Diphtheria with polyneuropathy in a closed community despite receiving recent booster vaccination

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Introducing and Methods: We report 20 patients aged 18–24 years from Latvia with diphtheritic polyneuropathy. All lived in a closed community and 80% were known to have been fully vaccinated against diphtheria until at least 14 years old. Diphtheria antitoxin had been administered within 3 days of the onset of upper respiratory tract infection in 16 patients and 15 received antibiotics.

Results: Neurological symptoms developed after a median of 43 days (range 35–58) compared to only 10 days in previous studies of unvaccinated patients. All showed evidence of mild limb polyneuropathy with electrophysiological evidence of polyneuropathy. Only 30% showed early bulbar abnormalities compared to the usual rate of over 75% in diphtheritic polyneuropathy. However, 45% had later bulbar deterioration coinciding with the limb polyneuropathy.

Conclusions: These patients show that an attenuated form of polyneuropathy of later onset, with less prominent early bulbar features, can occur in patients previously vaccinated against diphtheria according to schedule but living in a closed community in a country where diphtheria remains endemic.

METHODS

Of 149 (aged 18–40 years) diphtheria infected cadets, soldiers, and defence personnel, 20 were studied because of neuropathic symptoms. Suspected, probable, or confirmed cases of diphtheria were diagnosed according World Health Organization criteria. Available vaccination records were reviewed for vaccination dates, number of doses, dates, and type of diphtheria toxoid formulation, for example, DT (high antigen toxoid, 12 Lf) as given in childhood or Td (low antigen toxoid, 2 Lf) given as an adolescent booster.

The severity of the polyneuropathy was assessed according to a scale (motor disability grades 0–6, bulbar dysfunction grades 0–3, sensory symptoms grades 0–2) used previously. Seventeen subjects underwent nerve conduction studies using standard methods at a skin temperature of >34°C including motor conduction along four nerves (median, ulnar, peroneal, and peroneal) with electrophysiological evidence of polyneuropathy. Only 30% showed early bulbar abnormalities compared to the usual rate of over 75% in diphtheritic polyneuropathy. However, 45% had later bulbar deterioration coinciding with the limb polyneuropathy.

RESULTS

Patient characteristics

The 20 patients with DP were 18–24 year old males with an average age of 19.7 years. Bacterial culture for Corynebacterium diphtheriae (b.v. gravis) was positive in 10; it should be noted that antibiotic administration had been common prior to admission to hospital as prophylaxis, or on suspicion of diagnosis, during the 3 days over which this diphtheria outbreak developed. All 20 showed pharyngeal or tonsillar evidence of diphtheritic infection, two neck oedema, and 17 electrocardiographic myocarditis. Most (15 or 75%) were hospitalised in the Infectology Centre within the first 3 days of the localised infection. Five others were admitted from the 6th to 30th days. A total of 14 patients (70%) required

Abbreviations: DML, distal motor latency; DP, diphtheritic polyneuropathy; DTP vaccine, diphtheria and tetanus toxoids and pertussis vaccine; MCV, motor conduction velocity; SNCV, sensory nerve conduction velocity
treatment in specialised neurological departments. Antibacterial therapy was administered in 15: erythromycin in 12 (60%) and benzyl penicillin in three (15%). Diphtheria antitoxin was administered in 16 cases (80%) within 3 days of the first signs of disease; it was not administered in four (20%) due to late hospitalisation.

A total of 16 patients (80%) had been fully vaccinated against diphtheria including a booster given at age 14–16. Two patients (10%) were incompletely vaccinated and one patient (5%) did not recall vaccination; all three showed “protective” levels of IgG antibodies against diphtheria toxoid (ranging from 0.19 to >1 IU/ml). Vaccination records were unavailable for one patient (5%) who had low IgG antibody levels (0.08 IU/ml). The last booster dose had been a median of 4.1 years (range 1–8) previously. Detection of antibody response to diphtheria toxin was performed on admission and showed IgM negative in all (100%), and IgG >1.0 IU/ml in 13 (65%), 0.1–1.0 IU/ml in six (30%), and 0.08 IU/ml in one (5%).

Neurological features

The first neurological symptoms developed a median of 43 days (range 35–58) after the onset of localised tonsillar and pharyngeal diphtheria. Only seven patients (30%) manifested early local bulbar symptoms after the onset of infection with hoarseness in three and dysphagia in four. Late bulbar deterioration coinciding with limb polyneuropathy occurred in nine (45%); in two as grade 2 bulbar dysfunction (moderate dysphagia, nasal voice, palatal paresis) and in seven as grade 1 (minor symptoms and signs without dysphagia).

All 20 had neuropathic limb symptoms or signs: 10 (50%) experienced grade 1 disability in walking; two (10%) showed mild weakness of ankle dorsiflexion; 19 (95%) had distal limb tingling; 15 (75%) leg pain; seven (35%) arm pain; and 13 (65%) altered pain and touch sensation of “sock” distribution (hypoesthesia in nine, hyperaesthesia in four). Ten (50% of patients) had diminished tendon reflexes.

The four patients with an uncertain or incomplete vaccination history lay within the same spectrum as the other patients with onsets ranging from 37 to 55 days with one manifesting bulbar symptoms.

Improvement of neurological symptoms and signs generally occurred within 30 days of their onset.

Nerve conduction studies

Evidence of mild conduction slowing was found in all 17 patients. Sensory action potential amplitudes were normal in all.

Four patients (group 1) had decreased SNCV in leg nerves: tibial (four; average 41 m/s; range 35–44); sural (two; average 37 m/s; range 32–42); and peroneal (two; average 36 m/s; range 33–40).

Eight patients (group 2) had slowed motor conduction velocity (MCV) and SNCV in leg nerves only. Distal motor latency (DML) was prolonged in the peroneal nerve in seven patients (average 4.3 m/s; range 4.0–4.9; normal ≤3.8). Decreased MCV occurred in the peroneal nerve (average 40 m/s; range 37–44) and the tibial nerve (one; 42 m/s). SNCV was reduced in the tibial nerve (seven) to 35 m/s (range 29–45) and in the peroneal (five) to 43 m/s (range 38–45).

Five patients (group 3) had slowed MCV and SNCV in nerves of both arms and legs. D prolonged DML occurred in the peroneal nerve (four; average 5.1 m/s; range 4.1–6.3) and in the tibial (three; average 6.7 m/s; range 6.5–7.2). MCV was decreased in the forearm median nerve (one; 44 m/s) and in the peroneal (three; average 42 m/s; range 40–45). Slowed SNCV occurred in the tibial nerve (four; average 29 m/s; range 26–31) and in the median (two; average 46 m/s; range 40–44).

In summary, there was neurophysiological evidence of mild sensory motor polyneuropathy in legs alone in eight (47%) patients, mild generalised polyneuropathy in five (29%), and mild sensory neuropathy restricted to the legs in four (24%).

**DISCUSSION**

These recently vaccinated young adults from a closed community with diphtheria exhibited a milder form of polyneuropathy than previously associated with diphtheria. There was a lesser incidence of early bulbar weakness and subsequent limb symptoms were less severe. The previously described phenomenon of secondary, or late, bulbar deterioration at the time of limb polyneuropathy occurred at a similar frequency as previously (43%) but was also less severe. The onset of this attenuated polyneuropathy occurred later (median 43 days; range 35–58) in these previously vaccinated patients with attenuated disease compared to the median of 10 days (range 2–50 days) that we had observed previously. In part, this increased latency may reflect the greatly reduced incidence of early bulbar symptoms (only 30%) in these patients with attenuated disease compared to 98% in our previous study. The latency of onset of generalised neurological symptoms in these recently vaccinated patients was a median of 43 days, not dissimilar to the latency to occurrence of first limb symptoms (median 37 days) noted previously.

The recurrence of diphtheria in Latvia in the 1990s was acknowledged as an epidemic. After 17 years without diphtheria, cases had reappeared in 1986. During this initial epidemic, the incidence increased until 1994, with the disease usually occurring in middle aged adults. The maximum incidence was reached in 1995 with 369 cases and 27 deaths, a rate of 14.6 per 100 000. In 1995, the vaccination schedule was modified so that the second and third diphtheria booster doses were given at 7 and 14 rather than at 9 and 15 years of age. A mass vaccination campaign was initiated, targeted at providing at least 90% of adults between the ages of 25 and 60 with at least one booster dose of diphtheria toxoid vaccine. Single booster vaccination in Latvia produced protective antibody levels in 81% of adults compared to 38% prior to vaccination. These immunisation campaigns in Latvia succeeded in delivering three doses of diphtheria toxoid to approximately 53% of adults between 1995 and 1997. Recorded cases of diphtheria dropped to only 42 in 1997. However, cases began to increase again between 1998 and 2000, including these 20 military cadets with polyneuropathy, constituting 13% of the 149 cadets and other defence personnel who developed diphtheria in 2000.

There could be various reasons for the attenuated severity, delayed onset, and lesser bulbar symptoms of the diphteritic neuropathy occurring in these young adults with a history of recent booster vaccination. The protective effects of vaccination with diphtheria toxoid probably attenuated the effects of the exotoxin produced by pharyngeal infection. Renewed awareness, both of the diagnosis of diphtheria and of the need for early antitoxin administration, led to most of these patients receiving antitoxin within the first 3 days of disease; this therapeutic administration of antitoxin may have attenuated the neurological disorder. It should be noted that our previous study suggested that antitoxin was not effective in preventing polyneuropathy if given after the first 2 or 3 days.

The continued occurrence of diphtheria in Latvia, despite renewed and intensive vaccination programmes, raises a few points. First, doctors need to be aware of this diagnosis
in patients with neurological bulbar or limb symptoms, particularly if there is a history of travel to endemic regions. Second, a booster vaccination in recent years does not exclude diphtheria as a cause of polyneuropathy. Third, the continued occurrence of diphtheria emphasises the need for public health measures to ensure that adults receive booster vaccinations with toxoid because of waning immunity and a decline in previously provoked antibody levels.9 10

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