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Botulinum toxin therapy improves masseter spasticity in Amyotrophic Lateral Sclerosis

Abstract

Fifteen ALS patients with troublesome symptoms linked to masseter spasticity, benefited from BoNT-A injections in each masseter. Based on the medical records of patients, the effect of the first injection was assessed one month later. We retrospectively collected information for 12 patients. Eight of them reported a beneficial effect after the injection for the following symptoms: trismus, tongue, lip and cheek biting, and jaw clonus. Five patients indicated that dental care was easier after injection. Our study showed that injections of BoNT-A unequivocally reduced masseter spasticity in ALS patients who subsequently enjoyed greater comfort in their daily living.

Keywords: Amyotrophic Lateral Sclerosis – Spasticity - Botulinum toxin – Masseter - Trismus

Introduction

The spastic trismus consists of hypertonia of several masticatory muscles caused by an upper motor neuron syndrome, among them masseter muscles. Masseter hypertonia and spasticity have been described in patients who have Multiple Sclerosis, cerebral hypoxia, or ischemic brain lesions as well as after severe encephalitis [1]. This spastic hypertonia of the masseter muscles is a major contributor of the trismus and it severely impairs jaw movements, limiting the opening range of the oral cavity, and causing pain and difficulties in oral hygiene and feeding [2]. Past studies have found that Botulinum toxin injections into the masseter muscles effectively reduced hypertonia and provided better mouth opening [3].

Amyotrophic Lateral Sclerosis (ALS) is a progressive disorder characterized by upper and lower motor neuron degeneration. Spasticity can be a very debilitating issue in some ALS patients with upper motor neuron dominant phenotype. While spasticity concerns the limbs, hyperactivity may also affect other muscles in ALS such as the cricopharyngeal muscle, the upper esophageal sphincter or masseters [4]. Masseter spasticity in ALS is involved in some debilitating symptoms such as limited mouth opening and oral self-injuries. These symptoms are particularly prevalent in patients with bulbar involvement or pseudo-bulbar syndrome [5].

It is now well-established that Botulinum toxin type A (BoNT-A) is safe and effective for the reduction of adult limb spasticity in different neurological diseases [6]. However, very little is known about the effect of BoNT-A in ALS patients to reduce the severe disability induced by masseter spasticity.

In this work, we aimed to retrospectively assess the effect of BoNT-A injections in the masseters of ALS patients showing debilitating symptoms linked to masseter spasticity.

Observation

We retrospectively collected demographic and clinical information from the medical records of ALS patients treated for masseter spasticity with botulinum toxin that were seen at Pitié-Salpêtrière University Hospital and at University Avicenne Hospital between March 2016 and December 2017. Fifteen patients having laboratory-supported possible, probable, or definite ALS by revised El-Escorial criteria were enrolled [7] but all of them ended up having probable or definite ALS. Patients had to experience debilitating spasticity of masseters defined by: a) spasticity in masseters identified by palpation or presence of trismus; b) pseudo-bulbar signs (exaggerated jaw jerk reflex); c) one or more debilitating symptoms linked to masseter hypertonia (incomplete mouth opening, difficulties in feeding, pain, tongue, lip and cheek biting, jaw clonus, difficulties in oral hygiene). As for other injection sites of BoNT-A, all patients were informed of the procedure. This study was approved by the local ethics committee (CLEA-2019-86) and in accordance with the French law concerning retrospective studies, no

written informed consent was mandatory. The data were collected as a clinical care routine procedure, with the oral consent of the patients and/or caregivers (non-opposition to be used for research purposes). Demographic data including the Amyotrophic Lateral Sclerosis functional rating scale-revised (ALSFRS-R) and debilitating symptoms related to masseter hypertonia were identified. We used Clinical Global Impression – Severity scale (CGI-S, a scale going from 1 to 7, where 1 is normal and 7 is extremely severe) to evaluate the severity of the symptoms linked to masseter spasticity. Patients were given 20 to 40 units of incobotulinumtoxin A in each masseter muscle. As for other disorders needing botulinum injection, the injected dose was determined depending on two parameters: the intensity of the masseter hypertonia and its duration along the day. Two physicians (MM and BD) with experience in BoNT-A therapy conducted the injection without guidance, in the safe zone described by Peng and Peng [8]. Only one injection point was performed in each masseter.

As usually performed in our Neurology units, patients were re-evaluated by a neurologist during an ambulatory consultation or by phone around four weeks (formally called as visit 2) and six months (formally called as visit 3) after the injection. The patient or the primary caregiver was orally asked about the effects of the injection: improvements of debilitating symptoms, percentage of improvement, duration of the effect, time for treatment to be effective and side effects. We also used Clinical Global Impression – Improvement scale (CGI-I, a scale going from 1 to 7, where 1 indicates a large improvement and 7 indicates a significant worsening) – to evaluate the patient's impressions after treatment. For statistical analysis, values are expressed in mean (\pm standard deviation) or in percentage.

Twelve out of 15 ALS patients were finally included in the analysis (see Table 1 for details about clinical data). Three patients with a late-stage of ALS died before visit 3. Patients presented an advanced stage of the disease: half of them had a gastrostomy at the time of the injection and all of them were in a wheelchair. All patients were naive to a treatment for spasticity.

Initially reported symptoms and effects of the BoNT-A injection are shown in Table 2. Discomfort symptoms consisted in trismus or impairment of mouth opening, difficulties in oral hygiene and oral lesions (tongue, lip and cheek self-injuries) responsible for pain. Mean CGI-S was between 4 and 5 out of 7 (4=moderately ill; 5=markedly ill). Eight patients reported a clinical improvement after the injection (CGI-I \geq 3). Among these patients, the mean subjective percentage of improvement after BoNT-A injection was 38%. No worsening or side effects were reported. The onset of therapeutic response occurred after a period of 14 days on average (\pm 10 days). The mean duration of treatment efficiency was 48 ± 27 days.

Discussion

In our retrospective study, the majority of patients experienced improvement of the mouth opening after the first BoNT-A injection in their masseters. BoNT-A injections improved the daily living of ALS patients affected by masseter spasticity by reducing their pain and allowing them to maintain a good oral hygiene. We were particularly interested in maximizing the quality of life of ALS patients, which is essential in this severe and incurable disease.

To our knowledge, our study is the largest registry of ALS patients treated by BoNT-A injection in masseters. Some rare case reports showed improvement in patients treated for masseter spasticity in specific situations. For example, Winterholler et al. successfully treated one ALS patient who had recurrent trismus, stridor, and dyspnea with BoNT-A injection (onabotulinumtoxinA 6.25 mouse units, in each masseter) [9]. In our study, we used lower doses of BoNT-A than the ones used in the aforementioned studies. It would be interesting to gradually increase the doses in patients who presented a partial therapeutic response. Moreover, the treatment effectiveness is only temporary. It is necessary to repeat injections six weeks to three months after the first injection (depending on the dose of BoNT-A and on the patient responsiveness) to obtain an overlap between two injections and therefore maintain the positive BoNT-A effect. The dose should be adjusted for each patient, depending on symptoms' severity, clinical response after injection and duration of the injection's effect.

In our study, patients were at an advanced stage of ALS. Treating masseter spasticity is not only useful for patients' comfort but also to help perform gastrostomy. Restivo et al. described four ALS patients who could not undergo percutaneous endoscopic gastrostomy because of remarkable spastic closure of the mouth. After BoNT-A injections (onabotulinumtoxinA 75 units in each masseter), all patients showed significant reduction of masseter spasticity, such that the gastrostomy tube could be successfully inserted [10]. It could also provide benefits for patients with non-invasive ventilation: a better mouth opening would help clearing out the respiratory tract of these patients who are subject to bronchial congestion and hypersalivation.

In our preliminary study, no patients experienced side effects. In particular, there was no worsening of the bulbar signs, which indicates a low risk of toxin diffusion in the surrounding tissues. Systemic side effects and local complications are uncommon with BoNT-A. Systemic side effects are rarely reported and generally are not dose related. A large study of botulinum toxin injection in masseters in Asian people with masseter hypertrophy showed an excellent safety profile if injections were performed inside the recommended safety zone (the same used for this study): a quadrilateral within the muscle that avoids most important local structures [8].

This study has several limitations. First, the strength of our study is diminished by its retrospective nature. Second, the collection of data was therefore limited to information reported in patients' medical records. Third,

since this study was not designed as a clinical trial, we did not have any control group and evaluators were not blinded. To confirm our results, it would be necessary to perform a randomized double-blinded placebo-controlled study. Then, it would be possible to assess the impact of the masseter injection on the quality of life of patients, on their ability to eat and breath, on the convenience of nursing procedures and on their social impact.

Conclusion

The results of this study are encouraging: they suggest that injections of BoNT-A effectively and safely reduce masseter spasticity for advanced-stage ALS patients. To confirm the results of this study, it would be interesting to perform a randomized double-blinded placebo-controlled study.

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Disclosure of interest

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Table 1: Clinical data of the twelve patients

Sex	11♀ / 1♂
Age (years; mean ± standard deviation)	58 ± 6
Mean time-period between ALS-symptom onset and treatment (months)	37 ± 34
Patients with bulbar-onset (%)	42 %
Mean ALSFRS-R (*)	26 ± 10
Patients with gastrostomy (%)	50 %
Patients with non-invasive ventilation (%)	33 %

(*) Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised

Table 2: Initial symptoms and effects of the treatment

Debilitating symptoms	Affected patients [<i>number (% of total)</i>]	Improved after BoNT-A injections [<i>number (% of affected)</i>]
Trismus or limited mouth opening	9 (75%)	6 (75 %)
Difficulties in oral hygiene	9 (75%)	5 (55 %)
Tongue, lip and cheek self-injuries	8 (67%)	6 (75 %)
Jaw clonus	3 (25%)	2 (67 %)