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ORIGINAL RESEARCH

Single-Fiber Electromyography Analysis of Botulinum Toxin Diffusion in Patients With Fatigue and Pseudobotulism

Alexis Ruet, MD,[a] Marie Christine Durand, MD,[b] Pierre Denys, MD, PhD,[a] Frederic Lofaso, MD, PhD,[b] François Genet, MD, PhD,[a] Alexis Schnitzler, MD[a]

From the [a]Physical Medicine and Rehabilitation Department, Raymond Poincaré Hospital, Paris' Public Assistance Hospitals, University of Versailles Saint Quentin, Garches; and [b]Department of Physiology, Raymond Poincaré Hospital, Paris' Public Assistance Hospitals, University of Versailles Saint Quentin (EA 4497), Garches, France.

Abstract

Objective: To characterize electromyographic abnormalities according to symptoms (asymptomatic, fatigue, pseudobotulism) reported 1 month after botulinum toxin injection.

Design: Retrospective, single-center study comparing single-fiber electromyography (SFEMG) in the extensor digitorum communis (EDC) or orbicularis oculi (OO) muscles.

Setting: Hospital.

Participants: Four groups of adults treated for spasticity or neurologic bladder hyperactivity (N=55): control group (asymptomatic patients: n=17), fatigue group (unusual fatigue with no weakness: n=15), pseudobotulism group (muscle weakness and/or visual disturbance: n=20), and botulism group (from intensive care unit of the same hospital: n=3).

Interventions: Not applicable.

Main Outcome Measures: Mean jitter, percentage of pathologic fibers, and percentage of blocked fibers were compared between groups.

Results: SFEMG was abnormal for 17.6% of control patients and 75% of patients in the pseudobotulism group. There were no differences between the control and fatigue groups. Mean jitter, percentage of pathologic fibers, and percentage of blocked fibers of the EDC muscle were significantly higher in the pseudobotulism group than in the fatigue and control groups. There were no differences between groups for the OO muscle. The SFEMG results in the botulism group were qualitatively similar to those of the pseudobotulism group.

Conclusions: SFEMG of the EDC muscle confirmed diffusion of the toxin into muscles distant from the injection site in the pseudobotulism group. SFEMG in the OO muscle is not useful for the diagnosis of diffusion. No major signs of diffusion of botulinum toxin type A were found away from the injection site in patients with fatigue but no motor weakness. Such fatigue may be related to other mechanisms.

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Botulinum toxin was first used therapeutically in the 1970s to treat certain types of strabismus. The number of conditions treated is constantly increasing, and there are few side effects.[1] Localized side effects include pain, edema, erythema, bruising, headache, and hyperesthesia, which all resolve rapidly.[2] Diffusion of the toxin can occur both locally and systemically after injection.[3] Some local side effects resulting from diffusion to neighboring muscles have been reported (ie, regional diffusion), for example dysphagia after injection into the sternocleidomastoid muscle.[4] More generalized side effects of botulinum toxin type A (BoNTA) are nausea, rash, malaise, fatigue, and flu-like symptoms.[5] In extreme cases, death can occur. Between 1989 and 2003, 28 deaths after BoNTA were reported to the Food and Drug Administration in the United States.[6] Fatigue is a more frequent side effect with >5% of patients reporting fatigue after injection for the treatment of certain conditions.[7,8] Injection in upper-limb muscles leads to 7.6 times more generalized fatigue or flu-like

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symptoms than placebo injection.[9] The rate of flu-like symptoms or generalized fatigue varies from 1.7% to 20% depending on the study, and the mechanisms which cause these symptoms remain uncertain.[10] One cause of fatigue could be a generalized diffusion of the toxin to striated muscles distant from the injection site. Diffusion of the toxin away from the injection site causes clinical signs of pseudobotulism (eg, asthenia, muscle weakness, dysphagia, dysarthria, diplopia, ptosis, anomalies on single-fiber electromyography [SFEMG]).[11-13] The incidence of these signs appears to be very low because only case report studies have been published in the literature.

SFEMG is the criterion standard technique to assess the function of the neuromuscular junction in striated muscle. Botulinum toxin blocks the liberation of neurotransmitters at the axon terminal, modifying the electromyographic response in the injected muscles. This technique is used for the diagnosis of foodborne botulism and also the systemic diffusion of BoNTA.[14-19] The aim of this study was to investigate signs of BoNTA diffusion in patients with weakness in a muscle distant from the injection site or with fatigue. For that purpose, SFEMG was carried out in striated muscles distant from the injection site.

Methods

This was a retrospective, single-center study of adult patients treated with BoNTA for striated muscle hypertonia or detrusor muscle hyperactivity after a central nervous system lesion. The results of SFEMG were compared as a function of the symptoms (asymptomatic, fatigue, pseudobotulism) which occurred after BoNTA injection and with cases of foodborne botulism.

Participants

Between January 2003 and February 2011, 1809 consecutive patients received 2320 BoNTA injections to treat detrusor muscle hyperactivity, and another 1884 patients received 7490 BoNTA injections to treat striated muscle hypertonia. Detrusor muscle hyperactivity was a consequence of spinal cord injury (85%), multiple sclerosis (11%), or another cause of spinal cord lesion (4%). Striated muscle hypertonia was a consequence of stroke (45%), spinal cord injury (25%), cerebral palsy (15%), multiple sclerosis (7%), traumatic brain injury (4%), and dystonic disorders (4%). The doses injected and the frequency of injections followed the marketing authorization guidelines. Onabotulinum toxin A was the only toxin used for detrusor injections. Follow-up of patients systematically occurred approximately 1 month postinjection. A clinical examination was carried out, and any secondary effects were sought, no matter the number of injections previously received. Thirty-five patients were found to have unusual fatigue or weakness in muscles distant from the injection site, and all underwent SFEMG to ascertain if diffusion had occurred.

These patients were categorized into fatigue or pseudobotulism groups. The fatigue group consisted of 15 patients who responded in the affirmative to the following question: Did you feel unusual fatigue since the last BoNTA treatment? Unusual fatigue could not be evidently explained by another cause. The pseudobotulism group consisted of 20 patients. Sixteen patients had weakness of $\geq$1 muscle (shown by a decrease of 1 point on the Medical Research Council scale) at least 1 joint away from the injection sites; 1 patient also had swallowing difficulties. Four other patients had visual disturbances. All the symptoms were unrelated to the patients' initial pathologies. In the case of a visual disturbance (diplopia, accommodation disorders), a specialist ophthalmologic examination was carried out to screen for other causes. A control group of 17 asymptomatic patients from the same population of patients was included for comparison. These patients were treated for detrusor hyperactivity, and their data have previously been used in a study of toxin diffusion.[19] SFEMG results were compared statistically between these 3 groups. A botulism group consisting of the data of 3 patients with no neurologic pathology who contracted foodborne botulism confirmed by identification of the toxin and diagnostic SFEMG was also included. Their SFEMG results were provided for qualitative comparison.

According to French legislation, patient consent was not required for this study.

List of abbreviations:

ANS	autonomic nervous system
BoNTA	botulinum toxin type A
EDC	extensor digitorum communis
OO	orbicularis oculi
SFEMG	single-fiber electromyography

Single-fiber electromyography

SFEMG was carried out by the same trained examiner. A Neuropack M1[a] was used. SFEMG was carried out away from the site of BoNTA injection. Because pyramidal lesions can modify SFEMG results below the level of the lesion,[20] evaluations were carried out above the lesion muscles for patients with paraplegia and tetraplegia and on the nonparetic side for patients with hemiparesis. Neuromuscular junction function was therefore evaluated by axonal stimulation of the extensor digitorum communis (EDC) muscle for patients with paraplegia and hemiparesis and the orbicularis oculi (OO) muscle for patients with tetraplegia. The electromyographic technique used has been described previously.[19] Respective normative values for the mean jitter and individual jitter are 25 and 40μs for the EDC muscle and 20 and 30μs for the OO muscle, respectively.[21,22] Because the mean jitter of the EDC and OO muscles is different, they were compared separately between the control, fatigue, and pseudobotulism groups. In healthy subjects, the number of fibers with a prolonged jitter (pathologic fibers) is $<$10%, and there is no blocking of the action potential in the muscle fibers of the EDC or OO muscles.[21,22]

Statistical analysis

R statistical package[b] was used for statistical analysis. Because the data did not comply with the conditions of use of the parametric tests, a Kruskal-Wallis test was used to compare quantitative variables in $>$2 groups. A Wilcoxon test was used to compare quantitative variables between 2 groups and for post hoc analyses. A Bonferroni correction was used for the post hoc analyses. Fisher exact test was used to compare qualitative variables between groups when the conditions of use of a chi-square test were not fulfilled. The chi-square test was used to compare qualitative variables between groups.

Results

Incidence of complications

The incidence of unusual fatigue was 3 out of 1000 bladder injections, 1.1 out of 1000 striated skeletal muscle injections, and