A Case Of Fatal Diphtheria In A Paediatric Patient

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Citation

Z Z Rashid, N A Mohamed, T S Fong. *A Case Of Fatal Diphtheria In A Paediatric Patient*. The Internet Journal of Microbiology. 2016 Volume 14 Number 1.

DOI: 10.5580/IJMB.32981

Abstract

The introduction of diphtheria immunisation into the Expanded Program of Immunisation in the 1970s has markedly reduced the incidence of diphtheria diseases. We report a case of fatal diphtheria in a 2 year-old girl whose immunisation status was not known. She had presented with acute exudative tonsillitis and was treated with intravenous amoxicillin-clavulanate but showed progressive signs of upper airway obstruction; stridor, drooling of saliva and bull-neck appearance, with bilateral facial swelling around the parotid region that extended to submental and submandibular regions. Initial cultures from blood, throat, nasal and oral cavity revealed no significant organisms. Corynebacterium diphtheriae subspecies gravis which was resistant to penicillin, was isolated from pus specimen a day after her demise. Clinical suspicion is important to aid diagnosis, microbiological confirmation and management of diphtheria, as the disease is rare in the era of successful immunisation programs. Microbiological vigilance plays an important role in early detection of infection as well as outbreaks. Early institution of diphtheria antitoxin may save lives, while delay in diagnosis may increase mortality and the risk of transmission. This case reaffirms the vital role of immunisation and the importance of efforts to ensure a high uptake of the scheduled immunisations.

INTRODUCTION

The introduction of diphtheria immunisation into the World Health Organisation (WHO) Expanded Program of Immunisation (EPI) in 1970s, and Malaysia in 1980s, has markedly reduced the incidence of diphtheria diseases. There were 345 cases in Malaysia from 1980-1989, 42 in 1990-1999, 30 in 2000-2009, 3 in 2010, 4 in 2013 and 2 in 2014 (WHO 2015a). We report a probable imported case of fatal diphtheria in a 2 year-old girl in 2010, with doubtful immunisation history.

CASE REPORT

A previously well 2 year-old Malaysian-Siamese girl was brought to the emergency department with 3 days' history of fever, vomiting, runny nose and poor appetite. The fever was intermittent and relieved by antipyretics. There was no cough, seizure, abdominal symptom, jaundice, altered bowel habit or bleeding tendencies. Her antenatal period was uneventful. She was born at term via normal delivery at Kuala Lumpur Hospital with a birth weight of 3.2 kg. Her milestones were normal. She spent her first year of life in Narathiwat, Thailand with her mother and maternal grandmother and moved back to Kuala Lumpur a year ago, but returned regularly to visit their village in Thailand. Immunisation was claimed to be complete, but no documentation was available. She had a younger brother. Her mother was a housewife and her father a police officer. No other family members were sick recently.

On admission, her temperature was 39.8°C, with moderate dehydration. Her blood pressure was 97/45 mmHg and pulse was 170 beats/minute. She had bilateral grade III to IV tonsils with exudates, palatal petechiae and shotty cervical lymph nodes. Respiratory, cardiovascular and abdominal system examinations were unremarkable. Her total leucocyte count was 12.4 x 109/L, with normal haemoglobin and platelet counts. C-reactive protein was high at 7.66 mg/dL.

She was treated as acute exudative tonsillitis with intravenous amoxicillin-clavulanate. On the third day, she developed soft stridor, drooling of saliva and bull-neck appearance, with bilateral facial swelling around parotid region that extended to submental and submandibular regions. The surrounding tissue at oropharyngeal area was unhealthy with slough, which further compromised her upper airway. CT scan of the neck showed inflammatory changes of the tonsils, adenoids and pharyngeal mucosa with cervical lymphadenopathy causing airway compression. She was diagnosed as acute bacterial tonsillitis with bilateral

submental and submandibular cellulitis, and was transferred to the paediatric intensive care unit.

On the fifth day, friable slough areas bled. Full blood count showed increasing leucocytes with thrombocytopenia. Two units of platelet were transfused and amoxicillin-clavulanate was changed to ceftriaxone. She was intubated and direct laryngoscopy and nasoendoscopy were done. There was bilateral slough over the soft palate and tonsils extending posteriorly to the pyriform fossa, post cricoid areas and epiglottis, and anteriorly to the nasal cavities and nasopharynx. The slough peeled off easily revealing fairly normal mucosa with some ulceration of the soft palate. Her haemoglobin dropped to 8.1 g/dl, thus packed cells were transfused. Intravenous metronidazole was added. On day 6 she had haematuria, impaired renal function and oliguria. The next day, fresh bleeding recurred from oral and nasal cavity with blood-stained secretion from the endotracheal tube. She became tachycardic and hypotensive despite fluid resuscitation. No arrhythmias were noted. Otorhinolaryngology examination revealed bleeding from raw areas of her soft palate and tonsils that was controlled with gelaticel packing. Despite intensive support, her condition worsened and she passed away the same day.

Initial cultures from blood, throat, nasal and oral cavity revealed no significant organisms. Throat swab (pus) specimen sent on the day she died revealed pure growth of blackish colonies on cystine-tellurite agar, identified as Corynebacterium diphtheriae subsp gravis by API® Coryne (bioMerieux, France) identification system. The organism was sensitive to ciprofloxacin, erythromycin, gentamycin and vancomycin and resistant to penicillin and piperacillin. Unfortunately, the results were only available after her demise. Further test to establish toxigenicity of the strain was not available.

Public health officers visited the family when notified of the diagnosis of diphtheria. The mother, who had just returned from her village in Thailand, informed them that there had been several fatal cases of diphtheria in the village recently and mass immunisation of the villagers had been carried out.

DISCUSSION

Corynebacterium diphtheriae (C. diphtheriae) is a gram-positive bacillus that exists in 4 biotypes (gravis, mitis, belfanti and intermedius). Severe disease is associated with the gravis biotype, but any strain may produce toxin. The major virulent factor of C. diphtheriae is a potent exotoxin that inhibits protein synthesis. Clinically, an illness characterised by laryngitis, pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose plus laboratory isolation of C. diphtheriae by culture is required to confirm diphtheria. A clinically suspected case linked epidemiologically to a laboratory confirmed case may also confirm the diagnosis (WHO 2003). Overall case-fatality rate for diphtheria is 5%–10%, with higher death rates of up to 20% among persons younger than 5 and older than 40 years of age (Atkinson et al, 2007).

For C. diphtheriae isolation, swab specimens should be obtained from multiple, inflammed areas of oropharnyx, nasopharynx or cutaneous lesion, and in the presence of pseudomembrane, from beneath the membrane (Winn et al, 2006). Gram stain may show gram-positive rods that mimic Chinese characters. Most labs in non-endemic countries only screen for the organism, such as using a cystine-tellurite agar, upon request or with clinical indication. Gram stain is not a routine procedure for throat swab specimens in our laboratory, where only blood agar plate is inoculated for detection of hemolytic streptococcus. Other organisms including other corynebacterium species or ‘diphtheroids’ are considered as ‘normal mouth flora’. The presence of C. diphtheriae in the initial throat swab specimen might have been missed.

C. diphtheriae colonies appear small, greyish, smooth and non-haemolytic on blood agar. It grows on various selective media, including cystine-tellurite, modified Tinsdale or Loeffler medium. On modified Tinsdale medium, it produces black colonies surrounded by brown haloes (Winn et al, 2006). It is catalase positive, ferment glucose and maltose but not sucrose. Once diphtheria is suspected, toxigenicity test should be done. Traditionally, toxigenicity is determined by gel–diffusion immunoprecipitation reaction (Elek test). Other methods include enzyme immunoassays and nucleic acid amplification for detection of the regulatory gene for toxin production (dtxR) and diphtheria toxin gene (tox). None of the tests were readily available in Malaysia.

Clinical diagnosis of diphtheria is a matter of urgency. A suspected patient should be isolated to minimize the risk of toxigenic strain spread. Close monitoring and airway management are mandatory in severe cases. Prompt antibiotic therapy with penicillin or erythromycin eradicates the organism and hastens recovery. Early administration of diphtheria antitoxin, the cornerstone of diphtheria therapy (CDC 2012) neutralizes the exotoxin before it is bound by the host cell. Once the cell internalises the toxin, cell death is

imminent. The organism isolated in this case was resistant to penicillin and as the results were only obtained after her demise, no antitoxin was administered. Apart from the management of the index case, other measures including risk assessment, investigations, identification and management of contacts are required to reduce the risk of exposure to other individuals (Bonnet and Begg, 1999). The disease is usually not contagious 48 hours after antibiotic therapy is instituted. Elimination of the organism is documented by two consecutive negative cultures 24 hours after therapy is completed, and at least 24 hours apart. Index case and contacts should be immunised depending on age and immunisation history. Booster dose should be given if none was received in the past 12 months. If the strain is non-toxigenic, investigation of contacts can be discontinued (Atkinson et al, 2007). This case appeared to have occured following the outbreak in Narathiwat Province in Thailand in 2010 (Ministry of Public Health Thailand, 2012), where during that year a total of 77 cases were reported in the country (WHO 2015b).

Diphtheria vaccines are based on diphtheria toxoid, a modified bacterial toxin that induces protective antitoxin. Diphtheria toxoid combined with tetanus and pertussis vaccines (DTwP) has been part of the WHO EPI since its inception in 1974. Currently, the Malaysian EPI recommends 3 intramuscular doses of DPT (diphtheria toxoid, acellular pertussis vaccine and tetanus toxoid) for all children at 2, 3 and 5 months of age, with a fourth dose at the age of 18 months. A booster dose is given at 7 years of age. Immunisation coverage for the primary course of diphtheria vaccines in the country had been 90% or more since year 1980, and achieved coverage of 95-99% from year 1990 to date (WHO 2015c). In a study of 381 children diagnosed with diphtheria in Thailand, about 75% of patients had no history of immunisation (Pancharoen et al, 2002). Protective immunity may be boosted through exposure to circulating strains of toxigenic C. diphtheriae. Declining seroprevalence among adults, evidence for a recent shift in the age-distribution of cases, and the potential for outbreaks among susceptible populations support the immunisation of adults against diphtheria (Isahak, 2000). In adolescents and adults, the use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine is recommended (CDC 2011).

CONCLUSION

Fatal diphtheria in a patient who was most likely partially immunised or non-immunised reaffirms the vital role of the EPI and the importance of efforts to ensure a high uptake of the scheduled immunisations. Clinical suspicion is important to aid diagnosis, microbiological confirmation and management of diphtheria, as the disease is rare in the era of successful immunisation programs. Microbiological vigilance plays an important role in early detection of infection as well as outbreaks.

ACKNOWLEDGMENT

We would like to thank the Director of UKMMC and Dean of Faculty of Medicine, Universiti Kebangsaan Malaysia. Our thanks also to the staff of Bacteriology Unit, and the Head of Department of Medical Microbiology & Immunology, Faculty of Medicine, UKMMC for their assistance and support.

References

1. Atkinson W, Hamborsky J, McIntyre L, Wolfe S. Diphtheria, Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book), Washington DC. 2007; pp 75-86. Available at http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/dip.pdf.

2. Bonnet JM, Begg NT. Control of diphtheria guidance for consultants in communicable disease control. Commun Dis Public Health 1999; 2(4):242-249.

3. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunisation Practices, 2010. MMWR 2011; 60 (1): 13-15.

4. Centers for Disease Control and Prevention (CDC). Use of Diphtheria Antitoxin (DAT) for Suspected Diphtheria Cases, Atlanta. 2012. Available at http://www.cdc.gov/diphtheria/downloads/protocol.pdf. Accessed 20th September 2015.

5. Isahak I. Adult immunisation- A neglected issue in Southeast Asia. Southeast Asian J Trop Med Public Health 2000; 31 (1): 173-184.

6. Ministry of Public Health Thailand, Bureau of Epidemiology, Department of Disease Control. Investigations of Diphtheria Outbreak in Narathiwat Province, October 2010-March 2011. Weekly Epidemiological Surveillance Report 2012; 43 (5): 65-69. Available at
7. http://epid.moph.go.th/wesr/file/y55/H5552012-01-292012-02-04.pdf
8. Accessed 1st August 2015.

9. Pancharoen C, Mekmullica J, Thisyakorn U, Nimmannitya S. Clinical features of diphtheria in thai children: a historic perspective. Southeast Asian J Trop Med Public Health 2002; 33 (2): 352-354.

10. World Health Organization. Diphtheria. WHO-

recommended surveillance standard of selected vaccine-preventable diseases. WHO Geneva 2003; pp 10-12. http://www.who.int/immunization_monitoring/diseases/diphtheria_surveillance/en/index.html. Accessed 1st August 2015.

11. WHO vaccine-preventable diseases: monitoring system. 2015 a. Global Summary. Incidence time series for Malaysia (data as of 8 September 2015).
12. http://apps.who.int/immunization_monitoring/globalsummary/incidences?c=MYS. Accessed 1st October 2015.

13. WHO vaccine-preventable diseases: monitoring system. 2015 b. Global Summary. Incidence time series for Thailand (data as of 8 September 2015).
14. http://apps.who.int/immunization_monitoring/globalsummary/incidences?c=THA. Accessed 1st October 2015.

15. WHO vaccine-preventable diseases: monitoring system. 2015 c. Global Summary. Percentage target population vaccinated by antigen (data as of 8 September 2015). http://apps.who.int/immunisation_monitoring/globalsummary/coverages?c=MYS. Accessed 1st October 2015.

16. Winn WJ, Allen S, Janda W, Koneman E, Procop G, Schreckenberger P, Woods G. Aerobic and Facultative Gram-Positive Bacilli, Koneman's Color Atlas and Textbook of Diagnostic Microbiology (Sixth Edition), Lippincott Williams & Wilkins, Philadelphia. 2006; pp 765-840.

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