

Original Research Article

Clinical correlation of cardiac functions and troponin I and CPK-MB in dengue fever in children

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ABSTRACT

Background: Dengue is the most rapidly spreading mosquito-borne viral disease in the World. The spectrum of manifestations includes mild fever to severe and life-threatening disease, though uncommon complications such as myocarditis have also been reported in many cases. We conducted this study to analyze association between Clinical Profile, Cardiac Functions and Troponin I and CPK-MB (cardiac biochemical markers) in children with Dengue Fever. Aims and objectives of the study was the association between Clinical Profile, Cardiac Functions and Troponin I and CPK-MB (cardiac biochemical markers) in children with Dengue Fever.

Methods: This was a prospective observational study in which 80 paediatric patients who were hospitalized and diagnosed to be having Dengue fever were included. All patients were stratified into either of the 3 groups- Dengue without warning signs, Dengue with warning signs and severe Dengue. A detailed history and thorough clinical examination were done for all patients. A complete blood count, electrolytes, hepatic and renal function tests were done in all children. Cardiac function was assessed by 2D Echo, CPK-MB and Troponin-I, p value less than 0.05 was taken as statistically significant.

Results: Of the 80 studied cases there were 53 (66.25%) males and 27 (33.75%) females with a M:F ratio of 1.9:1. Dengue with and without warning signs was seen in 27.5% and 60% cases respectively whereas severe dengue was seen in 12.5% cases. The ejection fraction was comparable across the 3 groups. On 2D echo ejection fraction was 62.95%, 63.21% and 65.1% in cases with warning signs, without warning signs and severe dengue respectively. Additionally, ECG abnormalities were seen in 8.75% patients. All 80 patients had a normal CPK-MB and Troponin-I levels.

Conclusions: Cardiac markers (CPK-MB and Troponin-I) remain unaffected during Dengue illness and do not have significant correlation between Dengue without warning signs, Dengue with warning signs and severe Dengue.

Keywords: Cardiac markers, Dengue in paediatric age group, Electrocardiogram abnormalities, Myocarditis

INTRODUCTION

Dengue is the most rapidly spreading mosquito-borne viral disease in the World. In the last 50 years, incidence has increased 30-fold with increasing geographic expansion to new countries and, in the present decade,

from urban to rural settings. An estimated 50 million dengue infections occur annually and approximately 2.5 billion people live in dengue endemic countries.¹

Over the last 30 years the geographical distribution has greatly expanded, because of increased potential for breeding of *Aedes aegypti*, which is the primary vector of

dengue. This has been promoted by demographic explosion, rapid growth of urban centers with strain on public services, such as potable water and rainwater harvesting. Dengue Fever (DF) with its severe manifestations such as Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) has emerged as a major public health problem of international concern.²

Dengue Fever, also known as the break bone fever, is the most common arboviral disease in the world. It is a mosquito-transmitted acute viral infection caused by dengue virus. Virus has 1 of 4 virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) of the genus *Flavivirus*. Dengue Fever (DF) has been known for more than a century in the tropical areas of South East Asia and the Western Pacific regions. A significant increase in the incidence of this infectious disease has taken place in the last 20 years and Dengue has become a major international public health concern in recent years.² The actual numbers of dengue cases are underreported, and many cases are misclassified. One estimate indicates that 390 million dengue infections per year, of which 96 million manifests clinically. It is now endemic in more than 100 countries and an estimated 5,00,000 people of severe dengue require hospitalization every year, a large population of whom are children. About 2.5% of those affected die thereby making it an important cause of childhood morbidity and mortality.³

According to the older classification of the disease, it occurs in two forms: classic dengue, the milder form of the disease and Dengue Haemorrhagic Fever (DHF), the severe form. The severity of this disease falls into four grades. Grade I, which is milder form which is characterized by fever, general symptoms and positive tourniquet test and severe Grade IV which presents with shock and non-detectable arterial pressure. In all these phases, there is thrombocytopenia and hemoconcentration. The diagnosis of DF is based on clinical appearance in combination with serology. Definitive tests for Dengue Fever include Nonstructural protein 1 (NS1) antigen assay or Dengue serology (anti Dengue antibody).⁴ Dengue causes a spectrum of disease where the patient can develop cardiovascular compromise secondary to increased capillary permeability and plasma leak. Cardiac complications have also been reported including; reduced myocardial function, acute myocarditis and conduction disturbances. The nature and mechanism of the cardiac impairment and its contribution to severe disease has not been systematically defined.

Aims and objectives of this study was the association between Clinical Profile, Cardiac Functions and Troponin I and CPK-MB (cardiac biochemical markers) in children with Dengue Fever.

METHODS

This was a Prospective observational study conducted in the department of pediatrics of a tertiary Care medical

college situated in a metropolitan city. Institutional ethical committee duly approved the study and informed written consent was obtained from the parents or caregivers of the patients. 80 patients hospitalized with dengue fever confirmed through dengue NS1Ag and/or IgM were included in the study on the basis of a predefined inclusion and exclusion criteria. A detailed history was taken from the caretakers, parents or the patient himself/herself. Weight, height/length and Mid Upper Arm Circumference (MUAC) was measured using standard measuring tapes. WHO growth charts were used to plot the standard deviations and patients were labelled as either Moderate Acute Malnutrition (MAM) or Severe Acute Malnutrition (SAM). A detailed clinical examination was done with particular emphasis to detect presence of petechiae, purpura, ecchymoses, organomegaly (hepatomegaly, splenomegaly or hepatosplenomegaly). Respiratory distress if present was also noted. Pulse rate, respiratory rate and blood pressure was recorded in all the cases.

Complete blood count and liver function test, ECG, 2D-ECHO, CPK-MB and TROPONIN-I were also done in all the cases. CPK-MB and TROPONIN-I were determined with kits using ELISA method. Patients positive for dengue were classified as per Revised WHO dengue case classification 2011.

Echocardiography study was done as early as possible during the course of illness. Ejection fraction was calculated using standard formulae, which includes Teicholz method or Simpsons method. End diastolic volume and end systolic volume was documented in all patients. A 2-dimensional examination of the heart was performed and patients with any congenital and acquired disease were excluded. SSPS 21.0 software was used for statistical analysis and p value less than 0.05 was taken as statistically significant.

Inclusion criteria

- Dengue confirmed by NS1Ag and/or IgM antibodies.
- Parents/Caretakers gave informed written consent.
- Age less than 18 years.

Exclusion criteria

- Age more than 18 years.
- Parents/Caregivers Refused consent.
- Presence of congenital or acquired heart disease.
- Patients on drugs affecting the heart rate or rhythm.
- Patients with electrolyte imbalances affecting the heart rate/rhythm.
- Patients with any pre-existing severe systemic illness.

RESULTS

There were 80 cases of dengue based on clinical and laboratory profile were subjected to cardiac evaluation in

the form of 2D-echo, ECG, Chest x-ray, Troponin I and CPK-MB. Observations of these 80 cases were analyzed. Among 80 cases there were 53 (66.25%) males and 27 (33.75%) females with a M:F ratio of 1:0.509 (Figure 1).

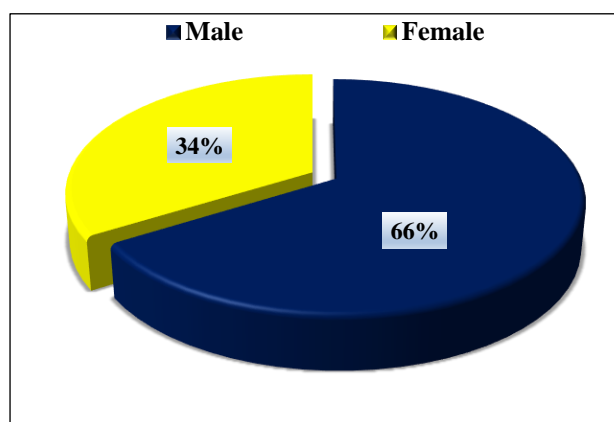


Figure 1: Gender distribution of the studied cases.

The analysis of age distribution of patients showed that the mean age of patients having Dengue with warning signs was 8.45 years whereas the mean age of patients without warning signs was found to be 6.83 years. In cases with severe dengue the mean age was found to be

7.2 years. The age difference was found to be statistically 'not significant' ($p=0.072$) (Table 1).

Table 1: Mean age of the studied cases.

Type of dengue	Mean age of affected cases
Dengue without warning signs	6.83 years
Dengue with warning signs	8.45 years
Severe dengue	7.2 years
$p=0.072$	

In this study of 80 cases, 60% presented without warning signs, 27.50% with warning signs and 12.50% had severe dengue. Whereas 38.75% were positive for IgM, 30% were positive for Ns1Ag and IgM and 31.25% were positive for Ns1Ag. The analysis of the nutritional status of these patients showed that majority of the cases (82.50%) had a normal nutritional status, whereas Moderate Acute Malnutrition (MAM) and Severe Acute Malnutrition (SAM) was present in 13.75% and 3.75% patients respectively.

Amongst the studied cases 28.75% had petechiae/purpura, 32.5% had rashes, 37.5% had hepatomegaly, 28.75% had splenomegaly (Table 2).

Table 2: Comparison of gender, duration of fever, nutritional status, serology, pallor and skin manifestation among the study groups.

Distribution of cases		Dengue with warning signs	Dengue without warning signs	Severe dengue	p value
Gender distribution	Male	81.8 %	64.6%	40%	$p=0.063$ (not significant)
	Female	18.2%	35.4%	60%	
Mean duration of fever (days)		6.64 days	7.02 days	8.5 days	$p=0.254$ (not significant)
Nutritional status	MAM	13.6%	12.5%	20.0%	$p=0.940$ (not significant)
	Normal	81.8%	83.3%	80.0%	
	SAM	4.5%	4.2%	0.0%	
Serological profile	IGM +VE	40.9%	37.5%	40%	$p=0.992$ (not significant)
	NS1 +VE	27.3%	33.3%	30%	
	IGM+NS1 +VE	31.8%	29.2%	30%	
Pallor	Present	45.5%	29.2%	100%	$p=0.000$ (significant)
	Absent	54.5%	70.8%	0 %	
Rash	Present	59.1%	8.3%	90%	$p=0.000$ (significant)
	Absent	40.9%	91.7%	10%	

Of patients with Dengue with warning signs 4.5% had cardiomegaly and 95.5% had normal X ray. Of patients with Dengue without warning signs 8.3% had cardiomegaly and 91.7% had normal X ray. Of patients with severe Dengue 20% had cardiomegaly and 80% had normal X ray. In total 91.75% had a normal Chest X ray and 8.75% had cardiomegaly. The p value by oneway ANOVA test was 0.353 and difference is not statistically

significant (Table 3). Among the 80 subjects 78.75% had a normal ECG, 8.75% showed ST, Twave Depression in lead V1-V4, 5% had sinus bradycardia and the remaining had varied changes of ST segment or AV block in various leads (Table 4).

All 80 patients had CPK-MB levels less than 0.1 ng/ml and Troponin-I levels less than 0.2 ng/ml (Table 5).

Table 3: Comparison of Mean HR, RR, Hb, Hematocrit, Platelet count, Chest Xray and 2DECHO findings in studied cases.

	Dengue with warning signs	Dengue without warning signs	Severe dengue	p value
Mean heart rate (HR)	79.14	78.40	80	p=0.898 (not significant)
Mean respiratory rate (RR)	26.73	25.08	24.90	p=0.418 (not significant)
Mean hemoglobin level (mg/dl) (HB)	9.53	9.91	8.15	p=0.007 (significant)
Mean hematocrit	30.36	31.17	28.60	p=0.183 (not significant)
Mean platelet count(lakh/mm ³)	1.15	2.07	0.67	p=0.000 (significant)
Chest x ray	Cardiomegaly	4.5%	8.3%	p=0.353 (not significant)
	Normal	95.5%	91.7%	
Mean ejection fraction	62.95%	63.21%	65.10%	p=0.777 (not significant)
Mean end systolic volume	30.18%	27.08%	28.7%	0.092 (not significant)
Mean end diastolic volume	62.45%	60.58%	62.90%	p=0.472 (not significant)

Table 4: Distribution of study group as per ECG findings.

ECG	Percentage
ST, T wave depression in V4-V6, Tall R waves in V5, V6	1.25%
Monophasic R wave in V1, right axis deviation	1.25%
Sinus bradycardia	5.00%
ST segment depression in V4- V6	1.25%
ST segment depression in V4-V6, 1ST degree AV block	1.25%
ST segment elevation in V1, V2	1.25%
ST, T wave depression in V3-V5, RSR' pattern in V1-V2	1.25%
ST, T wave depression in V1-V4	8.75%
Normal	78.75%
Total	100.00%

Table 5: Distribution of study group as per CPK-MB and troponin-I levels.

	Frequency	Percentage
CPK-MB <0.1NG/ML	80	100%
Troponin-I <0.2NG/ML	80	100%

DISCUSSION

This study aimed at evaluating the cardiac involvement in children with Dengue. Patients, proven seropositive with Ns1Ag or/and IgM where enrolled in the study and classified using WHO 2011 classification of Dengue as Dengue without warning signs, Dengue with warning signs and severe Dengue. A total of 80 patients where studied and each of these patients had a 2D-Echo, ECG, CXR, CPK-MB and Troponin-I assessed as soon as possible following admission. Patients hemoglobin, hematocrit, and platelets were also recorded. Patients were classified as either SAM or MAM based on anthropometry.

Mia MW et al, conducted a study on 100 patients as part of clinical and sonological evaluation of Dengue Fever (DF). Among these, 58% were males and 42% were females.⁵ In this study of 80 patients of Dengue fever, 67% were males and 33% were females. In this study Dengue fever was more common in males as compared to females which correlates with the study of Mia MW et al.

In a study conducted in 2005 on Vietnamese infants, male and female infants were at equal risk of developing DHF/DSS which correlates with this study in which 60% of patients with severe Dengue were females and 81.8% of patients with Dengue with warning signs and 64.6% of patients with Dengue without warning signs were males.⁶

In a study conducted in 2005 on Vietnamese infants, 6.9% were malnourished (underweight) of which 16 were MAM and 1 was SAM.⁶ In the same study it was concluded that there was no association between malnutrition status and severe complications in DHF infants. This correlates with this study in which out of 80 patients, 11(13.75%) were MAM and 3(3.75%) were SAM.

In the present study, of the 80 patients, non-severe dengue without warning signs was seen in 48 patients (60%), non-severe dengue with warning signs in 22 patients (28%) and severe dengue in 10 patients (12%). Abhinav Jain et al, in their study, found that out of 58 patients, 43(76%) were Dengue, 11(20%) were Dengue with warning signs, and 2 (3%) were Severe Dengue.⁷

In this study among the clinical signs petechiae was present in (28.75%), rashes in 32.5%, hepatomegaly in (37.5%) and splenomegaly in (28.75%) of the patients. These findings were similar to those found by C.V. Prathyusha et al, in the Paediatric department of Alluri Sita Ramaraju Academy of Medical Sciences, Eluru.⁸ Hepatomegaly was seen in 33.75% cases. In this study all patients with severe Dengue (100%) had hepatomegaly. It was also seen in Chukiat Sirivichayakul et al, study among children 3-14 yrs of age, who observed

hepatomegaly in approximately 40% of cases of DHF. This proportion was significantly higher than that found in Undifferentiated Fever and Dengue Fever.⁹

In the present study the mean platelet value and hemoglobin was significantly lower in patients with severe Dengue than in patients with Dengue without warning signs, dengue with warning signs. This correlates with a study in retrospective study done between 2011 and 2012 in Robert Reid Cabral Children hospital in Santo Domingo which showed that incidence of thrombocytopenia and anemia was more in patients with severe Dengue.¹⁰

In this study, all 80 subjects had undergone Chest X-Ray out of which 7 (8.75%) subjects had cardiomegaly on X-Ray. Of subjects with Dengue without warning signs, dengue with warning signs and severe dengue, 4 (8.3%), 1 (4.5%) and 2 (20%) respectively had cardiomegaly. The comparison shows that cardiomegaly is not significantly affected by severity of dengue. No previous study had compared the chest X-Ray findings in dengue patients.

In this present study, all 80 patients were subjected to ECG. 78.8% of the patient had a normal finding and 17 (21.2%) had an abnormal ECG, the most common ECG findings being ST, T wave depression in leads V1-V4 (8.8%) and sinus bradycardia (5%). Authors found no significant difference in the ECG patterns among subjects with Dengue without warning signs, dengue with warning signs and severe dengue. Kularatne SA et al, in their study of 120 dengue positive subjects, found 75 (62.5%) patients had electrocardiogram changes (T inversion, ST depression, bundle branch blocks), which is significantly higher than these present findings.¹¹

In this study, 2 D-ECHO was done for all patients as soon as possible in the course of illness. Mean ejection fractions in Dengue without warning signs, Dengue with warning signs and severe Dengue were 63.21%, 62.95% and 65.10% respectively and the difference was not statistically significant. The end systolic volume and end diastolic volume also did not show statistical difference between the 3 study groups. These findings do not correlate with a study done by Yacoub et al, in 2012, who found 42% of patients at admission had evidence of LV systolic impairment and 45% had impaired diastolic function.¹² Similarly, a study done in Chulalongkorn University, Bangkok, Thailand in 2003, showed that ejection fraction and VCFC/ESS were significantly lower during the toxic stage than after recovery. End-diastolic volume was low during toxic stage and returned to normal during convalescence and recovery.¹³

All 80 cases had normal age-based values of cardiac enzyme (CPK-MB and Troponin-I). Similarly, in a study done in 2007 by A Khongphatthanayothin et al, Serum troponin T analyzed in only nine of the 91 children with Dengue infection was not elevated.¹⁴

However, in a previous study done by Yacoub et al, of 79 cases with Dengue infection, Troponin I levels were analyzed in 17 cases and one severe dengue case had borderline elevated Troponin-I level of 0.31 ng/ml.¹² Also a study done in January 2011 on 81 Dengue patients, concluded that dengue viruses cause cardiac disease with clinical manifestations ranging from mild elevation of biomarkers to myocarditis and/or pericarditis.¹⁵

CONCLUSION

Authors found that ECG findings do occur in a significant number during Dengue illness, but do not have significant correlation between Dengue without warning signs, dengue with warning signs and severe dengue. 2D-ECHO findings and Cardiac enzymes (CPK-MB and Troponin-I) remain unaffected during Dengue illness and also do not have significant correlation between Dengue without warning signs, dengue with warning signs and severe dengue.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Murray NE, Quam MB, Wilder-Smith A. Epidemiology of dengue: past, present and future prospects. Clin Epidemiol. 2013;5:299.
2. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, et al. Early clinical and laboratory indicators of acute dengue illness. J Infe Dis. 1997 Aug 1;176(2):313-21.
3. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013 Apr;496(7446):504-7.
4. Chan HB, How CH, Ng CW. Definitive tests for dengue fever: when and which should I use?. Sing Med J. 2017 Nov;58(11):632.
5. Mia MW, Nurullah AM, Hossain A, Haque MM. Clinical and sonographic evaluation of dengue fever in Bangladesh: a study of 100 cases. Dinajpur Med Col J. 2010 Jan;3(1):29-34.
6. Nguyen TH, Nyugen TL, Lei HY, Lin YS, Le BL, Huang KJ, Lin CF, Do QH, Vu TQ, Lam TM, Yeh TM, Huang JH, Liu CC, Halstead SB. Association between sex, nutritional status, severity of dengue hemorrhagic fever and immune status in infants with dengue hemorrhagic fever. Am J Trop Med Hyg. 2005 Apr;72(4):370-4.
7. Jain A, Shah AN, Patel P, Desai M, Somani S, Parikh P, et al. A clinico-hematological profile of dengue outbreak among healthcare Professionals in a tertiary care hospital of Ahmedabad with analysis on economic impact. Nat J Comm Med. 2013 Apr;4:286-90.

8. Prathyusha CV, Rao MS, Sudarsini P, Rao KM. Clinico-haematological profile and outcome of dengue fever in children. *Int J Curr Microbiol Appl Sci.* 2013;2(10):338-46.
9. Sirivichayakul C, Limkittikul K, Chanthavanich P, Jiwariyavej V, Chokejindachai W, Pengsaa K, et al. Dengue infection in children in Ratchaburi, Thailand: a cohort study. II. Clinical manifestations. *PLoS Negl Trop Dis.* 2012 Feb;6(2):e1520.
10. Alfredo J. Lora M, Fernandez J, Brito MO. Disease severity and mortality caused by Dengue in a Dominican pediatric population. *Am J of Trop Med Hyg.* 2014 Jan 8;90(1):169-72.
11. Kularatne SA, Pathirage MM, Kumarasiri PV, Gunasena S, Mahindawanse SI. Cardiac complications of a dengue fever outbreak in Sri Lanka, 2005. *Trans Royal Soci Trop Med Hyg.* 2007 Aug 1;101(8):804-8.
12. Yacoub S, Griffiths A, Chau TT, Simmons CP, Wills B, Hien TT, et al. Cardiac function in Vietnamese patients with different dengue severity grades. *Crit Care Med.* 2012 Feb;40(2):477.
13. Khongphatthanayothin A, Suesaowalak M, Muangmingsook S, Bhattarakosol P, Pancharoen C. Hemodynamic profiles of patients with dengue hemorrhagic fever during toxic stage: an echocardiographic study. *Inte Care Med.* 2003 Apr 1;29(4):570-4.
14. Khongphatthanayothin A, Lertsapcharoen P, Supachokchaiwattana P, La-orkhun V, Khumtonvong A, Boonlarptaveechoke C, et al. Myocardial depression in dengue hemorrhagic fever: prevalence and clinical description. *Pediatr Crit Care Med.* 2007 Nov 1;8(6):524-9.
15. Miranda CH, Borges MD, Matsuno AK, Vilar FC, Gali LG, Volpe GJ, et al. Evaluation of cardiac involvement during dengue viral infection. *Clin Infe Dis.* 2013 Sep 15;57(6):812-9.

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