

CASE SERIES

Clinical and Laboratory Profile of Diphtheria Patients and Role of Diphtheria Antitoxin in Recent Outbreak of Diphtheria in Bageshwar District of Uttarakhand: A Case Series

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ABSTRACT

Background: Diphtheria is a vaccine-preventable disease despite universal immunization programs, outbreaks are reported from many Indian states with low immunization coverage since the last decade. Timely intervention and administration of diphtheria antitoxin (DAT) is the mainstay of treatment.

Aim material, and methods: In Uttarakhand state, an outbreak of diphtheria in the Bageshwar district was reported in August 2020 which resulted in high mortality due to limited resources, complications, and non-availability of DAT. Here, we describe the clinical-laboratory profile, the outcome of four patients admitted in our hospital who received DAT since October 2020, and also the intervention done by district and state authorities for prevention and early detection of diphtheria outbreaks along with to review the efficacy of the immunization program in the district.

Conclusion and significance: Diphtheria is still prevalent in our state; strict epidemiological surveillance for case detection and strengthening of immunization is needful. Timely management with empirical antibiotics with DAT results in a favorable prognosis.

Keywords: Diphtheria, Immunization, Vaccination.

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INTRODUCTION

Diphtheria is an acute, infectious disease caused by *Corynebacterium diphtheriae*, which is characterized by local inflammation of the upper respiratory tract, grayish-white membrane formation, and toxemia. The disease transmission occurs by contact or droplet infection from a case or carrier. The severity of the disease depends on the toxigenicity of the affecting strain and host immune response. The mortality rate, which is generally 5–10%, may be as high as 20% in children <5 years and adults over 40 years of age.¹

Being a vaccine-preventable disease, despite the universal immunization program offering three doses of diphtheria, pertussis, and tetanus vaccine (DPT) from 6 weeks of age, booster at 18 months and 4–6 followed by recent introduction of reduced diphtheria toxoid (Td) or acellular pertussis vaccine (Tdap) for >10 years of age every 10 years thereafter, there have been reports of re-emergence of diphtheria cases from many Indian states.^{2–9} In the state of Uttarakhand, one sporadic confirmed case was reported in 2018⁹ but after that, a recent outbreak was reported in the Bageshwar district of Uttarakhand in August 2020 till February 2021 with around 30 suspected and 14 laboratory-confirmed throat swab positive patients. Due to limited resources, complications, and non-availability of diphtheria antitoxin (DAT) majority of patients were referred to a higher center. After the availability of DAT in October 2020, we are reporting the clinical-laboratory profile and outcome of four patients admitted in our hospital who received DAT and intervention done by district and state authorities afterward.

CASE DESCRIPTIONS

Case 1

A 16-year-old male child, resident of Checheyi village, block Kanyalikot, Bageshwar district, was brought to the emergency

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room of District hospital, Bageshwar on October 26, 2020, with chief complaints of fever, sore throat, and odynophagia for 3–4 days. As per the mother's history, the patient was partially vaccinated (missed one or more of the three primary doses or booster doses of DPT). On examination, the patient was febrile with no signs of respiratory distress. A grayish-white membrane was present on the medial aspect of both tonsils extending up to the soft palate and uvula. Tonsils were hypertrophied (Grade III), a congested and posterior pillar was not visible. Prompt isolation was done. Diphtheria antitoxin at a dose of 100,000 IU was given as per recommendation (extensive disease of 3 or more days) under supervision after sensitivity. The patient was started on inj ceftriaxone and azithromycin with supportive management (penicillin was not available). A routine blood investigation was done. Throat swab culture for *C. diphtheriae* was positive. Electrocardiography suggestive of sinus tachycardia with ST elevation in lead V1 and V2, SGPT was raised (<2-fold rise), CPKMB

and Troponin-I were negative. The patient responded well with resolution of the white membrane by the 5th day of admission. The patient was advised for repeat electrocardiography after 2 weeks. All close contacts were given erythromycin prophylaxis.

Case 2

A 15-year-old female (2nd-degree sibling of case 1) was admitted a day after, i.e., October 27, 2020, hailing from the same village with a similar complaint of fever and sore throat for 2 days. The patient was partially immunized. On examination the patient was afebrile, bilateral tonsils were enlarged (Grade III), congested with grayish-white membrane patch over right tonsil and uvula. The patient was isolated and administered DAT at a dose of 30,000 IU (pharyngeal diphtheria of <48 hours duration) after sensitivity testing under strict monitoring. The patient was started on inj amoxiclav and azithromycin with supportive management. A routine blood investigation was done. Electrocardiography suggestive of ST elevation in lead V1 and V2, SGPT was normal, Troponin-I and CPKMB were negative. Throat swab culture for *C. diphtheriae* came negative. The patient too responded well with the resolution of the membrane by the 4th day. All close contacts were given erythromycin prophylaxis.

Case 3

A 4-year-old female resident of Dharamgarh, Bageshwar district was brought to the emergency room of District Hospital Bageshwar on November 6, 2020, with a complaint of fever, throat pain, dysphagia for 3–4 days, and dyspnea for 1 day. The patient was partially immunized. On examination, the patient was conscious, irritable, and febrile with a toxic look. Hoarseness of voice and bull neck was present. Throat was congested with bilateral tonsils enlarged (Grade III) with white membrane extending to uvula and nasopharynx? The patient was isolated, humidified oxygen with administered. Diphtheria antitoxin was started at dose 100,000 IU was given as per recommendation (extensive disease of 3 or more days) under supervision after sensitivity testing. Inj amoxiclav and azithromycin were given along with supportive measures. The high-risk condition and possible need for tracheostomy and pediatric ICU care were explained to parents. After 4 hours since admission patient developed nasal bleeding which was managed with local packing. The patient was referred to a higher center for better management and pediatric ICU care. Through telephonic follow-up, we came to know the patient succumbed to death after 3 days due to complications.

Case 4

A 9-year-old female, resident of Naugaon, district Bageshwar was admitted on February 15, 2021, with a complaint of fever, throat pain, hoarseness of voice, vomiting, and pain abdomen for 4 days. The patient was unimmunized. On examination, the child was conscious, febrile, and irritable. Bilateral tonsils were enlarged, congested (Grade III) white membrane was presented over both tonsils extending to uvula and soft palate. The patient was isolated, humidified oxygen started. Diphtheria antitoxin at a dose of 100,000 IU was given as per recommendation (extensive disease of 3 or more days) under supervision after sensitivity. Inj amoxiclav and azithromycin were given along with supportive measures. Routine blood investigation has been done suggestive of leukocytosis (21,390/mm³) with lymphopenia (11.9%) and monocytosis (10.3%) with thrombocytopenia (48,000/mm³) ESR was raised, although the patient does not have any signs of bleeding

manifestations. ECG was normal. Repeat CBC after 1 day suggested platelets 51,000/mm³ and TLC improved to 10,640/mm³. To rule out causes of thrombocytopenia, investigations were advised (due to limited resources at our center), however, considering underlying pathology toxin-induced thrombocytopenia was considered. Throat swab culture for *C. diphtheriae* was positive. The patient was advised for a hematology opinion at a higher center but their parents refused. The patient responded well with improvement in general condition and resolution of the white membrane by the 6th day of admission. All close contacts were given erythromycin prophylaxis (Table 1).

DISCUSSION

Diphtheria is an acute toxic infection caused by *Corynebacterium* species, namely *C. diphtheriae* and rarely, toxigenic strains of *Corynebacterium ulcerans*. *Corynebacterium diphtheriae* is an exclusive inhabitant of the human mucous membrane and skin. It causes a local inflammatory reaction by producing 62-kDa polypeptide exotoxin which causes tissue necrosis and forms a dense necrotic adherent coagulum called pseudomembrane. The primary focus of infection is tonsils and pharynx (94%) further extension into the larynx and bronchial airway leads to fatal airway obstruction.

Despite being vaccine-preventable disease diphtheria even after the introduction of the Universal Immunization Program in 1985, there have been several reports of re-emergence or persistence of diphtheria from many states of India over 2 decades.^{2–9} India contributes 19–84% of the global burden from 1998 to 2008.³ India reported 41,672 cases with 897 deaths during 2005 to 2014 (case fatality ratio: 2.2%). The immunization status in the state of Uttarakhand is worrisome because even the immunization coverage in 12–23 months old children has increased from 43.5% in NFHS-3 to 62% in NFHS-4 almost all states showed an improvement in immunization coverage except Uttarakhand where it decreased by about 3% with only 67% children have received three doses of DPT. Also, 9% of children have not received any vaccine to date.¹⁰ Coverage Evaluation Survey (CES) of UNICEF found that the reasons for partial immunization or non-immunization were “did not feel the need”, “not knowing about the need”, and “not knowing where to go for vaccination” in 28.2, 26.3, and 10.8% cases, respectively.¹¹

In the state of Uttarakhand, a study by Singh et al. reported a total of 61 suspected diphtheria cases from the Kumaon region between 2005 and 2010; however, microbiological and culture were negative in all cases.¹² One sporadic confirmed case was reported in 2018 but the patient did not survive owing to non-availability of DAT and toxin-mediated complications⁹ but after that, a recent outbreak was reported in August 2020 till February in Bageshwar district of Uttarakhand with 30 suspected and 14 laboratory-confirmed throat swab positive patients.

The mainstay of treatment is specific DAT and should be administered as soon as it is clinically suspected even before the bacteriological confirmation. The degree of protection offered by the DAT is inversely proportional to the duration of clinical illness.

Current CDC guidelines recommend administration of DAT to all laboratory-confirmed cases with respiratory diphtheria after testing for hypersensitivity to horse serum since about 10% get serum sickness but rarely anaphylaxis.¹³ The recommendation for antitoxin dosage by the Committee on Infectious Disease of the American Academy of Pediatrics is a single empirical dose of 20,000 to 100,000 units based on the degree of severity, size and

Table 1: Patients characteristics

Parameters	Case 1	Case 2	Case 3	Case 4
Age (years)	16	15	4	9
Gender	Male	Female	Female	Female
Residence (village)	Checheyi	Checheyi	Dharamgarh	Naugaon
Duration of illness (days)	3–4	2	3–4	4
Symptoms				
• Sore throat	Yes	Yes	Yes	Yes
• Fever	Yes	Yes	Yes	Yes
• Bloody nasal discharge	No	No	Yes	No
• Hoarseness of voice	No	No	Yes	Yes
• Difficulty breathing	No	No	Yes	No
• Difficulty swallowing	Yes	No	Yes	No
• Nasal regurgitation	No	No	No	No
• Grayish white membrane in the throat	Yes	Yes	Yes	Yes
• Bull neck	No	No	Yes	No
• Any other	–	–	–	Vomiting, pain abdomen
Immunization status	Partially	Partially	Partially	Unimmunized
Contact history	Yes	Yes	No	No
Management				
• Antibiotics (Crystalline Penicillin NA)	Ceftriaxone + Azithromycin	Amoxiclav + Azithromycin	Amoxiclav + Azithromycin	Amoxiclav + Azithromycin
• DAT (dosage)	100,000 IU	30,000 IU	100,000 IU	100,000 IU
Throat swab culture for <i>C. diphtheriae</i>	Positive	Negative	Positive	Positive
Investigations				
• CBC	WNL	WNL	–	Leukocytosis (21,390 → 10,640) Thrombocytopenia (48,000 → 51,000)
• ECG	ST elevation in V1, V2	ST elevation in V1, V2	NSR	NSR
• CPKMB	Negative	Negative	–	–
• Troponin-I	Negative	Negative	–	–
• SGPT	Raised (<2x)	Normal	–	Normal
Resolution of grayish-white membrane (days)	5	4	–	6
Outcome	Discharged	Discharged	Expired (post referral)	Discharged

extent of the membrane, and duration of illness. According to old studies, DAT should be administered within a week to reduce mortality but the best results were seen when treated within 24–48 hours.¹⁴

In our study, all patients received DAT (1,000 IU/mL) within 24 hours of admission as per recommendations with prior sensitivity testing. It resulted in a good prognosis and resolution of membrane between 4th and 6th days after admission except CASE 3 which was referred to a higher center in view of nasal bleeding and later succumbed to death owing to complication.

All patients in our study were between 4 years and 16 years and were unimmunized/partially immunized similar to previous outbreaks. This strengthens the fact that immunity acquired through primary immunization is waning in early childhood and booster dosages are also important similar to Mehta et al.¹⁵

Toxin absorption can lead to systemic manifestation and complications namely cardiomyopathy, acute tubular necrosis,

disseminated intravascular coagulation, thrombocytopenia, and/or polyneuropathy. The risk of complications also correlates directly with severity as well as delay in the administration of antitoxin. In CASE 4, the patient developed thrombocytopenia (cause? toxin-induced) as other causes could not be evaluated due to limited resources.

Toxic cardiomyopathy occurs in 10–25% of patients as early as 1st week of illness, can result in dysrhythmia and death. Tachycardia, prolonged P-R interval, and changes in ST-T wave are observed in ECG. Dilated and hypertrophic cardiomyopathy in echocardiogram is also seen.

In our study, ECG changes were noted in two patients (Cases 1 and 2) as ST-elevation although Troponin-I and CPKMB markers were not raised. Patients were advised for repeat ECG after 2 weeks for review.

Neither of any patients in our study showed neurologic complications like cranial neuropathies, bulbar palsy, or aspiration.

Intervention

District and state immunization officers were informed as soon as suspected diphtheria cases were detected in the district. House to house visits was done in the Checheyi village. Detailed immunization history was collected and mass vaccination was carried out. All suspected contacts were prescribed erythromycin prophylaxis. Health workers (ASHA, ANM, and AWWs) were advised to educate and report the suspected cases. Later under the Intensified Mission Indradhanush program all left-outs, drop-outs, and resistant cases were covered. At the district level, DAT stock was made available along with antibiotics which resulted in a favorable outcome as shown in our study.

CONCLUSION

The present study has shown that diphtheria is still prevalent in our state. Strict epidemiological surveillance and a high index of suspicion are needful in all cases of acute membranous tonsillopharyngitis for early detection and prevention of outbreaks. Diphtheria, pertussis, and tetanus vaccine immunization with emphasis on booster doses is a vital key for prevention. Implementation of replacing tetanus toxoid with Td beyond 4 years of age in immunization schedule will ensure sustained protection against diphtheria considering waning immunity following primary immunization as highlighted by WHO/UNICEF guidance note in September 2018. Early preparedness and timely administration of DAT is the mainstay of treatment along with antibiotic therapy as it subdues the effect of circulating toxin and results in a favorable prognosis.

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