Systemic effect of local botulinum toxin injections unmasks subclinical Lambert-Eaton myasthenic syndrome

In recent years botulinum toxin type A has been introduced as a new symptomatic therapy for focal dystonias. Generalised muscle weakness is reported after overdoses of botulinum toxin, but is a rare clinical phenomenon. However, botulinum toxin spreads to muscles distant from those injected, even in low doses, as shown by single fibre electromyography. There have been no reports of botulinum toxin in patients with a pre-existing alteration of neuromuscular transmission. In one of our patients suffering from blepharospasm local botulinum toxin injection uncovered a Lambert-Eaton myasthenic syndrome (LEMS).

A 63-year-old woman presented with a three year history of severe blepharospasm and mild oromandibular dystonia. A periorbital injection with a total dose of 12 nanograms of botulinum-toxin-A-complex (Porton Down, UK) had been performed in another hospital. After three days the blepharospasm had improved but a mild ptosis on the left eye, nausea, fatigue, and generalised muscle weakness had occurred, all of which resolved within eight weeks. Twelve weeks after the first injection, when we saw the patient for the first time, SFEMG from the right EDC-muscle showed no abnormality: fibre density 1-6, blockings 0%, MCD 22-2 μs (upper limits of our laboratory: fibre density 1-9, mean MCD 3-0 μs). There is a possible relation between the muscle weakness and the botulinum toxin injection remained unclear; the low dose would not be expected to cause generalised muscle weakness.

The blepharospasm recurred 20 weeks after the first treatment with botulinum toxin and the patient requested a further injection. We used a smaller total dose of 8 ng botulinum toxin. After four days the muscles of the pelvic and shoulder girdles became weak and fatigued. The patient had difficulties in rising from a chair and climbing stairs. We found normal motor conduction velocities in the peroneal and tibial nerves and normal sensory conduction velocity in the sural nerve. EMG of the right EDC muscle showed no abnormalities. Laboratory findings of blood and CSF, including immunological parameters, were normal. Anti-AChR antibodies were absent. SFEMG from the right EDC muscle showed a slightly increased fibre density of 1-6, blockings 1% and an increased jitter (MCD 46-2 μs) (fig b). EMG from the thenar muscles after repetitive median nerve stimulation revealed a slight increment of 118% after 3/sec-stimulation and an increment of 229% after 50 stimuli with a frequency of 20/sec (fig a).

These findings were not compatible with a systemic effect of a low dose of botulinum toxin, but suggested an additional presynaptic disturbance of the neuromuscular junction, particularly Lambert-Eaton myasthenic syndrome (LEMS). An intensive search for tumour formation was performed. X-ray of the chest was normal, but cytology of the bronchoscopy lavage showed malignant cells. CT of the lung showed a circular lesion in the upper-lobe of the left lung. Thoracotomy was performed and the left upper lobe was removed. The histopathological examination demonstrated an adenocarcinoma of the upper lobe of the left lung (UIJC-Stage 1; pT1, pN1, M0). The weakness had disappeared completely three months after removal of the tumour.

Botulinum toxin inhibits the release of acetylcholine from the presynaptic site of the motor nerve terminal. After overdoses of botulinum toxin, development of generalised muscular weakness was reported. In the majority of studies and in our own series of more than 2000 local injections, no patient experienced weakness of remote muscles. However, SFEMG can detect botulinum toxin induced disturbances of neuromuscular transmission in muscles distant from those injected before weakness is clinically evident. In our case both low-dose botulinum toxin injections coincided with a period of transient pelvic-girdle muscle weakness. If the weakness had been induced by the systemic botulinum toxin effect only, we would expect an involvement of more distal muscles. SFEMG findings of an increased jitter were not specific, but consistent with a botulinum toxin induced disturbance of neuromuscular transmission. However, electromyographic findings of a marked incremental response to high-rate repetitive stimulation could not be explained as an effect of the small botulinum toxin dose and it indicated an additional disturbance of neuromuscular transmission. Incremental responses are well known in systemic botulism, but they are not reported in cases who received only therapeutic doses of botulinum toxin. Lambert-Eaton myasthenic syndrome (LEMS) was therefore suspected and a malignant lung tumor was found.

LEMS is an acquired autoimmune disorder of neuromuscular transmission. Secondary to the IgG-induced blockade of voltage dependent calcium channels at the presynaptic site, quantal release of acetylcholine is reduced. Electromyographic findings confirm the clinical diagnosis by an increased compound muscle action potential amplitude during high-frequency repetitive nerve stimulation or following brief exercise. In single-fibre studies, increased jitter and blocking are found, which improve with high rates of stimulation and are worse after rest.

In our case the LEMS had been asymptomatic before the botulinum toxin injections. The additional and reversible effect of botulinum toxin on the neuromus-
cular transmission pushed the LEMS above the threshold of clinical manifestation. This case again demonstrates, that even low doses of botulinum toxin affect remote muscles by systemic effects and may act in combination with other neuromuscular disturbance. In mice the interaction between the two presynaptically acting agents LEMS-IgG and botulinum toxin was studied, and it was shown that LEMS-IgG did not prevent the binding and electrophysiological action of botulinum toxin. In conclusion it should be emphasised that patients with an underlying neuromuscular disease have an increased risk of developing generalised muscle weakness after local botulinum toxin injections. Patients with LEMS or myasthenia gravis and patients receiving substances that alter neuromuscular transmission should therefore be treated with caution if botulinum toxin injections are used to treat focal dystonia.

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Electrophysiological improvement after intravenous immunoglobulin in motor neuropathy with multifocal conduction block

Multifocal demyelinating motor neuropathy (MMN) with persistent conduction block may masquerade as multiple mononeuropathy or motor neuron disease. A careful electrophysiological study in these patients is necessary for diagnosis. Patients with chronic inflammatory demyelinating neuropathies may respond to high-dose intravenous immunoglobulin (IVIg). In view of the need for more effective therapy in MMN, we treated a patient with high-dose IVIg. A 53-year-old man had slowly progressive limb weakness over eight years. Weakness and fasciculations started in the right forearm, and left, and progressive right proximal arm, left forearm and hand involvement occurred. A year before admission he noticed slight weakness in both lower limbs. No bulbar symptoms were noticed. There was no known previous illness. Examination confirmed weakness in the limbs, 3/5 in the right arm muscles. The weakness was also prominent in extensor muscles of the left forearm (3/5) but grade 4/5 for flexion and extension of the left elbow, hand and shoulder girdle muscles. Foot dorsiflexion was weak on both sides (3/5). There was slight atrophy of all intrinsic hand muscles. Deep tendon reflexes were diminished. Occasional fasciculations were seen in both arms. Cranial nerves and all modalities of sensation were normal. Myokymia was seen in the right intrinsic hand muscles.

IgG and IgM antiganglioside antibodies measured by ELISA were not found. Other laboratory tests, including serological screening were either normal or negative. Sural nerve biopsy was normal. Muscle biopsy of the left peroneus showed signs of mild denervation atrophy.

Conventional electromyography revealed sparse fasciculation and fibrillation potentials, particularly in the right upper limb, and myokymic discharges in the right hand muscles. Motor unit potentials were often polyphasic and were followed by "satellites". Recruitment of the MUPS was considerably reduced. Bilateral distal and proximal sensory conduction along sural, superficial peroneal, median and ulnar nerves and amplitude of the nerve evoked potentials were normal. Motor conduction studies showed multifocal proximal conduction blocks involving nerves of both upper limbs (figure). A reduction in amplitude of ratio more than 40% at proximal supramaximal stimulation has been accepted as the criterion for conduction block, in the absence of increased duration of compound muscle action potential more than 20%. The block was not located at the usual sites of compression, and the segment blocked varied from nerve to nerve. More than one segment with blocks was possible in the same nerve (figure). The neuropathy was asymmetrical. Distal motor latencies were normal. There was proximal slowing in motor conduction velocity in the upper limb nerves (median, ulnar, musculocutaneous), but only moderate slowing in peroneal and tibial posterior nerves (knee-to-ankle segment) (figure). Right median and ulnar nerves F waves were absent. Central motor pathways conduction time was calculated by magnetic stimulation of the brain and this was normal (5-0ms). Radial conduction (C7-Erb's point) was prolonged.

The patient continued to deteriorate steadily until treatment with high-dose IVIg. He was started on 165 grams immunoglobulin divided into 5 daily doses (400 mg/kg/day). The patient noticed an increase in strength. Improvement started two to three days after infusion of IVIg. Clinical examination showed however, maximal improvement at seven to 10 days after infusion, with normal strength (5) except for extension muscles of left forearm and feet dorsiflexion (4/5). The improvement was, however, short-lived and five weeks later he returned to his initial pre-treatment level to the delayed dose administration. The patient improved again and regained strength upon restitution of the dose (165 grams) at four week intervals. After starting treatment with IVIg we have followed the patient for 18 months and no significant side effects were noted.

Electrophysiological study performed one week after the completion of the first IVIg infusion showed absence of myokymic discharges, increased MUPS recruitment, and full interference pattern. Conduction blocks were resolved after the first IVIg administration. Motor conduction block resolution was seen seven to 10 days after IVIg administration (figure) and correlated well with increased strength. After five weeks, conduction blocks were again seen, maximal less marked and observed in a smaller number of sites in each nerve than before IVIg administration. Slowing in motor conduction velocity did not show conclusive changes after treatment.

The present report provides evidence...