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Cardiac manifestations of Dengue in children: a hospital-based cross-sectional study.

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ABSTRACT

Objectives: **Primary objective**: To estimate the proportion of cardiac manifestations in children with Dengue admitted to hospital. **Secondary objective**: To describe the pattern of cardiac manifestations in children with Dengue admitted to hospital. **Methods**: Hospital-based cross-sectional study done over two years in children admitted with Dengue. Children were subjected to clinical examination, electrocardiograph and echocardiography, during defervescence and when Dengue Haemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS) was diagnosed based on WHO criteria. The information obtained was analysed using SPSS version 11.5. **Results**: The proportion of cardiac manifestations in children admitted with Dengue in our study was 30%. Relative bradycardia, clinically asymptomatic pericardial effusion, left ventricular ejection fraction (LVEF) less than 50%, and global hypokinesia on echocardiography was among our study's common cardiac manifestations**. Conclusions**: Asymptomatic, clinically silent cardiac involvement can occur in significant proportion of children with severe Dengue i.e.in, DHF and DSS.The cardiac involvement in Dengue in children is highly protean, can vary from relative bradycardia, minimal pericardial effusion to the more severe global hypokinesia, and reduced left ventricular ejection fraction on echocardiography.

Keywords: Cardiac manifestations; Dengue; Dengue Haemorrhagic Fever; Dengue Shock Syndrome; Pericardial effusion.

Introduction

Of the arthropod vector-borne viral diseases globally, Dengue is one of the most important and rapidly spreading [1, 2]. The disease incidence has increased in the last five decades by approximately 30 fold across the globe. Dengue has also spread its tentacles across various geographic locations worldwide with spread to new countries and across urban to rural areas. Approximately 2.5 billion people live in dengue-endemic countries, with an estimated 390 million infections occurring annually across 100 countries and 96 million clinical cases with a case fatality rate of around 1% [3].Dengue is caused by four distinct viral serotypes (DENV1, DENV2, DENV3, and DENV4) belonging to flaviviridae [3]. Life-long serotype-specific immunity occurs following infection with one serotype, whereas a second infection by a different serotype may lead to severe to fatal disease, characterised by shock to haemorrhage [4]. The mechanisms that lead to severe, fatal shock syndrome in Dengue remains an enigma, with acute plasma leakage from intravascular space being the ultimate pathophysiological phenomenon [5].

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In a majority of patients, Dengue occurs as a subclinical and asymptomatic infection. The natural history of symptomatic disease follows a clear pattern. In order to manage the clinical cases, the illness is divided into three phases: the febrile phase, the critical phase and the recovery phase. After an incubation period of about four to seven days, the febrile phase begins as an acute febrile illness without focus, with patients having high-grade fever, malaise, loss of appetite, retro-orbital pain, backache, myalgia, nausea and vomiting [1]. Defervescence heralds the onset of critical phase characterized by plasma leakage from intravascular space, which manifests as rising haematocrit, clinical and radiological third space fluid leakage and hypotension [6]. This plasma leakage usually lasts for approximately 24-48 hours after its onset and, if not treated appropriately at the right time, may progress to severe clinical and sometimes refractory shock, i.e. Dengue shock syndrome, which leads to coagulopathy with bleeding, i.e. Dengue haemorrhagic fever; both can culminate into death despite advanced critical care [7].

The principal mechanism leading to shock in Dengue is decreased intravascular volume due to plasma leakage [8], nevertheless, abnormal cardiac function may also contribute to shock states in patients. The incidence of atypical manifestations and various complications of Dengue reported are rising, as the number of Dengue cases is increasing [9], cardiac manifestations being one of them. Numerous studies have reported a spectrum of cardiac manifestations in Dengue, from clinically silent disease to myocarditis, pericarditis and cardiac failure, as well as functional and electrocardiographic abnormalities, especially in adults [6, 10-19]. There are not many studies of cardiac manifestations in paediatric patients of Dengue.

There has been an increasing incidence of Dengue in this part of central Karnataka with an increasing incidence of unusual systemic manifestations, with a concomitant increase in morbidity and mortality. As cardiac involvement in Dengue is not uncommon, and centres handling many dengue cases come across patients with cardiac manifestations, an attempt is made to estimate the proportion and pattern of cardiac involvement in Dengue in children as our centre is a paediatric referral hospital catering to many dengue patients.

Methods

This hospital-based cross-sectional study was carried out over two years at Chigateri Government Hospital (CGH) and Bapuji Child Health Institute (BCHI) attached to JJM Medical College, Davangere, Karnataka State.The following study was carried out to estimate the proportion of patients developing cardiac manifestations and describe the range of these cardiac manifestations in children with Dengue. After obtaining approval from Institution Ethics Committee and written, informed consent from the parent/s,100 consecutive children in the age group of 1yr to 18 yrs., admitted to CGH and BCHI who showed symptoms and signs of dengue fever and had positive IgM or IgG Dengue in the blood, were included in this study. Children aged < 1 year and patients >18 years of age and children with pre-existing congenital or acquired heart diseases and those with IgM or IgG negative Dengue like illnesses were excluded from the study. The patients meeting the inclusion criteria were examined clinically; routine blood investigations were done as needed for dengue management and then subjected to electrocardiography and echocardiography study in the first week of presentation to the hospital at the time of defervescence or when

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Dengue Haemorrhagic Fever and Dengue Shock Syndrome was diagnosed according to WHO criteria.

Data analysis

The information obtained was analysed using SPSS (Statistical Package for Social Sciences) version 11.5 for descriptive statistics, and the results were expressed in proportions, mean, and standard deviation. A p value of < 0.05 was considered as significant.

Results

The baseline characteristics of the admitted dengue patients are displayed in Table I. The mean age of the patients in our study was 6.92 years (±3.5), and the age ranged from 1.5 to 15 years. The mean age of children with cardiac manifestations was 6.1 years (±3.4), and the age ranged between 1.5 to 15 years. The mean age of children without cardiac manifestations was 7.24 years (±3.5), and the age ranged between 1.5 to 14 years. Out of all dengue patients with cardiac manifestations, 90% were in the age group 1 to 10 years, and in those without cardiac manifestations, 74% were in the age group 1 to 10 years. It was observed that the majority of the admitted dengue patients were males (n=67, 67%) than females (n=33, 33%). Furthermore, most patients with cardiac manifestations were males (n=20, 66.6%) compared to females (n=10, 33.3%).

TABLE I: Age and gender distribution of dengue patients with and without cardiac manifestations.

Demographic characteristics	Total Number of dengue patients (n =100)	Children with cardiac manifestations (n=30)	Children without cardiac manifestations (n=70)
Age group			
1-10 years	77	27	52
>10 years	23	03	18
Sex	(n=100)	(n=30)	(n=70)
Male	67	20	47
Female	33	10	23

Out of 100 cases studied, 60 children met World Health Organization (WHO) specified criteria of Dengue Fever (DF), 25 children met WHO specified criteria of Dengue Haemorrhagic Fever (DHF), and 15 children met WHO specified criteria of Dengue Shock Syndrome (DSS). Table II shows that out of 60 children who met WHO specified criteria of DF, none had cardiac manifestations or findings. The incidence of cardiac manifestations in children with DHF was

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80% (n=20) and in children with DSS was 66.6% (n=10). These manifestations were mostly clinically unapparent, except in two patients of dengue shock syndrome who had a refractory shock. In total, out of 100 cases of Dengue, 30 children had cardiac findings. Therefore, the incidence of cardiac manifestations in children with Dengue in our study was 30%.

TABLE II: Proportion of children with cardiac manifestations among various types of Dengue (n=30)

Type of Dengue	Number of children with cardiac manifestations , (n =30)
Dengue fever	0
Dengue haemorrhagic fever	20
Dengue shock syndrome	10

Table III shows the clinical spectrum of symptoms and signs in Dengue patients with and without cardiac manifestations. At the time of admission, fever was the predominant symptom in patients with cardiac manifestations (n=30,100%) and patients without cardiac manifestations (n=70,100%), followed by hepatomegaly, generalised lymphadenopathy, puffiness of face and splenomegaly in both the groups. However, petechial rash on the body (n=18, 60%) and melaena (n=06, 20%) were more commonly seen in those children with cardiac manifestations in comparison to petechial rash (n=13, 18.5%) and melaena (n=10, 14.2%) seen in children without cardiac manifestations. Abdominal pain was the only clinical feature seen more in patients without cardiac manifestations (n=32, 45.7%) than those with cardiac manifestations (n=10, 33.3%).

TABLE III: Clinical spectrum of symptoms and signs in patients with and without cardiac manifestations.

Symptoms and signs	With Cardiac Manifestation, n(%)	Without Cardiac Manifestation, n (%)
Fever	30 (100)	70 (100)
Hepatomegaly	20 (66.6)	59 (84.2)
Generalized Lymphadenopathy	19 (63.3)	54 (77.1)
Puffiness of face	19 (63.3)	50 (71.4)
Splenomegaly	18 (60)	35 (50)

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Petechiae	18 (60)	13 (18.5)
Abdominal pain	10 (33.3)	32 (45.7)
Headache	10 (33.3)	04 (5.7)
Arthralgia	07 (23.3)	15 (21.4)
Melena	06 (20)	10 (14.2)

Table IV shows the laboratory profile of essential parameters used in monitoring dengue patients. The mean haemoglobin value in patients with cardiac manifestations was 8.70 g/dl (±1.29) and ranged from 6.7 to 11.2 g/dl. In contrast, in patients without cardiac manifestations, the mean haemoglobin value was 9.22 g/dl (±1.77) and ranged from 5 to 13.2g/dl. The mean haematocrit value in patients with cardiac manifestations was 26.5% (±4.95) with a range of 19 to 35%, whereas in patients without cardiac manifestations, the mean value was 25.6% (±4.24) with a range of 16 to 34%. The lab parameters were consistent with moderate thrombocytopenia in patients with cardiac manifestations, with a mean platelet count of 0.72 lakhs/cu mm (±0.22) ranged between 0.20 to 1.20 lakhs/cu mm. In patients without cardiac manifestations, mild thrombocytopenia was seen, with a mean platelet count of 1.02 lakhs/cu mm (±0.53) ranged between 0.22 to 3.01 lakhs/cu mm.

TABLE IV: Laboratory parameters among patients with and without cardiac manifestations.

Cardiac manifestations	Total Cases (n=100)	Parameter	Mean	Standard deviation	p- value
Present	30	Haemoglobin (g/dl)	8.70	1.29	0.06
Absent	70		9.22	1.77	
Present	30	Haematocrit (%)	26.5	4.95	0.29
Absent	70		25.6	4.24	
Present	30	Platelet count (Lakhs/cumm)	0.72	0.22	0.000001*
Absent	70		1.02	0.53	

The cardiac findings are presented in Table V. The mean heart rate of children with cardiac manifestations was 93 bpm and ranged from 58 to 140 bpm. The mean heart rate of children without cardiac manifestations was 92 bpm and ranged from 75 to 120 bpm. In our study, ECG demonstrated a narrow QRS complex correlating in two children out of 30 children with cardiac manifestations. ECG was unremarkable in children with DF.ECHO showed that the mean left ventricular ejection fraction in children with DHF and DSS was 58.5 % and ranged from 20% to

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64%. The mean left ventricular ejection fraction in children with DF was 61.1% and ranged from 58 to 64 %.ECHO demonstrated minimal pericardial effusion in 80% of patients with DHF and 66.6% of patients with DSS. None of the children with DF had pericardial effusion. ECHO also demonstrated global hypokinesia in two patients with dengue shock syndrome.

TABLE V: ECG and ECHO findings in patients with cardiac manifestations.

ECG	Dengue Hemorrhagic Fever n = 25(%)	Dengue Shock Syndrome n=15(%)
Heart rate ≤ 60 bpm	2 (8)	2 (13.3)
Narrow QRS complex	1(4)	1 (6.6)
ECHO		
Pericardial Effusion	20 (80)	10 (66.6)
Left Ventricular Ejection Fraction < 50%	0 (0)	2 (13.3)

Discussion

Despite Dengue being one of the most important tropical infectious diseases globally and affecting both adults and children alike, much of the literature on cardiac findings in Dengue is in adult patients. These consist of mainly case reports and case series. These prospective studies have reported a variety of abnormal cardiac involvement in myocarditis and functional abnormalities. The hemodynamic status of patients with Dengue is a function of intravascular volume, cardiac function and appropriate autonomic response.

The present study extends our knowledge on cardiac involvement in Dengue in paediatric patients. Clinical assessment, including cardiac evaluation by electrocardiograph and echocardiography, and relevant laboratory parameters were assessed in paediatric patients of Dengue of varying severity ranging from uncomplicated dengue fever to severe dengue shock syndrome (DSS) during the critical phase of the illness. The data showed that most of the cardiac abnormalities were mild, clinically inapparent and correlated with disease severity with occasional severe involvement, similar to the findings in adult patients of Dengue.

In our study, all the cases enrolled fulfilled the clinical and laboratory criteria of dengue infection as laid out by World Health Organization [1], supported by serum IgM or IgG positivity for dengue infection. Out of 100 cases enrolled, 30 children had cardiac involvement in clinically

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silent, minimal pericardial effusion. Similar findings in the form of asymptomatic cardiac involvement in Dengue were observed in a study conducted in a cohort of adult patients [21]. Therefore, our study observes that even in paediatric patients of Dengue, asymptomatic clinically silent cardiac involvement is prevalent similar to in adult patients with Dengue. Our study's overall proportion of cardiac involvement was 30%, which was high compared to studies [7, 19, 24], but most of the findings were clinically silent and not severe to warrant therapeutic intervention.

The mean age of children with cardiac findings in our study was 6.1 years (±3.4), which was less compared to other studies, probably correlating with the lower mean age itself of children admitted with Dengue which was 6.9 years (±3.5) during the study period, which may be incidental and does not bear much significance. The ratio of male to female patients in the 100 cases of Dengue studied was 2:1; the ratio of male to female patients with cardiac findings was also 2:1. Therefore there was no sex predilection as far as the cardiac findings were concerning.

Asymptomatic, clinically unapparent cardiac involvement in the form of minimal pericardial effusion, diagnosed by ECHO, was present in children in our study. These findings were seen in those who met the World Health Organisation criteria of Dengue Haemorrhagic Fever and Dengue Shock Syndrome. Similar was the observation made by a few other studies [18, 21], probably because plasma leakage into third space is the pathophysiologic mechanism responsible for severe Dengue and pericardial space being one of the third spaces, might have led to pericardial effusion.

The left ventricular ejection fraction determined by ECHO was <50% in only two patients with DSS and was more than 50% in all other patients of DSS, DHF and DF. This proportion is less compared to a study done on myocardial depression in children with dengue haemorrhagic fever [18], where children belonging to all three whom grades of dengue infection showed LVEF <50% in varying proportions children with DSS showed the lowest LVEF. This probably points to the lesser tropism of the dengue virus towards the myocardial muscle in the cases we came across. In contrast, viral tropism for myocardial and skeletal muscle is known to occur and requires cardiac enzyme levels like CPK-MB, Troponin-I, NT Pro-BNP to be measured either [25] or immunochemistry for detection dengue virus in autopsied heart tissue [13].

ECG done in most of the patients were normal except for bradycardia in two patients of dengue haemorrhagic fever and two patients of dengue shock syndrome. Relative bradycardia is known to occur in dengue [13, 20-22]. ECG also revealed a narrow QRS complex in one patient, each of dengue haemorrhagic fever and dengue shock syndrome, which could be due to the pericardial effusion present in these cases. Although arrhythmias in the form of tachyarrhythmias, bradyarrhythmias, heart blocks, including first degree AV block and Wenckebach phenomena, are known to occur [21,22,26], we did not come across these findings. Nevertheless, clinicians should have a high index of suspicion and perform ECG in cases presenting with variations in heart rate, especially in those children with persistent bradycardia and tachycardia and persistent shock to look for arrhythmias.

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Conclusion

In light of our findings and analysis, we conclude that cardiac involvement can occur in significant proportion of children with severe Dengue, i.e. Dengue Haemorrhagic Fever and Dengue Shock Syndrome. The cardiac involvement in Dengue in children is highly protean, can vary from relative bradycardia, minimal pericardial effusion to the more severe global hypokinesia, and reduced left ventricular ejection fraction on echocardiography. As the disease is endemic and can have a fatal outcome in severe Dengue, we suggest doing baseline echocardiography and electrocardiography at the time of admission and repeating these investigations in patients during the critical phase and in patients that progress to Dengue Haemorrhagic Fever and Dengue Shock Syndrome to diagnose pericardial, myocardial involvement as well as arrhythmias in these sick children to guide in further treatment.

Limitations and Future Studies

Serial echocardiography on the day of admission, during the critical phase of illness, and after clinical recovery might add to better understanding of the continuum of cardiac changes in children with dengue. Second, we did not evaluate the cardiac biomarkers, namely CPK-MB, Troponin I, NT-proBNP, which are known to be elevated in myocarditis [13, 25]. As a result, we might have missed those cases, which had clinically silent myocarditis.Estimation of these biomarkers probably might throw light on viral cardiac tropism of dengue in children with clinically inapparent myocarditis.

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