LESSON OF THE MONTH

Diphtheritic polyneuropathy

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The very low incidence in the United Kingdom of diphtheritic infection with neurological complications is a testament to the efficacy of public health and vaccination programmes carried out over the past 50 years. Since 1990, only 19 cases of toxigenic diphtheria have been reported in England and Wales and most of these were acquired abroad.[1] However, recent large outbreaks spreading from eastern Europe indicate that increased awareness of the condition may be important in the near future. We report an instructive case of diphtheritic polyneuropathy that provides an opportunity to review its typical presentation and management.

Case history

A 53 year old man developed a severe sore throat and malaise on returning from a Spanish holiday. He was found to have a pyrexia, sloughing tonsillitis, and marked cervical lymphadenopathy. A bacterial throat swab culture (not cultured for *Corynebacteria*) was negative. He was treated with intravenous benzyl penicillin for a presumed bacterial throat infection and the condition resolved after 2 days.

Four weeks after the initial onset of symptoms, he experienced an episode of retrosternal chest pain lasting 30 minutes. An ECG and subsequent exercise test were normal. However, it was noted at that time that his voice had developed a nasal quality and he began to have nasal regurgitation.

Seven weeks after symptom onset, he developed proximal leg weakness which worsened over the next 4 weeks and became generalised. During this time, his feet became numb and his bulbar problems progressed so that he was no longer able to swallow safely. A diagnosis of Guillain-Barré syndrome was initially made but his weakness and sensory loss continued to deteriorate slowly despite treatment with intravenous immunoglobulin.

He was transferred to the National Hospital, Queen Square, where he was found to have bilateral palatal weakness, reduced palatal sensation, and tongue weakness. Visual accommodation, pupil reactions, eye movements, and facial movements were normal. Neck and trunk flexion were mildly weak and there was global limb weakness (MRC grade 4). Tendon reflexes and plantar responses were absent. He had distal sensory loss for all modalities in a glove and stocking distribution. General examination was normal with no abnormal fall in postural blood pressure. His vital respiratory capacity was never impaired.

Nerve conduction studies showed a demyelinating polyneuropathy. His CSF had a raised protein at 1.03 g/l, a normal glucose, and no pleocytosis or oligoclonal bands. Diphtheritic antitoxin serology was found to be strongly positive at 0.512 iu.

He continued to deteriorate until, at the nadir of his illness 13 weeks after the onset of sore throat, he was only able to walk a few steps with a Zimmer frame and had sensory loss to the elbows and midthighs with sensory ataxia. After this, his voice and swallowing, the second, assessed by video fluoroscopy, began to improve slowly, as did strength and sensation in the limbs. By 23 weeks after onset, with continued physiotherapy, recovery was complete.

Diphtheritic neuropathy was diagnosed on the basis of a pseudomembranous tonsillitis, a delayed bulbar palsy sparing the face, and a demyelinating peripheral neuropathy that eventually recovered completely over a period similar to that of the initial deterioration. Although the serological test is primarily conducted to check immune status rather than exposure to toxin, the result was supportive of the diagnosis as he had not been vaccinated against diphtheria.

Discussion

Diphtheria classically presents with a primary infection followed by biphasic secondary toxic effects (early local and late remote).[2] The primary infection is usually tonsillar, laryngeal, or nasal and is often accompanied by a characteristic membranous exudate. A "bull neck" may arise due to cervical lymphadenopathy and soft tissue swelling. Occasionally the initial site is cutaneous, vaginal or, in neonates, umbilical.

The secondary toxic effects of diphtheria arise by inhibition of protein synthesis through the ADP ribosylation and inactivation of ribosomal GTP-ase by toxin subunit A.[3] Local toxic effects occur by direct spread of toxin and result in the early bulbar problems while the ensuing generalised demyelinating neuropathy arises from haematogenous dissemination. The delay in onset of generalised neurological symptoms, the lack of efficacy of diphtheritic antitoxin given after such symptoms have developed and the proximal to distal spread of weakness all relate to the action via intracellular toxin and the long time for transport of

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Differential diagnosis of diphtheritic neuropathy

	Diphtheritic neuropathy	*Guillain-Barré syndrome*
Phases	Biphasic	Monophasic
Time course	Onset time equals recovery time	Rapid onset, slower recovery
Facial muscle involvement	Rare	Common
Autonomic	Cardiac vagal denervation, tachycardia	Sympathetic and parasympathetic
Other important features	Blurred near vision, palatal weakness, myocarditis	

newly synthesised protein down the axons. The latter determines the time for effects on myelin sheath integrity to become manifest and subsequently resolve. Thus the clinical course of complications of diphtheritic infection follows a stereotypical pattern with onset of bulbar symptoms 3–6 weeks after initial infection, onset of polyneuropathy at around 8 weeks, and a slow deterioration with subsequent resolution over a similar period.[2]

In addition to a peripheral motor and sensory neuropathy, generalised effects include oculomotor palsy, further bulbar problems, and phrenic nerve involvement. The toxin also affects myelinated parasympathetic autonomic nerves, resulting in blurred vision from impaired accommodation, abnormal pupil reactions, and vagal block. The last, in conjunction with direct myocardial involvement, may cause serious cardiovascular complications.

Nerve conduction and CSF findings are similar to those in Guillain-Barré syndrome. Pathologically, there is segmental demyelination mainly of the nerve roots and ganglia but also of peripheral nerves, with phagocytic macrophages and proliferation of Schwann cells.[4]

Management of diphtheritic infection involves administration of intravenous penicillin and diphtheritic antitoxin at the time of the initial illness. *Corynebacterium* should therefore be included as part of all routine throat swab cultures. The only management for the subsequent neurological complications is conservative, with attention paid to protection of the airway and to active physiotherapy.

This case has provided an opportunity to review the typical presentation and management of diphtheritic polyneuropathy. Diagnosis was difficult largely due to the lack of exposure of today's physicians to this once common condition. However, especially in view of the increasing number of European outbreaks, correct differentiation from Guillain-Barré syndrome (table) and other neuropathies is important because the treatment and prognosis are different and because of the importance of contact tracing.

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3 Taussig MJ. *Processes in pathology and microbiology*: Oxford: Blackwell, 1984:414–19.
4 Solders G, Nennesmo I, Persson A. Diphtheritic neuropathy, an analysis based on muscle and nerve biopsy and repeated neurophysiological and autonomic function tests. *J Neurol Neurosurg Psychiatry* 1989;**52**:876–80.