Original Article

Clinical Profile, Immunization Status and Antitoxin Administration of Diphtheria Cases During an Outbreak in Rural North India

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Abstract

Introduction: Diphtheria is an acute potentially fatal infectious disease caused by the toxigenic strains of Corynebacterium diphtheriae. Acute respiratory obstruction, toxic myocarditis and neurologic weakness are the most important complications of diphtheria. The clinical presentation and severity of diphtheria vary in immunised and non immunised children. Early diagnosis and prompt treatment including administration of diphtheria antitoxin and antibiotics minimise mortality.

Aim: To study the clinical profile of diphtheria during the 2019 outbreak and its association with immunisation status and antitoxin administration.

Methods: Records of 215 children admitted with the diagnosis of clinical diphtheria in a tertiary care teaching hospital in Nuh, Haryana, from January, 2019 to December, 2019 were analysed with respect to clinical features, immunization status, complications and mortality. Patients were divided into survivors and non-survivors' variables were compared between the two groups

Results: Data of 215 children was obtained. Young children (median age 5 year) were predominantly affected, and only 5(2.3%) children were fully immunized. Pseudomembrane was present in 113 (52.5%) cases. Albert staining and culture were positive in 57.2% (123) and 8.8% (19) cases, respectively. Complications developed in 38.1% (n=82) cases and included: airway compromise 15.3% (n=33), palatal palsy 4.7% (n=10), symmetric polyneuropathy 0.9% (n=2), diphtheritic cardiomyopathy 8.8% (n=19), acute kidney injury 2.3% (n=5), thrombocytopenia 6.6% (n=12) and hepatitis 0.4% (n=1) cases. Anti-diphtheritic serum (ADS) was administered to all admitted patients. Tracheostomy was done in (n=33) (15.3%) children. Case fatality rate was 12.1%.

Conclusion: Diphtheria mostly affected young unvaccinated or partially vaccinated children. Complications and mortality was high in unimmunized or partially immunized young children and those with bull neck, pseudomembrance, delayed (5 days) administration of ADS, acute kidney injury, thrombocytopenia and leukocytosis. Regular monitoring helped to detect asymptomatic myocarditis. The outbreak highlighted the need to improve awareness about diphtheria and better vaccination coverage. Administration of diphtheria antitoxin within 72 hours of presentation decreases the development of neurological complications. Regular anticipatory screening for cardiac involvement has a specific role in management.

Keywords: Leucocytosis, mortality, myocarditis, outcome.

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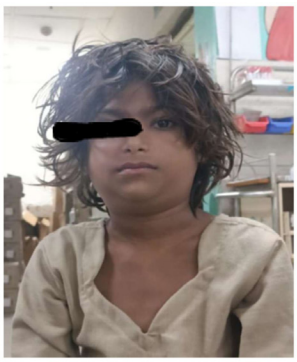
Diphtheria is an acute potentially fatal infectious disease caused by the toxigenic strains of Corynebacterium diphtheriae [1]. In the pre-vaccine era, more than 40% of cases occurred in children below five years. Recently an upward shift in age is observed both in developed and developing countries [2,3]. Acute respiratory obstruction, toxic myocarditis and neurologic weakness are the most important complications of this disease. Cardiac involvement may be asymptomatic {characterised only by changes in Electrocardiogram (ECG) and/or raised cardiac enzymes) or symptomatic (with clinical features of heart failure)} [4]. The main modality of treatment is administration of diphtheria antitoxin and antibiotics. The rapidity of seeking medical care and administering specific treatment is known to decrease the mortality [1]. Immunisation status of the individual affects the clinical presentation and severity of the disease [5]

Diphtheria has been virtually eliminated from developed countries but is still endemic in developing countries [6, 7]. World Health Organization (WHO) surveillance reports indicate that most cases of diphtheria worldwide occur in Southeast Asia and Africa regions [8]. Several outbreaks of diphtheria have been reported in various Indian states in recent times, including one in Mewat (Nuh) district of Haryana, in 2018-2020. Mewat is one of the socio-economically backward districts, with majority (90%) living in rural areas [9]. Coverage Evaluation survey (CES) conducted by Government of India in 2018 reported full vaccination coverage of 40.8% in Mewat [10]. The objective of this study was to report on the epidemiological profile, immunization status, clinical spectrum, outcome and the predictors of poor outcome in children with diphtheria during this outbreak.



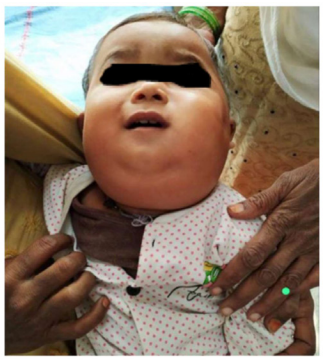


Figure 1 and 2: Images showing Bull's neck in diphtheria

Methods

This was a review of hospital records conducted in the department of pediatrics of a government medical college in Haryana after approval by the institutional ethics committee. The study population included children aged up to 15 years admitted over a period of three years (January, 2019 to December, 2019) with the clinical diagnosis of diphtheria. Diphtheria was defined as per World Health Organization (WHO) definition "an illness of upper respiratory tract characterized" by pharyngitis, naso-pharyngitis, tonsillitis or laryngitis and a firmly adherent greyish white, thick patchy to confluent membrane, which bleeds on dislodgement.

Inclusion criteria: Inclusion criteria: All children below 12 years of age who met the operational definition of diphtheria and were admitted to Paediatric Infectious Disease Unit from January 2019 to December 2019 were included in the study. A total of 80 children met the clinical case definition.

Exclusion criteria: included patients with age >15 years, known case of structural heart disease, those with an alternative diagnosis (other causes of membranous tonsillitis), absconded, discharge against medical advice (DAMA), referred and patients with incomplete data.

Procedure

Data regarding demography, clinical profile, immunization status, history of contact with a known case of diphtheria, site and extent of pseudomembrane, complications, laboratory and microbiological investigations, treatment details and outcome were collected from case records of all patients and recorded in predesigned case proforma. Patients were classified as survivors and nonsurvivors, depending on course during hospital stay.

The assessment of immunization status was done on the basis of immunization history mentioned in case files, which was assumed to be taken by recall method. Children who had received three primary doses of diphtheria-pertussis-tetanus (DPT) vaccine starting at 6 weeks of age followed by booster doses at 16-24 months and 5-6 years were considered 'immunized'. Those who had not received any dose

were considered 'Unimmunized'. Patients who had missed one or more of the primary doses or booster doses were considered 'Partially immunized'. Those in whom the immunization status was not known by the parents(s) or attendant were labelled as 'Unknow immunization status. Platelet count less than 150x109/L was considered as thrombocytopenia, and leukocytosis was defined as total leucocyte count more than 14 x109/L.

Throat swab culture: As per the protocol of the department, a case of membranous tonsillitis was evaluated by collecting throat and nasopharyngeal swabs, which were transported in Amies medium to the microbiology department of the hospital for Gram staining and Albert staining. Swabs of all Albert stain positive cases were sent to Maharishi Valmiki Infectious Disease Hospital (MVIDH), New Delhi for isolation, biochemical identification of the isolates, and testing for the toxigenicity.

Laboratory test: The laboratory tests include complete blood counts, Erythrocyte Sedimentation Rate (ESR), hepatic transaminases, renal function tests and urinalysis were done in all children at the time of admission and during clinical deterioration. ECG was taken soon after admission and was repeated on every alternate day during the inpatient stay, at the time of discharge and during follow-up visits.

Management: Albert stain positive cases were isolated and treated in a dedicated 10-bedded diphtheria (isolation) ward with Anti-diphtheritic serum (ADS), oral erythromycin or intravenous aqueous penicillin, and other supportive care as per standard guidelines. Patients with complications were treated in the pediatric intensive care unit (PICU) isolation rooms. Other causes of membranous tonsillitis were managed according to the underlying etiology.

Statistical Analysis

Statistical analysis was done using STATA v16. Normality of data was checked using Skewness and Kurtosis measurement. Since the continuous data was skewed, we report median (IQR) for quantitative variables. The outcomes were classified as survivors and non-survivors. Patients who absconded or were discharged against medical advice (DAMA) were excluded from multivariable analysis. The Wilcoxon ranksum test (Mann-Whitney U test) was used for comparison of the categorical or quantitative variables between the survivor and non-survivor groups. Comparison of the categorical variables between the two groups was done by the adjusted odds ratio (aOR) of complications in non-survivors against survivors, adjusted for potential confounding variables viz., age, duration of illness before admission; and history of contact with a known case of diphtheria. For all tests of significance, a Pvalue <0.05 was taken as significant.

Results

Records of 215 children were analyzed. Most cases were admitted between August to November. On comparing the variables between survivors and non-survivors, it was found that median age was significantly lower (P=0.001) and duration of illness before admission was significantly higher (P=0.026) in the non-survivor group. The Odds ratio (OR) for having airway compromise, myocarditis, cardiogenic shock, heart block, acute kidney injury (AKI), thrombocytopenia and leuko-cytosis were significantly higher for non-survivor group. Myocarditis was strongly associated with death [OR (95%CI) 140.54 (18.31-1078.37); P=<0.001]. The results were are follows

Demographic and Clinical Profile of Children With Diphtheria

Age group (y) 5yrs (3-8)

Male gender 163 (75.8%)

Immunization status

Unimmunized 210(97.7)

Immunized 5 (2.3)

Pseudomembrane 113(52.5)

Type of involvement

Pharyngeal 102 (47.5)

Laryngeal 10 (4.6)

Culture positivity

Albert stain positive 123(57.2)

Culture positive 19 (8.8)

Table 1: Clinical Features

Fever	96 (44.6%)
Dysphagia	94 (43.8%)
Breathing difficulty	41 (19%)
Bull neck	17 (7.9%)

Table 2 Complications

Palatal palsy	10 (4.7%)
Symmetric polyneuropathy	2 (0.9%)
Airway compromise / Tracheostomy	33 (15.3%)
Diphtheritic cardiomyopathy	19 (8.8%)
Acute kidney injury	5 (2.3%)
Thrombocytopenia	12 (6.6%)
Hepatitis	1 (0.4%)
Death	26 (11.9%)

Discussion

In our study, majority of the cases were aged less than 5 years; whereas, in previous Indian studies majority of the cases were older than five years, with 48.3% and 69% of children fully immunized for age [11, 12]. This is because in the absence of routine immunization, diphtheria mainly affects children less than 5 years of age, as was observed in the pre-vaccination era [13]. With increasing coverage of under-five children with primary vaccination schedule, an upward shift in the age for diphtheria has been observed from preschool to school age (5-15 year) [11]. Similar seasonal patternhas been previously reported [14, 15]. Increased mortality in those who presented late, with most ofthe deaths occurring within two days of admission were also noticed by other authors [10], similar to our study. Studies have shown a significant association between immunization status and disease severity. Low culture positivity rate observed in our study may be due to pre-treatment with antibiotics, improper swab collection technique, difficulty in collecting swabs from young/uncooperative children and delayed transportation of samples to the accredited laboratory.

Airway compromise seen in this study was higher than the reported incidence of airway compromise of 4-15% [16]. The incidence of diphtheritic cardiomyopathy in our study was much lower than the rate of 19-68% reported in previous studies [13, 17-19]. The mean interval between the onset of symptoms and cardiac abnormalities was similar to the reported range of 6.5-8.5 days, although the interval has been reported to be as long as 25 days [13, 17, 18]. Contrary to its classical description of occurrence between the second and third week of illness, the onset of diphtheritic cardiomyopathy was earlier in our study (first week of illness). This may be because of poor immunization status of our study population. Jayshree, et al. [13] observed that myocarditis more commonly developed in children who had severe respiratory symptoms, presence of bull neck, inadequate immunization, presence of pseudo-membrane and delayed administration of ADS [13]. The combination of pseudomembrane and bull neck strongly predicted the development of cardiomyopathy [20]. In a previous study from northern India, incidence of AKI was high (35.4%), and death occurred in 88.2% of AKI patients [13]. Only one child who received antitoxin within 72 hours of disease onset developed neurological complications and this was statistically significant (p-value <0.05). Higher incidence and mortality of AKI in this study may be because this study was conducted on diphtheria patients admitted in paediatric intensive care unit only [13]. Incidence of thrombocytopenia in the same study was 31.2% and mortality was observed in 66.7% cases [13].The case fatality rate (CFR) observed in our study was 12.1%. The mortality rate is generally between 5%-10% [21]. It may be as high as 20% in children below five years and adults over 40 years of age [21]. High mortality rate observed in our study might be due to young unimmunized Cases presenting late (> 5 days) with consequent delayed administration of ADS and development of complications. Another reason for high mortality rate in our study was lack of facilities like continuous ECG monitoring, pace-maker insertion and peritoneal dialysis.

Limitations

Details on nutritional status, socio-economic status, culture positivity and toxigenicity were not present, therefore, the impact of these variables on disease burden, severity and outcome could not be studied. Immunization status of patients may be inaccurate (presumed to be taken by recall method), which may affect the study results. Reason(s) for poor vaccination coverage could not be explored due

to lack of such data. Cases of underlying structural heart disease (when suspected)could not be ruled out due to lack of facility of echocardiography.

Conclusion

In conclusion, poor routine immunization coverage was an important factor for diphtheria outbreak in the study. Mortality was high in unvaccinated young children who develop complications, often multiple. Myocarditis, AKI, thrombocytopenia and leukocytosis were associated with poor prognosis. Mortality was high with delayed (> 5 days) administration of ADS even if the dose was adequate. AKI patients frequently developed concomitant thrombocytopenia with or without clinical bleeding. Characteristics which can help to anticipate the development of myocarditis include younger age (<5 year), unimmunized/partially/ unknown immunization status, bull neck, presence of pseudo membrane, administration of ADS three or more days after onset of illness andleukocytosis

Ethics clearance: Institutional Ethical Committee, SHKM GMC; No. SHKM/IEC/2020/149, dated Dec 07, 2020.

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