

Original research article

To Evaluate Cardiac Manifestations of Diphtheria in Children at GIMS Hospital Kalaburagi: A Retrospective Study

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Abstract

Diphtheria continues to be reported from many parts of the world. Complete heart block is rare but often fatal complication of diphtheric myocarditis. We report six children with diphtheric myocarditis who presented with complete heart block. Three patients survived, one with persistent complete heart block. Aggressive supportive management including transvenous pacing may result in complete recovery in a significant number of children with diphtheric myocarditis.

Material and Method: For this study, 67 patients having diphtheria presenting for the first time in a 3 year period were enrolled after obtaining informed verbal consent from the guardian of each child. Demographical profile, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded.

Results: Among the 67 enrolled children (M: F 2.4:1) with age ranging from 24 to 172 months (median 106 months), 56.7% subjects presented with diphtheria were non-vaccinated. Almost 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. Total 7.5% patient expired on follow up. Septal paradoxes had 76% sensitivity and 100% specificity with a positive predictive value (PPV) of 100%. Nasopharyngeal membrane had a PPV of 40.4% (P=0.42). Neck swelling had a PPV of 57.9% (P=0.02). Moderate severity score of diphtheria disease had a PPV of 90% and severe disease had a PPV of 100%. Tracheostomy at presentation having a PPV of 100% (p=0.001). Presence of arrhythmia was associated with the highest mortality (Odd Ratio 18.1; 95% CI 2.7-73.9; P = 0.0001). Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2-84.6; P = 0.0005)

Conclusion: Early prediction by alone or in combination of ECG and echocardiographic marker leads to early pick up of the disease and can decrease the burden of the disease in the community. Increased immunization coverage including booster dose of diphtheria and Tetanus (DT), easy availability of anti-diphtheritic serum (ADS), early prediction and recognition and effective treatment all may reduce the incidence and mortality.

Keywords: Diphtheria, cardiomyopathy, Children, Predictors

Introduction

Diphtheria once known as “the straggling angel of children” is a major preventable disease of childhood with high morbidity and mortality. Although it is no longer a public health problem in the developed nations, it continues to be reported from developing world. The toxin mediated disease affects multiple systems and cardiovascular involvement is a major contributor to the mortality varying from 50% to 75%. Cardiac manifestations include myocardial dysfunction as well as bradyarrhythmias and tachyarrhythmias; although the most feared one is complete heart block (CHB) with almost all cases being fatal despite ventricular pacing. There is scant literature available on this dreaded complication. Herein, we report six patients of diphtheria who presented to a tertiary care centre in India with CHB. Diphtheria remains an important cause of pediatric mortality in developing countries. The mortality rate is still ~10% and has changed little over the past 20 years with particular reference to developed world¹. A resurgence of diphtheria has been observed in developing nations, are largely attributed to waning vaccine immunity and social taboos leading to poor immunization coverage in children especially above 5 years of age. Acute mortality is due to toxin-mediated diphtheritic cardiomyopathy, suffocation by the pseudomembrane, disseminated intravascular coagulation, and renal failure^{2,3}. The incidence of diphtheritic cardiomyopathy following diphtheria is 10%–20%, and some Indian studies reported the occurrence of myocarditis is 16-66% and the associated mortality is ~50%. Myocarditis in diphtheria is reported to be the sole independent predictor of death with an adjusted Odds ratio 25, (95% confidence interval (CI) 3.4-210.3)⁴. Clinical signs of diphtheritic cardiomyopathy become apparent by the end of 2nd week of infection but, in severe cases, may be a presenting feature⁵. Severe conduction abnormalities including tachy or brady-arrhythmias or complete heart block are reported in 50% of patients presented with diphtheria cardiomyopathy and reported to be uniformly fatal for children^{6,7}. Most of the large series describing the clinical and electrocardiographic features of diphtheria were reported in old studies, before the availability of modern electrocardiographic, echocardiographic and bio chemical measurements⁸. These studies found that the development of severe conduction defects on the 12-lead electrocardiograph were associated with a poor prognosis⁹. We have recently observed on the prognostic and predictor utility of combined echocardiographic and electrocardiography and have shown that, in some cases of diphtheritic cardiomyopathy, intervention with temporary cardiac pacemaker or off label use of IV methylprednisolone may improve the outcome. The ability to predict from simple and readily available measures whether myocarditis will develop would aid in triage and clinical management. We aimed to examine clinical spectrum of diphtheric cardiomyopathy and diagnostic tools (serum markers, ECG, Echocardiography) to assess particular findings that might predict the development of diphtheritic cardiomyopathy and poor survival.

Material and Method:

For this study, 67 patients having diphtheria presenting cases in 3 year period (2018-2021) at GIMS, Hospital, Kalaburagi, Karnataka, were enrolled after obtaining informed verbal consent from the guardian of each child. Demographical profile, vaccination status, clinical spectrum, ECG interpretation and echocardiographic findings were recorded

Statistical Analysis

Data was entered in SPSS version 20 and analyzed using its statistical package. Frequency was calculated for qualitative variables including gender, vaccination status, and cardiomyopathy. Data was presented as mean, SD and median. Between groups comparison was done using Chi-square test for categorical data and Students' t-test and Mann Whitney U test for parametric and non-parametric data respectively. Univariate and multivariate analysis were performed to determine significance and to identify the predictors having a significant association with

cardiomyopathy and mortality. Odd's ratio with 95% CI was computed for the significant variables. All variables found to be significant on univariate analysis ($P < 0.05$).

Results

Sixty-seven subjects presented with diphtheria were recruited in the study in a 3 year period. There were 47 (70.1%) boys and 20 (29.9%) girls with boys to girl's ratio of 2.4:1. Median age at the time of presentation was 106 months (range 24-172 months). Median day of presentation to a tertiary care hospital was 3 days (range 1-9 days). Nearly 58.2% patients belong to rural areas. In total 38 (56.7%) subjects presented with diphtheria were non-vaccinated for diphtheria vaccine and 18 (26.9%) were completely vaccinated and 11(16.4%) were partially vaccinated. None of the subject in this cohort was given a booster vaccine at 5y of age. Total 70.1% patients had a nasopharyngeal membrane during initial presentation and 28.4% (n=19) had a neck swelling initially at presentation and 11.9% presented with stridor. All the patients who presented with stridor at initial clinical manifestation need a tracheostomy at subsequent days due to overt or impending upper airways obstruction. Majority (83.6%) of children presented with mild severity of the disease. Only 1.5% patients presented with severe disease and toxic look

Table 1: Comparison between cardiomyopathy VS no cardiomyopathy

Variable	Cardiomyopathy	No Cardiomyopathy	P value
Total patients	25	42	--
Age (months, Median, range)	110(48-157)	105 (24-172)	$P < 0.003$
Gender	M:F= 3 : 1	M:F= 2:1	NA
Un-Immunization (n, %)	13 (52%)	25(59.5)	$P = 0.213$
Partial immunization (n, %)	3 (12%)	8(19)	$P < 0.004$
Adequate immunization (n, %)	9 (36%)	9 (21.5)	$P < 0.002$
Neck swelling (n,%)	11(44%)	8(19%)	$P = 0.249$
Tracheostomy (n, %)	8 (32%)	0	$P = 0.650$
ECG (RBBB) (n, %)	3 (12)	1(2.4%)	$P = 0.389$
ECG (ST segment changes) (n, %)	6 (24)	1 (2.4%)	$P = 0.671$
Echocardiography (LV dysfunction) (n, %)	15(60)	0	$P = 0.690$
Septal paradoxes	19 (76%)	0	$P < 0.0001$
Mild LV dysfunction (>45%)	13 (52%)	0	$P < 0.001$
Time of presentation	3 (2-9)	3 (1-5)	$P < 0.0021$
Deaths (n, %)	5 (20%)	0	$P < 0.038$
EF <35% and death	5 (100%)	--	$P < 0.016$

In all the affected cases 25.4% patients had a positive throat culture for the *Corynebacterium diphtheriae*. Both the electrocardiography (ECG) and echocardiography were different at initial presentation and subsequent follow up. Out of these 76.1% (n=51) had a normal ECG at initial presentation (65.7% at subsequent ECGs), 4 (6.0%) had a right bundle branch block (RBBB),

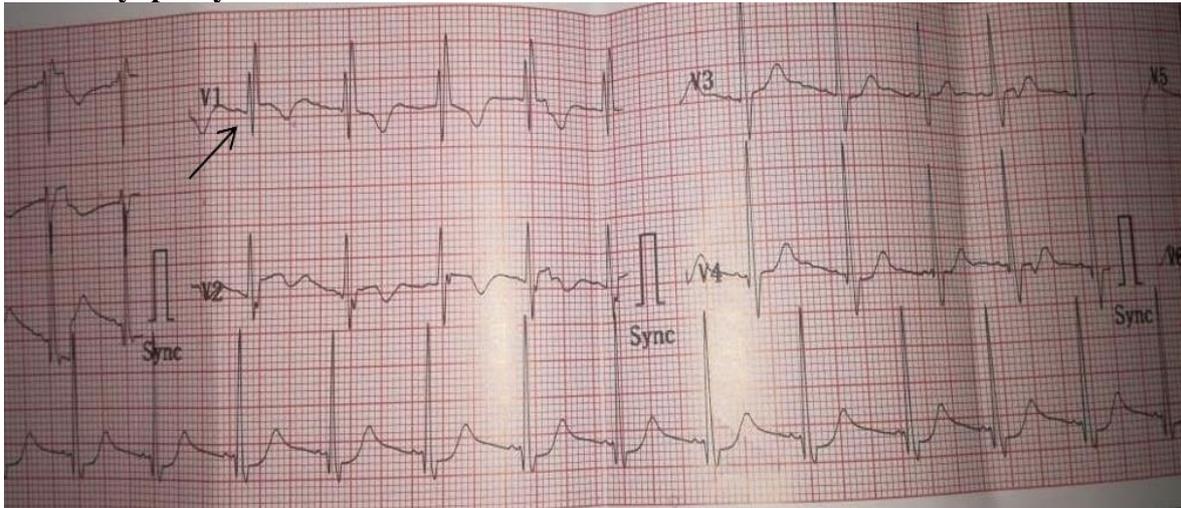
3% had a 1st degree heart block (10.4% on subsequent ECGs), 1.5% had complete heart block (3% on subsequent ECGs), 1.5% had VT (4.5% on subsequent ECGs). Forty- nine patients (73.1%) had a normal echocardiography at presentation, 23.9% (n=16) had septal paradoxes at initial echocardiography and 3% (n=2) had a LV systolic dysfunction (22.4% on subsequent echocardiography). Twenty-five (37.3%) had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9 ± 2.4 days (range 2-11 days). Among the cardiac involvement with LV dysfunction 52% had a mild LV dysfunction (EF>45%) on echocardiography and 18.8% had a moderate LV dysfunction (EF 35-45%). 7.5% (N=5) patient expired on follow up. Male had more commonly cardiac involvement as compared to female with a male: female 3:1 as compared to 2:1 among non-cardiomyopathy patients. Almost half (52%) were unimmunized in the group involve the heart but it is not statistically significant (p=0.213). patients who had neck swelling as initial presentation had a more cardiac involvement as compared to no neck swelling (44% vs 19%). Eight patients (32%) of patient who had a tracheostomy subsequently had cardiac involvement.

Table2: Comparison of Survivors vs Non-survivors (Complications) and risk

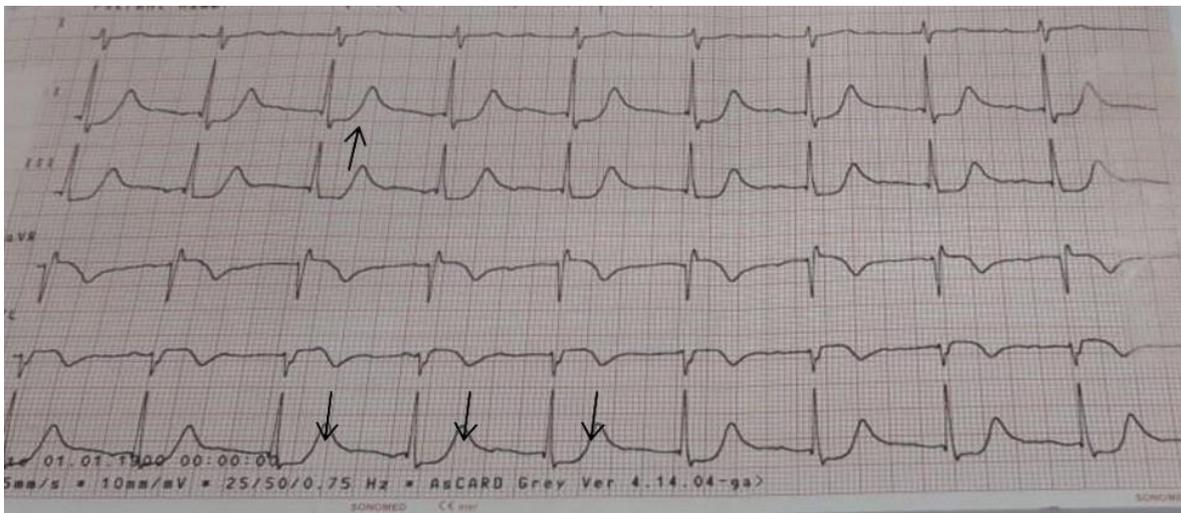
Complications	Survivors (n=62)	Non survivors (n=5)	Odd's Ratio (OR)	95% Confidence limit for OR	P value
Airway compromise	06	02	0.63	0.11-3.5	0.310
Neck swelling	17	02	1.7	0.31-9.2	0.480
Inspiratory stridor	07	03	4.9	1.0-25.1	0.002
Tracheostomy	07	01	1.8	0.2-14.5	0.009
Myocarditis	20	05	14.3	3.1-68.5	0.0001
Septal paradoxes	15	04	10.1	1.2-84.6	0.0001
Arrhythmia	11	05	18.1	2.7-73.9	0.0005

There were many predictors that predict the subsequent cardiac involvement and ultimately the outcome of the patient's. Septal paradoxes was an important marker in the prediction of the cardiomyopathy in patients with diphtheria. Septal paradoxes had 76% sensitivity and 100% specificity with a positive predictive value (PPV) of 100%. Nasopharyngeal membrane had a PPV of 40.4% (P=0.42). Neck swelling had a PPV of 57.9% (P=0.02). Moderate severity score of diphtheria disease had a PPV of 90% and severe disease had a PPV of 100%. Tracheostomy at presentation having a PPV of 100% (p=0.001). Some parameters had a very strong positive predictor value regarding outcome of the disease in the form of death. Ventricular tachycardia (VT) at presentation or on subsequent ECG had a PPV of 94% and complete heart block had a PPV of 82%. Out of 25 patients with myocarditis 5 (20%) died (Odd's ratio 14.3, 95% CI 3.1-68.5, P = 0.0001);. Presence of arrhythmia was associated with the highest mortality (OR 18.1; 95% CI 2.7-73.9; P = 0.0001). Presence of septal paradoxes on echo had association with the cardiac involvement (OR 10.1: 95% CI 1.2-84.6; P = 0.0005) **Table 2.**

Fig 1= ECG changes partial RBBB (i) and ST segment changes (ii) in diphtheria cardiomyopathy



(i)



(ii)

Discussion

Diphtheria, caused by toxigenic strains of *Corynebacterium diphtheriae*, is an ancient disease with a significant high incidence and mortality that has always been characterized by epidemic waves of occurrence and is more common in winter in India. There are sporadic cases of diphtheria and cardiomyopathy associated with diphtheria in the developed world¹⁰ but it is still a significant cause of mortality in developing world like India. In this study, we demonstrated the early predictors of diphtheria cardiomyopathy aiming at early detection and pick up of the disease and prompt response may alter the outcome of the disease. There was male pre dominance in our study and it is comparable with the literature^{11, 12}. The Male: Female is 2.3:1 which is comparable to regional literature as well¹¹. Median age at the time of presentation was comparable with other studies also had a range of presentation 62-120 months^{4, 12, 13}. In this study and the related literature the cluster of diphtheria among age group of 5-10y is possibly due to lack of booster dose (DT). Patients less than 5 year are possibly rare because of immunization effect and also maternal antibodies in the younger infants. So with advancing age due to possible modifying response of antibodies due to lack of booster dose is likely reason for common presentation of diphtheria at this age group. Almost half of subjects presented with diphtheria were non- vaccinated for diphtheria vaccine and 26.9% were completely vaccinated

which is comparable to the regional data⁴ in which 56.3% were non immunized. Although immunized and partially immunized children were also presented with diphtheria but their number is less and likely diminished efficacy of administered vaccine at early age group is the reason of this presentation. The diphtheria cardiomyopathy usually associated with exotoxins mediated myocardial injury produced by these microorganisms¹³. The incidence of diphtheritic cardiomyopathy following diphtheria is 10%–20%, and some Indian studies reported the occurrence of myocarditis is 16- 66% and the associated mortality is ~50%^{4, 13}. Our study showed 37.3% had a cardiac involvement in the form of diphtheria cardiomyopathy or arrhythmia. The mean interval between onset of respiratory symptoms and myocarditis was 5.9 ± 2.4 days (range 2-11 days). Majority of the patients with myocarditis were asymptomatic, had only ECG changes, SGOT elevation, and early changes in the echocardiography and had a favorable outcome. Out of 25 patients having diphtheria cardiomyopathy there was 20% expired during the course of treatment. Overall mortality among diphtheria patients was 7.4% which is comparable to the local and regional data^{11,12} where it was 8.9% and 5% but the 20% expiry among diphtheria cardiomyopathy is significantly low as compare to study by Jayashree M, Shruthi N et al⁴ where the frequency was above 70%. This expiry rate was irrespective of the anti-diphtheritic serum (ADS) administration because almost all the patient got the ADS at admission. It was observed that almost all patients developed cardiac involvement within first week of onset of respiratory symptoms and patients who had bull neck and extensive faucial patches had more incidence of cardiac involvement and this is comparable to the literature as well^{4,14}.

Conclusion

Diphtheria is still a public health problem in many developing countries and remains the major cause of morbidity and mortality due to lack of implementation of extended program of immunization (EPI) and also the booster dose of diphtheria in our setup. Diphtheria with its worst complications like diphtheria cardiomyopathy is still highly prevalent in this region of the world and major cause of mortality among diphtheria patients. Early prediction by alone or in combination of ECG and echocardiographic marker leads to early pick up of the disease and can decrease the burden of the disease in the community. Strict public health measures like an increased immunization coverage including booster dose (DT), easy availability of anti-diphtheritic serum (ADS), early prediction and recognition and effective treatment all may reduce the incidence and mortality.

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