Parkinsonism and dystonia in Lubag disease respond well to high pulse width/low-frequency globus pallidus interna DBS

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Practical Implications

Consider low-frequency stimulation in the programming of patients with dystonia-parkinsonism.

Lubag disease (*DYT3*), an X-linked neurodegenerative condition featuring dystonia and parkinsonism, is caused by mutations in the *TAF1* gene.¹ *DYT3* has been reported to respond to globus pallidus interna (GPi) deep brain stimulation (DBS) using frequencies above 100 Hz (table). We describe the first case of *DYT3* responding to high pulse width and low-frequency stimulation.

Case description

A 51-year-old man from Negros (Philippines) without known exposure to dopamine blockers or family history of movement disorders developed progressive involuntary tongue protrusion and laterocormia. His symptoms were refractory to amantadine and trihexyphenidyl. Fifteen months after symptom onset, he had progressed to develop severe dysarthria, sialorrhea, and dysphagia.

Examination at 17 months from symptom onset revealed dysarthria and hypomimia. Montreal Cognitive Assessment was abnormal (14/30). Kayser-Fleischer rings and square wave jerks were absent, but ocular pursuit was saccadic. Strength was normal, but he was rigid and bradykinetic. Dystonic right toe curling and right laterocormia were evident at rest and worsened with walking. Reflexes, sensation, and coordination were normal.

The combination of dystonia and parkinsonism in this Filipino man raised suspicion for *DYT3*. Sequencing the *TAF1* gene confirmed the disease-specific single nucleotide changes 3 and 12.

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Table Reported cases of Lubag disease treated with globus pallidus interna DBS, including DBS settings

Ref.	Age, y		Preoperative assessment			Reported DBS settings						Postoperative assessment	
	Onset	Surgery	Most disabling motor symptom (s)	BFM DRS score	UPDRS score	Months after surgery	Lead	Lead configuration	Voltage, volts	Pulse width, μ sec	Freq Hz	BFMDRS score (absolute/% improvement)	UPDRS score (absolute/% improvement)
2	31	45	Jaw dystonia, dysarthria	40	30	12	L	Single monopolar 0-case+	5	120	130	9.5 at 12 mo (30.5/76%)	8 at 12 mo (22/73%)
							R	Single monopolar 0-case+	5	210	130		
6	34	34	Oropharyngeal dystonia	77.5	37	12	L	NR	3.3	60	130	15 at 12 mo (62.5/81%)	8 at 12 mo (29/78%)
							R	NR	3.3	60	130		
3	32	40	Orofacial dystonia, opisthotonus	87	40	12	L	Double monopolar 0-1-case+	4.5	60	185	17 at 12 mo (70/80%)	38 at 12 mo (2/5%)
							R	Double monopolar 4-5-case+	4.5	60	185		
7	57	53	Right arm dystonia, shuffling gait	14	48	12	L	Double monopolar 2-3-case+	3.3	90	160	4.5 at 12 mo (9.5/68%)	43 at 12 mo (5/10%)
							R	Single monopolar, 2-case+	3.1	90	160		
4	30	32	Truncal dystonia, craniocervical dystonia	40	9.5	12	L	NR	4.5	90	145	4.75 at 12 mo (35.3/88%)	4 at 12 mo (5.5/58%)
							R	NR	3.2	90	145		
1	32	36	Orolingual dystonia, truncal dystonia	93.5	NR	9	L	Single monopolar 0-case+	4.5	120	140	36 at 9 mo (57.6/61%)	NR at 9 mo (NA)
							R	Single monopolar 0-case+	4.0	120	140		
Present study	49	51	Orolingual dystonia, truncal dystonia	89	33	10	L	Double monopolar 2-1-case+	3.6	180	75	16 at 10 mo (73/82%)	12 at 10 mo (21/63.6%)
							R	Double monopolar 3-2-case+	3.4	190	90		

Abbreviations: BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; DBS = deep brain stimulation; NA = not applicable; NR = not reported; UPDRS = Unified Parkinson's Disease Rating Scale.

Video

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By 30 months (see video 1 at Neurology.org/cp) he developed dystonic left arm elevation, was largely wheelchair bound, and had a percutaneous gastrostomy tube. He failed a clonazepam trial.

He underwent bilateral GPi DBS 32 months after onset. His preoperative Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) score was 89 and his Unified Parkinson's Disease Rating Scale (UPDRS) score was 33 (table).

Following a monopolar review, initial voltage/pulse width/frequency/lead configuration were as follows: left: 2.5 V/120 μ sec/60 Hz/0-case+; right: 2.5 V/120 μ sec/60 Hz/2-case+. Settings were titrated over time (most recent shown in the table).

Two months postoperative, swallowing, tongue protrusion, and gait all improved (BFMDRS score 48.5). By 6 months (see video 2), axial rigidity and ambulation also improved, although dystonic left arm elevation and laterocormia remained (BFMDRS score 41). Laterocormia and dysphagia improved significantly by 8 months (BFMDRS score 13) (see video 3). Ten months postoperative, increasing his left stimulator's frequency from 75 to 80 Hz worsened right shoulder dystonic pulling (BFMDRS score 16), prompting return to the previous settings which, again, reduced his BFMDRS scores. Parkinsonism also improved (see UPDRS scores in the table).

DISCUSSION

DYT3 affects roughly 18.9/100,000 Filipino men from the island of Panay,¹ with only a few female cases reported.² It typically debuts with segmental (craniocervical) dystonia that can generalize;³ parkinsonism evolves later.¹ In the right clinical setting, excluding other causes may allow for a presumptive clinical diagnosis.⁴

We herein report successful surgical treatment of Lubag disease using high pulse widths coupled with frequencies under 100 Hz, which suggests that these settings may be sufficient to correct aberrant GPi neuronal firing in *DYT3*. Data from our center previously described the usefulness of similar programming settings in the treatment of primary torsion dystonia,⁵ and since that report it is our practice to treat patients with low frequencies from therapy outset. However, we cannot exclude a therapeutic role of the high pulse widths (these were never reduced below 120 μ sec, unlike some of the cases shown in the table).

It is important to note that none of the other cases reporting the utility of DBS in *DYT3* described disadvantages from using higher frequencies. In fact, they were quite efficacious. We can only hypothesize that either our patient's lead positions or the contacts used were responsible for the clinical worsening experienced after increasing the stimulation frequency. Moreover, although continued voltage increments may have improved dystonia in our patient, we did not attempt this given adequate symptom control and our concern that voltage increments may trigger side effects similar to higher frequencies.

This case demonstrates that high pulse width and low-frequency stimulation provide comparable degrees of improvement in dystonia and parkinsonism in Lubag disease up to a year after surgery. The advantages of using these settings include minimizing stimulation-induced side effects and prolonging battery life. The latter reduces both the morbidity from repeated battery replacements and the lifetime cost of delivering DBS therapy.⁵ Continued follow-up and replication of our findings are warranted to document the persistence of these benefits, particularly as the disease progresses from the dystonic to the parkinsonian stage.

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