pumped out of a ventricle with each heart beat (Normal value – 67 ± 12%).²²
 - d) Pericardial effusion – Abnormal accumulation of fluid within pericardial cavity.

STATISTICAL ANALYSIS

The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test and Fisher's exact test. A probability value ('p' value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

RESULT

The mean age of children having cardiac manifestations was 10.43 yrs and without cardiac manifestations was 11.8 years. M: F ratio in children who had cardiac manifestations was 1.3:1, while in those without cardiac manifestation was 1.9:1. (Table 1)

Table 1. Characteristics of the two study groups

	With cardiac manifestations	Without cardiac manifestations
M:F ratio	1.3	1.9
Age (mean) (in years)	10.43	11.8

Cardiac involvement was seen mostly in patients who satisfied WHO criteria of Severe Dengue (SD) (7 out of 9 Severe dengue patients, 77.7%), followed by Dengue with Warning (DW) (21 out of 40 patients, i.e 52.5%) and only 4.4% (n=2) out of 45 Dengue fever (D) patients had cardiac manifestations. (Table 2)

Table 2. Incidence of cardiac manifestations in different types of dengue

	With cardiac manifestations, n(%)	Without cardiac manifestations, n(%)	Total patients, n (%)
D	2 (4.4)	43 (95.6)	45 (100)
DW	21 (52.5)	19 (47.5)	40 (100)
SD	7 (77.7)	2 (22.3)	9 (100)
Total	30 (31.9)	64 (68.1)	94 (100)

In patients with cardiac involvement mean platelet count was .35 lakh/cumm while in patients without manifestations it was found to be .55 lakh/cumm. Mean value of hematocrit was higher (mean 31.37) among patients who showed cardiac manifestations as compared to those without cardiac manifestations (mean 28.7). (Table 3)

Table 3. Mean hematocrit and platelet values in patients with and without cardiac manifestations

	With cardiac involvement, n(%)	Without cardiac involvement, n(%)
Hematocrit (mean value)	31.37	28.7
Platelet count (mean value)	.35 lakh	.55 lakh

In children with cardiac involvement, no specific symptoms referable to heart disease could be identified clearly or were overlapping with clinical features of dengue so were difficult to be identified separately. Minimum pericardial effusion was present in 5 patients and only one child had enlarged cardiac silhouette. ECG changes were found in 30 children (31.9%). ECHO showed minimal pericardial effusion in 5 cases (5.3%). And Left Ventricular Ejection Fraction was decreased in 7 cases which were all in severe dengue. Cardiac biomarkers including CPK-MB & Troponin I were increased in 9 patients, 5 patients had increased CPK-MB while 2 patients had only Troponin I raised and 2 patient had both CPK-MB & Troponin I raised. Among patients with high suspicion of having myocarditis on the basis of clinical picture, ECG, ECHO, x-ray findings and increased biomarkers (CPK-MB and Troponin I), Myocarditis was confirmed in 3 patients after performing cardiac MRI. (Table 4)

Table 4. Various cardiac manifestations found in our study

	D n(%)	DW n(%)	SD n(%)	P Value
ECG Changes				<.00001 *
Low voltage QRS	0	0	1 (11.1)	
ST elevation	0	0	2 (22.2)	
T wave inversion	0	0	1 (11.1)	
RBBB	0	0	1 (11.1)	
Inc. RR interval	2 (4.4)	12 (30)	2 (22.2)	
Dec. RR interval	0	9 (22.5)	5 (55.6)	
Pericardial effusion	0	2 (5)	3 (33.3)	.000082 *
Dec. LVEF (<55%)	0	0	7 (77.7)	<.00001 *
Inc. Troponin I	0	0	4 (44.4)	<.00001 *
Inc. CPK- MB	0	2 (5)	5	<.00001 *
Confirmed myocarditis (Cardiac MRI)	0	0	3 (33.3)	<.00001 *

DISCUSSION

The incidence of cardiac involvement among dengue patients in our study was 31.9% (30 out of 94) (Table 2). In a study conducted by Sidappa FD Et al²³, out of 39 patients 22 (56%) had cardiac abnormalities. Satarsinghe et al²⁴, found that 52 (24%) out of 217

patients had echocardiographic abnormality. Thus the incidence of cardiac involvement in dengue fever varied greatly between studies.

In our study, (Table 2) among children with dengue without warning signs the incidence of cardiac manifestation was 4.4% (2/45), 52.5% (21/40) in dengue with warning signs, and 77.7% (7/9) in severe dengue. Significant correlation was found in our study between increasing incidence of cardiac manifestations with increasing severity of dengue (p value < .05). Similarly, in a study by Sidappa FD et al²³, it was found that out of 22 (56%) patients having cardiac manifestations, 71% (5 out of 7 patients) had severe dengue, 53% (7 out of 13) had dengue with warning signs and 52% (10 out of 19) had dengue without warning signs. The difference among incidence of cardiac manifestations in different types of dengue maybe due to inclusion of small sample size or the parameters taken to label a patient as having cardiac manifestations.

In our (Table 3), it was found that in patients with cardiac manifestations mean platelet count was .35 lakh per mm³ and mean hematocrit 31.37 while in those without cardiac manifestations mean platelet count was .55 lakh per mm³ and mean hematocrit was 28.77. Thus in our study it was found low platelet count and higher hematocrit values were more related with cardiac manifestations. Similar findings were also found by Papalkar P et al²⁵, in which low platelet count (44.74% in patients < 1 lakh, while 18.18% in patients having platelet count > 1 lakh).and increased hematocrit (mean value 46.86 in patients which showed cardiac manifestations, while 40.41 in patients in which cardiac manifestations were absent) were more associated with cardiac manifestations.

In our study (Table 4), during electrocardiographic studies, 1 Patient had low voltage QRS complex, 1 had T wave inversion, 2 patients had ST elevation and 1 had Right bundle branch block. Decreased RR interval (Sinus tachycardia) was seen in 14.9% (14/94) patients and increased RR interval (Sinus bradycardia) in 17% (16/94) patients. The incidence of ECG changes in dengue patients without warning signs was 5% (2/40), in patients with warning signs was 46.6% (21/45) and 77.7% (7/9) in severe dengue patients. Overall incidence of ECG changes in our study among patients having dengue fever was 31.9% (30/94). Significant correlation was found between occurrence of ECG changes with increasing severity of dengue (all p values < .05). In a study by Sidappa FD et al²³, ECG changes were present in 13 (33%) cases of which sinus tachycardia disproportionate to fever was seen in 9 (23%) patients followed by T wave inversion in 7 (17%), low QRS complex and sinus bradycardia in 2 (5%) each, ventricular ectopic and supraventricular tachycardia in 1 (2%) patient each. So far there are limited studies available to correlate ECG changes with different types of dengue in children.

ECHO showed pericardial effusion in 5.3% (5/94) patients in our study. No patients in dengue without warning signs had pericardial effusion, while in dengue with warning signs 5% patients (2/40) (p value= .905) had pericardial effusion and in severe dengue the incidence was 33.3% (3/9), with a p value of .000082, showing significant correlation. Similar findings were noted by Sidappa FD et al²³, in which pericardial effusion was found in 2% patients (1/40). In a study by Papalkar et al²⁵, 3.33% (2/60) patients had pericardial effusion. The difference in incidence of pericardial effusion among these studies, maybe due to the difference in proportion of severe dengue patients included among them.

In Echocardiographic studies, it was found that 7 patients had Left ventricular ejection fraction less than 55. Decreased LVEF was found only in patients of severe dengue. The overall incidence of decreased LVEF was 7.4% (7/94), which was 77.7% in severe dengue cases (p value < 0.00001*). Similar to our study, in a study by Kabra SK et al²⁶, ejection fraction was reduced (< 50%) in 9/54 (16.7%) children. In a recent study by Shah C et al²⁷ in 2019, it was observed that 13.1% patients (42/320) had LVEF less than 40%. The incidence of decreased LVEF found in our study is similar to other studies.

In our study, Troponin I was increased in 4 patients belonging to Severe Dengue. Thus, overall incidence of increased Troponin I in our study was 4.25% (4/94), and incidence of increased Troponin I in severe dengue was 44.4% (4/9). CPK-MB was raised in 7 patients, out of which 5 patients had severe dengue and 2 had dengue with warning signs. In our study, overall incidence of increased CPK-MB was 7.4% (7/94), incidence of increased CPK-MB in severe dengue was 55.5%

(5/9) and incidence of increased CPK-MB in dengue with warning sign was 5% (2/40). In study of Kirawittaya et al²⁸, it was found that elevated Troponin levels were more common in severe dengue cases compared to DF (14.5% vs 5%, p = 0.028). Similar to our study in a study by Shah et al¹¹¹ in 2019, 10.6% (34/320) had elevated CPK-MB. In a study by Sidappa FD et al⁹³, CPK-MB was found to be raised in 2 (5%) patients out of 39 patients. Significant correlation was found in our study (p < 0.00001) between increased severity of dengue and elevated biomarkers.

Cardiac MRI was performed in clinically suspected cases of myocarditis having increased CPK-MB and Troponin I (Table 14). There were 9 patients having increased cardiac markers, 5 had increased CPK-MB, 2 had increased Troponin I and 2 had both CPK-MB & Troponin I raised. Myocarditis was confirmed in 3 patients based on Cardiac MRI findings. All these patients belonged to severe dengue, making the incidence of myocarditis in severe dengue 33.3% (3/9) and overall incidence 3.19% (3/94). Thus a significant correlation (p value < 0.00001*) was found in our study between occurrence of myocarditis in severe dengue.

CONCLUSION

Dengue is a major public health problem not only in Rajasthan or India but all over the world. Over the last few years, we have been observing varied clinical manifestations of dengue in addition to the classic WHO defined DF, DHF and DSS. Cardiac manifestations are one of them and most of the times they are asymptomatic. A wide range of cardiac manifestations were observed in our study. Bradycardia, Tachycardia, ECG changes like low voltage QRS, ST elevation and T wave inversion, pericardial effusion, left ventricular ejection fraction less than 50% were among the common manifestations.

It is difficult to easily differentiate cardiac manifestations in dengue because of overlapping signs and symptoms. But persistent shock despite adequate fluid resuscitation can be an important presentation of cardiac involvement and this should guide the treating physician to look for cardiac involvement such as diastolic and systolic dysfunction. Early detection of cardiac manifestations in dengue fever with appropriate intervention may change the outcome with better prognosis.

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