

### 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.<sup>1</sup> Systemic adverse effects 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 on conventional EMG in muscles distant from the site of the toxin injection have not been reported,<sup>2</sup> although single fibre EMG abnormalities have been previously documented.<sup>3</sup> 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 67 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 responded well to 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 moderately severe spastic paraparesis. Muscle tone was greatly increased in the hamstring muscles of the left leg. However, the patient was able to stand independently and walk indoors with a gutter frame rolater, 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 to hold her head up. Neurological examination confirmed severe flaccid paraplegia, severe weakness of neck flexors, dysphonia, and right partial ptosis. The rest of the physical 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 adductors, biceps femoris and flexor carpi radialis. Single fibre EMG confirmed the increase in jitter values and blocking. The jitter values ranged from 92.6 to 408  $\mu$ s (normal value < 57  $\mu$ s) 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 functional assessment were 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 based gait, a right extensor plantar response, and spasmodic torticollis. 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 anticholinergic drugs 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 mid-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 transient 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 dysarthria, diplopia, and generalised, moderately severe weakness involving the neck, trunk, and limb muscles.

Conventional intramuscular EMG of the right quadriceps femoris, tibialis anterior, first dorsal interosseus, and biceps muscles 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 weeks and four months later her condition was similar to that before the botulinum toxin injection. A repeat conventional intramuscular EMG was normal. The patient declined to have single fibre EMG studies.

The two patients reported here developed a syndrome which resembles 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 after only one dose, whereas in the second they developed after five years of regular treatment with the toxin. Clinically detectable weakness was present in the extraocular, 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 al*<sup>4</sup> 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 spasmodic torticollis. However, 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 recorded from muscles distant from the site of injection.<sup>3</sup> This suggests 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 supplied in 500 unit vials, a dispensing 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<sup>5</sup> of up to 5000 units Dysport was not associated with adverse effects. It is unlikely, therefore, that the generalised muscle weakness resulted from an overdose. An

increased sensitivity to the toxin seems unlikely to be present intermittently (patient 2) and it is possible that some of the toxin was inadvertently injected directly into the vascular capillaries.

The findings reported here suggest the need for regular long term monitoring of patients treated with BT/A. The absence of adverse effects at the commencement of treatment should not be relied on as evidence that a future injection would not cause an adverse response.

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### Feeling cold: an unusual brain injury symptom and its treatment with vasopressin

Some 12 years ago, a man was assessed for medicolegal purposes for the late effects of a severe head injury sustained almost five years earlier. After severe visual impairments from injury to the optic chiasma, he rated as his second worst problem the fact that ever since the injury he had always felt cold, although objectively he was no more than cool to the touch and had normal sublingual temperature. He and his partner described how even in high summer he would sit in front of a fire wearing two or more sweaters and a blanket or two, yet still feel uncomfortably cold. This was in stark contrast to his preinjury habit of driving his long distance lorry in rolled up shirtsleeves with the cab window open, summer and winter alike. Other residual disorders were total anosmia, mild brainstem motor deficits, and episodic dyscontrol.

He also had moderately severe impairments of attention and memory. At that time we were engaged in a formal study of the effects on such deficits of nasally administered vasopressin (now submitted for publication). Because the extant published studies using forms of arginine vasopressin (DDAVP and DGAVP)<sup>1-5</sup> were almost all negative, but several with lysine vasopressin<sup>6-9</sup> were positive, we were using the second, in the form of Syntopressin nasal spray. In animal studies, this version is reported to have little vasopressor action, and, compared with the arginine derivatives, relatively little antidiuretic but stronger mnemonic effects. In keeping with the procedures of the initial positive studies, a one month period of twice daily administration of about 5 units (one squirt to each nostril)