

Correlation of cardiac manifestations with severity of dengue fever

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Abstract

Background: Dengue is a serious problem in the tropics. Cardiac involvement is worrisome for both the clinician and patient. **Aim:** To correlate cardiac manifestations to the severity of dengue fever. **Material and Methods:** Total 110 confirmed cases of dengue fever by dengue serology were classified according to the World Health Organization criteria into dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The assessment of cardiac manifestations was done based on electrocardiogram (ECG), echocardiogram and cardiac markers. **Results:** Out of 110 dengue patients, 69.1% had dengue fever, 7.3% had dengue shock syndrome and 23.6% had dengue hemorrhagic fever. On ECG, 59.09% patients had normal sinus rhythm followed by 36.4% had sinus bradycardia. Eight patients were found to have DSS, of which one (0.9%) had pericardial effusion while two (1.8%) had systolic and diastolic dysfunction each. Of the eight patients with DSS, six patients (75%) had positive troponin I and 87.5% had raised CKMB levels. **Conclusion:** ECG, cardiac enzymes and echocardiography are the main tools to diagnose the myocardial involvement in dengue fever. DHF and DSS cases had higher degree of myocardial involvement as compared to DF cases.

Key Words: Dengue, cardiac, electrocardiography, Echocardiography, markers, severity

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INTRODUCTION

Dengue fever is a life-threatening arthropod-borne viral disease caused by dengue virus. It has four distinct serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) which are transmitted to humans mostly by the *Aedes aegypti* mosquito.¹ Dengue virus infection is currently an area of great concern due to its wide geographic spread and also due to the vast majority of world population under its potential influence. Dengue affects people of all ages. In Southeast Asia, where dengue is hyperendemic,

dengue hemorrhagic fever usually affects children younger than 15 years.² Several outbreaks of dengue have occurred over past decades in many countries, causing significant morbidity and mortality. Cardiac involvement in dengue infection is not uncommon and is encountered in centers handling large numbers of dengue cases. Clinical manifestations of cardiac involvement can range from asymptomatic bradycardia 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.^{3,4} The significance of cardiac involvement in dengue infection is not fully understood. Despite the evidence of myocardial dysfunction in severe dengue, the degree to which this contributes to shock syndrome is yet unclear and warrants further study. The present study was conducted to correlate cardiac manifestations to the severity of dengue fever.

MATERIAL AND METHODS

This study was conducted in the Department of Medicine, in tertiary care hospital on patients admitted in hospital

suffering with dengue fever. Prior to initiating the study, ethical clearance for same was obtained from the Institutional Ethics Committee.

Sample Size Determination

A total of 110 (calculated) cases were studied. Using the formula: $n = \frac{4pq}{L^2} = \frac{4 \times 0.37 \times 0.63}{(0.25)^2} = 108.90 \approx 110$. Where, n= Sample size; p= positive character=37%; q=1-p=1-37%= 63%; L=allowable error in p (25%)= 9.25.

Inclusion criteria

1. Age group of ≥ 13 years.
2. Patients admitted in Ward/ICU hospital with confirmed dengue serology (Dengue IgG/IgM/NS1 positive)
3. fulfilling the WHO criteria for dengue.
4. written and informed consent

Exclusion criteria

1. Patients on medications affecting the heart rate / rhythm.
2. Patients with history of preexisting heart disease.
3. Patients with electrolyte abnormalities affecting the heart rate/rhythm.
4. Patients not willing to give consent for the study.
5. Patients suffering from mixed infections (Malaria, leptospira).

Admitted patients were classified into dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome based on the World Health Organization (WHO) criteria.

Case definitions

Case definitions of dengue fever, DHF, and dengue shock syndrome were as follows:⁵

Dengue fever

Acute febrile illness with two or more of the following: headache, retro-orbital pain, myalgia, arthralgia/bone pain, rash, hemorrhagic manifestations, leukopenia (white blood cells ≤ 5000 cells/mm³), thrombocytopenia (platelet count $< 150,000$ cells/mm³), and rising hematocrit (5%–10%). And at least one of the following: supportive serology test, occurrence at the same location, and time as confirmed cases of dengue fever.

Dengue hemorrhagic fever

Four cardinal features of DHF as defined by the WHO are as follows:

1. Fever or history of fever lasting 2-7 days occasionally biphasic
2. Thrombocytopenia ($< 100 \times 10^3/\text{mm}^3$)
3. Hemorrhagic manifestations shown by anyone of the following – A positive tourniquet test,

petechiae, ecchymosis, or purpura, bleeding from the mucosa or injection site, hematemesis, melena, and hematuria

4. Evidence of plasma leakage owing to increased vascular permeability shown by any one of the following: rising hematocrit/hemoconcentration $\geq 20\%$ from baseline, signs of plasma leakage such as pleural effusion, ascites, or hypoproteinemia.

Dengue shock syndrome

DHF plus circulatory failure with signs of shock such as rapid and weak pulse, narrow pulse pressure (< 20 mmHg) or hypotension (< 90 mmHg), cold clammy skin, and mental status alteration.

Methodology

On the day of admission, patients underwent general physical examination, systemic examination, and tests that included complete blood count with platelet count and hematocrit, electrocardiography, two-dimensional echocardiography, and cardiac enzyme – creatine kinase-muscle/brain (CK-MB) (normal range: 0–20 IU). Electrocardiography was done on the day of admission when the patient was afebrile. The following parameters in the ECG were observed: heart rate, PR interval, ST-T changes, broad QRS complexes, and QT interval. Echocardiography changes were interpreted as systolic dysfunction which refers to impaired ventricular contraction and pericardial effusion which refers to abnormal accumulation of fluid in the pericardial cavity.

Statistical analysis

Statistical Package for Social Sciences (SPSS 18.0) was used for analysis of data. The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test and Fisher's exact test. The continuous data was expressed as mean \pm standard deviation (SD). A probability value ('p' value) of less than or equal to 0.05 at 95% CI was considered as statistically significant.

RESULTS

In the present study, 62% of the patients were males and 38% were females. The male to female ratio was 1.62:1. The mean age of the study population was 35.15 ± 13.2 with range of 16 to 68 years. The mean and median age among males was 33.9 ± 13.5 years and 30 (Range 16 to 63) years. In females the same was 37.05 ± 12.5 years and 34 (range 16 to 68 years) years respectively. Out of 110 dengue patients, 69.1% had dengue fever, 7.3% had dengue shock syndrome and 23.6% had dengue hemorrhagic fever. ECG at admission revealed normal ECG in 56.36% of the patients while ECG changes were noted among 43.64%. The second ECG done on day three showed normal ECG in 87.27% and ECG changes were

noted in 12.73% patients. At the time of discharge normal ECG was seen in all the patients (100%) indicating transient ECG changes in patients with dengue. In this study, 59.09% patients had normal sinus rhythm, 36.4% patients had sinus bradycardia; 3.6% patients had sinus tachycardia and 10.9 % patients had NSST-T changes. Also 0.9% patients had first degree AV block, 4.65% had

QTc prolongation and RBBB was noted in 1.8%. Some patients had overlapping changes like NSST changes with sinus bradycardia or normal sinus rhythm. Some patients had sinus bradycardia with QTc prolongation. Echocardiography showed pericardial effusion in 0.91% patients, systolic dysfunction in 1.82% patients; while 2.73% patients had diastolic dysfunction.

Table 1: Comparison of Echocardiography findings with dengue severity

		Dengue Severity			Total	P Value		
		DF	DHF	DSS				
Pericardial effusion	Absent	No.	76	26	7	109	0.002	
		%	69.1%	23.6%	6.4%	99.1%		
	Present	No.	0	0	1	1		
		%	0%	0%	0.9%	0.9%		
	Total		No.	76	26	8		110
			%	69.1%	23.6%	7.3%		100%
Systolic Dysfunction	Absent	No.	76	26	6	108	0.000	
		%	69.1%	23.6%	5.5%	98.2%		
	Present	No.	0	0	2	2		
		%	0%	0%	1.8%	1.8%		
	Total		No.	76	26	8		110
			%	69.1%	23.6%	7.3%		100%
Diastolic Dysfunction	Absent	No.	76	25	6	107	0.000	
		%	69.1%	22.7%	5.5%	97.3%		
	Present	No.	0	1	2	3		
		%	0%	0.9%	1.8%	2.7%		
	Total		No.	76	26	8		110
			%	69.1%	23.6%	7.3%		100%

In the present study based on abnormal cardiac enzymes, echocardiography and ECG 60.09% of the patients were found to have cardiac manifestations. Eight patients were found to have dengue shock syndrome of which one (0.9%) had pericardial effusion while two (1.8%) had systolic and diastolic dysfunction each. Of the 26 patients with DHF, one (0.9%) had diastolic dysfunction. The difference was statistically significant for all echocardiography findings with respect to dengue severity (P<0.05).

Table 2: Comparison of Troponin I with dengue severity

Dengue Severity		Troponin I		Total	P Value	
		Negative	Positive			
1	Dengue Fever	No.	76	0	76	0.000
		%	69.1%	0%	69.1%	
2	Dengue haemorrhagic fever	No.	19	7	26	23.6%
		%	17.3%	6.4%	23.6%	
3	Dengue shock syndrome	No.	2	6	8	7.3%
		%	1.8%	5.5%	7.3%	
Total		No.	97	13	110	
		%	88.2%	11.8%	100%	

Of the eight patients with DSS, six patients (75%) had positive troponin I. Out of 26 patients with DHF; seven patients (26.9%) had positive troponin I. None of the patients with DF had positivity of troponin I. This indicates the percentage of dengue patients having positive troponin I correlates with severity of dengue fever. The difference was statistically significant (P<0.001).

Table 3: Comparison of CKMB with dengue severity

Dengue Severity		CKMB		Total	P Value	
		25 or less	>25			
1	Dengue Fever	No.	46	30	76	0.03
		%	41.8%	27.3%		
2	Dengue haemorrhagic fever	No.	15	11	26	23.6%
		%	13.6%	10%		
3	Dengue shock syndrome	No.	1	7	8	7.3%
		%	0.9%	6.4%		
Total		No.	No.	48	110	
		%	%	43.6%	100%	

In the present study eight patients were found to have dengue shock syndrome with 87.5% of them having raised CKMB levels compared to 42.3% and 39.5% in dengue haemorrhagic fever and dengue fever respectively. This indicates the percentage of dengue patients having abnormal CKMB correlates with severity of dengue fever. The difference was statistically significant ($P < 0.05$). In the present study, all the dengue patients recovered from illness successfully and no mortality was recorded.

DISCUSSION

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.⁶ In our study the mean age of the study population is 35.15 ± 13.2 . The mean and median age among males was 33.9 ± 13.5 years and 30. In females the same was 37.05 ± 12.5 years and 34 years respectively. The youngest patient was 16 years old and the oldest patient was aged 68 years. The male to female ratio was 1.62:1 suggesting male preponderance. These findings were comparable to a study by Miranda *et al*,⁷ in which the mean age was 32 and M:F was 0.92:1. In another study by Malavige *et al*,⁸ the mean age was 26.6 years and M:F was 1.4:1. Another study by Guilarde *et al*,⁹ had mean age of 32 ± 12 years and M:F of 1.7:1. In this study, out of 110 dengue patients, 69.1% had DF, 7.3% had DSS and 23.6% had DHF. In a study conducted by Guilarde *et al*,⁹ 23.2% were classified as DHF and 50.3% were classified as DF showing almost similar finding compared to our study. Another study by Arora *et al*,¹⁰ showed 16.7% patients with DF, 70.8% patients with DHF and 12.5% patients with DSS thus having some variations compared to our study and with the other study as compared to previously. ECG and echocardiographic abnormalities are common during dengue infection. These are asymptomatic and most are transient among patients with dengue fever and DHF. These conduction abnormalities are most likely manifestations of involvement of the cardiac conduction system in dengue infection. In the present study, ECG at admission revealed normal ECG in 56.36% of the patients while ECG changes were noted among 43.64%. The second ECG done on day three showed normal ECG in 87.27% and ECG changes were noted in 12.73% patients. At the time of discharge normal ECG

was seen in all the patients (100%) indicating transient ECG changes in patients with dengue. In a study done by Prasanth *et al*,¹¹ ECG changes were seen in 30% of patients. In a study by Yadav *et al*,¹² 13% cases showed normal sinus rhythm, other findings seen were sinus bradycardia in 60%, first degree heart block in 11% and ventricular ectopics in 15% cases. In a study conducted by Gupta *et al*,¹³ sinus bradycardia ($HR < 60$) was present in 4 patients (14.28%), and sinus tachycardia in 6 patients (21.4%) and QRS and ST changes were not seen in any patient. In a study based on cardiac manifestations of dengue fever by Sheetal *et al*,¹⁴ the commonest rhythm abnormality was sinus bradycardia in 32% patients followed by 3% unexplained tachycardia and ventricular bigeminy, ventricular tachycardia in 1% each. In a study by Arora *et al*,¹⁰ 84.21% of them having normal heart rate, 8.77% having sinus bradycardia and 3.51% patients each having sinus tachycardia and NSST-T changes. Among 6 patients with abnormal rhythm at admission, 4 (66.67%) had first degree AV block and 2 had RBBB (33.33%). However, the second and third ECG done on day three and day seven (or at the time of discharge, whichever was earlier) showed normal rhythm. Hence, overall Sinus Bradycardia was the commonest ECG finding after normal Sinus rhythm. In the present study, based on abnormal cardiac enzymes, echocardiography and ECG 60.09% of the patients were found to have cardiac manifestations. In a study by Arora *et al*,¹⁰ the incidence of cardiac manifestations was found to be higher in patients with dengue shock syndrome with eight (53.33%) out of 15 patients having cardiac enzymes elevation compared to 30 (35.29%) out of 55 and six (30%) out of 20 patients with dengue hemorrhagic fever and dengue fever respectively. Although the difference was not statistically significant ($p = 0.325$). In our study, the correlation based on echocardiography, cardiac

enzymes compared with dengue severity showed statistical significance ($p < 0.05$) which entails higher cardiac involvement as dengue severity increases like in DHF and DSS. Cases of DSS had highest cardiac involvement as seen with cardiac enzymes, ECG and echocardiography.

Limitations of the study

- Testing for Troponin I was not done on quantitative basis, which could have provided better comparison with the severity of dengue fever.
- Cardiac biopsy which is the gold standard to diagnose myocarditis was not performed.
- Central venous pressure was not measured; correlation of the same to cardiac involvement was not done.

CONCLUSION

ECG, cardiac enzymes and echocardiography are the main tools to diagnose the myocardial involvement in dengue fever. DHF and DSS cases had higher degree of myocardial involvement as compared to DF cases.

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