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Original Article

Paediatrics Section

Diphtheria Remains a Threat to the Health System Even in the Era of Vaccination: A Cross-sectional Observational Study from Karnataka, India

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ABSTRACT

Introduction: Diphtheria is an infectious disease caused by a gram-positive facultatively anaerobic bacilli, Corynebacterium (C.) diphtheriae. The present health statistics and data from the few studies that have been carried out suggest that our war with this disease is still going on and is far from being over inspite of the vaccine that's freely available.

Aim: To study clinical profile, complications, and outcome of diphtheria in Karnataka population and to correlate with immunisation status.

Materials and Methods: This was a hospital-based prospective cross-sectional observational study done in the Department of Paediatrics, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India, from January 2018 to November 2018. Patients admitted with history suggestive of diphtheria were enrolled and categorised into probable and confirmed cases. The age, sex, area of residence, religion, immunisation status, mean time of presentation to hospital from onset of illness, use of inotropes and mechanical ventilation were recorded in a predesigned proforma. Throat swab smear for *C.diphtheria* and culture, complete blood count, Renal Function Tests (RFT) with serum electrolytes, chest radiograph, Electrocardiogram (ECG) and 2-Dimensional (2D) Echocardiogram (ECHO) were also recorded.

Results: Out of total 28 cases, 18 fulfilled the inclusion criteria. Male to female ratio was 2:1 and the mean age of presentation was 9.7 years. Highest incidence (n=14, 77.8%) was seen in the age group of 09-11 years. Most common clinical presentation was fever and sore-throat present in all 18 (100%), neck swelling in 13 (72.2%), dysphagia in 05 (27.7%). Examination revealed tonsillar hypertrophy and pseudomembrane in 17 (94.4%) patients, whereas one patient had laryngeal diphtheria, which was diagnosed when swab was sent while intubating in view of membranous laryngitis. Mean time of presentation to hospital after the onset of symptoms was 5.65 days. All children received appropriate antibiotics and Antidiphtheritic Serum (ADS). Total of seven patients were ventilated, of which 5 (27.7%) succumbed, and two were extubated. Four (22.2%) patients developed myocarditis in the second week, and all succumbed to resistant arrhythmias. One patient developed sepsis with ventilator dependency, and succumbed to inotrope resistant septic shock. On follow-up, 5 (27.7%) developed palatal palsy among which three had associated polyneuropathy; all these children recovered with only supportive care.

Conclusion: Diphtheria is down but not out, the present study unmasks the fact that the disease is equally prevalent in immunised and older children with the changing epidemiology of diphtheria in the era of vaccines.

Keywords: Arrhythmias, Immunisation, Partially immunised, Upper respiratory tract

INTRODUCTION

Diphtheria is an upper respiratory tract infection involving anterior nasal, pharyngeal, tonsillar or laryngeal mucous membranes. The organisms are locally invasive and secrete soluble exotoxins, which can lead to fatal consequences mainly involving the heart muscle and nervous system. The mortality rate, which is generally 5-10%, may be as high as 20% in children below 5 years and adults over 40 years of age [1]. Incidence of the disease, which was more than a million per year during the first half of the 19th century declined by over 95% during the past three decades due to widespread immunisation [2]. However, after this sharp decline in cases, there seems to be a plateau in the world incidence of the disease with India contributing as much as 78% of all cases between 2000-2017 [2,3].

Due to the vaccine-preventable nature of the disease and initial steady decline, not much attention has been given towards this disease which has not only continued over the past decade in India but has also been sixth in the list with highest mortality rate in India. Current statistics show that diphtheria has been re-emerging [3,4]. This re-emergence is despite a reported increase in coverage of the National Immunisation Programme (NIP). The recent national health profile reports about 11270 cases of diphtheria in India with a mortality rate of 2% [3]. Certainly, this information is a compilation of the data which is mostly limited to reports obtained from routine surveillance systems functioning in respective states and union territories in the country. Detailed literature on occurrence of diphtheria as cases or outbreaks has been very scanty. Literature that is available includes those cases and outbreaks in Vijayapura district of Karnataka and also mostly in northern India and also in Mumbai [5-7].

The present health statistics and data from the few studies that have been carried out suggest that the war with this disease is still going on and is far from being over inspite of the vaccine that's freely available. At a global level there has been outbreaks of diphtheria in Rohingya refugees [8,9]. There have been recent outbreaks of this vaccine preventable disease in Venezuela, due to the tumbling economy and authoritarian rule prevailing in the country leading to a massive gap in immunisation coverage [10]. Similar outbreak has been noticed in Yemen with the ongoing civil war since March 2015, which has severely affected the country's infrastructure including health services. Less than 50% of existing health facilities is fully functional and there is a serious shortage of staff, medicine and equipment, this in turn, has led to outbreaks of

vaccine preventable diseases and arthropod borne diseases [11]. This research was taken up to study the clinical profile, vaccination status and predictors of mortality in the era of intensified routine immunisation in Hubballi, Dharwad district of Karnataka, India.

MATERIALS AND METHODS

This was a hospital-based prospective cross-sectional observational study done in the Department of Paediatrics, Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India, from January 2018 to November 2018. Ethical clearance was obtained from the ethical committee of the institute. (EC no:KIMS/PGS/456/2017-2018). An informed written consent was taken from the parent/guardian.

Inclusion criteria: Patients presenting with fever, sore throat and membrane over tonsil were included in the study.

Exclusion criteria: Those patients with non adherent tonsillar membrane were excluded from the study.

Patients admitted with history suggestive of diphtheria were enrolled and categorised into probable and confirmed cases based on the following definitions [8]:

- Probable diphtheria is an upper respiratory tract illness characterised by sore throat, low-grade fever, and an adherent membrane of the tonsils, pharynx, and/or nose.
- Confirmed diphtheria is a probable case supported by laboratory evidence either by: i) isolation of the organism from a clinical specimen; or ii) demonstration of a four-fold or greater rise in serum antibody titres in paired sera samples (only if both serum samples are obtained before the administration of diphtheria toxoid or antitoxin).

Study Procedure

The relevant information of study population was collected by interviewing the parents or guardians of the child, using a predesigned proforma. Demographic data including age, sex, areas of residence, religion, parental education and economic status were recorded. Detailed clinical history including immunisation status, mean time of presentation to hospital from onset of illness, use of inotropes and mechanical ventilation were recorded. Chest X-ray, Electrocardiogram (ECG) and 2-Dimensional (2D) Echocardiogram (ECHO) were done as and when indicated. Chest X-ray was done for all, ECG and ECHO helped in diagnosis of myocarditis. Children who had received three primary doses of Diphtheria Pertussis Tetanus (DPT) vaccine at 4-6 week intervals starting at six weeks of age, followed by booster doses at 18 months and five years were recorded as "immunised". Those who had not received any dose were categorised as "unimmunised". Partially immunised patients were the one who had missed one or more of the three primary doses or booster doses. However, for better comparison both unimmunised and partially immunised children were taken as one category. Detailed history of immunisation was taken orally and then crosschecked from immunisation cards of children whenever available. All children received appropriate antibiotics and Antidiphtheritic Serum (ADS). Details about antibiotics given and ADS administration were recorded for analysis.

STATISTICAL ANALYSIS

All the data was entered into Microsoft excel sheet and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software version 21.0. Data was expressed as mean±standard deviation for continuous metric data or median Interquartile Range (IQR) for those with the skewed distribution. Nominal categorical data between the groups was expressed as relative frequency, percent distributions and compared with Chi-square test or Fischer's-exact test as appropriate. The comparison of normally distributed continuous variables between the groups was done by student t-test. The p-value of <0.05 was denoted as statistically significant.

RESULTS

Out of 28 cases who presented with fever, sore throat, and membrane on tonsil, a total of 18 cases (64.28%) fulfilled inclusion criteria. Male to female ratio was 2:1 and the mean age of presentation was 9.7±0.9 years. Highest incidence (n=14, 77.8%) was seen in the age group of 09-11 years. Majority were from rural area 14 (77.8%), however all belonged to lower socio-economic status (modified Kuppuswamy classification). Out of 18 children, 5 (27.8%) were completely immunised, and 4 (22.2%) were unimmunised, and 9 (50%) were partially immunised.

Most common clinical presentation was fever and sore-throat present in all 18 (100%) patients, neck swelling in 13 (72.2%), dysphagia in 5 (27.7%). Examination revealed tonsillar hypertrophy and pseudomembrane in 17 (94.4%) patients, whereas one was a case of laryngeal diphtheria which was diagnosed when swab was sent while intubating in view of membranous laryngitis. Total of 13 (72.2%) cases had cervical lymphadenopathy and 4 (22.2%) had halitosis. Mean time of presentation to hospital after the onset of symptoms was 5.65 days. Only 8 (44.4%) patients presented within three days of onset of symptoms [Table/Fig-1].

Clinical features	Immunised (n=5) n (%)	Partially immunised/ unimmunised (n=13) n (%)	p-value (Fisher-exact test)
Fever (n=18)	5 (100)	13 (100)	1.0000
Sore throat (n=18)	5 (100)	13 (100)	1.0000
Dysphagia (n=5)	1 (20)	4 (30.7)	1.0000
Halitosis (n=4)	1 (20)	3 (23.07)	1.0000
Respiratory distress (n=9)	3 (60)	6 (46.2)	1.0000
Laryngeal involvement (n=2)	1 (20)	1 (7.6)	1.0000
Bull neck (n=13)	1 (20)	12 (92.3)	**0.0077**
Membrane (n=18)	5 (100)	13 (100)	1.0000
Requirement of inotropes (n=4)	2 (40)	2 (15.3)	1.0000
Need for Mechanical ventilation (n=9)	4 (80)	5 (38.4)	1.0000
Duration of hospital stay (days) (Mean±SD)	5.2±1.6	11.5±2.1	t=-6.0256, **0.0001**
Sequelae			
a) Myocarditis	2 (40)	2 (15.3)	1.0000
b) Palatal palsy	0	5 (38.4)	0.2480
Death (5)	1 (20)	4 (30.8)	1.0000

[Table/Fig-1]: Comparison of profile of diphtheria in immunised/partially immunised and unimmunised.
p-value in bold font indicates statistically significant value

Albert stain was positive in 13 (72%) cases, culture was positive for *C.diphtheriae* in remaining 5 (27.7%) cases. Seventeen (94.4%) children had pharyngeal/tonsillar involvement and 2 (6.6%) of them also had laryngeal involvement. All 18 were confirmed cases of *C.diphtheria.*

Total of seven cases were ventilated of which five succumbed and two were extubated. Out of all, 4 (22.2%) patients developed myocarditis in the second week and all succumbed to resistant arrhythmias. One patient also developed complete airway obstruction, was tracheostomised immediately in view of difficult intubation, however, direct cause of death was cardiac arrhythmia. One patient developed sepsis with ventilator dependency and succumbed to inotrope resistant septic shock. So, a total of 5 (27.7%) patients succumbed to the disease [Table/Fig-2]. On follow-up, 5 (27.7%) developed palatal palsy among which three had associated polyneuropathy; all these children recovered with only supportive care over a period of 16-24 weeks.

High mortality rate in the study was probably due to late presentation to hospital (mean time of presentation from the day of onset of symptoms=5.65 days) leading to delay in administration of ADS.

Complications	Total patients (n)	Mortality n (%)
Myocarditis	4	4 (100)
Palatal palsy	5	0
Airway obstruction	5	1 (20)
Renal failure	1	1 (100)

[Table/Fig-2]: Complications witnessed in the cohort.
*One case developed complete airway obstruction, requiring emergency tracheostomy in view of difficult airway intubation, however patient succumbed to cardiac arrhythmia a week later

Other factors contributing to mortality include patient's immunisation status, age at infection, clinical type, time of intervention and time of administration of antitoxin. [Table/Fig-3] compares the profile between survived and death patients.

Variables	Survivors (n=13)	Death (n=5)	p-value (Fisher-exact)/t-test
Mean age (years) (Mean±SD)	8.28±1.2	11.2±2.2	t=-3.7672, **0.0017**
Mean time of presentation (days) (Mean±SD)	4.5±1.4	6.8±2.3	t=-2.6155, **0.0187**
Laryngeal involvement (n)	0	2	1.0000
Bull neck (n)	9	4	-
Confirmed (Albert stain positive) (n)	8	5	0.2489
Culture positive (n)	5	0	**0.0001**
Mechanical ventilation (n)	2	5	1.0000

[Table/Fig-3]: Comparison of profile of diphtheria in children who survived and died.

DISCUSSION

Diphtheria, if not detected early and treated promptly with antibiotics and ADS, can lead to significant mortality and morbidity because of critical complications such as myocarditis, obstructive airway disease, polyneuritis, cranial nerve palsies, disseminated intravascular coagulation and secondary pneumonia [12]. Due to good vaccine coverage worldwide, a shift in age incidence has been observed from preschool to school age (5-15 years) with more and more cases being reported in adolescents and adults. The reported incidence for diphtheria in India has been 9622 and 8788 cases in the years 2019 and 2018, respectively as compared to 5293 and 3380 in the years 2017 and 2016, respectively [13]. Countries like Yemen, Venezuela which are facing humanitarian crisis, civil war have witnessed outbreak of vaccine preventable diseases in the recent years and is largely attributed to lack of medical care and very poor immunisation coverage due to the crisis [10,11].

The present study shows higher incidence of diphtheria in the age group of 09-11 years. Similar observations were made by other studies, about change in epidemiology of diphtheria that the disease which was common among under five children was now more prevalent in older children [14,15]. This change may be owing to the fact that immunity against all three components of DPT vaccine wanes over the next 6-12 years and thus emphasising the need for regular booster doses.

The signs and symptoms of diphtheria depend upon the site of infection, the immunisation status of the host, and whether or not toxin has been distributed to the systemic circulation. It was interesting to note that in the present study 27.8% were completely immunised and 22.2% were unimmunised and 50% were partially immunised. There is a report of occurrence of diphtheria with ocular manifestations in a fully immunised child [16]. In a clinico-epidemiological study by Meera M and Rajarao M on a large sample in Andhra Pradesh 41% of the children were completely immunised [12]. The possible explanation of occurrence of the disease in immunised patients could be individual variations in immune response to vaccines or failure of vaccine response [16]. However, vaccine ineffectiveness (due to non maintenance of cold chain) at the time of use and improper technique of administration can also contribute to the disease burden. Also, greater number of cases among the partially immunised population emphasises the need for booster doses to combat this disease. In the present study, it was found that symptoms like bullneck was more in partially immunised and unimmunised population and was statistically significant. Also, total duration of hospital stay was also prolonged in partially immunised population (p-value <0.05). There is shift of epidemiology of diphtheria to early and mid-adolescence which necessitates the need of diphtheria booster dose at the beginning of adolescence. This point needs to be brought to notice before national immunisation advisory committee.

Myocarditis was observed to be the most common complication. In a study by Havaldar PV, 13 patients had left or right bundle branch blocks, or second degree or complete atrioventricular block associated with 58% mortality [17]. Stockins BA et al., reported a mortality of 50% in patients with bundle branch block [18]. Celik T et al., also demonstrated that the patients with left bundle branch block and T wave inversion had lower survival rates than that of patients without these ECG changes [19]. In the present study, the mortality rate was 27.8%. It has been shown that use of antitoxin significantly reduced the mortality (3.3% in treated compared to 12.2% in untreated patients [20].

Neurologic complications appear after a variable latent period, are predominantly bilateral, are motor rather than sensory, and usually resolve completely. Paralysis of the soft palate is common and generally appears in the 3rd week. Patients who were immunised did not suffer from fatal complications like myocarditis and most of them recovered uneventfully.

When comparing the profile of survivors and death cases in this study, authors found that mean age of those who died was more and was statistically significant (p-value=0.0017). This was probably because the diphtheria severity was more in later ages when the effect of vaccination would have waned off. Also, late presentation to hospital was associated with higher chances of causing death. (p-value=0.018). This finding could be attributed to spread of toxin in systemic circulation and its adverse effects before antitoxin was administered.

Persistence of diphtheria is due to low coverage of booster immunisation. As immunity acquired by primary immunisation wanes over time, adequate coverage of booster doses is equally important. Administration of antitoxin serum definitely plays an important role, early administration was found to have a favourable outcome. Creating awareness among general population about the disease and preparedness among healthcare givers to fight the disease including accessibility to ADS should be prioritised [17].

Limitation(s)

The sample size was small due to the time-bound nature of the study. Genetic study of *C. diphtheria* and further categorisation into genotypes were not done.

CONCLUSION(S)

Diphtheria is down but not out, this series unmasks the fact that the disease is equally prevalent in immunised and older children with the changing epidemiology of diphtheria in the era of vaccines. It was found in this study that immunised population definitely had less fatal complications and recovered better when compared to the unimmunised group. The outcome of patients also depended on the day of illness at presentation, late arrival to the hospital had more complications as the toxin would have already caused the damage. To conclude, it is high time to introspect on our immunisation practices and emphasise the need for "booster doses in routine immunisation" practices before diphtheria hits mankind like never before.

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