

Original Research Article

To study cardiac manifestations in patients presenting with dengue infection and to find out the correlation of cardiac manifestations to warning signs of dengue

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Received: 08 March 2017

Accepted: 15 March 2017

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ABSTRACT

Background: This study was done to observe the presence of Electrocardiographic (ECG) changes in patients presenting with dengue infection and to evaluate whether there were any related clinical cardiac manifestations and to find out the correlation of cardiac manifestations to warning signs of dengue.

Methods: The study was conducted at MLN Medical College, Allahabad in the Department of Medicine between July 2016 to December 2016. One hundred consecutive patients aged 18 years or more with positive dengue serology were interviewed and examined. ECG was done for all patients. The data was analyzed using statistical significance tests.

Results: Thirty-six patients had no warning signs, 64 patients had warning signs, out of which 43 patients had two or more warning signs while 21 patients had single warning sign. Most common warning sign in this study was abdominal pain (50%) and Vomiting (45 %) while hepatomegaly was the least common warning sign. The most common cardiac abnormalities noted were rhythm abnormalities of which the commonest was sinus bradycardia, found in 60 percent. There was statistically significant correlation between cardiac manifestations and all the warning signs except lethargy/restlessness and hepatomegaly.

Conclusions: The most common cardiac manifestations noted were transient rhythm abnormalities, of which sinus bradycardia was the commonest. There was no evidence of myocarditis in any of the patients. There was statistically significant correlation between cardiac manifestations and all the warning signs except lethargy/restlessness and hepatomegaly.

Keywords: Cardiac abnormality, Dengue fever, Warning signs of dengue

INTRODUCTION

Dengue fever (DF) is caused by any of four closely related viruses, or serotypes: dengue 1-4. Infection with one serotype does not protect against the others, and sequential infections put people at greater risk for dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).¹

Dengue is transmitted between people by the mosquitoes *Aedes aegypti* and *Aedes albopictus*, which are found

throughout the world. Insects that transmit disease are vectors. Symptoms of infection usually begin 4 - 7 days after the mosquito bite and typically last 3 - 10 days. In order for transmission to occur the mosquito must feed on a person during a 5- day period when large amounts of virus are in the blood; this period usually begins a little 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 8-12 days incubation before it can then be transmitted to another

human. The mosquito remains infected for the remainder of its life, which might be days or a few weeks.

In many parts of the tropics and subtropics, dengue is endemic, that is, it occurs every year, usually during a season when *Aedes* mosquito populations are high, often when rainfall is optimal for breeding. These areas are, however, additionally at periodic risk for epidemic dengue, when large numbers of people become infected during a short period. Dengue epidemics require a coincidence of large numbers of vector mosquitoes, large numbers of people with no immunity to one of the four virus types (DENV 1, DENV 2, DENV 3, DENV 4), and the opportunity for contact between the two.

Today about 2.5 billion people, or 40% of the world's population, live in areas where there is a risk of dengue transmission. Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean. The World Health Organization (WHO) estimates that 50 to 100 million infections occur yearly, including 500,000 DHF cases and 22,000 deaths, mostly among children.²

Dengue viral infection has emerged as most important arboviral disease in India. Dengue is endemic in most of tropical and subtropical countries. India have recorded increasing incidence of dengue viral infections 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 of DF/DHF occurred in Delhi, with 10,252 cases and 423 deaths being reported (country total being 16,517 cases and 545 deaths). In 2006, the country witnessed an outbreak of DF/DHF with 12,317 cases and 184 deaths. The incidence of dengue is increasing in the last few years. During 2010, a total of 28,292 cases were reported, which increased to 50 222 in 2012 and 75 808 in 2013 – the highest since 1991.^{3,4} The case fatality ratio (CFR – deaths per 100 cases) has declined from 3.3% in 1996 to 0.4% in 2010 after the national guidelines on clinical management of DF/DHF/dengue shock syndrome (DSS) were developed and circulated in 2007.⁵ This further declined to 0.3% in 2013. Overall mortality rate at an experienced center in the tropics is probably as low as 1%.

With rising disease burden, atypical manifestations have increased as well which are missed most often due to lack of awareness. Our aim of the study was to look for the atypical manifestations of dengue fever. A small percentage of persons who have previously been infected by one dengue serotype develop bleeding and endothelial leak upon infection with another dengue serotype. This syndrome is termed dengue hemorrhagic fever (DHF). Some patients with dengue hemorrhagic fever develop shock (dengue shock syndrome [DSS]), which may cause death. Severe dengue infections may give rise to many complications such as liver failure, disseminated intravascular coagulation, encephalopathy, myocarditis,

acute renal failure, and hemolytic uremic 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 capillary leakage of plasma into the interstitial space, 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, myocarditis 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 association with in-hospital morbidity and mortality.

The present study was undertaken with the following aims

- To observe the presence of Electrocardiographic (ECG) changes in patients presenting with dengue infection.
- To evaluate whether there were any related clinical cardiac manifestations, and their possible association with in-hospital morbidity and mortality.
- To find out the correlation of cardiac manifestations to warning signs of dengue.

METHODS

This was an observational study. All consecutive patients of dengue fever admitted to the Department of Medicine, MLN Medical College, Allahabad between July 2016 to December 2016 were included in the study. 140 patients admitted with suspected dengue fever were selected for the study. Out of them, 124 ELISA confirmed IgM-dengue sero-positive cases were satisfying WHO criteria. Out of this 100 were selected after exclusion.

Inclusion criteria

- Age group of ≥ 18 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 abnormalities affecting the heart rate/rhythm

The local ethical committee approved the research.

Study protocol

A written informed consent was taken. Baseline clinical characteristics including age, sex, socio- demographic

data, diabetes mellitus, hypertension, history of coronary artery disease, any other chronic illness and smoking history were obtained. The diagnosis of dengue fever was based on WHO criteria for dengue fever (Table 1).

Table 1: WHO case definition of dengue fever.

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 haemorrhagic manifestations.
Dengue haemorrhagic fever (DHF)
a). A case with clinical criteria of dengue Fever plus
b). Haemorrhagic tendencies evidenced by one or more of the following
1. Positive tourniquet test
2. Petechiae, ecchymoses 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 haematocrit for age and sex $>20\%$
2. A more than 20% drop in haematocrit 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).

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 admission plasma glucose, complete blood count including hematocrit, liver and renal function tests, serum electrolytes including calcium and magnesium. ECG was done daily to monitor changes during illness. 2D-ECHO, cardiac enzymes (CPK-MB, TROPONIN-T, SGOT) and Chest radiograph and

ultrasound abdomen were performed in patients suspected to have DHF.

All patients received standard medical treatment on the basis of the current standards of care recommended by published guidelines. Patients were followed during admission by daily vitals monitoring, pulse pressure measurement, evidence of fluid leak in form of pleural effusion or ascites and intake output monitoring.

Study end points

The primary end point of the study was death of patient during hospitalization. In-hospital major adverse clinical events (MACEs) (major bleeding [requiring blood transfusion], severe thrombocytopenia [platelet counts <20,000/ microlitre], acute pulmonary edema [with or without the need for mechanical ventilation], clinically significant tachyarrhythmia's, and acute kidney injury) were evaluated as secondary end points.

Statistical analysis

In this study the chi square test (χ^2 test) for independent samples was used for data analysis, with data presented as mean \pm SD unless otherwise specified. Pearson's correlation was applied and P value <0.05 considered significant.

RESULTS

A total of 100 dengue fever patients were studied. Table 2 shows baseline clinical characteristics of dengue patients. Mean age was 29.3 \pm 12 years, a youngest patient was 18 years and oldest was 50 years old. There were 64 males and 36 females. In the study group 90 patients presented within 1st week and only 10 patients presented after one week of onset of symptoms. Tourniquet test was positive in all patients included in this study. No patient died in present study.

Table 2: Baseline clinical characteristics of dengue patients (n= 100).

Character	Number of patients
Age range (years)	
15-30	29
31-46	45
45-60	26
Sex	
Males	64
Females	36

Clinical presentation in this study includes Fever (95 %), Headache (70%), Restlessness (30%), Abdominal pain (50%) Vomiting (45%), Petachial manifestation (25%), Hematemesis (5%), Hematuria (5 %), Shock (25%), Altered sensorium (5%). Minimum platelet count in this study was 8000/cmm, while mean platelet count in this study was 19471.42/cmm. Severe hepatic derangement (SGPT >1000) was not detected in this study, highest SGOT/SGPT was 256/338 in this study. 20 patients had mild renal dysfunction. Warning signs and symptoms includes respiratory distress, oxygen desaturation, severe abdominal pain, excessive vomiting, altered sensorium, confusion, convulsions, rapid and thready pulse, narrowing of pulse pressure less than 20 mmHg, urine output less than 0.5 ml/kg/h, laboratory evidence of thrombocytopenia/ coagulopathy, rising Hct, metabolic acidosis, derangement of liver/kidney function tests.

Table 3 shows warning signs of dengue present in present study. Thirty-six patients had no warning signs, 64 patients had warning signs, out of which 43 patients had two or more warning signs while 21 patients had single warning sign. Most common warning sign in this study was abdominal pain (50%) and Vomiting (45%) while hepatomegaly was the least common warning sign.

Table 3: Warning signs of dengue.

Warning signs	Number of patients (n=100)
Persistent vomiting	45
Abdominal pain	50
Mucosal bleed	20
Fluid accumulation	25
Lethargy/restlessness	30
Hepatomegaly >2 cm	12
Shock	25
Respiratory distress	20
ARDS	25

Table 4 shows ECG changes in dengue patients in our study. Sinus bradycardia was the most common ECG finding in present study while first degree heart block was least common.

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

ECG changes	Number of patients (n=100)
Sinus rhythm	13
Sinus bradycardia	60
Sinus tachycardia	27
First degree heart block	11
Ventricular ectopics	15

Table 5 shows the correlation between warning signs and ECG changes in dengue patients. There was statistically significant correlation between ECG abnormalities and all the warning signs except lethargy/restlessness and hepatomegaly (P value <0.05).

Table 5: Correlation of warning signs to ECG abnormality.

Warning signs	ECG abnormality		P Value
	Yes	No	
Persistent vomiting	26	19	0.680
Abdominal pain	32	18	0.034
Mucosal bleed	14	06	0.021
Fluid accumulation	20	05	0.027
Lethargy/restlessness	18	12	0.194
Hepatomegaly >2 cm	05	07	0.889
Shock	21	04	0.011
Respiratory distress	15	05	0.020
ARDS	14	01	0.007

DISCUSSION

Many infectious diseases cause relative bradycardia, such as typhoid fever, chlamydia pneumoniae, 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, and self-limited and are attributed to subclinical viral myocarditis. Cardiac manifestation in dengue fever ranges from asymptomatic bradycardia to severe myocarditis. Cardiac abnormalities including various ECG abnormality (sinus bradycardia, and prolongation of PR interval, transient AV block, transient ventricular arrhythmias), 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 ectopics, have also been reported during convalescence period of dengue fever.⁸

Mean age group of present study is 29.3 years youngest was 18 years and oldest was 50 years and age group that is mostly affected in other studies like Gupta et al New Delhi was 5-20 years, Dash PK et al Gwalior was <15 years, and Neeraja M in Hyderabad was 20 -39 years.⁹⁻¹¹ In this study most of the patients are males (64) in comparison to females (36) and ratio is 1.7:1. In other studies like Dash PK et al, Gwalior male female ratio was 1.28:1, Neeraja M Hyderabad was 2:1, Gupta et al New Delhi, was 1.8 :1. Difference in this may be due small number of patients taken in this study group or it may be due to because of male dominated region where male seeks more medical help in comparison to females.⁹⁻¹¹ This needs study with more numbers of patients.

Most common warning sign in this study was abdominal pain (50%) and Vomiting (45%). In the study by Thien et al with dengue patients fever and persistent vomiting was noted in 39% of cases and was most common warning sign.¹² Hepatomegaly was least common warning sign in our study and seen in only 12% of cases. In this study 25% patients had shock, 20% had respiratory distress and 40% had malena. Severe hepatic derangement (SGPT >1000) was not detected in this study, highest SGOT/SGPT was 256/338 in this study. Renal impairment was present in 20% cases, ARDS in 15% cases, impaired consciousness in 5% of cases. In the study of thein leo et al 4% had severe hepatic impairment and 4 patients had renal impairment, maximum creatinine was 2.1 mg /dl, and 4 patients had ARDS.¹³

In this study cases showed sinus bradycardia in 60%, first degree heart block in 11%, and ventricular ectopics in 15% cases. While in other studies Gupta V et al showed 18% Brady cardia, 64% relative bradycardia, and 14% sinus tachycardia.¹⁴ Mean pulse rate in this study is 49.97 /min, minimum pulse rate was 33/ min, and maximum pulse rate was 123/min. In the study by Lathief et al mean heart rate 87.6/min, the commonest rhythm abnormality

was sinus bradycardia was found in 32% of cases.¹⁵ In the study by Gupta 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 was resolved in 24 hours. Kaushik et al have described AV dissociation and SA exit block in child from dengue fever.¹⁶ In present study ECG abnormalities were fairly common but all the ECG changes were reversible and no patient died in our study

Table 5 shows the correlation between warning signs and ECG changes in dengue patients. There was statistically significant correlation between ECG abnormalities and all the warning signs except lethargy/restlessness and hepatomegaly (P value <0.05). Kabra et al found no correlation between myocardial involvement and clinical severity of dengue fever.¹⁷ Obeyesekere et al have described direct cardiac involvement in dengue fever patients as evident by positive cardiac biomarkers. association between warning signs and cardiac manifestation was significant.¹⁸

Limitations of the study

First, we included a population admitted to a single center. Second, the study population was possibly underpowered to detect a significant difference in in-hospital mortality. Third, our data are only hypothesis generating, because they do not provide evidence to support a causal relationship, and they require confirmation in suitably designed clinical trials.

CONCLUSION

Sinus bradycardia was predominant manifestation in dengue viral fever patient, which resolved spontaneously over period of 24 to 48 hours. First degree heart block and ventricular ectopics were other ECG manifestation in these patients. There was no evidence of myocarditis in any of the patients. 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 manifestation in dengue patients except lethargy /restlessness and hepatomegaly.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. P C Saxena, MD, DM, Professor, Department of Cardiology, MLN Medical College and Hospital for help in management of patients. Authors are grateful to Dr. Sarita Bajaj, Professor, Head of department, department of medicine for her guidance. Authors would also like to thank Dr Shivprakash for statistical analysis.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Gibbons RV, Vaughn DW. Dengue: an escalating problem. *BMJ.* 2002;324:1563-6.
2. World Health Organization and Tropical Diseases Research. Dengue: Guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization. 2009.
3. Baruah K, Biswas A, Suneesh K, Dhariwal AC. Dengue fever: Epidemiology and clinical pathogenesis. Chapter 13, Major tropical diseases: Public health perspective. Goa: Broadway publishing House. 2014:255-71.
4. Dutta AK, Biswas A, Baruah K, Dhariwal AC. National guidelines for diagnosis and management of dengue fever/dengue hemorrhagic fever and dengue shock syndrome. *J Ind Med Assn.* 2011;109(1):30-5.
5. World Health Organization. Comprehensive guidelines for prevention and control of dengue and dengue hemorrhagic fever. New Delhi: WHO, SEARO; 2011: revised and expanded edition.
6. Wiwanikit. Dengue Cardiac Infection, A Brief Review; *Acta Cardiol Sin.* 2008;24:226.
7. Wichmann D, Kularatne S, Ehrhardt S, Wijesinghe S, Brattig NW, Abel W, et al. Cardiac involvement in dengue virus infections during the 2004/2005 dengue fever season in Sri Lanka: *Southeast Asian J Trop Med Public Health.* 2009;40:727-30.
8. Sheetal S, Jacob E. A Study on the Cardiac Manifestations of Dengue. *JAPI.* 2016;64:30-5.
9. Gupta E, Dar L, Kapoor G, Broor S. The changing epidemiology of dengue in Delhi, India. *Virol J.* 2006;3:1-5.
10. Dash PK, Saxena P, Abhavankar A, Bhargava R and Jana AM. Emergence of dengue virus type 3 in Northern India. *Southeast Asian J Trop Med Public Health.* 2005;36:370-7.
11. Neeraja M, Lakshmi V, Teja VD, Umabala P and Subbalakshmi MV. Serodiagnosis of dengue virus infection in patients presenting to a tertiary care hospital. *Indian J Med Microbiol.* 2006;24:280-2.
12. Thein S, Aung MM, Shwe TN, Aye M, Zaw A, Aye K, et al. Risk factors in dengue shock syndrome. *Am J Trop Med Hyg.* 1997;56:566-72.
13. Thein T-L, Leo Y-S, Fisher DA. Risk Factors for Fatality among Confirmed Adult Dengue Inpatients in Singapore: A Matched Case-Control Study. Salluh JI, ed. *PLoS ONE.* 2013;8(11):e81060.
14. Vishal Kumar Gupta, AK Gadpayle. Subclinical Cardiac Involvement in Dengue Hemorrhagic Fever. *JACM.* 2010;11(2):107-11.
15. Lateef A, Fisher DA, Tambyah PA. Dengue and Relative Bradycardia. *Emerg Infect Dis.* 2007;13(4):650-1.
16. Kaushik JS, Gupta P, Rajpal S, Bhatt S. Spontaneous resolution of sinoatrial exit block and atrioventricular dissociation in a child with dengue fever. *Singapore Med J.* 2010;51:e146-8.
17. Kabra SK, Verma IC, Arora NK, Jain Y, Kalra V. Dengue haemorrhagic fever in children in Delhi *Bulletin of the World Health Organization.* 1992;70:105-8.
18. Obeyesekere I, Hermon Y. Arbovirus heart disease: Myocarditis and cardiomyopathy following dengue and chikungunya fever—a follow-up study. *Am Heart J.* 1973;85:186-8.

Cite this article as: Yadav RK, Kumar S. To study cardiac manifestations in patients presenting with dengue infection and to find out the correlation of cardiac manifestations to warning signs of dengue. *Int J Adv Med* 2017;4:323-8.