Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases

Botulinum toxin type A (BT/A) is commonly used nowadays in the treatment of patients with localised muscle spasticity. The toxin, in therapeutic doses, is considered to be effective and safe.1 Systemic adverse effects of BT/A are rare and include flu-like symptoms, anaphylactic reactions, and excessive fatigue. Generalised clinically detectable muscle weakness has not been reported in patients treated with BT/A. Similarly, changes in cardiovascular function are not detectable at clinically recommended doses. These symptoms were well tolerated by the patient presented in this report. A single fibre EMG abnormalities have been previously documented.2 We report two patients in whom treatment with therapeutic doses of BT/A resulted in a generalised muscle weakness with widespread EMG abnormalities which were typical of botulism.

Patient 1 was a 57 year old woman with longstanding spastic paraparesis due to multiple sclerosis. Four years after diagnosis the patient presented with painful spasticity of her hip adductors and "scissoring" of her gait. These symptoms resolved well with intermittent obturator nerve blocks with 50% alcohol. However, she started to develop severe spasticity of the hamstring muscles for which she was referred for treatment with BT/A.

She had moderate severe spastic paraparesis. Muscle tone was greatly increased in the hamstring muscles of the left leg. Hand grip was weak. She was able to stand independently and walk indoors with a gutter frame roller, although she could not fully extend her left knee in stance.

The patient was treated with a total of 250 units BT/A Dysport which was divided between the medial and lateral hamstring muscles of the left leg. Four days after the injections she complained of sudden onset of hoarseness of her voice, inability to walk, and she could not hold her head up. Routine neurological examination confirmed severe flaccid paraplegia, severe weakness of neck flexors, dysphonia, and right partial ptosis. The rest of the examination was unremarkable. Routine investigations including a full blood count, erythrocyte sedimentation rate, and urine culture were normal. An EMG showed evidence of denervation in the left hip flexors, neck flexors, and facial muscles with carpal radialis. Single fibre EMG confirmed the increase in jitter values and blocking. The jitter values ranged from 926 to 408 μs (normal value < 57 μs) and blocking ranged from 14% to 36%.

The lower limb and neck muscle weakness improved gradually and four weeks later the findings on clinical examination and function were assessed similar to those before treatment with BT/A. EMG studies were not repeated.

Patient 2 was a 34 year old woman with multisystem atrophy who developed mild dysphagia, neck pain, and stiffness. Over the next few months her chin started to progressively turn to the left. She had dysarthria, intention tremor of both hands, ataxic broad base gait, and sensor plantar responses. Routine blood fasting and spasmidic torticolis. Serum copper studies were normal and there were no acanthocytes on a blood film. Brain MRI showed brain stem and cerebellar atrophy. A trial of anticholinergics was unsuccessful.

The patient was then treated with BT/A: 250 units of Dysport were injected into the right sternomastoid and left splenius capitis muscles and 500 units into the left middle trapezius. The neck pain resolved and the neck posture improved considerably for about two months. No adverse effects were reported. The injections were repeated every two to three months using the same protocol and dosage schedule each time. One week after the third treatment session the patient developed difficulty in dysphagia lasting 10 days. There were no further adverse effects until five years later, when three weeks after the injection, the patient presented with dysphagia, severe dysthria, diplopia, and generalised, EMG confirmed widespread denervation. Similarly, single fibre EMG of the right extensor digitorum communis was abnormal with very prolonged jitter values and increased blocking.

The patient's neurological symptoms and signs gradually improved over the next four weeks and four months later her condition was similar to that before the botulinum toxin injection. A repeat conventional intra muscular EMG was normal. The patient declined to have single fibre EMG studies.

The two patients reported here developed a syndrome of botulism after intramuscular injections of therapeutic doses of BT/A drawn from two different batches of the drug. In the first patient these symptoms occurred only after one dose, whereas in the second they developed after five years of regular treatment with the toxin. Clinically detectable weakness was present in the extracocular, bulbar, trunk, and limb muscles and EMG changes were recorded in all muscles tested. The muscle weakness and EMG changes resolved a few weeks later.

Generalised muscle weakness has not been reported previously in patients treated with BT/A. Anderson et al4 have described a patient with longstanding paralytic polio who reported deterioration in pre-existing lower limb muscle weakness after the injection of BT/A (Botox) into his neck muscles for spasmidic torticolis. Although muscle weakness was not confirmed on physical examination. Some patients treated with BT/A had prolonged jitter values and increased blocking on single fibre EMG from muscles distant to the site of injection. This suggests the spread of the toxin to distant muscles even though the patients did not exhibit objective weakness in these muscles or have abnormalities on conventional EMG. The co-occurrence of generalised muscle weakness and abnormalities on conventional EMG in our patients may be an indication of the severity of the neuromuscular transmission block.

It is difficult to explain the generalised botulism-like syndrome in our patients given that the great majority of patients do not show such an effect. The total dose of the toxin given per session did not exceed 1000 units of Dysport, which is well below the maximum recommended dose. Since the toxin is injected into a defined muscle, a dosing error could not have resulted in a total dose higher than 500 units in patient 1 or 1000 units in patient 2. The use by some authors of the terms "resembles botulism" was not associated with adverse effects. It is unlikely, therefore, that the generalised muscle weakness resulted from an overdose.