SHORT REPORT

Problems with botulinum toxin treatment in mitochondrial cytopathy: case report and review of the literature

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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 sialorrhoea, 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 cytopathies. Clinicians should be cautious when using BTXA injections in such patients because of the significant risk of side effects.

Botulinum toxin type A (BTXA) is widely used in neurological therapeutics for indications as varied as focal dystonia, spasticity, hemifacial spasm, hyperhidrosis, and drooling of saliva. It acts by inhibiting acetylcholine release from nerve terminals, producing muscle paralysis. It does this by disrupting exocytosis at the nerve ending. Exocytosis requires the interaction of multiple proteins that are embedded in the vesicle, the cytosol, and the nerve terminal membrane. These proteins are responsible for the attachment of the vesicle to the presynaptic membrane to facilitate exocytosis. BTXA cleaves SNAP-25, a cytosolic protein attached to the presynaptic membrane. The dosage used clinically reduces but does not completely block neuromuscular transmission.^{1 2}

BTXA is relatively contraindicated in the following circumstances:

- in individuals with a known hypersensitivity to any component of the formulation;
- when there are disorders of neuromuscular transmission (such as myasthenia gravis);
- when aminoglycoside antibiotics or streptomycin are already used or are likely to be used;
- when there are bleeding disorders of any type, anticoagulant therapy, or any reason to avoid intramuscular injections;
- during pregnancy.

There are also isolated case reports describing repeated specific problems: marked ptosis in a patient with mitochondrial cytopathy and blepharospasm treated with botulinum toxin injection; general weakness in a patient with amyotrophic lateral sclerosis (ALS) after focal botulinum toxin injection; and severe and prolonged dysphagia complicating BTXA injections for dystonia in Machado-Joseph disease.^{3–5}

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 sialorrhoea.

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, dentatorubropallidoluysian 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

Abbreviations: ALS, amyotrophic lateral sclerosis; BTXA, botulinum toxin type A

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 II/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 drooling, especially in children,⁶⁻⁹ while papers on the use of BTXA in hypersalivation, either idiopathic or secondary to diseases such as Parkinson's disease, progressive supranuclear palsy, ALS, subacute sclerotic panencephalitis, and cancer¹⁰⁻¹⁶ in adults, have included only small numbers of patients. Even the larger studies included only 10 to 13 patients,^{11 12 16} with the dose and method of administration varying. As reported previously, small doses of botulinum toxin are not sufficient to produce benefit, but doses of 50 to 100 mU of Botox® (mean dose 76.6 mU) in the salivary glands seem to be more effective, with long lasting results.¹² This dose appeared not to produce side effects in the patients treated. In a study comparing the two BTXA preparations (Botox and Dysport), a unit of Botox was three to four times as potent as a unit of Dysport,¹⁷ suggesting that the maximum total dose of Dysport in patients with hypersalivation should be 300 to 400 mU. As the submandibular glands produce up to 70% of the saliva,¹² it is important to inject them to obtain a significant reduction in total saliva. As far as technique is concerned, our experience and that in previous reports^{12 16 18} suggests that ultrasound guidance for submandibular gland BTXA treatment is useful for localisation and promotes efficacy and safety.

Our two patients had excessive distressing sialorrhoea. Their muscle biopsy revealed complex II and III deficiency

of the mitochondrial respiratory chain. In the absence of any other defects, and in view of the enzymology and clinical picture, we believe these siblings have a primary mitochondrial disorder. The total dose of Dysport did not exceed the suggested maximum dose in either of them, neither were they underweight (brother 82 kg, sister 56 kg), and the injections were ultrasound guided. Unfortunately they both developed side effects, which we believe reflected a vulnerability to BTXA because of their mitochondrial cytopathy, because the same doses used in other patients with sialorrhoea secondary to Parkinson's disease or stroke have not caused such problems. However, although our patients never had difficulty in swallowing before, we cannot entirely rule out the possibility that they had subclinical dysphagia owing to brain stem and cerebellar involvement.

Dysphagia after injections of botulinum toxin result from weakness of the swallowing musculature caused by local toxin diffusion.⁵ Other proposed mechanisms include systemic distribution by blood flow¹⁹ and retrograde axonal transport to the ipsilateral spinal anterior horn cells, following anterograde transport through the respective axon.^{19 20} Patients who already suffer from diseases of the neuromuscular junction are extremely sensitive to botulinum toxin, and myasthenia gravis and Lambert-Eaton syndrome are contraindications for its use. Subclinical Lambert-Eaton syndrome can even be unmasked after local botulinum toxin injections.²¹ Patients with anterior horn cell disorders, such as ALS or Machado-Joseph disease, are also reported to have hypersensitivity to botulinum toxin.^{4 5}

In addition to our cases, there is a report describing marked bilateral ptosis, weakness of other facial muscles, impairment of speech and chewing, and local swelling in a patient with blepharospasm resulting from mitochondrial cytopathy who was treated with botulinum toxin injections (60 mU of Dysport per eye).³ However, the mechanism resulting in hypersensitivity to botulinum toxin in patients with mitochondrial cytopathies is not fully understood. Patients with mitochondrial myopathies have an increased sensitivity to rocuronium and atracurium, drugs acting by blocking the neuromuscular junction.²² This suggests there is neuromuscular junction dysfunction. Indeed, there are reports mentioning the association of mitochondrial cytopathies with myasthenic symptoms. All patients presented with ptosis and fatigability. The neostigmine test was positive in five of 13 cases, negative in three, and not done in five. Anti-AChR antibodies were negative in seven patients, positive in one, and not tested in five. Thymus enlargement was not found. Neuromuscular block was found in six cases, absent in four, and not sought in three. The types of mitochondrial respiratory chain defect in these cases varied.²³⁻³⁵ In an electrophysiological study of nine patients with mitochondrial myopathy where classical electrostimulation and single fibre EMG were used, normal neuromuscular transmission was found in five cases, slight abnormalities of neuromuscular transmission in three, and in one case the neuromuscular transmission disturbances were of neurogenic origin.²⁴ 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.³⁶

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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