www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i11.102

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Cardiac Manifestation involvement in Dengue Infection

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Abstract
Background and Objectives: *Dengue is endemic in the tropics, and complications involving organ systems are seen with varying incidence.*
The present study was conducted to find out the proportion of dengue fever cases with cardiac involvement.
Materials and Methods: *This is a descriptive study. 211 successive dengue fever cases were selected for the study. Appropriate investigations were done.*
Results: *It was found that a significant number of patients of dengue developed asymptomatic involvement of heart as evidenced by electrocardiography changes, raised cardiac enzymes.*
Conclusion: *Myocardial involvement in most of the cases was found to be subclinical on 2-D echo.*
Keywords: *Dengue, Myocardial Involvement.*

Background and Objectives

Introduction

Dengue is one of the most important mosquito-borne illnesses worldwide[1]. It is a caused by a flavivirus with four distinct serotypes (DENV1, DENV2, DENV3, and DENV4). Current estimates project that 390 million infections occur annually, in over 100 countries, of which 96 million result in clinical disease with a case fatality rate of around 1% [2]. Infection with one of the serotypes is thought to result in lifelong serotype-specific immunity. Serious disease is thought to occur mainly, though not exclusively, as a result of a second infection by a different serotype[3]. The mechanisms that result in the development of the severe, life-threatening dengue shock syndrome remain an enigma. The primary pathophysiological phenomenon of the disease that occurs is acute vascular leakage, which lasts for 24–48 hours after its onset.

Despite being traditionally considered a disease of children, dengue is now known to affect individuals of any age, and results in significant economic impact. Dengue infection is difficult to control; no specific treatment or vaccine is available, and vector control is fraught with difficulties. There is no specific treatment for dengue [4].

The natural history of dengue infection usually follows a clear pattern. The majority of infections are asymptomatic and subclinical. Symptomatic disease follows an incubation period of four to seven days, and begins as an acute febrile illness with high temperature, malaise, retro-orbital

headache, myalgia, backache, nausea, loss of appetite, and vomiting[5]. For management purposes, clinical illness is divided into three phases: the febrile phase, the critical phase, and the recovery phase. Around the third to seventh day of illness, the critical phase, which is associated with a dropping platelet count, recovery of leukopenia, and defervescence, may begin. The critical phase is defined by the occurrence of features of plasma leakage: rising hematocrit, clinical or radiological evidence of third-space fluid leakage, and, in some cases, hypotension.

A proportion of patients develop severe clinical shock, of which a minority proceed to develop relentless severe intractable shock, coagulopathy with bleeding, and multi-organ failure, which can culminate in death[6]. As the incidence of dengue increases, reports of atypical manifestations are also on the rise, although these may be underreported because of lack of awareness and under-diagnosis of dengue[7]. The incidence of various complications, in both serologically diagnosed patients and those with merely a clinical diagnosis without supporting serology, is quite similar[8]. A variety of atypical manifestations of dengue have been described [7]. In one study of 913 schoolchildren with dengue, a wide variety of complications were observed: hepatitis (27%), neurological alterations (25%), renal impairment (7%), cardiac involvement (8%), pulmonary changes (9%), acalculous cholecystitis (9%), hemophagocytic syndrome (2.5%), pancreatitis (1%), and acute abdominal pain (11%) [9].

Cardiac involvement is not uncommon and is encountered in centers handling large numbers of dengue cases. Clinical manifestations of cardiac involvement can vary widely, from silent disease to severe myocarditis resulting in death. Rhythm abnormalities, hypotension, arrhythmias, myocarditis, myocardial depression with symptoms of heart failure and shock, and pericarditis have been reported. Involvement of multiple organs as well as the presence of metabolic derangement can further confuse the picture[10,11]. Still, the significance of cardiac involvement in dengue infection is not fully understood. Myocarditis, pericarditis, and cardiomyopathy after dengue have been reported in the literature from the 1970s [12-15]. During outbreaks, incidence of myocarditis as high as 13% has been reported; electrocardiographic changes have been noted in up to 62.5% of patients [16-17].

The purpose of this study was to assess whether there is any form of cardiac involvement (Clinical or subclinical) in dengue and DHF, because most of our dengue patients had raised cardiac markers.

Aims & Objectives

To find out the proportion of Dengue Fever cases with cardiac involvement.

Materials & Methods

This study was conducted in the Rajarajeshwari Medical College & Hospital, Mysore road, Bangaluru. It was a hospital based observational descriptive study and was carried out from April 2017 to September 2017. 211 eligible dengue fever cases fulfilling inclusion criteria were included basis after beginning of the study.

Inclusion Criteria

- Both primary dengue (NS-1 antigen or IgM or both positive) and secondary (NS-1 antigen or IgM and IgG antibody positive) dengue cases were included.

Exclusion Criteria

- All patients with fever who are Dengue IgM/NS1 Ag negative.
- Patients who had any known cardiac disease, chronic kidney disease, diabetes mellitus, hypertension were excluded.

The following parameters were considered and/or measured in all patients: Age, gender, blood pressure, routine blood inv., NS-1 antigen, IgM and IgG antibody, CK-MB, ECG, Trop-T, 2-D echo. Inferences were drawn with use of appropriate test of significance. The categorical data were presented as numbers (percent) and

were compared among groups using Chi square test. Groups were compared for demographic data, were presented as mean and standard deviation and were compared using by students t-test. Probability P value <0.05 was considered statistically significant.

Results

Table 1 Age Wise Distribution of Cases

Age (Yrs)	No. Of Cases	Percentage %
<20	43	20.37
21-29	71	33.64
30-39	49	23.22
40-49	18	8.53
50-59	18	8.53
>59	12	5.68

Table 2 Gender Wise Distribution of Cases

Gender	No. of Cases	Percentage %
Male	110	52.13
Female	101	47.87

Table 3 Geographical Distribution of Cases

Address	Cases	Percentage%
Ramnagar	97	46
Channpatna	54	26
Bidadi	30	14
Kumbalgowdu	16	8
Kambipur	09	4
Kangeri	05	2

Table 4 ECG changes

ECG changes	No.of Patients	Percentage
With in normal limit	154	72.98
Involved	57	27.01
Generalized T wave inversion	06	10.52
Sinus bradycardia	18	31.57
Sinus tachycardia	14	24.56
ST depression in V1-V6	6	10.52
ST depression in V1-V4	6	10.52
T wave inversion in V2-V5	4	7.01
T wave inversion in V2-V5	8	14.03
Generalised ST elevation	1	1.75
Low voltage	7	12.28
ST-T changes in V2-V5	4	7.01
ST-T changes in V3-V6	4	7.01
T wave inversion in lead 2,3	6	10.52

Table 5 Dengue Cases According to CKMB with Cardiac Involvement

CK-MB (U/L)	No. of Patients	Mean	Std. Deviation	P value LS
Normal	132	22.05	0.32	<0.0001S
Elevated	79	94.62	5.64	<0.0001S

Table 6 Distribution of Dengue Cases According to Abnormal Troponin T test with Cardiac Involvement

Troponin T test	No of cases	Percentage
Positive	12	5.68
Negative	199	94.32
Total	211	100

Table 7 Echo Finding with Cardiac Involvement

Echo Finding	No. of Patients	Percentages
Global hypokinesia, LVEF-50%	2	3.50
Grade 1 diastolic dysfunction	2	3.50
LV systolic dysfunction, EF-49%	2	3.50
Mild MR, trivial TR	2	3.50
Mild pericardial; effusion	10	17.54
Severe LV dysfunction	2	3.50
RA,RV dilated, RV hypokinesia	2	3.50
Grade 1 LVDD, EF-53%	2	3.50
Lt. Ventrivular hypokinesia LVEF-45%	2	3.50
Severe TR,Mild MR, LVEF-46%	2	3.50

Table 8 Assessment of Cardiac Involvement via Various Investigation Modalities

Finding	No. of cases	Percentage
Abnormal CK-MB(U/L)	79	37.4
Abnormal ECG	57	27.01
Abnormal Echo findings	18	8.53
Abnormal Troponin T	12	5.68

Table 9 Distribution of Dengue Cases According to Cardiac Involvement

Cardiac Involvement	No. of cases	Percentage
Present	57	27.01
Absent	154	72.99
Total	211	100

In our study, maximum patients were within 20 to 39 years of age group. Out of 211 patients, most were male. (Table1,2)

Out of 211 dengue patients, abnormal ECG findings were in 57 patients, most common ECG

finding was sinus bradycardia in 18 patients (31.57%), next was sinus tachycardia in 14 patients (24.56%) and T-wave inversion in V1-V4 and V2-V5 was in 8 and 4 patients respectively. ST depression in V1-V4 and V1-V6 was in 6patients each, generalised T inversion in 6 patients and low voltage in 7 patients, ST-T changes in V2-V5 and V3-V6 both were in 4 patients each, generalised ST elevation in 1 patient and T wave inversion in lead 2, 3 were in 6 patients. (Table 4). Among these 57 patients, abnormal echo finding was present in 18 patients (31.57%). The most common finding was mild pericardial effusion in 10 patients (17.54%). (Table 7).

Among these 211 patients, the mean Value of CK-MB (U/L) was significantly higher in the cases with cardiac involvement as compared to normal which was statistically significant (P<0.0001S) (Table 5).

Out of 211 patients, 12 patients (5.68%) were troponin T positive and 199 (94.32%) were troponin T Negative (Table 6).

Out of 211 patients, 79 patients (37.4%) had elevated CK-MB and 57 patients (27.01%) had abnormal ECG findings, and 18 patients (8.53%) had abnormal 2-D echo and abnormal Troponin T seen in 12 patients (5.68%) . (Table 8).

Out of 211 patients, 57patients (27.01%) had cardiac involvement and 154 patients (72.99) did not have cardiac involvement. (Table 9).

Discussion

Dengue fever is known to affect several systems in the human body. As in any viral myocarditis, only a portion of the patients (8.65%) had 2-D echocardiographic evidence of myocarditis. 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.

Clinical features, electrocardiographic abnormal-ities, abnormal cardiac biomarkers, and echocardiographic findings have been evaluated in various studies as possible markers of cardiac involvement in dengue.

In the present study, a total of 211 patients of Dengue fever were analyzed. The most common age group affected in our study was 20-39 years (53%).

Table 10

SI.No.	Author	Year	Place	Age (yrs)
1.	Baruah J	2002	MANIPAL	5-20
2.	Dash PK et al	2003	Gwalior	<15
3.	Neeraja M	2004	Hyderabad	20-39
4.	Present study	2017	RRMCH, Mysore road	20-39

This is comparable to the study done by Neeraja et al in 2004, in Hyderabad.[18]

The mean age in the present study is 30.45 years. This is comparable to the study done by Gupta et al (30.15 years) in 2008, in New Delhi.[19] In our study, the incidence among males and females is almost equal. This is comparable to the study done by Dash P K et al in 2003, in Gwalior. [20]

Table 11

SI.No.	Author	Year	Place	M:F Ratio
1.	Dash PK et al	2003	Gwalior	1.28:1
2.	Neeraja M	2004	Hyderabad	2:1
3.	Gupta et al	2008	New Delhi	1.8:1
4.	Present study	2017	RRMCH, Mysore road	1.08:1

Amongst the cases in our study, 46% cases were from Ramnagara, 26% cases were from Channpatna, 14% cases from Bidadi, 8% cases from Kumbalgowdu, 4% from Kambipura & 2% case from Kangeri

In present study, above findings also observed for cardiac involvement in dengue. The presence of electrocardiogram (ECG) abnormalities has been used by some authors to denote cardiac involvement in dengue.[21] A diverse range of ECG abnormalities have been reported with dengue, including rate and rhythm abnormalities, heart block, wave form abnormalities, and voltage abnormalities.[22-33]

Reported rhythm abnormalities include relative bradycardia,[23] sinoatrial block,[24] disorders of

atrioventricular conduction (Junctional rhythm),[24,25] second-degree[26] and complete heart block,[22,27] and monomorphic premature ventricular contractions on a background of heart block,[26] atrial flutter,[28] transient[22,29] and persistent[30] atrial fibrillation, self-limiting tachy-brady arrhythmia,[34] sinoatrial block, and uniform ventricular ectopics progressing to ventricular bigeminy.[31] Electrocardiographic features mimicking acute myocardial infarction have also been reported.[33] ECG abnormalities may go undetected or asymptomatic.

Cardiac arrhythmias are other clinical manifest-ations of myocarditis. Various arrhythmias have been described during dengue virus infection such as atrial fibrillation, ventricular tachycardia and even atrioventricular blocks. These arrhythmias are associated to syncope and even sudden death. [35-37]

In present study, out of 211 dengue patients, abnormal ECG findings were in 57 patients (27.01%), most common ECG finding was sinus bradycardia in 18 patients (31.57%), next was sinus tachycardia in 14 patients (24.56%), and T wave inversion in V1-V4 and V2-V5 was in 4 and 2 patients respectively. ST depression in V1-V4 and V1-V6 was in 6 patients each, generalised T inversion in 6 patients and low voltage in 7 patient, ST-T changes in V2-V5 and V3-V6 both were in 4 patients each, generalised ST elevation in 1 patient and T wave inversion in lead 2, 3 were in 6 patient. Sinus bradycardia (Nimmannitiya S. et al) [36] was the most conspicuous ECG finding with dengue fever but heart rate not useful.

Clinical manifestations suggesting cardiac involvement in dengue are diverse and include chest pain, palpitations, pleurisy, irregularities of pulse, bradycardia, hypotension, pulmonary oedema, and features of shock.[38,34]

It is known that tachycardia and hypotension is more frequently seen in DSS (Ranjit S et al).[37] Also in our study 5 patients had hypotension and 11 patients had tachycardia, that is more common in DSS/DHF. Thus, although this study provides some evidence that patients with ECG changes were more likely to develop hypotension and tachycardia or bradycardia, it does not provide convincing evidence that cardiac involvement was present.

In present study out of 211 dengue patients, we observed elevated CK-MB in 79 (37.4%), troponin T test was positive in 12 (5.68%) patients. Myocardial involvement was subclinical as 2-D echo was normal in 17 patients (60.71%). Possible cause of raised cardiac enzymes in these patients is subclinical myocarditis.

Cardiac biomarkers may indicate the presence of cardiac involvement in dengue. A prospective study in Sri Lanka (Wichmann, et al)[39] evaluated several cardiac biomarkers (myoglobin, CK-MB, Troponin T, NT- pro-brain natriuretic peptide, heart-type fatty acid-binding protein), in patients. with dengue 25% of patients had abnormal results in one or more biomarkers. However, the correlation between biomarkers and cardiac function has not been clearly demonstrated.

A study (Gupta V K et al) [19] was conducted in New Delhi for estimating cardiac enzymes in 28 patients of Dengue fever. Estimation of cardiac enzymes was done in all patients. 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%). Myocardial involvement was subclinical as 2-D echo was normal in 23 patients (82%). Possible cause of raised cardiac enzymes in these patients was subclinical myocarditis.

Out of 211 dengue patients, the cardiac involvement was in 57 patients. Among these 57 patients, abnormal echo finding was present in 18 patients (31.55%). The most common finding was mild pericardial effusion in 10 patients (17.54%).

Echocardiographic evidence of myocardial involvement in dengue has been clearly demonstrated.[40,41,42]

In a study of 91 children with dengue, LVEF <50% was observed in 6.7%, 13.8%, and 36% of patients with DF, DHF, and DSS, respectively.

Similarly, in our study LVEF<50% was observed in 3.50%, 3.50% and 7% of patients with DF, DHF, and DSS, respectively.

In another study of 54 children under 12 years of age, LVEF was reduced (< 50%) in nine cases, and two had LVEF below 35% (Kabra SK, et al) [43]

Satarasinghe et al[40] demonstrated echocardiographic evidence of myocarditis in 24% of patients with dengue, cardiac dilatation, the most commonly demonstrated echocardiographic evidence of myocarditis, more commonly affected - the right ventricle (57%), and associated with tricuspid regurgitation. Left ventricular dilatation was seen in 21% of patients, and biventricular dilatation in 16%.

In our study, we also observed that right ventricle dilation (7%) was more common and it was associated with tricuspid regurgitation. Left ventricular dilatation was seen in 3.50% of patients.

Sengupta et al [44] also demonstrated similar evidence of myocarditis in patients with dengue, and suggest that two-dimensional (2-D) speckle tracking echocardiography may be a more sensitive tool for the detection of early and subtle myocarditis.

Cardiac magnetic resonance (CMR) imaging, where available, may be of value in confirming the diagnosis of myocarditis, with a positive predictive value of 95% if at least two of the three diagnostic criteria are present.

Conclusion

Dengue is a serious problem in the tropics. Cardiac involvement is worrisome for both the clinician and patient. A significant number of patients of dengue developed asymptomatic involvement of heart as evidenced by electrocardiography changes, raised cardiac enzymes (CPK-MB, S. trop. T, LDH and SGOT). Myocardial involvement was subclinical as 2-D echo was normal in 34 patients (60%). Possible cause of raised cardiac enzymes in these patients is subclinical myocarditis. Asymptomatic myocarditis appears to be common in dengue, and spontaneous uneventful recovery is the norm.

Sinus bradycardia was the most conspicuous ECG finding; however, an echocardiogram is the gold standard for diagnosing myocardial involvement.

Further studies are needed to evaluate the hemodynamic impact of myocardial involvement in patients with severe dengue. Most forms of treatment currently are purely supportive, but with better understanding of the pathophysiology of dengue, targeted treatment may become possible.

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