NEUROLOGICAL RARITY

Wound botulism

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Practical Neurology, 2005, 5, 46–51

INTRODUCTION

Wound botulism used to be a rare form of a rare disease but recent outbreaks among injecting drug users in the USA and UK have changed this epidemiological pattern. Three years ago when I saw my first patient it was very unfamiliar territory. But once seen, never forgotten. When some months ago I was asked to see a patient in the Intensive Therapy Unit (ITU), a known drug user, who had collapsed with respiratory failure, the history sounded unmistakable and I had little doubt what the diagnosis would be. This was the fourth case in an injecting drug user seen in our centre over the last three years.

BOTULISM

Botulism is caused by the spore-forming strict anaerobic bacterium, *Clostridium botulinum*, found in soil and aquatic sediments. It produces the most potent neurotoxin known in nature. Botulinum toxin spreads systemically and binds irreversibly to the presynaptic portion of cholinergic synapses, preventing release of acetylcholine at the neuromuscular junctions, autonomic ganglia and parasympathetic synapses.

There are three naturally occurring forms of botulism: food-borne, infant, and wound botulism (Hughes *et al*. 1997). The classic food-borne botulism is caused by ingestion of a finite amount of preformed toxin. In contrast, both infant and wound botulism are due to continuous toxin production and release *in vivo*. Infant botulism occurs after ingestion of spores in food (e.g. honey) with subsequent gut colonization. In wound botulism spores contaminate a wound, germinate and release toxin.

Seven types of *C. botulinum* (A–G) have been identified, based on the type of neurotoxin they produce. Human disease is mainly caused by types A, B, E (present in aquatic sediments and associated with fish products) and rarely C and F. (Hughes *et al*. 1997). All confirmed cases of wound botulism have been caused by types A and B.

EPIDEMIOLOGY

Wound botulism, first described in the USA in 1951, can develop after traumatic injury, surgery, sinusitis after sniffing cocaine and, rarely, in abscesses. Most of the early cases were after trauma, often in an agricultural setting. In 1982 the first case of wound botulism in an injecting drug user was reported in New York and since the late eighties has occurred almost exclusively in drug users injecting into muscle, or subcutaneously ('skin popping'). In the largest published series, from California, comprising 127 patients between 1951 and 1998, the last 102 occurred in the nineties and all but one were due to 'black tar' heroin. This was a 20-fold increase compared to the previous years (Werner *et al*. 2000). The USA cases comprise 90% of all cases of wound botulism worldwide, and 75% have occurred in California (Werner *et al*. 2000). In the USA, 'black tar' heroin from Mexico and South America, so named because of its appearance, accounts for most of the heroin consumed west of the Mississippi river, which explains the geographical clustering of wound botulism. Contamination of heroin with *C. botulinum* spores can occur at any stage between production and injection, and addition of bulking agents ('cutting') is particularly risky. In 'black tar' heroin, bulking agents reportedly included shoe polish and even dirt.

In the UK, the first case of wound botulism was recorded in March 2000 in an injecting heroin user. Since then a total of 74 suspected cases, all in 'skin popping' injecting drug users, have been reported to the Health Protection Agency's (HPA) Communicable Disease Surveillance Centre (CDSC) (Hope *et al*. 2004; Brett *et al*. 2004;. All these patients were diagnosed clinically and microbiological confirmation was possible in 34, i.e. about half the cases (Table 1). Both in the American and British patients type A toxin accounted for 80–90% of the cases. There have also been small clusters of cases in injecting drug users in Norway and Switzerland. In marked contrast, there have been no cases of food-borne botulism reported in the UK since 1998.

The European cases of wound botulism have been associated with the use of heroin in powder form originating from Asia. Heroin is

Year	No. of reported cases	No. (%) micro-biologically confirmed	*C. botulinum* type (no. of patients)
2000	6	3 (50%)	A (3)
2001	4	3 (75%)	A (3)
2002	23	14 (61%)	A (12)
			B (2)
2003	14	7 (50%)	A (6)
			A + B (1)
2004	27	7 (26%)	A (6)
			B (1)

Table 1 UK cases of wound botulism (Brett *et al*. 2000; unpublished data, Health Protection Agency)

poorly soluble and is dissolved by mixing with a weak solution of citric acid and then gentle heating – these conditions encourage germination of spores and kill other organisms that could compete with *C. botulinum*. Moreover, repeated injection of an acidic solution damages tissues and facilitates anaerobic conditions (Brett *et al*. 2004). Cleaning the skin before injection does not seem to reduce the risk significantly.

Intravenous injection or snorting/sniffing drugs are much less likely to cause wound botulism.

In the Californian series, drug-injecting patients were older than those with wound botulism from other causes (median age 40 years vs. 28 years; Werner *et al*. 2000). Many had resorted to 'skin popping' after they had 'used up' their veins. There were more women compared to non-injecting patients, apparently because female drug users preferred a non-intravenous route of administration. In the British series, the age range was 22–51 years with a mean of 29 and 37% were females (Brett *et al*. 2004).

CLINICAL PICTURE AND DIFFERENTIAL DIAGNOSIS

The clinical picture is similar in food-borne and wound-borne botulism, although only the former causes gastrointestinal symptoms at the onset (Hughes *et al*. 1997). Classically, botulism presents as a descending, symmetrical, flaccid paralysis. The median incubation period from injury to onset of neurological symptoms in wound botulism unrelated to drug abuse is 6.5 days (range 4–13 days) (Werner *et al*. 2000) compared to 18–36 h (range 6 h to 8 days) in food-borne botulism (Hughes *et al*. 1981). In injecting patients the incubation period is difficult to determine because they inject regularly, and there usually are multiple skin lesion.

Patients develop signs of ocular paresis with blurred vision, diplopia and ptosis accompanied by, or closely followed by dysphonia, dysarthria, dysphagia and facial weakness. In some patients bulbar or facial paresis precedes ocular weakness. The pupils may be sluggish from onset or become poorly reactive and dilated later, but pupillary abnormalities are present in only about half the cases. Patients typically complain of dry mouth. A descending paralysis of the neck, limbs and respiratory muscles then develops. Atypical presentations have been described with weakness of the neck muscles before cranial nerve palsies, or fulminant respiratory failure before oculobulbar and limb weakness is fully developed (Brett *et al*. 2004). Deep tendon reflexes may be normal or depressed, but areflexia does not develop until the relevant muscles are completely paralysed. Sensation is normal and patients are alert and apyrexial (unless another concomitant infection is present). The blood and CSF investigations are unremarkable. Creatine kinase level is normal and the tensilon test may be weakly positive.

The differential diagnosis includes other paralytic illnesses most importantly myasthenia gravis and the Guillain–Barré syndrome, particularly the Miller–Fisher variant. Poliomyelitis, viral encephalitides, brain-stem stroke, tick paralysis, organophosphate and magnesium poisoning should also be considered (Table 2, see also Merrison *et al*. 2002).

CASE REPORT

A 47-year-old male, who had been using drugs for 20 years and recently had been 'skin popping', woke up with blurred vision and then developed double vision, slurred speech and swallowing difficulties. In the evening he presented to his local hospital where initial examination revealed bilateral ptosis, restriction

Table 2 UK cases of wound botulism (Hope *et al*. 2004; Brett *et al*. 2004)

		Investigations			
Disease	Clinical features differentiating from wound botulism	Neuro-physiology	CSF	Tensilon test	Serum antibodies
Guillain–Barre syndrome	Ascending paralysis Sensory symptoms/signs, pain Ophthalmoplegia rare (3–5%) Areflexia/hyporeflexia	Slowing of nerve conduction (denervation in axonal variant) No post-tetanic facilitation	Elevated protein	– ve	Campylobacter jejuni (15–20%) Antiganglioside antibodies (GM1, GD1a)
Miller–Fisher syndrome	Ataxia › weakness (ascending) External ophthalmoplegia (may be some pupil involvement) Areflexia	Normal or mild reduction of muscle action + sensory action potentials	Elevated protein	– ve	GQ1b antiganglioside
Myasthenia gravis	Fatiguable weakness No descending pattern Asymmetric and less severe external ophthalmoplegia Normal pupils Normal reflexes	Decrement of muscle action potential on repetitive stimulation	Normal	+ + ve	Acetylcholine receptor
Brain-stem stroke	Pyramidal weakness Hyperreflexia, extensor plantars Isolated cranial nerve palsies or brain-stem eye movement disorder Sensory findings/ataxia	Normal	Normal or mildly elevated protein	– ve	_
Poliomyelitis	Pyrexia and altered conscious level Asymmetric flaccid paralysis legs › arms Ocular weakness very rare	Denervation (after 2–4 weeks)	Pleocytosis	– ve	Increased viral titre in convalescent sample
Tick paralysis	Ascending weakness Cranial muscles rarely involved Paraesthesia of affected limbs Presence of a tick	Reduced muscle action potential Abnormalities of neuromuscular ransmission	Normal	– ve/(+)	_
Organophosphate poisoning	Altered mental state Ascending weakness Fasciculation Muscarinic symptoms, myosis	Repetitive discharges after single shock Decremental response on repetitive stimulation	Normal	– ve	_
Lambert– Eaton myasthenic syndrome (LEMS)	Mainly proximal muscle weakness No ocular or bulbar weakness usually Paraneoplastic in 50%	Low amplitude muscle action potential Decrement on repetitive stimulation at 3–5 Hz Much greater post-tetanic facilitation than in botulism	Normal	+ ve	Voltage-gated calcium channel
Diphtheria	Slow evolution (weeks) Bulbar weakness followed by accommodation paresis/ opthalmoplegia Predominantly sensory neuropathy	Sensory › motor demyelinating polyneuropathy	Normal or elevated protein	– ve	_
Magnesium poisoning	High Mg^{2+} level	Similar to LEMS	Normal	– ve	_

of eye movements, diplopia in all directions of gaze and dysarthria, but no limb weakness and no long tract signs. He had a buttock abscess, which was drained, and multiple smaller lesions at other injection sites, which did not appear infected. He was admitted with a suspected diagnosis of brain-stem stroke. His brain CT scan was normal. On the third day he had a respiratory arrest and was ventilated. On admission to the ITU he was noted to have some limb weakness which, over the next two days, progressed to nearly complete flaccid paralysis of all limbs. At that stage a neurological opinion was obtained. Examination revealed a conscious, ventilated patient with bilateral complete ptosis and external ophthalmoplegia, dilated and poorly reactive pupils, absent gag reflex, flaccid paralysis of all limbs except for some distal movement, depressed reflexes and flexor plantar responses. Sensation appeared to be intact. A clinical diagnosis of wound botulism was made and he was given trivalent botulinum antitoxin followed by further surgical debridement of skin lesions and a 10 day course of benzylpenicillin 1.8 g qds plus metronidazole 500 mg tds. Six weeks later he was still in ITU but had been gradually weaned off the ventilator. There had been a steady improvement of his oculobulbar and limb function, and he had started to stand with support. The microbiology investigations for botulinum toxin in the serum and *C. botulinum* isolation from the abscess were negative.

This patient's presentation was very similar to that of our previous patient (Merrison *et al.* 2002) and many others in the literature (Werner *et al.* 2000; Brett *et al.* 2004). The evolution of symptoms, as in this case, was rapid (1–3 days), but wound botulism may develop more gradually over 7–14 days suggesting a slow release and cumulative effect of the toxin (Brett *et al.* 2004). Because the binding of botulinum toxin at the neuromuscular junction is irreversible, recovery can only occur through terminal axonal sprouting and reinnervation which takes from a few weeks to about a year (Wilcox *et al.* 1990). Recovery is usually complete but patients may complain for a long time of reduced physical stamina and a dry mouth. Case fatality is about 10%.

INVESTIGATIONS

All suspected cases in the UK should be reported to the CDSC and referred to the HPA Food Safety Microbiology Laboratory for microbiological investigations which include:

- examination of serum samples for botulinum toxins in a standard mouse bioassay and identification of toxin type by neutralization antibodies;
- isolation of *C. botulinum* in samples of tissue and pus from wounds;
- detection of toxin in tissue specimens.

In the Californian series, toxin detection in serum was positive in 95% of injecting patients and 83% of non-injecting patients, and *C. botulinum* was isolated from wounds in 65% of cases (Werner *et al.* 2000). In the UK patients, the yield of microbiological investigations has been much lower (Table 1). In all these cases a firm clinical diagnosis of botulism was made with no diagnostic alternative.

There are several possible reasons for failing to confirm the diagnosis microbiologically: insufficient sample size, low levels of circulating toxin either because it has already been irreversibly bound or because it has been released slowly in small amounts, or samples being taken after starting antibiotics.

Neurophysiology studies are diagnostically helpful (Cherington 1998). The most consistent abnormality is a small muscle action potential after a single supramaximal stimulus in a clinically affected muscle. Post-tetanic facilitation, similar to but less spectacular than in the Lambert–Eaton syndrome, can be found in some muscles after rapid (50Hz) supramaximal nerve stimulation (or isometric exercise) in about 60% of patients, but this is not absent in more severely affected muscles. Sensory nerve amplitudes and sensory and motor nerve conduction velocities are normal. After an appropriate interval, needle EMG shows features of denervation.

TREATMENT

Treatment consists of trivalent (A, B, E) equine antitoxin, thorough surgical debridement of suspected sites of infection, some of which may look very innocuous but still harbour *C. botulinum*, and high dose intravenous bezylpenicillin often combined with metronidazole. In mild cases antitoxin may not be necessary. About 75% of patients require mechanical ventilation and ITU care.

Botulism caused by type A strains of *C. botulinum* tends to be more severe; the mean period of mechanical ventilation has been reported to be 58 and 26 days for type A and type B cases,

PRACTICE POINTS

- Wound botulism occurs in 'skin popping' heroin users as a result of contamination of the injection sites with *C. botulinum* spores and production of botulinum toxin *in situ*.
- Contaminated injection sites often do not look infected.
- There is descending paralysis with oculobulbar, respiratory and limb weakness in a conscious, apyrexial patient.
- The diagnosis should be considered in any paralytic illness in an injecting drug user.
- About 75% of patients develop respiratory failure and require mechanical ventilation.
- Gastrointestinal symptoms at the onset are not a feature but there often is autonomic involvement (e.g. dilated pupils, dry mouth).
- Neurophysiology can be helpful in the diagnosis, but essentially the early diagnosis is clinical.
- Microbiology investigations include detecting botulinum toxins in serum and isolation of *C. botulinum* from tissue samples but are positive in only about half the cases, or less.
- Early treatment is with trivalent (A, B, E) botulinum antitoxin
- Surgical debridement of suspected skin lesions and antibiotic therapy are essential.

Wound botulism among drug users in the UK shows no signs of subsiding and in 2004 there were considerably more suspected cases than in 2003

respectively (Hughes *et al*. 1981). In retrospective studies, early administration of botulinum antitoxin has been reported to reduce case fatality from 46% in untreated cases to 10% in those treated within 24 h and 15% in those treated after more than 24 h (Tacket *et al*. 1984), and appears to be associated with a shorter period of artificial ventilation and fewer pulmonary complications (Sandrock & Murin 2001). It is therefore essential not to delay treatment in clinically diagnosed cases while waiting for microbiological confirmation, which may be negative anyway. Twenty-four hour advice on the supply of botulinum antitoxin is available from the CDSC.

Wound botulism among drug users in the UK shows no signs of subsiding and in 2004 there were considerably more suspected cases than in 2003 (Table 1). Whether this is a true increase or due to increased awareness of the problem among physicians, and improved reporting, is not clear. Indeed, has there been an underestimate of the problem? Could some cases of sudden death among injecting drug users have been due to botulism? It seems likely that we shall see more of it in the future and it is essential that this diagnosis is considered at the very start in any case of paralytic illness in an injecting drug user, and treatment given as early as possible to prevent respiratory failure and a lengthy stay in ITU.

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