CASE REPORT

Respiratory Diphtheria in Three Paediatric Patients

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Summary

From August till November 1998, the Paediatric and Anaesthetic Units of Hospital Kuala Terengganu managed three patients from Kuala Terengganu District who were ventilated for respiratory diphtheria. Their ages were 5, 4 and 7 years old and their immunisation for diphtheria were not complete. All three patients presented with respiratory distress and were ventilated for upper airway obstruction. Their treatment included intravenous penicillin and diphtheria antitoxin. One patient died of cardiogenic shock with secondary pneumonia. Pharyngeal and tonsillar swabs of all three patients grew toxigenic *Corynebacterium diphtheriae* biotype mitis. There were 765 throat cultures taken from contacts. The confirmed positive cultures grew 2 toxigenic and 3 non-toxigenic *Corynebacterium diphtheriae* biotype mitis and surprisingly, 10 non-toxigenic biotype gravis. A prevalence study is needed to document the endemicity of diphtheria in Kuala Terengganu and to determine the carrier rate of both biotypes. Steps have been taken to increase the immunisation coverage in children. The giving of regular booster doses of diphtheria toxoid to the adult population should be considered.

Key Words: Diphtheria, Upper airway obstruction, Ventilation, Paediatric patients, Contacts

Introduction

Diphtheria has been known to affect human beings for more than a hundred years. The introduction of diphtheria vaccination in the past fifty years has greatly reduced its incidence. Nevertheless, the disease has re-emerged recently as epidemics in the independent states of former Russia[1] from 1990 to 1995 and in Thailand[2] in 1994. Vaccination against diphtheria was introduced in Malaysia in the 1960's. The last significant diphtheria outbreaks in Malaysia[3] occurred in isolated unimmunised communities in Klang and Kuala Terengganu in 1988 and 1989. The incidence rate of reported diphtheria cases in Malaysia was less than 0.2 per 100,000 population since 1992. There were two last reported cases in Terengganu in 1990 and no reported case of diphtheria in Peninsular Malaysia from 1994 to 1997. However, we have recently managed three children with diphtheria who required artificial ventilation. Steps must be taken to contain the spread of this infection through the intensification of vaccination.

Patient Report

Case No. 1

Patient A.H. was a 4-year 9-month old boy who presented in August 1998 with a history of noisy breathing of two days' duration and severe breathlessness on the day of admission. His fever was said to be mild. He was not immunised for diphtheria before. On admission, he was drowsy but was still able to obey simple commands. Central cyanosis was present. His respiratory rate was 50 per minute with presence of

intercostal and subcostal recession. Air-entry over both lungs was markedly reduced. His perfusion was normal. The provisional diagnosis was acute epiglottitis. Laryngoscopic examination under general anaesthesia done three hours after admission revealed white plagues over both tonsils and an inflammed pharygeal wall. The epiglottis, supraglottis and vocal cords were normal. He required mechanical ventilation and was started on intravenous ampicillin. Chest radiograph revealed pneumonic opacities in right upper and left mid-zones.

On the fourth day of admission, the tonsil swab taken at admission grew *Corynebacterium diphtheriae*. A re-examination of his throat showed white membrane over both tonsils. His antibiotic was changed to intravenous penicillin and intravenous diphtheria antitoxin was given. His progress was satisfactory and he was ventilated for a total of eight days. Post-extubation chest radiograph showed mild secondary pneumonia.

With regards to his heart, his heart rate increased to 160 per minute on third day of admission. He was afebrile then. The serum lactate dehydrogenase LDH peaked at 1169u/L (normal range 240 to 480u/L) on third day of admission. He had muscle weakness and was only able to sit up at day 11 and walked at day 14 of admission. EMG and nerve conduction tests were not done. He was discharged home on day 22 of admission.

The throat swabs taken on admission and three days later grew *Corynebacterium diphtheriae* (identified by morphology and carbohydrate fermentation tests). This was confirmed and biotyped as mitis by Microbiology Division of Institute Medical Research, Kuala Lumpur and was toxigenic by the Elek test (toxin-antitoxin precipitation assay). Throat swabs were taken from 624 contacts and the results were as shown in Table II. The positive cultures were biotypes mitis and gravis. The age range of these 13 positive-culture contacts was 10

Table I
Comparison of the Three Ventilated Paediatric Patients

Features	Case 1	Case 2 (died)	Case 3
Age	4 years 9 months	3 years 10 months	6 years 9 months
Presenting Complaints	Noisy breathing 2d breathlessness 1d	breathlessness 3d	breathlessness 3d
Immunisation for Diphtheria	none	none	3 doses, primary series
Temperature on Admission	37.8°C	37.8°C	37.0°C
Site of Diphtheria	tonsillar	'bull-neck'	tonsillo-pharyngeal
Total white/mm^3 on Admission	23,200	24,100	11,500
Neutrophil %	87	82	78
Lymphocyte %	10	15	18
Diphtheria Antitoxin Dose	60,000u	150,000u	60,000u
Ventilation			
Instituted	3 hours after admission	on admission	on admission
Duration	8 days	17 days	12 days
Complications			
Secondary Pneumonia	Yes	Yes	Yes
Myocarditis	Yes	Yes	Yes
Muscle Weakness	Yes	Yes	Yes

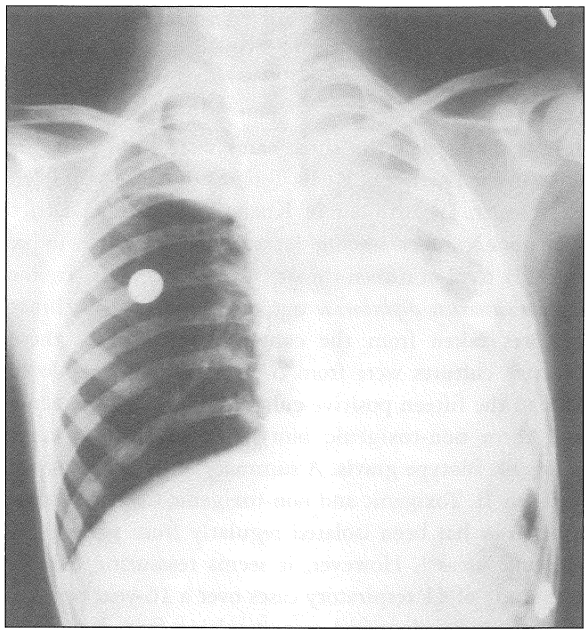

Figure 1: CXR of case 2 on admission.

months to 15 years and the average age was 7.2 years. All culture positive contacts were asymptomatic and they were isolated and given ten days of oral erythromycin together with DPT vaccination. They were discharged home when two throat cultures were negative for diphtheria.

Case No. 2

Patient A.A. was a 3-year 10-month old girl who presented in October 1998 with a history of fever and breathlessness for three days. There was hoarseness of voice for two days and poor oral intake. She did not receive any diphtheria-pertussis-tetanus DPT vaccination before. On admission, she was in severe respiratory distress, pale, cyanosed and restless. The respiratory rate was 40 per minute. Stridor was present with intercostal and subcostal recession. There was absent breath sounds bilaterally. The heart rate was 160 per minute and capillary refill was delayed more than two seconds. During intubation, white membrane was seen at the post-pharyngeal wall and soft palate. There was significant bilateral cervical lymphadenopathy resembling 'bull-neck diphtheria'. Chest radiograph showed collapse consolidation of the left lung and right upper lobe (Fig. 1). She was started on intravenous penicillin and diphtheria antitoxin.

There was evidence of myocarditis with persistent tachycardia of 150 to 160 per minute upto fifth day of admission with a peak serum LDH of 2047u/L on day 14 of admission. Pancuronium and midazolam infusion were stopped on 14th and 15th day of admission respectively. She was on endotracheal CPAP (continuous positive airway pressure) on the 18th day of admission. She looked alert and could follow simple instructions. She could open her mouth slightly and moved her fingers on command. However, there was no movement of her shoulders, elbows and whole of lower limbs and there was hardly any chest rise on inspiration. Her reflexes were diminished with down-going Babinski and these signs were suggestive of lower motor neuron weakness. This was followed by desaturation and cardiorespiratory failure 10 hours later and she was put back on positive pressure ventilation. The repeat chest radiograph showed severe lung infection. She finally succumbed to cardiogenic shock with third degree heart block on day 19 of admission.

The slough from membrane taken on admission grew *Corynebacterium diphtheriae* and this was confirmed as toxigenic biotype mitis. Throat swabs of 122 contacts were taken and the results are as shown in Table II. The two positive-culture contacts were 4 and 11 years old and their management was as described in case 1.

Case No. 3

Patient W.A. was a 6-year 9-month old boy who presented in November 1998 with breathlessness, cough and poor oral intake for three days. He had noisy breathing and poor oral intake one day prior to admission. He had completed his primary series of three DPT vaccination in infancy. On examination, he was in respiratory distress with intercostal and subcostal recession. Air-entry on both lungs was diminished. He had normal perfusion. White membrane was present in posterior pharyngeal wall with no membrane over the enlarged tonsils. The impression was upper airway obstruction due to diphtheria. He was ventilated within one hour of admission. Chest radiograph showed mild haziness over left lower zone. He was started on intravenous penicillin and diphtheria antitoxin.

There was evidence of myocarditis on day 7 of admission. He developed pulseless supraventricular tachycardia requiring four doses of synchronised

cardioversion and finally responded to intravenous adenosine. His highest serum LDH was 1228u/L on the fifth day of admission.

He had a generalised tonic-clonic convulsion of uncertain origin on the day 11 of admission. He self-extubated while on low ventilator settings on the following day. Chest radiograph revealed secondary pneumonic patches and cefotaxime was continued. He was able to walk unaided twenty days after admission and was discharged home.

Culture from the slough of his throat membrane on admission grew *Corynebacterium diphtheriae* which was confirmed as toxigenic biotype mitis. Contact tracing was done and all nineteen throat cultures was negative for diphtheria.

Discussion

During the 4-month period from August to November 1998, three very ill patients presented with upper airway obstruction due to respiratory diphtheria. They required mechanical ventilation almost immediately after admission. The tonsillar and pharyngeal membrane due to diphtheria was characteristic although the diagnosis of the first patient was delayed for 4 days due to lack of awareness of the disease. One death was due to cardiogenic shock with secondary pneumonia. The pathogen responsible for all three cases was toxigenic *Corynebacterium diphtheriae* biotype mitis. A summary of the clinical presentation of the three cases is shown in Table I. A previous lack of awareness of this disease might have resulted in 'missed' cases in the past presenting as pneumonia or even sequelae of motor weakness or cardiomyopathy.

It was noted that the three cases were from different areas in the District of Kuala Terengganu. The staff from the Health Department of Kuala Terengganu District had done contact tracing for each of the three index cases. A total of fifteen throat cultures were positive for *Corynebacterium diphtheriae* out of a total of 765 throat cultures taken from the contacts. Thirteen of these positive cultures were from contacts of case one alone. Out of the fifteen positive cultures, two were toxigenic and three non-toxigenic biotype mitis and ten non-toxigenic biotype gravis. A summary of results is shown in Table II. Toxigenic and non-toxigenic *Corynebacterium diphtheriae* has been isolated regularly from patients in endemic areas[4,5]. However, it seems reassuring that in one study of 41 respiratory cases over a 16-year period[4], there were no identified cases resulting from secondary transmission.

The possible causes of the occurrence[1,2,4,6,7] of these three serious cases included the importation of cases due to population movement across national boundaries. Secondly, the coverage of immunisation of children in the community may not be adequate. The third reason could be the lack of immunity in the adult population as the second and final booster of diphtheria vaccination in Malaysia is given at 7 years of age. This could result in the occurrence of asymptomatic carriers who are important in disease transmission to susceptible unimmunised children.

Table II
Summary of Positive Cultures from Contacts of the Three Index Cases with Toxigenic *Corynebacterium Diphtheriae* Biotype Mitis

Index Case Number	Number of Contacts Swabbed	POSITIVE CULTURES			
		Toxigenic Mitis	Non-toxigenic Mitis	Non-toxigenic Gravis	Total
1	624	1	3	9	13
2	122	1	0	1	2
3	19	0	0	0	0
Total	765	2	3	10	15

In the outbreak in Saraburi, Thailand[2] in 1994 it was found that the carriage rates among household and school contacts were 4% and 8% respectively. Carriers may harbour the organism on the throat as well as on skin sores[4,5,6]. A cross-sectional prevalence study of throat and skin sores cultures for *Corynebacterium diphtheriae* could be done to determine the carrier rate. Toxigenic and non-toxigenic strains of diphtheria of biotypes mitis and gravis are possibly endemic in Kuala Terengganu district. If this is so, then booster doses of vaccination with a lower dose of diphtheria toxoid (as in the Td preparation) should perhaps be recommended every ten years to the adult population[4,7]. Even though immunisation does not necessarily prevent asymptomatic carriage of the organism[6], it does protect against both severe disease and death[4]. Control strategies recommended by WHO in countries with high incidence rates included mass immunisation rates[7] to achieve an uptake of 95% in children and 90% in adults.

Even if the children of a country are highly immunised, the population could still be at risk of carriage and infection[7] with non-toxigenic *Corynebacterium diphtheriae* from imported cases or carriers. This is the result of previous success in eradicating the organism from the community through high coverage vaccination during childhood. Thus the large majority of adult population would be unprotected in the absence of regular booster doses of diphtheria vaccination.

Therefore eradicating the disease from the community depends on improving the socio-economic status of the community, high coverage of immunisation during childhood, and most probably regular booster doses for the adult population.

Conclusion

Three cases of respiratory diphtheria occurred over a 4-month period in 1998 in Kuala Terengganu District. They presented with upper airway obstruction and secondary pneumonia requiring artificial ventilation. Two of them did not have vaccination against diphtheria while the remaining one completed only the primary series. Cultures taken from the tonsillo-pharyngeal membrane of the three cases grew toxigenic *Corynebacterium diphtheriae* biotype mitis. Throat culture of contacts revealed a mixture of biotypes mitis and gravis. Reasons for this outbreak included the strong possibility of endemicity of diphtheria, inadequate coverage of immunisation in children and lack of immunity in the adult population. Immediate actions need to be taken including the intensification of vaccination in children and adult population in order to stop the spread of this disease.

Acknowledgement

We wish to thank the Director-General of Health for permission to publish this paper. Special thanks to Director of Health, Terengganu and the Microbiology Division of Institute of Medical Research, Kuala Lumpur.

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