

Original Research Article

Diphtheria: a re-emerging infectious disease

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ABSTRACT

Background: Diphtheria is a fatal bacterial infection which affects the mucous membranes of oropharyngeal and nasal cavity, caused by aerobic gram-positive bacteria *Corynebacterium diphtheriae*. Clinical diphtheria is on the increase worldwide, mainly affecting developing countries and leading cause of morbidity and mortality. We sought to understand its presentation among patients and also early intervention of the disease. The objective of the study was to study the clinico-demographic profile of cases, the relationship between immunization status and clinical disease, the role of microbiological investigations and to identify complications in diphtheria cases.

Methods: This study is a hospital based observational study from September 2019 - September 2020 at a tertiary care centre, S.Nijalingappa Medical College and HSK hospital, Bagalkot, Karnataka. The cases were analysed with respect to demographic details, clinical features, immunization status, microbiological confirmation and complications of diphtheria cases.

Results: 32 cases were suspected to have diphtheria on clinical examination. The mean age of presentation was 15 years. Fever, sore throat, difficulty in swallowing, neck swelling and pseudomembrane in oral cavity were the common signs and symptoms. Airway compromise, myocarditis and neurological complications were noted. Antidiphtheric serum (ADS) was tried in all 32 cases and 8 cases had adverse reactions. Case fatality rate was 12.5%.

Conclusions: Shifting of occurrence of diphtheria in the age group of >5 years suggest the need to improve and strengthen the immunization program specially the booster doses.

Keywords: Diphtheria, Antidiphtheric serum, Albert stain, Myocarditis

INTRODUCTION

Diphtheria is an infectious disease caused by the exotoxin produced by *Corynebacterium diphtheriae*.¹ The organisms are locally invasive and secrete soluble exotoxins, which can lead to serious consequences mainly involving the heart muscle and nervous system. Death can occur due to circulatory failure within the first 10 days of infection.² If diagnosed early, the infection responds to appropriate antibiotics and prompt antitoxin therapy.

The incidence of diphtheria is high in India, especially in the region of North Karnataka. Factors contributing to morbidity and mortality include patient's immunization status, age at infection, time of infection, clinical type, and time of intervention.³ An accurate microbiological diagnosis of diphtheria is crucial and is always regarded as being complementary to clinical diagnosis because diphtheria is often confused with other conditions, such as severe streptococcal sore throat, Vincent's angina, or glandular fever.⁴

As per World health organization (WHO) data from 2000 to 2016, over 82% of diphtheria cases occurred in children above 5 years and over 40% occurred in individuals over 15 years of age.⁵ This second shift is due to the waning immunity as the child grows older and is the reason why regular booster doses are recommended. India has the maximum number of diphtheria cases in the world, from 2011 to 2015 India had a total of 18,350 cases of diphtheria.⁶ Over 40% of cases reported in India are from individuals over 15 years and about 20% cases are reported from children under the age of 5 years.⁷

Aims and objectives

To study the clinico-demographic presentation of diphtheria cases. To know the immunization status in diphtheria cases. To know the role of microbiological investigations in diphtheria cases. To identify the complications in diphtheria cases.

METHODS

Place of study

S. Nijalingappa Medical College and HSK Hospital.

Study population

All cases with clinical suspicion of diphtheria admitted in HSK hospital.

Exclusion criteria

Patient who already treated with antibiotic prior throat swab

Study period

September 2019 to September 2020.

Type of study

Observational case series study.

The case data was analysed with respect to demographic details, clinical features, pseudomembrane, microbiological confirmation, complications and mortality by using openepi software version 2.3.1.

The management of a patient with suspected diphtheria includes: administration of antidiphtheritic serum (ADS) as soon as possible after assessing for hypersensitivity to horse serum, establishing the diagnosis through appropriate bacterial cultures, administration of antibiotics and appropriate supportive care – to maintain an adequate airway in the presence of laryngeal or extensive pharyngeal membrane and to carefully monitor for cardiac rhythm disturbances or other manifestations of myocarditis.

The following data were recorded: age, sex, clinical symptoms and signs. Patients were categorized into four age groups: <5, 5–20, 20–40 and >40 years. Immunization status was documented as per the information given by the parents/ patients. 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 and not known immunization status were considered as “Unimmunized”/ “Unknown status”. Patients who had missed one or more of the three primary doses or booster doses were included as “Partially immunized”.

Microbiological investigations

Sample collection

Under aseptic precautions, two throat swabs were taken from all suspected cases of diphtheria. Swabs should be collected underneath the pseudomembrane or a piece of membrane should be removed. One swab was used for direct microscopy and the other for culture.

Table 1: Paediatric and Adult ADS (antidiphtheritic serum) dose.

Diphtheria clinical presentation	ADS dose in IU (# of ampoules)
Pharyngeal or laryngeal disease of 2 days duration	20000-40000 (2-4)
Nasopharyngeal disease	40000-60000 (4-6)
Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck	80000-100000 (8-10)
Skin lesions only (rare case)	20000-40000 (2-4)

Direct microscopy

Gram staining and Albert staining of swab smears were carried out.

Culture and sensitivity

Throat swab was inoculated on blood agar, Mc conkey agar and Potassium tellurite agar. Growth after 24–72hr incubation was identified using standard methods.

Toxigenicity testing

The isolates confirmed by biochemical reaction was sent to CMC vellore for PCR test and it detects the tox-bearing gene.

All the patients registered under the study were given appropriate antibiotics and antidiphtheritic serum (ADS).

Desensitization was done in case of adverse reaction to ADS such as rashes, hypotension, serum sickness etc.

1 ml (antitoxin) + 9.0 ml saline = 1:10 dilution

1 ml (1:10 dilution) + 9.0 ml saline = 1:100 dilution

0.1 ml (1:10 dilution) + 9.9 ml saline = 1:1000 dilution

1 ml (1:100 dilution) + 9 ml saline = 1:1000 dilution.

Table 2: Desensitization to ADS- intravenous route.

Dose number	Dilution of ADS in normal saline	Amount of injection(cc)
1	1:1000	0.1
2	1:1000	0.3
3	1:1000	0.6
4	1:100	0.1
5	1:100	0.3
6	1:100	0.6
7	1:10	0.1
8	1:10	0.3
9	1:10	0.6
10	undiluted	0.1
11	undiluted	0.2
12	undiluted	0.6
13	Undiluted	1.0

Administer at 15 minute intervals.

RESULTS

Out of 32 patients, 2 patients (6.2%) were less than 5 years age group, 24 patients (75%) were between 5-20 years and 6 patients (18.8%) were above 20 years. Paediatric age group - 21 cases; adults - 11 cases. 16 patients (50%) were males and 16 (50%) were females.

Table 3: Age distribution.

Age group (years)	Number of patients (%)
>5	2 (6.2)
5-20	24 (75)
20-40	5 (15.5)
>40	1 (3.3)
Total	32 (100)

Immunization status

9 (28.1%) were fully immunized and 17 (53.2%) were partially immunized and 6 (18.7%) were unimmunized/unknown status.

Bull neck

Out of 32 patients,19(59.3%) presented with bull neck at presentation.

Table 4: Immunization status.

Immunization status	Number of patients (%)
Fully immunized	9 (28.1)
Partially immunized	17 (53.2)
Unimmunized/ Unknown status	6 (18.7)
Total	32 (100)

Table 5: Clinical presentation.

Clinical presentation	Number of patients (%)
Fever	32 (100)
Throat pain	32 (100)
Cough	18 (56.25)
Bull neck swelling	19 (59.3)
Dysphagia	12 (37.5)
Epistaxis	1 (3.12)

Table 6: Microbiological investigations.

Lab parameter	Data (%)
Albert stain	
Positive	18 (56.2)
Negative	14 (43.7)
Throat swab culture	
Positive	21 (65.6)
Negative	11 (34.3)

Myocarditis

Out of 32 patients,12 (37.5%) developed myocarditis and 4 (12.5%) patients died.



Figure 1: ADS adverse reaction- rashes over legs.

Microbiological investigations

Albert staining was performed in 32 cases of which 18 (56.2%) were positive. Culture was performed in 32 cases of which 21 were positive (65.6%). In our study 20 isolates were found to be toxigenic and 1 isolates was contaminated in the transportation and toxigenicity testing was not done for that isolate.

Antidiphtheritic serum (ADS) administration

ADS was administered in all 32 cases out of which 8 patients developed ADS reaction and desensitization was done.

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 adults. 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.⁸

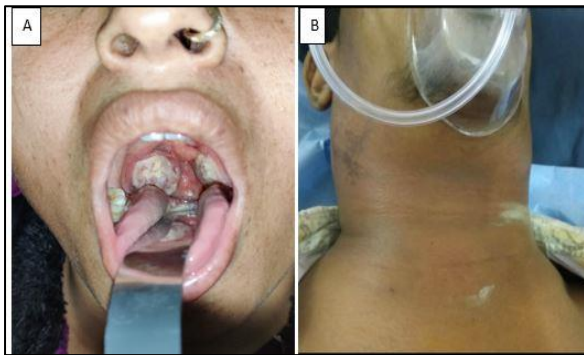


Figure 2: (A): Pseudomembrane over tonsils; (B): Bull neck.

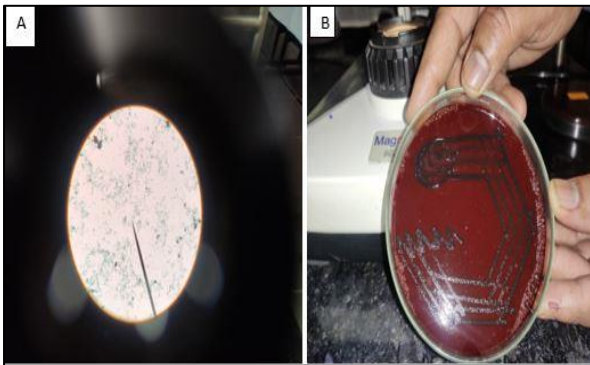


Figure 3: (A): Albert's stain: Smear showing green colored bacilli with bluish black metachromatic granules arranged in L or V shape. (B): Potassium tellurite agar - Black colored colonies.

In present study 93.8% patients were more than 5 years of age (Table 3). However, Meshram et al (55.32%) Basavaraja et al (74.1%), Bandichhode et al (66.66%) also reported resurgence of disease in children of more than 5 years of age.⁹⁻¹¹

In present study, males and females were equally affected giving sex ratio 1:1 which is almost similar to Meshram et al.⁹ Similar types of sex distribution was reported by many authors, while Mehariya et al observed male predominance below 10 years of age and few studies noted predominantly female involvement.¹²

Most of the patients in the present study were from rural area and lower socioeconomic class, could be because our hospital mainly serves to socioeconomically deprived rural population who have poor access to immunization and health care system. Similarly, high incidence of disease in rural and lower socioeconomic class were reported by Mehariya et al and Singh SN et al.^{12,13}

Present immunization coverage in India is around 61%, with geographical, religion, rural, urban and gender variation.¹⁴ Minimum immunization coverage of 90% in children and 75% in adult is required to prevent spread of diphtheria and current coverage rate in Karnataka is 77.6% which remains inadequate.

Factors contributing to the low immunization coverage include lack of awareness, misconception, avoiding immunization for trivial reasons, migration, decline in enthusiasm to routine immunization, unilateral focus on pulse polio campaign, short supply of vaccine, not maintaining proper storage of vaccine (cold chain), 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.¹⁵

In present study, 9 (28.1%) patients were fully immunized, 17 (53.2%) were partially immunized and 6 (18.7%) were unimmunized/unknown status (Table 4). This denotes unsatisfactory immunization coverage with DT/DPT (Diphtheria, Pertussis and Tetanus) vaccine in respective rural area.

The clinical manifestation can vary from mild to severe to the life threatening depending on immune status of host and severity of infection. All patients presented with fever, pseudomembrane in throat and throat pain (100%) followed by bull neck 19 (59.3%), dysphagia 12 (37.5%), epistaxis 1 (3.2%) (Table 5). Similar clinical details were reported by various authors from various parts of India. 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.^{11,16}

In our study Albert stain was positive in 18 cases (56.2%) and growth in culture was seen in 21 cases (65.6%) out of 32 tested (Table 6). False negative reports are seen because of prior antibiotic use, difficulties in proper throat swab collection due to lymphadenopathy, bull neck and delayed transportation of sample to the laboratory. Low *Corynebacterium* yield were reported by Basavaraja

et al (16.1%), Bandichhode et al (33.33%), Singh et al (30.63%).¹⁰⁻¹²

Myocarditis was the commonest complication 12 (37.5%) followed by palatal palsy 3 (9.3%), airway obstruction 2 (6.2%). Case fatality rate was 12.5% and cause of death was cardiopulmonary arrest. In India, incidence of diphtheric myocarditis varies from 16 to 66% because 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.^{9,17,18}

Palatal palsy was characterized by a nasal quality of voice, nasal regurgitation commonly occurring in second and third week and is the earliest neurological complication which may occur alone or in association with other types of paralysis. However in Meshram et al study, 7 (14.89%) patients had palatal palsy and 4 (8.51%) had polyneuropathy with or without cranial nerve involvement.⁹

In present study we analyzed all the cases of diphtheria hospitalized in S N Medical College from a period of September 2019 to September 2020. Data collected showed mean age of affected is 15 years. In present study, 32 cases (100%) were found to have a pseudo membrane. Authors consider a pharyngeal membrane that is difficult to peel off and leaves a bleeding area on the mucous membrane after an attempt to remove it pathognomonic for diphtheria. All patients were treated with anti-diphtheritic serum as recommended by WHO and UNICEF. The most commonly administered antibiotics were penicillin or erythromycin following recommendations of the WHO and UNICEF. Every patient in present study had a throat swab taken and 65.6% of cases had microbiologically confirmed disease. There was 12.5% mortality in present study and one patient was COVID positive. This observation suggests that complete vaccination is essential in preventing fatalities. 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 rural areas. Present study showed complete immunization, high index of suspicion and microbiological confirmatory diagnosis and early prompt administration of antitoxin prevent the complication and mortality.

CONCLUSION

Although, we have reduced the incidence of vaccine preventable diseases by vaccination, diphtheria is still a matter of concern for public health. Shifting of occurrence of disease above 5 years age group suggest the need for completing the immunization schedule, especially booster doses. A high degree of suspicion and early initiation of appropriate management as well as

close monitoring for development of complications are key factors in successful management of individual cases. Therefore, serious efforts have to be made to increase immunization coverage and good surveillance systems ought to be put into place to enable optimum reporting of disease.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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