Arrhythmia spectrum and outcome in children with myocarditis

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ABSTRACT

Introduction	:	**Myocarditis remains an under-diagnosed entity among children. We evaluated the spectrum of electrocardiogram (ECG) changes and arrhythmias in children with myocarditis.**
Methods	:	**A single-center prospective observational study was conducted over a period of 18 months at a public university hospital, which included all cases with myocarditis from the ages of 1 month to 12 years. Myocarditis was diagnosed according to standard criteria. Arrhythmias were detected by 12-lead ECG or by multiparameter monitors.**
Results	:	**There were 63 children with myocarditis. Sinus tachycardia remained the most important ECG finding (61, 96.8%) followed by ST-T changes (30, 47.6%), low voltage QRS complexes (23, 36.5%), and premature complexes (11, 17.4%). Sustained arrhythmias were seen in 14/63 (22.2%) of the children (Group A), while the remaining 49 patients were designated as Group B. There were 11 (17.5%) cases with sustained tachyarrhythmias, comprising 5 with supraventricular tachycardia, 4 with ventricular tachycardia, and 2 with atrial flutter/fibrillation. Bradyarrhythmias were seen in 3 patients, including 2 children with atrioventricular block and 1 with severe sinus bradycardia. A longer hospital stay of 18.5 (4.75) days vs. 13 (4) days, $P = 0.001$), and more ST-T changes [12 (85.7%) vs. 18 (36.73%), $P = 0.003$] were seen in Group A. Multivariate regression analysis found only the presence of ST-T changes as predictors for arrhythmia.**
Conclusions	:	**A variety of arrhythmias and other ECG changes were commonly seen in children with myocarditis. Sustained arrhythmias were seen in one-fifth of the patients, being associated with ST-T changes and a longer hospital stay.**
Keywords	:	Cardiomyopathy, electrocardiography, pediatric arrhythmias

INTRODUCTION

Myocarditis is commonly caused by viral infections which can be seen in both children and adults. Alternate etiologies include other infections, toxins, systemic diseases, autoimmune process, or hypersensitivity reactions.[1] The true incidence of myocarditis is unknown, mainly because a considerable number of patients are asymptomatic and hence not diagnosed.[2] The diagnosis could also be challenging during infancy because it can masquerade as a respiratory or gastrointestinal

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ailment.[1,2] Studies have shown that boys are more susceptible to viral myocarditis[3,4] and there is a bimodal peak in infants, and teenagers.[5] Myocarditis has a wide clinical spectrum, ranging from asymptomatic cases and subclinical myocarditis, to severe symptoms including chest pain, arrhythmias, acute heart failure with dilated cardiomyopathy, fulminant myocarditis, and sudden cardiac death.[6] Cardiac arrhythmias are commonly seen in patients with myocarditis, with incidence of arrhythmia at presentation reported as 29%–45%,[7,8] to as high as 100% in patients with fulminant myocarditis.[9]

METHODS

This was a single-center prospective observational study, conducted between October 2016 and March 2018 at a teaching hospital in Mumbai, India. Institutional Ethics Committee approval was obtained, and informed consent was taken from the parents/caretaker. Consecutive patients admitted in the pediatric intensive care unit, between ages 1 month to 12 years with the diagnosis of myocarditis were included in the study. The criteria for the diagnosis of myocarditis were: A clinical context of myocardial injury with cardiovascular symptoms with at least one of the following: (A) biomarkers of cardiac injury raised, (2) electrocardiogram (ECG) findings suggestive of cardiac injury, and (3) abnormal cardiac function on echocardiogram.[10] The children were observed in the intensive care unit for a minimum of 24 h, where they were constantly monitored using 12-lead ECG, and on multiparameter monitors. Stable patients were shifted to the wards. Continuous ECG monitoring using Holter could not be performed, due to logistic constraints, hence rhythm was monitored manually, with 12-lead ECG recorded every 12 h and additionally as needed. The types and frequency of arrhythmia, duration of stay, treatment course, as well as invasive and noninvasive therapeutic procedures (including the need of mechanical ventilator, electrical cardioversion, and inotropic support) were recorded. Based on standard ECG criteria, the documented arrhythmias were classified as tachyarrhythmias (ventricular tachycardia, supraventricular tachycardia, and atrial flutter/atrial fibrillation) and bradyarrhythmia (atrioventricular block, sinus bradycardia, and junctional escape rhythm). Isolated premature complexes, sinus tachycardia, and PR prolongation were noted. ECG findings of low voltage complexes and ST-T changes were also noted. Low voltage was defined as QRS complexes of <0.5 mV in all limb leads and 1.0 mv in all precordial leads. ST-T changes were defined as J point elevation by >0.25 mv in boys or >0.15 mv in girls in leads V2–3 and >0.1 mv in all other leads; ST depression was defined as horizontal or downsloping ST segment ≥1 mV. Cardiac enzymes, transthoracic echocardiography, and routine biochemistry were performed in all the cases.

Treatment included supportive and symptomatic care. Guideline-directed medical therapy was given to all patients who developed symptomatic heart failure, which included diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blockers. Patients with cardiogenic shock received inotropic and vasopressor support. Rhythm control was attempted with amiodarone or synchronized DC cardioversion, as and when appropriate. Corticosteroids, mainly prednisolone, alone or in combination with cyclosporine or azathioprine were given to patient with fulminant myocarditis.

Statistical analysis

All analyses were performed using SPSS (version 20.0, IBM Corp., Armonk, NY, USA). Categorical variables were expressed as percentages, whereas continuous variables were presented as mean ± standard deviation, and these continuous variables were approximated to the form of the normal distribution and compared by Student's *t*-test. Skewed variables were presented as median with interquartile range and compared using Mann–Whitney U-test. Z-test was used to check for significance of association for mortality. Chi-square test was used for the categorical variables between the two groups. While arrhythmia was taken as a dependent variable, and risk factors of arrhythmia in patients with myocarditis were identified by using univariate analysis and multivariate logistic regression. Odds ratio (OR), *P* value, and 95% confidence interval (CI 95%) were calculated. Binary multivariate logistic regression was used to screen the risk factors, and the regression model was established using backward Wald method and was then expressed as Forest Plot. All hypothesis tests of significance were two-tailed, and significance was defined as $P < 0.05$.

RESULTS

The study group had 63 children: 40 boys and 23 girls, aged 5.7 ± 4.2 years. The ECG abnormalities included sinus tachycardia in 61 children (96.8%), ST-T changes in 30 (47.6%), low voltage QRS complexes in 23 (36.5%), and premature complexes in 11 (17.4%). Children with sustained arrhythmias were classified as Group A, while the remaining were designated as Group B. There were 14 children (22.2%) in Group A, of whom 11 had tachyarrhythmia [4 with ventricular tachycardia, 5 with supraventricular tachycardia, and 2 with atrial flutter/fibrillation, Figure 1] and 3 had bradyarrhythmia (2 with high degree AV block and 1 with severe sinus bradycardia). There were 49 patients (77.8%) in Group B. All the arrhythmias developed within the first 7 days of hospital admission [Table 1]. Adverse events consisted of need for inotropic support or mechanical ventilation were seen in 34 out of 63 (53.9%) patients. The overall mortality was 14.3% (9 patients).

Table 1: Demographics, clinical presentation, and parameters of the whole cohort (*n*=63)

Parameters	*n* (%)	Mean±SD
Average age (years)	-	5.66±4.21
Gender distribution (males)	40 (63.49)	-
Duration of hospital stay (days)	-	
Low voltage ECGs	23 (36.50)	14.14±4.25
ST-T changes	30 (47.61)	
Sinus tachycardia	61 (96.82)	
Baseline heart rate		
Ectopics (APCs VPCs)	11 (17.4)	142.66±17.4
Arrhythmias	14 (22.22)	
Atrial fibrillation	2 (3.17)	
Atrial tachycardia	3 (4.76)	
Atrial flutter	0	
SVT	2 (3.17)	
PJRT	0	
VT	4 (6.34)	
Junctional rhythm	1 (1.58)	
High degree AV block	2 (3.17)	
LVEF (%)		
Cardiogenic shock	20 (31.74)	39.92±8.05
Mechanical ventilation requirement	19 (30.15)	
Inotropic support	34 (53.9)	
DC cardioversion	6 (9.52)	
Mortality	9 (14.3)	

(2 acute VT, 1 sub-acute VT, 1 acute + sub-acute VT). ECG: Electrocardiogram, APCs: Atrial premature complexes, VPCs: Ventricular premature complexes, SVT: Supraventricular tachycardia, PJRT: Permanent junctional reciprocating tachycardia, VT: Ventricular tachycardia, AV: Atrioventricular, DC: Direct current, SD: Standard deviation, LVEF: Left ventricle ejection fraction

Figure 1: Upper panel shows supraventricular tachycardia; lower panel shows ventricular tachycardia in another patient

There was no significant difference between groups A and B with respect to age at presentation, gender distribution, presence of low voltage complexes on ECGs, left ventricular ejection fraction, need for inotropic support or development of cardiogenic shock, requirement of mechanical ventilation, or mortality [Table 2]. The hospital stay in Group A was longer with median (interquartile range) of 18.50 (4.75) days versus 13 (4) days in Group B, *P* = 0.001. ST-T changes [Figure 2] were more frequent in Group A than in Group B, 12 (85.7%) versus 18 (36.7%), *P* = 0.003. All surviving patients in group A had a complete recovery with control of arrhythmia at discharge.

A Forest plot to express mutivariate binary logistic regression [Figure 3] was performed to test the likelihood for arrhythmia in patients with myocarditis. This was done to exclude confounding factors and screen independent risk factors for the development of arrhythmia. A level of significance was achieved only for the presence of ST-T changes (OR = 10.095, CI: 1.7–61.7, *P* = 0.01).

DISCUSSION

Myocarditis can range from being asymptomatic to having a fulminant course riddled with arrhythmias, need for inotropic support, mechanical ventilation, and death. In our study, infants comprised of 16 (25.4%) of the 63 patients, while children in the age group 10–12 years comprised of 18 (28.6%) of the 63 patients. This was similar to the findings in the study done by Ghelani *et al.*[5] There was a male predominance seen (40, 63.5%), consistent with findings of Caforio *et al.*[1] and Fairweather *et al.*[4] The exact reason for the gender differences is not known, but studies[4,11,12] have noted that exercise and hormonal factors may be important, testosterone being contributory and estrogen being protective.

Arrhythmias form an important feature in the spectrum of myocarditis and can affect the in-hospital stay, clinical course, outcome, and prognosis.[13] We found sustained tachyarrhythmias in 11 (17.5%) of the patients, and these were both supraventricular and ventricular in origin. Bradyarrhythmias were infrequent. There were other ECG changes that were even more common, such as ST-T abnormalities and low voltage QRS complexes.

Morimoto *et al.*[14] performed endomyocardial biopsy in 50 patients with acute myocarditis, to study the role of myocardial interstitial edema, as a cause for conduction disturbances and found a significant association for both ventricular tachycardia and complete AV block with the presence of edema. A Japanese working group document on myocarditis[15] stated that sinus

Figure 2: Marked ST segment elevations in one of the children with myocarditis

bradycardia, prolonged QRS duration, increased left ventricular hypokinesia on echocardiography, and persistent or fluctuating troponin level may predict life-threatening arrhythmias. We found no predictive factors for the development of arrhythmias, though all the arrhythmias were observed within the first 7 days after hospital admission. This was similar to the findings of Ichikawa *et al.*,[9] who also reported that arrhythmias which were seen in the active phase of myocarditis, resolved during convalescent and remote phases. This suggests that patients of myocarditis should undergo vigilant ECG monitoring at least for a week after presentation.
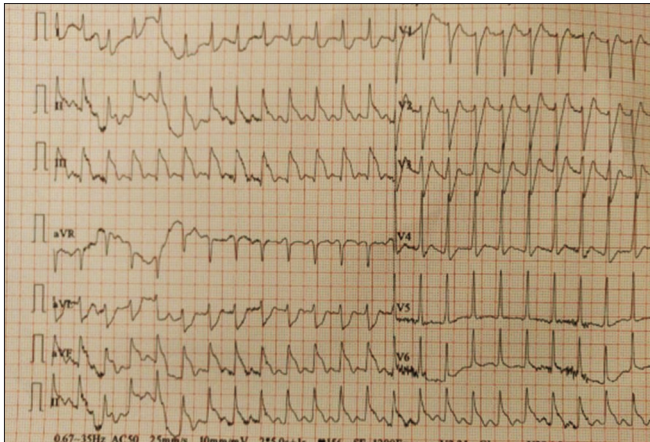
We observed that four-fifths of the arrhythmia group required inotropic support, mostly before the development of arrhythmia. This signified that more severe cases are at risk of arrhythmia, with an added proarrhythmic potential of the inotropes. None of the participants with ventricular tachycardia or high degree AV block required a subsequent pacemaker or implantable defibrillator, suggesting that once the inflammation settles, at least the part of damage is reversible. However, the number of patients with high
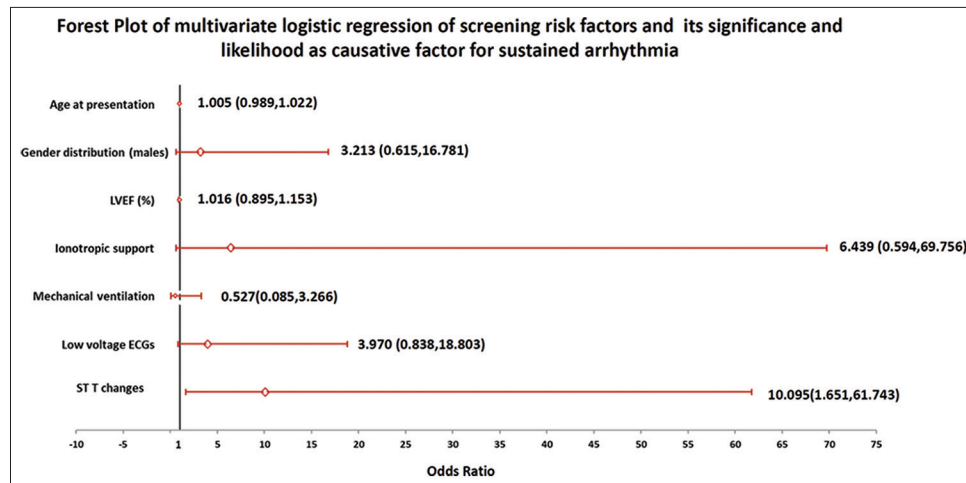

Figure 3: Forest plot for multivariate logistic regression to screen risk factors and determine their likelihood as causative factors for sustained arrhythmia

Table 2: Comparison between the two groups

Parameters	Group A (*n*=14)		Group B (*n*=49)		*P*
	n (%)	Central parameter	*n* (%)	Central parameter	
Age at presentation		66 (72)		60 (115)	0.94
Gender distribution (males)	10 (71.42)		30 (61.22)		0.48
Duration of hospital stay		18.50 (4.75)		13 (4)	0.001
Baseline heart rate		152.14±12.14		139.96±17.82	0.006
ST-T changes	12 (85.7)		18 (36.73)		0.003
Low voltage ECGs	8 (57.14)		15 (30.61)		0.06
LVEF (%)		37±8.21		40.75±7.89	0.144
Cardiogenic shock	7 (50)		13 (26)		0.096
Inotropic support	11 (78.57)		23 (46.93)		0.07
Mechanical ventilation	6 (42.85)		13 (26.53)		0.24
Mortality	4 (28.6)		5 (10.20)		0.19

ECG: Electrocardiogram, LVEF: Left ventricle ejection fraction

degree AV block in our study was too few, to derive any meaningful conclusion regarding their course. Batra *et al.*[16] studied 40 patients of myocarditis with complete heart block and found that only 27% of them required permanent pacemaker implantation. Ichikawa *et al.*[9] found complete resolution of rhythm abnormalities in survivors at follow-up, including those with complete heart block. Wiles *et al.*[17] performed endomyocardial biopsy of 33 consecutive children with ventricular ectopic rhythm but a structurally normal heart on examination and found that approximately 50% of these patients had subclinical cardiomyopathy or unsuspected myocarditis. Friedman *et al.*[18] studied whether resolution of occult myocarditis in children with associated ventricular arrhythmia correlated with the presence of arrhythmia at late follow-up. They found that complex arrhythmias could persist after apparent resolution of occult myocarditis, though these are easier to control, and may require patients to be kept on long-term anti-arrhythmic therapy.

Limitations

An important limitation of our study is the lack of cardiac magnetic resonance imaging (MRI) in our diagnostic protocol, so our patients are classified as probable at best, but we tried to evaluate all the patients with echocardiographic suggestion in the form of left ventricular dysfunction or dilatation. An endomyocardial biopsy may be indicated for such patients but there are limitations to the sample obtained and the site of inflammation. As most diagnosis of myocarditis was made clinically, and patients with dilated cardiomyopathy were excluded, we could have missed cases of chronic myocarditis. Continuous ECG monitoring was also not possible for patients who had been shifted to general wards, so late arrhythmias could have been missed. There is also lack of data in patients who died, as autopsy was not conducted in majority of cases.

CONCLUSIONS

Sustained and varied arrhythmias were seen in over one-fifth of children with myocarditis, developing within the 1st week of admission. These arrhythmias were associated with ST-T changes and a longer hospital stay.

Conflicts of interest

There are no conflicts of interest.

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