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LETTER TO THE EDITOR

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Systemic effect of local and small-dose botulinum toxin injection to unmask subclinical myasthenia gravis

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Dear Editor:

In recent years botulinum toxin A (BTX) has been introduced as a new symptomatic therapy for focal dystonias such as blepharospasm [2]. BTX therapy for blepharospasm is effective and simple. The treatment is widely studied, but few reports have been made on the side effects of the therapy, especially the systemic effects. We report a patient who experienced serious adverse systemic effects after the administration of relatively small doses of BTX for blepharospasm.

A 78-year-old woman with a medical history of cholecystectomy and no notable family history, was diagnosed with spasmodic torticollis and blepharospasm in 1992, and was treated with oral agents. For the spasmodic torticollis, BTX was injected, 60 units in December 2003 and 80 units in March 2004. The spasmodic torticollis symptoms improved after the injections. In April 2004, BTX was administered, 20 units in each eyelid for a total 40 units, because the blepharospasm had worsened gradually since 1992 and the patient's eyes had essentially become closed. One week after the injection, the symptoms in her eyes had markedly improved. However, on the following day, systemic complications were observed. The patient developed significant dysphagia preventing oral intake, requiring hospital admission, necessitating central intravenous hyperalimentation, and subsequently a gastrotomy tube for nutritional support. The patient also developed severe dysarthria and systemic weakness in the muscles preventing her from walking. One month after BTX treatment, the dysarthria minimized her ability to talk. In July 2004, the patient was capable of safe oral intake and her muscle strength had essentially recovered to baseline so the systemic complications associated with BTX were considered resolved.

To our knowledge, the recommendation to use BTX therapy is lacking the requirement of an evaluation of the anti-cholinergic antibodies prior to BTX injection. Few prior reports have been made on severe dysphagia following BTX administration. In a report by Tuite and Lang, two patients with Machado–Joseph disease who were given 320 units or 250 units of BTX to treat dystonia experienced dysphagia lasting half a year [5]. Thobois et al. reported that the administration of 250 units to a patient suffering from multisystem atrophy with Parkinsonian manifestations resulted in severe dysphagia of unknown etiology lasting 4 months [4].

Our patient did not have brain MRI or MRA abnormalities, and the results of the CT of the thorax were negative for thymoma. The patient did not have a history of abnormal MRI, MRA or thymoma. There was no history of receiving large doses of BTX. One week after the BTX treatment for blepharospasm, the efficacy was evident; however, at this 1 week post-

treatment point, systemic side effects also became evident. When one considers that the initial 140 units of BTX for spasmodic torticollis did not cause systemic complications, it does not seem plausible that a lower dose of 40 units administered to the eyelids had complications that resolved in approximately 3 months while BTX efficacy at this dose lasted for about 6 months.

In our patient the anti-acetylcholine (Ach) antibody was high at 1.8 nmol/l (normal: less than 0.3 nmol/l), strongly suggesting the existence of myasthenia gravis (MG). This patient showed no response to Mestinon administration, had a negative tensilon test, and had no other abnormalities suggestive of MG, but these test results do not exclude the presence of MG. Elevated levels of anti-Ach antibody is extremely specific to MG, so it is quite possible that the patient had asymptomatic, latent subclinical MG when she was treated for blepharospasm and the MG only became apparent after BTX was administered. Since local administration of BTX has been shown to increase jitters in distant muscles, considering a BTX effect detected by single-fiber electromyography, it is possible that BTX has both local and systemic effects on neuromuscular junctions [3]. BTX administration for spasmodic torticollis followed 1 month later with a dose for blepharospasm is therefore thought to have caused botulinus toxin to accumulate and MG symptoms to appear.

It has been reported that administration of small doses of BTX to a patient with Eaton–Lambert syndrome, which is an impairment of the neuromuscular junction similar to MG, improved blepharospasm, but weakened muscles systemically [1]. Therefore, as in our patient, it is thought that in patients with latent, subclinical neuromuscular junction abnormalities prior to BTX administration the appearance of the neuromuscular symptoms may be triggered. It should be considered that patients with an underlying neuromuscular disease are at increased risk of developing generalized muscle weakness after local BTX injection. We emphasize that patients with suspected latent, subclinical neuromuscular junction abnormalities, such as MG and Eaton–Lambert syndrome, should have systemic testing performed prior to BTX administration, and then be treated with caution even if BTX is to be used focally and in small doses.

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