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Botulinum toxin injection following deep brain stimulation in generalized dystonia

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Introduction

Deep brain stimulation (DBS) has emerged as an effective treatment for idiopathic generalized and some focal dystonias [1,2]. It is also increasingly utilized in patients with symptomatic or secondary dystonias, such as those due to cerebral palsy, post-traumatic dystonia, post-stroke dystonia, tardive dystonia, neurodegenerative or metabolic disorders such as pantothenate [3]. kinase-associated neurodegeneration (PKAN), and other disorders, although they may be less responsive to DBS [1,4-8].

For dystonia, DBS usually targets the GPi and is often reserved for patients who are poorly controlled with oral medications and botulinum toxin (BoNT) injections. DBS typically improves generalized dystonia by about 50% on rating scales such as the Burke-Fahn-Marsden dystonia rating scale [1,9].

BoNT plays a limited role in management of generalized dystonia as toxic doses would be required to treat all body areas. However, BoNT can successfully relieve spasm in discrete body areas [9-11]. Patients with generalized dystonia often receive BoNT injections for symptomatic control of specific symptoms before undergoing DBS. Since residual symptoms are present in patients with generalized dystonia following DBS, continuing BoNT injections after DBS placement may be helpful. There is, however, little literature available on the utility of botulinum toxin after DBS surgery and whether the dose, selection of muscles or response to BoNT is altered by DBS. In this small retrospective study, we evaluated the utility of BoNT following DBS surgery in patients with generalized dystonia.

Methods

The National Institute of Neurological Disorders and Stroke Human Motor Control Section clinical database was queried for patients with generalized dystonia who received BoNT injections for at least 1 year after DBS. The muscles injected, BoNT dose, and response to injection were recorded for the last injection session prior to DBS (when applicable) and followed yearly from date of DBS surgery (Table 1).

Results are described as mean (range). Response to BoNT was scored using a patient self-reported visual analog scale ranging from 0% (no improvement) to 100% (no dystonic symptoms). DBS settings were adjusted during the period of BoNT treatment by patient physicians independent of those injecting BoNT.

Results

Patients

Patient #1 DYT1: Patient #1 had delayed motor milestones; she sat at 1 year of age and walked at 2½ years. Initial dystonic symptoms were noted at age 9, when she developed difficulty writing, using utensils, and buttoning and "overlapping toes". No treatment was sought. Neck involvement, which was not prominent until age 19, progressed over 6 months to a fixed laterocollis. Neck pain and concerns about her appearance led to medical evaluation. The patient was of Ashkenazi Jewish descent and family history revealed a maternal aunt with generalized dystonia and a father with cervical dystonia. MRI of the brain and cervical spine was normal. Genetic testing was positive for DYT-1.

After a brief trial of levodopa without response, BoNT injections were started, targeting the neck and right hand. Injections over the next 10 years brought 50-80% improvement in neck and hand symptoms. However, the dystonia gradually worsened and spread to other body areas. Injections became less effective, yielding only about 30% benefit. She underwent bilateral globus pallidus internus (GPi) DBS surgery at age 29. BoNT injections were resumed after DBS. The injections targeted a similar number of muscles and used a dose similar to that previous to surgery. Over the next 2 years, she had a consistent response of about 40% improvement in residual dystonic symptoms with injection of 503 units (range 500 to 505) of onabotulinumtoxinA to neck muscles. She has had no adverse effects.

Patient #2 Intrauterine Rubella: Patient #2 had motor and cognitive development delays attributed to intrauterine rubella infection. As a child, she was able to walk and swim without difficulty. However, she gradually developed laterocollis, scoliosis, and myoclonic jerking of her neck as well as abnormal arm and leg movement and postures during her 30s, by age 41, she was unable to walk without assistive devices. She was unable to tolerate oral medications including trihexyphenidyl and amantadine. She received up to 200 units

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Table 1. Number of muscles and doses before and annually after DBS.

Diagnosis	Time of injection	Muscles	Total dose*	Response**
DYT1	Before DBS	5	505	30
	1 y	5	500	40
	2 y	5	505	
Intrauterine Rubella	Before DBS	4	200	0
	0y (immediately p-dbs)	4	320	75
	1 y	8	500	75
	2 y	9	500	75
	3y	7	370	75
	4y	6	360	75
	5y	6	310	75
	6y	7	330	75
	7y	3	320	75
PKAN2	Before DBS	9	215	25
	1 y	Salivary glands only		
DYT1	0y (immediately p-dbs)	8	200	15
	1y	9	660	20
	2y	11	555	55
	3y	12	660	75
	4y	11	610	50
	5y	13	595	60
	6y	12	560	40

*dose = units onabotulinumtoxinA
**Response assessed by patient/family as % improved (0=none to 100= complete response)

onabotulinutoxinA to the neck and trunk without noticeable response at another institution. She underwent GPi DBS implantation at age 42. At BoNT treatment sessions over the subsequent 7-year period with ongoing DBS, 3-9 muscles (mean = 6) were injected with a mean total dose of 37 units onabotulinumtoxin A (range 310-500 units). She has had a stable response to injection, which she and her family assessed at 75% improvement. There have been no adverse effects other than temporary mild weakness in injected muscles.

Patient #3 PKAN2: Patient #3 had clumsiness and behavioral problems dating to early childhood. She was initially diagnosed with attention deficit/hyperactivity disorder and treated with antidepressants and stimulants, which elicited vocal and motor tics. During childhood and adolescence, she also received risperidone and topiramate for behavioral symptoms. When writing, she had a tight grip on the pen and switched from writing with her right hand to the left hand in 7th grade. Slurred speech, involuntary jaw opening and dystonic posturing of her arm and leg were first noticed at age 16. Dystonia gradually worsened to involve all extremities, the trunk and the face and jaw. CT scan of the brain showed basal ganglia calcification. Genetic testing was positive for PKAN 2. Levodopa was tried without response. She began BoNT injections for hand dystonia with moderate response at another institution according to prior physician notes. When first seen at NIH, her main impairment from the generalized dystonia included slurred speech, jaw opening dystonia, hypersalivation, and difficulty walking. Injections at NIH with up to 440 units onabotulinumtoxin A before DBS brought about 10% improvement. She underwent GPi DBS at age 25. Following DBS, she only had a onetime injection of 10 units to each lateral pterygoid for her dystonia. She discontinued limb and neck injections because of remarkable improvement from DBS. However, she elected to continue BoNT injections for sialorrhea only with mean 80 units (range 60 to 100) to each parotid, and 32 units (range 15 to 60) to each submandibular gland. Switching to rimabotulinumtoxinB did not result in further improvement.

Patient #4 DYT1: Patient #4, a Guatemalan woman of Chinese ancestry, with otherwise normal birth and delivery and early childhood milestones, was diagnosed as having a psychogenic movement disorder when she developed abnormal hand and feet posturing at age 10. Symptoms worsened despite psychiatric therapy and neurologic therapy, including trial of benzodiazepines, antidepressants, levodopa, baclofen and trihexiphenidyl, such that by age 24, dystonia had generalized to involve the trunk and all extremities and she required a wheelchair. Genetic testing was positive for DYT1. She had GPi DBS initiated at age 30. BoNT injections were first started after DBS to address residual dystonic symptoms. Over the next 6 years, she received a mean dose 627units (range 200-785) with a stable response rated 50 ± 8% improvement. She has reported no adverse effects of injection.

Discussion

While the first line treatment for focal dystonia, botulinum toxin injection is not uncommonly used in patients with generalized dystonia to address focally disabling symptoms. GPi DBS, however, is a better approach for these patients, reducing generalized dystonic symptoms by 50-80% and improving quality of life, comfort and function [1,9]. Although patients with generalized dystonia that is acquired or due to a degenerative underlying disease have a less robust response to DBS, they often benefit sufficiently to justify the risks of surgery [7]. DBS is increasingly being used in this population. Both BoNT injections and DBS offer the advantage of being safe to use in combination with other therapeutic modalities, including each other. The lack of published literature on the utility of botulinum toxin injection after DBS implantation leaves little to guide physicians on their combined use.

This report of 4 cases, 2 patients with DYT-1 dystonia, 1 with acquired dystonia from perinatal infection and 1with dystonia due to the neurodegenerative disease PKAN, provides the first information on the utility of BoNT in combination with DBS. Although we have followed only a small number of patients receiving BoNT after DBS for generalized dystonia, their cases are informative. These patients show that botulinum toxin can continue to be effective in managing residual dystonic symptoms over up to at least 7 years and that the dose and response can remain stable with DBS, including stimulator setting adjustments. Further study is needed to better delineate the role for BoNT in management of dystonia in combination with DBS.

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