Research Article

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A Study of Cardiac Involvement in 200 Cases of Dengue Fever

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ABSTRACT

Objective: *This study was done to find out the prevalence of cardiac involvement in dengue fever in patients presented to our hospital and to find out the correlation of cardiac manifestations to warning signs and severe dengue hemorrhagic fever/dengue shock syndrome. (DHF/DSS).*

Methods: *The one year descriptive study was undertaken at Shanti Infectious diseases clinic and Metro Hospital and Research Institute in Vadodara (Gujarat state) India. Two hundred patients aged 14 years or more with positive dengue serology were interviewed and examined. E.C.G was done for all patients and selected patients underwent Echocardiography evaluation. The data was analyzed using statistical significance test.*

Results: *In present study 116 (58%) had warning signs and remaining 84 (42%) patients were not having warning signs. 46 patients had one warning sign and remaining 70 patients had more than 1 warning signs. 71 (35.5%) patients were having severe dengue shock syndrome (DSS). Most common warning sign was abdominal pain (52%) and persistent vomiting (45%) while hepatomegaly was the least common warning sign. The minimum pulse rate was 34 beats/minute. The most common cardiac abnormalities noted in ECG were rhythm abnormalities of which the commonest was sinus bradycardia found in 66 (33%) patients and 45 (22.5%) patients with AV block,19 cases (9.5%) with ventricular ectopic and 22 (11%) were having sinus tachycardia. Echocardiography was in selective cases showed ECG abnormality, the mean ejection fraction was 47.05 (3.8%). In 71 patients with dengue shock syndrome the mean ejection fraction was 39.63%, 57 (28.5%) patients had myocarditis with ejection fraction below 35% and global hypokinesia. Echocardiography was repeated in these 71 patients after treatment and 3 weeks of follow up and ejection fraction was 50%& global hypokinesia was also improved and ECG changes reverted to normal after 3 weeks follow up. Thus acute reversible cardiac insult was observed in dengue shock syndrome in 71 (35.5%) patients and it could be responsible for hypotension/ shock seen in these cases. Further studies are required to establish pathogenic mechanism of cardiac dysfunction in dengue shock syndrome. There was statistically significant correlation between cardiac manifestations and all warning sign except persistent vomiting. 71 (35.5%) patients with dengue shock syndrome were having mucosal bleed, fluid accumulation, respiratory distress, bradycardia with hypotension was found to have significant correlation with cardiac manifestations. Cardiac manifestation in the form of myocarditis was observed in 57 (28.5%) patients with positive correlation with severity of dengue fever defined as by W.H.O criteria.*

Conclusions: *The most common cardiac manifestation noted wee transient rhythm abnormalities of which sinus bradycardia was seen in 66 (33%) patients, 45 (22.5%) patients had AV block and 71 Patients (35.5%) were having Dengue hemorrhagic fever/ dengue shock syndrome of which 47 (35.5%) patients had myocarditis. Patients with dengue fever are at high risk of developing myocarditis and rhythm disturbance and therefore require close monitoring.*

Keywords
Dengue fever, Infectious diseases, Mosquitoes.

Introduction

Dengue fever is an acute febrile infectious disease, caused by any of four serotypes (1, 2, 3 or 4) of a virus from genus flavivirus called dengue virus. The highest incidence of dengue is seen in South East Asia, India and American tropics. Infection with one serotypes does not protect against the others and sequential infections put people at greater risk of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [1].

Dengue is transmitted between people by mosquitoes Aedes Aegyptus and Aedes albopictus which are found throughout the world. Insects that transmit disease are vectors. Symptoms of infection usually begin 4 to 8 days after the mosquito bite and typically last 3 to 10 days. In order for transmission to occur the mosquito must feed on a person during a 5 day period when a large amount of virus is in the blood; this period usually begins before the person become symptomatic. Some people never have significant symptoms but can still infect mosquitoes. After entering the mosquito in the blood meal, the virus will require an additional 8-to 12 days incubation before it can then be transmitted to another human. The mosquito's remains infected for remainder of its life, which might be days or few weeks. In many parts of the tropics and subtropics, dengue is endemic, that is, it occur every year, usually during a season when Aedes mosquito population are high, often when rainfall is optional for breeding. These areas are however additionally at periodic risk for epidemic dengue, when large number of people becomes infected during a short period. Dengue epidemics require a coincidence of large number of vector mosquitoes, large numbers of people with no immunity to one of the four virus sero types (DEN V1, DEN V2, DEN V3, and DEN V4) and the opportunity for contact between the two. Today about 2.5 billion people or 40% of world's population, live in areas where there is a risk of dengue transmission. Dengue is endemic in at least 100 counties in Asia the Pacific, the America, Africa and the Caribbean.

The World health Organization (WHO) estimated that 50 to 100 million dengue infections occur in the world including 500,000 DHF and 22,000 deaths mostly among children [2]. Dengue is endemic in most of the tropical & subtropical countries. Dengue viral infection has emerged as most important arboviral disease in India, Malaysia, Indonesia and other countries of South East Asia and Africa. India have recorded increasing incidence in recent years. Dengue viral infection was first reported in India from Chennai in 1780. Today dengue viral infection is documented in almost all parts of India. During 1996, one of the most severe outbreaks DF/DHF occurred in Delhi with 10, 252 cases and 423 deaths being reported. In 2006 the country witnessed an outbreak of DF/DHF with 12,317 cases & 185 deaths. The incidence of dengue is increasing in last few years. During 2010 a total of 28,292 cases were reported which increased to 50,222 in 2012 and 75808 in 2013 the highest since 1991 [3,4]. The case fatality ratio (CFR deaths per 100 cases.) has declined from3.35 in 1996 to 0.4% in 2010 after national guidelines on clinical management of DF/DHF. Dengue shock syndrome (DSS) were developed and circulated in 2007 [5]. Overall mortality rate at an expected center in tropics is probably as low as 1%.

With rising disease burden, a typical manifestation causing metabolic syndrome have increased as well which are missed most often due to lack of awareness. Our aim of study was to look for cardiac manifestations of dengue fever. A small percentage of persons who have previously been infected by one of dengue sero types develop bleeding and endothelial leak upon infection with another serotype. This syndrome is termed as dengue hemorrhagic fever (DHF). Some patients of dengue hemorrhagic fever develop shock (Dengue shock syndrome (DSS) which may cause death. Severe dengue infection may give rise to many complications such as liver failure, disseminated intravascular coagulation (DIC), encephalopathy, myocarditis, and acute renal failure & hemolytic renal syndrome. Although these complications are generally rare in recent years they have been reported with increasing frequency. Although shock in DHF/DSS has been attributed largely to decreased intravascular volume due to plasma leakage into interstitial spaces, a few recent studies have reported that it may be due to cardiac involvement. Cardiac manifestations in dengue virus infection can range from asymptomatic bradycardia to life threatening myocarditis [6]. Various studies have quoted several cardiac manifestations of dengue infection like sinus bradycardia, transient Av blocks, transient ventricular arrhythmias and pericardial effusion [7,8].

The purpose of this study was to determine the presence of Electrocardiographic (ECG) changes in patients presenting with dengue infection and to see whether there were any related clinical cardiac manifestations and their possible associations with in-hospital and mortality.

Objectives of the Study

- To study the prevalence of cardiac manifestations of dengue fever in patients presented to our hospital.
- To evaluate whether there were any related clinical cardiac manifestations and their possible association with in-hospital morbidity and mortality.
- To study the Electrocardiographic (ECG) changes in patients presenting with dengue infection.
- To find out the Correlation of cardiac manifestation's to warning signs of dengue fever.

Patients & Method

This was observational study and was undertaken at Shanti Infectious diseases clinic & department of medicine, Metro hospital & research institute which is tertiary care hospital in Vadodara of south Gujarat India from June 2015 to December 2015. Two hundred patients aged 14 years or more with positive dengue serology (ELISA confirmed IGM dengue seropositive cases were satisfying WHO criteria) were admitted in medical wards in Metro hospital & research institute Vadodara. All 200 cases were interviewed and examined in detail. ECG was done

for all patients and selected patients underwent Echocardiography evaluation and troponin testing.

Inclusion criteria

- Age group of >14 years.
- Fulfilling the WHO criteria for dengue.
- Confirmed dengue serology.

Exclusion criteria

- Patients on medications affecting the heart rate/rhythm.
- Patients with history of pre-existing heart disease.
- Patients with electrolyte abnormality affecting the heart rate and rhythm.

Study protocol

Baseline clinical characteristics including age, sex, socio-demographic data, diabetes mellitus, and hypertension, history of coronary artery diseases, any other chronic illness and smoking history were obtained. The diagnosis of dengue fever was done on WHO criteria (Table 1).

WHO case definition of dengue fever
Clinical features of DF
An acute febrile illness of 2-7 days duration with two or more of the following manifestations: Headache, retro-orbital pain, myalgia, arthralgia, rash, or hemorrhagic manifestations
Dengue haemorrhagic fever (DHF)
a). A case with clinical criteria of dengue Fever plus b). Hemorrhagic tendencies evidenced by one or more of the following 1. Positive tourniquet test 2. Petechial, ecchymosis or purpura 3. Bleeding from mucosa, gastrointestinal tract, injection sites or other sites Plus c). Thrombocytopenia (<100 000 cells per cumm) plus d). Evidence of plasma leakage due to increased vascular permeability, manifested by one or more of the following: 1. A rise in average hematocrit for age and sex >20% 2. A more than 20% drop in hematocrit following volume replacement treatment compared to baseline 3. Signs of plasma leakage (pleural effusion, ascites, hypoproteinemia) <20%
Dengue shock syndrome (DSS)
All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure (<20 mm Hg) or hypotension for age, cold and clammy skin and restlessness
Case definition
Probable DF/DHF
A case compatible with clinical description of dengue Fever during outbreak. OR Non-ELISA based NS1 antigen/ IgM positive. (A positive test by RDT will be considered as probable due to poor sensitivity and Specificity of currently available RDTs.)
Confirmed dengue Fever
A case compatible with the clinical description of dengue fever with at least one of the following Isolation of the dengue virus (Virus culture +VE) from serum, plasma, leucocytes. Demonstration of IgM antibody titre by ELISA positive in single serum sample. Demonstration of dengue virus antigen in serum sample by NS1-ELISA. IgG seroconversion in paired sera after 2 weeks with Four fold increase of IgG titre. Detection of viral nucleic acid by polymerase chain reaction (PCR).

Table 1: WHO case definition of dengue fever.

Occurrence of symptoms like fever, bleeding and abdominal pain were noted. Cardiac symptoms like chest pain, dyspnea and palpitations were identified. Blood samples were collected for plasma glucose, complete blood count including haematocrit, liver and renal function test, serum electrolytes including calcium magnesium. E.C.G was done in all 200 cases. 2D Echo cardiac enzymes (CPK, troponin T) chest radiographs and ultrasound were performed in patients suspected to have DHF.

All patients received standard medical treatment on the basis of current standards of case recommended by published guidelines; patients were followed during admission by daily vital monitoring, pulse, B.P measurement, and evidence of fluid leak in the form of pleural effusion or ascitis and intake output monitoring.

Study End Points

The primary end point of study was death of patient during hospitalization. In-hospital major adverse clinical events e.g. major bleeding (requiring blood transfusion for severe thrombocytopenia platelets count< 20,000 micro liter) acute pulmonary edema, clinically significant tachyarrhythmia's and acute kidney injury were evaluated as secondary end points.

Statistical Analysis

In this study the chi square test (X2 test) for independent samples was used for data analysis. With data presented as mean + SD unless o was applied otherwise specified. Pearson's Co-relation was applied and P value <0.05 considered significant.

Result

A total of 200 dengue fever patients were studied. Table 2 shows baseline clinical characteristics of dengue patients. Mean age was 28.2+_ 10 years, a youngest patient was 14 years and oldest was 55 years old. There were 128 males and 72 females. In the study group 180 patients presented within 1st and 2nd week and 20 patients presented in third week of onset of symptoms. Tourniquet test was positive in all patients included in this study. No patient died in present study.

Character		**Number of Patients**	**Percentage**
Age Range (Years)	14-28	58	29%
	28-46	90	45%
	47-60	52	26%
Sex	Males	128	64%
	Females	72	36%

Table 2: Baseline clinical characteristics of dengue patients (Number= 200).

Clinical presentation in this study includes fever (96%), Headache (70%), Restlessness (30%), Abdominal pain (52%), Vomiting (45%), Petechiae rashes (35.5%), Hematuria (5%), haemetmasis (7%) Shock (35.5), Altered sensorium (10%), minimum platelet count in this study was 7000 cmm, severe hepatic derangement (SGPT >1000) was not detected in this study, highest SGOT/ SGPT was 260/350 in this study.

Warning signs & symptoms includes respiratory distress, ARDS, severe abdominal pain, excessive vomiting, altered sensorium, confusion, lethargy, restlessness, rapid and thready pulse, hypotension, mucosal bleed, hepatomegaly, fluid accumulation, shock, narrowing pulse pressure less than 20 mmHg and laboratory evidence of thrombocytopenia/coagulopathy, rising HCT and some cases with metabolic acidosis.

Table 3 shows warning signs of dengue in present study 116 (58%) had warning signs and remaining 84 (42%) patients were not having warning signs. 46 patients had one warning sign and remaining 70 patients had more than 1 warning signs. 71 (35.5%) patients were having severe dengue shock syndrome (DSS). Most common warning sign was abdominal pain (52%) and persistent vomiting (45%) while hepatomegaly was the least common warning sign.

Sr No	Warning Signs	Number of Patient (n=200)	Percentage
1	Persistent vomiting	90	45%
2	Abdominal pain	104	52%
3	Mucosal bleed	70	35%
4	Fluid accumulation	50	25%
5	Lethargy/restlessness	60	30%
6	Hepatomegaly>2CM	24	12%
7	Shock	71	35.5%
8	Respiratory distress	40	20%
9	ARDS	35	17.5%

Table 3: Warning signs of dengue fever.

Table 4 shows ECG changes in dengue patients in our study. Sinus bradycardia was the most common ECG finding in present study and some cases showed First degree AV block and ventricular ectopic.

Sr No	Ecg Changes	Number of Patients (n=200)	Percentage
1	Sinus rhythm	48	24%
2	Sinus bradycardia	66	33%
3	Sinus tachycardia	22	11%
4	First degree AV block	45	22.5%
5	Ventricular ectopic	19	9.5%

Table 4: Electrographic (ECG) changes in dengue patients.

Table 5 shows the correlation between warning sign and ECG changes in dengue patients. There was statistically significant correlation between ECG abnormalities and all warning signs except lethargy/restlessness & hepatomegaly (P value <0.5).

Sr No	Warning Signs	ECG Abnormality		P value
		Yes	No	
1	Persistent vomiting	52	38	0.00035
2	Abdominal pain	68	36	0.0987
3	Mucosal bleed	50	20	0.8327
4	Fluid accumulation	40	10	00889
5	Lethargy/restlessness	36	24	0.03304
6	Hepatomegaly>2cm	10	14	0.0009
7	Shock	59	12	0.0037
8	Respiratory distress	30	10	0.4853
9	ARDS	20	15	0.0564

Table 5: Correlation of warning signs to ECG abnormality.

Discussion

Many infectious diseases cause relative bradycardia, such as typhoid fever, Chlamydia pneumoniae and legionnaire's disease. Various viral infections cause myocardial damage either by invasion or an autoimmune reaction resulting in myocardial inflammation. The cardiac abnormalities in dengue are invariably benign, transient self-limited and attributed to subclinical viral myocarditis. Cardiac manifestation's in dengue fever ranges from asymptomatic bradycardia to severe myocarditis. Various ECG abnormality (sinus bradycardia, prolongation of PR interval, transient AV block, and transient ventricular arrhythmia.), myocarditis, systolic and diastolic dysfunction and pericardial effusion have been observed during acute phase of viral dengue infection [6,7].

Rhythm disturbance such as sinus bradycardia and ventricular ectopic, have also been reported during a convalescence period of dengue fever [8]. Mean age group of present study is 28.2 years youngest was 14 years and oldest was 55 years and age group that is mostly affected in other studies like Gupta E et al. New Delhi was 5 to 20 years, Dash PK et al. Gwalior was <15 years and Neeraja M in Hyderabad was 20-39 years. In this study most of patients are males (128) in comparison to females (72) and ratio is 1.77: 1. In other studies like Dash PK et al. Gwalior male female ratio was1.28:1, Gupta E et al. was 1.8:1, Neeraja M, et al. Hyderabad was 2:1. It may be due to because of male dominated region where male seeks more medical help in comparison to females [9-11].

Most common warning sign in this study was abdominal pain 54% and vomiting 45%.In the study by Thien S et al. with persistent vomiting was noted in 39% and it was most common warning sign [12]. Hepatomegaly was least common warning sign in present study and seen only in 12% of cases. In this study 35.5% were cases of Dengue shock syndrome (DSS), 20% had respiratory distress. Severe hepatic derangement (SGPT>1000) was not detected in this study. Highest SGPT/SGOT was 260/350 in this study. In the study of Thein, Leo et al. 4% had renal impairment and maximum creatinine was 2.1/dl and 4 patients had ARDS [13].

In this study 66 cases (33%) showed sinus bradycardia, 22 cases (11%) has sinus tachycardia, 48 cases (24%) had sinus rhythm. First degree hear block was seen in 45 (22.5%) cases and ventricular ectopic in 30 cases (15%), While in other studies Gupta V et al. showed 18% bradycardia, 64% relative bradycardia and 14% sinus tachycardia [14]. Mean pulse rate in this study was 51 beats per minute, minimum pulse rate was 34 beats/per minute, maximum pulse rate was 125 beats per minute. In the study by Lateef A, et al., mean heart rate was 87/minute, the commonest rhythm abnormality was sinus bradycardia32% of cases [15]. Echocardiography was

done in 71 cases of Dengue shock syndrome which revealed 57 cases 28.5% had myocarditis and all these cases of myocarditis ejection fraction was below 35%. All 57 cases of myocarditis showed global hypokinesia in echocardiography. After treatment 12 weeks follow up echocardiography was repeated in 57 cases and there was marked improvement 50% Ejection fraction which indicated reversible cardiac insult.

In the study by Gupta V, et al. sinus bradycardia was found in 14.28% cases and sinus tachycardia in 21.4% cases. AV dissociation was observed in one patient which were resolved in 24 hours, Kaushik JS et al. have described AV dissociation and SA exit block in child from dengue fever [16]. Table 5 shows correlation between warning signs and ECG changes. There was statistically significant correlation between ECG abnormalities and all warning signs except lethargy/restlessness and hepatomegaly (p value<0.05). Kabra SK, et al. found no correlation between myocardial involvement and clinical severity of dengue fever [17].

Obeyeserkere I, Hermon Y, have described cardiac involvement in dengue fever patient as evident by positive cardiac biomarkers association between warning signs and cardiac manifestation was significant [18].

Conclusion

Sinus bradycardia was predominant manifestation in dengue viral fever which was resolved spontaneously over period of 24 hours to 48 hours. First degree heart block and ventricular ectopic were other ECG abnormalities was observed in our study. 57 patients (28.5%) showed myocarditis with poor ejection fraction below 35% and global hypokinesia on echocardiography. 71 cases (35.5%) were having dengue shock syndrome (DSS).

In present study ECG abnormalities were common but all the ECG changes were reversible and no patient died in our study. There was statistically significant correlation between warning signs and ECG changes in dengue viral fever except lethargy/ restlessness and hepatomegaly.

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