RESEARCH

RESURGENCE OF DIPHTHERIA AT A TERTIARY CARE CENTRE, OUR EXPERIENCE OF 417 PATIENTS: A RETROSPECTIVE STUDY FROM RURAL HARYANA

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Abstract

Background: Diphtheria continues to be one of the main infectious diseases in countries where implementation of the full course of the DPT vaccination programme is not effective, and poses a public health threat in developing countries. The objective is to study clinical features, treatment and outcome after management of patients who presented with clinical features of Diphtheria, during recent upsurge in cases. **Materials and Methods:** The present study is a retrospective observational study conducted at a tertiary care hospital in the state of Haryana, India. Institutional records of total 417 patients who were admitted to the hospital with clinical features of diphtheria were analysed for clinical history, examination, immunisation status, investigations, management and outcome. **Result:** All the patients underwent throat swab examination, out of which 62% were confirmed on throat swab and additional 32% were confirmed on culture. The patients presented with symptoms like, throat pain and odynophagia in 358 (85.8%) patients, fever in 316 (75.77%) patients, neck swelling 112 (26.85%), respiratory distress with stridor was seen in 71 (17.02%). 263 (63.06%) patients were discharged after full recovery, 57 (13.66%). Out of total patients, 97 (23.26%) patients succumbed due to cardiorespiratory complications. **Conclusion:** Diphtheria is a life-threatening disease that requires early detection, rapid treatment and intensive care interventions in very severe cases. Diphtheria must be recognised as another important vaccine-preventable disease of the modern age. Prevention via immunisation programmes along with booster doses must be prioritised.

INTRODUCTION

Diphtheria is an infectious disease caused by toxigenic bacteria of the Corynebacterium genus. Corynebacterium diphtheriae is the most common bacteria followed by other closely related species, namely C. ulcerans and C. pseudo- tuberculosis. The Corynebacteriaceae family comprises >100 species of aerobic, Gram-positive rods that exhibit a club-shaped morphology.[1]

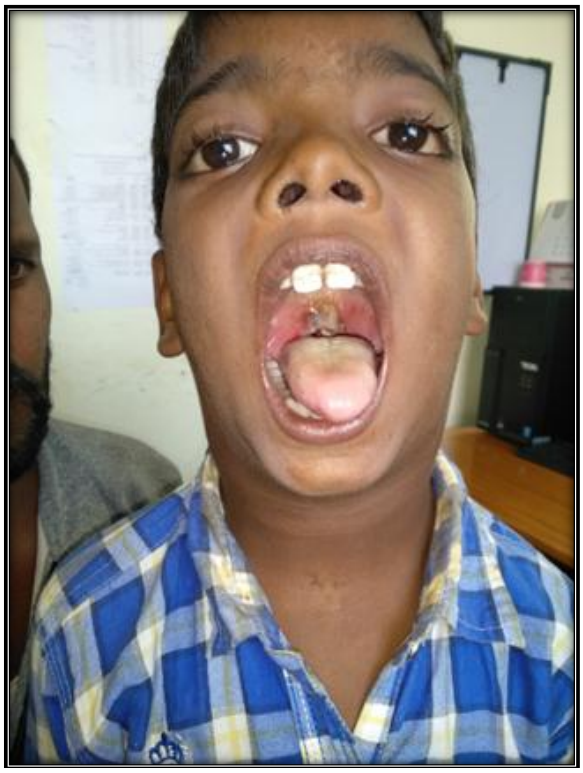
Diphtheria, a potentially life-threatening condition which remains a problem in a number of low-income countries with poor immunization coverage. Several outbreaks have been reported in sub-Saharan Africa (e.g. Nigeria and Madagascar) since 2000.[2] Bangladesh experienced recently an outbreak in a large refugee camp for the Rohingyas in 2017.[3] Currently, India, Indonesia and Nepal have the highest number of diphtheria cases in Asia. 2 Even in countries with rather good immunization coverage, such as Thailand and Iran, outbreaks of 157 and 513 cases respectively, have been reported in recent years.[2] Since the last major outbreaks of diphtheria in the 1990s, cases continue to be reported from Europe as well. In 2014, for example, 22 cases of confirmed diphtheria were reported in the European Union, and about half of these cases were in Latvia.[4] No age group is completely immune, but unimmunized children are commonly affected before 5 years of age.[1] Clinical features of diphtheria incudes presence of pseudo-membranous pharyngitis. The other typical features of acute diphtheria include enlarged lymph nodes in the neck which is commonly known as bull neck, myocarditis and inflammation of cranial nerves. Diphtheria continues to be one of the main infectious diseases in

countries where implementation of the full course of the DTP vaccination program is not effective, and poses a public health threat in developed countries.

The present study is done at a tertiary care center located in Nuh district of Haryana, India. This area has been designated as the most backward district of the country as per the report of Sadoh AE.[5] The literacy rate, poor sociocultural practices prevailing in this area, and neglect to immunization programs have led to resurgence of disease from time to time.

The aim of present study is to observe the various clinical features, its management, need for tracheostomy and fatality of the cases of diphtheria, during a recent upsurge in the cases at our center.

MATERIALS AND METHODS



Picture 1: Characteristic diphtheria Membrane in throat.

The present study is a retrospective observational study conducted at a tertiary care hospital in the state of Haryana of cases of diphtheria admitted from January 2018 to December 2021. Institutional records of total 417 patients who were admitted to the hospital were analysed for patient clinical history, examination, immunisation status, investigations, management and outcome after clinical management. The approval was taken from institutional ethical committee.

Picture 2: Bull neck in Diphtheria.

Picture 3: Bull neck and cutaneous ulcers in a 19 day old female.

All patients who presented to the hospital with high clinical suspicion of diphtheria based on history of dysphagia, fever, odynophagia, respiratory distress, bull neck, whitish membrane in throat etc. [Picture 1-3], were admitted to a separate isolation ward designated as Diphtheria ward. Detailed history was taken and all patient underwent throat swab

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examination. Two throat swabs were taken and sent for Albert stain and bacterial culture. Patients with high clinical suspicion of diphtheria were administered with anti-diphtheritic serum (ADS) in doses ranging from 20,000 IU -80,000 IU based on dosage recommended by WHO. Antibiotic cloxacillin, paracetamol for fever was also started in patients with mild symptoms, ADS was given only to patients after throat swab/ culture tested positive for diphtheria, or the patients with high clinical suspicion of Diphtheria. Routine blood investigations were done and ECG was done in patients having abnormal pulse. Patients having respiratory distress were tracheostomised with appropriate post tracheotomy care. The patients were discharged only after two consecutive throat swabs were negative on Albert staining.

The data was collected from the hospital records and entered in a proforma. Patients demographics, presenting signs and symptoms, diagnostic investigations including throat swab, radiological imaging, medical and surgical outcomes were tabulated and Analysed.

Inclusion Criteria

Clinical records of:

1. All patients clinical diagnosed cases of Diphtheria
2. All patients with throat swab positive for Diphtheria

Exclusion Criteria

Incomplete records

RESULTS

Total of 417 patients were admitted from January 2018 to Dec 2021. The yearly distribution as per [Table 1].

Out of total 417 patients, 263 (63%) were males and 154(37%) were females [Figure 2]. The most common age group affected was 1-5 years (63.54%) [Figure 3]. The youngest patient admitted was 19 days old female, [Picture 3], while the eldest patient was 36 years female. 5 patients of total were health care professionals who were involved in patient care. 376 (90.16%) patients were un-immunised / incompletely immunised.

All the patients underwent throat swab examination, out of which, 62% were confirmed on throat swab and additional 32% were confirmed on culture. The patients presented with symptoms like, throat pain and odynophagia in 358 (85.8%) patients, fever in 316 (75.77%) patients, neck swelling 112 (26.85%), respiratory distress with stridor was seen in 71 (17.02%). All patients were treated as per guidelines for the management of diphtheria, depending on duration of onset of symptoms and presentation to hospital since onset of symptoms, 11(2.6%) patients received 20,000 units, 108 (25.8%) patients received 40,000 units, 109 (26.13%) patients received 60,000 units, and 189 (45.32%) received 80,000 units [Figure 4]. 69 patients were tracheostomised because of respiratory distress, all the patients who were tracheostomised either had respiratory distress at the time of admission or developed distress within 2 days of admission.

263 (63.06%) patients were discharged after full recovery, 57 (13.66%) patients developed cardiac complications and were referred to higher center due to non-availability of paediatric cardiac unit, 97 (23.26%) patients expired. [Figure 5]

Table 1: Yearly distribution of cases

Year/Month	Jan-March	April-June	July-sept	Oct-Dec
2018	0	0	0	123
2019	7	3	95	110
2020	8	2	14	29
2021	3	0	9	13

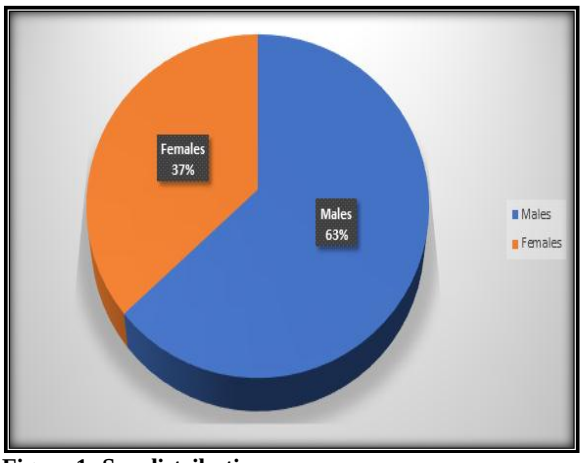

Figure 1: Sex distribution

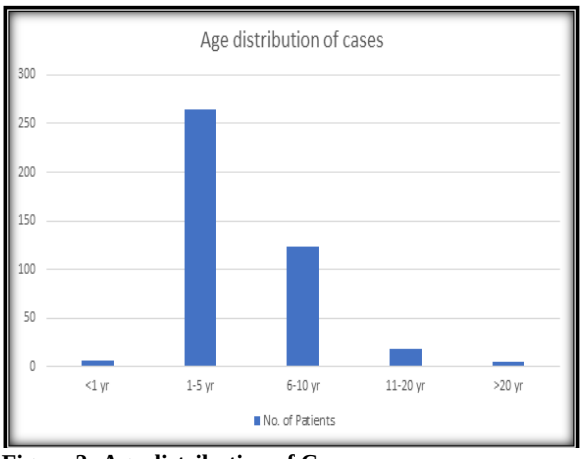

Figure 2: Age distribution of Cases

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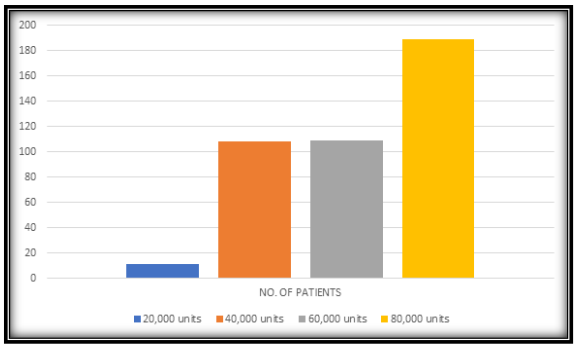

Figure 3: Dose of Diphtheria antitoxin given to patients

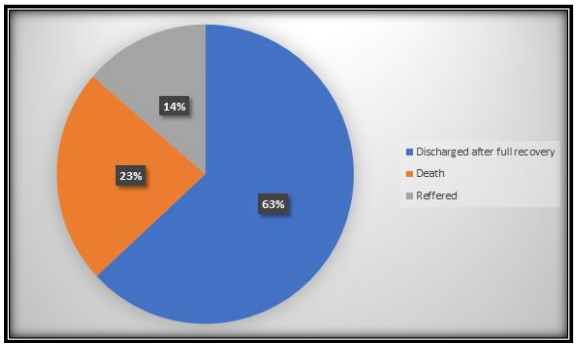

Figure 4: Outcome after management

DISCUSSION

In the past decade, there have been 4,000–8,000 diphtheria cases reported annually worldwide. 5 Global diphtheria cases reported to WHO are likely an underestimation of the real burden of disease due to under-reporting, exclusion of non-respiratory diphtheria cases and exclusion of cases caused by the other potentially toxigenic species.[6]

Diphtheria is caused by Corynebacterium species. The most commonly associated organism is toxin-producing Corynebacterium diphtheriae, and rarely by toxin-producing strains of C. ulcerans and C. pseudotuberculosis. The classic respiratory diphtheria is caused by the exotoxin produced by the bacteria which causes the formation of a pseudomembrane in the upper respiratory tract. This exotoxin enters the blood circulation and damages other organs such as the myocardium and peripheral nerves. Acute respiratory obstruction, acute systemic toxicity, myocarditis and neurologic complications are the usual causes of death. The infection can also affect the skin (cutaneous diphtheria). Rarely, it can affect mucous membranes at other non-respiratory sites, such as genitalia and conjunctiva. The diphtheria toxin binds epithelial, nerve and muscle cells which leads to severe local and systemic manifestations of the disease. This toxin interferes with enzymes of protein synthesis, leading to cell damage and death. Local effects include severe inflammation and formation of pseudomembrane in the nose, pharynx and larynx. A diphtheria pseudomembrane is the result of an exudate released in response to the infection, that is greyish, thick, firmly adherent and patchy to confluent. Dislodging the pseudo membrane is likely to cause profuse bleeding. Laryngeal pseudo membrane can cause life-threatening airway obstruction. The absorption of diphtheria toxin into the blood stream can lead to systemic effects which include myocarditis, polyneuritis, and, sometimes renal failure.[7,8]

The disease is insidious in onset with an incubation period of 1-5 days. It begins with low-grade fever followed by development of pharyngeal pseudo membrane over 2-3 days, along with enlarged neck nodes known as “bull neck”. Gradually the systemic toxicity sets in, resulting in a rapid, thready pulse, weakness, and irritability. Although the systemic effects of diphtheria can occur in the first week of illness, they usually occur later (1-2 weeks after onset for myocarditis, 2-8 weeks for neuritis). The hallmark of suspected respiratory diphtheria is a low-grade febrile, membranous pharyngitis of insidious onset.[7,8]

Case fatality ratios up to 10% have been reported in diphtheria outbreaks, and are higher in settings where diphtheria antitoxin (DAT) is unavailable. 1 We reported Case fatality rate of 23.26%, this could be explained by delay in presentation to a tertiary care centre, vaccine hesitancy in the rural population, high bacterial load at time of infection, poor nutritional status, overcrowded living conditions. Due to lack of awareness of severity and sequalae of disease, people seek local practitioners at the village level and present very late to a tertiary care centre, when the disease becomes advanced or, already complications like respiratory distress, cardiotoxicity sets in.

As per the national immunisation programme, Diphtheria toxoid, the vaccine to prevent diphtheria, should be given to infants as a primary series of three doses, at 6 weeks, 10 weeks and 14weeks, followed by three appropriately spaced booster doses yearly thereafter till 5 years of age, to ensure long-term protection.[1]

According to WHO, the definition of a suspected case of diphtheria is an illness of the upper respiratory tract characterized by the following:

- Pharyngitis, nasopharyngitis, tonsillitis or laryngitis AND
- Adherent pseudo membrane of the pharynx, tonsils, larynx and/or nose.

All suspected diphtheria cases should be isolated and have two specimens collected prior to initiation of antibiotic treatment. The sample should be obtained under direct visualization, preferably from the edge of or directly beneath the pseudomembrane. If possible, a sample of the pseudomembrane should also be collected and placed in saline (not formalin). Treatment of the suspected cases should begin promptly without waiting for laboratory confirmation.

Treatment

The management of a patient with suspected diphtheria includes:

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1. Administration of DAT as soon as possible after assessing for hypersensitivity to horse serum; early administration of DAT is critical for survival.[9]
2. Establishing the diagnosis through appropriate bacterial cultures;
3. Administration of antibiotics; and
4. Appropriate supportive care including special attention to maintaining an adequate airway in the presence of laryngeal or extensive pharyngeal membranes and to careful monitoring for cardiac rhythm disturbances or other manifestations of myocarditis.

The IV route is the preferred route of administration of DAT, especially in severe cases. The antitoxin dose should be mixed in 250 –500 mL of normal saline and administered slowly over 2 – 4 hours, closely monitoring for anaphylaxis. The antitoxin may be given IM in mild or moderate cases.

Dosage

1. Perform sensitivity tests, and desensitization if necessary.
2. Give the entire treatment dose of antitoxin IV (or IM) in a single administration
3. The recommended DAT treatment dosage ranges are as per [Table 2].
4. Give children the same dose as adults.
5. Repeated doses of DAT after an appropriate initial dose are not recommended and may increase the risk of adverse reactions.

Table 2. Paediatric and Adult DAT Dose.[10]

Diphtheria clinical presentation	DAT dose in IU (# of ampoules)
Pharyngeal or laryngeal disease of 2 days duration Nasopharyngeal disease	20,000 – 40,000 (2-4)
Extensive disease of 3 or more days duration, or any patient with diffuse swelling of neck	40,000 – 60,000 (4-6) 80,000 – 100,000 (8-10)
Skin lesions only (rare case where treatment is indicated)	20,000 – 40,000 (2-4)

The present study successfully highlights the importance of adequate vaccine coverage to prevent the upsurge of cases in a given population. Failure to do so results in high mortality and morbidity. It also leads to overburdening of health care system and additional expenditure for procurement of Diphtheria antitoxin. Limitations of the study are that being a retrospective study molecular analysis of the strains and their toxigenic potential could not be done. Further studies needs to be done to analyse the toxigenicity of antitoxins produced by the bacteria.

CONCLUSION

In areas where frequent outbreaks are reported, provision of adequate infrastructure and availability of adequate stock of DAT should be maintained for timely management of such cases. Ten yearly booster dose should be included in ongoing immunisation programme, and should be made compulsory for health care professionals involved in patient care. A better understanding of the molecular epidemiology of this pathogen might assist in directing and strengthening public health interventions.

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