DOI: 103126/JNPS.V4113

Original Article

Clinico-epidemiological Profile of Children with Diphtheria in Tertiary Care Hospital of Nepal

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Article History
Received On : Oct 24, 2021
Accepted On : Apr 05, 2022

External Funding: None

Conflict of interest: None

Keywords:
Anti diphtheria serum; myocarditis; tonsillopharyngeal diphtheria

Online Access

DOI:https://doi.org/10.3126/jnps.v42i1.40546

Abstract

Introduction: This study was conducted with the aim to describe the clinical presentation of diphtheria in children, relationship between clinical disease and immunization status, complications of the disease and adverse events due to anti diphtheria serum (ADS).

Methods: All patients admitted at Tribhuvan University Teaching Hospital, Kathmandu from July 2016 to November 2018 with clinical diagnosis of diphtheria were included in this study.

Results: There were total 12 children and age ranged from five to 15 years, out of which seven (58%) were males and five (42%) were females. All of them were immunized except one whose immunization status was unknown. All of them had tonsillopharyngeal diphtheria. Four patients (33%) also had nasal and five (42%) patients had additional laryngotracheal diphtheria. Seven patients had bull neck on presentation. Four patients had airway obstruction due to laryngotracheal diphtheria requiring tracheostomy. Throat swab for Corynebacterium Diphtheria by Albert stain and Gram stain were positive in 10 patients, and in nine, diagnosis was confirmed by culture. Six patients (50%) were given anti diphtheria serum (ADS) out of which four patients (66.66%) developed anaphylaxis. Myocarditis was the commonest complication seen in four patients (25%). All children with myocarditis developed complete heart block (CHB) and none of them survived.

Conclusions: Tonsillopharyngeal diphtheria was the most common clinical presentation and myocarditis was highly fatal complication. This study emphasizes on the need for careful surveillance, early laboratory confirmation and careful administration of ADS in patients with clinical diagnosis of diphtheria.

Introduction

Diphtheria is an acute, toxin-mediated disease caused by the bacterium Corynebacterium diphtheria.[1] This disease is usually localized to upper respiratory tract but can lead to serious toxin related complications mainly involving the heart muscle and nervous system. Death can occur due to circulatory failure within the first 10 days of infection. Diphtheria is fatal in 5% to 10%, with higher death rates (Up to 20%) among persons younger than five years.[2] The case-fatality rate for diphtheria has changed very little during the last 50 years.

The data on vaccine-preventable diseases provided by the Government of Nepal to the World Health Organization indicate persistent occurrence of 100 to 200 cases of diphtheria per year over the past 10 years. However, there was rapid increase in rate

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to 1079 in the year 2014.[3] The reporting of these cases is based on appearance of an adherent membrane of the nose, pharynx, tonsils, or larynx without laboratory confirmation or epidemiologic linkage. Since the diagnosis of diphtheria by this definition is clinical, many conditions apart from diphtheria are also falsely reported as diphtheria, the larger chunk being of streptococcal membranous tonsillitis. On the other hand, the diphtheria patients who come to hospital with complications like myocarditis or neurological involvement are likely to be missed as by the time of occurrence of these complications, membrane disappears. Also, due to infrequent reporting and lack of laboratory facility to identify carriers, the exact prevalence of diphtheria in our part of the world is largely unknown.

Diphtheria is one of the vaccine preventable diseases. Three doses of Diphtheria Pertusis Tetanus toxoid (DPT) at 6, 10 and 14 weeks are given in Nepal. The vaccine coverage of third DPT dose is 86%. [4] Due to low reported cases and high DPT vaccine coverage, diphtheria is thought to be declining in Nepal. There is paucity of literature describing clinical manifestation and management of diphtheria in Nepal. A prospective observational study was conducted to describe the clinical presentation of diphtheria in children, relationship between clinical disease and immunization status, complications of the disease and adverse events due to Anti Diphtheria Serum (ADS).

Methods

This study was done at Tribhuvan University Teaching Hospital, Institute of Medicine, Maharajgunj, Kathmandu, Nepal from August 2016 to November 2018. All children less than 16 years, presenting with fever and sore throat having difficulty in swallowing with a greyish white membrane and diagnosed as diphtheria were included in the study. The immunization status was documented as per the information given by the parents. Those who had received three doses of DPT vaccine at four to six week intervals starting at one month of age were recorded as "Immunized". Swabs were taken from the membrane and the area beneath soon after admission. Smears were immediately sent to microbiology laboratory and were stained by Gram stain and Albert–stain method. Smear was considered positive if Gram stained smears showed a large number of Gram positive bacilli with the appearance of Chinese letters, and Albert stain showed bacilli with numerous metachromatic granules. Similarly, Loeffler's serum slope and Tellurite blood agar culture was examined after 18 hours of incubation at 37 degree Celsius. Culture were considered positive if there was appearance of grayish white, raised, glistening colonies on Loeffler's serum slope or black hemolytic colonies (Slate coloured) with greyish margin on Tellurite blood agar. Nerve Conduction study (NCV), electrocardiography (ECG) were done as and when indicated. Similarly, tracheostomy was done for patients with airway obstruction.

The following data were recorded: age, sex, ethnicity, and region of residence, clinical symptoms and signs, laboratory findings including smear for throat swab for Corynebacterium diphtheria and culture, complications, treatment with antibiotics and / or ADS and outcome. Data analysis was carried out using IBM SPSS statistic 20.

Results

There were total of 12 patients admitted with diphtheria during this period. The age range was five to 15 years (Table 1). Out of 12 patients, seven (58.33%) were males and five (41.66%) were females. Half of them were from province number two and two of them were siblings. As per the history given by parents / caretakers, all of them were immunized except one whose immunization status was unknown. We noticed striking occurrence of cases from July to November months of the year. Duration of illness ranged from three to 10 days at the time of presentation. Seven patients had bull neck on presentation. We found that all had tonsillopharyngeal diphtheria, four (33.33%) patients also had nasal and five (41.66%) patients also had laryngotracheal diphtheria. Among five patients with laryngotracheal diphtheria, tracheostomy was done in four patients, out of whom three died due to myocarditis and one survived who was discharged home with tracheostomy tube in situ and was closed later. Throat swab for Corynebacterium diphtheria by Albert stain & Gram stain were positive in 10 patients and in nine patients, diagnosis was confirmed by culture in Tellurite blood agar. Among remaining two, one had membranous tonsillitis followed by myocarditis and heart block and the other had palatal palsy with peripheral neuropathy following membranous tonsillitis.

All patients were treated with injection crystalline penicillin. Six patients were given ADS. Rest of them did not receive ADS either due to unavailability or the duration of illness was more than seven days at the time of presentation. Though hypersensitivity test was done in all patients receiving ADS, four (66.66%) out of six patients developed anaphylaxis and one of them died due to anaphylaxis. Rest of the children with anaphylaxis were managed successfully with intravenous adrenaline and desensitizing dose of ADS.

Myocarditis was the commonest complication recorded after first week of illness seen in four patients (33.33%). All children with myocarditis developed complete heart block (CHB) and none of them survived. Temporary pacemaker was kept in one patient and was improving but due to displacement of pacemaker, child again developed CHB and died. One patient developed palatal palsy and peripheral neuropathy on second and fourth week of illness respectively.

Seven out of 12 patients were discharged and five (42%) patients died. The immediate cause of death was myocarditis with CHB in four cases and ADS anaphylaxis in the remaining one case. Erythromycin prophylaxis was given to household contacts and booster dose of DPT or dT was also given to patients and their household contacts.

Table 1. Clinicoepidemiological profile of children with diphtheria

	N (%)
Age: Mean age (± SD) Range Age distribution: 5 – 10 year 10 - 15 year	 10 years (± 3.22) 5 - 15 years 5 (41.66%) 7 (58.33%)
Sex distribution: Male Female	 7 (58.33%) 5 (41.66%)
Residence: Province 1 Province 2 Province 3 Province 4 Province 5 Province 6 Province 7	 0 6 (50%) 1 1 1 2 1
Type of diphtheria: Nasal Tonsillopharyngeal Laryngotracheal	 4 (33.33%) 12 (100%) 5 (41.66%)
Complications: Myocarditis Airway obstruction requiring tracheostomy* Palatal palsy and peripheral neuropathy	 4 (33.33%) 4 (33.33%) 1 (8.3%)
Microbiological confirmation Albert stain & Gram stain positive Culture positive	10 (83.33%) 10 (83.33%) 9 (90%)
ADS treatment Anaphylaxis to ADS	6 (50%) 4 (66.66%)
Total deaths Immediate cause of death: Myocarditis Anaphylaxis to ADS	5 (41.6%) 4 (33.33%) 1 (8.3%)
Immunization status: Complete Not known	 11 (91.66%) 1 (8.3%)

* Three patients had myocarditis as well.

Discussion

This study describes clinical profile of 12 children with diphtheria, treated at TUTH, Maharajgunj, Kathmandu, Nepal from July 2016 to November 2018. In the present study diphtheria was diagnosed mainly on clinical findings and microbiological confirmation was available in 10 (83.33%) cases. We observed that tonsillopharyngeal type and bull neck were commonest presentations. Myocarditis was the most common fatal complication. Anaphylaxis was observed in two third patients during ADS administration.

Our study shows that diphtheria is still prevalent in Nepal. Half of the patients in this study were from province number two. Whether this is mere coincidence due to close proximity to our center or there is actual high prevalence of diphtheria in this particular province need to be further investigated. This finding indicates need for strict disease surveillance in this particular area with the possible epidemiological linkage.

In this study, all the cases presented to hospital between July to November months of the year. In the study done at tertiary care hospital at Ahmedabad, India, among 38 cases of diphtheria over one year period, greater number of increase in cases was seen during month of August to December.[5] Similarly in the retrospective study done from 1985 to 2002 at Medical College, Rajkot, Gujarat, India, on 126 possible cases of diphtheria, maximum number of cases was seen in the month of August to October.[6] The increased incidence of disease in particular season needs to be confirmed from further such outbreaks.

In our study, myocarditis occurred in four (25%) cases. All of them developed CHB and died. Our finding is similar to the findings reported in an Indian series on diphtheria where myocarditis was reported in 10 (66%) cases with mortality rate of 60 to 70% and was the most common cause of death in diphtheria.[11,12] Myocarditis is also the only independent predictor of death with an adjusted odds ratio (OR) 25, {95% confidence interval (CI) 3.4-210.3}.[12] Severe conduction abnormalities including CHB develops in approximately 50% of patients with diphtheria myocarditis and is considered to be uniformly fatal.[13-15] We noticed death rates of 42% which is higher than mentioned in the literature.[3] Case fatality rate of upto 20% was noticed in studies done in India.[17] Most of the patients were referred late when complications are expected so it might not reflect the true fatality rate in our community.

Diphtheria immunization decreases local tissue spread, prevents toxic complications and diminishes transmission of the organism. In the present study, 11 out of 12 patients were immunized against diphtheria as per immunization schedule of Nepal which includes only three doses of primary series. This finding of our study is in contrary to the finding of the study done in India where diphtheria had been reported in less than 5% of fully immunized children and none were fatal.[5,6] In India, five doses of DPT are included in immunization schedule and those who are fully immunized had received at least five doses which might have conferred higher immunity. The recent WHO vaccine position paper recommends six doses of diphtheria containing vaccine which includes three primary plus three booster doses prior to adolescence.[7] Three primary doses of DTwP- or DTaP-containing vaccines should be administered as early as six weeks of age, and given with a minimum interval of four weeks. The first booster dose with DTwP- or DTaP is recommended at 12 to 23 months and a second booster dose with Td/ DT at four to seven years. A third booster dose with Td or or Tdap is recommended at 11 to 12 years of age. Immunization by itself is reported to confer up to 95% protection.[8] Despite this recommendation, only three doses of primary series are given in Nepal. After three doses of primary diphtheria toxoid immunization, most children achieve antitoxin titers greater than the minimally protective level.[9] However, in the absence of ongoing exposure, immunity wanes over time, requiring booster doses of diphtheria toxoid to maintain protective antitoxin levels. In the absence of a booster dose at four to six years, protection may not be maintained throughout the school-age years. Disease despite primary immunization has been reported earlier in few

studies from the past.[6,10] Since none of our patients had received booster doses, plausible explanation for diphtheria on them is due to waning immunity. The findings of the study justify the need of emphasizing importance of booster diphtheria immunization at appropriate ages for effective control of diphtheria. We noticed anaphylaxis during ADS administration in two third cases which is much higher than reported anaphylaxis of 0.6%.[16] This higher rate of anaphylaxis demands meticulous monitoring of patient during ADS administration.

Since the study done is done in small population of children, the findings lack generalizability. Still, this is the first study on diphtheria with microbiological confirmation from Nepal. We recommend keeping high index of suspicion of diphtheria not only in children presenting with membranous tonsillitis but also those with myocarditis or palatal palsy and send appropriate investigation for microbiological confirmation. Also we believe that introducing DPT booster doses in immunization schedule of Nepal helps to reduce burden of this disease.

Conclusions

Diphtheria is prevalent among immunized children in Nepal. Tonsillopharyngeal diphtheria is the most common clinical presentation. Laboratory documentation of clinical diphtheria should be done whenever possible. Myocarditis is highly fatal complication which can be prevented by early administration of ADS. This study also recommends introducing booster doses of diphtheria immunization at appropriate ages for effective control of diphtheria.

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