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The prevalence and clinical significance of major acute cardiovascular events after dengue infection: A observational study.

[1]Dr. Prabhakar Telawade, [2]Dr. Kaushik Kumar Bhol, [3]Dr. B Chaitanya Kiran

[1]Medical Officer, Panvel Municipal Corporation, Navi Mumbai, Maharashtra
[2]Assistant Professor, Department of Medicine, Institute of Naval Medicine, INHS, Asvini
[3]Assistant Professor, Department of Medicine, Base Hospital, Delhi Cantt, New Delhi

Corresponding Author
Dr. B Chaitanya Kiran
Assistant Professor, Department of Medicine, Base Hospital, Delhi Cantt, New Delhi
Email id: ckps5193@gmail.com

Abstract

Background: Dengue infection is one of the common tropical infectious diseases. Clinicalmanifestations of cardiacinvolvement can vary widely, from an incidental finding to severe cardiac failure resulting in death.

Aim:To assess the prevalence and clinical significance of major acute cardiovascular events after dengue infection.

Methods:A comprehensive longitudinal investigation took place at a tertiaryhealthcare facilitylocated inRaigad (Maharashtra). The sampling techniqueinvolved the inclusion of 140 eligible dengue fever cases who were selected on a first come first serve basisafter the beginning of the study.A previous history of any cardiac disease, history of chronic kidney disease(CKD), pregnant women and children, as well as admission ECG suggestive of old ischemicchanges, and use of medications affecting heart rate were excluded from the study,

Results: Prevalence of cardiac inflammation in dengue fever cases were 26.4%. The elevatedhs-Troponin-T (pg/ml) in 25.0% cases and elevated CK-MB (U/L) in 23.6% cases.1st-degree heart block in 10.8%,2nd-degree heart block in 2.7%, complete heart block in 2.7%, atrial fibrillation in 10.8%, ST elevation in 5.4%, ventricular tachycardia in 2.7% and sinus tachycardia in 13.5%. 37.8% cases found EF <40.0% echocardiography, 24.3% cases EF 40-50% and regional wall motion abnormality (RWMA) in 51.4% cases.

Conclusion: Our study revealed that patients withnormal echo, ECG and serum levels of markers of cardiac injury are atlow risk for mortality and hence may need less monitoring or therapeutic intervention.Our study elucidates various significantfindings that advocate for tailored interventions, heightened awareness of cardiac involvement, andstrategic use of diagnostic tools.

Keywords: Dengue, Denguevirus infection,Cardiac involvement, Haemodynamic,Myocarditis.

Background

Dengue virus infection (DVI) is a major health problem in more than 100 countries in tropical and subtropical regions. Approximately 96 million people develop DVI annually.[1] Dengue is a mosquito-transmitted virus and the leading cause of arthropod-borne viral disease in the world. It is also known as breakbone fever due to the severity of muscle spasms and joint pain, dandy fever, or seven-day fever because of the usual duration of symptoms. Although most cases are asymptomatic, severe illness and death may occur. A few people who were previously infected with one subspecies of the dengue virus develop severe capillary permeability and bleeding after being infected with another subspecies of the virus. This illness is known as dengue hemorrhagic fever.[2] The complications arising from severe dengue infection, including liver failure, disseminated intravascular coagulation, dengue encephalopathy, acute renal failure, and hemolytic uremic syndrome, present substantial risks to patients' overall health.[3] Cardiac complications are amongst the important consequences of DVI.Cardiac manifestations of Dengue fever can present with a mildly raised cardiac enzyme tosevere myocarditis leading to congestive heart failure, arrhythmias, cardiogenic shock, anddeath.[4] Cardiac complications during the illness carry significance in predicting length ofstay (LOS) and in-hospital mortality.[5]Traditionally, the pathogenesis of dengue fever has been linked to capillary leakage, leading to decreased intravascular volume and the development of DHF/DSS. However, studies have highlighted the potential involvement of the heart in dengue-related shock.[6,7,8] Authors have reported cases of direct cardiac involvement in dengue fever patients, suggesting a plausible connection between cardiac dysfunction and the development of shock.[6,9]The definitive diagnosis of myocarditis depends on an endomyocardial biopsy. However, theclinically suspected diagnosis is based on history, clinical examination, and biochemical andradiological profile. The European Society of Cardiology (ESC) 2013 consensus statementsuggested the presence of at least one clinical and one diagnostic criterion for the diagnosisof clinically suspected myocarditis. Clinical criteria include acute new-onset, or worseningdyspnea, palpitations, and/or unexplained shock. The diagnostic criteria include ECG or Holterchanges, raised cardiac biomarkers, functional and structural abnormalities on cardiac imaging,and tissue characterization on cardiac magnetic resonance (CMR) imaging.[10]The exact prevalence of dengue myocarditis is unknown. It is essential to recognize the burdenof cardiac manifestations in dengue fever. There is a need for preparedness at the physician'send for early

recognition and prompt management for patients with dengue fever beingcomplicated by cardiovascular manifestations. Additionally, determining prognostic factors isessential for the risk stratification of patients. With dengue fever continuing to be a major healthcare concern, more studies are needed to predict in-hospital outcomes and mortality. In thisobservational study, we looked at the prevalence and clinical significance of major acute cardiovascular events after dengue infection.

Material & Methods

A comprehensive longitudinal investigation took place at a tertiaryhealthcare facility located inRaigad Districtin Maharashtra. This study conducted from Jan 2022 to Dec 2023. A samplesize of 140 cases was determined, based on an expected 14.9% prevalence of cardiac involvement in denguefever cases [11], with a 95% confidence level, 80% power, and 5.0% absolute error. The sampling techniqueinvolved the inclusion of 140 eligible dengue fever cases who were selected on a first come first serve basisafter the beginning of the study. Patients were selected based on specific inclusion and exclusion criteria.

Inclusion criteria included dengue fever cases in individuals aged 18 years and above, with eithernon-structural protein 1 (NS-1) antigen or immunoglobulin M (IgM) antibody positive or both positive.

Exclusion criteria comprised a previous history of any cardiac disease, history of chronic kidney disease(CKD), pregnant women and children, as well as admission ECG suggestive of old ischemicchanges, and use of medications affecting heart rate.

Data collection methods

All patients clinically suspected to have dengue fever underwentevaluation as per the WHO classification and guidelines (2009) for thediagnosis of dengue infection [11]. Serological diagnosis was based onDengue IgG/IgM rapid card test (J. Mitra). All patients with confirmeddiagnosis of dengue underwent detailed clinical evaluation, a12-leadelectrocardiography (ECG), assay for cardiac markers (troponinT, CK-MB) and 2-d echocardiography (ECHO). All echocardiographic data were acquired using a standard ultrasound machine(Vivid E9, GE Vingmed, Horten, Norway) with a 2.5 or 3.5 Mhz multi-phased array probe and the images were digitally stored for off lineanalysis.

Criteria for identifying cardiac involvement in patients with dengue fever:

1. Symptoms such as chest pain, dyspnoea at rest or during exercise, palpitation,syncope or signs such as hypotension, bradycardia or tachycardia, or signs ofheart failure
2. Electrocardiographic changes
    A. Cardiac arrhythmias
    B. Heart block of any type
    C. ST segment or T wave changes
3. Echo Doppler studies
    A. LVEF < 50%
    B. Global or regional wall motion abnormalities
    C. Pericardial effusion
4. Serum levels of markers of myocardial injury
    A. Elevated hs Troponin T > 25 pg/ml
    B. Elevated CK-MB > 5 mg/ml

Statistical analysis: Confirmed cases of dengue fever meeting the inclusion criteria were enrolled, and data on socio-demographic profiles and investigations were collected and entered into Excel 2019 (Microsoft, Redmond,WA, USA). Statistical analysis was performed using SPSS-20. Categorical data were presented asnumbers (percent) and compared among groups using the Chi-square test, while continuous data werepresented as mean and standard deviation and compared using the student's t-test. A P-valueless than 0.05 was considered statistically significant to draw inferences based on the study's aims andobjectives.

Result:

Over a period of two year, we had 160 patients with dengue fever asdetected by serology. During screening, 17 patients were excluded fromthe present study because of pre-existing heart disease; 3 patients didnot give consent for participation. We investigated the remaining 140eligible patients.In our study 58.6% cases were male gender and rest 41.4% were female gender. 37.9% cases were belonging to >50 years followed by 35.0% in 31-50 years and 22.9% were in ≤30 years age group. 44.3% cases were overweight and 39.3% were normal weight while16.4% were belonging to underweight. 16.4% dengue fever cases were having hypertension,12.9% diabetes and 10.7% were dyslipidaemia. In this study noted that 37 (26.4%) dengue fever cases noted cardiac indolent i.e prevalence of cardiac inflammation in dengue fever cases were 26.4%.It was found that major symptoms chest pain in 89.2%, followed by palpitations in 56.8%, irregularities of pulse in 35.1% cases,

bradycardia in 24.3%, hypotension in 13.5% and pulmonary edema in 8.1% cases.In this study we noted that the elevatedhs-Troponin-T (pg/ml) in 25.0% cases and elevated CK-MB (U/L) in 23.6% cases. Our study also noted that the significant difference between normal level and elevated biomarkers ($p<0.05$).From 140 patients only 37 showed abnormal ECGS. Among the ECG changes observed in the studypopulation that is Sinus bradycardiain 16.2%, 1st-degree heart block in 10.8%,2nd-degree heart block in 2.7%, complete heart block in 2.7%, atrial fibrillation in 10.8%, ST elevation in 5.4%, ventricular tachycardia in 2.7% and sinus tachycardia in 13.5%. 37.8% cases found EF <40.0% echocardiography, 24.3% cases EF 40-50% and regional wall motion abnormality (RWMA) in 51.4% cases.

Table 1: Clinical characteristics of patients with dengue fever

		Frequency (n=140)	Percentage
Gender	Male	82	58.6%
	Female	58	41.4%
Age	≤30	32	22.9%
	31-50	49	35.0%
	>50	53	37.9%
Obesity	Underweight	23	16.4%
	Normal weight	55	39.3%
	Overweight	62	44.3%
Comorbidity	Diabetes mellitus	18	12.9%
	Hypertension	23	16.4%
	Dyslipidaemia	15	10.7%

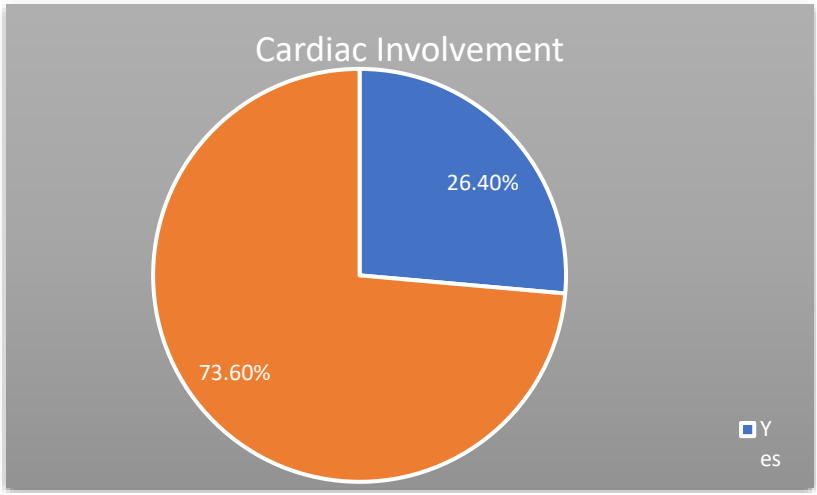


Table 2: Sign and symptoms of cardiac involvementin dengue fever

	Frequency (n=37)	Percentage
Chest pain	33	89.2%
Palpitations	21	56.8%
Irregularities of pulse	13	35.1%
Bradycardia	9	24.3%
Hypotension	5	13.5%
Pulmonary edema	3	8.1%

Table 3: Rise in serum levels of biomarkers of cardiac injury

Biomarkers		Number (%)	Mean±SD	P value
hs-Troponin-T (pg/ml)	Normal	105 (75.0%)	18.34±2.51	<0.001
	Elevated	35 (25.0%)	36.48±6.21	
CK-MB (U/L)	Normal	107 (76.4%)	19.83±2.78	<0.001
	Elevated	33 (23.6%)	68.22±9.46	

Table 4: Changes seen in electrocardiogram & echocardiography

		Frequency (n=37)	Percentage
Electrocardiogram	Sinus bradycardia	6	16.2%
	1st-degree heart block	4	10.8%
	2nd-degree heart block	1	2.7%
	Complete heart block	1	2.7%
	Atrial fibrillation	4	10.8%
	ST elevation	2	5.4%
	Ventricular tachycardia	1	2.7%
	Sinus tachycardia	5	13.5%
Echocardiography	EF < 40%	14	37.8%
	EF 40-50%	9	24.3%
	Regional Wall Motion Abnormality (RWMA)	19	51.4

Discussion

Dengue fever has become a notable public health concern in India. Currently, a variety of methods areemployed on both the national and state levels to gauge its severity and monitor the occurrence of dengueoutbreaks. These approaches are implemented through various National and State Sentinel SurveillanceSystems across the country. The National Vector Borne Disease Control Programme and the IntegratedDisease Surveillance Programme (IDSP) work together in a passive sentinel surveillance endeavor, focusedon the prevention and management of dengue.[12]This study adopted a hospital-based longitudinal approach, enrolling 140 patients with dengue fever whowere admitted at a tertiaryhealthcare facility located in Raigad District in Maharashtra. The study aims to uncover potential cardiacinvolvement in these patients. Inclusion criteria were guided by WHO Criteria-10 for dengue diagnosis,requiring serology (IgM antibody and NS-1 Ag) and aligning with pre-established inclusion and exclusionconditions.In our study 58.6% cases were male gender and rest 41.4% were female gender. 37.9% cases were belonging to >50 years followed by 35.0% in 31-50 years and 22.9% were in ≤30 years age group. 44.3% cases were overweight and 39.3% were normal weight while16.4% were belonging to underweight. 16.4% dengue fever cases were having hypertension,12.9% diabetes and 10.7% were dyslipidaemia. **Jadav Net al[13]** reported that the males accounted for 77 (74%), while females constituted 27 (26%). The mean age,represented by mean ± standard deviation, was 29.12 ± 0.92 years. The age spectrum ranged from 19, theyoungest patient, to 53, the oldest.Other research carried out in India by **Agarwal et al[14], Ray et al[15],** and **Wali et al[16]** individually demonstrated a greateroccurrence of dengue infection among male patients in comparison to females. The male-to-female sexratios reported were 1.9:1, 1:0.57, and 2.5:1, respectively.In this study noted that 37 (26.4%) dengue fever cases noted cardiac indolent i.e prevalence of cardiac inflammation in dengue fever cases were 26.4%.The reported incidences of cardiac involvement and myocarditis indengue infection are varied in different studies. **Salgado et al[17]**in astudy of 102 patients with DF, found myocarditis in14%; these patientshad dengue hemorrhagic fever (DHF). **Wichmann D et al[18]** from SriLanka reported a 25% incidence of cardiac involvement in DF. **Li Y et al[19]** from China had recorded evidence of myocarditis in 201(11.43%) among 1782 patients they studied. A study from southIndia specifically looking at cardiac manifestations in 100 patientswith dengue infection did not observe any patient with echocardiographic evidence of myocarditis.[20] In their analysis of 17 consecutivepatients with DHF/ DSS, **Wali PJ et a[21]** at New Delhi found five patientswith ST and T segment changes in the electrocardiogram. They concluded that DF can result in an acute reversible cardiac injury, whichwas responsible for the changes they observed in their patients.In a recent study in north India, **Laul A et al[22]** observed among 115 patients only 1 with evidence of myocarditis and LV dysfunction.**Yadav R et al[23]** did not find evidence of myocarditis in any of the 36 patients they studied.It was found that major symptoms chest pain in 89.2%, followed by palpitations in 56.8%, irregularities of pulse in 35.1% cases, bradycardia in 24.3%, hypotension in 13.5% and pulmonary edema in 8.1% cases.The common biomarker which is elevated in the serum of patients with dengue infection and cardiac involvement is troponin. In patients with clinically suspected myocarditis, cardiac troponins are more sensitive of myocyte injury than CK-MB and BNP levels, which are non-specific and when normal do not exclude myocard.[24,25]In this study we noted that the elevated hs-Troponin-T (pg/ml) in 25.0% cases and elevated CK-MB (U/L) in 23.6% cases. Our study also noted that the significant difference between normal level and elevated biomarkers ($p<0.05$).**Miranda CH et al[26]** found elevation of serum levels of troponin I and NT-proBNP in12of their 81 patients. In a study from south India,12 out of 120 patients had isolated CK-MB elevation and 4 had isolated troponin I elevation.[20]**Arora M et al[27]** reported troponin I elevation in serum in 48 (26.7%) and rise of CK MB in serum in 34 (33.3%) of their patients. This study noted that from 140 patients only 37 showed abnormal ECGS. Among the ECG changes observed in the

studypopulation that is Sinus bradycardiain 16.2%, 1st-degree heart block in 10.8%,2nd-degree heart block in 2.7%, complete heart block in 2.7%, atrial fibrillation in 10.8%, ST elevation in 5.4%, ventricular tachycardia in 2.7% and sinus tachycardia in 13.5%. The most common abnormal finding in the ECG is sinus bradycardia.[28,29] Other ECGchanges include rate and rhythm abnormalities, heart block, wave form as well as voltage abnormalities.[30]Khongphatthallayothin A et al have noted a patient with Mobitz type 2 block.[31] Sinus bradycardia, prolonged QRS duration, ECHO evidence for increased left ventricular hypokinesis and persistently raised or fluctuating serum troponin levels may precede a life-threatening arrhythmia. A few patients with complete atrioventricular block may require temporary pacing. There are reports of occasional patients with dengue myocarditis who had life-long arrhythmias and required a permanent pacemaker or insertion of an implantable cardioverter defibrillator. Electrocardiographic features mimicking acute myocardial infarction have also been reported.[32] The present study was noted that 37.8% cases found EF <40.0% in echocardiography, 24.3% cases EF 40-50% and regional wall motion abnormality (RWMA) in 51.4% cases.

Limitations

Several limitations are present within this study. The reliance on a single-centre methodology could restrictthe applicability of the results to more extensive demographics. Additionally, the absence of extendedfollow-up data and the lack of a control group for comparative purposes introduce constraints onestablishing conclusive connections between cardiac engagement and dengue fever as causal relationships.

Conclusion

Our findings confirmed dengue cases found significant links between dengue infection andcardiac engagement, unveiling uncommon cardiac manifestations beyond the typical symptoms. The study'smale predominance (58.6%) aligns with prior Indian research, possibly reflecting gender-related factors. The most common abnormalitiesare in the electrocardiogram. Our study revealed that patients withnormal echo, ECG and serum levels of markers of cardiac injury are atlow risk for mortality and hence may need less monitoring or therapeutic intervention.Our study elucidates various significantfindings that advocate for tailored interventions, heightened awareness of cardiac involvement, andstrategic use of diagnostic tools. Furthermore, future research should focus on conducting multicentrestudies with larger sample sizes and diverse populations to validate the findings of this study.

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