Thalamic Deep Brain Stimulation Ameliorates Mixed and Abductor Spasmodic Dysphonia: Case Reports and Proof of Concept

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BACKGROUND AND IMPORTANCE: Spasmodic dysphonia (SD) is a dystonia of the vocal folds causing difficulty with speech. A recent randomized controlled trial showed that thalamic deep brain stimulation (DBS) was safe and could improve this condition in the most common subtype—adductor SD. We investigated if thalamic DBS could also improve the other subtypes of abductor SD and mixed SD. These prospective blinded trials of 1 were designed to assess the safety of thalamic DBS in mixed and abductor SD and to quantify the magnitude of any benefit from unilateral or bilateral thalamic stimulation.

CLINICAL PRESENTATION: One patient with mixed SD and one patient with abductor SD received bilateral thalamic DBS. After optimizing their DBS settings for vocal improvement, they were blinded and prospectively randomized to receive 1 mo of left, right, both, or neither hemisphere stimulation. Outcome was assessed by a speech language pathologist, blinded to the settings, rating voice recordings with the Unified Spasmodic Dysphonia Rating Scale, and by patient self-reported quality-of-life questionnaires. Additional outcomes included scores of mood and cognition. There were no complications. Both patients reported a subjective improvement of their voice and quality of life with blinded left thalamic DBS. The quality of their voice was also objectively rated as improved with blinded left thalamic DBS.

CONCLUSION: This small proof-of-concept study suggests that left thalamic DBS can improve the quality of voice and quality of life of patients with mixed SD and abductor SD.

KEY WORDS: Abductor spasmodic dysphonia, Deep brain stimulation, Spasmodic dysphonia, Quality of life

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Spasmodic dysphonia (SD) is a neurological disorder of the voice compromising a patient's ability to speak due to involuntary contractions of the laryngeal muscles.[1] It is a task-specific, focal dystonia affecting approximately 1 to 4/100 000/yr.[2] The most common subtype is adductor SD (80%-90%) where the vocal folds spasm together causing a strained, choppy voice. In the rare subtype of abductor SD (10%-15%), the vocal folds intermittently spasm apart causing a breathy, quiet, whispering voice. In mixed SD (1%-5%), there are components of both. The current standard of care is repeated botulinum toxin A injections in the affected muscles.[3] Most (not all) patients with adductor SD are satisfied with this therapy.[4-6] Unfortunately, the treatment response for patients with abductor or mixed SD can be poor.[4]

ABBREVIATIONS: BDI-II, Beck Depression Inventory version 2; **SD,** spasmodic dysphonia; **USDRS,** Unified Spasmodic Dysphonia Rating Scale; **V-RQOL,** voice-related quality of life; **VHI,** voice handicap index

A recent randomized controlled trial of thalamic deep brain stimulation (DBS) for adductor SD showed that the therapy was safe and improved both objective quality of voice and subjective quality of life.[7] We offered DBS to a patient with mixed SD expecting improvement in their adductor component and allowing assessment of their abductor component. Following the reported benefit on both components, we offered DBS to a patient with abductor SD.

In this new field of neuromodulation for vocal disorders, it is not yet clear if patients require bilateral[8] or just unilateral stimulation[9] in their speech-dominant hemisphere. This study

TABLE 1. DBS Parameters

	Mixed SD		Abductor SD	
	Left	Right	Left	Right
Blinded	case +, 1− 185 Hz, 60 μs, 1.5 V	8+, 9− 185 Hz, 60 μs, 1.5 V	case +, 2− 185 Hz, 60 μs, 2.0 V	case +, 9− 185 Hz, 60 μs, 1.0 V
Unblinded (1 yr)	0−, 1−, 2−, 3+ 185 Hz, 120 μs, 2.5 V	–	case +, 2− 185 Hz, 60 μs, 2.0 V	–

The active DBS contacts are numbered 1-4 on the left (1 deepest) and 8-11 on the right (8 deepest). Monopolar settings used the implantable neural stimulator as the anode (case +). Bipolar settings report the anode (+) and cathode (−).

TABLE 2. Mixed SD Subjective Voice Scores During Blinded Stimulation

	Preoperative	Left DBS	Right DBS	Bilateral DBS	No DBS
V-RQOL	Fair	Good	Poor	Fair	Poor
VHI	77	67	77	75	76
BDI-II	6	2	12	9	10
VAS	7	5	9	7	9

DBS = deep brain stimulation, V-RQOL = voice-related quality-of-life subjective assessment, VHI = voice handicap index (lower scores are better), BDI-II = Beck Depression Inventory version 2 (lower scores reflect less depression), VAS = visual analog scale of voice pathology (lower is better).

TABLE 3. Mixed SD Objective Voice Assessment During Blinded Stimulation

	Preoperative	Left DBS	Right DBS	Bilateral DBS	No DBS
USDRS overall	4	3	3	3	6
USDRS breathy-voice	4	3	3	3	6
USDRS strained-voice	4	3	2	2	5
Number of adductor spasms	15	3	2	3	4
Number of abductor spasms	8	1	3	5	7

USDRS = Unified Spasmodic Dysphonia Rating Scale (0-7 scale, lower is better).

was designed to add information about the benefits from unilateral or bilateral thalamic DBS for SD.

CLINICAL PRESENTATION

The CARE (CAse REport) guidelines were followed for this case report. Ethics approval was obtained from our university [Ethics Board # H19-00359] and both patients provided a written consent.

Mixed Spasmodic Dysphonia

A 55-yr-old right-handed woman presented with a 3-yr history of mixed SD. She was diagnosed by consensus by a laryngologist and speech language pathologist. Treatments included voice therapy and repeated botulinum toxin injections, but the benefits were not enough to stop the condition from interfering with her work. The patient had bilateral thalamic DBS during 1 operation using the same targeting method as reported to be effective for adductor SD.[7] A postoperative computed tomography (CT) scan was merged with the preoperative magnetic resonance imaging (MRI) and the deepest contacts (for both patients) were <2 mm from the expected location. Stimulation began 1 mo later and was optimized over several visits (Table 1). Settings with side-effects (paresthesia or contractions) were not allowed to avoid unblinding. The patient was then blinded and randomized to 1 of 4 settings for 1 mo each: left DBS, right DBS, bilateral DBS, or no DBS. After each setting, the patient completed the following forms: voice handicap index, Beck Depression Inventory version 2, voice-related quality of life, and also rated their voice on a visual analog scale (Table 2). Recorded voice samples were rated by a speech language pathologist blinded to the settings using the Unified Spasmodic Dysphonia Rating Scale, and the number of abductor and adductor spasm events was counted with the patient reading standardized sentences

(Table 3). Voice recordings are provided during blinded-DBS "off" in Video 1A and blinded-left "on" in Video 1B.

There was a subjective and objective improvement in her voice with DBS in the left hemisphere. After 12 mo of left stimulation (unblinded), the patient reported sustained improvement, but the DBS parameters had been changed (Table 1).

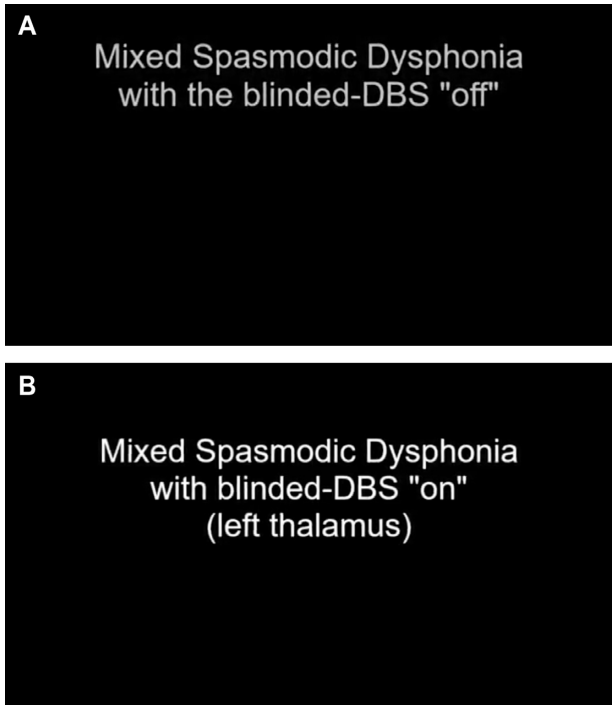
Abductor Spasmodic Dysphonia

A 50-yr-old right-handed man presented with a 3-yr history of abductor SD. He was diagnosed by consensus by a laryngologist and speech language pathologist. His breathy, quiet voice was initially intermittent but became constant and interfered with his work and socializing. Treatments included voice therapy and repeated botulinum toxin injections. He declined further injections. The patient had bilateral thalamic DBS. Results are presented in Tables 4 and 5, and voice recordings are provided during blinded-DBS "off" in Video 2A and blinded-left "on" in Video 2B.

There was a subjective and objective improvement in his voice with DBS in the left hemisphere. The objective measurements of abductor SD, USDRS breathy-voice and number of abductor spasms, improved with DBS in the left but not in the right hemisphere. Montreal cognitive assessments before and after the study were unchanged for both patients. After 12 mo of left stimulation (unblinded), the patient reported sustained improvement without further adjustment of the DBS parameters.

DISCUSSION

The field of DBS for vocal disorders is new. There are a few retrospective case reports of serendipitous improvement of



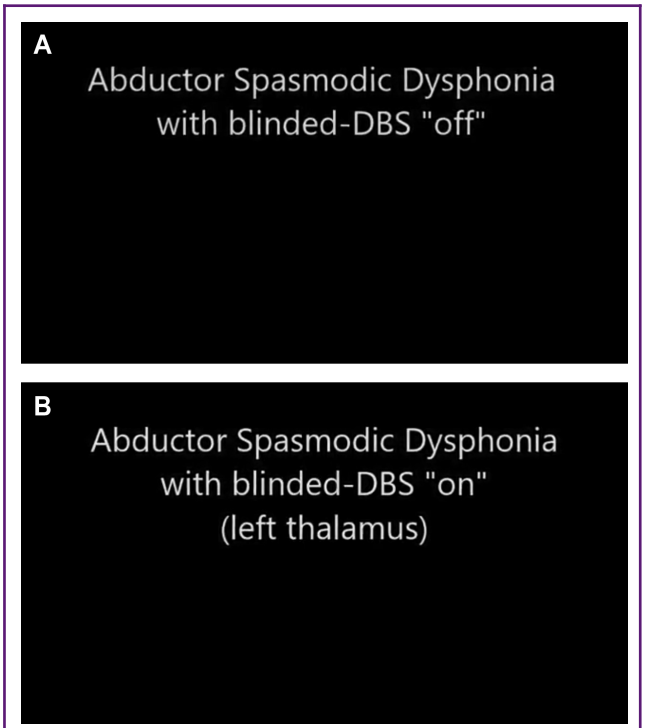
VIDEO 1. *Voice recordings for mixed SD. The patient with mixed SD is reading standardized sentences and the rainbow passage, describing the "cookie thief" scene, and speaking spontaneously with blinded-DBS "off"* **A** *and blinded-left thalamic DBS "on"* **B**.

TABLE 4. Abductor SD Subjective Voice Scores During Blinded Stimulation

	Preoperative	Left DBS	Right DBS	Bilateral DBS	No DBS
V-RQOL	Poor	Fair	Poor	Fair	Poor
VHI	78	51	81	50	69
BDI-II	17	2	3	4	1
VAS	8	3	9	3	10

TABLE 5. Abductor SD Objective Voice Assessment During Blinded Stimulation

	Preoperative	Left DBS	Right DBS	Bilateral DBS	No DBS
USDRS overall	5	3	6	5	6
USDRS breathy-voice	5	2	6	3	7
USDRS strained-voice	5	3	4	4	2
Number of adductor spasms	0	0	1	0	0
Number of abductor spasms	22	13	25	13	28



VIDEO 2. *Voice recordings for abductor SD. The patient with abductor SD is reading standardized sentences and the rainbow passage, describing the "cookie thief" scene, and speaking spontaneously with blinded-DBS "off"* **A** *and blinded-left thalamic DBS "on"* **B**.

adductor SD following thalamic DBS for concomitant tremor.[10] There is a single prospective case report of blinded DBS for adductor SD.[9] The first randomized controlled trial of DBS for adductor SD has only just been published in *Neurosurgery*.[7] This report is the first to describe DBS for the rare subtypes of abductor and mixed SD. In both our prospective, randomized, blinded trials of 1, there were no adverse or unanticipated events. There was subjective and objective improvement in the voice and subjective improvement in the quality of life for both patients. Botulinum toxin injection for SD is often effective for the adductor but not for the abductor subtype.[4] Neuromodulation may provide a new treatment for abductor SD as well as an additional treatment option for those with adductor SD who are refractory to their current therapies. Initial examination of the limited data suggests that unilateral left DBS may provide a similar benefit to bilateral DBS in right-handed patients. The small number treated so far makes any definitive statement on this premature, but a recent study has also shown left dominance for thalamic speech control (in right-handed patients).[7] Speech as well as language appears to be lateralized. The benefit of thalamic (ventrointermediate nucleus) neuromodulation for SD[7-10] coupled with the lack of benefit following pallidal DBS[11] suggests that the neural circuits for vocal fold movement are predominantly if not exclusively under cerebellar control.

CONCLUSION

These prospective case reports of blinded thalamic DBS for abductor and mixed SD provide a proof of concept that neuromodulation can be effective for this vocal pathology.

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