### 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 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,[2] although single fibre EMG abnormalities have been previously documented.[3] 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 interosseous, 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*[4] 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.[3] 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[5] 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)[1–5] were almost all negative, but several with lysine vasopressin[6–9] 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 mnesic 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)

was completed, cognitive measures being repeated one month after completion.

On review, this patient reported no subjective change in his concentration or memory, although significant improvements in recall memory and new word learning were apparent on neuropsychological reassessment. Quite unexpectedly he declared that he no longer felt cold at all, the change having appeared briskly after about two weeks of treatment and persisting despite the discontinuation after one month. A further contact six months later, after the winter, disclosed that his temperature perception had remained normal without further treatment, although he had continued to take carbamazepine (which stimulates release of endogenous vasopressin) because it successfully controlled his episodic dyscontrol. Follow up 11 years later confirmed that the symptom had never recurred, despite his having discontinued carbamazepine some seven years earlier. (He had remained totally anosmic.) This permanent improvement after only a month's treatment parallels what was reported in earlier studies of Syntopressin in memory disorders, as well as our experience of those whose cognitive states improved in our own study.

Since this unexpected finding, I have seen a further 12 patients with the same symptom, 11 after severe traumatic brain injuries (coma range 3–70 days, mean 16·8, median 8, SD 17·8; post-traumatic amnesia 6–150, mean 58·1, median 42, SD 39·8 days) and one after carbon monoxide poisoning (coma 14 days, post-traumatic amnesia 150 days). In 10 of the 13, the patient or a relative spontaneously mentioned the symptom; in three with very poor communicative ability it was inferred from the consistent wearing of excessive clothing. All were slightly cool to the touch, but not cold. In no case was the sublingual temperature abnormally low. Three patients had thyroid function tests performed, the results being normal in each case. The patients were culled from three settings: three were from 659 seen in a general hospital head injury clinic (0·5%), five among 502 seen medicolegally (1%), and five from 167 treated in a residential rehabilitation unit (3%). The symptom thus seems to be quite rare. The relative frequencies, given the different kinds of populations, raise the possibility of an association with more severe injury, although they might simply reflect the greater opportunities for observation and comment with inpatients.

Nine patients were male, the male:female ratio of 2·25:1 being within the range typically seen in traumatic brain injury. There did not seem to be any uniformity in the patterns of injury or of residual disorders. Seven of the 13 were anosmic, three unilaterally, although two with bilateral anosmia recovered olfaction after 23 and 47 months and one with unilateral anosmia at nine months. Four had diabetes insipidus in the acute stage (three of them were anosmic), but in none of these did it persist. Ten had residual disabilities due to brainstem dysfunction. The only feature common to all 13 was that the acute brain injury was complicated by considerable global brain swelling identifiable on CT. Despite this, age at injury did not seem to be important, the range being 15 to 57 (mean 30·8, median 29, SD 12·4).

Of the 13 patients, 11 stopped feeling cold completely and permanently after one month's treatment with Syntopressin; one was much improved, but not to a normal level. One of two 15 year old girls (not anosmic) was unchanged. The duration of the symptom (3 to 88 months, mean 35·5, median 34, SD 21·4) did not seem to be a factor determining the response, the girl who did not respond being 33 months from injury. Indeed no specific aetiological or prognostic factors could be identified. (The occurrence of significant brain swelling in all patients suggests the possibility of compressive injury to the diencephalon, where vasopressin is produced, but this is unlikely to be a specific causal factor, as large numbers of patients with this complication do not develop the symptom.) In view of the earlier literature discussed above, it was interesting that four of the responders had previously been treated (for other reasons) with DDAVP, without any effect on the symptom of feeling cold. It has been argued that intranasal vasopressin might reach the base of the brain via nervous or lymphatic structures in the olfactory nerves, so it is of interest that traumatic anosmia clearly did not impede responsiveness.

Although vasopressin is known to be present in neurons distributed widely through the diencephalon and limbic areas, and to have effects on mechanisms of arousal and possibly learning that are distinct from its extracerebral effects on renal function,[10] no clear explanation of this effect on temperature perception is apparent. Nor is it easy to see how such short term treatment should produce lasting improvement, although there is a parallel with some effects of dopamine agonists on post-traumatic motivational deficits.[11 12]

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## Nerve growth factor concentrations in human cerebral blood vessels

The nerve supply to cerebral blood vessels plays an important part in migraine and cerebral vasospasm, via sympathetic fibres containing the vasoconstrictors noradrenaline and neuropeptide Y (NPY), and sensory fibres containing vasodilators substance P and calcitonin gene related peptide (CGRP). As evidence in rodents and humans supports the view that sympathetic fibres and sensory neuropeptides are dependent on nerve growth factor (NGF),[1] we have studied NGF concentrations in human cerebral vessels.

The circle of Willis was collected postmortem from subjects with no known neurological disorder (mean age 72 years, range 61 to 79 years; postmortem delay: mean 23 hours, range 18 to 28 hours), and dissected before storage at $-70^{0}$C. A specific enzyme linked immunoassay was used to measure NGF-like immunoreactivity, with recombinant human NGF as standard.[2] The table shows that NGF concentrations were lower in anterior than in posterior cerebral vessels in the circle of Willis, with a significant age related decline.

This is the first demonstration of NGF in human cerebral blood vessels. The NGF concentrations measured in cerebral blood vessels are similar to those in human skin and nerve. There seems to be a decline of NGF with aging, and we propose to extend the range of study to younger subjects. NGF is produced by vascular smooth muscle cells and fibroblasts, and processes such as atheromatous change may contribute to decreased NGF production in old age. The relevance of the regional differences in NGF concentrations in the circle of Willis is unknown; as there is evidence that the density of the sensory and sympathetic peptidergic innervation is greater in the anterior circle of Willis, there seems to be an inverse correlation with NGF concentrations. One explanation for this may be less uptake and transport of NGF away from the blood vessels by the fewer fibres in the posterior circle of Willis, perhaps analogous to the higher NGF concentrations found in the frontal cortex when cholinergic fibres that take up NGF from this region and transport it to basal regions have degenerated in Alzheimer's disease.

The presence of NGF in blood vessels is consistent with the neurotrophic theory—that is, that NGF regulates the density of vascular sympathetic and peptidergic sensory fibres. There is increasing evidence to support the hypothesis that NGF may regulate nociception in humans,[1] and that NGF in blood vessels may regulate the presentation of migraine and other vascular head pain. The frequency and severity of migraine declines with age, as do NGF dependent substance P, CGRP and NPY concentrations in human cerebral vessels.[3] The target organ (the blood vessel) has been shown to be responsible for the reduced cerebral vessel innervation in aged rats, and NGF infusion can reverse this neuronal atrophy.[4] Biopsies of tender superficial temporal arteries in migraine may show oedema, attributed to local release of substance P, and in cluster headache they may show increased mast cells during headache free intervals.[5] NGF sensitises nociceptor fibres, produces neurogenic inflammation via substance P and CGRP, and is associated with increased numbers of mast cells.[1] Oestrogens upregulate NGF receptor mRNA in sensory neurons: migraine is commoner in women, and may be related to menstruation. Corticosteroids help inflammatory vascular head-