CLINICAL/SCIENTIFIC NOTES

Myasthenia Gravis After Botulinum Toxin A for Meige Syndrome

Botulinum toxin A (BTX-A) produces muscle weakness by blocking presynaptic release of acetylcholine at the neuromuscular junction. Following treatment with usual clinical doses, weakness is limited to local or adjacent muscles without clinically important effects on muscles in other body regions. However, abnormal neuromuscular transmission1–5 and remote type II muscle atrophy6 without clinical weakness have been identified in muscles remote from the site of BTX-A injection. Recently, several patients with underlying neurologic disorders have been reported in whom BTX-A administration has produced exaggerated muscle weakness.7–11 We are reporting follow-up information concerning a previously reported patient12 with Meige syndrome who developed acute, generalized myasthenia gravis immediately after BTX-A administration.

Case Report

An 80-year-old woman with a 13-year history of essential blepharospasm and oromandibular dyskinesia (Meige syndrome) was successfully treated on 18 occasions over 13 years with periorcular and lower facial BTX-A (Botox) injections (30–120 units) without adverse effects. There was a remote history of breast carcinoma without recurrence and thyroidec- tomy 30 years previously for an enlarged gland.

In January 1998, 4 days after receiving 120 units BTX-A into periorcular and lower facial muscles, she experienced dysphagia and neck weakness for the first time. Within 3 weeks she developed ptosis, oculomotor weakness, facial diplegia, neck extensor weakness, dysarthria, and pulmonary aspiration. Vials of Botox® (Allergan, Irvine, CA, USA) from the same lot were checked for potency by the manufacturer and were consistent with the labeled dose. Modified barium swallow confirmed oral, lingual, and pharyngeal weakness. A 14-week hospitalization ensued and feeding by gastrostomy was initiated. An edrophonium test was negative followed within several weeks by a positive response. Acetylcholine receptor antibody was 6.9 (normal <0.07). Single-fiber electromyography 2 months after BTX showed increased jitter in posterior cervical and upper extremity muscles. Repetitive stimulation studies were normal. Conventional electromyography showed fibrillations in paraspinal muscles and mildly increased polyphasic units in shoulder, arm, and forearm muscles. Trapezius muscle biopsy showed minor, nonspecific inflammatory changes. Chest computed tomography (CT) scan, thyroid functions, brain CT scan, and lumbar puncture were normal.

Pyridostigmine was not tolerated because of gastrointestinal side effects and exacerbation of dystonia, although the latter was not well documented. Neostigmine and prednisone were followed by gradual improvement in myasthenic symptoms accompanied by the reappearance of blepharospasm and oromandibular dyskinesia. She returned to baseline status 5 months after onset of myasthenic symptoms and neostigmine and predni- sone were discontinued. Baclofen, benztropine, and diphen- hydramine were unhelpful for the dystonic symptoms.

BTX-A was not repeated, but in September 1998 she was rehospitalized for increasing neck extensor weakness, dyspha- gia, dysarthria, bifacial weakness, and fluctuating diplopia. Modified barium swallow again showed pharyngeal weakness and aspiration. Over the next 2 months she developed increasing trunk weakness, fluctuating ophthalmoplegia, bilateral ptosis, facial diplegia, tongue weakness, hoarseness, and weakness of trunk and extremity muscles. Electromyography showed normal neuromuscular transmission. CT of the chest and neck showed a multinodular thyroid goiter and absence of thymoma. Acetylcholine receptor antibody was 30.0. She was treated with plasmapheresis, 50 mg prednisone alternating with 10 mg every other day, and 150 mg azathioprine per day. She improved rapidly and by late January 1999 again had no myasthenic findings.

Blepharospasm and oromandibular dyskinesia reappeared coincident with clearing of myasthenia. Acetylcholine receptor antibody remained elevated at 2.9. BTX-A antibodies (mouse protection bioassay) were absent. BTX-A was injected at a dosage of 7.5 units around the left eye, 4.5 units around the right eye, and 15 units into masseters bilaterally for a total of 42 units. There was marked improvement in blepharospasm, no change in oromandibular dyskinesia, and no reappearance of myasthenic weakness. Rejection of 45 units BTX-A into each masster 2 weeks later was unhelpful for jaw dyskinesia. Predni- sone was tapered and discontinued while she remained on azathioprine. Blepharospasm returned 3½ months after BTX-A treatment and once again subsided after injection of 7.5 units BTX-A around each eye. She remains on 150 mg azathioprine per day without recurrent muscle weakness 12 months after her last episode of myasthenia gravis.

Discussion

This patient with Meige syndrome developed signs of acute and generalized myasthenia gravis immediately after administration of BTX-A after 13 years of previously uncomplicated BTX-A therapy. Initially, it was unclear whether she was ex- periencing an unusual systemic response to BTX-A or had developed coincidental myasthenia gravis unmasked by BTX-A treatment. However, the remission of myasthenia, fol- lowed by its spontaneous reappearance 10 months after her last exposure to BTX-A, established the diagnosis of coincidental myasthenia gravis. Remission of myasthenia and return of normal muscle strength was accompanied on two occasions by the reappearance of dystonia.

Myasthenia is well known to remit and relapse early in its course, either spontaneously13 or, more commonly, in response to immunosuppressive therapy.14 The diagnosis was further supported by typical clinical signs of generalized myasthenia, elevated serum acetylcholine receptor antibodies on three oc- casions, and remission of myasthenia after immunosuppressive therapy on two occasions. Although the normal repetitive stimulation studies were surprising, this does occur in a sig-
<table>
<thead>
<tr>
<th>Authors</th>
<th>Dystonia treated (age, sex)</th>
<th>Underlying neurologic disorder</th>
<th>Muscles injected</th>
<th>Total BTX-A dose</th>
<th>Result (latency)</th>
<th>Duration of weakness</th>
<th>EMG</th>
<th>Prior BTX-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tarsy et al. (this report)</td>
<td>Blepharospasm; Oromandibular dystonia (80, F)</td>
<td>Myasthenia gravis</td>
<td>Periorbital, lower facial</td>
<td>120 units (Allergan)</td>
<td>Generalized myasthenic weakness (4 days)</td>
<td>5 months</td>
<td>† jitter</td>
<td>13 years of regular treatment without weakness</td>
</tr>
<tr>
<td>Emmerson⁷</td>
<td>Spasmodic torticollis (51, F)</td>
<td>Myasthenia gravis</td>
<td>Right SCM, bilateral SC</td>
<td>600 units (Dysport)</td>
<td>Dysphagia (9 days)</td>
<td>1 week; 5 days (two injections)</td>
<td>† jitter</td>
<td>Once 3 months previously without weakness</td>
</tr>
<tr>
<td>Egburth et al.⁸</td>
<td>Blepharospasm; Oromandibular dystonia (63, F)</td>
<td>Lambert—Eaton syndrome</td>
<td>Periorbital</td>
<td>8 ng (Dysport)</td>
<td>Pelvic, shoulder, and hip weakness (4 days)</td>
<td>?</td>
<td>† jitter, blocking Incremental response</td>
<td>None</td>
</tr>
<tr>
<td>Backheit et al.⁹</td>
<td>Spasticity (67, F); Torticollis (34, F)</td>
<td>Multiple sclerosis</td>
<td>Left hamstrings</td>
<td>250 units (Dysport)</td>
<td>Hoarseness, paraparesis, neck flexor weakness, dysphonia, ptosis (4 days)</td>
<td>4 weeks</td>
<td>† jitter, blocking Incremental response</td>
<td>None</td>
</tr>
<tr>
<td>Mezaki et al.¹⁰</td>
<td>Spasticity (56, F)</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Bilateral thigh adductors</td>
<td>300 units (Chiba)</td>
<td>Proximal upper and lower limb weakness (3 days)</td>
<td>2 months</td>
<td>† jitter, blocking Incremental response</td>
<td>None</td>
</tr>
<tr>
<td>Tuite and Lang¹¹</td>
<td>Oromandibular dystonia; retrocollis (20, M)</td>
<td>Machado-Joseph disease</td>
<td>Masseters, temporalis, digastrics, bilateral SC</td>
<td>320 units (Allergan)</td>
<td>Dysphagia (4 days)</td>
<td>6 months</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Machado-Joseph disease</td>
<td>Retrocollis (21, M)</td>
<td>Bilateral TR, bilateral SC</td>
<td>250 units (Allergan)</td>
<td>Dysphagia (1 week)</td>
<td>6 months</td>
<td>—</td>
<td>None</td>
</tr>
</tbody>
</table>

SCM, sternomastoid; SC, splenius capitis; TR, trapezius.
significant proportion of patients with myasthenia gravis. In increased jitter with SFEMG testing is a more sensitive test and is consistent with either myasthenia gravis or a systemic effect of BTX-A. The conversion from a negative to positive edrophonium response was possibly the result of waning BTX-A effect between the two tests.

Caution is recommended when treating patients with BTX-A who have coexisting neuromuscular disorders. However, there is no specific warning concerning this in the package label for Botox. The package label for Dysport® (Seywood, UK) advises caution “in patients with subclinical or clinical evidence of marked defective neuromuscular transmission.” Two patients with underlying disorders of neuromuscular transmission and five with central nervous system motor disorders have been reported in whom administration of BTX-A has produced exaggerated muscle weakness (Table 1). Similar to our patient, weakness was generalized in four of these seven cases. We think our patient with Meige syndrome coincidentally developed subclinical myasthenia gravis following which BTX precipitated generalized muscle weakness by its well-established but usually subclinical effect on remote muscles. In this case, once remission of myasthenia was insistent on being treated for her disturbing symptoms, and was administered much lower doses than those that had precipitated her initial episode of myasthenia. Nonetheless, cautious dosing and muscle selection are strongly recommended if BTX-A is used in the presence of underlying neurologic disorders characterized by weakness because even relatively low doses can apparently precipitate remote muscle weakness in this setting.

Acknowledgments: Supported in part by the Shirley and Edgar Grossman Movement Disorders Fund.

The authors thank Dawn Mechanic and Loren LaBelle for technical assistance.

Daniel Tarsy, MD
Neil Bhattacharyya, MD
Beth Israel Deaconess Medical Center
Boston, Massachusetts, U.S.A.

Gary Borodic, MD
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts, U.S.A.

REFERENCES


Test–Retest Reliability of Patient Information on Age of Onset in Essential Tremor

Age of onset and disease duration are important variables in essential tremor (ET) research. First, in several prevalence studies, diagnostic criteria for ET have stipulated that tremor must be present for a defined period of time. Second, in genetic studies and clinical trials of movement disorders, patients may be stratified into those with older versus younger ages of onset; estimates of genetic and therapeutic effects may differ substantially in the two groups. Third, disease duration is one of the more commonly reported clinical characteristic in therapeutic trials of ET. Finally, in epidemiologic studies, information about the variable rates of disease progression in different patient groups are based on age of onset data.

The scientific quality of the information obtained from patients on their age of onset depends on the validity of their reports. Validation of these data would require an incidence study in which initially normal subjects would be followed over time until they developed tremor. Even among individuals with the highest annual incidence (≥80 years of age), the annual incidence is only 843 cases per 100,000, meaning that an investigator would have to evaluate more than 20,000 subjects annually for 5 years to ascertain 84 ET cases. While validity

Received January 5, 2000; revision received April 4, 2000. Accepted April 5, 2000.

Address correspondence and reprint requests to Elan D. Louis, MD, MS, Unit #198, Neurological Institute, 710 W. 168th St., New York, NY 10032, U.S.A.