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Case Series

Out of the blue presentation out of the box management: diphtheria cases in Vadodara

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ABSTRACT

Diphtheria cases continue to be reported in India despite the national immunization programme although there has been an age shift to older children and adults in the recent outbreaks. This case study follows 17 patients of diphtheria treated at Sir Sayajirao General Hospital Vadodara between September 2022 and September 2023, their clinicoepidemiological profile and management. There were 4 females and 13 males, ages from 7 months to 11 years. While most cases had pharyngeal disease (grade 1), one case had nasopharyngeal disease (grade 2) and three had diseases for more than 3 days and extending to the neck (grade 3). Albert stain was reported positive in 10 cases and culture was not grown in any. Most cases were unimmunized or partially immunized. Mean duration of hospital stay was 9.3 days, longest being 35 days. Three cases died on day 2,4 and 21. In addition to crystalline penicillin, majority were administered Metronidazole and carnitine. DAT was used in doses of 40000, 60000 or 80000 IU uneventfully. When therapy is started based on clinical findings, adding metronidazole increases the spectrum of coverage and using levocarnitine protects against cardiomyopathy. In our series none of our cases died of cardiomyopathy. DAT was not involved in any of the deaths and was found safe and effective in all the cases. Diphtheria persists in different pockets in India and the only way of controlling it by increasing vaccine coverage

Keywords: Diphtheria, Diphtheria anti toxin, DAT, Metronidazole, levocarnitine

INTRODUCTION

Diphtheria is generally considered a childhood disease. In India, DTP vaccine was introduced in the national immunization programme in 1978. The incidence of Diphtheria in the paediatric population has fallen drastically, but the infection has shifted to older age groups, especially in those who were unimmunized or partially immunised.[1] Central Bureau of Health intelligence (CBHI), publishes National Health profile every year. As per the 17th issue, for the period January to December 2021, there were 3677 reported cases of Diphtheria with 47 deaths. Few states like West Bengal 2227, Odisha 760, Rajasthan 160, Andhra Pradesh 157, Karnataka 153 and Telangana 105 had a high number of reported cases.[2] Diphtheria, presents as sore throat, low grade fever and cervical lymphadenopathy. The bacterium releases an exotoxin that creates a membrane of dead tissue over the throat and tonsils making breathing and swallowing difficult. In severe cases the toxin can also cause myocarditis and neuropathy.[3]

Administration of diphtheria antitoxin (DAT) reduces mortality by 76%.[4] DAT is composed of equine antibodies. Being of heterologous origin, the presence of these foreign proteins could cause hypersensitivity reactions. Text books suggest that the risk of adverse reactions to DAT is between 5 and 20% with a 0.6% risk of anaphylaxis.[4] There are only a couple of published reports regarding the safety of DAT in the population.[4,5]

This retrospective study records the clinico epidemiological profile of patients with diphtheria and its management.

CASE SERIES

Cases of diphtheria treated at Sir Sayajirao Hospital Vadodara between September 2022 and September 2023 have been covered. During this period, only DAT manufactured by premium serums and vaccines private ltd (PSVPL) had been supplied. After receiving approval from the Ethics Committee of Sir Sayajirao Hospital, all cases of Diphtheria from the medical records were reviewed for vaccination status, use of DAT, antibiotics, and adjunct therapy as well as adverse events. This has been tabulated in Table 1.

Table 1: Demographics, vaccination history, clinical grade, drug usage among the 17 cases.

Patient, age, sex,	Clinical grade	Albert's stain	Culture	Immune status	Indoor stay days	DAT in units	Antibiotics used	Others	ADRs
1) M/ 10mths	1	0	0	Unimmunised	21 *	60000	CP, M		Nil
2) M/10 mths	1	0	0	Unknown	6	60000	CP, M	L	Nil
3) M, 1 yr	1	0	Diphtheroid forms	Unknown	7	40000	CP, M	L	Nil
4) F, 7 yrs	1	0	DF	Partially Imm	4	40000	CP, M	L	Nil
5) M, 6 yrs	1	1	DF	Unimmunised	10	60000	CP, M	L	Nil
6) M,1 yr	1	1	DF	Unknown	4 DAMA	60000	CP, M	L	Nil
7) F, 10 mths	1	0	DF	Unknown	4 *	80000	CP, M		Nil
8) M, 4 yrs	1	1	DF	Unknown	7	80000	CP, M	L	Nil
9) M, 7 mths	2	1	DF	Unknown	8	60000	CP, M	L, Cef	Nil
10) M, 7 yrs	3	0	DF	Unknown	2 *	40000	CP, M		Nil
11) M, 3 yrs	1	1	DF	Unimmunised	9	40000	CP, M	L	Nil
12) F, 11 yrs	1	0	0	Unimmunised	8	40000	CP, M	L	Nil
13) M, 4 yrs	3	1	DF	Partially Imm	6	60000	CP, M	L	Nil
14) M, 5 yrs	1	1	DF	Partially Imm	7	60000	CP, M	L	Nil
15) F, 3 yrs	1	1	DF	Partially Imm	11	40000	CP, M		Nil
16) M, 21 mths	1	1	DF	Partially Imm	9	60000	CP, M	L	Nil
17) M, 4 yrs	3	1	DF	Unknown	35	80000	CP, M	Cef, Col, Lin	Nil

CP-Crystalline penicillin, M-Metronidazole, L-Levocarnitine, C-Carnitine, Cef - Ceftriaxone, Col-Colistin, L-Linezolid. * Death, DAMA–Discharged Against Medical Advice, Albert's stain and culture 0- negative, 1- positive DF=Diphtheroid forms, Clinical grade: Pharyngeal or laryngeal disease–Grade 1, Nasopharyngeal disease–Grade 2, Extensive disease of 3 or more days duration, or diffuse Swelling on the neck–Grade 3.

We started diphtheria anti toxin therapy based on clinical findings, while at the same time sending a throat swab for culture and Albert's staining. Antibiotic and supportive therapy was administered as per standard of care. The disease was graded clinically as per CDC guidelines. Pharyngeal or laryngeal disease-grade 1, nasopharyngeal disease-grade 2, extensive disease of 3 or more days duration, or diffuse swelling on the neck-grade 3.[6] The planned dose of DAT was diluted in normal saline and administered as a single dose. Immunization history was elicited from parents and matched with immunization cards if available. Patients who had not received even one dose of primary vaccination were categorized as unimmunized. Those who had received at least one dose of DPT but not completed the 5-dose schedule were categorized as partially immunised, and those who had received all 5 doses were classified as fully immunised.[3] Unfortunately 8 patients could not provide any information about vaccinations. Albert stain was reported positive in 10 cases and no culture was grown in 3 cases while in others the laboratory reported Diphtheroid forms, to be confirmed clinically. Most cases were unimmunised

or partially immunised. Mean duration of hospital stay was 9.3 days, longest being 35 days. Three cases died on day 2,4 and 21. In addition to crystalline penicillin, majority were administered Metronidazole and carnitine. DAT was used in doses of 40000, 60000 or 80000 IU uneventfully.

DISCUSSION

Diphtheria continues to occur in India despite the ongoing immunization programme. The presentations are still rare and strike out of the blue. However, a shift has been noted to older children and adults.[3] In our series we had 6 cases up to one year, 7 cases 1 to 5 years, and remaining 4 were 6,7,7 and 11 years clearly showing a shift to higher aged children. Diphtheria is recorded in cases who are unimmunized or partially immunised.[3] In our series, 4 cases were unimmunized, 5 were partially immunised and the rest could not give any information. Even an illiterate mother can tell if her child was given any vaccination or injection since there are many rounds of the hospital to be completed. So, instead of classifying them as status unknown, if we label them as unimmunised, it would mean 12 of 17 (70%) were unimmunised.

Diagnosis of respiratory diphtheria is usually made based on clinical presentation because it is imperative to begin presumptive therapy quickly. Persons with suspected diphtheria are given diphtheria antitoxin and antibiotics in adequate dosage, without waiting for laboratory confirmation. This is accompanied by a booster shot of immunisation.[7]

In our department too, we begin therapy on clinical suspicion of diphtheria while at the same time sending a swab for Albert's staining and culture. In this case series only 10 cases showed positivity on Albert stain. 3 cases were culture negative and the remaining grew diphtheroid organisms to be confirmed clinically. Even if these reports are negative, if clinical situation demands we continue therapy. We administer DAT and begin antibiotics. CDC has proposed ascending doses of DAT as per the grades. The clinical grades proposed by CDC relate to the location of the diphtheritic membrane, duration of illness and other comorbidities. In the present situation in case of a grade 1 illness confined to the pharyngeal area, if the clinical severity demanded we have administered higher doses of DAT, and lesser than prescribed dose if the clinical condition was not so alarming. Crystaline penicillin is the go-to drug for Diphtheria.[7] In private practice penicillins are avoided for fear of anaphylaxis, hence we have a penicillin naïve population which responds well. However, we also added metronidazole in all cases to cover for anaerobes that are rampant in the oral cavity.

Per IAP guidelines 2022, toxic cardiomyopathy can occur in up to 25 % cases and is the cause of death in 50-60% cases. Carnitine (P-hydroxy-y-Ntrimethyl-ammonium butyrate) is an indispensable cofactor for the transport of fatty acids into the mitochondria. Fatty acids are oxidized to obtain ATP.[8] Diphtheric toxin interferes in protein synthesis. This could lead to an impairment in carnitine transport and a loss of carnitine molecules readily utilizable in the oxidative metabolism.[9] Ramos et al, in a comparative study involving 625 cases of diphtheria, observed that administration of Levocarnitine 100 mg/kg/day for 4 days lead to a significant reduction in mortality due to cardiac causes. We routinely use levocarnitine in all our patients. Surprisingly during literature search, we have not come across many institutions where levocarnitine is routinely used. Of the three instances of death, case 10, passed away in 2 days. The cause of death was attributed to delay in bringing the case to the hospital and severity of disease. The other two cases 1 and 7 succumbed to hospital related infection and sepsis. None had cardiomyopathy. The case that was discharged against medical advice was stable at discharge.

DAT was found to be effective in controlling progression of disease and recovery at the recommended doses of dose of 40,000 to 80,000 IU.DAT is expected to have adverse effects, in 5 to 20% cases with a 0.6% risk of anaphylaxis.[4] In our case series it was well tolerated with no adverse event reported in any case. In the death cases too, there was no suspicion of a DAT adverse event.

CONCLUSION

Diphtheria persists in different pockets in India and the only way of controlling it by increasing vaccine coverage. When therapy is started based on clinical findings, adding metronidazole increases the spectrum of coverage and using levocarnitine protects against cardiomyopathy. In our series none of our cases died of cardiomyopathy. DAT was safe and well tolerated in all cases with no adverse events following administration and no death was attributable to DAT.

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