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Importance of the initial response to GPi deep brain stimulation in dystonia: A nine year quality of life study

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A B S T R A C T

Background: Long-term efficacy of deep brain stimulation (DBS) on health-related quality-of-life (HRQoL) for isolated dystonia is not well established. This study aims to determine the long-term impact of DBS on HRQoL outcomes and identify clinical predictors.

Methods: We retrospectively investigated 16 inherited or idiopathic isolated dystonia patients treated with bilateral globus pallidus internus DBS who were followed beyond 9 years at our center. The cohort consisted of 9 males, 7 females; 10 generalized, 6 segmental; mean (range) age at implantation, 37.0 (8–67) years; mean follow-up duration after implantation, 10.9 (9–13) years. We employed the Unified Dystonia Rating Scale for motor and Short Form Health Survey for HRQoL assessments to monitor the change longitudinally. We analyzed the changes in motor and HRQoL at 1–2 years (short-term) and ≥9 years (long-term) follow-up as compared to baseline with a Wilcoxon signed-rank test. We assessed the factors that predicted motor and HRQoL improvement with univariate regression analyses.

Results: Motor (41.6%; $p = 0.004$) and HRQoL (total score, $p = 0.039$) improvements remained significant at long-term follow-up and, in the regression analysis, change in HRQoL outcomes correlated significantly with change in motor outcomes ($R^2 = 0.384$, $p = 0.010$). Additionally, short-term motor and HRQoL improvements predicted the long-term motor ($R^2 = 0.384$, $p = 0.010$) and HRQoL (total score, $R^2 = 0.594$, $p < 0.001$) outcomes, respectively.

Conclusion: Motor and HRQoL improvements with DBS in isolated dystonia remain sustained for nearly a decade and may largely be predictable by the short-term response to DBS.

1. Introduction

Deep brain stimulation (DBS) is an effective surgical therapy for medication refractory inherited or idiopathic isolated dystonia (formerly, primary dystonia) [1,2]. Dystonia is primarily a disabling motor disorder but can impact all aspects of health-related quality-of-life (HRQoL) including the mental, pain, and social domains [3]. Prospective studies have demonstrated that improvements in motor dysfunction, disability, and HRQoL sustained for up to 5 years after bilateral globus pallidus internus (GPi) implantation [1,2]. Although a few retrospective studies have reported favorable motor outcomes with GPi DBS beyond 5 years [4–6], there has been little assessment on the long-term impact on HRQoL. Hogg et al. recently reported improvements in HRQoL with either GPi or subthalamic nucleus (STN) DBS at a mean postoperative period of 10.5 years in a dystonia cohort of mixed etiologies. However, limitations of this study were the lack of motor outcomes and preoperative HRQoL assessments [7]. Another study reported that patients with isolated dystonia experience sustained HRQoL improvements at 10 or more years after STN DBS but there was no analysis of predictive factors for the long-term outcomes [8].

In the current study, we present motor and HRQoL outcomes of patients with inherited or idiopathic isolated dystonia who underwent bilateral GPi DBS at our center and were followed longitudinally for 9 or more years after surgery. We aimed to determine if the motor benefits with DBS could inform a parallel improvement in HRQoL and we sought to identify clinical factors that may predict long-term outcomes.

2. Methods

2.1. Subjects

The inclusion criteria for this retrospective IRB-approved study were as follows. (1) diagnosis of isolated dystonia according to the consensus criteria [9], (2) DBS targeted to bilateral GPi between 2003 and 2008 with pre and serial postoperative assessments for motor and HRQoL scores, (3) no prior brain surgery, (4) no acquired etiologies, and (5) all participants maintaining ≥ 9 years of follow-up after surgery.

2.2. Surgical and postoperative management

DBS electrodes (model 3387; Medtronic, USA) and the latest pulse

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Table 1
Participant baseline characteristics and DBS outcomes beyond 9 years.

Pt	Sex	Age at surgery (yr)	Disease duration (yr)	Follow-up after surgery (yr)	*TOR1A* mutation	Body distribution before surgery	Region of onset	Preoperative UDRS score						Postoperative total UDRS score (%improvement)		New regions after surgery	Medications		Additional implantations
								UF	LF	N	UL	LL&T	Total	Short-term (1–2 yrs)	Long-term (≥9 yrs)		Before surgery	≥9 yrs	
1	F	40	2	12	N.A.	Generalized	UL	0	2	6	16	28	52	5 (90%)	6 (88%)	UF	a,b,c,d	e,f	
2	F	24	12	13	+	Generalized	LL	0	7	4	13	26	50	15 (70%)	26 (48%)	UF	b,e,g	b,d,e,g	
3	M	15	7	9	–	Generalized	LL	0	3	7	10	19	39	18 (54%)	25 (36%)	UF	b,f		
4	M	48	5	13	N.A.	Segmental	UF	7	13	4	0	0	24	15 (38%)	6 (75%)		b		
5	F	16	2	12	–	Generalized	UL	4	9	7	22	18	60	7 (88%)	29 (52%)		a,b	b,e	
6	F	60	32	11	N.A.	Segmental	N	0	0	7	5	0	12	7 (42%)	6 (50%)				
7	F	14	13	10	–	Generalized	UL	0	6	2	28	40	76	35 (54%)	34 (55%)		a,g	g	
8	M	32	24	11	+	Generalized	UL	2	2	0	26	14	44	14 (68%)	6 (86%)				
9	M	62	14	9	N.A.	Segmental	N	0	0	7	0	5	12	4 (67%)	2 (83%)		e		
10	M	35	8	10	N.A.	Segmental	N	0	0	8	0	0	8	0 (100%)	2 (75%)			f	
11	M	67	10	9	N.A.	Segmental	UF	8	6	5	0	0	19	7 (63%)	5 (74%)		e,g	g	
12	M	8	2	12	+	Generalized	UL	0	3	0	20	10	33	36 (−9%)	55 (−67%)	UF	a	e	R GPi, R STN
13	F	42	9	11	–	Segmental	N	0	0	8	3	0	11	7 (36%)	6 (45%)		f	e,f	L GPi, Bil STN
14	F	47	9	13	N.A.	Generalized	N	0	3	5	12	10	30	8 (73%)	39 (−30%)	UF	d,h	f,h	Bil Vim
15	M	11	6	9	+	Generalized	LL	0	5	7	24	19	55	38 (31%)	41 (25%)	UF	a	b	L STN
16	M	33	20	10	–	Generalized	N	2	20	6	20	19	67	36 (46%)	58 (13%)		b,c,f	b,f	Bil STN

DBS = deep brain stimulation; N.A. = Not Assessed; UDRS = Unified Dystonia Rating Scale; Regions: UF = Upper face, LF = Lower face, N = Neck, UL = Upper limb, LL = Lower limb, T = Trunk. Lower face subscores include lower face, jaw, tongue, and larynx items. Upper limb subscores include arm and hand items. Trunk and lower limb subscores include trunk, leg, and foot items; Medications: a = Anticholinergics, b = Antispasmodics, c = Levodopa/carbidopa, d = Antiepileptics, e = Benzodiazepines, f = Analgesics, g = Botulinum toxin injection, h = Beta blockers; Additional implantations: Bil = Bilateral, GPi = globus pallidus internus, L = Left, R = Right, STN = Subthalamic nucleus, Vim = ventral intermediate nucleus.

Table 2
Outcomes of motor function and quality of life beyond 9 years.

	Baseline	1–2 yrs	3–5 yrs	6–8 yrs	≥9 yrs	*p* value 1–2 years vs baseline	*p* value 3–5 years vs baseline	*p* value 6–8 years vs baseline	*p* value ≥9 yrs vs baseline
UDRS									
Total	37.0 (21.7)	15.8 (13.1)	17.9 (18.2)	14.9 (18.3)	21.6 (19.4)	< 0.001	< 0.001	< 0.001	< 0.001
Upper face	1.4 (2.6)	0.8 (1.7)	0.7 (1.8)	0.6 (1.3)	1.3 (1.7)	0.084	0.236	0.046	0.117
Lower face	4.9 (5.4)	3.3 (4.0)	3.6 (5.0)	3.5 (5.7)	5.0 (6.2)	0.134	0.307	0.081	0.017
Neck	5.2 (2.6)	2.7 (2.7)	1.9 (2.2)	2.0 (2.0)	2.9 (2.6)	0.008	< 0.001	0.002	0.001
Arm	12.4 (10.2)	3.6 (4.8)	5.1 (5.8)	3.8 (5.4)	6.1 (6.6)	0.002	0.002	< 0.001	< 0.001
Leg & trunk	13.0 (12.1)	5.4 (5.7)	6.7 (8.5)	4.9 (6.9)	6.4 (8.0)	0.005	0.025	0.049	0.003
SF-36									
Physical function	60.3 (30.1)	76.9 (27.4)	75.0 (32.5)	66.9 (32.4)	61.6 (34.9)	0.021	0.133	0.244	0.452
Role physical	37.5 (44.7)	84.4 (27.2)	87.5 (34.2)	81.3 (33.5)	71.9 (32.8)	0.006	0.013	0.030	0.043
Bodily pain	52.9 (28.9)	72.3 (25.1)	67.4 (24.0)	67.1 (23.5)	61.7 (23.7)	0.073	0.078	0.062	0.167
General health	63.7 (12.7)	79.1 (19.8)	73.3 (21.5)	66.4 (22.2)	69.5 (18.5)	0.013	0.078	0.535	0.256
Vitality	54.7 (20.0)	73.1 (15.4)	68.1 (23.2)	63.4 (21.3)	60.3 (24.5)	0.018	0.031	0.073	0.190
Social function	66.6 (28.7)	85.3 (19.9)	84.5 (18.9)	83.0 (22.2)	77.4 (21.9)	0.028	0.013	0.007	0.101
Role emotional	70.8 (38.3)	95.8 (16.8)	87.5 (34.2)	79.1 (38.3)	85.4 (34.3)	0.055	0.368	0.527	0.121
Mental health	73.0 (20.1)	87.5 (15.1)	83.5 (15.0)	79.5 (17.5)	81.8 (15.5)	0.021	0.083	0.299	0.068
Total	42.8 (9.4)	52.4 (5.6)	50.9 (7.3)	48.9 (7.8)	47.7 (8.3)	0.002	0.009	0.013	0.039
PCS	39.5 (9.6)	47.1 (10.5)	46.6 (9.5)	44.5 (10.2)	43.9 (10.2)	0.011	0.034	0.098	0.056
MCS	46.1 (10.1)	57.6 (9.1)	55.1 (8.1)	53.3 (12.2)	51.5 (9.1)	0.005	0.010	0.011	0.039

Values are mean ± SD. Changes in UDRS and SF-36 over time were assessed using Wilcoxon signed-rank test. P value < 0.05 was considered significant. Lower face subscores include lower face, jaw, tongue, and larynx items. Upper limb subscores include arm and hand items. Trunk and lower limb subscores include trunk, leg, and foot items. MCS = Mental component summary; PCS = Physical component summary; SF-36 = Short Form Health Survey-36; UDRS = Unified Dystonia Rating Scale.

generators available at the time of surgery (Activa PC/SC, Soletra, or Kinetra; Medtronic) were implanted. The detailed information of surgical procedures and electrode measurements are available in Supplementary material. Following the surgery, each patient underwent monthly adjustment of stimulation settings and medications until optimal control of symptoms was established. Patients had visits at least annually for clinical assessments and adjustment of stimulation settings and medications.

2.3. Outcome measures

Motor and HRQoL were evaluated at baseline. The follow-up evaluations after surgery were sorted into four time intervals (1–2 years, 3–5 years, 6–8 years, and ≥9 years). Dystonia motor severity was recorded with the Unified Dystonia Rating Scale (UDRS) administered by fellowship-trained movement disorders specialists [10]. Items were summarized into five subdomains: upper face, lower face (including lower face, jaw, tongue, and larynx), neck, upper limb (arm and hand), trunk and lower limb (trunk, leg, and foot). Total scores of UDRS were also calculated. Patients filled out a standard HRQoL questionnaire, Short Form Health Survey-36 (SF-36), during their follow-up visits [11]. The eight domains of SF-36 were assessed and summarized into Total, physical component summary (PCS) and mental component summary (MCS) scores. The SF-36 total score was calculated by averaging the value of PCS and MCS.

2.4. Statistical analysis

The follow-up evaluations at 1–2 years were regarded as short-term and ≥9 years were regarded as long-term follow-up. Primary non-responders were defined as patients who had < 25% improvement on UDRS at 1–2 years. Secondary non-responders were patients who had > 25% improvement at 1–2 years with subsequent loss of benefits (< 25%) at ≥ 9 years. Wilcoxon signed-rank test was applied to compare UDRS and SF-36 at follow-up intervals with baseline scores. Adjustment for multiple comparisons was not performed because of the low statistical power arising from a small sample size. The % change in UDRS total score ($UDRS_{\%change}$) after surgery was calculated with the following formula: (preoperative UDRS – postoperative UDRS)/preoperative UDRS × 100. Change in SF-36 Total, PCS and MCS was calculated by subtracting the postoperative score from the preoperative score ($Total_{\Delta}$, PCS_{Δ} and MCS_{Δ}). Univariate regression analysis was employed to identify factors that predicted motor and HRQoL outcomes at long-term. These factors included age at onset, age at DBS, disease duration before surgery, body distribution before surgery, preoperative total UDRS, $UDRS_{\%change}$ and SF-36 $Total_{\Delta}$, PCS_{Δ} and MCS_{Δ} at short-term. Statistical significance was set to p values < 0.05. Statistical analysis was performed with IBM SPSS statistics 25 (Armonk, NY, IBM Corp).

3. Results

3.1. Study sample

Twenty-four patients with inherited or idiopathic isolated dystonia who underwent bilateral GPi DBS between 2003 and 2009 were enrolled. Eight patients were excluded due to the following reasons. Five patients relocated to other states, one died unexpectedly, one was lost to follow-up for unclear reason and one did not have the preoperative evaluation. The mean motor improvement for the excluded patients was 42% with the mean follow-up after surgery of 2.9 ± 2.1 years. The final cohort comprised of 16 patients with 9 males, 7 females; 10 generalized, 6 segmental; mean (range) age at onset, 23.7 (1–57) years; age at implantation, 37.0 (8–67) years; disease duration before implantation, 10.9 (2–32) years; and follow-up period after implantation, 10.9 (9–13) years. There were four generalized dystonia patients carrying *TOR1A* mutation. Five patients developed dystonia symptoms in new body regions after surgery (patients 1, 3, 12, 14 and 15). Further details on body distribution, UDRS, and medications are provided in Table 1. Additionally, DBS programming data, electrode coordinates, and medication are summarized in Supplementary Results and Table 1.

3.2. Motor outcomes

UDRS scores at baseline and at each follow-up interval are shown in Table 2 and Fig. 1A. Compared to baseline, UDRS scores significantly

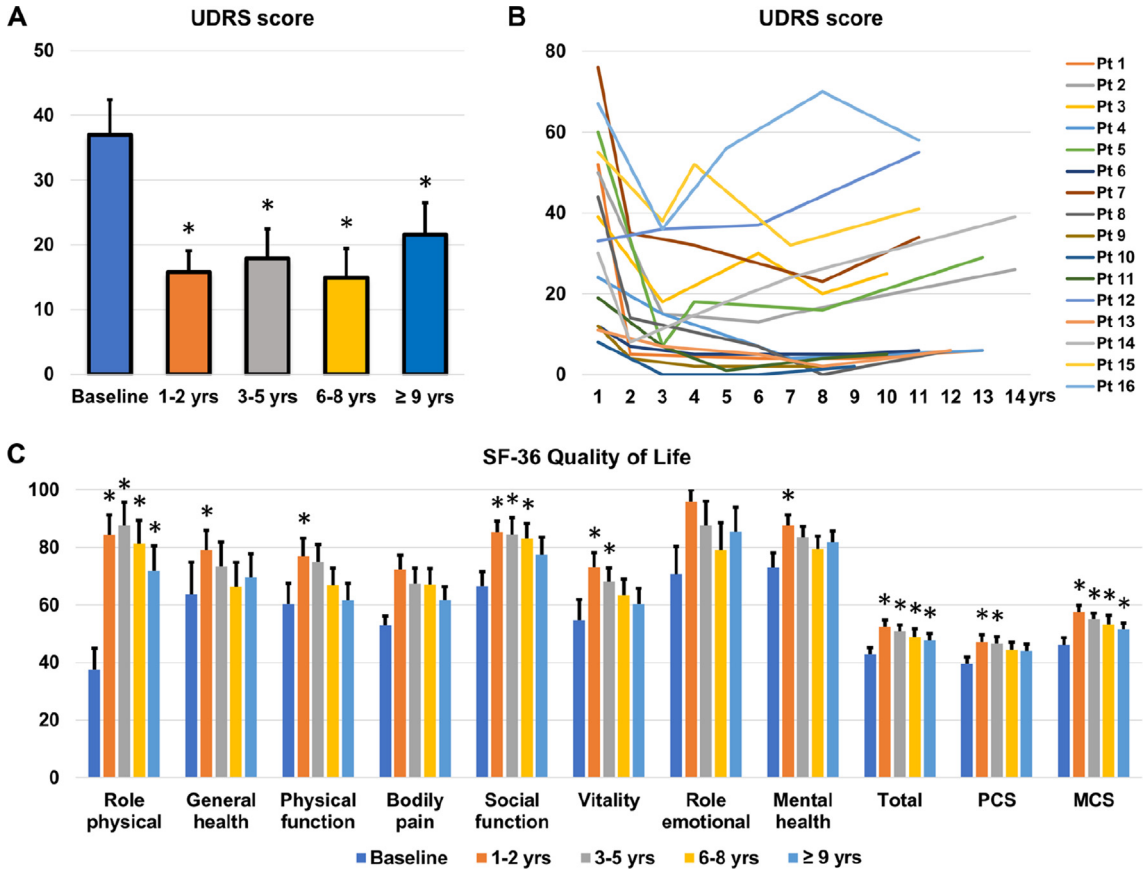

Fig. 1. (A) Longitudinal changes in UDRS total scores. Bars represent the mean and whiskers represent the standard error. (B) Line graphs show individual UDRS scores at baseline and at multiple follow-up intervals after surgery. (C) Longitudinal changes in SF-36. Bars represent the mean and whiskers represent the standard error. * indicate significant improvements as compared to baseline according to Wilcoxon signed-rank tests ($p < 0.05$). MCS = mental component summary; PCS = physical component summary; SF-36 = Short Form Health Survey-36; UDRS = Unified Dystonia Rating Scale.

improved at 1–2 years (57.3%, $p < 0.001$), 3–5 years (51.6%, $p < 0.001$), 6–8 years (59.7%, $p < 0.001$), and at ≥ 9 years after surgery (41.6%, $p = 0.004$). UDRS subdomains for neck, arm, and leg & trunk also significantly improved at all follow-up intervals (all $p < 0.05$).

UDRS changes in individual patients are provided in Table 1 and Fig. 1B. Patients 1–11 experienced sustained benefits with bilateral GPi DBS with a mean 66.1% (range, 36–88%) improvement in UDRS at ≥ 9 years. In contrast, patients 12–16 required additional implantations during the follow-up to rescue the worsening dystonia symptoms. All the electrodes except for the initial left GPi electrode in patient 13 were placed within the posteroventrolateral GPi, the STN, or the Vim.

The responder analysis showed a clinically-relevant response (> 25% improvement) in 15 patients (93.8%) at 1–2 years and 12 patients (75.0%) at ≥ 9 years. One patient (6.3%) was a primary non-responder and 3 patients (18.8%) were classified as secondary non-responders.

Patients 12 and 15 carrying *TOR1A* mutation were primary and secondary non-responders, respectively. These patients developed dystonia in their childhood and underwent GPi DBS with a relatively short disease duration. However, both patients developed dystonia in the upper face during the follow-up. The bilateral GPi electrodes in patient 12 were replaced one year after the initial implantation because of migration. Dystonia symptoms were worse on the left side and worse in the lower extremity compared to the upper extremity. Thus, a second right GPi electrode anterior to the initial electrode was implanted and an electrode was subsequently implanted in the right STN. However, these additional implantations did not improve symptoms. The left GPi electrode in patient 15 migrated possibly because of growth and was replaced eight years after the implantation. Considering that dystonia symptoms were worse on the left side, the patient underwent right STN implantation but did not have meaningful improvements.

Patients 14 and 16 responded well in short-term (% improvement in UDRS; 73% and 46%, respectively) but turned out to be secondary non-responders. Both patients initially presented with adolescent onset neck dystonia which later spread to involve multiple body regions at the time of surgery. Dystonia symptoms continued to worsen in these two patients during the follow-up. Vim DBS for patient 14 provided remarkable benefits in dystonic head tremor with little improvement of neck posturing.

Patient 13 with segmental dystonia who did not show initial good response to left GPi DBS due to the suboptimally-placed electrode (anterior to the posteroventrolateral GPi). Additional targeting of left posteroventrolateral GPi was performed and electrodes were subsequently implanted in the bilateral STN which led to 45% UDRS improvement at long-term.

3.3. HRQoL outcomes

In regards to SF-36 (Table 2 and Fig. 1C), there were significant improvements in Total ($p = 0.002$), PCS ($p = 0.011$), and MCS ($p = 0.005$) scores at 1–2 years follow-up whereas improvements remained significant at ≥ 9 years only for Total ($p = 0.039$) and MCS ($p = 0.039$). In the individual domain analysis, role physical ($p = 0.006$), physical function ($p = 0.021$), general health ($p = 0.013$), vitality ($p = 0.018$), social function ($p = 0.028$), mental health ($p = 0.021$) significantly improved at 1–2 years whereas bodily pain ($p = 0.073$) and role emotional ($p = 0.055$) showed only a tendency to

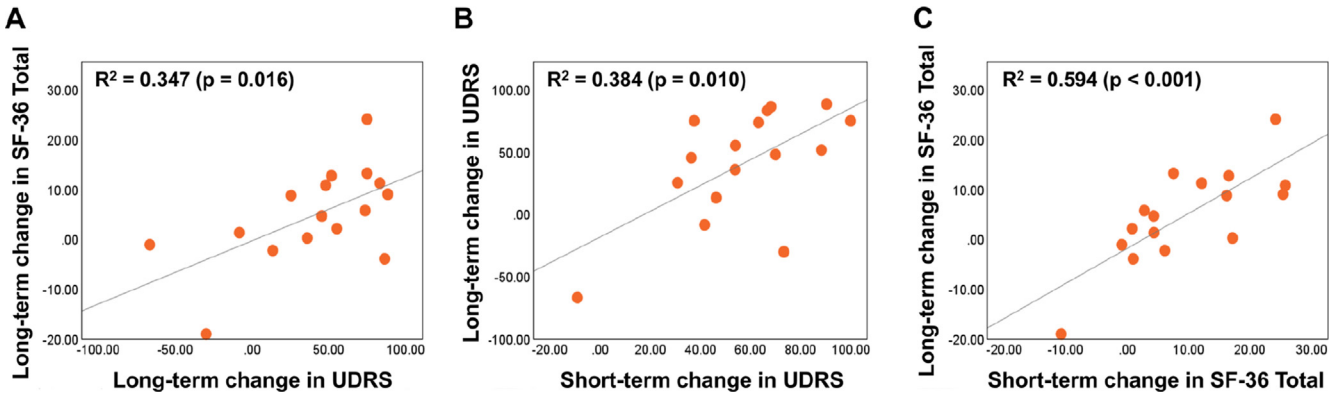

Fig. 2. Univariate analyses with regression lines show significant relationships between long-term changes in UDRS and long-term changes in SF-36 Total scores (A), between short- and long-term changes in UDRS (B), and between short- and long-term changes in SF-36 Total scores (C). SF-36 = Short Form Health Survey-36; UDRS = Unified Dystonia Rating Scale.

improve. Role physical ($p = 0.013$), vitality ($p = 0.031$), and social function ($p = 0.013$) remained significantly improved at 3–5 years. Then, at 6–8 years follow-up, role physical ($p = 0.030$) and social function ($p = 0.007$) remained significantly improved. Finally, at long-term follow-up at ≥ 9, only role physical ($p = 0.043$) maintained significance.

3.4. Univariate regression analysis

SF-36 Total$_{\Delta}$ at long-term follow-up was associated with UDRS$_{\%change}$ at long-term ($R^2 = 0.347$, $p = 0.016$, Fig. 2A). None of the baseline factors predicted long-term motor and HRQoL improvements (all $p > 0.05$). However, UDRS$_{\%change}$ at short-term follow-up predicted UDRS$_{\%change}$ at long-term ($R^2 = 0.384$, $p = 0.010$, Fig. 2B). Similarly, SF-36 Total$_{\Delta}$, PCS$_{\Delta}$ and MCS$_{\Delta}$ at short-term follow-up predicted SF-36 Total$_{\Delta}$, PCS$_{\Delta}$ and MCS$_{\Delta}$ at long-term ($R^2 = 0.594$ $p < 0.001$, Fig. 2C; $R^2 = 0.384$, $p = 0.010$; $R^2 = 0.293$, $p = 0.030$, respectively).

3.5. Adverse effects

Nine hardware-related adverse events occurred during the follow-up (three electrode breakage; one stimulator malfunction; two extension cable fracture; and two electrode migration). Five patients experienced subcutaneous infection, which required removal of the devices. Stimulation-related adverse events included dysphagia in one patient treated with GPi DBS, ataxia in patient 14 treated with both bilateral GPi and Vim DBS, and apathy in patient 13 who was treated with both bilateral GPi and STN DBS. Apathy resolved immediately after the left STN stimulation was stopped.

4. Discussion

In the present study on patients with inherited or idiopathic isolated dystonia who underwent bilateral GPi DBS surgery at our center, motor and HRQoL remained significantly improved at 9 or more years after surgery compared to baseline status. The improvements in HRQoL at long-term were closely correlated to the motor outcomes. Furthermore, most of patients with favorable short-term outcomes in motor and HRQoL domains, continued to demonstrate sustained improvements at long-term follow-up. A minority of patients experienced secondary worsening of dystonia symptoms after brief initial improvement during the course of their follow-up.

Motor improvement by 57.3% at 1–2 years (short-term) and 41.6% at ≥ 9 years (long-term) with a responder rate of 93.8% at 1–2 years and 75.0% at ≥ 9 years were comparable to previously published cohorts with generalized and/or segmental dystonia [1,2,5,12]. All the electrodes except for the initial left GPi electrode in patient 13 were placed within the posteroventrolateral GPi which is considered as an optimal target for dystonia patients [1,4,13]. A recent study using diffusion tensor imaging showed considerable variability of functional parcellation of the GPi among patients [13], which might contribute to the variable DBS outcomes in our cohort. Furthermore, we will discuss other possible factors responsible for poor outcomes in non-responders in the subsequent paragraphs.

Patients 12 and 15 who carried *TOR1A* mutation did not respond well to DBS even with additional bilateral STN implantation. These patients had childhood onset dystonia, a rapid clinical course before surgery, and facial dystonia which is uncommon in patients with DYT-*TOR1A*. *TOR1A* mutation has been proposed as a factor influencing positive outcomes with GPi DBS [15–17]. However, there are individual cases which have revealed a suboptimal response to GPi DBS. For example, two child patients with DYT-*TOR1A* responded poorly to GPi DBS with optimally-placed electrodes [18]. Cif et al. also reported that, in their case series of 26 patients with DYT-*TOR1A*, that 4 patients experienced suboptimal outcomes after bilateral GPi DBS even after implanting a second pair of companion electrodes within bilateral GPi [4]. Non-c.907_909delGAG variants/mutations in *TOR1A* gene or additional mutations in distinct genes may possibly affect clinical phenotypes and response to DBS [19].

Patients 14 and 16 responded well in the short-term but had secondary worsening despite optimally-placed electrodes. In patient 14, additional bilateral Vim implantation provided an excellent control of head tremor but did not improve the neck posturing. Given that the UDRS does not measure dystonic tremor, the scores at long-term could not reflect these improvements. Moreover, the DBS target for patients with dystonia and dystonic tremor remain less clear. Small case series have reported good tremor suppression after Vim DBS with or without improvement in dystonia [20,21]. Dystonia has been reported to worsen with time, emerging in previously unaffected body regions despite initial improvement with DBS [22,23]. One possible underlying reason that was not completely explored in our cohort was the genetic factors, such as the *THAP1* mutation. The *THAP1* mutation has been linked to worse long-term DBS outcomes [24,25]. Further researches on genetic contributions may prove critical.

HRQoL outcomes have been widely regarded as a reliable and important marker for therapeutic outcomes [14]. However, there is limited data on HRQoL outcomes in patients with isolated dystonia with most studies reporting up to 5 years after GPi DBS. In our study, although there were significant improvements in SF-36 Total and MCS throughout the follow-up, PCS improvements did not reach significance at long-term. Possible reasons for this difference included a relatively small sample size of our cohort and a lower degree of motor improvement at long-term compared to short-term. With regard to specific domains, there were three domains with significant improvements at

3–5 years follow-up. This was consistent with other prospective studies with 3–5 years follow-up [1,2]. However, at long-term follow-up, we found only one domain (role physical) demonstrated significant improvements. In contrast, the Hogg et al.'s study reported improvements across all domains at a mean postoperative period of 10.5 years [7]. There are several possibilities to explain these discrepancies. Their study included patients who responded to invitations sent through social media (potential selection bias). Additionally, they did not longitudinally track the HRQoL outcome, and instead asked these patients to recollect the baseline HRQoL status 10 years before (potential recall bias). In the present study, we enrolled all patients who underwent GPi DBS surgery at our center and included the reasons for exclusion. Additionally, there was no risk of recall bias as all HRQoL assessments were performed regularly during each follow-up visit.

Previous studies showed that a shorter disease duration, younger age, DYT-*TOR1A*, and less severe motor impairment may be favorable prognostic factors although there remains some degree of disagreement between reports [15,16,26–29]. Early intervention with DBS is considered beneficial to avoid potential secondary skeletal deformities [26]. A recent meta-analysis demonstrated that higher motor and disability scores before surgery and a younger age at implantation were the main factors associated with better motor outcomes [30]. These discrepancies may be related to the inherent differences in the cohorts included and the statistical methods used in these analyses. In our cohort, we did not find these baseline factors to predict long-term outcome. However, an important finding of our regression analysis was that improvements in motor scores observed early in the course of follow-up at 1–2 years predicted long-term motor outcome. Likewise, improvement in HRQoL according to Total, PCS and MCS at 1–2 years also predicted favorable outcome for Total, PCS and MCS at long-term, respectively. These observation have a high likelihood of informing clinical practice.

The most frequent adverse events in our study were hardware-related, and this finding was consistent with other reports [1,26]. Electrode migrations, likely a consequence of growth in stature, were observed in two patients who underwent DBS during childhood. One patient developed ataxia after additional thalamic implantation, which has also been reported commonly with thalamic DBS [31]. Stimulation-induced apathy was observed in one patient who underwent additional STN implantation. This may have been related to spread of current into the limbic region of the STN [32].

Our sample was well-defined and there was clear delineation of the reasons for excluded patients, and this minimized any potential selection bias. We included only patients who reached a 9 year milestone in order to clarify the determinant of very long-term HRQoL outcomes. However, we acknowledge the interpretation of the current study findings may have been limited because the data was analyzed retrospectively and all assessments were open label. Because of the low statistical power arising from a small sample size, we did not perform adjustment for multiple comparisons which may lead to a potential increase of Type I error. Although our HRQoL outcomes at 3–5 years were consistent with prospective studies, verification of the long-term outcomes is warranted in large samples.

5. Conclusion

In the present study, we demonstrated that, in patients with inherited or idiopathic isolated dystonia, motor and HRQoL improvements after bilateral DBS remains sustained 9 or more years after surgery. Importantly, motor and HRQoL improvements seen at short-term may predict favorable long-term outcomes. A minority of patients demonstrate secondary worsening and a small number of individuals may improve with electrode implantations in additional targets. The genetic variants/mutations that may factor into optimal or suboptimal response to DBS remain undefined. Understanding the clinical phenotypes and the genetic factors influencing DBS outcomes can help clinicians advising individuals on the potential response and sustainability of the intervention.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.04.024.

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