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Diphtheria in Andhra Pradesh–a clinical-epidemiological study

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SUMMARY

Objectives: Clinical diphtheria is on the increase worldwide, mainly affecting developing countries. We sought to understand its presentation among patients at Sir Ronald Ross Institute of Tropical and Communicable Diseases in Hyderabad, Andhra Pradesh, India.
Methods: Diphtheria patients presented with fever, pharyngitis, and a patch in the throat. Data collected for each patient included age, clinical presentation, morbidity, mortality, bacteria isolated from culture, and immunization status.
Results: Of 61 950 admissions from January 2008 to December 2012, 2925 (4.7%) had clinical diphtheria; 1194 had been immunized and 1731 were non-immunized. Immunized patients had a milder disease. Culture-positive immunized patients were positive for *Corynebacterium* other than *diphtheriae* (COD; $n = 104$) or *Corynebacterium diphtheriae* (CD; $n = 23$); these patients suffered mild disease and recovered completely. In contrast, culture-positive non-immunized patients were positive for COD ($n = 11$) or CD ($n = 412$). Eighty-one patients (3%) died, 77 of whom were non-immunized; death was usually as a result of myocarditis. Seventy-three percent of deaths were in patients aged <5 years.
Conclusions: The clinical presentation of diphtheria and its severity and morbidity differ considerably in immunized and non-immunized patients. Disease caused by CD can be deadly, while disease due to COD is mild and responds to treatment.

1. Introduction

Diphtheria is an acute infectious disease of the upper respiratory system caused by toxigenic strains of *Corynebacterium diphtheriae*/*Corynebacterium* other than *diphtheriae*. The organisms are locally invasive and secrete soluble exotoxins, which can lead to serious consequences mainly involving the heart muscle and nervous system. Death can occur due to circulatory failure within the first 10 days of infection.[1] If diagnosed early, the infection responds to appropriate antibiotics and prompt antitoxin therapy.

The incidence of diphtheria is high in India, especially in the state of Andhra Pradesh. Factors contributing to morbidity and mortality include patient's immunization status, age at infection, time of infection, clinical type, and time of intervention. Clinical correlation with laboratory findings (microscopy and culture) helps in the confirmation of the diagnosis, and onward transmission of data helps the health authorities to spread awareness, boost immunization programs, and prevent community spread. Early diagnosis and timely intervention help to reduce the incidence, containing the infection in the community and decreasing morbidity and mortality in the affected individuals.[2,3]

The aim of this study was to assess the incidence of clinical diphtheria and its mode of presentation, trends of the disease, such as the frequency in children and adults, seasonal variation, gender predisposition, relationship between clinical disease and immunization status, the role and limitations of laboratory investigations, and most importantly, the variation in clinical presentation of disease due to *Corynebacterium diphtheriae* (CD) and *Corynebacterium* other than *diphtheriae* (COD).

2. Materials and methods

This study was done at Sir Ronald Ross Institute of Tropical and Communicable Diseases (SRRITCD), Hyderabad, India from January 2008 to December 2012. A total 61 950 patients were admitted during this period. Of these, 2925 cases of clinical diphtheria were admitted to the isolation ward of the hospital.

Study inclusion criteria were those of US Centers for Disease Control and Prevention;[4,5] patients of all ages presenting with fever and a sore throat with a grayish white membrane were included. The following patients were excluded: those who died

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before any therapeutic measure could be undertaken; those who left the hospital against medical advice.

The immunization status was documented as per the information given by the parents those attending with the patient/individuals. Those who had received three primary doses at 4–6-week intervals starting at 1 month of age, followed by booster doses at 18 months and 5 years were recorded as immunized. Those who had not received any dose were considered unimmunized. Patients who did not receive all three primary doses or booster doses were included as partially immunized. For statistical purposes unimmunized and partially immunized patients were considered together as non-immunized.

The following data were recorded: age, sex, clinical symptoms and signs, laboratory findings including smear for Klebs–Löffler bacillus (KLB) and culture, complete blood picture (CBP), erythrocyte sedimentation rate (ESR), and albuminuria, and the outcome. Patients were categorized into five age groups: <5, 5–20, 20–30, 30–40, and >40 years. Clinical features other than those of the inclusion criteria were noted for each patient.

Throat swabs for direct microscopy for KLB and culture for corynebacteria were collected soon after admission and repeated on day 5 for each patient. Staining of the smears was done by Albert–Laybourn method and culture on Löffler's serum (early growth, 4–6 h), blood agar (enriched medium), potassium tellurite medium (selective for corynebacteria), and Tinsdale/diphtheria virulence agar (supports the growth of toxigenic strains). Growth after 24–72 h incubation was processed biochemically (glucose, maltose, sucrose, trehalose, starch, glycogen, urease, cysteinase, and gelatin liquefaction). Practically, growth on Tinsdale/diphtheria virulence agar was taken as evidence of toxigenicity of the strain. CD and COD (*Corynebacterium ulcerans*, *Corynebacterium jeikeium*, and *Corynebacterium arcanobacterium*) were identified based on differences in biochemical reactions, as per standard methods.[6] Other investigations included CBP, ESR, and examination of urine for albumin. An electrocardiogram (ECG) was taken for each patient soon after admission, on every alternate day during the inpatient stay, and at the time of discharge.

The statistical analysis was done using SPSS software v. 17.0 (SPSS Inc., Chicago, IL, USA).

3. Results

All patients (N = 2925) presented with fever, sore throat, and a pseudomembrane. Mild to moderate laryngitis was observed in 67%, rhinorrhea in 63%, and lymphadenopathy and edema in the neck region were seen in 33% of cases. Features of acute respiratory obstruction in the form of stridor were seen in 9% of cases at the time of admission. Vomiting and abdominal pain were seen in 29% of patients. Signs and symptoms suggestive of myocarditis developed in 16% of cases (vomiting and abdominal pain along with low blood pressure and tachycardia) 1–2 days after admission (Table 1).

One thousand one hundred and ninety-four (41%) patients gave a history of complete immunization (Table 1), 236 (8%) cases were partially immunized, and 1257 (43%) were unimmunized; the immunization status was not known for 238 cases (8%). For statistical analysis, the partially immunized, unimmunized, and those with an unknown immunization status were considered as non-immunized individuals – 1731 cases (59%) (Table 1).

Females were found to be more affected (60%) in comparison to males (40%) (Figure 1). A binomial test was done to show the statistical significance of gender susceptibility ($p > 0.05$).

The distribution of cases by age showed 1540 out of 2925 cases (52.6%) were adults (≥20 years), while 1385 (47.3%) were children and adolescents. The disease occurred at an earlier age in the immunized, peaking between 5 and 20 years of age, while in the non-immunized the disease peaked in those aged 20–30 years (Table 2).

Table 1
Characteristics of the two diseases: *Corynebacterium diphtheriae* (CD) and *Corynebacterium* other than *diphtheriae* (COD)[a]

Clinical features	CD (n = 435)	COD (n = 115)	Immunized (n = 1194)	Non-immunized (n = 1731)
Fever	435	115	1194	1731
Throat pain/dysphagia	435	115	1194	1731
Membrane	435	115	1194	1731
Rhinorrhea	184	41	603	1240
Vomiting and abdominal pain	45	14	417	431
Laryngitis	435	46	960	1028
Lymphadenitis/neck edema	187	93	424	553
Stridor	91	-	-	270
Evidence of myocarditis	83	-	-	540
Soft tissue swelling	187	-	91	553
Pneumonitis	47	-	40	101
% Immunized	5	95	-	-
No. of deaths	-	-	4	77
Raised ESR	435	115	601	1231
Albuminuria	435	74	507	1047
KLB	92	-	-	-

ESR, erythrocyte sedimentation rate; KLB, Klebs–Löffler bacillus.
[a] Interpretation: (1) There was a significant occurrence of lymphadenitis, stridor, myocarditis, soft tissue swelling, and pneumonitis in CD positive and non-immunized patients compared to COD positive and immunized patients; (2) 95% of immunized patients were COD positive compared to 5% CD; (3) the number of deaths was significantly greater in the non-immunized (n = 77) than in the immunized.

The disease showed seasonal variation (Figure 2), with a peak incidence in the month of September (71 cases on average). The peak of disease among the vaccinated cases occurred in the month of October (33 cases on average) and the peak among the unvaccinated occurred in September (45 cases on average).

Culture was done for 2905 patients. CD/COD were isolated from throat swab cultures of 550 (18.8%) patients. Among the immunized patients, CD was isolated from 23 (5%) and COD from 104 (95%), while among non-immunized patients, CD was isolated from 412 and COD from 11 ($p < 0.0001$), as shown in Table 3.

The clinical illness was found to be milder in COD-positive cases (n = 115) when compared to CD-positive cases (n = 435). All features of complicated diphtheria were seen in CD-positive and non-immunized cases (Table 1). Apart from the inclusion criteria, laryngitis was seen among COD-positive cases, while laryngitis, lymphadenitis, stridor, myocarditis, soft tissue swelling, and pneumonitis were seen among CD-positive cases (Table 1).

Ninety-five percent of COD-positive cases were immunized, while the rate of immunization was 5% among CD-positive cases (Table 1).

KLB were seen in smears of 92 CD-positive cases. A raised ESR and abnormal CBP showing leukocytosis with relative neutrophilia were reported in all CD- and COD-positive (100%) cases. Severe albuminuria was observed in all CD-positive (100%) and 74 COD-positive cases. While KLB detected 21% of CD-positive cases, ESR, CBP, and albuminuria did not distinguish between CD- and COD-positive cases.

Two thousand three hundred and four (81%) cases were completely cured and discharged. The average duration of inpatient stay was 7–10 days.

Five hundred and forty patients (16%) who had mild myocarditis were followed up until complete recovery. Of these, 13% suffered from dyspnea and 3% complained of chest pain, while 80% showed ECG abnormalities in the form of conduction blocks and arrhythmias.