Complete heart block due to diphtheritic myocarditis in the present era

Mithun J Varghese, Sivasubramanian Ramakrishnan, Shyam S Kothari, Akhil Parashar, Rajnish Juneja, Anita Saxena
Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India

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.

Keywords: Complete heart block, diphtheria, myocarditis

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.[1-4] The toxin mediated disease affects multiple systems and cardiovascular involvement is a major contributor to the mortality varying from 50% to 75%.[5,6] 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.[7] 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. Three representative cases are presented in detail.

Case 1

A 10-year-old boy had presented with history of fever of 10 days duration along with progressive swelling of neck. Three days prior to admission he also developed difficulty in swallowing with nasal regurgitation of food associated with progressive dyspnea and orthopnea. There was no reliable history of adequate immunization against diphtheria. On examination his pulse rate was 42 beats per minute, regular, low volume with blood pressure of 86/64 mmHg, and there was bilateral cervical lymphadenopathy. His clinical assessment revealed a membrane over right tonsil and posterior pharyngeal wall with features of bulbar palsy as well. Electrocardiogram (ECG) showed CHB with a ventricular escape rate of 40. A temporary transvenous pacemaker was inserted immediately in view of the low heart rate. An emergency echocardiogram showed global hypokinesia with left ventricular ejection fraction (LVEF) of 15%. His investigations showed raised white blood cell (WBC) count of 38100/mm^3 with neutrophilic preponderance as well as elevated renal parameters. Although his throat swab cultures and blood cultures were sterile, a provisional diagnosis of bulbar diphtheria with myocarditis was made and he was started on intravenous erythromycin and crystalline penicillin along with diphtheria antiserum. Although he was afebrile throughout the hospital stay, he continued to be in CHB and developed progressive hypotension, which was treated with inotrops. He sustained a ventricular tachycardia (VT) on day six of admission, which was refractory, and he expired on the same day due to progressive cardiogenic shock.

Case 2

The second patient was an 8-year-old boy who presented with complaints of fever and cough of 10 days duration along with progressive neck swelling. He developed

Access this article online

Quick Response Code:

Website: www.annalspc.com

DOI: 10.4103/0974-2069.107231

Address for correspondence: Dr. Sivasubramanian Ramakrishnan, Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India.
E-mail: ramaaiims@gmail.com

bulbar symptoms including nasal regurgitation of food and nasal twang after six days into the illness. Since the onset of neurological symptoms he was admitted in a tertiary pediatric hospital with a provisional diagnosis of diphtheria based on presence of extensive membrane formation in both tonsils and pharynx. Treatment given to him included penicillin, erythromycin, and diphtheria antitoxin although no positive culture reports were available. On the tenth day of illness he developed significant bradycardia and was referred to our center as a suspected case of diphtheria myocarditis. Clinical examination revealed cervical lymphadenopathy, features of bulbar palsy and generalized diminished tendon reflexes in addition to bradycardia. ECG showed CHB with a ventricular escape rate of 40 beats per minute; hence a temporary pacemaker was inserted immediately. He had severe biventricular dysfunction (LVEF = 20%) and moderate mitral regurgitation (MR) and tricuspid regurgitation (TR) by echocardiography. After admission he was continued on antibiotics and antiserum and other supportive measures. His blood work up was unremarkable except for mild leukocytosis. During the hospital stay he had two episodes of accelerated junctional rhythm lasting few minutes and subsided on its own. On day six of admission his ECG reverted to normal sinus rhythm after an intermediate few hours of atrial flutter with variable conduction. He continued to have a favorable course in hospital with LVEF showing remarkable improvement to 50% along with improvement in neurological symptoms and hence was discharged after 22 days of hospital stay.

Case 3

A 5-year-old boy was referred to our outpatient clinic as a case of CHB. Forty days prior, he was admitted in a pediatric tertiary hospital with fever and neck swelling of seven days duration followed by bulbar symptoms, cranial nerve palsies, and respiratory difficulty. His ECG done was unremarkable except for sinus tachycardia although no echocardiography was done during the acute stage. He was diagnosed as a case of bulbar diphtheria and was given antiserum as well as antibiotics and other supportive measures. He required intubation and ventilator support for 15 days. Meanwhile his throat swab culture grew Corynebacterium diphtheriae thus confirming the diagnosis. Over the next month he showed significant improvement, but noted to have relatively slow heart rate while in hospital. A repeat ECG done revealed CHB with ventricular rate of 62 beats per minute and had narrow QRS escape [Figure 1]. As his neurological recovery was near complete he was discharged and referred to our center. An echo done then revealed mild left ventricle (LV) dysfunction with LVEF of 50% while ECG showed persistence of CHB. Hoping for recovery, it was decided to keep child on close medical follow-up as the he was asymptomatic. But even after five months, he continued to be in CHB and hence a pacemaker implantation was advised. This was not agreeable to the parents and he was lost to follow-up subsequently. The baseline features and investigation findings in the patients are summarized in Tables 1-3.

DISCUSSION

Diphtheritic myocarditis occurs in 10-20% of patients presenting with oropharyngitis.[8] Relatively recent Indian series on diphtheria report a 16-66% occurrence of myocarditis;[6,9] the wide variation is probably related to the type of set up whether primary or tertiary care and the method used to diagnose myocarditis. Diphtheritic myocarditis is associated with a mortality rate of 60-70%, and is the most common cause of death in diphtheria.[6] Myocarditis is reported to be the only independent predictor of death with an adjusted Odds ratio (OR) 25, (95% confidence interval (CI) 3.4-210.3).[6] Severe conduction abnormalities including CHB develops in approximately 50% of patients with diphtheria myocarditis and is considered to be uniformly fatal.[7,8,10]

Conduction system involvement in diphtheria is shown to be due to acute inflammation of sinoatrial and atrioventricular nodes leading to even their disruption in fatal cases.[11] Toxin mediated inhibition of protein synthesis is the essential mechanism for all systemic manifestations in diphtheria. Diphtheria toxin is directly cardiotoxic and it causes DNA fragmentation and cytolysis by inhibiting the elongation factor-2 activity in protein synthesis.[12] The myocardium apart from interstitial inflammation shows hyaline degeneration and necrosis. Conduction tissue is also affected.[13] In this context, it is difficult to explain the recent reports of occurrence of myocarditis by nontoxigenic strains of C. diphtheriae.[14]

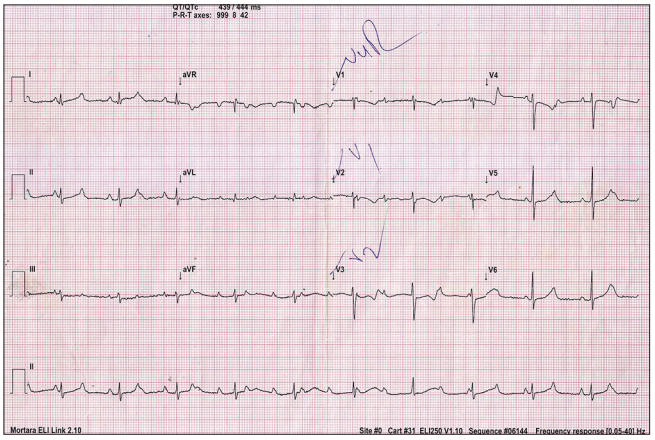

Figure 1: Complete heart block persisting nearly a month after recovery from proven diphtheria myocarditis in a 5-year-old child

Table 1: Baseline features of the six patients

Case	Age (years)	Sex	Immunization	Day of presentation (days)	Duration of hospital stay (days)	Bacteria isolated	Antitoxin before D10 of illness	Survival
1	10	M	Nil	10	6	No	No	Died
2	8	M	Partial	10	22	No	No	Survived
3	5	M	Partial	7	35	Yes	Yes	Survived with long-term CHB
4	6	F	Nil	9	3	Yes	Yes	Died
5	5	M	Not known	21	8	No	No	Survived
6	9	F	Nil	8	5	No	Yes	Died

CHB: Complete heart block

Table 2: Clinical features and basic investigation results of the six patients

Case	Fever	Bull neck	Nasopharyngeal membrane	Bleeding tendency	Airway compromise	Neurological manifestation	Total WBC count (per mm^3)	Creatinine	LFT
1	Yes	Yes	Yes	No	No	Bulbar palsy	38000	4.2	Normal
2	Yes	Yes	Yes	No	No	Bulbar palsy	14500	1.5	Normal
3	Yes	Yes	-	No	Yes	Quadriparesis	-	-	-
4	Yes	Yes	Yes	Yes	No	Delirium, quadriparesis	41000	3.4	Elevated
5	Yes	Yes	Yes	No	No	Bulbar palsy quadriparesis	16800	0.9	Normal
6	Yes	Yes	Yes	Yes	No	Bulbar palsy	29000	2.8	Elevated

LFT: Liver function tests, WBC: White blood cell

Table 3: Echo and ECG findings of the six patients

Case	LVEF (%)	Other echo findings	Pulmonary edema	Cardiogenic shock	Presentation ECG	Documented arrhythmias
1	15	Severe global biventricular dysfunction, mild mitral regurgitation (MR) and tricuspid regurgitation (TR)	Yes	Yes	CHB with wide low voltage QRS complex	VT
2	20	Severe global biventricular dysfunction, mild MR, mild pericardial effusion	No	No	CHB with LBBB pattern escape, low atrial rhythm	Junctional rhythm, atrial flutter
3	50	Mild LV dysfunction	No	No	-	-
4	25	Severe LV dysfunction, mild MR	No	Yes	CHB with LBBB pattern QRS complex	Junctional rhythm, VT
5	15	Severe global biventricular dysfunction, mild MR and TR	No	No	Low junctional rhythm at 36 bpm and intermittent CHB	IntermittentJunctional rhythm
6	30	Severe global biventricular dysfunction, moderate MR and TR, mild pericardial effusion	No	Yes	Low atrial rhythm, CHB with broad QRS escape	VT

ECG: Electrocardiogram, LVEF: Left ventricular ejection fraction, LV: Left ventricle, CHB: complete heart block, LBBB: Left bundle branch block, VT: Ventricular tachycardia

Data regarding CHB associated with myocarditis including those due to diphtheria is limited in recent literature. Conduction system disturbances in patients with diphtherial myocarditis are markers of severe myocardial damage and are uniformly fatal despite ventricular pacing.[7] However, in our series, three of the six patients survived with proper supportive measures including airway management and temporary pacemaker insertion. This better survival may be due to the improvement in supportive measures provided over the years. A recent study from Vietnam also reports similar findings with 27% survival rate in patients who underwent cardiac pacing.[15] In that study, 7 (26%) of the 27 patients who received a temporary cardiac pacemaker survived, compared with 0 of the 16 patients who did not receive a cardiac pacemaker.

Diphtheria myocarditis can result in long-term CHB as seen in case number three in our series. This is not intuitively obvious as all manifestations of diphtheria including cardiac function recover with no residual effect. However, recent studies have documented a variety of nonsustained bradyarrhythmias and tachyarrhythmias occurring even after discharge from the hospital. The time course of recovery from diphtheritic myocarditis is longer than has been appreciated previously.[16] Left bundle branch block (LBBB) is also recognized as an independent predictor of long-term survival in diphtheritic myocarditis.[17] However, long-term CHB seems rare as literature search revealed only two case reports[18,19] of diphtheria myocarditis in preimmunization era, which resulted in long-term CHB.

All patients who developed cardiogenic shock and secondary ventricular arrhythmias died. VT occurs in the later stages of illness and is usually refractory and all the patients who developed this arrhythmia in our series expired. Although junctional rhythm and supraventricular arrhythmias including atrial flutter was seen in three patients these complications were not uniformly fatal unlike the case with VT. Elevated renal

and liver function tests probably denotes an advanced stage of illness and was seen in all the patients who died thus serving as markers of poor prognosis. Finally, vaccination although not fully protective, may afford some benefit as two of the survivors received at least partial immunization while all the patients who died never received any form of preventive coverage.

Apart from supportive measures, treatment options in diphtheria myocarditis are limited. Antitoxin is of proven value in the early stages of the illness, but it has limited action against penetrating toxin or toxin already absorbed into the cell. Hence, it is unlikely to have made much of a difference in our patients as all of them presented at a much later time course of illness. Yet, antitoxin administration to all who are suspected of diphtheria myocarditis is recommended as this is the only specific antidote available and may neutralize any unbound toxin. The role of immunosupressive therapies such as steroids and immunoglobulins are not proven yet[20,21] and were not used in any of our patients. In a study of 66 patients with diphtheria, steroid therapy did not prevent the occurrence of myocarditis and of neuritis.[20] A study reported that carnitine showed a significant reduction in incidence of myocarditis and a significant reduction in mortality as compared with controls.[22]

It is important to remember the preventive measures against diphtheria for the care givers. We provided standard droplet infection prophylaxis to all the suspected diphtheria cases. Moreover, all were given antibiotic prophylaxis with Azithromycin 500 mg once daily or erythromycin 500 mg QID for the duration of contact. All traceable contacts of these patients were advised to get throat cultures done and to watch for symptoms. Close household contacts of these patients were also given prophylactic course of antibiotics.

Limitations

The report pertains to only 6 patients, and the outcome reported here would have a wide confidence interval. The organism was isolated in only 2 children, but the diagnosis was reasonably secure. Mechanical support devices or ECMO was not used in the patients with cardiogenic shock that could influence the outcomes potentially.

CONCLUSIONS

Diphtheria myocarditis continues to occur among the poor under vaccinated children and is associated with very high mortality. CHB from diphtheric myocarditis is not uniformly fatal.

REFERENCES

1. Singh J, Harit AK, Jain DC, Panda RC, Tewari KN, Bhatia R, *et al.* Diphtheria is declining, but continues to kill many children: Analysis of data from a sentinel center in Delhi, 1997. Epidemiol Infect 1999;123:209-15.
2. Lodha R, Dash NR, Kapil A, Kabra SK. Diphtheria in urban slums in north India. Lancet 2000;355:204.
3. Anima H, Malay M, Santanu H, Rajashree R, Sita C, Baran SA. A study on determinants of occurrence of complications and fatality among diphtheria cases admitted to ID and BG hospital of Kolkata. J Commun Dis 2008;40:53-8.
4. Ornek E, Ureyen CM, Kurtul A, Oksüz F. Diphtheria myocarditis in Turkey after years. Anadolu Kardiyol Derg 2012;12:279-80.
5. Kneen R, Pham NG, Solomon T, Tran TM, Nguyen TT, Tran BL, *et al.* Penicillin vs. erythromycin in the treatment of diphtheria. Clin Infect Dis 1998;27:845-50.
6. Jayashree M, Shruthi N, Singhi S. Predictors of outcome in patients with diphtheria receiving intensive care. Indian Pediatr 2006;43:155-60.
7. Stockins BA, Lanas FT, Saavedra JG, Opazo JA. Prognosis in patients with diphtheric myocarditis and bradyarrhythmias: Assessment of results of ventricular pacing. Br Heart J 1994;72:190-1.
8. Hoyne A, Welford N. Diphtheritic myocarditis, a review of 496 cases. J Pediatr 1934;5:642-53.
9. Havaldar PV, Sankpal MN, Doddannavar RP. Diphtheritic myocarditis: Clinical and laboratory parameters of prognosis and fatal outcome. Ann Trop Paediatr 2000;20:209-15.
10. Smith S. Heart rhythm in diphtheria. JAMA 1922;77:765-71.
11. James TN, Reynolds EW Jr. Pathology of the cardiac conduction system in a case of diphtheria associated with atrial arrhythmias and heart block. Circulation 1963;28:263-7.
12. Collier RJ. Dipheria toxin: Mode of action and structure. Bacteriol Rev 1975;39:54-85.
13. Hadfield TL, McEvoy P, Polotsky Y, Tzinserling VA, Yakovlev AA. The pathology of diphtheria. J Infect Dis 2000;181(Suppl 1):S116-20.
14. Kanungo R, Vijayalakshmi N, Nalini P, Bhattacharya S. Diphtheria due to non-toxigenic corynebacterium diphtheriae: A report of two cases. Indian J Med Microbiol 2002;20:50-2.
15. Dung N, Kneen R, Kiem N, Bethell DB, Phu NH, Solomon T, *et al.* Treatment of severe diphtheritic myocarditis by temporary insertion of a cardiac pacemaker. Clin Infect Dis 2002;35:1425-9.
16. Bethell DB, Dung NM, Loan HT, Le Minh TN, Dung NQ, Day NP, *et al.* Prognostic value of electrocardiographic monitoring of patients with severe diphtheria. Clin Infect Dis 1995;20:1259-65.
17. Celik T, Selimov N, Vekilova A, Kursaklioglu H, Iyisoy A, Kilic S, *et al.* Prognostic significance of electrocardiographic abnormalities in diphtheritic myocarditis after hospital discharge: A long-term follow-up study. Ann Noninvasive Electrocardiol 2006;11:28-33.
18. Butler S, Levine SA. Diphtheria as a cause of late

heart-block. Am Heart J 1930;5:592-8.

19. Sayers EG. Diphtheritic myocarditis with permanent heart damage. Ann Intern Med 1958;48:146-57.
20. Thisyakorn U, Wongvanich J, Kumpeng V. Failure of corticosteroid therapy to prevent diphtheritic myocarditis or neuritis. Pediatr Infect Dis 1984;3:126-8.
21. Mason JW, O'Connell JB, Herskowitz A, Rose NR, McManus BM, Billingham ME, *et al*. A clinical trial of immunosuppressive therapy for myocarditis. The myocarditis treatment trial investigators. N Engl J Med 1995;3:333:269-75.
22. Ramos AC, Barrucand L, Elias PR, Pimentel AM, Pires VR. Carnitine supplementation in diphtheria. Indian Pediatr 1992;29:1501-5.

How to cite this article: Varghese MJ, Ramakrishnan S, Kothari SS, Parashar A, Juneja R, Saxena A. Complete heart block due to diphtheritic myocarditis in the present era. Ann Pediatr Card 2013;6:34-8.

Source of Support: Nil, **Conflict of Interest:** None declared