ORIGINAL RESEARCH

Clinical Profile and Predictors of Outcome in Patients with Diphtheria in a Tertiary Care Center

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Abstract

Introduction: Diphtheria, a potentially fatal upper airway infection, caused by *Corynebacterium diphtheriae*, still continues to be significant cause of morbidity and mortality in India, despite extensive immunization.

Aims and objectives: This article aims to generate information about the clinical profile of patient of diphtheria in present times, assess association between immunization and severity of the disease and evaluate predictors that affect final outcome of the disease.

Materials and methods: This is a retrospective study from June 2017 to June 2020 at a tertiary care teaching hospital. The relevant data of 33 cases who were either suspected or confirmed cases of diphtheria, were analyzed with respect to demographic details, clinical features, immunization status, treatment provided, complications, and final outcome.

Results: Out of 33 cases, 72.7% were of age more than 5 years. Eighteen (55%) were nonimmunized, 10 (30%) were partially immunized, and 5 (15%) were immunized. The clinical features included fever, throat pain in all cases, membrane over tonsil in 93.7%, and bull neck in 78.1% cases. Albert stain was positive in 20 (60.6%) cases. Antidiphtheric serum (ADS) was given in 28 out of which 18 cases (64.3%) survived. Five cases did not receive ADS and out of these two (40%) survived. Case fatality rate was 55% in nonimmunized, 30% in partially immunized, and nil in immunized group. Overall, case fatality rate was 42.4%, and survival rate was 57.6%.

Conclusion: As disease nowadays is affecting older children more, awareness about booster doses is required. Complete immunization, early ADS therapy irrespective of result of Albert stain, helps to decrease complications and improve survival.

Keywords: Albert stain, Antidiphtheric serum, Diphtheria, Immunization, Membrane over tonsil, Suspected diphtheria.

Otorhinolaryngology Clinics: An International Journal (2021): 10.5005/jp-journals-10003-1398

Introduction

Diphtheria is a vaccine preventable infectious disease and has been eliminated in many developed countries by effective and extensive immunization. It is a potentially fatal upper respiratory tract infection caused by a gram-positive bacteria, *Corynebacterium diphtheriae*, which is transmitted from person to person via oral or respiratory droplets. Incubation period is 2–5 days. Classical clinical presentation of diphtheria is throat pain, fever, a membrane over oropharynx and usually associated with cervical lymphadenopathy (bull neck) of acute onset with history of 4–7 days.[1] Most important characteristic feature of diphtheria is the "pseudomembrane" which typically develops over the tonsils. This superficial pseudomembrane is tough, dirty-gray to gray white which is formed by necrotic sloughed epithelial cells and numerous colonies of *C. diphtheriae*.[2] Pharynx, larynx, trachea, and the main bronchi may be covered by adherent pseudomembrane which on peeling leaves behind a bleeding surface.

The diagnosis of diphtheria is confirmed by Albert staining of swab from oropharynx/larynx which is a rapid test. Bacterial growth in culture takes about 8 hours.[3]

Medical management in form of antidiptheric serum (ADS) is the mainstay of the treatment. It neutralizes bacterial toxin.[4] Diphtheria can lead to many serious complications. Complications are mostly due to exotoxin-mediated inhibition of protein synthesis. Various complications of this disease are cardiac (myocarditis, arrhythmia, CHF), polyneuropathy, respiratory distress/failure, renal failure.[5,6] This can cause mortality within 10 days of infection.[7] Death occurs in 5–10% of cases, and it is usually due to myocarditis and respiratory failure.[4]

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How to cite this article: Kumar L, Bist SS, Dhasmana G, *et al*. Clinical Profile and Predictors of Outcome in Patients with Diphtheria in a Tertiary Care Center. Int J Otorhinolaryngol Clin 2021;13(3):77–81.

Source of support: Nil

Conflict of interest: None

Diphtheria vaccination is part of national immunization program in India. It had been included in Expanded Programme of Immunization, with the aim of preventing and eradicating the disease in the country. This program was launched in the year 1978. At present, it is part of National immunization program.[8] Primary immunization doses for diphtheria include three doses at the age of 6, 10, and 14 weeks followed by booster doses at 18 months and 5 years.[8] Despite this, the disease still is endemic in India and continues to be one of the leading causes of morbidity and mortality among pediatric population. Recent reports show that the disease is making a comeback despite vaccination. The National Health Profiles indicate that India reported 5,826 cases and 68 deaths in 2005,[9] which decreased in 2011 to 2,525, but the data increased back in 2014, where there were 6,094 cases and 104 deaths.[10] In

2015, India contributed 2,365 cases (52.21%) of the total 4,530 cases reported globally.[11]

The present study intends to make ENT surgeons and pediatricians aware of this disease in the population in the present times.

Although there have been many studies on diphtheria in the past, it is because of this recent resurgence that this study was done to find out the clinical profile, which will help us to recognize the patient with diphtheria early and start the appropriate treatment quickly. This can result in decrease in the morbidity and mortality of case.[12]

Aims and Objectives

- To generate information about clinical profile of patient of diphtheria in present times.
- To evaluate relation between immunization status and the final outcome of the disease.
- To study predictors affecting outcome in patients with diphtheria.

Materials and Methods

We did a retrospective observational study from June 2017 to June 2020 at a tertiary care teaching hospital. All the cases that were either confirmed or suspected for diphtheria as per WHO guidelines were included in the study. A suspected case is the one having upper respiratory tract infection characterized by pharyngitis, nasopharyngitis, tonsillitis, or laryngitis and having adherent pseudomembrane of the tonsils, pharynx, nose, or larynx. A confirmed case is suspected case which is laboratory confirmed case of isolation of *C. diphtheriae*.[13] All the cases that presented in the hospital with acute onset fever, severe throat pain, odynophagia, and grayish-white membrane over the tonsils or oropharynx were included in the study. After obtaining approval from the ethical committee of the institute to carry out the study, the relevant data were analyzed and complete information regarding name, age, gender, clinical signs and symptoms, immunization status for diphtheria, laboratory tests, treatment provided, complications, and the outcome was noted. Data were compiled and analyzed according to various parameters. Depending upon immunization history, patients were divided into three groups. Those who did not receive any dose of diphtheria vaccine were put in unimmunized group, those who received few doses but did not take all recommended doses including booster doses at 18 months and 5 years were put in partially immunized group and those who received all recommended doses were put in immunized group. Data were then analyzed to know the clinical profile of diphtheria in the present scenario and also to see whether any correlation exists between the immunization status of the patient and the outcome of the disease. Data were also analyzed to derive any correlation between administration of ADS and final outcome of the disease. The consent had already been taken at the time of admission by the patients included in this study for the use of data for any research work.

Results

A total of 33 patients with diagnosis of diphtheria were taken in the study.

The age of patients ranged from 3 to 15 years out of which 9 patients (27.3%) were below age of 5 years, while 24 (72.7%) were more than 5 years of age. There were 19 (57.6%) males and 14 (42.4%) females. The male to female ratio was 1.35:1. All of them except three (91%) were from the rural area. Thirty-one cases (94%) were from the lower socioeconomic class, while two (6%) were from middle class. By religion, 17 (51%) of them were Hindus, 15 (46%) were Muslims, and 1 (3%) patient was Sikh (Table 1).

Clinically, all patients presented with fever and severe throat pain. On clinical examination, 31 cases (93.7%) had a membrane over the tonsils, 26 (78.1%) had bullneck (multiple, cervical lymph node enlargement), and 28 (84.8%) had breathing difficulty at time of presentation in hospital (Table 1).

Majority of patients, i.e., 18 (55%) were unimmunized, while 10 (30%) were partially immunized. Only five (15%) were completely immunized.

These patients were subjected to laboratory test, i.e. Albert Stain. In present study, in 20 (60.6%) patients, this test was positive, while in 12 (36.3%) patients, the result was negative. In one (3.1%) patient, the test was nonconclusive.

ADS was given to 28 (84.8%) patients, while five (15.2%) patients did not receive ADS. Dose given was according to the severity of disease and varied from 50,000 to 100,000 units, given by intravenous route, after test dose. Out of 28 patients who received ADS, 18 (64.3%) patients survived and 10 (35.7%) died. While, out of those five who did not receive ADS, two (40%) patients survived and three (60%) died (Table 2).

Table 1: Demographic data and clinical features ($n = 33$)

Parameter	*Number*
Age	
<5	09 (27.3%)
6–10	14 (42.4%)
11–15	10 (30.3%)
Gender	
Male	19 (57.6%)
Female	14 (42.4%)
Residence	
Rural	30 (91%)
Urban	03 (9%)
Economic status	
Upper	00
Middle	02 (6%)
Lower	31 (94%)
Religion	
Hindu	17 (51%)
Muslim	15 (46%)
Sikh	01 (3%)
Immunization status	
Unimmunized	18 (55%)
Partially immunized	10 (30%)
Immunized	05 (15%)
Clinical features	
Fever	33 (100%)
Membrane over tonsil/ oropharynx	31 (93.7%)
Bull neck	26 (78.1%)
Odynophagia	33 (100%)
Breathing difficulty	28 (84.8%)

Out of 28 patients who were given ADS, 19 (67.8%) had complications. There were five patients who were not given ADS and all of them (100%) had complications (Table 2).

Twenty-four (72.7%) out of 33 patients had complications, among which cardiac complications and respiratory distress were the commonest and seen in 15 cases (45.5%) each, followed by palatal palsy in 24.3% cases, polyneuropathy in 21% cases, and bleeding or disseminated intravascular coagulation (DIC) in 21% cases. Nine percent patients had acute renal failure, 3% patient had convulsions, and 3% had septicemia (Table 3).

Out of 15 cases who developed respiratory distress, 12 (80%) patients had to be given ventilatory support. Out of 12, 7 (58.3%) expired while 5 (41.7%) cases survived. Six (40%) patients underwent tracheostomy out of whom one patient could be decannulated. Out of six tracheostomized patients, two (33.3%) survived and four (66.6%) died (Table 2).

Fifteen (83.3%) out of 18 unimmunized patients had complications, 11 (61%) of them died. Among 10 partially immunized patients, 8 (80%) cases had complications and 3 (30%) of them died. While only one (20%) out of five immunized patients had complication, and the rest four had less severe course and all five (100%) patients survived (Fig. 1).

Out of total 33 patients, 14 expired, making case fatality rate of diphtheria 42.4%, while 19 (57.6%) patients survived (Table 3).

Discussion

Vaccination against diphtheria has reduced the mortality and morbidity of the disease dramatically; however, it is still a significant child health problem in developing countries.

In present study, out of 33 cases, only 9 (27.3%) cases were less than 5 years of age and 24 (72.7%) were above 5 years, whereas prior to the vaccination era, children less than 5 years of age were affected more, due to their poor immunity while adolescents and adults were saved because of their developed immune system. However, in the recent years, when the vaccination coverage has been improved, it is noticed that there has been a shift in age for occurrence of disease. It is now seen more in older children and adults. This is probably because of lack of booster doses that are recommended at 18 months and at 5 years of age. Child with missed booster dose becomes susceptible to infection due to fall in antibody titers, whereas infants and younger children are better protected due to initial three doses which are least likely to be missed now a days. Such shift in age group was observed in two other recent studies in India. Basavraja et al.'s[14] study had 25.8% patients who were less than 5 years and 74.1% patients who were over 5 years, while in study by Bandichhode et al.,[15] 33.33% cases were less than 5 years of age, whereas 66.66% were more than 5 years of age.

In present study, males outnumbered females by ratio 1.35:1. Ninety-one percent patients belonged to the rural area, and 94% were from the lower class. This may be attributed to the fact that socioeconomically weaker may have lesser access to the immunization/health facilities compared to economically richer population, also there could be challenges in rural areas to maintain the cold chain. Similar observations were made by Meshram et al.[16] and Maheriya et al.,[17] but male to female ratio was almost similar in the former i.e. 0.95:1. Hindus and Muslims were almost same in number.

We observed, out of 33 patients, 55% cases were unimmunized, 30% patients were partially immunized, and only 15% were completely immunized. Similar observation regarding immunization status was reported by Maheriya et al.[17] and Bandichhode et al.[15] In the study by Bandichhode et al.,[15] 36 patients were taken, out of which 58.33% were unimmunized, 30.55% were partially immunized, and only 11.11% children were fully immunized. This lack of complete immunization may be due to non-availability of immunization services especially in rural/hilly area. Other factors include delaying or postponing vaccination in minor childhood illness, lack of awareness, and illiteracy.

In our study, 83.3% of unimmunized patients had developed complications while 55% of them died. Among 10 partially immunized patients, 80% cases had complications and 30% died. In immunized group, one (20%) out of five patients had complication but all the patients (100%) survived. These data strongly favor the point that prior immunization plays a key role in preventing the complications and fatal outcome of the disease. Disease had run more fulminant course in unimmunized patients. It proves that proper immunization is necessary for the reduction of the mortality associated with the disease.

In total, 24 (72.7%) out of 33 patients had complications, out of which respiratory and cardiac complications were the most common i.e. 45.5%. It was comparable to study by Meshram et al.[16] and Ujjwal et al.,[18] which showed myocarditis as the most common complication, i.e., 42.5 and 63.3%, respectively.

Table 3: Complications and final outcome ($n = 33$)

Complications	*Number*
Cardiac	15 (45.5%)
Respiratory distress	08 (24.3%)
Polyneuropathy	07 (21%)
Palatal palsy	15 (45.5%)
Acute renal failure	03 (9%)
Convulsions	01 (3%)
Septicaemia	01 (3%)
DIC/bleeding	07 (21%)
Final outcome	
Survived	19 (57.6%)
Expired	14 (42.4%)

Table 2: Relation between treatment given and course of disease ($n = 33$)

Treatment	*Total*	*Complications present*	*Complications absent*	*Expired*	*Survived*
ADS given	28 (84.8%)	19 (67.8%)	9 (32.2%)	10 (35.7%)	18 (64.3%)
ADS not given	5 (15.2%)	5 (100%)	0 (0%)	03 (60%)	02 (40%)
Ventilatory support	12 (36.4%)			7 (58.3%)	5 (41.7%)
Tracheostomy	6 (18.2%)			4 (66.6%)	2 (33.3%)

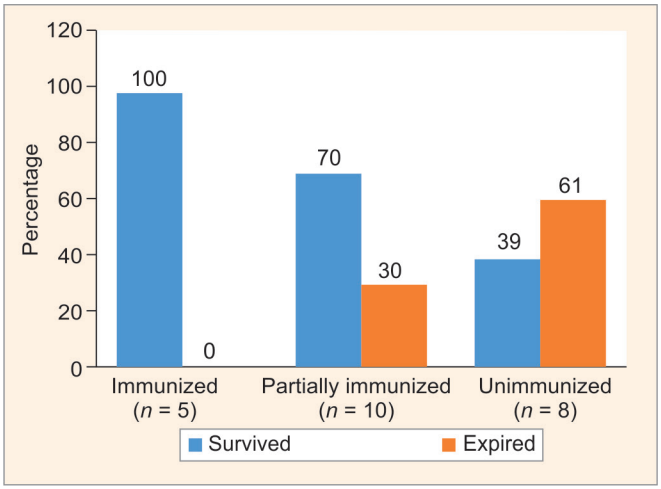

Fig. 1: Relation of disease outcome with immunization status in diphtheria patients ($n = 33$)

Respiratory distress was seen in 15 cases (45.5%), out of whom 12 patients required supportive intervention in the form of ventilatory support, 6 had undergone tracheostomy. A similar observation regarding respiratory distress was made in study by Jayshree et al.[19]

Lab test for Albert stain was positive in 20 (60.6%) cases and negative in 12 (36.4%) cases. Other studies done by Basavaraja et al.,[14] Bandichhode et al.,[15] and Singh et al.[19] observed positive Albert stain in 16.1, 33.33, and 30.63% cases, respectively. Due to low sensitivity rate, we should not depend completely on result of lab test, thereby initiating therapy on clinical suspicion of diphtheria without delay, in form of ADS.

In our study, out of 28 patients who were given ADS, 64.3% survived, 67.8% had complications, and 35.7% died. The cause of occurrence of these complications may be history of incomplete immunization, delay in starting the treatment or inadequate dosage. However, there were five patients who were not given ADS, probably as Albert stain was negative in them. Forty percent of them survived, all of them (100%) had complications and 60% expired, suggesting that prompt antitoxin therapy is important in preventing the fulminant course and lethal outcome. ADS neutralizes free toxin circulating in the blood and can thus reduce complications as well as mortality of diphtheria. This observation implies that we should start the therapy as soon as possible, based on the clinical suspicion.

Out of 33, 14 patients died, making case fatality rate of diphtheria 42.4%, in present study. Similar mortality rate (48%) was seen in study done by Singh et al.[20] A higher mortality (56.3%) was noted in study by Jayshree et al.,[19] while in study by Ujjwal et al.,[18] it was 18.18%, and in study by Meshram et al.,[16] it was 21.28%. It indicates that diphtheria remains a potentially fatal disease, even in present times. This high mortality rate could also be due to delay in clinically diagnosing the disease, possibly as clinicians do not suspect diphtheria as the possibility, thereby delaying the treatment in form of ADS. We observed that delay in initiating ADS therapy resulted in high morbidity and mortality.

Therefore, the present study showed that complete immunization, high index of suspicion, early clinical diagnosis, and prompt antitoxin therapy are the essential key factors in preventing the mortality and complications.

Conclusion

- Creating awareness about the disease and the immunization, especially the booster doses among people in the rural areas is of utmost importance.
- Diphtheria, if not diagnosed early, or if not treated promptly with ADS, may lead to deadly complications and mortality, especially in unimmunized children.
- Antitoxin therapy should be started early, based upon high degree of clinical suspicion, irrespective of Albert stain report.
- Therefore, from the present study, we conclude that complete immunization with emphasis on taking booster doses, early diagnosis and prompt treatment with ADS help in controlling/treating this dreaded infectious disease.

Acknowledgments

The authors acknowledge with gratitude the Institute and associated Hospital for providing all support for the conduct of this study.

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References

1. Meera M, Rajarao M. Diphtheria in Andhra Pradesh–a clinical-epidemiological study. Int J Infect Dis 2014;19:74–78. DOI: 10.1016/j.ijid.2013.10.017.
2. Tsinzerling AV, Sizemov AN, Miasnikova TI, et al. Tonsils in diphtheriae and the *Corynebacterium diphtheriae* carrier state, Arkh Patol 1980;42(8):75–80. PMID: 7406725.
3. Begg N. Diptheria-manual for the management and control of diphtheria in the European region. Copenhagen: WHO Publication; 1994.
4. Ghai OP. Essential pediatrics. 9th ed. New Delhi, India: CBS Publishers and Distributers Private Limited; 2019. p. 236–237.
5. Atkinson W. Epidemiology and prevention of vaccine-preventable diseases. Department of Health & Human Services, Centers for Disease Control and Prevention; 2006.
6. Verghese MJ, Ramakrishnan S, Kothari SS, et al. Complete heart block due to diptheric myocarditis in the present era. Ann Pediatr Cardiol 2013;6(1):34–38. DOI: 10.4103/0974-2069.107231.
7. Government of India. Annual report 2012. India: Ministry of Health; 2012.
8. Park K. Park's textbook of preventive and social medicine. 25th ed. Madhya Pradesh, India: Bhanot Publishers; 2019. p. 134–135 [NIS, immunization].
9. Central Bureau of Health Intelligence, Directorate General of Health Services, Government of India. National Health Profiles; 2011. Available from: http://www.cbhidghs.nic.in/index1.asp/linked=267 [Last accessed on December 31, 2016].
10. World Health Organisation. Vaccine preventable diseases: monitoring system 2016 global summary. Updated on March 3, 2017. Available from: http.//www.who.int.tsincidencediptheria.com [Accessed on March 27, 2017].
11. United Nations International Children's Fund. Immunisation report. Available from: www.unicef.in/whatwedo/3/immunisation [Accessed on March 27, 2017].
12. Park K. Park's textbook of preventive and social medicine. 16th ed. Madhya Pradesh, India: Bhanot Publishers; 2000. p. 125–128 [early diagnosis reduces morbidity].

13. World Health Organisation vaccine preventable diseases surveillance standards. 2018.
14. Basavaraja GV, Chebbi PG, Joshi S. Resurgence of diphtheria: clinical profile and outcome—a retrospective observational study. Int J Contemp Pediatr 2016;3(1):60–63. DOI: 10.18203/2349-3291.ijcp20160058.
15. Bandichhode ST, Jatti GM, Anita MS, et al. A clinical study of diphtheria cases in a pediatric population in tertiary care hospital in western Maharashtra. Indian J Child Health 2016;3(3):251–253. DOI: 10.32677/IJCH.2016.v03.i03.018.
16. Meshram RM, Patil A. Clinical profile and outcome of diphtheria in central India: a retrospective observational study. Int J Contemp Pediatr 2018;5(4):1600–1605. DOI: 10.18203/2349-3291.ijcp20182572.
17. Maheriya KM, Pathak GH, Chauhan AV, et al. Clinical and epidemiological profile of diphtheria in tertiary care hospital. Gujarat Med J 2014;89(2):105–108.
18. Ujwal MV, Pol RR, Vanaki R, et al. Resurgence of diphtheria in rural north Karnataka: clinical profile and outcome. Int J Med Paediatr Oncol 2019;5(1):17–20. DOI: 10.18231/j.ijmpo.2019.004.
19. Jayshri M, Shruti N, Singhi S. Predictors of outcome in patients with diphtheria receiving intensive care. Indian Pediatr 2006;43:236–238. PMID: 16528112.
20. Singh SN, Singh A, Chandra S. Clinical profile and predictors of poor outcome of hospitalized diphtheria cases in children from Lucknow region of North India. Clin Epidemiol Global Health 2014;2(2):75–79. DOI: 10.1016/j.cegh.2012.11.005.