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Deep Brain Stimulation in Isolated Dystonia With a *GNAL* Mutation

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Mutations in *GNAL* are a rare cause of dystonia.[1,2] Most patients have cervical onset with spread to cranial muscles, and a minority becomes generalized. It is unclear how genetic etiology dictates pharmacological and surgical response, as *DYT1-TOR1A* mutation carriers show excellent benefit from deep brain stimulation (DBS), but *DYT6--THAP1* carriers show a more mixed response.[3] Here we report a series of 3 patients with *GNAL* dystonia who responded to bilateral globus pallidus pars interna (GPi) DBS (Table 1). Our cases were ascertained post-DBS; thus, charts were reviewed retrospectively, and formal pre- and post-DBS rating scales were only available for cases 2 and 3. All cases had other family members with dystonia, and their family mutations were included in the initial report of the *GNAL* gene.[1]

Case 1 developed head tremor at age 38, which progressed to antero- and laterocollis, then retrocollis, bilateral shoulder elevation, bilateral arm tremor, and writer's cramp. DBS was performed at age 53, and after 1 year, pain and neck posturing markedly improved. After 2 years, arm tremor was reduced, and there was mild residual laterocollis, but writer's cramp persisted.

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Case 2 developed laterocollis at age 42 and had partial initial improvement with botulinum toxin injections. However, symptoms markedly worsened at age 44 with the development of left retrocollis, right shoulder elevation, and limited range of motion with intense pain. He had mild dysphagia, hoarseness, and changes in speech. DBS was performed at age 53. Three years after surgery, dystonic posturing improved, with residual mild left torticollis, right laterocollis, and retrocollis, but pain and dysphagia persisted. Twelve months after surgery the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) part 1 score had decreased from 24 to 17 and is now 13 after 8 years of follow-up (Table 1).

Case 3 developed laterocollis at age 18. The dystonia spread to both arms and feet as well as the upper and lower face, including jaw, tongue, and pharynx, and was associated with severe dysarthria. At 41, DBS was performed for worsening laterocollis. After 1 year, neck tilt improved significantly, from 90 to 15 degrees. Although foot cramping improved markedly, left arm dystonia continued to progress and was significantly worse 8 years after DBS. Despite this and persistent severe dysarthria, both the patient and her neurologist reported considerable improvement, and TWSTRS part 1 scores decreased from 21 to 15 after the first year and to 9 after 2 years of follow-up (Table 1).

Our cases extend and support prior limited literature that suggested that cervical dystonia from *GNAL* mutations may significantly improve with GPi DBS.[4,5] Although cranial (including speech) and limb dystonia did not improve, severe and prolonged cervical dystonia lessened in all cases. Furthermore, all demonstrated significant benefit at the first year, which was always sustained in the neck. The progression of dystonia in the setting of DBS, as seen in case 3, has been reported in other forms of dystonia.[3]

The underlying different pathophysiologic mechanisms in genetic forms of dystonia may contribute to heterogeneous DBS response. There is limited imaging data in *GNAL* although in 1 case with laryngeal dystonia functional MRI demonstrated increased activity in the frontoparietal cortex and decreased activity in the cerebellum.[6] Gαolf mutations may precipitate dystonia by interfering with adenylate cyclase activity in dopamine D1 receptors of striatal medium spiny neurons,[1,2] but it remains unclear how this pathophysiologic mechanism is related to DBS response. Larger prospective studies, including with formal rating scales, are necessary.

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TABLE 1.

Clinical features and deep brain stimulation response in *GNAL* mutation carriers

Case	Age/sex	Mutation	Age at onset	Site of onset	Preoperative affected sites	Preoperative medications	Postoperative medications	Age at surgery	Neurologist report at last follow-up	DBS settings	TWSTRS[a] part I score	TWSTRS[a] total score
1	56 F	T197fsX09	38	Neck	Neck, R arm, L arm,	Trihexyphenidyl, clonazepam, TBZ,[b] propranolol, fentanyl, baclofen, botulinum toxin	Clonazepam, cyclobenzaprine, gabapentin	53	2 Years; improved: 85% neck and Arms	L GPi: 0–3+, 4 V/90 microseconds/185 Hz R GPi: 8–11+, 6 V/120 microseconds/185 Hz	n/a	n/a
2	56 M	R21X	42	Neck	Neck	Cyclobenzaprine, botulinum toxin	botulinum toxin	53	8 Years; improved: 50% neck[c]	L GPi-1: C+0−, 3 V/90 microseconds/125 Hz L GPi-2: C+1−, 3 V/90 microseconds/125 Hz R GPi-1: C+1−, 3 V/90 microseconds/125 Hz R GPi-2: C+0−, 3 V/90 microseconds/125 Hz (interleaving settings)	Preop TWSTRS part 1: 241 year postop part 1: 172- to 4-years postop part 1: 18 5- to 7-years postop TWSTRS part 1: 158 years postop part 1: 13	n/a
3	44 F	S95fsX09	18	Neck	Neck, pharynx, upper and lower face, tongue, jaw, both arms, legs	Ethopropazine, botulinum toxin	None	41	8 years; improved: neck 85% (from 90- to 15-degree tilt), foot cramps improved 90%, continued progression of dysarthria and L hand dystonia	L GPi: C+1−, 4.5 V/60 microseconds/145 Hz R GPi: C+5−, 4.2 V/90 microseconds/145 Hz	Preop part 1: 211 year postop part 1: 152 years postop part 1: 9	Preop total: 681 year postop total: 312 years postop total: 23

[a]TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

[b]TBZ, trabenazine.

[c]Prior to surgery, his laterocollis caused his right ear to touch his right shoulder (90 degrees). This markedly diminished after surgery but remained at a level 3 or 4 (16 to 35 or >35 degrees).