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Tremor and Other Hyperkinetic Movements

Article

Low-Frequency Deep Brain Stimulation for Dystonia: Lower is Not Always Better

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Abstract

Background: It has been observed that low-frequency stimulation (LFS) may be effective for dystonia, and the use of LFS may alleviate the need for frequent battery changes in a subset of patients. The aim of this study was to analyze LFS as a strategy to treat deep brain stimulation (DBS) patients with various dystonias.

Methods: Subjects had to receive a minimum of 6 months of clinical follow-up at the University of Florida, and were required to have a minimum of 3 months on a LFS trial. Twenty-seven dystonia DBS patients were retrospectively analyzed from the UF-INFORM database.

Results: Thirteen subjects met inclusion criteria. Of the 13 subjects, all had bilateral internal pallidum (GPi) DBS, and five (38.5%) remained with at least one side on LFS settings at their last follow up (average follow up 24 months, range 6–46 months). Within the first 6 months, six (46%) subjects remained on LFS and seven (54%) were changed to high-frequency stimulation (HFS). Those who remained on LFS settings at 6 months were characterized by shorter disease durations than those on HFS settings. There were no significant differences in dystonia severity (Unified Dystonia Rating Scale and Burke–Fahn–Marsden Dystonia Rating Scale) at baseline between the two settings. The estimated battery life for LFS (79.9 ± 30.5) was significantly longer than for HFS settings (32.2 ± 13.1, $p<0.001$)

Discussion: LFS was ultimately chosen for 38.5% of all subjects. Although this study failed to yield solid predictive features, subjects on LFS tended to have shorter disease durations.

Keywords: Deep brain stimulation, dystonia, voltage, rate, complications, outcome

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Introduction

Dystonia is a complex neurological syndrome characterized by repetitive, involuntary muscle co-contractions. The syndrome can be classified by the pattern of distribution (focal, segmental, multifocal or generalized), the etiology (primary or secondary), or the age of onset of symptoms (early vs. late).[1] Medical treatment for generalized dystonia can be challenging, and in many cases disappointing. In recent years, bilateral globus pallidus internus (GPi) deep brain stimulation (DBS) surgery has emerged as a reasonable therapeutic modality for well-selected and for well-screened cases of disabling, medication refractory dystonia.[1–6] Among the many advantages of DBS, flexibility in programming has been one of the most attractive features, as this type of flexibility may facilitate the achievement of a more tailored and potentially better clinical response. The parameters on the DBS device that can be adjusted by the clinician, including the active contacts (and their array), the amplitude, the frequency, and the pulse width (PW) of stimulation. There remains, however, little consensus regarding the optimal parameters, and most DBS experts would argue that in dystonia programming is highly empiric and patient specific. Historically, programming for dystonia has been performed with higher PWs (210 μseconds up to 450 μseconds), and higher frequencies (130 Hz up to 185 Hz);[1,3,6–9] however, recently lower PWs (<210 μseconds) and lower frequencies (<100 Hz) have been employed. There are currently few available data addressing high-frequency stimulation (HFS) versus low-frequency stimulation (LFS) clinical outcomes in dystonia. Also absent from most datasets are the

many differing presentations of dystonia (e.g. focal, segmental, generalized). Isaias et al.[5] in a record review of 30 consecutive patients with primary generalized dystonia (PGD) implanted with GPi DBS reported that there was no difference in the overall clinical outcome of HFS versus LFS DBS. The authors noted that shorter PWs and lower frequencies had an added benefit for prolonged battery life. We introduced a clinical protocol to enroll a consecutive group of mixed dystonia patients (regardless of dystonia subtype), and to administer a minimum of 3 months of LFS. Following this trial, if a less than anticipated clinical outcome was achieved, patients were subsequently converted to HFS in an attempt to improve their outcomes. The patients were then followed and their outcomes and stimulation settings recorded.

Methods

This study employed an Institutional Review Board (IRB) approved database (UF-INFORM). Data were retrospectively obtained on the general demographics (age, gender, type of dystonia, disease duration, DYT-1 gene test results), stimulation parameters (voltage, rate, pulse width) as well as the Unified Dystonia Rating Scale (UDRS) and Burke–Fahn–Marsden Dystonia Rating Scale (BFM–DRS) motor subscores when available. The maximal total score of the UDRS and BFMDRS were 112 and 120 respectively.[10] The scales were recorded from 6 month and 12 month post-DBS follow-up visits, and they were drawn from all available data. Subjects were started on LFS (defined as a frequency of less than 100 Hz) and all outcomes were documented. The analysis was designed to elucidate the characteristics that potentially predicted who remained at LFS, and who converted to HFS. Subjects had to receive a minimum of 6 months of clinical follow-up at our institution (UF) to be included in the study, and they must have received a minimum of a LFS trial for the first 3 months after DBS surgery. The 3 month LFS trial was introduced in our DBS programming clinic in 2004. Excluded from the cohort were patients who had previous DBS surgery for dystonia at any outside institution, the use of multiple DBS targets for dystonia, or the use of double leads on a single target. Patients were also excluded if any programming occurred outside of our institution, or if they did not complete a minimum of 3 months of a LFS trial after DBS implantation.

All patients signed an informed consent and underwent DBS surgery by the same neurosurgeon (KDF) and neurologist (MSO) team at the University of Florida Center for Movement Disorders & Neurorestoration between 2004 and 2009. The bilateral GPi DBS procedure was staged for some subjects: one side followed by a second hemispheric surgery 2–4 weeks later, or alternatively subjects had bilateral surgery on the same day. All subjects underwent bilateral quadripolar electrode (3387 Medtronic, Minneapolis) implants. Implantable pulse generators (IPGs) were placed in another procedure, under general anesthesia, and 1 month following the second DBS lead surgery. Patients were seen 1 week after IPG placement for screening of benefits and side effects at each of the four DBS lead contacts. A monopolar configuration, with a set PW of 90 μseconds and a set frequency of 135 Hz was utilized for these trials. Side effects were monitored by increasing the stimulation amplitude until the patient developed sensory, motor or visual phenomena. After checking thresholds and confirming lead placement by a post-operative magnetic resonance imaging–computed tomography (MRI–CT) fusion study, each patient underwent subsequent programming utilizing LFS over 3 months, pushing the voltage toward maximally tolerated thresholds at each visit if clinical improvement was not evidenced, or improvement was judged suboptimal. Programmers were permitted to add cathodes (more active contacts) if there was a lack of response, or a less than anticipated clinical improvement. The estimates of battery life were obtained by calling Medtronic technical support and by using the programming parameters at the last clinical follow-up visit. All data were retrospectively collected from the UF-INFORM database, and then used to compare LFS and HFS. The Mann–Whitney test was utilized for continuous data because of the small sample size, and because the data were not normally distributed. The chi-square test was utilized for categorical data.

Results

A total of 27 dystonia subjects were identified in the database as potentially being eligible for the study. These subjects were operated between 2004 and 2009. From the 27 database records, 14 subjects (seven male and seven female, mean age 20.9 ± 16.6, median age 12.5, range 7–55 years) were excluded from further analysis because they failed to meet the inclusion criteria. Ultimately 13 subjects (10 male and three female, mean age 25.5 ± 19.8, median age 27.0 and range 0–62 years) were included. There were no statistical differences between the included and excluded groups in terms age (Mann–Whitney test, $p=0.627$) and sex (chi-square, $p=0.248$). The reasons for exclusions were as follows: multiple targets (n=2; one with GPi and Vim and the other with GPi and Subthalamic Nucleua (STN) targets), STN surgery for mitochondrial disease (n=1; not a GPi target), double leads placed on single GPi target (n=2), DBS surgery at an outside institution (n=1), surgery prior to the year 2004 when the LFS protocol was instituted (n=3), failed to meet the minimum 3-month period of LFS prior to converting to HFS (n=2), DBS programming performed outside of our institution (n=1), no follow-up at our institution for the first 6 months after DBS surgery (n=1), and initiation of HFS after infection and replacement of the subject's hardware 1 month post-DBS (n=1).

General characteristics, dystonia patterns and DYT-1 status

Of the 13 subjects who qualified for analysis of outcomes, 10 subjects were male and three were female. One of these subjects had a left GPi DBS lead revision 27 months post-operatively because of a fracture; however, he met all inclusion criteria. The baseline and 6-month post-DBS programming parameters were obtained prior to the lead fracture and his last clinical follow-up was obtained after his lead replacement. The disease characteristics of the subjects are summarized in Table 1.

The mean age of symptom onset was 25.5 years (range 0–62 years). Most of the subjects had generalized dystonia (n=7). The other clinical

Table 1. Demographics of patients who had minimum of 3 months of low-frequency stimulation

Subject #	Gender	Age Symptom Onset	Age at First Surgery	DYT-1 Status	Fixed Skeletal Deformities	Dystonia Type (1° vs. 2°)	Distribution	Baseline UDRS	Baseline BFM–DRS M
1	F	29	35	N/A	YES	1	Cervical + larynx	7	N/A
2	M	8	31	pos	NO	1	Gen	44	31
3	M	birth	34	N/A	NO	2 (CP)	Gen	69	64.5
4	M	39	43	N/A	NO	2 (TD)	Gen	82	72
5	M	48	62	N/A	NO	1	Cervical	12	8
6	F	51	73	N/A	NO	1	Cervical	8	8
7	M	15	35	neg	NO	1	Gen	N/A	N/A
8	M	62	67	N/A	NO	1	Craniofacial	29	N/A
9	M	6	8	pos	NO	1	Gen	71	N/A
10	F	29	60	N/A	YES	1	Cervical	12	6
11	M	27	34	N/A	NO	1	Cervical	8	8
12	M	5	11	pos	NO	1	Gen	55	116
13	M	13	33	neg	NO	1	Gen	63	66.5

UDRS, Unified Dystonia Rating Scale; N/A, not available; pos, positive; neg, negative; Gen, generalized dystonia; CP, cerebral palsy; TD, tardive dystonia; BFM–DRS M, Burke–Fahn–Marsden Dystonia Rating Scale Motor subscore.

dystonia patterns included: focal (cervical) dystonia (n=4), segmental (cervical and larynx, n=1), and craniofacial (n=1). Two subjects had secondary dystonia: one subject had generalized dystonia secondary to cerebral palsy, and the second subject had generalized tardive dystonia secondary to neuroleptic exposure for a psychiatric condition. Of the cohort, 11 had a primary dystonia, and of the primary dystonias, three had documented DYT-1 gene mutations. There were two subjects who were DYT-1 gene mutation negative, and the remaining eight subjects in the cohort did not have documented genetic testing. Two subjects had a fixed skeletal deformity (FSD), and, of these, one had a primary dystonia and the other had a secondary dystonia. Baseline UDRS scores were not available for all subjects (not available, n=1). Using the available scores the mean UDRS at baseline was 38.3 (range 7–82). Baseline BFM–DRS motor subscores were not available for all subjects (not available, n=4), but from those available the baseline motor mean score was 42.2 (range 6–116), see Table 1.

Initial programming settings

All of the 13 subjects were initiated on a low frequency of 60 Hz on both DBS leads (see Table 2). Initially, the PWs ranged from 150 to 210 μseconds, with amplitudes ranging from 2 to 3.5 V. Most of the subjects were programmed with a monopolar configuration (n=12) using contacts 1 or 2 (leads numbered 0–3, with 0 representing the ventral contact). There was one subject (subject #6) who was initially programmed on a bipolar configuration for the right lead, and another subject (subject #10) who had a double monopolar configuration on the left lead.

Six months post-DBS follow up

After 6 months of chronic stimulation, six subjects (46%) remained on LFS. The clinical pattern of dystonia distribution for those who remained at LFS 6 months post DBS was generalized in four subjects (66%), focal (cervical) dystonia (16%) in one subject, and segmental (craniofacial) dystonia (16%) in one subject. One of the subjects had HFS settings on the left lead and a LFS setting on the right lead, and this subject was included because at least one lead was at LFS. All six subjects were male. Dystonia was primary in all but one of the subjects. The DYT-1 status in the primary dystonia subjects in the cohort revealed two subjects who were gene mutation positive (33%), one subject was gene mutation negative (33%), and two subjects did not have genetic testing. The secondary dystonia subject was a tardive dystonia case that resulted from neuroleptic exposure for treatment of a psychiatric condition.

Seven subjects (n=54%) were changed from LFS to HFS within the first 6 months. The clinical pattern of dystonia distribution in this group was as follows: generalized (n=3, 43%), focal (cervical) (n=3,

Table 2. Programming settings at baseline and at the last follow-up for the deep brain simulation (DBS) leads.

Subject #		Baseline parameters				Parameters 6 months				Parameters at last follow-up					
		Contacts	Amp	PW	Freq	Contacts	Amp	PW	Freq	Months[1]	Contacts	Amp	PW	Freq	EBL
1	R	1-	2.2	180	60	1-	3	180	135	28	1-	2.3	180	135	46
	L	1-	2.2	180	60	1-	3.1	180	135	28	1-	2.3	180	60	89
2	R	5-	2.8	180	60	5-	1.7	180	135	42	5-	1.8	180	135	39[3]
	L	2-	3.3	180	60	2-	2.4	180	135	41	2-	2.5	180	135	39[3]
3[2]	R	1-	2.1	210	60	2-	2	450	185	13	1-/2-	3.0	120	5	>120[3]
	L	2-	2.1	210	60	1-/2+	2	450	185	13	1-/2-	2.0	120	5	>120[3]
4	R	6-	3.0	180	60	5-/6-	2.1	180	60	35	5-/6-	3.1	180	185	21[3]
	L	1-	3.0	180	60	1-/2+	3	450	185	9	1-/2+	3.0	450	185	21[3]
5	R	2-	2.2	150	60	1-/2+	3	150	135	6	1-/2+	3.0	150	135	45
	L	2-	2.2	150	60	1-/2+	2.6	150	135	7	1-/2+	2.6	150	135	54
6	R	1-/2+	2.0	180	60	1-/2+	2.3	210	185	12	1-/2+	3.0	330	185	20
	L	2-	2.3	180	60	1-	2.5	210	185	12	0-/1+	3.5	330	185	16
7	R	1-	2.5	180	60	0-/1+	2.2	150	135	27	1-	3.0	180	60	72
	L	1-	2.5	180	60	0-/2+	3	150	135	27	1-	3.1	180	60	70
8	R	5-	3.5	180	60	5-/6-	3.2	60	10	6	5-/6-	3.2	60	10	>120[3]
	L	1-	3.4	180	60	1-/2+	3.2	60	10	6	1-/2-	3.2	60	10	>120[3]
9	R	2-	2.6	180	60	2-	3.2	180	60	46	1-/2-	3.6	180	90	40
	L	1-	2.8	180	60	1-	3	180	60	46	1-/2-	3.6	180	60	68
10	R	1-	2.0	180	60	1-/2-/3+	2.3	450	135	39	1-/2-/3+	3.3	330	145	25
	L	0-/1-	2.0	180	60	1-/2-/3+	4.5	450	135	38	1-	3.1	330	185	17
11	R	2-	2.5	180	60	2-	3.2	180	60	24	2-	3.5	180	60	58
	L	2-	2.5	180	60	2-	3.2	180	60	24	2-	3.5	180	60	52
12	R	2-	2.1	150	60	2-	2.8	180	60	25	0-/2+	2.3	210	80	44
	L	1-	2.0	150	60	1-	2.8	180	60	25	1-/2-	2.3	180	80	66
13	R	2-	2.2	180	60	2-	3.2	180	80	23	2-	3.0	210	160	30
	L	2-	2.2	180	60	2-	3.2	180	80	23	2-	3.5	180	100	46

DBS contacts are monopolar unless noted with a positive contact which indicates bipolar configuration.
[1]Months after placement of DBS lead at their last follow up.
[2]Subject 3 had failure of DBS and all hardware was removed 13 months post DBS, at last follow up devices were turned off. EBL: estimated battery life using programming parameters at last clinical follow up.
[3]Kinetra IPGs, otherwise subjects had Soletra IPGs.
Abbreviations: Amp, amplitude of stimulation in volts; PW, pulse width; Freq, frequency of stimulation.

43%), and segmental craniofacial (n=1, 14%). Three subjects were female (43%) and four were male (57%). The etiology for dystonia was secondary in one subject (cerebral palsy), and primary in the other six subjects. In the primary group, one subject was DYT-1 gene mutation positive, one was negative, and four did not have documented genetic testing.

There were no differences in age between the LFS group (25.3±22.2, median 20) and the HFS group (mean 25.7±19.4, median 29, Mann–Whitney test, p=0.775). Disease duration was significantly shorter in the LFS cohort (mean 7.3±6.4, median 5.5) versus the HFS cohort (mean 21.4±9.6, median 22, Mann–Whitney test, p=0.015). Also there were no significant differences between two groups in BFM-DRS score at baseline (LFS; mean 65.6±44.3, median 69.25, HFS; mean 23.5±25.1, median 8, Mann–Whitney test, p=.081) and at 6 months (LFS; mean 35.1±19.4, median 32.25, HFS; mean 35.4±19.6, median 26.5, Mann-Whitney test, p=.592). There were no significant differences between the LFS group and HFS group in UDRS score at baseline (LFS; mean 52.0±28.1, median 61, HFS; mean 25.3±25.5, median 12, Mann–Whitney test, p=0.127) and at 6 months (LFS; mean 37.7±19.5, median 38.5, HFS; mean 28.6±22.3, median 23, Mann–Whitney test, p=0.352). None of the subjects in the LFS group had any fixed skeletal deformities (FSD). Two subjects in the HFS cohort had FSDs.

Last clinical follow-up

Subjects were followed for an average of 24.0±13.1 months (range 6–43 months) post DBS. A total of six out of 13 subjects (46.1%) remained on LFS settings at their last clinical follow up. It is noteworthy, that one of the subjects (patient #3) was at a very LFS setting (vLFS) of 5 Hz, and had his devices turned off at the last clinical follow-up. His hardware was removed because of lack of clinical efficacy 13 months after DBS placement. This subject had a secondary dystonia due to cerebral palsy. Examination of the subjects who were at LFS at their last clinical follow-up revealed they were all male. Subjects that were maintained on LFS settings at their last clinical follow-up were not all identical subjects that were on LFS 6 months post DBS. Two of the subjects who remained on LFS settings 6 months post DBS were subsequently converted to HFS. Both of these subjects had generalized dystonia without fixed skeletal deformities, and both were male. One had a primary dystonia (DYT-1 mutation negative), and the other had secondary dystonia. Furthermore, one subject who had been changed to HFS at 6 months post DBS was later changed back to LFS at the last clinical follow-up, and it was unclear whether one state was superior to the other. There was no significant difference in age (LFS; mean 20.6±21.4, median 15, HFS; mean 31.3±17.9, median 34, Mann–Whitney test, p=0.224) or in follow-up duration (LFS; mean 23.9±14.4, median 23, HFS; mean 24.1±12.1, median 25, Mann–Whitney test, p=0.718) between the LFS group and the HFS group. Furthermore, there was no significant difference in disease duration between the LFS group (mean 11.4±11.5, median 6) and the HFS group (19.0±9.1, 21, Mann–Whitney test, p=.223). Additionally, there were no significant differences between two groups in UDRS baseline (LFS; mean 39.8±29.2, median 42, HFS; mean 37.5±31.8, median 28, Mann–Whitney test, p=0.936) and at 12-month post-DBS visit (LFS; mean 33.0±23.8, median 33, HFS; mean 31.5±24.6, median 31.5, Mann–Whitney test, p=0.915). Also there were no significant differences between the two groups in BFM-DRS at baseline (LFS; mean 62.8±54.0, median 64.5, HFS; mean 31.9±30.4, median 19.5, Mann–Whitney test, p=0.431) and at the 12-month post-DBS visit (LFS; mean 32.6±23.6, median 32.5, HFS; mean 39.0±35.9, median 35, Mann–Whitney test, p=0.773).

Cohort of subjects at LFS at 6 months and at the last clinical follow-up

There were 4 (30.8%) subjects who remained with at least one side on LFS settings 6 months post DBS, and who continued on LFS settings at their last clinical follow up. All four were male and all four had a primary dystonia (two were DYT-1 gene mutation positive). One of the subjects had the right lead at HFS (100 Hz) and the left lead at LFS (60 Hz), and this subject was therefore included in the LFS group. The clinical pattern of distribution for these four subjects was generalized (n=2, 50%), focal (cervical) (n=1, 25%), and segmental (craniofacial) (n=1, 25%). The average disease duration for this group was 5 years, and ranged from 2 to 7 years. None of the subjects had a FSD. The mean UDRS baseline score for this group was 40.75 (range 8–71), and the BFM-DRS motor subscore was not available for two of the subjects.

Implantable pulse generator changes

There were four subjects that had dual channel IPGs (Kinetra), and the remainder of the cohort had single channel IPGs (Soletra). There were three subjects in the cohort who had an implantable pulse generator (IPG) replaced at some point during the clinical follow-up, and all were replaced as a result of the end of battery life. One of the three subjects had two IPG-Soletra changes. The first IPG replacement was performed 16 months post implant, and the second replacement occurred at 20 months following this replacement. One of the subjects had a single IPG-Soletra change on each side at 36 months post implant. The other subject had a single IPG change on the right side at 25 months post implantation, and no changes of the left IPG. Both subjects who had bilateral IPG changes were at HFS parameters at 6 months post DBS. The one subject with a unilateral IPG change remained at LFS at 6 months and also at the last clinical follow-up.

Estimates of battery life were obtained for all the subjects in the cohort using the parameters derived from the last clinical follow-up, with the assumption that the devices were kept in the "On" state for 24 hours (see Table 2). The overall average battery life for the right Soletra IPGs was 42.2 months (range 20–72 months) and for the left side it was 53.1 months (range 16–89 months). The overall average battery life for the Kinetra IPGs was 75 months (range 21–120 months). There were two subjects with a Kinetra that had an estimated battery life of greater than 120 months, and this was felt to be due to very-low-frequency settings (vLFS; 10 and 5 Hz). The Medtronic

Technical Support system does not allow calculating estimates of battery life if the frequency is less than 15 Hz, and this frequency had to be used to calculate the estimate of battery life for these two subjects as it was felt that it would not alter the final estimate. The estimated battery life of the IPG (left or right) programmed for LFS (mean 79.9 ± 30.5, median 70) was significantly longer than the IPG programmed for HFS (mean 32.2 ± 13.1, median 30, $p<0.001$).

Discussion

The results of this study revealed that up to 46% of dystonic patients in a DBS clinic benefited from a trial with LFS. Further, 30.8% of subjects in the cohort remained on LFS settings during the course of their follow-up. The majority of subjects in the cohort were maintained on HFS. The results from the study could be divided into three categories: 1) those patients who remained on LFS during their clinical follow up, 2) those who started on LFS and were subsequently changed to HFS within the first 6 months of DBS programming, and 3) those that were changed back to LFS at some point following their 6-month visit. The study results revealed that the majority of the subjects in this clinical cohort were changed to HFS within the first 6 months of stimulation, and only four subjects (30.8%) ultimately remained on LFS. There was not a clear predictive pattern that emerged for subjects remaining on LFS. There was however a clinical trend for subjects with shorter disease durations tending to be more likely to remain on LFS settings. Interestingly, male subjects also had a more promising response with LFS settings. DYT-1 status was recently reported in the literature to be important in generalized dystonia patients; however, in our small dataset, we could neither confirm nor refute this relationship. Although there was a small sample size of three DYT-1 subjects, one had to be changed to HFS within the first 6 months of stimulation initiation. There were not clear predictive factors in clinical dystonia subtype and the response to LFS. The majority of our cohort had a generalized distribution of dystonia ($n=7$), and of the generalized dystonia subjects ($n=2$), 28.5% remained on LFS. Although it was not statistically significant, the baseline BFM-DRS and UDRS scores tended to be severe in the LFS group. Interestingly, the one subject with craniofacial dystonia remained on a LFS setting with a positive response. It is known that patients who have FSDs may reveal a less robust response to DBS, and in our cohort, the two subjects with FSDs both required HFS.

Recent observations in the literature have revealed that lower frequencies of stimulation were equivalent to higher frequencies in clinical outcomes for generalized dystonia, and our data in general support comparable outcomes for both types of stimulation.[2] In our small cohort, all of our subjects were started on LFS and less than half remained at LFS settings 6 months post DBS. Further, following 6 months of therapy there were more conversions to HFS.

Disease severity was diverse as highlighted by the subjects' differing baseline UDRS and BFM-DRS motor scores. In the group that was maintained on LFS during clinical follow up, the baseline UDRS scores ranged from 8 to 71, and the baseline BFM-DRS motor subscores ranged from 8 to 116, suggesting that disease severity was not a likely predictive factor of a favorable LFS outcome. Moreover, in our cohort some focal and segmental dystonias seemed to benefit from a trial of LFS.

It is reasonable to expect that HFS parameters will deplete the battery more quickly in DBS. In our cohort, there were three subjects who had IPG replacements as a result of end of battery life. Overall, the group on HFS had a lower estimated battery life for both sides than the LFS group. More frequent battery changes represent an important clinical issue as battery changes increase the likelihood for infections, are an inconvenience to the patients, and also increase cost. Battery issues proved a definite advantage for the LFS group.

There were several limitations to our study. A prospective trial of HFS vs. LFS will be needed to exclude the many possible biases of an open case series. Other programming variables such as the active stimulation contacts, the amplitude, and the pulse width of stimulation were not considered in this series, and therefore these variables may have affected the outcome. Additionally, although there has been a recent review on programming approaches for dystonia DBS,[11] no standardized approach has been adopted across continents. Programming for dystonia DBS can be tricky, as clinical improvements are not usually manifested at the bedside. Another weakness was that the statistical power for this study was low because of the small sample size. Additionally, the small cohort was diverse in dystonia subtypes, DYT-1 status, and disease duration. The majority of the subjects in the case series did not have genetic testing for DYT-1, and in a larger study this could proven to be an important outcome predictor for LFS vs. HFS. Finally the variable and broad age range could have influenced outcome.

In our clinical experience, LFS was effective for only a subset of patients. The data on predictive factors was not conclusive. There was a trend for subjects with shorter disease durations to remain on LFS settings. Taking into careful consideration that there exists a group of patients who may have a favorable clinical outcome with LFS, it is reasonable to offer this option to dystonia patients, regardless of DYT-1 status, dystonia distribution pattern, gender, disease severity, or age. We suspect that underlying physiology may play an important role in response to LFS versus HFS, and this question remains to be addressed by future studies. LFS, if successful, has the advantage of consuming less battery, being more cost effective, and having less surgical related comorbidity.

References

1. Tagliati M, Shils J, Sun C, Alterman R. Deep brain stimulation for dystonia. *Expert Rev Med Devices* 2004;1:33–41, http://dx.doi.org/10.1586/17434440.1.1.33.

2. Isaias IU, Alterman RL, Tagliati M. Outcome predictors of pallidal stimulation in patients with primary dystonia: the role of disease duration. *Brain* 2008;131:1895–1902, http://dx.doi.org/10.1093/brain/awn120.

3. Ostrem JL, Starr PA. Treatment of dystonia with deep brain stimulation. *Neurotherapeutics* 2008;5:320–330, http://dx.doi.org/10.1016/j.nurt.2008.01.002.

4. Magarinos-Ascone CM, Regidor I, Gomez-Galan M, et al. Deep brain stimulation in the globus pallidus to treat dystonia: electrophysiological

characteristics and 2 years' follow-up in 10 patients. *Neuroscience* 2008;152:558–571, http://dx.doi.org/10.1016/j.neuroscience.2008.01.001.

5. Isaias IU, Alterman RL, Tagliati M. Deep brain stimulation for primary generalized dystonia: long-term outcomes. *Arch Neurol* 2009;66:465–470, http://dx.doi.org/10.1001/archneurol.2009.20.

6. Krause M, Fogel W, Kloss M, et al. Pallidal stimulation for dystonia. *Neurosurgery* 2004;55:1361–1368; discussion 68–70, http://dx.doi.org/10.1227/01.NEU.0000143331.86101.5E.

7. Bereznai B, Steude U, Seelos K, Botzel K. Chronic high-frequency globus pallidus internus stimulation in different types of dystonia: a clinical, video, and MRI report of six patients presenting with segmental, cervical, and generalized dystonia. *Mov Disord* 2002;17:138–144, http://dx.doi.org/10.1002/mds.1250.

8. Vasques X, Cif L, Gonzalez V, et al. Factors predicting improvement in primary generalized dystonia treated by pallidal deep brain stimulation. *Mov Disord* 2009;24:846–853, http://dx.doi.org/10.1002/mds.22433.

9. Katsakiori PF, Kefalopoulou Z, Markaki E, et al. Deep brain stimulation for secondary dystonia: results in 8 patients. *Acta Neurochir (Wien)* 2009;151:473–478; discussion 78, http://dx.doi.org/10.1007/s00701-009-0281-x.

10. Comella CL, Leurgans S, Wuu J, et al. Rating scales for dystonia: a multicenter assessment. *Mov Disord* 2003;18:303–312, http://dx.doi.org/10.1002/mds.10377.

11. Tagliati M, Krack P, Volkmann J, et al. Long-term management of DBS in dystonia: response to stimulation, adverse events, battery changes, and special considerations. *Mov Disord* 2011;26 Suppl 1:S54–62.