Botulinum toxin type A (BTXA) is widely used in neurological therapeutics for a variety of indications such as dystonia, spasticity, hyperhidrosis, and hypersalivation. It is relatively contraindicated in disorders of neuromuscular transmission, in individuals with known hypersensitivity or bleeding disorders, and during pregnancy. Two patients are presented with initially undetermined multisystem neurological disorders and excessive sialorrhea, later diagnosed as mitochondrial cytopathy, who had side effects after treatment with ultrasound guided BTXA injections. Published reports on the use of BTXA injections in hypersalivation of various causes are reviewed, along with the proposed mechanisms of hypersensitivity to BTXA in patients with mitochondrial cytoptathies. Clinicians should be cautious when using BTXA injections in such patients because of the significant risk of side effects.

We report two patients (a brother and sister) who had an unexpected reaction to botulinum toxin injections into their parotid and submandibular glands for the treatment of sialorrhea.

CASE REPORTS
Patient 1
The first patient was a 30 year old man with an insidious onset of intellectual and movement disorders in infancy. He had delayed motor and intellectual development. He was wheelchair bounded, while his language was limited to single words or simple phrases. He had good comprehension and memory, and normal sphincter function. He had no difficulty in swallowing.

Neurologically, multiple systems were affected, resulting in spasticity, pigmentary changes in both eyes on fundoscopy, marked startle response, intention tremor (improved on CoQ10), right foot dystonia, variable dyskinesias of the neck, trunk, and arms, and hypersalivation. His full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, C reactive protein, coagulation screen, vitamin B-12, thyroid function tests, antinuclear antibody screen, protein electrophoretic strip, α-fetoprotein, glucose, folate, acanthocytes, and vitamin E were normal. Plasma lactate was normal. His white cell enzymes and very long fatty acids were normal. Copper studies (Cu and caeruloplasmin) were normal. Genetic testing for spinocerebellar ataxias, DYT-1, Huntington’s disease, dentatorubropallidolysian atrophy, and Friedreich’s ataxia was negative. Cranial MRI showed volume loss of cerebellum and brain stem. Electroencephalography, electromyography, and nerve conduction studies were normal.

In December 2002 the patient received botulinum toxin A (Dysport®) injections as follows: 120 mU in each parotid gland for excessive drooling, 100 mU into the right tibialis anterior muscle and 200 mU into the right tibialis posterior muscle for right foot inturning. There was moderate reduction of saliva secretion and mild muscle relaxation of the right leg. At this stage there were no side effects. The benefit lasted for about two months.

When the effect started to wear off he had further injections, by the same physician, of 120 mU Dysport in each parotid gland and 60 mU in each submandibular gland under ultrasound guidance. He also received 300 mU of Dysport in the right tibialis anterior muscle and 100 mU in the right tibialis posterior muscle. Ten days after this second course of injections the patient started having difficulty in swallowing. He was admitted to hospital for 10 days, needing a nasogastric tube. He improved, but required a fluid diet. The dysphagia had a fluctuating course necessitating a nasogastric tube from time to time. One month after the onset of dysphagia the patient had an episode of pneumonia. He never had fatigue. Dysphagia subsided completely two
months after the second course of injections. A repetitive nerve stimulation test in the proximal and distal muscles (accessory, axillary, and ulnar nerves) of his right upper limb showed no significant compound muscle action potential decrement. Single fibre electromyography of the orbicularis oculi and extensor carpi radialis muscles showed normal muscle fibre jitter and no blocks.

Results of a muscle biopsy carried out a few days before the botulinum toxin treatment showed muscle fibres containing mitochondria with disrupted internal architecture and whorled membranous material within them. Mitochondrial respiratory chain enzymes suggested complex I/III deficiency, as follows:

NADH ubiquinone reductase, 0.141 (normal, 0.104 to 0.268); succinate cytochrome C reductase, 0.019 (0.040 to 0.204); cytochrome oxidase, 0.014 (0.014 to 0.34).

**Patient 2**

The second patient was the first patient’s 32 year old sister. There was a normal pregnancy and a normal neonatal course. She had delayed motor and intellectual development. She sat alone at 9 to 10 months, crawled at one year, and did not walk until 18 months. She never developed speech, but was able to recognise some words. The neurological features of her disorder included spasticity, tremor, and mental retardation. Her neurological condition was very similar to that of her brother, as was her cranial MRI.

As her main problem was excessive drooling she was treated for the first time with botulinum toxin injections (120 mU of Dysport in each parotid gland and 50 mU in each submandibular gland under ultrasound guidance) at the time when her brother had his second course of injections. Her reaction was very similar, with fluctuating dysphagia requiring a nasogastric tube from time to time for a few days, and aspiration pneumonia. The dysphagia was never so severe as to require a percutaneous endoscopic gastric tube during the two months it lasted.

**DISCUSSION**

Sialorrhoea can decrease the quality of life because it causes difficulties in speech and feeding, skin maceration, and social embarrassment. Unfortunately, there have been no double blind placebo controlled studies of BTXA in hypersalivation. There are a few reports describing its use in excessive patients.27 The type of neuromuscular junction defect in these cases is not clear. It may be the result of an associated peripheral neuropathy producing immature newly formed end plates because of reinnervation phenomena.23 24 34 In another single fibre electromyography study in patients with chronic progressive external ophthalmoplegia, increased jitter or block was found in at least one muscle in 13 of 16 patients.27 The type of neuromuscular junction defect in these cases is not clear. It may be the result of an associated peripheral neuropathy producing immature newly formed end plates because of reinnervation phenomena.23 24 34 Indeed, in an ultrastructural study on the neuromuscular junction in patients with mitochondria cytopathy nerve terminals were found to be shrunken.60

Further research is obviously needed to clarify the precise mechanisms underlying these disorders. We suggest that
clinicians should be careful when treating patients with mitochondrial cytopathies with botulinum toxin injections, or even avoid doing so, because of the significant risk of side effects.

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