

Original Research Article

Clinical profile and outcome of diphtheria in central India: a retrospective observational study

Rajkumar M. Meshram¹, Ashwini Patil^{2*}

¹Department of Paediatrics, ²Department of Microbiology, Government Medical College, Nagpur, Maharashtra, India

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***Correspondence:**

Dr. Ashwini Patil,

E-mail: dr_rajmeshram@rediffmail.com

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ABSTRACT

Background: Although, diphtheria is eliminated by many developed countries by effective immunization, still diphtheria continues to be endemic in India and leading cause of morbidity and mortality, especially in areas in the border of the two states. The objective of the present study was to recognize the clinical profile, morbidity and mortality pattern of diphtheria and to study their immunization status as a retrospective observational study performed in pediatric wards and paediatric intensive care unit.

Methods: The medical records were recovered from the case files, searching for cases diagnosed as diphtheria from the Medical Record Section and Statistical Service of the institute. A pre-established protocol was formed after approval from institutional ethical committee. Case study included suspected, probable and confirmed cases of diphtheria as per the WHO definition guidelines. All the relevant data and information regarding age, gender, residence, socioeconomic status, immunization status, clinical details, laboratory investigation, complications, and treatment provided, and outcome were recorded.

Results: Amongst 47 patients, 55.32% were >5years and mean age was 6.46±3.08 years with no difference in sex distribution. 2(4.25%) patients were completely immunized, 27(57.45%) were partially immunized and 18(38.30%) were not immunized. An immunization rate was less in females as compared to males. All patients presented with fever and membrane in throat followed by throat pain 95.74%, enlarged/congested tonsils 80.85%, respiratory difficulty 68.08%, dysphagia 59.57% bull neck 48.94% and voice change 36.17%. Myocarditis was the commonest (42.55%) complication followed by palatal palsy (14.89%), polyneuropathy (8.51%), acute renal failure (4.25%) and DIC & shock (4.25%) were observed. Case fatality rate was 21.28%. Maximum numbers of cases were noted during the rainy season.

Conclusions: Shifting of occurrence of diphtheria in the age group of 5-15 years suggest the need to improve and strengthen the immunization activity specially booster doses in the border districts as most of the cases were from areas at the border of two states.

Keywords: Diphtheria, Immunization status, Myocarditis, Polyneuropathy

INTRODUCTION

Diphtheria is an acute fatal bacterial toxin induced disease caused by *Corynebacterium diphtheriae*, known from ancient times. Its name is derived from the Greek word meaning "Leather" pointing towards pseudo

membrane, the hallmark of the disease. In Ayurveda it's called "Ghatsarpa" suggesting a snake winding tightly around neck of a pot. In the pre-vaccination era it was a leading cause of mortality in childhood.¹ The disease has been almost completely eradicated in many developed countries and many European countries. On the contrary, in developing countries, although the incidence has

declined, still account for 80-90% of global burden. In 2015, India contributed 2365 (52.21%) of the 4530 diphtheria cases reported globally.² Though the immunization programme in India was started with the aim to reduce the morbidity and mortality of vaccine preventable diseases completed almost four decades are still responsible for over 5 lakhs death annually and national coverage for full immunization is 61% and around 7.4 million children are not immunized with DPT-3.^{3,4}

There is large inter-state variation in the coverage of immunization. Goa, Sikkim, Punjab and Kerala covers >80% of children between 12-23 months of age are fully immunized while Bihar, Madhya Pradesh, UP, Nagaland and Arunachal Pradesh are less than 50%. So many outbreaks of diphtheria from various states in India have been reported in recent times.⁵⁻⁹ Because of inadequate vaccine coverage, waning vaccine induced immunity, mass population movements, poor living standards, delay reporting to hospital and non-availability or delay in administering antitoxin appears to be main factors contributing to re-emerging of the disease and high mortality at border district areas of the states. Our institute is serving to population of Vidhrabh and nearby states and there is paucity of literature from central India. We planned to study the clinical profile and mortality of the children admitted with suspected diphtheria and to study their immunization status in the tertiary care hospital.

METHODS

This case series was retrospectively studied at one of the largest tertiary care and referral hospital that provide care to underprivileged, socioeconomically deprived population of central India (including Vidhrabh region of Maharashtra, parts of Madhya Pradesh, Telangana state and Chhattisgarh) from January 2010 to December 2016. The medical records were recovered from medical case files by searching for cases diagnosed as diphtheria from the Medical Record Section and Statistical Service of the institute and the information was collected to conform to a pre-established protocol after approval from institutional ethical committee.

The patients included in the study came from different socioeconomic status, religions and region of residence, giving diversity in the subjects and practices. A clinical diagnosis of diphtheria was included as children having symptoms of pain in throat, cough, fever, difficulty in swallowing and breathing and presence of pseudomembrane anywhere in the throat with or without bull neck. Case study was including suspected, probable and confirmed cases of diphtheria as per the WHO definition guidelines.¹⁰

All the relevant data and information regarding age, gender, residence, socioeconomic status, immunization status, clinical details, laboratory investigation,

complications, treatment provided, and outcome was recorded. The immunization status was documented as per the information given by the parents. Those who had received three primary doses at 4-6 weeks interval starting at 6 weeks of age, followed by booster doses at 18 months and 5 years were recorded as "Immunized". Those who had not received any doses were considered as "Unimmunized". Patients who had missed one or more of the three primary doses or booster doses were included as "Partially immunized". We classified our patients according to Modified Kuppuswamy's Socioeconomic Scale into Lower, middle and upper socioeconomic class.¹¹

Throat swab for direct microscopy of *Corynebacterium diphtheriae* and culture were collected immediately after admission. Staining of the smear was done by Gram Stain and Albert-stain method and culture was done on Blood Agar, potassium Tellurite Agar and Loeffler's serum slope and identified as per standard methods.

All patients were treated with appropriate antibiotics and antidiphtheric serum. Those patients who developed complications were treated with appropriate support in pediatric intensive care unit.

Statistical analyses

The data regarding the numerical variables were summarized through average, medium and deviation pattern. Categorical data were summarized and presented inform of frequency. The $P < 0.05$ was considered significant.

RESULTS

There was a total of 47 patients admitted with diphtheria during the study period, 16 patients were from Madhya Pradesh, 1 from Uttar Pradesh, 3 from Chhattisgarh and 27 from Vidhrabh. The mean age of study population was 6.46 ± 3.08 years, 26 (55.32%) cases were ≥ 5 years and 2 cases were below 1 year (1 was 9 months and 1 was 11 months old). Both were from Madhya Pradesh and unimmunized. Male and female ratio was almost equal (0.95:1). Most of patients were from lower socioeconomic class and from rural area.

Only 2 patients were completely immunized, 27(57.45%) were partially immunized and 18(38.30%) were not immunized. Immunization was less in females as compared to males. All the non-survivors were unimmunized. Immunization rate among children from Madhya Pradesh was less as compared to children from Maharashtra.

All patients were presented with fever and membrane in throat followed by throat pain in 95.74%, enlarged/congested tonsils in 80.85%, bull neck in 48.94% and respiratory difficulty in 68.08%. (Table1). Cases of diphtheria was seen throughout the year and

great number of increase was seen during month of June to September (Figure 1).

Table 1: Demographic and clinical parameters of diphtheria patients.

Parameters	N=47	%
Age (years) mean±SD	6.46±3.08	
<1	02	4.25
1-5	19	40.43
5-12	26	55.32
Gender (male)	23	48.94
Residence(rural)	30	63.83
Socioeconomic status		
Lower	31	65.96
Middle	16	34.04
Clinical details		
Fever	47	100
Throat pain	45	95.74
Voice change	17	36.17
Dysphagia	28	59.57
Respiratory difficulty	32	68.08
Bull neck	23	48.94
Membrane	47	100
Enlarged/congested Tonsil	38	80.85
Bleeding manifestation	02	04.25
Albert stain (KLB seen)	15	31.91
Culture report (KLB grown)	07	14.89

Out of 47 patients only 15(31.91%) were positive for Klebs-Loffler bacillus (KLB) on smear examination by Albert stain while on throat swab culture, 7(14.89%) were positive for KLB.

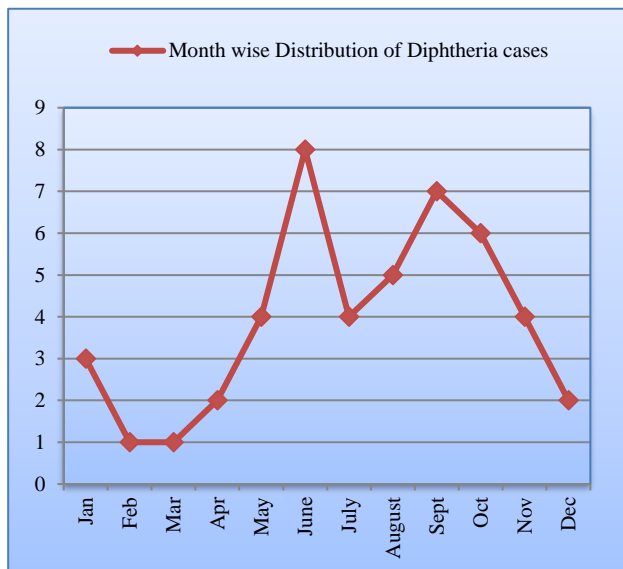


Figure 1: Month wise distribution of diphtheria cases

20 (42.55%) patients had myocarditis, out of which 12 were symptomatic and 8 had ECG abnormalities including inappropriate sinus tachycardia, left bundle branch block, right bundle branch block. Amongst,

symptomatic myocarditis 8 patients were in frank cardiac failure and expired. Out of 7 (14.89%) palatal palsy 4 were presented with aspiration pneumonia and severe respiratory distress and required mechanical ventilation, 2 of them died. Polyneuropathy was observed in 4(8.51%); one patient was presented with multiple cranial nerve palsy and required ventilation. Out of 2 patients of acute renal failure, one required peritoneal dialysis. Bleeding manifestation and shock was noted in 2(4.25%) patients (Table 2).

Table 2: Complications of diphtheria patients.

Complications	N=47	%
Myocarditis	20	42.55
Palatal Palsy	07	14.89
Polyneuropathy	04	08.51
Acute renal failure	02	04.25
DIC and shock	02	04.25

Out of 47 patients 10 were expired, giving case fatality rate 21.28%. Average duration of hospital stay for all patients was 9.5 days. All succumbed patients were unimmunized, from rural area and lower socioeconomic class and 4 from Madhya Pradesh, one from Uttar Pradesh and 5 from Maharashtra.

DISCUSSION

In the pre-vaccine era, disease was common among children less than 5 years of age due to natural boost to the development and maintenance of immunity in adolescence and adult. However, after widespread immunization in children, lack of or inadequate booster doses in children and adult and decrease incidence of cutaneous diphtheria, there is shift of age for the occurrence of disease in older children and adults. Such a shifting of age of occurrence was observed in developed and developing countries including India.

In present study 26 (55.32%) patients were more than 5years of age. Similarly, Basavaraja JC et al (74.1%), Bandichhode ST et al (66.66%) were reported resurgence of disease in children more than 5 years of age.

Disease is also common in unimmunized infant. Infantile diphtheria was also reported by various authors as well as we observed 2 unimmunized infants of 9 months and 11 months old from nearer state (Madhya Pradesh).^{9,12-15} As secondary attack rate is very high all cases needs to be isolate and their family members thoroughly examined and treated. We found two siblings were admitted 4 days duration apart and both were unimmunized.

In present study, males and females are almost equally affected giving sex ratio 0.95:1. Similar types of sex distribution were reported by many authors, while Mehariya et al, Sardar JC et al and Kole AK et al observed male predominance below 10 years of age and

few studies noted predominantly female involvement.^{8,12,13,14,16}

Most of the patients in present study from rural area and from lower socioeconomic class, could be because of our hospital mainly served to socioeconomically deprived rural population have poor access to immunization, health care system and overcrowding. Similarly, high incidence of disease in rural and lower socioeconomic class were reported by Mehariya et al and Singh SN et al.

Though, the Expanded Programme of Immunization (1978) and Universal Immunization Programme (1985) was launched almost four decades before in aim to reduce childhood morbidity and mortality of vaccine preventable diseases by offering full immunization coverage. Present immunization coverage in India is around 61%, with wide state wise, geographical, religion, rural urban and gender variation.³

Minimum immunization coverage of 90% in children and 75% in adult is required to prevent spread of diphtheria and current coverage rates in Maharashtra and nearby states remain rather inadequate.

Factors contributing to the low immunization coverage include lack of awareness, misconception, avoiding immunization for trivial reasons, migration, decline enthusiasm to routine immunization, unilateral focus on polio campaign, short supply of vaccine, poor clinic organization, non-availability of immunization services on all day of week, not opening a multidose vial if enough children are not present and delaying or postponing vaccination in minor childhood illness.¹⁷

In present study, 2 (4.25%) patients were fully immunized, 27 (57.45%) were partially immunized and 18 (38.30%) were unimmunized. This denotes unsatisfactory immunization coverage with DT/DPT vaccine in respective areas and their residence. Such types of observation were reported by various authors.^{5,13} There is does not exist any surveillance system for vaccine preventable diseases except poliomyelitis and measles, now days. Many authors have highlighted deteriorating health infrastructure and significant drop out between 1st and 3rd dose of DPT because of DPT is known for adverse effect due to its pertussis component.¹⁸

The clinical manifestation can vary from mild to severe to the life threatening depending on immune status of host and severity of infection. The present study showed fever and membrane in throat in all patients. Other presentation includes throat pain 45(95.74%), enlarged/congested tonsils 38(80.85%), respiratory difficulty 32(68.08%), dysphagia 28(59.57%), bull neck 23(48.94%), voice change in 17(36.17%) patients. Similar clinical details were reported by various authors from various parts of India.^{8,9,13,16,19} Cases of diphtheria were seen throughout the year but more number of cases was observed during month of June to September during

rainy season. Some authors reported peak during the winter season and some in rainy season.^{5,13} In view of poor specimen collection on usual throat swab, delayed transportation to the lab, delayed inoculation to the special culture media and prior antibiotic therapy, Albert stain revealed KLB in 15 of 47(31.91%) and microbiologic confirmation could be established in only 7(14.89%). Low Corynebacterium yield were reported by Basavaraja et al (16.1%), Bandichhode et al (33.33%), Singh SN et al (30.63%).^{9,12,13}

Since toxin mediated inhibition of protein synthesis is known to be the essential mechanism of all complications of diphtheria, especially myocarditis, as the exotoxin is directly cardiotoxic and can cause DNA fragmentation and cytolysis by inhibiting elongation factor-2 activity in protein synthesis leading to tissue damage, non – immunized and CD-positive patients developed complications associated with diphtheria.^{20,21}

Myocarditis 20 (42.55%) was the commonest complication in present study amongst that 12 were symptomatic and 8 had ECG abnormality including inappropriate sinus tachycardia, left bundle branch block, right bundle branch block. Out of, 12 symptomatic myocarditis, 8 were in frank cardiac failure and expired and predominantly contributing in mortality. In India, incidence of diphtheric myocarditis varies from 16 to 66%.²²⁻²⁴

Palatal palsy characterized by a nasal quality of voice, nasal regurgitation commonly occurring in second and third week and earliest neurological complication which may occur alone or in association with other types of paralysis. In present series, 7 (14.89%) patients had palatal palsy and 4 (8.51%) had polyneuropathy with or without cranial nerve involvement.

Most palatal palsy with polyneuropathy required mechanical ventilation and complicated with secondary infections and pneumonia. Our 4 patients were required mechanical ventilation and two of them succumbed to death because of secondary pneumonitis. Acute renal failure and disseminated intravascular coagulopathy and shock are also common in diphtheria. We observed each of 2 patients and none of them died. Similar types of complications are reported by various investigators.^{5,9}

Diphtheria, if not detected early and treated can lead to significant mortality and morbidity because of critical complication. Early recognition is dependent on a high index of suspicion as other common cause's pharyngotonsillar disease such as streptococcal, Epstein Barr Virus, Vincent angina and Candida may form pseudomembrane in throat. The early and prompt treatment prevents mortality.

Specific antitoxin is mainstay of management, where a horse serum is used without waiting for laboratory confirmation to neutralize the unbound toxin in blood.

Corynebacterium is susceptible to antimicrobials like penicillins, erythromycines, clindamycine and metronidazole. Therapy is to be given for 14 days and it is important to maintain isolation, treatment of carriers and prevent spread. Case fatality was 21.28% in our patients where as it is ranged from 9-14% in Maharashtra, 32-56.3% in different centers in north India and 23.67% in West India.^{5,9,12,13,19} Diphtheria is still not a lost entity as cases are coming to tertiary care level. Immunization activity needs to be improved and strengthened in borderline districts as most of the cases in present study were from the borderline states. Present study showed complete immunization, high index of suspicion and diagnosis and early prompt administration of antitoxin prevent the complication and mortality.

CONCLUSION

Although, we reduce the incidence of vaccine preventable diseases, diphtheria is still a matter of concern for public health. Shifting of occurrence of disease in 5-15 years age group suggest the need for completing the immunization schedule, especially booster doses.

High mortality was observed with cardiac involvement and neurological complication denotes need of early diagnosis and prompt antitoxin therapy to prevent mortality. Immunization activity needs to be improved and strengthened in border districts as most of the cases in present study were from areas at the border two states.

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