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Diphtheria: A Case Series From Central India

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ABSTRACT

Background: Diphtheria continues to be a public health problem in India as it is re-emerging in several regions of the country. In recent times, apart from preschool-aged children, diphtheria outbreaks are seen to affect older children and adults. Recent emergence of cases highlights the risk diphtheria poses when civil unrest interrupts vaccination and healthcare access. An improved understanding of the nature of each outbreak is therefore essential to generate a pool of evidence regarding the current disease status in India. Here we describe the case series of diphtheria from Central part of India so as to better understand the natural history of disease, key epidemiological factors, the role of asymptomatic carriers in transmission and effectiveness of control measures so as to improve clinical practices and support alternative strategies for response to future diphtheria outbreaks.

Results: Among the 10 patients admitted with clinical suspicion of oropharyngeal diphtheria. Microbiological diagnosis was achieved in 3 cases and one was diagnosed clinically. All the 3 bacteriological positive cases were of pediatric age group with incomplete immunization. All the positive cases were found to be originated from inmates of boarding school inhabiting the same residential area. Of the 10 patients, eight (80%) recovered, one (10%) succumbed to death while one took discharge against medical advice. Clinical presentations, vaccination history and microbiologic findings points towards the persistence of toxigenic strain of C. diphtheriae (gravis type) along with other rare corynebacterium spp. that clinically mimic as oropharyngeal diphtheria in the community and their role in disease transmission with potential for future outbreaks.

Conclusion: Awareness among people, widespread universal immunization coverage especially in cohorts of children, availability of modern microbiological support, and rapid early diagnosis are the cardinal steps to control diphtheria resurgence.

Keywords: *Diphtheria, Central India, Universal Immunization*

1. INTRODUCTION

Diphtheria is a highly contagious infection caused by toxin-producing gram-positive bacterium *Corynebacterium diphtheriae* [1,2] and sometimes by toxigenic strains of *C. ulcerans* & *pseudotuberculosis*.[3,4] Transmission of *C. diphtheriae* seems to occurs either via contact with respiratory droplets or skin secretions of an infected individual. An infected person generates an estimated 2–4 cases. Though Globally, there has been a decline in diphtheria cases following effective national vaccination programs; India still contributes to a large proportion of global burden of diphtheria. As per CBHI data, during 2005–2014, India documented 41,672 cases (average: 4167 per year) and 897 deaths (case fatality ratio: 2.2%). Ten Indian states namely Assam, Kerala, Maharashtra, Delhi, Karnataka, Gujarat, Haryana, Nagaland, Rajasthan, and West Bengal accounted for 84% of these cases.[5] Several factors impact the incidence of diphtheria such as low vaccination status, overcrowding, migration, nutritive status and improper hygiene of children, home ventilation, and humidity or moisture in the house.[6]

Diphtheria is a vaccine preventable disease, but multiple doses and booster doses are needed to maintain sustained immunity. For unvaccinated individuals, without adequate treatment, diphtheria can lead to death in around 30% of cases upholding younger children at higher risk of disease progression and death.[7] Recent outbreaks highlights the threat diphtheria poses when civil activities interrupts vaccination and healthcare access. Lack of interest over the last century resulted in knowledge gaps about diphtheria's epidemiology, transmission, and control. Hence we aimed to add further to existing knowledge of diphtheria and related outbreaks in Central part of India so as to improve clinical practices and support alternative strategies for response to future diphtheria outbreaks.

2. METHODS

This case series studied 10 patients admitted to tertiary care hospital located in Central part of India with clinical suspicion of oropharyngeal diphtheria over a period of six months. In each case; two throat swabs were collected and primary identification of Corynebacterium diphtheriae was done by direct microscopy (Gram and Albert stain), bacteriological culture and biochemical tests as per the standard procedure.[8] Culture isolates were sent to a reference laboratory for further confirmation by polymerase chain reaction(PCR), toxigenicity testing by Elek's gel precipitation test[9] and detection of *tox* A gene by PCR.

3. RESULTS

Hereby we are describing the case summary of 3 microbiolocally confirmed cases of diphtheria on direct microscopy among 10 patients admitted with clinical suspicion of oropharyngeal diphtheria(overview in Table I):

CASE	AGE IN YRS	SEX	VACCINATION HISTORY	MICROSCOPY AND CULTURE	TOX GENE	ANTIDIPHTHERIC SERUM	COMPLICATING FATORS	OUTCOME
1.	8	M	Vaccinated	Negative	Negative	Not Given	None	Recovered
2.	21	F	Partially Vaccinated(No booster)	Negative	Negative	Given	None	Recovered
3.	6	M	Partially Vaccinated	Positive	Positive	Not Given	Myocarditis	Death
4.	7	M	Partially Vaccinated	Positive	Negative	Given	None	Recovered
5.	6	F	Partially Vaccinated	Positive	Positive	Given	Congenital heart disease	Recovered
6.	8	M	Partially Vaccinated	Negative	Negative	Not Given	None	Recovered
7.	10	M	Partially Vaccinated	Negative	Negative	Not Given	None	Recovered
8.	6	F	Partially Vaccinated	Negative	Negative	Given	None	Recovered
9.	38	M	Vaccinated(No booster)	Negative	Negative	Given	Myocarditis	Lost to follow up
10.	8	F	Vaccinated	Negative	Negative	Not Given	None	Recovered

Table I: Distribution of vaccination history, microbiological findings and patient outcome

Case 1:

A six year old male child reffered from district hospital with history of unresolving fever since 10 days, cough, cold, sore throat since 8 days and increased difficulty in breathing since 2 days. He was resident of Aadiwasi Aashram Shaala and in view of membranous tonsillitis had received preliminary oral treatment at Primary health clinic. His immunisation history was incomplete with only 3 doses of DPT. Thorough examination, revealed tonsilar hypertrophy with white membrane which didn't bleed on touch. His vitals were stable and on systemic examination he has normal heart sounds, chest clear , abdominal, CNS examination normal and also urine output was normal. The throat swab microscopy revealed gram positive bacteria on gram stain with KLB like organisms on albert stain. Growth on Lofflers serum slope with subsequent jet black colonies on potassium tellurite agar was subsequently tested by standard biochemical tests which raised the suspicion of *C. diphtheriae*. Patient was started on injectable antibiotics, IV fluids and supportive treatment. Antidiphtheric serum was deffered as the patient was found to stable on presumptive management .But unfortunately on day seven patient developed periorbital puffiness, tachycardia, low BP and decreased urine output. His renal function tests were deranged and ECG reports were suggestive of Conduction Block. Despite the rigorous treatment patient died of cardiorespiratory arrest secondary to diphtheria with myocarditis with acute kidney injury. At the same time our Reffrence lab CMC Vellore confirmed the strain to be toxigenic strain of *C. dipththeriae*

Case 2:

Simultaneously within two days of death of primary index case, a seven year old male, sharing the same environment with the index case admitted to the hospital with fever, sore throat since 5 to 6 days with difficulty in swallowing in last three days. On history his immunisation was found to be incomplete. He was non-toxic and his vitals were stable. His systemic examination was also normal. Considering the contact with index confirm case and history of incomplete immunisation, anti-diphtheric serum was administered and started on injectable antibiotics and supportive treatment. Throat swab for Microbiologic evaluation reveled KLB like organism on albert stain. The isolate recovered from culture on potassium tellurite agar and Lofflers serm slope was tested by standard biochemical test and on further evaluation found to be nontoxigenic strain of other Corynebacteria. The patient recovered subsequently.

Case 3:

A 6 year old female with congenital heart disease admitted to hospital with unresolving fever since 10 days and respiratory complaints. Her tonsils were enlarged bilaterally, and a grayish-white exudate extended from the tonsil to the posterior pharyngeal wall. The uvula and soft palate were erythematous ,edematous, and tender cervical lymphadenopathy was present. Direct microscopy of throat swab was positive by albert stain. Presumptive clinical diagnosis of respiratory diphtheria was made. In view of incomplete vaccination history and potential for disease progression and complications she received antidiphtheric serum immediately and started with injectable penicillin. The isolate from this patient was confirmed as toxigenic strain of *C. ulcerans* by PCR. The patient recovered subsequently.

All the 10 patients had presentation like oropharyngeal diphtheria with pseudo membrane formation as depicted in Figure I. Eight cases were of the pediatric age-group and two were adults. Among eight pediatric cases microbiological diagnosis was attained by direct microscopy in throat swab of 3 cases which demonstrated green Kleb Loffelers Bacillus in chinese letter arrangement with blue metachromatic granules on albert stain(figure II). Isolates grown on Loffelers serum slope and jet black colonies on potassium telluride agar (Figure III) were subsequently tested by standard biochemical tests for confirmation of *C. diphtheriae*. Among 8 pediatric cases; six had history of incomplete immunization including the 3 positive cases on direct microscopy. All the 3 microbiologically confirmed cases were admitted during the same timeframe of around 10-15 days and on enquiry they were found to share the same residential habitat i.e Boarding school. Of the 10 patients, eight (80%) recovered. One patient deteriorated despite the treatment with injectable antibiotic like amoxyclav and vancomycin; into complications like myocarditis with conduction block followed by acute kidney injury and succumbed to death due to cardiorespiratory arrest. At the same time, reference centre CMC Vellore confirmed the strain isolate to be toxigenic strain of *C. dipththeriae* mitis biotype.

Simultaneously within two days of death of primary index case; 2 inmates sharing the same residential environment were admitted to hospital with clinical presentation of oropharyngeal diphtheria. In both the cases, considering the contact with index confirm case and history of incomplete immunization; anti-diphtheric serum was administered immediately with injectable antibiotics and supportive treatment. Both patients recovered subsequently. Though the direct microscopy of throat swab in both cases were positive by gram and albert stain; the isolates from patient were further confirmed to be non toxigenic strain of other Corynebacteria spp. by reference centre implying the role of other rare species mimicking faucial diphtheria clinically with potential for outbreak particularly in immunocompromised or partially vaccinated persons.

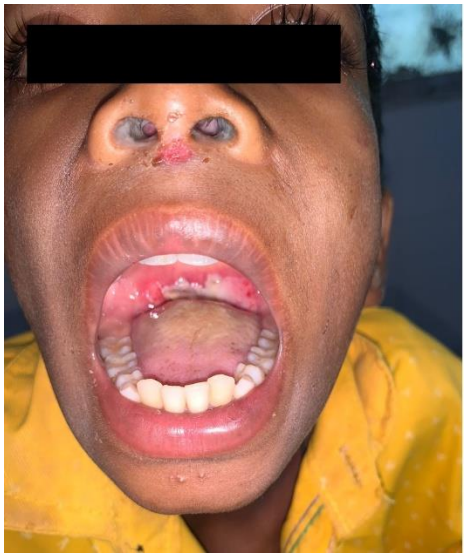

Figure I. Clinical Presentation of oropharyngeal diphtheria with pseudomembrane

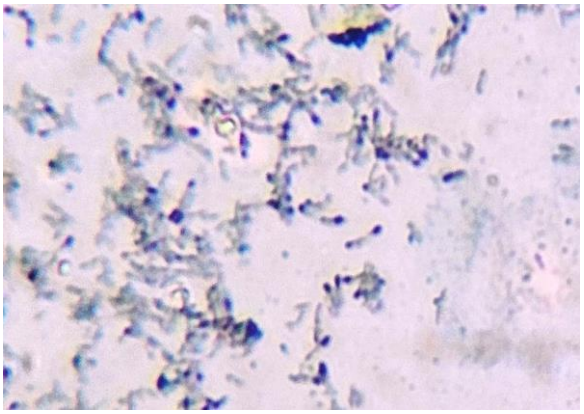

Figure II. Albert stain showing green bacilli with blue colored metachromatic granules.

Figure III. Potassium tellurite agar with black colored colonies of *C. diphtheriae*

4. DISCUSSION

Diphtheria once considered as a leading cause of childhood mortality; since the initiation of routine childhood immunization has been found to be almost completely eradicated in many developed countries. Developing countries though still accounts for 80–90% of the global burden of diphtheria.[10,11] It is a toxin-mediated, potentially fatal, acute infectious disease of the upper respiratory system caused by Corynebacterium diphtheria progressing to damage to the myocardium or other tissues.[12] Though diphtheria toxin is considered to be the main virulence factor of *C. diphtheriae* leading to pseudo membrane formation in faucial diphtheria[13]; several possibilities could explain the presence of a pseudo membrane in infections with nontoxigenic corynebacterium strains. First, toxigenic and nontoxigenic colonies of the same species can coexist in a patient; this phenomenon has been reported in diphtheria[14] or it is possible that the symptoms in our patient were caused by a nontoxigenic corynebacteria or other corynebacterial spp. and that the pseudo membrane was simply an inflammatory exudate.

Diphtheria is a vaccine preventable disease, but multiple doses and booster doses are needed to produce sustainable immunity. For unvaccinated individuals, diphtheria can be fatal in around 30% of cases without proper treatment with young children at higher risk of death as occurred in our index case.[7] Furthermore, in our study all the 3 confirmed cases were under- immunized posing them to be at risk of disease development and progression. Also, Under vaccination in successive cohorts of children can lead to outbreaks of diphtheria as in our case where all the confirmed cases belong to the same residential locality implying the circulation and transmission of strain in the inmates. Considering the verge of impending diphtheria outbreak; all the children who have been in contact with cases of diphtheria and other residents of boarding school were screened and treated with antibiotics prophylactically to prevent illness. The immunization status of all the contacts were checked and those not fully vaccinated were offered vaccination.

In our study; 2 cases in contact with confirmed index case were promptly administered with anti-dipththeric serum to neutralize the toxin limiting the progression of disease. For this reason, if diphtheria is suspected, testing to confirm the disease should be done promptly and treatment should be started as soon as possible.

Inability to measure the serum antibody titre against diphtheria toxin and inability to perform genetic sequencing of the isolates are the limitations of our study which necessitates further research.

5. CONCLUSION

Clinical presentations, vaccination history and microbiologic findings points towards the persistence of toxigenic strain of *C. diphtheriae* (gravis type) in the community along with other rare corynebacterium spp. that clinically mimic as oropharyngeal diphtheria and their role in transmission of disease with potential for future outbreaks. Our study also updates clinical and epidemiological metrics of diphtheria in Central India that may contribute to improve clinical practices and support alternative strategies for response to future diphtheria outbreaks

Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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