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DIPHTHERIA MORTALITY IN NIGERIA: THE NEED TO STOCK DIPHTHERIA ANTITOXIN

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ABSTRACT
INTRODUCTION: Diphtheria had been a major of cause of childhood mortality until the advent of an effective vaccine. Even in Nigeria with low to moderate coverage with the third dose of DPT the number of reported cases of diphtheria had been reducing. However, in a recent report we noted an increase in the incidence of diphtheria. The mainstay of management of diphtheria is the Diphtheria antitoxin. Diphtheria antitoxin is not available in Nigeria. We present the mortalities from diphtheria to highlight the need to stock the diphtheria antitoxin.
METHODOLOGY: A review of the case notes of patients managed for diphtheria between August 2008 and 2010 was done and relevant data extracted.
RESULTS: Nine cases of diphtheria were seen and three mortalities were recorded giving a mortality rate of 33.3%. One of the deaths was from myocardial involvement and acute renal failure while another was from possible septicaemia. The third mortality occurred at home after discharge from hospital
DISCUSSION: Most of the symptoms of diphtheria are due to the effects of the diphtheria exotoxin. The non availability of the antitoxin for the management of these children contributed to their mortality.
CONCLUSION: As long as diphtheria remains uneradicated the need for the antitoxin is imperative.

INTRODUCTION

Diphtheria, a disease caused by *Corynebacterium diphtheria* and its exotoxin is characterised by high case fatality (1-3). Diphtheria commonly affects the tonsils, pharynx and larynx. The C. diphtheria remains in the superficial mucosa or skin and elaborates its exotoxin. The diphtheria exotoxin, a potent 62 kd polypeptide inhibits protein synthesis leading to local tissue necrosis (2). The exotoxin is absorbed into the mucous membranes and causes destruction of epithelium and a superficial inflammatory response (3). The necrotic epithelium becomes embedded in exuding fibrin and red and white cells, resulting in a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes (3,4). This advances – commonly over the tonsils, pharynx, or larynx, and becomes a gray-brown, leather-like adherent **pseudomembrane** (*Diphtheria* is Greek for leather). With increase in the concentration of toxin, it is spread to other tissues through haematogenous dissemination (2).

Laryngeal involvement, which may occur on its own or as a result of membrane extension from the nasopharynx, presents as hoarseness, stridor, croupy cough and dyspnea (3). These patients are at significant risk for suffocation because of local soft tissue edema and airway obstruction by the diphtheritic membrane (3).
There may be toxin-mediated paralysis of soft palate, posterior oropharynx and hypopharynx (4). Although the toxin has no target organs the myocardium and peripheral nerves are most affected.[2]Other toxin mediated complications of diphtheria are toxic cardiomyopathy which occurs in 10–25% of patients with respiratory diphtheria and is responsible for 50–60% of deaths (3). Neurotoxicity and renal damage can also occur. Some of these features may present up to six weeks after the onset of the illness suggesting an immunological basis for the pathophysiologic mechanism for these delayed features of diphtheria (2).

The mainstay of management of diphtheria is the antitoxin. WHO (5) recommends immediate administration of diphtheria antitoxin and antibiotics following clinical diagnosis. The diphtheria vaccine is one of the major approaches for the control and prevention of diphtheria. In the pre-vaccine era diphtheria was common place with annual reported cases of 125,000 and 10,000 annual deaths from diphtheria being reported in the United States of America (3). With the advent of an effective vaccine against diphtheria and following the introduction of mass immunization the incidence of diphtheria fell to such levels that at the beginning of the 1980s many countries in the world were progressing toward the elimination of diphtheria (6). It in fact became a medical rarity (3). This was until the striking resurgence of diphtheria in the Newly Independent States (6).

The numbers of reported cases of diphtheria in Nigeria have been declining. Reported cases from Nigeria were 5,039 in 1989, 3,995 in 2000, 2,468 in 2001, 790 in 2002 and 312 in 2006 (7). Immunization coverage with three doses of DPT in Nigeria has been inconsistent reaching an all time low in 2003 (8). Current DPT 3 coverage in Nigeria is 72% (7). There are few reports on clinical diphtheria in Nigeria but most of these are old reports corroborating the possible declining prevalence of diphtheria in Nigeria. However, we reported 5 cases over a one year period in 2009 with 40% mortality and speculated on the possible resurgence of the disease (9).

In this report we note the continued presence of cases suggesting the possible veracity of resurgence of the disease in Nigeria. The focus of this report however, are the mortalities recorded among the cases of diphtheria between 2008 and 2010 with a discussion on the need to stock the diphtheria antitoxin which is the mainstay of management of diphtheria.

MATERIALS AND METHODS

Records of patients managed for diphtheria over the period 2008 and 2010 in the University of Benin Teaching Hospital, Benin City were reviewed. In all cases diagnosis was clinical and confirmed microbiologically. The relevant clinical data were extracted. Each child received intravenous crystalline penicillin once the diagnosis was made or strongly suspected. Resection of the pseudomembrane was done in two children both of whom eventually required tracheostomy. No child received the diphtheria antitoxin as this is not available in Nigeria. The public health unit investigated each case and reported the cases to the appropriate authorities. Family and close contacts were treated with erythromycin while unimmunized children were immunized

RESULTS

Nine patients were admitted over the two year period. Their ages ranged 11 months to 10 years with a mean of 5.8±3.5 years. There were 4(44.4%) males and 5(55.6%) females. Three mortalities were recorded giving a mortality rate of 33.3%. The three deaths were one male infant (11months old) and two females aged 8 and 10 years. All three mortalities presented with fever, dysphagia/drooling of saliva and enlarged cervical lymph nodes. Other clinical features are as shown in table 1.

Case A in addition to the features in table 1 had had measles two weeks prior to the onset of pharyngotonsillar symptoms. In fact he did not recover from the measles as he continued to have fever before the onset of the pharyngotonsillar symptoms. He also had visited a traditional healer who had made scarifications on his abdomen. Although he had been seen earlier in the General Practice Clinic of the hospital diphtheria was not suspected until he presented in the children's emergency room with symptoms of pharyngotonsillar disease.

TABLE 1: CLINICAL FEATURES OF CHILDREN WHO DIED FROM DIPHTHERIA

Clinical features	Individual cases of diphtheria		
	a	b	c
age	11mth	8yrs	10yrs
sex	male	female	female
fever	+	+	+
cough	+	-	+
nasal discharge	+	+	-
nausea/vomiting	+	-	-
diarrhea	+	-	-
dysphagia/drooling/ inability to suck	+	+	+
*duration of symptoms (in days)	2	3	4
neck swelling/enlarged lymph nodes	+	+	+
enlarged tonsils	+	+	-
membrane on tonsils	-	+	+
im status	dpt2	?complete	complete
contact**	-	-	-
mother's loe	pry	?	pry

+ attribute present - attribute absent
im – immunization status * symptoms of pharyngtonsilar disease
****contact with a case of diphtheria loe – level of education**

pry – primary dpt – diphtheria, petussis, tetanus vaccine

Even so the initial diagnosis was septicaemia. He developed severe anaemia for which he was transfused. Thereafter he started bleeding from the nostrils and rapidly deteriorated and died.

Case B improved following treatment and was discharged home after a week on admission. She developed nasal speech and regurgitation of water one week after discharge and died at home four days later

Case C in addition to the features in table 1 developed bradycardia and hypotension two days after admission. Electrocardiogram showed abnormalities of the ST segment. She was adjudged to have toxic cardiomyopathy and managed with fluids (including blood transfusion) and dopamine infusion. She subsequently developed acute renal failure with pulmonary oedema and died

DISCUSSION

The major features of morbidity resulting from diphtheria are from the exotoxin and once bound is not amenable to treatment. It is thus imperative that antitoxin is available for the management of cases of diphtheria. In fact, it is recommended that antitoxin be administered once diphtheria is suspected(3, 10). Worsening outcomes have been associated with

delays in administration of the antitoxin (2). The antitoxin has been recommended to be given at an empirical dose based on the degree of toxicity, site and size of the membrane, and duration of illness (2). Similar doses are given to adults and children (3). The intravenous route is preferred (2).

Diphtheria is associated with high mortality and one of the prognostic factors is the speed with which the antitoxin is administered (2). For those in whom the disease is recognized on the first day and appropriate treatment instituted mortality is 1% but those in whom such treatment is delayed till the fourth day mortality rises to 20%.[2]The high mortality rate recorded in this series may have been due to the lack of antitoxin. The high mortality recorded in this series is similar to that reported from India in which a case fatality rate of 30.8% was recorded during an outbreak of diphtheria in which none of the patients benefited from antitoxin since none was available (11).
The role of antimicrobial therapy in diphtheria is to halt toxin production, treat localized infection and prevent transmission of the organism to contacts (2, 3). Delay in making the diagnosis occasioned by late presentation of patients and a low index of suspicion in the first mortality in this series may also have contributed to the high mortality recorded. Delays allow time for multiplication of the organism and elaboration of toxins before the administration of effective antibiotics. Bound toxin is not amenable to treatment and in this series even the unbound toxin could not have been treated as there was no antitoxin. In a series reported from Thailand, early recognition and prompt treatment reportedly decreased complications and mortality (12).

Early recognition of diphtheria is dependent on a high index of suspicion of the attending physician as there are other common causes of pharyngotonsillar disease such as exudative pharyngitis due to streptococcus pyogenes and Epstein-Barr virus, Vincent's angina, bacterial epiglottitis, severe laryngotracheobronchitis, staphylococcal or streptococcal tracheitis.[3] Since diphtheria had hitherto become uncommon it is necessary for practicing medical personnel to be reminded of diphtheria through continuing medical education programmes. Caregivers also need to be sensitized concerning diphtheria to improve care seeking behaviour.

Rarely diphtheria may result in septicaemia with uniformly fatal outcome (2). While this is a possibility in the first mortality it was not confirmed by a positive blood culture. The possibility of septicaemia in this child is also likely given the fact that he had suffered from measles which is known to impair immunity and the causative organism may not necessarily be Corynebacterium diphtheria since he had scarification marks which may have served as portal of entry for other organisms.

Some of the complications of diphtheria can occur as late as six weeks after the illness (2, 3). Thus in the second case death occurred after the child had been discharged home in the third week of the illness. Although the history suggested that the child had neurological complications as evidenced by the nasal speech and the regurgitation of water, it is possible that the child may have had other more life threatening complications such as myocarditis. Complete recovery is often the expected outcome for neurological complications of diphtheria however in a series from India fatal aspiration led to mortality in a minority of cases with palatal paralysis (13). In the same series poor outcome was associated with delay in instituting diphtheria antitoxin. Since a post mortem examination was not done in the current case it is not possible to state the definitive cause of death. It can however be speculated that if the child had received antitoxin the outcome may have been different.

Early complication of the illness with myocardial disease has been associated with high mortality as was the case with the third mortality (3). The additional complication of acute renal failure may have been due to the effect of the toxin. It could also have resulted from the repeated episodes of cardiogenic shock with resultant hypoperfusion of the kidneys.

In developed countries such as the United States where diphtheria is all but a medical rarity the antitoxin is still stocked at Centre for Disease Control (CDC) and can be obtained within 24hours. While prevention by effective vaccination remains the best option, until the disease is eradicated the antitoxin should be available.

Two of the three mortalities occurred in older children one of whom is said to have had complete immunization in infancy. It has been documented that the level of immunity wanes with time such that booster doses of DPT are required (14). This becomes more pertinent in the face of improving social environments with fewer opportunities for cutaneous diphtheria which is believed to serve as boosters in developing countries. Research is needed to determine the levels of immunity in Nigerian children to guide policy decisions on the need for booster doses for diphtheria.Of importance is the need to strengthen the immunization programme. One of the mortalities had received only two doses of DPT and had not received measles vaccine despite being 11months old. He suffered measles prior to developing diphtheria a classic case of "double jeopardy"

In conclusion Diphtheria would seem to be increasing in incidence in Nigeria. There is therefore a need to strengthen the immunization services as a means of prevention. However, as long as Diphtheria is not eradicated Diphtheria antitoxin should be available to treat clinical cases of diphtheria so as to reduce case fatality rates. The presence of diphtheria in any given community remains a potential risk for the rest of the world since the world has become a global village.

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