

Diphtheria: the patch remains

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Abstract

This study analysed the number of patients admitted with diphtheria to a teaching hospital in the state of Assam in India over a period of five years and compared the disease characteristics and management with outcomes and incidences of diphtheria reported in the literature. It was a retrospective analysis of data elicited from clinical records of patients admitted to hospital.

A total of 101 admissions were recorded during a five-year period between March 1997 to March 2002, mostly with pharyngeal diphtheria (90 per cent). The majority of patients had no history of immunization (70 per cent). Significant presenting features were a tonsillar patch, sore throat, respiratory distress and fever. All patients were treated with anti-diphtheritic serum and intravenous antibiotics. Steroids were given to 81 per cent of patients and tracheostomy was carried out in 10 per cent of cases. The mortality was 16 per cent.

Diphtheria of the respiratory tract remains a potentially fatal disease commonly presenting with membranous pharyngitis. Early diagnosis and treatment with anti-diphtheritic serum and antibiotics remain the cornerstone of treatment. Inadequate immunization cover is deemed responsible for the continued menace of diphtheria.

Key words: Diphtheria; Immunisation

Introduction

Diphtheria, a potentially life-threatening condition, has re-appeared over the past decade in parts of Europe and in the continents of Asia and Africa.¹ The causative organism, *Corynebacterium diphtheriae* is a Gram positive bacillus that produces exotoxins, which are responsible for the clinical effects of the disease.² In the pre-vaccination era, diphtheria was one of the leading causes of childhood deaths.¹ Unfortunately, immunization coverage remains very poor in developing countries. Outbreaks have been reported in India and elsewhere in the past decade.

For the purpose of the study, a case of diphtheria was defined as a patient with a sore throat and a pharyngeal membrane diagnosed as diphtheria by a physician or a patient with catarrhal symptoms (sore throat without a membrane and a culture positive for *C. diphtheriae*). The severity of diphtheria cases were defined according to WHO criteria. The form is determined by the extent of the membrane. The 'catarrhal' variety describes erythema of the pharynx without membrane but with culture positive for *C. diphtheriae*. The 'follicular' variety presents with patches of exudates over the pharynx and tonsils.

The 'spreading' variety describes a membrane covering the tonsils and posterior pharynx. In 'combined' cases there are usually two anatomical sites involved, i.e. throat and skin.³

The aim of this undertaking is to try and increase awareness of this disease which is undergoing a resurgence. This is especially important in today's world with ease of travel.

Methods

A retrospective study was conducted in a teaching hospital in the state of Assam in India of cases of diphtheria admitted between March 1997 to March 2002. Information pertaining to the age, sex, immunization status, clinical features at presentation, length of hospital stay and the outcome of treatment was obtained from the clinical records.

These cases were reviewed in an effort to establish the prevalence of the disease, methods of treatment and outcome. We also attempted to compare the incidence of this disease in this remote part of the world with the incidence reported elsewhere in the country and abroad.

Data gathered were analysed by using simple statistical methods.

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TABLE I
CLINICAL DETAILS

Prior vaccination	Yes	No
Immunization status	70%	30%
Pseudomembrane	38%	62%
Microbiology-positive	65%	35%

Results

There were 101 cases of diphtheria admitted to the hospital in the five-year period between March 1997 and March 2002. All these patients met inclusion criteria for the study. The medical records were analysed retrospectively.

There were 46 female patients. Only 30 per cent of the patients had prior vaccination as shown in Table I. Patients less than five years old were 41 per cent of the cases in our study. Children between the ages of six and 10 constituted 30 per cent and 12 per cent of patients were between 11 and 15 years old. Those over 15 years of age made up the remaining 18 per cent.

Fever and sore throat were the most common complaints, 84 per cent and 30 per cent respectively. A tonsillar patch was noted in 38 per cent of the cases as shown in Figure 1. Sixty-five per cent of cases were microbiologically confirmed cases of *C. diphtheriae*.

Most patients had pharyngeal or faucial diphtheria (90 per cent), five per cent had laryngeal diphtheria and five per cent had nasal diphtheria, as shown in Figure 2.

Every patient received anti-diphtheritic serum, between 20 000 to 100 000 units intravenously, depending on clinical severity. Intravenous antibiotics (i.v. penicillin usually and erythromycin in patients allergic to penicillin) were routinely administered. Dexamethasone was administered in 81 per cent of patients in order to reduce inflammation and the toxicity of the disease.

Of 101 patients admitted with diphtheria 75 per cent of the patients recovered and were discharged. Patients who left the hospital with some residual complaints constituted five per cent. Four per cent of patients left hospital against medical advice. The

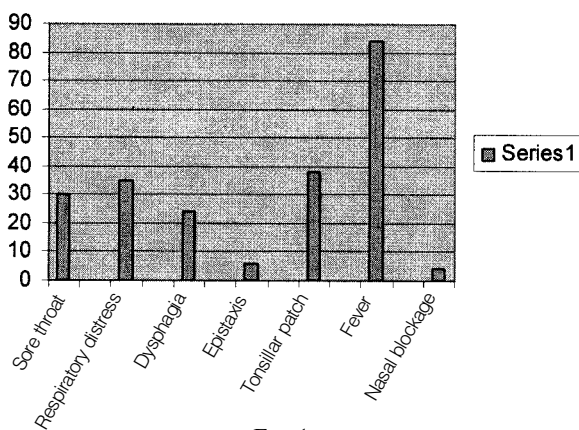


FIG. 1
Clinical presentations.

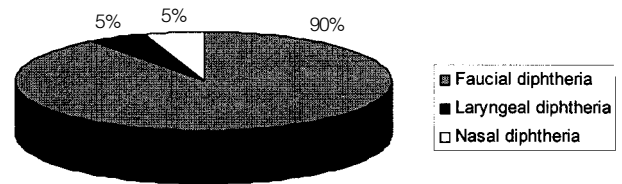


FIG. 2
Types of diphtheria.

mortality was 16 per cent. Six patients died within 24 hours of admission. Most of the deaths occurred in patients less than four years of age. The cause of death was noted as respiratory failure. Cardiac failure due to myocarditis was also noted.

Discussion

Diphtheria is an acute communicable disease produced by a Gram positive exotoxin producing bacillus, *Corynebacterium diphtheriae*. It usually localizes in the upper respiratory tract causing ulceration of the mucosa followed by formation of an inflammatory pseudomembrane.

The toxin released is absorbed into the circulation subsequently causing other organ damage and ultimately death. It is usually transmitted by direct contact or droplets.⁴ Non-immune children below the age of five are commonly affected.⁵

With the introduction of immunization, the disease has been completely eradicated from certain western countries. Only 41 cases were reported in the United States during 1980 and 1985.⁶ With the advent of immunization, the demography has shifted to the adult population.^{7,8} The vaccine against diphtheria is given at the second, third and four months, four to five years and 15 to 18 years of age (National Immunisation Schedule).⁹ To detect the presence of active antibodies to diphtheria blood samples can be tested for serum antitoxin levels (a level of >0.1 IU/ml is accepted as adequate).¹⁰

The diphtheria toxin is the primary virulence factor and studies have shown that the toxin is highly conserved at the amino acid level indicating that the diphtheria toxoid used for immunization is both specific to *C. diphtheriae* and highly effective.¹¹ The developing world is yet to achieve full immunization cover of the population and this has translated into the disease being reported in high numbers. As the number of immunized children is very small in this part of the developing world as shown in our series (un-immunized 70 per cent in our cohort), the disease is very common in both children and young adults.⁷

There are also reports of the resurgence of diphtheria in both developed and developing countries such as the former states of the Soviet Union.¹² The incidence of diphtheria probably is on a slight decline in India with only 1336 cases being reported in 1997.¹³ The figures quoted may possibly be a gross underestimate because of the lack of a good surveillance system.

A recent series of 606 cases over a period of five years (1989 to 1993) was reported from the state of West Bengal where most of the diagnoses were clinical with only seven per cent cases being confirmed microbiologically.¹⁴ Disparity in the reported incidence of the disease in various parts of India has been attributed to variability in the rate of immunization and equally important, lack of uniform recording and reporting procedures. As Singhal *et al.* reported in the *Indian Paediatric Journal*, the percentage coverage with three doses of the 'triple vaccine' of DPT (diphtheria pertussis and tetanus) varied between 27 to 88.5 per cent in different states of the country.¹² The survey also reported a significant drop-out rate between the administration of the first and second doses of the DPT vaccine of 22 per cent. Details of booster doses DPT vaccines were not available.¹⁵⁻¹⁷

The data thus presented is very heterogenous but allows some general conclusions:

- (1) Vaccine coverage varies widely throughout the country with significant urban and rural differences.
- (2) There are some independent surveys, which estimate coverage to be significantly lower than official claims. This is also shown in our study (immunization coverage of only 30 per cent).
- (3) There is a significant drop out rate between the administration of the first and second doses of DPT.
- (4) Administration of booster doses of the vaccine in those previously vaccinated was extremely low.

Reasons for poor immunization coverage in India are: a short supply of vaccines, poor logistical organization, poor screening facilities and postponing vaccination because of minor childhood illnesses.^{18,19} This is also compounded by widespread illiteracy and low awareness about the utility of vaccination and vaccine preventable diseases.^{18,19} Other factors are ignorance about the total doses required, improper or absent counselling, vaccine side-effects and migration of families. Therefore we can emphasize the fact that there is an urgent requirement for resources to address the issue of proper immunization cover in countries such as India in order to increase the herd immunity of the population and prevent outbreaks of the disease.

Herd immunity in populations with good immunization cover has prevented outbreaks of the disease. A need for routine immunization of adults in these populations (as in the former Soviet Union) is debated.²⁰ However, if there is a drop in childhood immunization an epidemic may be triggered as was seen in the newly independent states of the former Soviet Union (This epidemic began in the Russian Federation at the end of the 1980s and affected 15 newly independent states of the former Soviet Union by the end of 1994. The states most severely involved were Belarus, Russia, Ukraine and the Baltic states of Estonia, Latvia and Lithuania). Therefore routine immunization of adults with low strength booster

doses is considered appropriate by many people.²¹ This applies to individuals previously immunized who need to have a booster dose at 10 year intervals. Immunity in adults is thought to be maintained by the use of Td vaccine (diphtheria toxoid with tetanus toxoid) or 'd' vaccine (an adult type monovalent diphtheria toxoid for persons with a high immunity against tetanus).²¹

In our study we analysed all the cases of diphtheria hospitalized in a teaching institute in eastern India over a period of five years. Data collected shows that children as well as young adults were affected, with one case being reported in a person of 33 years age. This indicates a lack of herd immunity in the population. The sex difference was not as marked as that reported in the Russian federation.²

The clinical characteristics of diphtheria among the hospitalized patients in our study reflect a larger incidence of the catarrhal form (without membrane) – 62 per cent. In our study 38 per cent of patients were found to have a pseudomembrane. We consider a pharyngeal membrane that is difficult to peel off and leaves a bleeding area on the mucous membrane after an attempt to remove it pathognomic for diphtheria. However, it is of course not exclusive to diphtheria and equally, diphtheria can also manifest as an ulcer in the oropharyngeal mucosa. There were a few cases of laryngeal diphtheria in our study (five per cent). Another five per cent had nasal involvement and the remainder of cases in our study had pharyngeal diphtheria.

An interesting shift in the age distribution of the disease is noted with 18 per cent of patients seen in the age group of 15 or more (there being also an adult male of 33 years age). Lack of herd immunity in the population studied with no evidence of booster vaccination doses are thought to be responsible for the disease occurring in adolescents and young adults.⁹

All patients were treated with anti-diphtheritic serum as recommended by WHO and UNICEF.¹⁹ The most commonly administered antibiotics were penicillin or erythromycin following recommendations of the WHO and UNICEF.^{22,23}

Every patient in our study had a throat swab taken and 65 per cent of patients had microbiologically-confirmed disease.

There was 16 per cent mortality in our study. This is comparable to other studies in the literature i.e. three to 23 per cent.²⁴ Only three patients who died were recorded to have had a full course of immunization and their deaths can be deemed to have been due to immunization failure. This observation suggests that complete vaccination is essential in preventing fatalities. Our study shows that the clinical features of the disease amongst the unvaccinated patients were similar to those observed and reported in the pre-vaccination era. Despite the shift to an older age group among diphtheria patients, this remains a potentially fatal disease with patients presenting with sore throat and respiratory distress.

- **Five year analysis of 101 patients admitted with diphtheria to a teaching hospital in Assam, India**
- **Ninety per cent had pharyngeal diphtheria. The majority (70 per cent) had no history of immunization**
- **Presenting features included tonsillar patch, sore throat, respiratory distress and fever**
- **All patients were treated with antidiphtheritic serum and intravenous antibiotics. Steroids were given to 81 per cent and a tracheostomy was carried out in 10 per cent of cases. The mortality was 16 per cent**
- **Diphtheria remains a potentially fatal disease commonly presenting with membranous pharyngitis. Early treatment with antidiphtheritic serum and antibiotics remain the cornerstone of treatment. Inadequate immunization cover results in the persistence of diphtheria**

Conclusion

Based on our study and a review of the literature, the immunization coverage against diphtheria is far from satisfactory in India. Therefore serious efforts have to be made to increase immunization coverage and good surveillance systems ought to be put into place to enable optimum reporting of disease.

There remains a risk of the disease being introduced into areas of the world where it is now non-existent by the simple method of a carrier of the bacillus travelling long distances.

Age appropriate immunization, early diagnosis, full treatment of cases with anti-diphtheritic serum and antibiotics (penicillin or erythromycin), and chemoprophylaxis of close contacts of cases remain the cornerstones of effective prevention and treatment.

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References

- 1 Vitek CR, Wharton M. Diphtheria in the former Soviet Union: re-emergence of pandemic disease. *Emerg Infect Dis* 1998;**4**:539–50
- 2 Zamiri I. Corynebacterium. In: Colles JG, Fraser AG, Marmion DP, Simmonds A, eds. *Practical Medical Microbiology*, 14th edn. Edinburgh: Churchill Livingstone, 1996:299–308
- 3 Kadirova R, Kartoglu HU, Strebel PM. Clinical characteristics and management of 676 hospitalized diphtheria cases, Kirgыз Republic, 1995. *J Infectious Dis* **181**:S110–S115
- 4 Hadfield TL, Mcevoy P, Polotsky Y, Vsevolod A, Yakovlev AA. The pathology of diphtheria. *J Infect Dis* **181**:S116–S120
- 5 Robins SL. Infectious diseases. In: *The Pathologic Basis of Disease*. Philadelphia: W.B. Saunders, 1974:390–2
- 6 Vitek CR, Wenger J. Diphtheria. *Bull WHO* 1998;**76**(suppl. 2):129–30
- 7 Galazcka AM, Robertson SE. Diphtheria: changing patterns in the developing world and the industrialized world. *Eur J Epidemiol* 1995;**11**:107–17
- 8 Eskola J, Lumio J, Vuopio-Varkila J. Resurgent diphtheria – are we safe? *Br Med Bull* 1998;**54**:635–45
- 9 Collier J, Longmore M, Scally P. *Oxford Handbook of Clinical Specialities*. Oxford: Oxford University Press, 6th edn, 2003
- 10 Khetsuriani N, Music S, Deforest A, Sutter RW. Evaluation of a single dose of Diphtheria toxoid among adults in the Republic of Georgia, 1995: Immunogenicity and Adverse Reactions. *J Inf Dis* 2000;**181**(suppl 1):S208–12
- 11 Popovic T, Mazurova IK, Efstoration A, Vuopio-Varkila J, Reeves MW, De Zoysa A. *et al.* Molecular epidemiology of Diphtheria. *J Inf Dis* 2000;**181**(suppl 1):S168–77
- 12 Singhal T, Lodha R, Kapil A, Jain Y, Kabra S. Diphtheria – down but not out. *Indian Pediatr* 2000;**37**:728–38
- 13 World Health Organization. Immunization profile – India. Information accessed from WHO website. http://www.who.int/vaccines-surveillance/WHOUNICEF_Coverage_Review/
- 14 Ray SR, Gupta SD, Shaha I. A report of diphtheria surveillance from a rural medical college. *J Indian Med Assoc* 1998;**96**:236–8
- 15 Department of Family Welfare. Annual Report 1998-1999. New Delhi. Ministry of Health and Family Welfare, Govt of India, 1999:63–71
- 16 Mukherjee B, Kar M, Biswas R. Coverage evaluation surveys amongst children in some blocks of West Bengal. *Indian J Public Health* 1990;**34**:209–14
- 17 Singh MC, Singh MP. Immunization coverage and knowledge and practice of mothers regarding immunization in rural India. *Indian J Public Health* 1994;**38**:103–7
- 18 Singh J, Ichchujani RL, Prabha S, Chandra R, Khare S, Pande RC. Immunity to Diphtheria in women of child bearing age in Delhi 1994: evidence of continued *C. diphtheriae* circulation. *South East Asian J Trop Med Public Health* 1996;**27**:274–8
- 19 Ichchujani RL, Grover SS, Joshi PR, Kumar S, Varghese T. Prevalence of diphtheria and tetanus antibodies in young adults in Delhi. *J Communicable Dis* 1993;**25**:27–9
- 20 Prospero E, Raffo M, Bagnok M, Appignanesi R, D'Errico MM. Diphtheria: Epidemiological update and review of prevention and control strategies. *Eur J Epidemiol* 1997;**13**:527–34
- 21 Galazka AM, Robertson SE. Immunization against diphtheria with special emphasis on immunization of adults. *Vaccine* 1996;**14**:845–57
- 22 Begg N. Diphtheria: manual for the management and control of Diphtheria in the European Region, Copenhagen: World Health Organization, 1994; WHO ICP/EPI 038 (B)
- 23 Fazio KM, Strebel PM, Chen RT, Kimbler A, Cleary TJ, Cochi SL. Fatal respiratory disease due to *C. diphtheriae*: a case report and review of guidelines for management, investigation and control. *Clin Infect Dis* 1993;**16**:59–68
- 24 Hardy IRB, Dittmann S, Sutter RW. Current situation and control strategies for the resurgence of diphtheria among school children in the Russian Federation in relation to time since last vaccination. *Lancet* 1999;**353**:355–8

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