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Original Article

Clinical profile and predictors of poor outcome of hospitalized diphtheria cases in children from Lucknow region of North India

S.N. Singh^{a,*}, Anita Singh^b, Surabhi Chandra^c^a Associate Professor, Department of Paediatrics, Chhatrapati Shahuji Maharaj Medical University (Erstwhile K.G.M.C.), Shahmina Road, Chowk, Lucknow 226003, Uttar Pradesh, India^b Senior Resident, Department of Paediatrics, Chhatrapati Shahuji Maharaj Medical University (Erstwhile K.G.M.C.), Lucknow 226003, Uttar Pradesh, India^c Resident, Department of Paediatrics, Chhatrapati Shahuji Maharaj Medical University (Erstwhile K.G.M.C.), Lucknow 226003, Uttar Pradesh, India

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ABSTRACT

Objectives: Diphtheria is a re-emerging disease with changing epidemiology. We aimed to identify clinical and demographic characteristics of diphtheria cases and predictors of mortality, reported scarcely.

Methods: This was a retrospective study of 279 diphtheria cases admitted at tertiary care hospital over 2 years. Demographic, clinical details & outcome were recorded. Clinical diagnosis was based on presence of typical membrane or palatal palsy with febrile illness. Microbiologic confirmation could be established in 34 of 111 cases investigated. Categorical variables were analysed by Chi-square test and continuous variables by independent t-test or Mann–Whitney U test. Complications found significant on univariate analysis were analysed by logistic regression to find predictors of mortality.

Results: The 1–5 yr age group represented 49.5% of the cases & 5–10 yr represented another 43%. Most cases were either unimmunized (79.6%) or partially immunized (18.3%). Majority (83.9%) presented with illness of less than 14 days. The overall case fatality was 48%. Airway obstruction (adjusted OR = 21.7), respiratory paralysis (adjusted OR = 57.7), bradyarrhythmia (adjusted OR = 7.0), renal failure (adjusted OR = 5.5) and shock at admission (adjusted OR = 2.9) were independent predictors of mortality.

Conclusion: Diphtheria among children reflects poor immunization coverage. Airway obstruction, respiratory paralysis, bradyarrhythmia, renal failure and shock at admission predicted mortality.

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* Corresponding author. Tel.: +91 9415202124 (mobile).

E-mail address: drsn.singh@rediffmail.com (S.N. Singh).

1. Introduction

Many outbreaks of diphtheria from various states in India have been reported in recent times.^{1–5} In 2010, India shared 3123 (77.1%) of 4053 diphtheria cases contributed by 24 countries, reported to WHO,⁶ which may possibly be a gross underestimate due to lack of a good surveillance system & facility for microbiologic diagnosis.⁷ Inadequate vaccine coverage in young children, waning vaccine induced immunity in adults, mass population movements, poor living standards, delayed reporting to hospital and non-availability or delay in administering antitoxin appears to be the main factors contributing to re-emergence of the disease and high mortality.^{8,9}

In scenario of changing epidemiology of diphtheria, studies reporting clinical profile remains scanty.^{9,10} A large number of diphtheria cases are treated at our hospital. It was therefore decided to analyse the information to bring out the clinical and demographic profile of diphtheria cases and predictors of mortality. This would help in early recognition of cases and referring them timely to higher medical care facility and to prioritize intensive care, which may reduce morbidity and mortality.

2. Methods and materials

This was a retrospective study of consecutive, clinically diagnosed diphtheria cases admitted to Paediatric emergency of a tertiary teaching hospital over a period of two years from January 2009 to January 2011. Clinical diagnosis of diphtheria was considered in any child who had fever, throat pain/dysphagia or neck swelling and demonstrated either typical membrane or developed palatal palsy. The case record of 279 consecutive diphtheria cases were reviewed and information regarding age, gender, residence, immunization status, clinical details, complications, laboratory investigations, treatment provided and outcome was recorded. Variables are compared among survivors and expired to find out predictors of outcome. Outcome was defined as either survived or expired. Children were considered completely immunized if they had received all the recommended doses of diphtheria toxoid for the age including booster as per national immunization schedule. All patients with a diagnosis of diphtheria were put on parenteral crystalline penicillin. Antidiphtheric serum (ADS) was administered to most of the patients in a single dose as recommended¹¹ depending on the site and extent of the disease & availability of ADS. All patients were kept in isolation area of Paediatric emergency for monitoring and management. All cases received L-carnitine 50–100 mg/kg/day in three divided doses routinely.

Data were analysed by SPSS software version-16. The data were presented as mean (SD) and median (range) for continuous variables and as frequency & percentage for categorical variables. Between groups comparison was done using Chi-square test for categorical data. The normal distribution of quantitative variables was tested by Kolmogorov–Smirnov test and were compared by independent t-test (parametric data), or Mann–Whitney U test (nonparametric data).

A p-value of <0.05 was considered to be statistically significant difference. Various complications found to be significantly associated with mortality on univariate analysis were analysed further by multiple logistic regression to determine the independent predictors of mortality.

3. Results

Of 279 admitted diphtheria cases, 134 expired (case fatality rate of 48%). The detailed demographic and clinical profile of admitted diphtheria cases are shown in Table 1. *Corynebacterium diphtheriae* was seen in smear among 34 patients out of 111 specimens sent to microbiologic laboratory. Culture was positive in 23 patients, all of them were smear positive also. The mean $\pm$ SD age (yr) of patients at presentation was 4.77 ± 2.77 (survived: 5.13 ± 2.99 vs expired: 4.39 ± 2.99 ; $p = 0.024$). Only six (2.2%) patients had received complete immunization. Majority (83.9%) of patients presented in the acute phase of the illness, less than 14 days duration. Those presented in the later phase (14 days or later) had neurologic complications. Among 34 *Corynebacterium* positive cases, fever was present in 33 (97.1%), throat pain/dysphagia in 31 (91.2%), neck swelling in 22 (64.7%), palatal palsy in 6 (17.6%), and membrane was seen in 33 (97.1%) cases.

Table 2 shows various complications among hospitalized diphtheria cases. Of 144 patients having airway obstruction, 92 (63.9%) had neck swelling, 110 (76.4%) had pharyngolaryngeal or laryngeal membrane and 29 (20.1%) had isolated pharyngeal membrane, and 41 (69.7%) had cardiac complication. Tracheostomy was performed in 105 patients. Intubation was done to relieve airway obstruction at arrival to emergency room in 54 patients, 13 of them died during intubation, and tracheostomy was done subsequently in 15. Of 59 patients with cardiac involvement, 20 (33.9%) had tachyarrhythmia $\pm$ gallop and 39 (66.1%) had bradyarrhythmia which progressed to complete heart block in 8 patients. Temporary pacing was done in 2 patients but none of patients with complete heart block survived. Of 31 patients having shock at admission, 12 (38.7%) had bradyarrhythmia, 1 (3%) tachyarrhythmia, 7 (22.6%) polyneuropathy, 8 (25.8%) renal failure, 21 (67.7%) swelling neck, 27 (87.1%) membrane, and 24 (77.4%) had airway compromise. Of 37 patients with acute renal failure, 5 dialysed (3 survived), 32 (86.5%) had cardiac complication and 8 (21.6%) had shock at admission.

Table 3 shows clinical parameters including complications of diphtheria cases in different age groups. Various complications found to be significant on univariate analysis among survived and expired patients were further analysed and shown in Table 4.

4. Discussion

In view of poor specimen collection on usual throat swab, delayed transportation to the lab, delayed inoculation to the special culture media and prior antibiotic therapy, microbiologic confirmation could be established in only 34 of 111 specimens sent to lab. Low *Corynebacterium* yield (7–12%)

Table 1 – Demographic and clinical parameters of diphtheria cases.

Parameters	All cases n = 279 (%)	Survived n = 145 (%)	Expired n = 134 (%)	p-Value
Age (yr) median (range)	4.0 (0.4–13)	5.0 (0.4–13)	4.0 (0.6–12)	0.056
Age frequency (yr)				
<1	9 (3.2)	7 (4.8)	2 (1.5)	0.012
1–5	137 (49.1)	59 (40.7)	78 (58.2)	
5–10	121 (43.4)	70 (48.3)	51 (38.1)	
>10	12 (4.3)	9 (6.2)	3 (2.2)	
Male:Female	160:119	83:62	77:57	0.970
Urban:Rural	95:184	49:96	46:88	0.925
Admission				
Jan–June	13 (4.7)	5 (3.4)	8 (6.0)	0.318
July–Dec	266 (95.3)	140 (96.6)	126 (94.0)	
Vaccination				
Complete	6 (2.2)	6 (4.1)	0	0.017
Incomplete	51 (18.3)	31 (21.4)	20 (14.9)	
None	222 (79.6)	108 (74.5)	114 (85.1)	
Illness prior to admission				
<7 days	114 (40.9)	47 (32.4)	67 (50)	0.003
7–14 days	131 (47)	89 (61.4)	42 (31.3)	0.000
>14 days	34 (12.2)	9 (6.2)	25 (18.7)	0.001
Fever at presentation	271 (97.1)	140 (96.6)	131 (97.8)	0.724
Neck swelling	164 (58.8)	73 (50.3)	91 (67.9)	0.003
Throat pain/dysphagia	239 (85.7)	121 (83.4)	118 (88.1)	0.272
Voice change	143 (51.3)	75 (51.7)	68 (50.7)	0.870
Nasal regurgitation	61 (21.9)	31 (21.4)	30 (22.4)	0.839
Respiratory difficulty	194 (69.5)	70 (48.3)	124 (92.5)	0.000
Limb weakness	35 (12.5)	16 (11.0)	19 (14.2)	0.428
Membrane: all cases	243 (87.1)	125 (86.2)	118 (88.1)	0.645
Faucial/pharyngeal	111 (39.8)	77 (53.1)	34 (25.4)	0.000
Pharyngolaryngeal	128 (45.9)	45 (31.1)	83 (61.9)	0.000
Nasal	2 (0.7)	2 (1.4)	0	–
Laryngeal	2 (0.7)	1 (0.7)	1 (0.7)	–

Figures in parentheses depict % unless specified.

have also been reported by Ray et al¹² and Patel et al,¹ thus emphasizing the relevance of clinical diagnosis, and one should not delay immediate and specific treatment of the patient. Presence of membrane in throat which is hallmark for clinical diagnosis of diphtheria¹³ was present in 243 (87.1%) cases in our series. Palatal palsy characterized by a nasal quality to the voice and nasal regurgitation commonly occurring in 2nd or 3rd week is the most common and earliest

neurological complication which may occur alone or in association with other type of paralysis.¹⁴ In our series 68 (24.4%) patients had palatal palsy following a febrile upper respiratory tract illness, 30 (44.1%) of these had neck swelling.

The higher mortality among children with shorter duration of illness prior to hospitalization (<7 days) compared to those with duration 7 days or more represents more fulminant course, and had more often neck swelling (67.5% vs. 32.5%:

Table 2 – Complications among diphtheria cases.

Complication	All cases n = 279	Survived n = 145	Expired n = 134	p-Value
Neuropathy				
Palatal	23 (8.2)	14 (9.7)	9 (6.7)	0.377
Palatal + polyneuropathy	43 (15.4)	20 (13.8)	23 (17.2)	
Palatal + ataxia	2 (0.7)	2 (1.7)	0	
Carditis (clinical)				
Tachyarrhythmia ± Gallop	20 (7.2)	9 (6.2)	11 (8.2)	0.517
Bradycardia	39 (14.0)	4 (2.8)	35 (26.1)	0.000
Acute renal failure	37 (13.3)	6 (4.1)	31 (23.1)	0.000
Bleeding	22 (7.9)	5 (3.4)	17 (12.7)	0.004
Shock at admission	31 (11.1)	4 (2.8)	27 (20.1)	0.000
Airway compromise	144 (51.6)	41 (28.3)	103 (76.9)	0.000
Respiratory paralysis	23 (8.2)	3 (2.1)	20 (14.9)	0.000

Figures in parentheses depict % unless specified.

Table 3 – Clinical parameters of diphtheria in different age groups.

Parameters	Age < 1 yr n = 9	Age 1–5 yr n = 137	Age 5–10 yr n = 121	Age > 10 yr n = 12	p-Value
Illness prior to admission					
<7 days	4 (44.4)	55 (40.1)	52 (43.0)	3 (25.0)	0.671
7–14 days	5 (55.6)	60 (43.8)	58 (47.9)	8 (66.7)	0.434
>14 days	0 (0)	22 (16.1)	12 (9.9)	0 (0)	0.144
Fever at presentation	9 (100)	130 (94.9)	120 (99.2)	12 (100)	0.179
Neck swelling	4 (44.4)	72 (52.6)	81 (66.9)	7 (58.3)	0.099
Throat pain/dysphagia	5 (55.6)	118 (86.1)	107 (88.4)	9 (75.0)	0.036
Voice change	1 (11.1)	75 (54.7)	63 (52.1)	4 (33.3)	0.045
Nasal regurgitation	3 (33.3)	35 (25.5)	21 (17.4)	2 (16.7)	0.333
Respiratory difficulty	8 (88.9)	109 (79.6)	73 (60.3)	4 (33.3)	0.000
Limb weakness	0 (0)	16 (11.7)	7 (5.8)	1 (8.3)	0.293
Membrane	9 (100)	114 (83.2)	110 (90.9)	10 (83.3)	0.180
Neuropathy					
Palatal	0 (0)	13 (9.5)	8 (6.6)	2 (16.7)	0.182
Palatal + polyneuropathy	1 (11.1)	29 (21.2)	12 (9.9)	1 (8.3)	
Palatal + ataxia	0 (0)	2 (1.5)	0 (0)	0 (0)	
Tachycardia ± Gallop	2 (22.2)	7 (5.1)	10 (8.3)	1 (8.3)	0.243
Bradycardia	0 (0)	16 (11.7)	22 (18.2)	1 (8.3)	0.245
Acute renal failure	1 (11.1)	16 (11.7)	20 (16.5)	0 (0)	0.349
Bleeding	0 (0)	8 (5.8)	13 (10.7)	1 (8.3)	0.618
Shock at admission	2 (22.2)	13 (9.5)	15 (12.4)	1 (8.3)	0.618
Airway compromise	7 (78.8)	73 (53.3)	60 (49.6)	4 (33.3)	0.219
Respiratory paralysis	0 (0)	15 (10.9)	8 (6.6)	0 (0)	0.303

Figures in parentheses depict % unless specified.

$p = 0.013$) and airway compromise (67.5% vs. 32.5%: $p = 0.000$). Conversely, those with longer duration of illness more than 14 days had respiratory paralysis more commonly than those with illness 14 days or less (67.6% vs. 32.4%: $p = 0.000$).

47.7% children in our series were of above 5 year of age. Similar age shift affecting children above 5 year have been reported by other authors.^{2,9,15} This indicates changing epidemiology of diphtheria and the lack of protective antibodies against diphtheria due to poor coverage with booster doses & declining immunity. Seasonal incidence of the disease between July to December was in accordance to earlier findings.³

The commonest complication observed in present study were airway compromise (144 patients, 51.6%) and neuropathy including palatal paresis (68 patients, 24.3%) followed by clinical carditis (59 patients, 21.2%). Jayshree et al.¹⁰ have also reported airway obstruction (70.8%) and myocarditis (66.7%) as the most common complications among 48 children admitted in intensive unit, however, Kadirova et al.¹⁶ mentioned myocarditis (121 patients, 22%) and neuritis (33 patients, 5%) as common complication in their series

which included adult patients also. Only 110 (76.4%) of patients in present series having airway obstruction demonstrated laryngeal membrane. The other possible mechanism for upper airway obstruction may be soft tissue oedema, extensive pharyngeal disease, bleeding into airway or paralytic closure of larynx.¹⁷ Tracheostomy is always preferable to procure patent airway in patients with upper airway obstruction as intubation may not be successful and can lead to dislodgement of fragile membrane causing further obstruction, bleeding and patient may succumbed during procedure as observed by us and others also.¹⁰ Serial ECGs from admission until a few days after convalescence have shown changes in as many as 84% of patients.¹⁸ However, clinically detectable myocarditis have been reported to occur in 16.5–27% cases, similar to ours (21.2%) and bradycardia was most frequently reported findings and carry poor prognosis.^{19,20} The clinical picture of carditis was characterized by cardiac failure in 18 patients, circulatory failure in 23, and 12 patients had sudden death possibly due to fatal cardiac arrhythmia in our series. Diphtheritic polyneuropathy is a dangerous late complication of diphtheria, especially its

Table 4 – Comparison of survived vs. expired (complications) – logistic regression analysis.

Complication	Survived n = 145	Expired n = 134	Adjusted Odd's ratio	95% CI for aAdjusted OR	p-Value
Airways compromise	41	103	21.71	9.73–48.44	0.000
Respiratory paralysis	3	20	57.72	13.66–243.82	0.000
Tachycardia + Gallop	9	11	0.67	0.17–2.59	0.561
Bradycardia	4	35	7.02	1.70–29.02	0.007
Acute renal failure	6	31	5.52	1.16–26.29	0.032
Bleeding	5	17	1.22	0.34–4.39	0.763
Shock at admission	4	27	2.93	0.83–10.27	0.093

severe form with bulbar, respiratory and circulatory disturbances resulting in aspiration, respiratory failure and shock. Mortality due to these forms of diphtheritic polyneuropathy surpassed 50% even in the specialized hospitals,¹⁷ also found in our study. Two of our patients had sensory ataxia, reported to occur in severe cases.¹⁷

Case fatality was 48% in our patients, similar to reports from different centres (32–56.3%) in north India.^{9,10,21} Higher case fatality in our patients may be attributed to more severe cases, late presentation with complications, delayed administration or non-availability of antitoxin, and lack of optimal facilities to manage the complications especially those with respiratory paralysis.

Decline in childhood immunization coverage appears to be main reason in facilitating disease spread. Immunization coverage in Uttar Pradesh as shown in NFHS-3 is only 44%.²² Vaccinated children found to suffer from mild disease and had less fatality. All 6 patients in our study who were completely immunized and who developed diphtheria, survived. The mortality was significantly higher ($p = 0.017$) in unimmunized than those who were either partially or fully immunized in present series, also observed by others.³ Thus there is urgent need to re-strengthen the immunization.

5. Conclusion

Diphtheria was equally prevalent in children of age group 1–5 yr and 5–10 yr, and reflects poor immunization coverage. Clinical diagnosis of diphtheria based on presence of typical membrane or palatal palsy in children with fever, throat symptoms/neck swelling may be useful for initiating prompt treatment. Occurrence of airway obstruction, respiratory paralysis, bradyarrhythmia, acute renal failure and shock are independent predictors of mortality.

Contribution

SN Singh conceptualized the study, analysed the data and finalized the manuscript. Anita Singh & Surabhi Chandra collected data, helped in analysis and manuscript writing.

Conflicts of interest

All authors have none to declare.

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