

Spasmodic Dysphonia in Multiple Sclerosis Treatment With Botulin Toxin A: A Pilot Study

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Summary: Objectives: This study aims to evaluate the effect of botulin toxin A in patients with multiple sclerosis (MS) affected by spasmodic dysphonia (SD) and to show the safety and effectiveness of this treatment in long-term observation.

Materials and methods: This is a pilot study on three relapsing-remitting MS patients with SD and their response to botulin toxin A.

Results: None of the patients reported dysphagia or other adverse events. Significant improvement was observed in terms of both voice quality and laryngostroboscopy results. The treatment effect was durable for 6–8 months.

Conclusions: Botulin toxin A is a safe treatment that can be successfully used to treat SD in patients with MS. Larger studies are necessary to confirm our results.

Key Words: Multiple sclerosis—Dysphonia—Spasmodic dysphonia—Treatment—Botulin toxin A.

INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease affecting the central nervous system (CNS). It presents with a variety of symptoms, such as motor weakness, balance impairment, visual loss, and sensory disturbances.¹ According to Hartelius et al, voice and speech are affected in 44% of patients with MS.^{2,3} Acoustic analysis of voice revealed dysphonia in 70% of this population.⁴ Subjective and perceptual analysis of voice quality found 44% of patients with MS (52% of female patients) have voice disorders.⁵

Yamout et al reported vocal breaks and vocal fatigue as the most common vocal symptoms found in 25% of patients with MS.⁶ Vocal breaks and vocal fatigue are also the common symptoms of spasmodic dysphonia (SD). Darley et al found that approximately 72% of patients with MS present with harsh voice quality, strained voice, and excess tone in vocal cords.⁷

SD is a rare focal dystonia of the intrinsic laryngeal muscles characterized by spasms of the vocal folds only during speech. It manifests as a strained voice quality, effortful speech, and voiceless gaps. It can coexist with other focal dystonias such as blepharospasm, tremor, torticollis, and writer's cramp. Neurologic disorders such as Parkinson disease, amyotrophic lateral sclerosis, mitochondrial disorders, and central pontine myelinolysis might be associated with SD.^{8–11} In addition, SD can complicate valproic acid or neuroleptic administration.¹²

SD is centrally mediated⁸ and it is mainly due to the involvement of the basal ganglia or cerebellum.¹¹ Diagnosis

is challenging because of the anatomy of the larynx and its similarity to other voice disorders (muscle tension dysphonia, voice tremor, and dysarthria). In addition, no objective test is conclusive for a definite diagnosis. Diagnosis is clinically based on perceptual voice evaluation and task specificity and it is made by an experienced ear, throat, and nose (ENT) or speech pathologist.

In 2009, Bernitsas et al identified a 1.6% prevalence of SD in patients with MS—five cases on 297 observed patients—whereas the prevalence of SD reported on general population is 0.0005%.¹³ SD successfully responds to botulin toxin A (BTX), which induces a chemical denervation on the muscle by blocking neurotransmitter release at cholinergic nerve-ending level. Several studies showed the efficacy of BTX to treat SD,^{14–17} but until today, there is only one case report that described the use of BTX for treating SD in a patient with MS.¹⁵

We present three patients affected by MS and SD and their response to BTX.

MATERIALS AND METHODS

The study was conducted in a tertiary reference center. The patients enrolled in the study were previously informed about the risks and benefits of treatment before signing a written informed consent. The study was conducted with respect to the Declaration of Helsinki and in accordance with institutional review board policies of both hospitals.

Three patients affected by relapsing-remitting MS have been diagnosed with SD based on the voice-quality pressed and choked during speech and the results of laryngostroboscopy that has been performed to exclude other diseases that can mimic SD. All patients underwent treatment with BTX by percutaneous technique under cutaneous local anesthesia¹⁸ first in the thyroarytenoid muscle (TA) and then in the lateral cricoarytenoid muscle (LCA) (Figure 1) during the same treatment. A 30-gauge needle was used during the procedure. Injection of BTX was performed under electromyography to identify precisely the hyperfunction of the

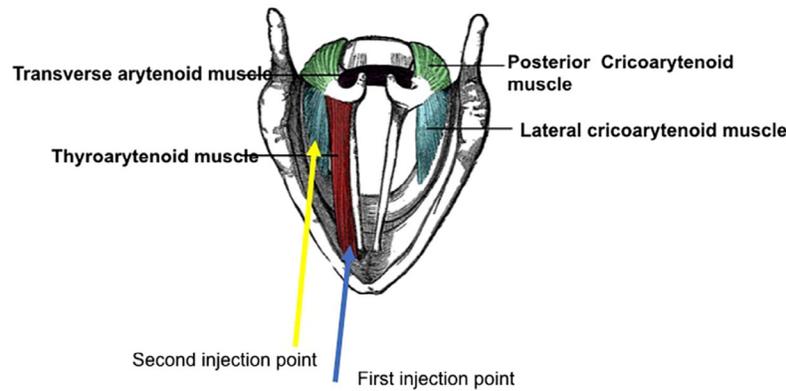
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The angle of needle insertion is 180° for the first injection, parallel to TA, the second 210° to reach better the LCA

FIGURE 1. The angle of needle insertion is 180° for the first injection, parallel to the thyroarytenoid muscle, the second 210° to reach better the lateral cricoarytenoid muscle. This method was used for patients 1 and 2 only, because patient 3 was affected from abductor paralysis.

muscles and its position. We treated each vocal fold separately in each session.

THEORY

This study aimed to demonstrate that BTX is a safe treatment in MS patients with SD. BOTOX is safe and effective for several symptoms, such as headaches and neurogenic bladder; however, it seems to be less effective in other disorders, such as blepharospasm, especially in the second treatment. This failure could be related to the immunological resistance resulting from BTX antibody formation due to large cumulative dosage dose of the toxin.¹⁹

In our pilot study, we report that BTX can be used safely and successfully in repeated treatments in patients with MS.

RESULTS

Clinical case 1

We report a 32-year-old woman affected by relapsing-remitting MS. Her first manifestation was right optic neuritis in July 2001. A definitive diagnosis of MS was made in September 2003 per McDonald criteria.¹⁹ An abnormal lumbar puncture supported the diagnosis.²⁰

The patient had been on high-dose, high-frequency interferon beta-1a injections three times a week for 10 years (from October 2003 to February 2013). Her response to

treatment was not satisfactory; she experienced recurrent relapses with incomplete recovery and disability progression. In February 2013, a repeat magnetic resonance imaging (MRI) scan showed interval progression and severe medullary involvement. Then, the patient switched to fingolimod. In July 2012, while on interferon injections, she experienced an episode of SD during a relapse. She was treated with high dose of steroids (methylprednisolone 1 g i.v. daily for 5 days) with 2 months of temporary resolution.

The patient's symptoms included a 6-month duration of pressed and choked voice and vocal asthenia. She was referred to an ENT specialist; a diagnosis of adductor SD was made and supported by laryngostroboscopy results. Subsequently, she was started on BTX (Allergan, USA) injections. After the BTX treatment, her speech has significantly improved. She prefers to have the treatment on one vocal cord at a time. She received a total of 12 injections. BTX is repeated every 6–8 months. Laryngostroboscopy, repeated 30 days after the first treatment, showed normal findings. She is currently followed up in our center. Table 1 shows the BTX received until 2017.

Clinical case 2

A 39-year-old woman presented to the emergency department 6 months after her initial diagnosis of relapsing-remitting MS

TABLE 1.
Treatment Schedule With Botox Patient 1

Treatment schedule patient 1				
2013	January: 3 IU right	April: 1 IU left	July: 1 IU right	November: 1 IU left
2014	Mars: 1 IU right	July: 1 IU left	December: 1 IU right	
2015	May: 1 IU left	September: 1 IU right		
2016	April: 2 IU left	June: 1 IU right	November: 1 IU left	
2017	Mars: 1 IU right			

Abbreviation: IU, international units.

TABLE 2.
Treatment Schedule With Botox Patient 2

Treatment schedule patient 2				
2016	January: 5 IU bil	April: 2.5 IU right	August: 2 IU left	December: 2 IU left
2017	May: 2 IU right	September: 2 IU left		

TABLE 3.
Treatment Schedule with Botox Patient 3

Treatment schedule patient 3				
2014	June: 5 IU bil	August: 2.5 IU right	November: 2 IU left	
2015	February: 2 IU right	May: 2.5 IU left	September: 2 IU right	
2016	January: 2 IU left	April: 2 IU right	October: 2 IU left	
2017	February: 2 IU right	July: 1 IU left	November: 1 IU right	

in 2015. The patient was otherwise healthy with no additional comorbidities. For her MS, she was on immunomodulatory treatment with glatiramer acetate. Her symptoms included effortful speech with vocal tremor, difficulty swallowing, and balance impairment. MRI scan revealed a T2-enhancing lesion in the brainstem. After treatment with intravenous steroids, her balance and swallowing improved. She noticed vocal changes. A vocal tremor associated with strained voice was identified during the examination, and after ENT evaluation, she was diagnosed as adductor SD. The diagnosis was supported by flexible videostroboscopy. Treatment with BTX injections to the vocal cord adductors was initiated with good control of her symptoms. The patient received a total of six treatments and she is clinically stable. During her last visit, laryngostroboscopy showed normal motility of the vocal folds. The treatment was repeated every 6–8 months. [Table 2](#) shows the BTX frequency of administration.

Clinical case 3

A 45-year-old man, with a 2-year history of right facial spasm, noticed strained voice with voiceless gaps. After an extensive workup, he was diagnosed with abductor SD in 2014. The diagnosis was confirmed by flexible videostroboscopy. Subsequently, he was started on BTX injections in the posterior cricoarytenoid muscles. Fourteen months later, he noticed difficulty ambulating that was getting progressively worse. He was referred to neurology service for further evaluation. An MRI scan of the brain and cervicothoracic spine, followed by Cerebrospinal Fluid analysis, confirmed the diagnosis of primary progressive multiple sclerosis. His SD has improved and he is on treatment with ocrelizumab for his MS. He has received a total of 12 injections of BTX and he tolerates it well. Videostroboscopy after treatment showed normal vocal fold motility; the results were concordant with voice quality. As with our two previous patients, the BTX was repeated each 6–8 months to maintain vocal stability. [Table 3](#) shows the treatment details for this patient.

DISCUSSION

We report excellent results in terms of voice quality and laryngostroboscopy findings in all three patients after treatment with BTX.

In a small, retrospective study, Bernitsas et al¹³ found the prevalence of SD in patients with MS to be 1.6%, whereas it is only 0.0005% in the general population; moreover, SD can precede the diagnosis, being the first manifestation or following the diagnosis of MS.¹³

Ludlow et al explained the mechanism of speech production,²¹ focusing on the pathways involved. In addition, she related the voice alteration to lesions in the emotional area of the brain.^{9,11,22} She has described neurodegenerative phenomena in specific areas of the brain involved in speech and emotional functions. These areas include the solitary tract, spinal trigeminal, nucleus ambiguus, inferior olive, pyramid, substantia nigra, and locus coeruleus. Demyelinating lesions in the CNS structures related to speech production may contribute to the development of SD in MS.^{9,12,23} Although voice quality and speech production are affected in MS, there is lack of data in the literature focusing on MS-related voice disorders. Furthermore, there is only anecdotal evidence regarding MS-associated SD. The causative factor and mechanism involved in the MS-related SD is still unclear and speculative.

The use of BTX is widely accepted as off-label treatment for SD.^{15,16} Maronian et al²⁴ supported the use of BTX on LCA in the adductor SD. Then, the injection site was switched to TA to reduce the vocal tremor and voice breaks; we used the same technique for treating our patients and we can confirm its validity in our case series.

In our patient with adductor SD, we inject 5 international units (IU) of BTX by percutaneous technique,¹⁸ first in the TA and then in the LCA ([Figure 1](#)). We observed symptom resolution 15 days after the BTX, and the results of the treatment were stable in long-term observation, repeating a maximum of two injections per year for each vocal fold. The stability of voice quality we observed in this sample is concordant with that of patients without MS who have SD;

in fact, we always repeat the BTX twice per year. We may conclude that in the presence of MS, BTX has been equally effective.

Even though we started our BTX treatment with dose higher than the one suggested by other authors,^{15,25} we did not observe dysphagia²⁴ in any of our patients. In our opinion, this is due to the method we used for BTX dilution and to the precision of the injection point. In general, to activate the BTX, it is necessary to add 1.25 mL of tonic solution to the ampulla of 50 units of toxin, to have 4 units each milliliter. In our practice, we use 1.50 mL for 50 units, and a solution of 3 units/mL is produced; higher dilution allows higher spread of the toxin in the injected muscles, which may reduce the likelihood of adverse events.

BTX acts in periphery by blocking acetylcholine release at the neuromuscular junction, and Ludlow et al attributed the effectiveness of BTX in treating SD to an alteration in sensory feedback to the CNS²¹ and possibly to retrograde transmission of the toxin to the interneurons in the CNS affecting motor neuron firing, thus reducing muscle activity.^{17,26,27}

BTX with its double action directly reduces muscle spasticity and, by retrograde action, alters the centrally mediated vocal fold movements, thus normalizes the phonation and improves the speech emission and fluency.^{1,16,21}

To confirm the long-term effectiveness of this therapy and its clinical implications, larger scale studies are warranted.

CONCLUSIONS

The prevalence of SD in patients with MS might be higher than in the general population. We presented three cases of SD associated with MS, successfully treated with BTX injection. Patients with MS experience voice problems, such as weak voice, vocal tremor, and voiceless gaps. The clinician should be aware of the possibility of SD, and he or she should always include it in the differential diagnosis of vocal problems in patients with MS.

BTX, thanks to its double effect directly on vocal folds and indirectly on brain, should always be considered as first choice in MS-associated SD.

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