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Original Research Article

Study of cardiac function in adults with dengue

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ABSTRACT

Background: Medical literature has reports of isolated cases of atrioventricular conduction disorders, supraventricular arrhythmias, and myocarditis in dengue fever (DF). There is a paucity of data available in the published literature on the cardiac manifestations of DF from India. The aim of the present study was to assess the cardiac manifestations of DF.
Methods: The 140 patients aged ≥18 years with DF confirmed with a serology-dengue non-structural protein 1 antigen-positive were included for this prospective observational study. Three serial ECGs were taken on day one, day three and day seven or day of discharge. All the patients were evaluated using 2D echo on day one, day seven or day of discharge. The primary outcome measures were to find the incidence and type of echocardiographic abnormalities and electrocardiographic changes in dengue.
Results: The incidence of cardiac abnormalities on ECG and 2D echo was 30 (21.4%), and 5 (7.0%) respectively. On ECG, 14 (10%) 9 (6.4%) 3 (2.1%) 3 (2.1%) and 1 (0.7%) patients had sinus bradycardia, sinus tachycardia, non-specific ST-T changes, right bundle branch block and atrio-ventricular block respectively. On 2D echo, 7 (5.0%), 5 (3.6%) and 1 (0.7%) patient had systolic dysfunction, ejection fraction (<45.0%) and diastolic dysfunction respectively.
Conclusions: The incidence of cardiac abnormalities on ECG and 2D ECHO in dengue patients was considerable. ECG and 2 D echo should be undertaken in patients with DF.

Keywords: DF, Cardiac abnormalities, ECG, 2 D echo

INTRODUCTION

Dengue fever (DF) has emerged as one of the most important mosquitos borne viral disease in the world.[1] The disease can range from mild DF to the severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). Dengue has been endemic in the tropical areas of the world where the environmental factors favor breeding of the Aedes aegypti mosquito.

It is postulated that dengue rarely affects the heart. Medical literature has reports of isolated cases of atrioventricular conduction disorders (junctional rhythm and atrioventricular block), supraventricular arrhythmias, and myocarditis.[2] On the other hand, the ventricular dysfunction associated with the acute phase of DHF has been described and is probably under diagnosed in clinical practice.[2] Although cardiac manifestations specific to dengue are rare, depression of myocardial function is frequent in the hemorrhagic form of the disease or in the associated shock.[3]

There is a paucity of data available in the published literature on the cardiac manifestations of DF from India. The aim of the present study was to find the cardiac manifestations of DF and to identify subclinical/ latent cardiac involvement.

METHODS

This prospective observational study was conducted between June 2018 and May 2019 at Poona hospital and

research Centre, Pune, India. After the approval from the institutional ethics committee (Letter No: RECH/EC/2018-19/0083), a written informed consent was obtained from all the patients prior to enrolment explaining the risks of the study. Patients above 18 years of age admitted in the intensive care unit and wards with DF confirmed with a serology-dengue NS1 antigen positive and/or IgM antibody tests were included. Patients who had a previous history of any type of cardiac illness, an admission electrocardiogram (ECG) suggestive of old myocardial infarction or on medications affecting the heart rate (e.g., β-blockers, β-agonists, calcium channel blockers or xanthine derivatives) and other concomitant infection were excluded.

Baseline demographic information was collected. The patients underwent general physical examination, systemic examination and laboratory tests such as complete blood count, serum sodium, serum potassium, serum calcium and serum magnesium. Three ECGs were taken on day one, day three and day seven or day of discharge (whichever was earlier). All the patients were evaluated using two-dimensional echocardiography on day one, day seven or day of discharge (whichever was earlier) and if required in between.

Patients with features suggestive of rhythm disturbance, heart rate changes like sinus tachycardia or bradycardia, abnormal ECG such as sinus tachycardia, sinus bradycardia, non-specific ST-T wave changes, inverted T waves, first degree heart block and right bundle branch block were noted. Echocardiography changes were interpreted as systolic dysfunction (impaired ventricular contraction), diastolic dysfunction (abnormality in filling during diastole), ejection fraction, pericardial effusion.

Patients classified on basis of WHO criteria as follows:[4,5]

DF

Lived in/travel to the dengue-endemic area, fever and two of the following-nausea, vomiting/rash/aches and pains/tourniquet test positive/leucopenia/any warning sign such as abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation-generalized oedema, pedal oedema, abdominal ascites, pleural effusion, mucosal bleed, lethargy, restlessness, liver enlargement >2 cm on palpation, increase in haematocrit concurrent with a rapid decrease in platelet count.

DHF

Fever or history of fever lasting 2-7 days, occasionally biphasic, a hemorrhagic tendency shown by at least one of the following: a positive tourniquet test; petechiae, ecchymoses or purpura; bleeding from the mucosa, gastro-intestinal tract, injection sites or other locations; or hematemesis or melena, thrombocytopenia [≤100,000 cells/mm^3 (100×10^9/L), evidence of plasma leakage owing to increased vascular permeability shown by an increase in haematocrit ≥20% above the average for age, sex and population; a decrease in the haematocrit after intervention ≥20% of baseline; signs of plasma leakage such as pleural effusion, ascites or hypo-proteinaemia.

DSS

All the criteria for DHF, in addition to evidence of circulatory failure manifested by rapid, weak pulse and narrow pulse pressure (<20 mm of Hg) manifested by hypotension for age and cold, clammy skin and restlessness or lethargy.

The primary outcome measures were to find the incidence and type of echocardiographic abnormalities and electrocardiographic changes in DF, DHF and DSS, whereas the secondary outcome measure was to find the risk factors associated with cardiac abnormalities. Assuming the incidence of 10.0% of cardiac manifestations in dengue, the sample size was calculated by a formula $N^6=(Z_\alpha)^2p(1-p)/d^2$ We have taken Z_α a standard normal variate at 5% type 1 error (1.96). A total sample size of 140 was calculated by the above method.

Statistical analysis

Data collected were entered in excel 2007 and analysis of data was done using statistical package for social sciences for Windows, version 20.0 from IBM corporation, Armonk, NY, USA. The data on categorical variables are shown as n (% of cases). The data on continuous variables are presented as mean and standard deviation (SD). Comparison of the distribution of categorical variables was done using the Chi-square or Fisher's exact test. Comparison of continuous variables was done by unpaired t-test. The underlying normality assumption was tested before subjecting the study variables to an unpaired t-test. Multiple logistic regression analysis was done. The confidence limit for significance was fixed at 95% level with a $p<0.05$.

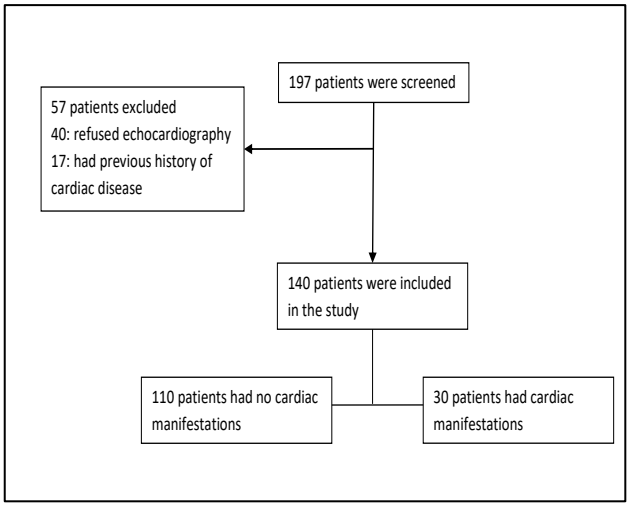

Figure 1: Consort diagram.

RESULTS

Of 197 patients screened, 57 were excluded from the study. One hundred-forty patients were included in the study (Figure 1). Of 140 patients, 11 (7.9), 23 (16.4%), 27 (19.3%), 41 (29.3%), 30 (21.4%), and 8 (5.7%) were ≤ 20, 21-30, 31-40, 41-50, 51-60 and ≥61 years respectively. The mean ± SD of age was 41.6±13.2 years. Of 140 patients, 87 (62.1%) were males. Of 140 patients, 47 (33.6%), 69 (49.3%) and 24 (17.1%) had DF, DHF and DSS respectively. Of 140 patients, one patient died. One hundred thirty-two (94.3%), 127 (90.7%), 110 (78.6%), 46 (32.9%), 30 (21.4%), 24 (17.1%), 14 (10.0%) and 7 (5.0%) had myalgia, fever, retro-orbital pain, rash, bleeding, shock, chest pain and dyspnea respectively. Thirty-four (24.3%), 26 (18.6%), 25 (17.9%), 12 (8.6%), 10 (7.1%) and 9 (6.4%) had blanching, systolic BP<90 mm of Hg, hepatomegaly, pericardial rub, splenomegaly and pulse rate ≥100 per min respectively. Of 140 patients, 30 (21.4 %) patients had cardiac manifestations. Of 140 patients, 110 (78.6%) 14 (10.0%) 9 (6.4%) 3 (2.1%) 3 (2.1%) and 1 (0.7%) had normal sinus rhythm, sinus bradycardia, sinus tachycardia, non-specific ST-T changes, right bundle branch block (Figure 2) and atrio-ventricular block (Figure 3) on ECG respectively. One hundred thirty-three (95.0%), 7 (5.0%), 5 (3.6%) and 1 (0.7%) had normal 2D echo findings, systolic dysfunction, ejection fraction (<45.0%) and diastolic dysfunction respectively.

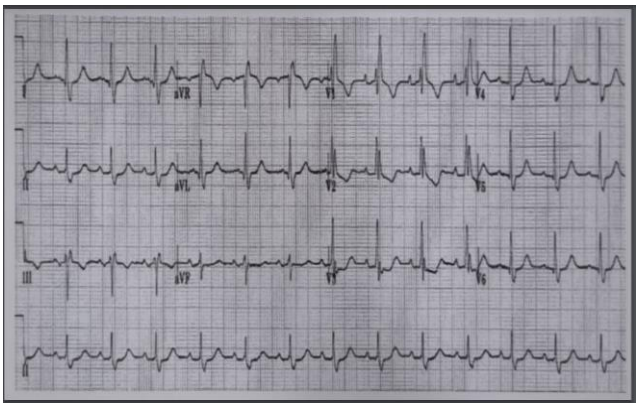

Figure 2: Right bundle branch block.

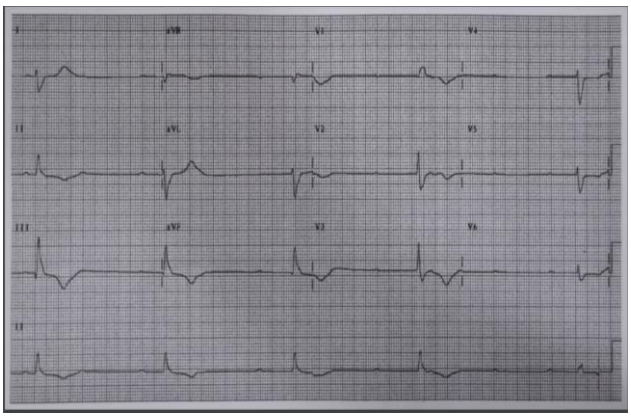

Figure 3: AV block.

The ECG and 2D echo status did not differ significantly across various age groups of the patients (p>0.05). The ECG status did not differ significantly across various categories of severity of dengue (Table 1). The 2 D echo status did not differ significantly across various categories of severity of dengue (Table 2). The mean duration of hospital stay was 6.9±1.1 days and 6.6±1.1 days in patients who had abnormal ECG and normal ECG respectively (p=0.183). The mean duration of hospital stay was 6.6±1.3 days and 6.6±1.1 days in patients who had abnormal 2 D echo and normal 2 D echo respectively (p=0.183). The logistic regression analysis showed that the parameters such as age, gender, type of dengue, platelet count, did not show significant association with the cardiac abnormalities (Table 3).

Table 1: Distribution of ECG status according to severity of dengue.

Severity of dengue	ECG status		Total, n (%)	P
	Abnormal, n (%)	Normal, n (%)		
DF	8 (17)	39 (83)	47 (100)	0.270
DHF	14 (20.3)	55 (79.7)	69 (100)	
DSS	8 (33.3)	16 (66.7)	24 (100)	
Chi-square test was used				

Table 2: Distribution of 2D echo status according to severity of dengue.

Severity of dengue	2D echo status		Total, n (%)	P
	Abnormal, n (%)	Normal, n (%)		
DF	3 (6.4)	44 (93.6)	47 (100)	0.875
DHF	3 (4.3)	66 (95.7)	69 (100)	
DSS	1 (4.2)	23 (95.8)	24 (100)	
Fisher's exact test was used				

Table 3: Multivariate logistic regression analysis for the independent determinants of cardiac abnormality (ECG/ECHO).

Variables	Category	Odds ratio	95% CI OR	P
Age group (years)	<40	1.00 (Ref)	--	--
	≥40	1.84	0.84-2.57	0.149
Gender	Female	1.00 (Ref)	--	--
	Male	1.67	0.79-2.38	0.262
Type of dengue	DF	1.00 (Ref)	--	--
	DHF	1.41	0.62-2.53	0.421
	DSS	1.95	0.92-2.96	0.085
Platelet count	>100000	1.00 (Ref)	--	--
	≤100000	1.57	0.81-2.48	0.208

DISCUSSION

The mechanism and severity of myocardial injury by dengue has not been extensively studied in the literature. Dengue can affect cardiac function both by direct invasion as well as by autoimmune reaction causing myocardial inflammation. Cardiac manifestations of dengue are usually transient and self-limited. Cardiac abnormalities seen during the acute phase of dengue infection include ECG abnormalities such as sinus tachycardia, sinus bradycardia, non-specific ST-T changes, right bundle branch block, A-V nodal block, an ECHO abnormalities such as systolic dysfunction, diastolic dysfunction, reduced ejection fraction, pericardial effusion.[7] Yacoub et al opined that where available, echocardiography should be performed in patients with dengue, particularly in those with severe disease and refractory shock, to tailor their management.[7]

Arora et al reported that the mean age of the patients was 33.0±12.7 years.[3] Sukhawani et al reported that the mean age of the patients was 27.9 years.[8] Wali et al reported that the mean age was 29.8 years.[9] In the present study, the mean ± SD of age was 41.6±13.2 years which is higher than the above studies. Arora et al, Sukhawani et al and Wali et al reported that 85 (70.83%), 36 (62.1 %) and 70.6 % patients were males.[3,8,9] In the present study, 62.1 % patients were males. This is comparable to above studies.

Arora et al reported that the commonest clinical presentation was myalgia (97.5%) followed by fever (92.5%).[3] Sukhawani et al reported that the major presenting complaint among patients was fever and body ache. The study further reported that rashes, subconjunctival hemorrhage, nose bleeding, gum bleeding and hematemesis were observed in 17 (29.3%), 6 (10.3%), 5 (8.6%), 3 (5.2%), and 2 (3.4%) cases respectively.[8] Wali et al reported that haemorrhagic manifestations were seen in 14 (82.4%) patients. The study further reported that bleeding manifestations included petechiae, gum bleeding, epistaxis, haemoptysis, melaena, and haematemesis in 9 (52.9%), 7 (41.2%), 6 (35.3%), 2 (11.8%), 1 (5.9%), and 3 patients (17.6%) respectively.[9] In the present study, 132 (94.3%), 127 (90.7%), 110 (78.6%), 46 (32.9%), 30 (21.4%), 24 (17.1%), 14 (10.0%) and 7 (5.0%) had myalgia, fever, retro-orbital pain, rash, bleeding, shock, chest pain and dyspnea respectively.

Arora et al reported that on clinical examination 33.3% of the patients had petecheia and only 9 patients having active bleeding manifestation at the time of presentation.[3] In the present study, 34 (24.3%), 25 (17.9%), 12 (8.6%), and 10 (7.1%) patients had blanching, hepatomegaly, pericardial rub, and splenomegaly respectively.

Sukhawani et al, Datta et al, and Mansanguan et al reported that 9/58 (15.5%), 15/120 (12.5%). and 22.2% of patients had cardiac manifestations respectively.[8,10,11] In the present research, 30/140 (21.4%) patients had cardiac manifestations which are similar to above studies.

Arora et al reported that rhythm disturbance was noted in 5% of the patients with AV block being the most common (66.7%).[3] Gupta et al reported that of 28 patients, 4 (14.3%) and 6 (21.4 %) patients had sinus bradycardia and sinus tachycardia respectively.[12] Datta et al, Sheetal et al reported that 8 (6.6%) and 32/100 (32.0%) patients had bradyarrhythmias respectively.[10,13] Sheetal et al reported that of 100 patients, sinus bradycardia was found in 32 % of patients.[13] Wali et al reported that of 17 patients, ECG was abnormal in 5 patients with horizontal ST elevation (2-3 mm) and T inversion and bradycardia (heart rate 60/min) was present in 3 patients.[9] In the present study, 14 (10.0%) 9 (6.4%) 3 (2.1%) 3 (2.1%) and 1 (0.7%) had sinus bradycardia, sinus tachycardia, non-specific ST-T changes, right bundle branch block and atrio-ventricular block on ECG respectively.

Gupta et al reported that in 2D echo, 4 (14%), and 1 (3.5%) patient had grade 1 diastolic dysfunction and mild pericardial effusion respectively.[12] Datta et al reported that 4 patients had left ventricular systolic dysfunction (ejection fraction 35-45%) and 2 patients had pericardial effusion.[10] Sukhawani et al reported that diastolic dysfunction and pericardial effusion were presented in only 1 (1.7%) cases.[8] Mansanguan et al reported that 3 (3.7%), 3 (3.7%), and 6 (7.4%) patients had left ventricular systolic dysfunction, transient diastolic dysfunction, and small pericardial effusion respectively. The study further reported that myocarditis was suspected in only two DHF patients.[11] In the present study, 7 (5.0%), 5 (3.6%) and 1 (0.7%) had systolic dysfunction, ejection fraction (<45.0%) and diastolic dysfunction respectively.

In the present study, an increasing trend was observed in incidence of ECG abnormalities and severity of dengue-17.0% in DF, 20.3% in DHF, and 33.3% in DSS. However, there was statistically no significant association between ECG abnormalities and the severity of dengue. Only 7 (5%) patients had abnormal echo findings. Sukhawani et al reported that the incidence of cardiac manifestations was more common in DHF and DSS which was 15.5% and 3.4%, respectively.[8] In the present study, the patients that had echo abnormalities also had ECG abnormalities.

Determining the risk factors that might be useful in predicting cardiac abnormalities can help in management of dengue patients.[7] For instance, decisions regarding investigations like echocardiography, need for in-patient or intensive care in dengue patients can be informed based on the presence of these risk factors. In the present study, multivariate logistic regression analysis to determine independent predictors of cardiac abnormalities as seen on ECG and echo showed no significant association of age, gender and platelet count and severity of dengue.

Limitations

As this was a single centre study, it is difficult to generalise its findings to other populations. Cardiac biomarkers were not included in this study. Cardiac magnetic resonance

imaging was not done to determine the presence of myocarditis. This may have led to an underestimation of the cardiac abnormalities in dengue patients included in the study. Multicentric prospective studies with a large sample size should be undertaken to substantiate the research findings described in this paper.

CONCLUSIONS

The incidence of cardiac abnormalities on ECG was 30 (21.4%), whereas the incidence of cardiac abnormalities on echo was 5 (7%). On ECG, 14 (10%), 9 (6.4%), 3 (2.1%), 3 (2.1%) and 1 (0.7%) had sinus bradycardia, sinus tachycardia, non-specific ST-T changes, right bundle branch block and atrio-ventricular block respectively. On 2D echo, 7 (5.0%), 5 (3.6%) and 1 (0.7%) had systolic dysfunction, ejection fraction (<45.0%) and diastolic dysfunction respectively. Parameters as- age, gender, type of dengue, and platelet count did not show significant association with cardiac abnormalities. ECG should be obtained in all patients diagnosed with dengue.

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