NEURO-OPHTHALMIC FINDINGS IN BOTULISM TYPE B

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SUMMARY

In June 1989, the largest recorded outbreak of food-borne botulism occurred in the United Kingdom. Twenty-seven patients were affected during the outbreak with type B botulism. A case note review of 14 patients admitted with this condition was performed and the neuro-ophthalmic findings are presented. Patients with severe disease presented with a combination of ocular and bulbar symptoms; in mild cases dysphagia was noted first and visual disturbance followed within 24 hours. Clustering of cases and bilaterality of cranial nerve signs aided in the diagnosis. Accommodative paresis and sixth cranial nerve palsy were frequent early signs. When there was respiratory paralysis and ventilatory failure, it occurred within 12 hours of the onset of a third cranial nerve palsy.

The organism responsible for botulism was discovered by Professor Emile van Ermengem in 1896 after investigating an illness in a group of musicians who had eaten raw salted ham after playing at a wake. Three of the musicians died. The organism, *Clostridium botulinum*, is an anaerobic, spore-forming, Gram-positive bacillus with a world-wide distribution. Food-borne botulism is rare in the United Kingdom. It is a potentially lethal condition that may present initially to an ophthalmologist due to visual impairment. The organism produces a polypeptide toxin with a molecular weight of 15 000 daltons. It is one of the most potent toxins known to man. Three serologically distinct toxins (A, B and E) are found in human botulism. The toxin acts on neuromuscular junctions and cholinergic sites within the autonomic nervous system (all ganglionic synapses, and post-ganglionic parasympathetic synapses) by binding irreversibly to receptors on the pre-synaptic membrane. This is followed by endocytosis, and through a process of enzymatic coupling the toxin prevents the normal calcium-associated quantal release of acetylcholine from the pre-synaptic nerve terminal.[1] Recovery can occur only by the formation of new axon terminals, with the regenerating axon forming contacts at the original synaptic sites.[2]

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Patients present clinically within 12–36 hours of ingestion of contaminated food. They may state that the food had an abnormal taste. One third of those affected may develop transient nausea and vomiting, abdominal pain and diarrhoea or constipation. There then develop oculobulbar signs followed by a descending paralysis. Clinical features include blurring of vision, dilated pupils, ptosis, external ophthalmoplegia, dysphagia and dysarthria. These features are often bilateral and may progress to weakness affecting the upper then the lower limbs, and in some cases respiratory muscle weakness requiring assisted ventilation. Important negative findings are a lack of fever, no sensory symptoms and no change in mental state. The differential diagnosis includes Guillain–Barré syndrome (however in this condition the paralysis is ascending), Miller–Fisher syndrome, myasthenia gravis, diphtheria, and brain stem stroke.

In June 1989, the largest recorded outbreak of food-borne botulism in the United Kingdom occurred in the North-West of England and North Wales. The neuro-ophthalmic features of this outbreak are now presented.

PATIENTS AND METHODS

A total of 27 patients (10 male, 17 female; age range 14 months to 74 years) were affected during the outbreak. The case notes of 11 patients admitted with botulism to the Victoria Hospital, Blackpool, and 3 patients admitted elsewhere were reviewed. All patients initially presented to the acute medical services. Clinical information was therefore obtained from the findings of the admitting physicians in all 14 patients. Eleven of the patients were subsequently reviewed by a consultant ophthalmologist with a formal orthoptic assessment.

RESULTS

Of the 27 patients affected, 25 had eaten one brand of hazelnut yoghurt before the onset of symptoms. Critchley *et al.*[3] reviewed the main symptoms of all the patients in the outbreak and noted that 21 (77.7%) complained of blurring of vision, 15 (55.5%) complained of drooping lids and 8 (29.6%) complained of double vision. The duration between consumption and onset of symptoms was 2

Table I. Neuro-ophthalmic findings in 14 patients with type B botulism

Clinical findings	No. of patients	% bilateral
Third cranial nerve palsy		
Accommodative paresis	13	100
Ptosis	12	92
Ophthalmoparesis	8	75
Dilated pupils	2	100
Sixth cranial nerve palsy	11	64
Seventh cranial nerve palsy	8	75
Nystagmoid eye movements on lateroversions	3	100
Conjunctival injection	4	75
Epiphora	4	100

hours to 5 days (mean 1 day). In severe cases ocular and bulbar signs were present simultaneously; in milder cases, difficulty in swallowing was noted first and visual disturbance followed within 24 hours. Those patients admitted within 48 hours of the initial symptoms had both ocular and bulbar signs. Disease progression with spread of neurological deficit followed rapidly over the successive 3 days. Twelve patients were admitted to the Intensive Therapy Unit, 8 required artificial ventilation, and one 74-year-old woman died from aspiration pneumonia.

The neuro-ophthalmic finding of the 14 patients with case note review are summarised in Table I. Seven patients with ophthalmoparesis secondary to third cranial nerve palsy had restriction of elevation of the eye, and 1 patient had restriction of both adduction and elevation. No patient was documented as having a fourth cranial nerve palsy. Eleven patients had restriction of eye abduction. A full recovery of cranial nerve signs was noted in all the survivors in the case note review, with the exception of 1 patient who had a previously diagnosed V pattern esotropia. The speed of recovery of the ocular signs was related to the severity of the disease. Those patients requiring assisted ventilation had the most prolonged recovery, with a mean inpatient stay of 38 days compared with 14 days in patients not requiring ventilation.

DISCUSSION

The early ophthalmic signs of botulism included accommodative paresis and sixth cranial nerve palsy. The severity of the ophthalmoparesis was a good indicator of the overall severity and progression of the disease. When there was ventilatory failure, it occurred within 12 hours of the onset of a third cranial nerve palsy. Terranova *et al.*[4] noted that sixth cranial nerve palsy may be the initial neurological manifestation of type B botulism. He also noted that 8 of 11 (73%) patients with evidence of a third cranial nerve palsy eventually developed respiratory insufficiency.

Double vision was noted to be a symptom in only 8 (29.6%) of the patients in the outbreak; however, 11 of the 14 patients in the case note review had evidence of sixth cranial nerve palsy. It is probable that associated lid ptosis reduced the frequency of this complaint in these patients.

Accommodative paresis was seen in 13 of the 14 (93%) case notes reviewed and symptoms of blurring of vision were noted in 21 (77.7%) of the patients in the outbreak. A more benign form of type B botulism has been reported where the major symptom was blurring of vision, together with a dry mouth and dry eye and no progression to a descending paralysis.[5–7]

Three patients had nystagmoid eye movement on lateral gaze. Hedges *et al.*[8] examined 2 patients with botulism who had rapid quivering eye motions during attempts to re-fixate laterally placed objects. Oculographic studies showed multiple hypometric saccades and Hedges *et al.* postulated that the toxin limits the duration of saccadic burst innervation to the extraocular muscles.

In this outbreak there was a wide dispersion of cases geographically which initially added to the difficulty in diagnosis. There were four family groups with the disease (together with one cat who remained well after eating the remains of a yoghurt carton!) Clustering of cases, together with rapid onset of symptoms and symmetry of physical findings, all suggest the clinical diagnosis. Eighty-seven per cent of neuro-ophthalmic signs in the case notes reviewed were bilateral.

Public Health Laboratory investigations showed that the processing of the hazelnut conserve for the yoghurt was inadequate to destroy the *Clostridium botulinum* spores. Type B toxin was identified (by the mouse bioassay test) from the stool of 1 patient, 1 tin of hazelnut puree, and 2 cartons of hazelnut yoghurt from the patient's home.[9] All serological tests for botulism in affected patients were negative.

Some unusual features of the outbreak were noted, including sore throats in 7 patients, watering eyes in 4, and fever in 8. Electrodiagnostic tests were also unusual in that they showed evidence of segmental demyelination as seen in post-infectious neuropathy. Classical electrodiagnostic findings in this condition show normal motor and sensory conduction velocities, with reduced amplitude of the evoked compound muscle action potential in affected muscles, with increment in the muscle action potential with rapid repetitive nerve stimulation (50 Hz) or after exercise (as also seen in other pre-synaptic disorders such as Eaton–Lambert syndrome).[10,11]

Medical treatment of botulism is essentially supportive. Antitoxin has been shown only to shorten the duration of illness in type E botulism, but it should still be given to patients with botulism as soon as the diagnosis is suspected as it can only act before the toxin is irreversibly bound to its receptor on the pre-synaptic membrane.[12,13] Adverse reaction to the antitoxin may be seen in up to 20% of patients. Guanidine is a compound that enhances release of acetylcholine from the pre-synaptic nerve terminal. It has been used in botulism but has only a slight effect on limb and ocular muscles and no effect on respiratory muscle.[14]

Patients presenting with oculobulbar symptoms may undergo a tensilon test to exclude myasthenia gravis, but false positives may occur in mild forms of botulism.[3,14–16]

Clinical improvement occurs over weeks to months. In the United States the mortality from this condition is

7.5%.[17] In less well developed countries the mortality is higher.[18] The combination of poor oropharyngeal function, respiratory muscle paralysis and a paralytic ileus results in a high risk of aspiration pneumonia, with subsequent respiratory failure and septicaemia. Patients with suspected botulism should have regular monitoring of respiratory function, but care should be taken with conventional respiratory monitoring in the presence of orofacial weakness.[19]

There are some clinical differences between the three neurotoxins producing botulism. Type E botulism is usually associated with eating seafood, and pupillary abnormalities and ptosis may be seen as early signs.[20–23] Preceding gastrointestinal symptoms are more prevalent in type E and type B botulism.[24] Type A botulism is the most severe form of the disease and carries the highest need for ventilatory support and also has the highest mortality.[16,25–28]

The most important aspect of management of an outbreak of food-borne botulism, however, is the early recognition of the condition, and an appropriate public health investigation to determine the source of the outbreak and prevent further spread of the disease.

Key words: Botulism, Ophthalmoplegia, Pupils, Vision disorders.

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