The changing epidemiology of diphtheria in Jordan*

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Outbreaks of diphtheria used to occur regularly in Jordan, the last such outbreak being in 1977–78. Since that time, a massive immunization programme targeted at preschool-age children has been markedly successful. Hence, when an outbreak of diphtheria occurred in 1982–83, it was unexpected. Of the 35 patients who were treated at the Jordan University Hospital, two died and the remaining 33 recovered uneventfully. Contrary to our findings in previous diphtheria epidemics in Jordan, this outbreak largely involved adolescents and young adults.

Since the introduction of a vaccine against diphtheria in the early part of this century, the disease has almost been eradicated in developed countries. Occasional outbreaks, however, do occur, especially if the immunization level in the general population drops below 70% (1); for example, such outbreaks have been reported in the USA and the United Kingdom (2, 3). In Jordan, where the immunization level in the general population was suboptimal in the past, outbreaks of diphtheria continued to occur on a regular basis every 3–4 years (4). The last such outbreak was in 1977–78 and has already been described (4). The age group infected with diphtheria in Jordan has traditionally been young children, and in the 1977–78 outbreak we described 27 cases, 22 of which were less than 10 years of age; four were aged between 10 and 14 years and only one was an adult (a 25-year-old). This age distribution, with young children primarily being infected, might indicate the presence of naturally acquired immunity among older individuals caused by subclinical infection. In 1979 the Ministry of Health with the help of the WHO Expanded Programme on Immunization embarked on one of the most comprehensive immunization programmes ever carried out in Jordan.

The following immunization schedule is used: diphtheria–pertussis–tetanus toxoid (DPT) and oral polio vaccine (OPV) are given to infants aged 3–5 months and repeated when they are 1.5 years old and upon school entry. The programme has been targeted against children less than 5 years of age. A recent survey showed that more than 70% of children younger than this age have received three doses of DPT and OPV. When an outbreak of diphtheria occurred in 1982 it was, therefore, unexpected. Here, we describe the cases seen at Jordan University Hospital, and discuss the implications that the outbreak has for the future epidemiology of the disease in Jordan.

MATERIALS AND METHODS

After admission of the first suspected case, a diphtheria follow-up committee, consisting of a paediatrician, an internist, an otolaryngologist, and a microbiologist, was set up. Both paediatric and medical residents and interns examined all suspected diphtheria patients when they presented to the emergency admission room of the hospital.

Patients who complained of a sore throat but had no grey-white pseudomembrane were categorized as marginally suspected cases, and, after a throat culture had been made, those who were older than 6 years of age received 1.2 million IU of benzathine penicillin G, while those who were less than this age received 600 000 IU. Patients who refused injections were given penicillin orally for 7 days, while penicillin-allergic patients were given erythromycin orally for 7 days. Suspected cases were asked to leave details of their address and telephone number, whenever available, before being allowed to leave the hospital and were requested to return for daily medical examinations and follow-up.

The second group of patients had a pseudomem-
brane and were highly suspected of having diphtheria, especially if the tissues beyond the tonsils were involved or the submandibular area was swollen. Such patients were admitted to the isolation ward of the hospital and were kept in strict isolation. Throat cultures were obtained from these patients immediately upon admission. Those who had been ill for less than 48 hours and in whom the pseudomembrane was confined only to the tonsils received 20,000–40,000 IU of diphtheria antitoxin. Patients in whom the pseudomembrane involved the pharynx beyond the tonsils received a dose of 40,000–80,000 IU of antitoxin, while those who had been ill for longer than 3 days before presenting to the hospital or in whom the pseudomembrane involved the larynx or nose, or who had submandibular swelling, received 80,000–120,000 IU. The antitoxin was given after performing a skin test and the whole amount was diluted in 100 ml saline and administered intravenously over 1.5 hours. All patients aged more than 6 years were also given penicillin or erythromycin for 1 week as follows: 600,000 IU of procaine penicillin G every 12 hours for 3 days followed by 250 mg oral penicillin every 6 hours for the remaining 4 days. Children less than 6 years of age received half these amounts. All patients had vital signs recorded every 4 hours and electrocardiograms (ECGs) twice daily; those whose ECGs showed pathological changes were placed on a cardiac monitor. Patients’ contacts were given prophylaxis with benzathine penicillin G after throat cultures had been obtained. Non-immunized contacts were advised to receive diphtheria vaccine from the Ministry of Health.

The bacteriological methods used in the study were as follows: at the beginning of the outbreak, throat swabs obtained from patients suspected of having diphtheria were inoculated onto plates containing blood agar and potassium tellurite blood agar. Later, during the surveillance for diphtheria organisms among patients’ contacts and convalescing diphtheria patients, only tellurite blood plates were used. All plates were incubated for 24–48 hours at 35°C. Suspicious colonies were checked by Gram stain/Löffler’s alkaline methylene blue stain and for catalase. When diphtheria-like organisms were detected, the physician was informed. A single colony of the suspicious organisms was then subcultured on tellurite blood agar, and after 24–48 hours the pure culture was examined biochemically for glucose, sucrose, and maltose fermentations as well as for the production of urease.

Toxigenicity was demonstrated in vitro by Elek’s method for the first two Corynebacterium diphtheriae isolates only. Seven representative isolates of C. diphtheriae were sent to the Centers for Disease Control, Atlanta, GA, USA, for confirmation and proved to be the mitis biotype and toxigenic.

RESULTS

Only eight patients were admitted with diphtheria to Jordan University Hospital from January 1979 to November 1982, one of whom died. In contrast, during the period December 1982 to January 1983, 35 patients were admitted to the hospital with signs of diphtheria. Table 1 shows the symptoms at the time of admission in the bacteriologically confirmed and suspected cases.

A pseudomembrane was present in 28 cases (Table 2). Also the ECGs of nine patients were consistent with the presence of pathological changes and two of these patients died. For five of the patients who developed ECG changes, bacteriological confirmation of diphtheria could not be made.

Bacteriological confirmation of diphtheria was made in only 11 patients. Of the remaining 24 patients who had negative cultures, 20 had received antibiotics for at least 2 days before admission to hospital; and five of these patients exhibited ECG changes consistent with myocarditis.

The immunization status of the patients was as follows: 12 had been immunized, 15 had not, while that of a further eight was uncertain, although they were most probably not immunized.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat</td>
<td>33 (94.3)*</td>
</tr>
<tr>
<td>Fever</td>
<td>33 (94.3)</td>
</tr>
<tr>
<td>Pain on swallowing</td>
<td>32 (91.4)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>12 (34.3)</td>
</tr>
<tr>
<td>Oedema of the neck</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Weakness</td>
<td>1 (2.9)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Signs</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomembrane:</td>
<td></td>
</tr>
<tr>
<td>Tonsillar</td>
<td>22 (62.9)*</td>
</tr>
<tr>
<td>Beyond the tonsils</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Electrocardiogram changes</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Polyneuritis</td>
<td>1 (2.9)</td>
</tr>
</tbody>
</table>

* Figures in parentheses are percentages of the total number of cases (n = 35).
After the death of the first two patients who had been prescribed 60,000 IU of antitoxin, the dose was increased to 120,000 IU for those with extensive pseudomembranes, regardless of the duration of their illness. This dose was well tolerated, and no patients were found to have serum sickness upon follow-up.

The age distribution of the patients in the study is depicted in Fig. 1. Ages ranged from 2 years to 44 years, the greatest number being among adolescents and young adults (age range: 10–30 years). This age distribution is unusual for diphtheria in Jordan, where thus far the most frequently affected group has been children aged <10 years. It is noteworthy that this was the age distribution of diphtheria patients who were admitted to hospitals during the inter-epidemic years 1979–82 and also of the cases in Jordan as a whole from December 1982 to January 1983 (Fig. 2).

DISCUSSION

Man is the only host for *C. diphtheriae*. Hence, persistence of the organism in the community is usually due to the presence of asymptomatic carriers or undiagnosed mild infections. Another possible source is avirulent *C. diphtheriae* strains. For example, Freeman has demonstrated that commensal diphtheroids of the throat are able to convert into toxigenic organisms by infection with an appropriate bacteriophage and that these can then serve as a source of spread of diphtheria in a community (5). Skin infections with *C. diphtheriae*, which are easily confused with impetigo, can also serve as an effective means of dissemination of the organism in the community (6). The role of such infections in previous epidemics in Jordan is unclear. However, it is not likely that skin infection played an important role, since most outbreaks occurred in the autumn and early winter, when impetigo-like skin lesions are uncommon among the population. Hence, it is probable that the regular occurrence of sporadic cases was due to asymptomatic infections or contact with respiratory carriers.

Despite the implementation of a vigorous programme of immunization of young children, sporadic cases of diphtheria have continued to occur in Jordan. The most recent previous epidemic occurred in 1977–78, which was prior to the immunization programme, and the majority of affected individuals were less than 10 years of age. Subsequently, the sporadic number of patients who presented to the Jordan University Hospital with diphtheria were not limited geographically to any particular location of the country, but most belonged to the less privileged, lower socioeconomic groups, and one out of eight died.

Before 1979 the immunization level against diphtheria for children in Jordan did not exceed 20%. Hence, many individuals born prior to this must have acquired immunity against the disease by subclinical infection; that such immunity must occur is clear from the results of the epidemiological studies in many communities (7). Subsequently, with the effective elimination of diphtheria among younger children, susceptible older children and young adults in the community presumably became infected. Interestingly, two of the hospitalized patients were school teachers, while three of their pupils were identified as asymptomatic carriers.

In the 1982–83 epidemic the indiscriminate self-administration of antibiotics by patients before admission to hospital made it difficult to isolate
C. diphtheriae from many who were judged to be highly suspicious for diphtheria. In the diphtheria epidemic in San Antonio, Texas, C. diphtheriae was effectively eliminated from the pharynx of 75% of the patients by therapy with penicillin or erythromycin for 2 days (3). Many of the patients presented to us after 2–3 days of self-administered antibiotic therapy at home, which made isolation of the organism almost impossible. The actual number of bacteriologically proved cases in the country as a whole was similarly affected.

Among our patients, dysphagia and sore throat were very common, which is similar to the findings of McLosky et al. in the San Antonio outbreak (3).

The unusual feature of this epidemic in Jordan was the age distribution of those affected, the majority of whom were older than 10 years. This is very similar to the epidemiological patterns for diphtheria in developed countries, where childhood immunization is efficient (3), and may be similar to recent trends in measles infection in the USA, where the majority of cases are now young adults (8). It therefore appears that in Jordan immunization of children aged 12–16 years with diphtheria vaccine before they leave school may help to decrease this pool of susceptible individuals. Another strategy would be to administer tetanus–diphtheria vaccine to all army recruits. Since there is mandatory conscription in Jordan, this should benefit all young men in the country, while immunization of adult females can be carried out at mother and child health centres. The implications of the age distribution for diphtheria reported here should be further elucidated by screening for the level of immunity against the disease in the community.

RÉSUMÉ

L’ÉVOLUTION DE L’ÉPIDÉMILOGIE DE LA DIPHTÉRIE EN JORDANIE

Le présent article décrit les cas de diphtérie observés au Jordan University Hospital au cours d’une épidémie qui a eu lieu en Jordanie entre le 19 décembre 1982 et le 16 janvier 1983. Cette épidémie a été assez inattendue, car dans la majeure partie du pays, plus de 70% des enfants de moins de 5 ans avaient été vaccinés contre la diphtérie dans le cadre d’un programme de vaccination de masse des enfants d’âge préscolaire lancé en 1979.

Au total, 35 malades ont été admis à l’hôpital, et 33 se sont rétablis sans incident. Les cas les plus suspects ont été isolés et placés sous surveillance. Des prélèvements de gorge ont été effectués dès l’admission et l’on a prescrit de la pénicilline, de l’Érythromycine et de l’antitoxine diphérique à des doses allant de 20 000 à 120 000 UI selon la gravité de l’infection.

Trente-trois malades (94%) avaient de la fièvre et se plaignaient de maux de gorge, 32 (91,4%) étaient atteints de dysphagie et 28 présentaient une pseudo-membrane amygdalienne. Cette pseudo-membrane s’étendait au-delà des amygdales chez six d’entre eux (17,1%). De plus, chez neuf patients (25,7%) on a observé au cours de la maladie des modifications pathologiques de l’électrocardiogramme évocatrices d’une cardite diphérique.

A l’examen bactériologique, 11 malades (31,4%) se sont révélés positifs pour la diphtérie, et deux d’entre eux sont décédés. Sept isolements représentatifs de Corynebacterium diphtheriae ont été confirmés aux Centers for Disease Control d’Atlanta (GA, États-Unis d’Amérique) et se sont avérés appartenir au biotype bénin et être toxigènes.

Dans 24 cas pour lesquels les signes cliniques de diphtérie étaient très nets, C. diphtheriae n’a pu être isolé. Vingt de ces malades avaient pris des antibiotiques pendant au moins 2 jours avant d’être admis à l’hôpital et cinq d’entre eux l’électrocardiogramme faisait penser à une myocardite.

Douze malades (34,2%) avaient été vaccinés contre la diphtérie, alors que 15 (42,8%) ne l’avaient pas été; huit autres (22,8%) ne savaient pas s’ils avaient été vaccinés, mais ne l’avaient probablement pas été.

L’âge des malades allait de 2 à 44 ans, mais la plupart étaient des adolescents ou de jeunes adultes (de 10 à 30 ans). Cette répartition est très inhabituelle pour la diphtérie en Jordanie, où les épidémies précédentes touchaient surtout les enfants de moins de 15 ans. On pense que ce décalage vers les classes d’âge plus élevées est dû au succès des campagnes de vaccination menées chez les jeunes enfants.

REFERENCES