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Original Article

Paediatrics Section

Diphtheria in Children- Clinical Profile of Cases during an Outbreak in Kerala, India

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ABSTRACT

Introduction: Diphtheria is an acute potentially fatal infectious disease caused by the toxigenic strains of *Corynebacterium diphtheriae.* Acute respiratory obstruction, toxic myocarditis and neurologic weakness are the most important complications of diphtheria. The clinical presentation and severity of diphtheria vary in immunised and non immunised children. Early diagnosis and prompt treatment including administration of diphtheria antitoxin and antibiotics minimise mortality.

Aim: To observe the changing trends in the clinical presentation of diphtheria during the 2016 outbreak and its association with immunisation status and antitoxin administration.

Materials and Methods: This longitudinal prospective study was conducted among children admitted to Government Medical College, Kozhikode, Kerala, a tertiary care centre with a diagnosis of diphtheria during January 2016 to December 2016. Details of socio-demographic data, clinical presentation, investigations, immunisation status, treatment and complications were collected using a semi-structured performa. These children were managed by an interim guideline provided by the state authorities. They were followed-up for 3 months i.e. till March 2017. The data was analysed using Statistical Package for Social Sciences (SPSS), version 18.0.

Results: Among 76 children, 62(81.6%) were from Malappuram and Kozhikode districts, which have relatively low immunisation coverage. Most admissions were in July 2016. Majority 58 (76.3%) of children belonged to Muslim community. The mean age was 8.1 years with male to female ratio 1.53:1. Most of the children 47 (61.8%) were unimmunised or partially immunised. Cultures were positive for *C. diphtheriae* in 20 children. Complications were noted in 36 children, which included asymptomatic myocarditis in 31, symptomatic myocarditis in one, palatal palsy in nine, loss of accommodation in four and distal weakness in five. Only one child who received antitoxin within 72 hours of disease onset developed neurological complications. Complications were common in children who received less than minimum three doses of diphtheria vaccines compared to those who received three or more doses (54% vs. 44%). There was no mortality.

Conclusion: There was an upward shift in age of affected children. Neurological complications were significantly less in those who received antitoxin within 72 hours of disease onset. Regular monitoring helped to detect asymptomatic myocarditis. The outbreak highlighted the need to improve awareness about diphtheria and better vaccination coverage, especially in older children.

Keywords: Clinical presentation, Complications, Diphtheria antitoxin, Immunisation status, Vaccination

INTRODUCTION

Diphtheria is an acute potentially fatal infectious disease caused by the toxigenic strains of *Corynebacterium diphtheriae* [1]. In the pre-vaccine era, more than 40% of cases occurred in children below five years. Recently an upward shift in age is observed both in developed and developing countries [2,3]. Acute respiratory obstruction, toxic myocarditis and neurologic weakness are the most important complications of this disease. Cardiac involvement may be asymptomatic {characterised only by changes in Electrocardiogram (ECG) and/or raised cardiac enzymes) or symptomatic (with clinical features of heart failure)} [4]. The main modality of treatment is administration of diphtheria antitoxin and antibiotics. The rapidity of seeking medical care and administering specific treatment is known to decrease the mortality [1]. Immunisation status of the individual affects the clinical presentation and severity of the disease [5].

An outbreak of diphtheria was reported from the northern districts of the state of Kerala India in 2016, starting from June 2016. A total of 533 cases were reported accounting for about 7% of globally reported cases [6]. But this was based on surveillance data alone and did not analyse the clinical features or treatment response. This was the largest epidemic in Kerala over the last decade. Majority of cases were reported from Kozhikode, Malappuram, and Kannur districts where the routine immunisation coverage was low at that time.

The aim of this study was to find out the changing trends in the clinical presentation and complications of diphtheria in children during the epidemic. The study also had attempted to find out the association of complications seen in the epidemic with immunisation status and the time of antitoxin administration.

MATERIALS AND METHODS

This longitudinal prospective study was conducted in the Paediatric Infectious Disease Unit at Government Medical College, Kozhikode, Kerala, India (tertiary care teaching institute in North Kerala). The study period was from January 2016 to March 2017. All children satisfying the inclusion criteria were included in the study. This study was approved by Institutional Ethical Committee of Government Medical College Kozhikode (Ref No: GMCKKD/RP 2016/ EC/171). Informed consent was obtained from parents.

The operational definition for clinical diphtheria was taken as an illness characterised by laryngitis, pharyngitis or tonsillitis and an adherent membrane on the tonsils, pharynx or nose as per World Health Organisation (WHO) case definition or a child with clinically compatible history with typical complications such as palatal palsy, myocarditis or peripheral neuropathy [7].

Inclusion criteria: All children below 12 years of age who met the operational definition of diphtheria and were admitted to Paediatric Infectious Disease Unit from January 2016 to December 2016 were

included in the study. A total of 80 children met the clinical case definition.

Exclusion criteria: Children in whom an alternate diagnosis was made during evaluation were excluded. So, two cases were diagnosed subsequently as infectious mononucleosis, one case as streptococcal pharyngitis, and one turned out to be a case of acute lymphoblastic leukaemia, were excluded from the study.

Procedure

Details of socio-demographic data, clinical presentation, laboratory investigations, immunisation status, treatment and complications were collected using a semi-structured proforma and from the hospital records. Immunsation status was documented after crosschecking with the available records. Those children who had completed recommended age-appropriate doses of diphtheria toxoid as per national immunisation schedule were considered as completely immunised [8]. Those who did not receive even a single dose were considered as non immunised and those who had received less than the recommended doses for age were classified as partially immunised.

Clinical examination: Detailed clinical examination was done to determine the degree of involvement and presence of cardiac and neurological complications. A child with clinical diphtheria and ECG showing non specific changes and or raised cardiac enzymes in the absence of clinical features of cardiac failure was classified as having asymptomatic myocarditis. Throat was examined to determine the type and extent of the diphtheritic membrane.

Laboratory test: The laboratory tests includes complete blood counts, Erythrocyte Sedimentation Rate (ESR), hepatic transaminases, renal function tests and urinalysis were done in all children at the time of admission and during clinical deterioration. ECG was taken soon after admission and was repeated on every alternate day during the inpatient stay, at the time of discharge and during follow-up visits. Further investigations including echocardiography and nerve conduction study was done for cases with features of cardiac or neurological involvement. Troponin-I assay was done in 32 children with ECG abnormalities.

Management and follow-up: All cases were managed as per the interim guidelines provided by the Directorate of Health Services, Kerala state [9] at the time of outbreak. The details of treatment with antitoxin (dose, route, and day of administration) and antibiotics were documented. These children were followed-up at 4 and 6 weeks and at 3 months.

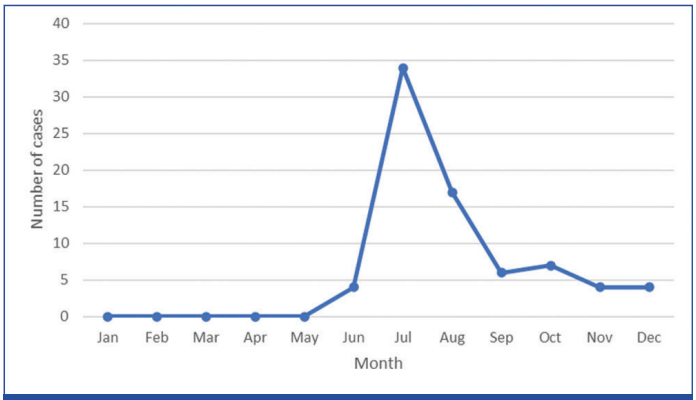
Throat swab culture: Throat swabs for *Corneybacteria* were collected and cultured immediately on blood agar and potassium tellurite agar. Cultures were done soon after admission and repeated on days 15 and 16. The isolates were confirmed from World Health Organisation Vaccine Preventable Disease Surveillance Laboratory at Thiruvananthapuram using Polymerase Chain Reaction (PCR) and standard biochemical tests. Sugar fermentation tests were done using Hiss's serum sugar media. Other biochemical reactions tested included urease test, nitrate reduction test, catalase and oxidase reaction. The toxigenicity was detected by PCR for *tox*+ gene (tox A and tox B) and the phenotypic expression was confirmed using modified Elek's gel precipitation test [10,11]. Real-time PCR (qPCR) assays were done using hydrolysis probes (TaqMan, Applied Biosystems). The qPCR targets for the RNA polymerase β-subunit-encoding gene (rpoB) and the tox A gene were used. Extraction of DNA was performed using Magna pure 24 System (Roche Life Science). Oligonucleotide primers and probe were designed using the software Primer 3 to target rpoB and the tox gene [12]. Elek's test was done with Elek's test agar base supplemented with calf serum. A sterile filter paper with 10 IU/mL of antitoxin was used. The test organisms were streaked at 10 mm from the disk along with positive and negative controls. The plates were observed after 24 hour incubation at 37°C. Formation of precipitin lines, due to binding of toxins produced by the strains with the antitoxin released from the filter paper, between the disk and the inoculum was taken as positive.

STATISTICAL ANALYSIS

The data was analysed using Statistical Package for Social Sciences (SPSS) version 18.0. Chi-square test was used as test of significance for qualitative variables. A p-value <0.05 was considered as statistically significant.

RESULTS

Total of 80 children met the clinical case definition. Among these, four children were excluded from the study as they had an alternate diagnosis during the hospital stay. Of these, two cases were diagnosed subsequently as infectious mononucleosis, one case as streptococcal pharyngitis, and one turned out to be a case of acute lymphoblastic leukaemia. The remaining 76 children were followed-up for 3 months and details were analysed. The mean age of the study population was 8.1 years, and the youngest child was 7 months old. There were more boys with a male to female ratio 1.53:1. Most of these children were from Malappuram and Kozhikode districts. The epidemic started in June with the first case admitted on 13th June 2016. Maximum numbers of cases were admitted in July 2016, at the peak of monsoon season in this state. Thereafter cases started declining and reached a plateau by November 2016 [Table/Fig-1].



[Table/Fig-1]: Month wise distribution of diphtheria cases 2016.

Among the study subjects, 22 children were unimmunised and 25 partially immunised [Table/Fig-2]. None of the older children received Tetanus and adult Diphtheria (Td) vaccination since it was not included in the immunisation schedule at that time.

Details	Male (n=46)	Female (n=30)	Total (N=76)	Non immunised	Partially immunised	Fully immunised
Age group						
0-5 years	15	4	19 (25.0)*	5	5	9
6-10 years	24	15	39 (51.3)	10	17	12
11-12 years	7	11	18 (23.7)	7	3	8
Total	46 (60.5)	30 (39.5)	76 (100)	22	25	29
District-wise distribution						
Malappuram	19	13	32 (42.1)	12	10	10
Kozhikode	17	13	30 (39.5)	4	12	14
Kannur	3	4	7 (9.2)	4	1	2
Palakkad	1	0	1 (1.3)	1	0	0
Wayanad	4	0	4 (5.3)	0	2	2
Kasarkode	2	0	2 (2.6)	1	0	1
Religion						
Christian	2	0	2 (2.6)	0	1	1
Hindu	7	9	16 (21.1)	1	1	14
Muslim	37	21	58 (76.3)	21†	23	14

[Table/Fig-2]: Epidemiological details of children admitted during the diphtheria outbreak.
*The number in parenthesis show percentages; †p-value=0.001

In this study, 25 (32.9%) cases were diagnosed within 48 hours of the disease onset. One child presented around third week of illness with palatal palsy and another one presented with generalised weakness after one month of illness. All of them had pharyngo-tonsillar lesions [Table/Fig-3]. Bull neck was present in 15 (19.7%) cases [Table/Fig-4].

Type of involvement	Number of children* (n,%)
Pharyngo-tonsillar	76 (100)
Laryngeal	2 (2.63)
Nasal	1 (1.32)
Cutaneous	0

[Table/Fig-3]: Type of diphtheria (N=76).
*More than one type observed in some children

Clinical feature	Number of children* (n,%)
Fever	75 (98.7)
Sore throat	74 (97.4)
Dysphagia	34 (44.7)
Bull neck	15 (19.7)

[Table/Fig-4]: Clinical features (N=76).
*More than one symptom observed in many children

Corynebacterium diphtheriae was isolated from throat swabs of 20 children (26.3%). All isolates were sensitive to penicillin and erythromycin. Repeat cultures after 14 days of treatment were negative except in one child who became culture-negative after a course of erythromycin for 14 days. Culture positive cases included five fully immunised children as well. Thirty four (44.7%) children had leukocyte count above 15000. Erythrocyte Sedimentation Rate (ESR) was above 50 mm in 28 (36.8%) children. Ten (13.2%) of them had elevated Alanine Aminotransferase (ALT) level [Table/Fig-5].

Laboratory parameter	Mean	Range	Standard deviation
Haemoglobin (gm/dL)	11.6	8.6-13.9	0.87
Total count (cells/mm^3)	15459	7500-49930	6739
Platelet count (lakh cells/mm^3)	3.21	1.03-6.90	1.27
Erythrocyte sedimentation rate (mm at 1st hour)	49	3-125	27
Alanine aminotransferase (U/L)	28	10 -204	32
Creatinine (mg/dL)	0.56	0.3-0.9	0.11

[Table/Fig-5]: Laboratory investigations (N=76).

Injection crystalline penicillin was given in a dose of 150000 units /kg/day in four divided doses for 14 days to all subjects (including those who presented late) except one who developed hypersensitivity reaction to penicillin. This child was treated with erythromycin 40 mg/kg/day four divided doses for 14 days. Diphtheria antitoxin was administered to 74 children but could not be given to two since they were admitted two weeks after the onset of symptoms. Antitoxin was given in varying doses (20,000 to 1,00,000 units) depending on the day of presentation and the severity of the illness [Table/Fig-6]. For all the children antitoxin was administered intravenously. Less than half 34 (44.7%) of the children received antitoxin within 72 hours of the onset of the disease. Fourteen children had allergic reactions following antitoxin administration. Three of them developed severe allergic reactions and needed desensitisation. Full dose of the antitoxin could not be administered to these three children.

Quantity of Diphtheria antitoxin (units/kg/day) administered intravenously	No. of children (N=76)
0	2
20,000	27
30,000	1
40,000	26
50,000	1
60,000	10
80,000	8
1,00,000	1

[Table/Fig-6]: Details of antitoxin administration.

Complications were noted in 36 children while on treatment or follow-up [Table/Fig-7]. Palatal palsy was noted in 9 (11.8%) children of whom two developed weakness in the first week itself and 7 after second week. Five children developed distal weakness during 4-6 weeks of illness. One child required ventilator support for 5 days. Four children developed loss of accommodation reflex during follow-up visit but improved without any sequelae. None had any airway compromise. None had jaundice or features of hepatic failure. There was no mortality.

Major complications observed*	Number of cases (n,%) N=76	Non immunised	Partially immunised	Fully immunised
Asymptomatic myocarditis	31 (40.8)	11	9	11
Symptomatic myocarditis	1 (1.3)	1	0	0
Palatal palsy	9 (11.8)	6	1	2
Symmetric polyneuropathy	5 (6.6)	5	0	0
Accommodation palsy	4 (5.3)	2	1	1
Proteinuria	1 (1.3)	1	0	0
Thrombocytopenia	2 (2.6)	2	0	0

[Table/Fig-7]: Complications observed.
*More than one complication was observed in some children

These children were followed-up till 3 months after the onset of illness. New complications noticed during the follow-up visits as well [Table/Fig-8]. All affected children recovered completely by three months.

Time of follow-up visit	No of children came for follow-up	Newly detected complications*			
		Asymptomatic myocarditis	Palatal palsy	Loss of accommodation	Distal weakness
4th week	75	1	3	2	2
6th week	73	1	3	2	3
3rd month	76	0	0	0	0

[Table/Fig-8]: Details of follow-up visits.
*More than one complication was observed in some children

Association between day of administration of antitoxin and complications: Only one child who received antitoxin within 72 hours of disease onset developed neurological complications and this was statistically significant (p-value <0.05).

Association between immunisation status and complications: Complications were common in children who received less than 3 doses of diphtheria toxoid compared to those who received three or more doses (54 vs 44%). However, this was not statistically significant (p-value=0.2). Children who received five doses of vaccine did not develop diphtheritic polyneuropathy or accommodation palsy. Those children with bull neck had developed more complications and it was statistically significant (p-value=0.001).

DISCUSSION

Out of the 533 reported diphtheria cases in Kerala in 2016, 76 cases were admitted in this hospital [Table/Fig-9]. This includes 58 children in the under 10 years of age. The upward shift in age in the study by Sangal L et al., is evident in our study as well with relatively lesser number of children in the 0-5 year age group [6]. The upward shift of age was reported from various parts of the world [2,3,13]. Some areas of India continue to have a predilection to younger age groups. In a hospital-based study conducted by Maheriya KM et al., [14] from Ahmadabad (Gujarat), children in the 0-5 year age

category were more affected. More boys were affected in current study, which was consistent with the above study. Majority of cases were from Malappuram and Kozhikode districts, which have relatively low immunisation coverage for even primary doses of Diphtheria Pertussis Tetanus (DPT) (80.8% and 86.9%; NFHS 4).

District	Total reported cases in Kerala by Sangal L et al., [6] (N=533*)	Case in present study (N=76) Number (%)
Malappuram	229	32 (14%)
Kozhikode	190	30 (15.8%)
Kannur	64	7 (1.6%)
Wayanad	16	4 (25%)
Palakkad	15	1 (6.7%)
Kasaragod	3	2 (66.7%)
Other Districts†	16	0

[Table/Fig-9]: District wise breakup of Diphtheria cases in 2016.
†(Thrissur, Ernakulam, Alappuzha, Thiruvananthapuram)

Twenty nine (38.15%) immunised children developed the disease. This is contrary to most of the studies from India where many were unimmunised [Table/Fig-10] [14,15]. But in a recent (2015) epidemic reported from Delhi, a significant number of immunised children developed the disease [16]. More than 90% of children developed protective level of antibodies against diphtheria following three primary doses [17]. But Gowin E et al., demonstrated that only 70% polish children developed protective antibodies after adequate immunisation pointing to the fact that variation can occur in protective antibody production in different populations [18]. So, in the present study, the observation of occurrence of the disease in children adequately immunised points the need for population-based studies for estimating protective antibody levels in India. Recent change in the national policy to give Td instead of Tetanus Toxoid (TT) at 10-year, 15 year and during pregnancy may decrease the disease in these age groups [19]. This also reminds us that the protection through immunisation is not an absolute one. Thus, any child presenting with fever and sore throat must be carefully examined for the presence of a diphtheritic membrane irrespective of the immunisation status. It is especially important in an epidemic setting in the background of low immunisation coverage in the community. Bull neck was more common among who had received less than five doses of vaccine. Higher mortality of children with bull neck had been described in an earlier study [16].

Variables	Maheriya KM et al., [14]	Dandinarasaiah M et al., [15]	Present study, 2022
Period of study	2013	1997 to 2007	2016
Place of study	Hubli, Karnataka	Ahmedabad, Gujarat	Kozhikode, Kerala
Study design	Prospective	Retrospective	Prospective
Total cases	38	52	76
Age <5 years	22 (58%)*	21 (40.38%)	19 (25%)
Fully immunised	6 (16)	6 (11.53%)	29 (38.15%)
Male female ratio	1.8:1	1:1.7	1.53:1
Season	August to December	Not mentioned	January to December
Culture positivity	3 (7.89%)	8 (15.38%)	20 (26.3%)
Bull neck	9 (23.68%)	Not mentioned	15 (19.7%)
Myocarditis	20 (52.63%)	Not mentioned	32 (42.1%)
Palatal palsy	2 (5.26%)	Not mentioned	9 (11.8%)
Polyneuropathy	2 (5.26%)	Not mentioned	5 (6.6%)
Accommodation palsy	Not mentioned	Not mentioned	4 (5.3%)
Antidiphtheritic serum given	37 (97.36%)	16 (30.76%)	74 (97.36%)
Case fatality	9 (23.68%)	19 (36.53%)	0

[Table/Fig-10]: Comparison with previous studies from India.
*The number in parenthesis show percentage

Diphtheritic polyneuropathy is under reported in India [20]. The latency of the diphtheritic polyneuropathy can vary from 10 days to 3 months [21]. In this study, neurological complications appeared within 6 weeks of illness, during follow-up. Lack of follow-up may be the reason for under reporting of neurological complications. Accommodation palsy is not a reported complication in other studies [Table/Fig-10]. It was noted that neurological complications were significantly low for those who had received antitoxin early. This observation underscores the importance of early initiation of antitoxin in suspected cases (even before a definite diagnosis is established by bacterial culture).

Cardiac involvement was present in 32 children (42%) of which all except one had asymptomatic myocarditis noted in routine electrocardiogram monitoring. Other studies from India have reported varying incidence of myocarditis from 16 to 66% [4,5,14,22]. This highlights the importance of routine ECG monitoring in all children suspected to have diphtheria.

Most of the Indian studies have reported a high case fatality rate varying from 23.67% to 56.3% [5,14,15,16]. There was no mortality in current study. The reasons may be due to relatively higher immunisation status, early administration of antitoxin and antibiotics and a protocol based institutional case management for all children with suspected diphtheria.

Limitation(s)

Since this was a hospital-based study, true nature of illness in the community would not be reflected here.

CONCLUSION(S)

Occurrence of diphtheria in various parts of India including states like Kerala where immunisation coverage in children is significantly high compared to other states, is a matter of grave public health concern. It is important to note that diphtheria may occur in immunised children as well. The clinical profile is also changing with an increased incidence in older children. It is gratifying to note that mortality can be prevented or reduced significantly with institutional care and protocol-based management, which includes routine screening for the development of complications. Administration of diphtheria antitoxin within 72 hours of presentation decreases the development of neurological complications. Regular anticipatory screening for cardiac involvement has a specific role in management.

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